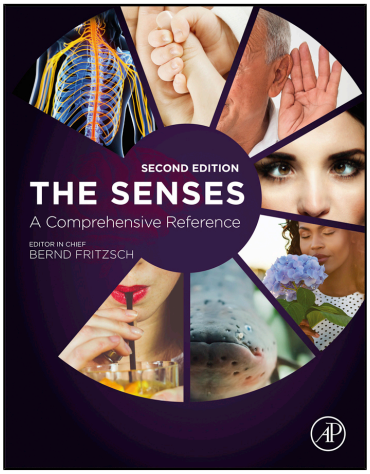

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3.35 Role of Olfaction for Eating Behavior

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Glossary

Acinar cell the exocrine cell of the pancreas that synthesizes and releases digestive enzymes for the purposes of reaching the duodenum

Ad libitum from the Latin "as you desire" frequently vulgarized into "as needed"

Adenylate cyclase a regulatory enzyme that catalyzes ATP to cycle adenosine monophosphate, or cAMP

Adipose tissue loose connective tissue used for fat storage; made of adipocytes (fat cells)

Anorexigenic a signal or drug that reduces appetite, resulting in lower food consumption

Anosmia the loss of the sense of smell

Anxiolytic a drug or behavior that is used to reduce the symptoms and presence of anxiety

Astrocytes from the Greek 'astron' or star; star-shaped glial cells located in the brain and spinal cord

Beta adrenergic receptors G-protein-coupled-receptors responsible for binding catecholamines such as norepinephrine and epinephrine, involved in the adrenaline response

Biotinylation process involving the attachment of biotin to a protein, nucleic acid, or other molecule; commonly used for non-radioactive labeling.

Bowman's Glands (olfactory glands) a nasal gland found in the main olfactory epithelium; secretes mucus to moisten the olfactory surface and possibly to enhance the detection and binding of odor molecules

Bulbectomy surgical removal of the olfactory bulbs

Carbodiimide a synthetic organic chemical functional group with formulas RN=C=NR

Cribriform plate part of the ethmoid bone of the nasal cavity that supports the olfactory bulb

Ectopic expression abnormal gene expression, outside of the normal time or location for that gene to be expressed

Electroolfactogram a recording device that measures the change in potential of the olfactory epithelium as a result of odor presentation

Electrogenic transport movement of ions across the cell membrane such that a net charge is transported across the membrane

Endocannabinoids lipid-based neurotransmitters that bind to cannabinoid receptors often regulating or fine tuning homeostasis in vertebrates.

Entorhinal cortex a region of the brain located in the medial temporal lobe. The interface between the hippocampus and neocortex, participates in memory, navigation, and the perception of time

Euglycemia state in which the body's glucose concentration levels are normal

Fiber photometry a technique that uses calcium indicators to record the activity of specific neuronal populations; data is collected through the implantation of optical fibers near the brain region of interest

fMRI Functional Magnetic Resonance Imaging used to detect changes in blood flow and map brain activity non-invasively.

G protein a guanine nucleotide-binding protein, able to hydrolyze GTP to GDP to signal cellular events

G-protein-coupled-receptor a seven-transmembrane domain receptor proteins that detects events outside of a cell, activating internal signaling pathways by way of a coupled G-protein

GABA (gamma-aminobutyric acid) a primary inhibitory neurotransmitter of the central nervous system

Ghrelin an orexigenic hormone that promotes appetite and food intake

Glomerulus (olfactory bulb) a small cluster of nerve endings wherein the terminals of the olfactory nerve (olfactory sensory neuron axons) synapse to the dendrites of mitral cell, periglomerular cells and tufted cells

Glutamatergic a neuron that releases or a drug that impacts excitatory glutamate or aspartate neurotransmitters in the brain

Glycaemia a measure of the amount of glucose present in the blood

Hedonic pertaining to or achieving a level of pleasantness

Hyperphagia a significant increase in appetite or food intake

Immunolocalization the use of immunological techniques such as antibody labeling to identify the location or expression level of a target protein or molecule

Incretin hormones metabolic hormones that augment the release of insulin in response to food intake

Intracerebroventricular infusion administration of a drug directly into the ventricles of the brain, bypassing the blood-brain barrier that would otherwise prevent drug entry into the brain
Islets of Langerhans cells of the endocrine pancreas named for Paul Langerhans who first discovered them; their functions include the production of metabolic hormones such as insulin and glucagon
Juxtaglomerular positioned near but separate from a glomerulus
Kv1.3 voltage-dependent potassium channel, type 1, member 3
Lamina propria thin layer of tissue beneath the epithelium present in mucosa
Malaise a feeling of unease and discomfort that is not easily identifiable
Margatoxin a pore blocking peptide that binds the vestibule of Kv1.3 voltage-dependent ion channels
Mesolimbic the dopaminergic reward pathway in the brain
Mitophagy degradation of the mitochondria by autophagy as a result of damage or high levels of stress
Mitral (cell) the primary projection neurons of the olfactory bulb, named for the characteristic mitre shape of their cell bodies
Occludin transmembrane protein that is important for the stability and function of tight junctions
Optogenetics a technique that uses genetically encoded light-responsive proteins to selectively control the activity of cells in live animals or preparations; allows for the study of function at the level of neurons and neural networks
Orexigenic a drug or hormone that stimulates appetite or food intake
Orexin (alpha or beta) orexigenic hormones produced by the hypothalamus
Piriform cortex brain region that receives input from the olfactory bulb and serves as a higher-order processing center for olfactory information
Plethysmograph an instrument used to measure changes of volume within a system of study, particularly an organ
Postprandial the period after a meal
Preprandial odor sensitivity an increase in odor sensitivity before a meal thought to enhance food-seeking behavior
Pyramidal cells neurons with multiple dendritic projections that act as primary excitation centers for signaling
Slice electrophysiology a technique for measuring the *ex vivo* activity of neurons in brain sections or slices
Sniffin' Sticks pen-like delivery device used to test olfactory performance by using gradations of scents in psychophysical tests on humans
Stellate neuron any neuron that has a star-like appearance, usually GABAergic
Suprachiasmatic nuclei a region of the hypothalamus that regulates physiological circadian rhythms
Sustentacular cell a non-neuronal cell in the apical layer of the pseudostratified ciliated columnar epithelium that affords structural and metabolic support
TDI score an olfactory metric of the Sniffin' Stick Test representing threshold, discrimination, and identification measures, a TDI of < 16.5 is anosmic, > 30 is normosmic (normal olfactory detection ability)

3.35.1 Abstract

Richard Axel, a Nobel Laureate in Physiology and Medicine in 2004, has described how odorant chemicals are transduced into an internal representation of our external world (Axel, 2005). We are now starting to uncover that the olfactory system not only encodes external chemical cues but importantly detects internal chemical cues, or the chemistry of metabolism, nutrition, and eating. There is a world of communication between the gut and the brain (Mayer, 2011) and the olfactory system is not excluded from that pathway of communication. Moreover, signaling pathways that are comprised of metabolic hormones and nutritionally important molecules are highly expressed in the olfactory system and act locally to adjust olfactory physiology, the detection of odorants, and ultimately eating behaviors (Palouzier-Paulignan et al., 2012; Julliard et al., 2017). Herein, we will describe the distribution and function of these pathways and how they regulate physiology and olfactory behaviors, we will explore how fasting, circadian biology, eating, and excess nutrition (obesity) affect olfactory structures and function, will reflect on how a number of animal models and drug delivery approaches have revealed a link between olfactory behaviors and metabolism, and finally discuss how human olfaction is changed with altered eating, metabolism, or nutrition.

3.35.2 Olfaction Is an Intriguing Sensory Modality

Of all our sensory modalities, olfaction captures a unique dimension of our environment and can transport us to another place, time, or mood within the span of a few milliseconds. Essential for mating and survival among animals, it may provide another trajectory of function in humans in terms of shaping quality of life (Croy et al., 2014) and our eating behavior (Fedoroff et al., 1997). Interestingly, neurodegeneration, dementia, and metabolic dysfunctions demonstrate deficits in our olfactory function

(Murphy et al., 1990; Mesholam et al., 1998; Palouzier-Paulignan et al., 2012) and can even be utilized as a predictor of longevity and health (Pinto et al., 2014). On top of our curiosity for olfactory physiology and operation of this sense, is a neuroanatomically fascinating laminated structure (Internet 3), the home of the discovery of the largest superfamily of G-protein coupled receptors (Buck and Axel, 1991), a haven of second-messenger signaling cascades to transduce olfactory information (Antunes and Simoes de Souza, 2016), and a high level of intrigue for synaptic regulation and information coding of the odor message (Shepherd, 1972; Jordan et al., 2018). Scientists have probed the olfactory physiology of the sense of smell for over a century (Ramon y Cajal, 1911; Figueres-Onate et al., 2014), and along the way have applied an array of methods and advancing technologies in each age, to open a small window of understanding of how chemical signals in our environment can ultimately drive behavior.

3.35.3 The Olfactory System Is Home to Metabolic Hormones and Energy Important Molecules that Regulate Eating Behaviors

The hedonic evaluation of food that ultimately results in food choice and consumption heavily depends upon the olfactory sensory system. A classic experiment was performed by Jacques Le Magnen in the 1950s and later translated to English thirty years ago (Le Magnen, 1999). He was the first to observe meal size increases, or hyperphagia, when he presented rats with identical diets that were only varied by the addition of an odor! Such "sensorily varied dishes", as he referenced them, caused over-eating behavior. Today, the endocrine changes that accompany consumption of a meal have been well characterized. Hormones and nutritionally important molecules that govern our state of satiety and hunger are classically defined as either orexigenic or anorexigenic signals, meaning those that stimulate or inhibit food intake, respectively (**Table 1**). When we consume a meal, anorexigenic signals are released from our gastrointestinal tract and peripheral organs into the bloodstream, where they are carried to the central nervous system to modify eating behavior and ultimately drive satiation. While the hypothalamus plays a predominant role in this feedback loop as the center of the neuroendocrine axis that balances homeostatic set-point of body weight and metabolism, the olfactory system also receives these metabolic factors and responds (**Fig. 1**). In fact, the olfactory bulb is only four synapses away from the hypothalamus and recent evidence suggests that odor activation can intercept with sympathetic circuits to modify metabolism (Riera et al., 2017). Likewise, during the interlude between meals or when there is fasting, orexigenic signals build up and initiate a drive to eat so that food consumption matches nutritional need. Receptors for these molecules of appetite regulation, therefore, are not restricted to the hypothalamus and are expressed broadly across the olfactory system, where scientists have been exploring their physiological targets for over forty years.

3.35.3.1 Receptors for Hormones and Energy Important Molecules Are Distributed Broadly Across the Main Olfactory Epithelium, Olfactory Bulb, and Piriform Cortex

From the periphery to higher cortical centers, olfactory structures express a variety of receptors for hormones and metabolic factors. The anatomical distribution of these signaling molecules provided the rationale to explore physiological function and then seek correlative olfactory behavioral responses through activation, deletion, developmental or other manipulation of the signaling pathway. For further reading, readers are referred to a comprehensive report outlining the protein and mRNA expression of both orexigenic or anorexigenic peptides and their receptors as compared across the main olfactory epithelium (MOE), the olfactory

Table 1 Hormones and Metabolic Peptides are Classified as Inducing or Inhibiting Food Intake

orexigenic		anorexigenic	
endocannobinoids	brain	insulin	pancreas
orexin	hypothalamus	leptin	adipose
ghrelin	stomach	GLP-1	intestine

A short table of the major orexigenic (inducing food intake) and anorexigenic (inhibiting food intake) hormones discussed in this chapter. Circle = location where the major source of the hormone is released.

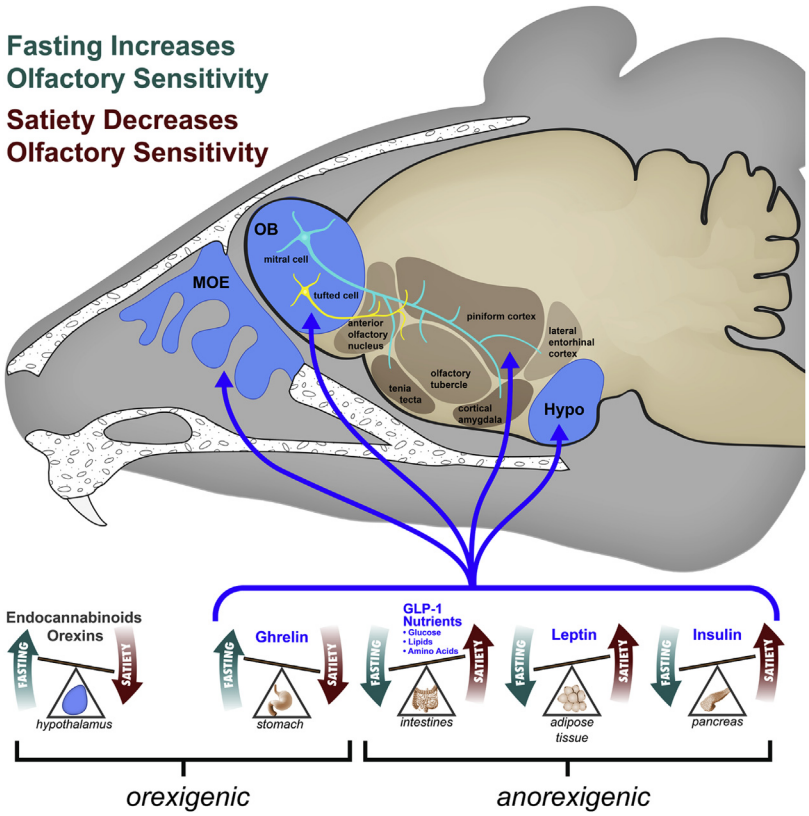

Figure 1 **The Detection of Orexigenic (Stimulating Food Intake) and Anorexigenic (Inhibiting Food Intake) Hormones and Metabolic Factors Across the Olfactory System.** Some of the prominent central and peripheral endocrine hormones and metabolic factors are featured with the position of the 'teeter totter' as a reflection of the change in circulating concentration with nutritional status; fasting (*green*) or satiety (*red*), respectively. The location of the major production of the hormone or factor is indicated within the triangle. Each send neural relays, are transported through the blood brain barrier, or are produced locally in the CNS to modulate physiological activity in the main olfactory epithelium (MOE), olfactory bulb (OB), piriform cortex, and hypothalamus (Hypo). Note the broad synaptic connection to higher olfactory cortices of a prominent output neuron of the OB, the mitral cell (blue), that is discussed frequently in the chapter. Tufted cells also serve as projection or output neurons to different higher regions (yellow). Schematic of mitral and tufted cells and brain regions modified from Imai (2014) by C. Badland.

bulb (OB), and the hypothalamus (Palouzier-Paulignan et al., 2012). Herein, we update a schematic for the major known metabolic receptors expressed in both the MOE and the OB and expand the reported distribution to include the piriform cortex (PC) (Fig. 2). In our text that follows, we discuss the discovery of the expression pattern for a select number of hormone or metabolic receptors and receptors for energy or nutritional factors that pique interest in the chemosensory field and for which there is substantial physiological and behavioral known correlates, which follow in the subsequent section. Included in our text discussion is the olfactory signaling involving insulin, glucose, ghrelin, leptin, endocannabinoids, and glucagon-like peptide-1, or GLP-1.

3.35.3.1.1 Insulin

Insulin is an essential anabolic hormone required to mobilize glucose from the bloodstream for storage of energy in the liver, skeletal muscles, and adipose tissue. Pancreatic β cells within the Islets of Langerhans secrete insulin in response to a well-orchestrated series of responses initiated by consumption of a meal. In the periphery, the rise in blood glucose evokes a depolarization in response to a closure of ATP-dependent potassium channels, followed by a rise in cytoplasmic calcium through voltage-gated calcium channels, which permits exocytotic release of insulin (Bertram et al., 1995; Bertram and Sherman, 2004; Bertram et al., 2010; Henquin, 2011; Henquin et al., 2012). Paul Langerhans was the first to describe "islands of acinar cells" in the pancreas in 1869 that were later named Islets of Langerhans in his honor (Williams et al., 2011). When Joseph von Mering and Oskar Minkowski removed a pancreas from a dog, the first discovery of severe diabetes was reported (Houssay, 1952; Karamanou et al., 2016). In the early 1920s, Frederick Banting and Charles Best successfully were able to extract insulin from the islets (originally called isletin), which they used to reverse diabetes in a pancreatectomized dog and then later almost fully corrected the disease by injecting their extract into a teenager (Banting and Best, 1990; Bliss, 1993).

In the mid-1980s and early 1990s, there was a resurgence of interest in insulin and its role in brain function (Schwartz et al., 1992; Myers, Jr. and White, 1993; White, 1997; Wickelgren, 1998). Curiously, it was found that the highest brain insulin-binding affinities, insulin receptor (IR) density, and IR kinase activity were localized to the OB compared with those found in all other brain regions (Baskin et al., 1983; Hill et al., 1986; Gupta et al., 1992; Banks et al., 1999; Fadool et al., 2000;

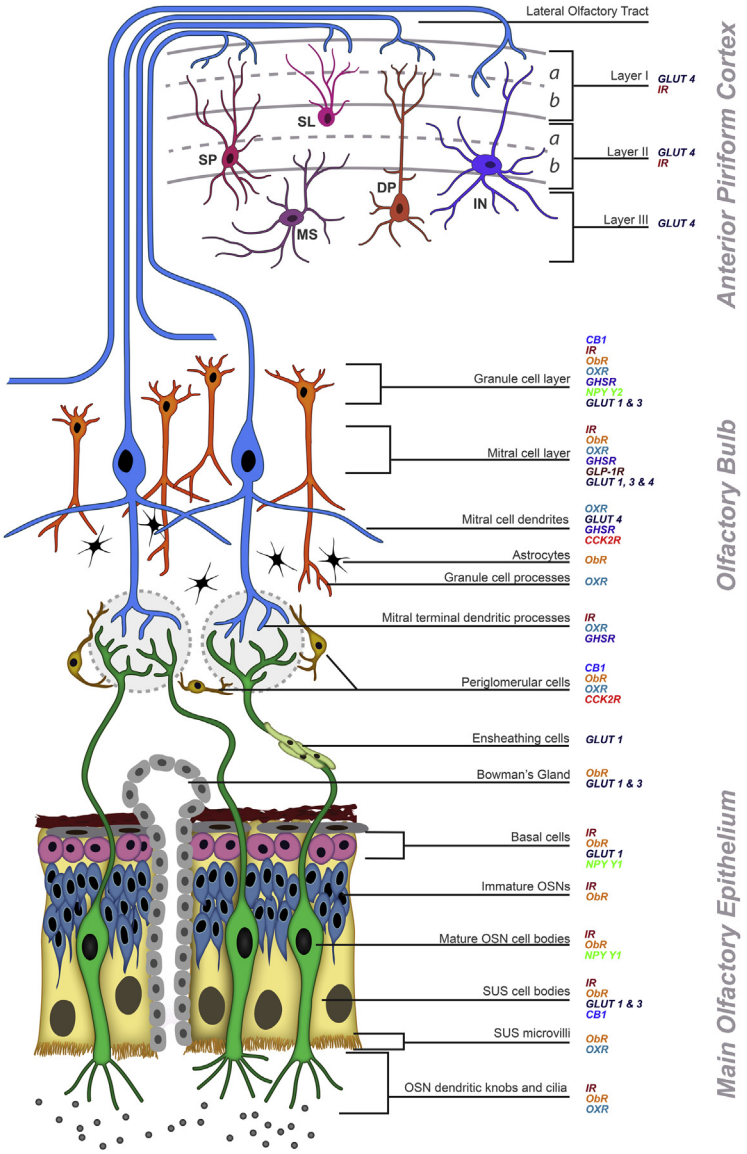

Figure 2 Map of Noteworthy Metabolic and Hormone Receptors and Receptors for Energy Important Molecules that Are Distributed Across the First Three Olfactory Centers. Schematic cartoon designating the expression of metabolic and hormone receptors and receptors for energy important molecules across the main olfactory epithelium, olfactory bulb, and anterior piriform cortex. Odorant molecules (*circles*, bottom) bind to cilia of the olfactory sensory neurons (OSN) to initiate a second-messenger-activated signal transduction cascade that generates the action potential message, which propagates down the axons that terminate in specialized glomerular synaptic foci (*dashed circles*) in the olfactory bulb. The pattern of glomerular activity creates a topographical map of odorant information that is then relayed through action potential patterned information through the mitral cells, whose axons collate to form the lateral olfactory tract with connections to the various layers of the anterior piriform cortex. OSN = olfactory sensory neuron, SUS = sustentacular, IR = insulin receptor kinase, ObR = leptin receptor, OXR = orexin receptor, GLUT 1, 3, 4 = glucose transporter 1, 3, or 4, CB1 = endocannabinoid receptor 1, NPY Y1, 2 = neuropeptide Y receptor 1 or 2, CCK2R = cholecystokinin receptor 2, GHSR = ghrelin receptor, GLP-1R = glucagon-like receptor 1, SP = superficial pyramidal, MS = multipolar spiny, SL = semilunar, DP = deep pyramidal, IN = interneurons (deep layers; a variety of classes), *a/b* = denotes upper (a) and lower (b) divisions of the anterior piriform cortex layers. Original Art by C. Badland.

Aimé et al., 2012). Because the brain was once considered an insulin-independent organ, scientists began to reconsider its physiological role and that it might be important for sculpting and shaping synaptic circuitry (Schwartz et al., 1992). With some exception, historical evidence is weak for a central source of insulin (Baskin et al., 1983), therefore brain insulin is thought to be largely derived from peripheral insulin secreted into the circulation, thus a pancreas to brain communication. A notable exception is intriguing work by Kuwabara et al. (2011) who derived adult neuronal progenitor cells from the OB, and remarkably report a reduction in serum glucose as evidenced by an improved glucose tolerance test when grafted to the pancreas of diabetic mice (Kuwabara et al., 2011). Nonetheless, brain insulin and that found within olfactory structures is likely largely derived from receipt from the peripheral circulation and thus must be transported through the specialized vascular structure of the blood brain barrier (BBB).

The method of BBB transport is not known, and yet a number of factors appear to influence the rate of transport including status of nutrition, level of blood glucose, and obesity (Banks et al., 2012; Rhea et al., 2017). Early radioimmunoassay studies, whereby peripheral infusions of insulin yielded non-linear elevations of insulin content in the cerebral spinal fluid (Margolis and Altszuler, 1967), suggested to Banks (Banks, 2004) the presence of a saturable insulin transport system across the BBB. Recent models from this group show evidence that the signaling-related insulin receptor may not be required to transport insulin across the BBB (Rhea et al., 2018). It is important to underscore that all regions of the BBB are not equally permeable to insulin and that passage into the OB can be actually quite leaky. In fact, transport into the OB has been measured as two to eight times faster than that into the whole brain (Banks et al., 1999). Interestingly, following a meal when circulating plasma levels of insulin are increased, that found in the OB are low. Moreover, OB insulin is elevated in animals fasted for 72 hours even when the circulating plasma insulin levels are low (Fadool et al., 2000). It has been demonstrated that feeding does modulate OB insulin content where it is higher in satiated vs. fasted rats (Aimé et al., 2012) - a result not unlike that reported for refeeding activities governed in other brain regions (Strubbe et al., 1988; Woods et al., 2003). Collectively these types of studies demonstrate that insulin in the OB could be derived centrally or peripherally, but that hormone levels appear to be highly controlled using a mechanism of regulation that is still as yet unknown.

Regardless of the source and transport of insulin into olfactory structures, IR kinase, the receptor to which the hormone binds, is ubiquitously found throughout the MOE, OB, and PC (**Fig. 2**). Within the MOE, IR kinase immunolabeling is prominent in the external border of the olfactory sensory neurons and their dendritic knobs (Lacroix et al., 2008; Marks et al., 2009) and is observed to a lesser extent in some immature olfactory sensory neurons (OSN), sustentacular cells, and the endothelium of the lamina propria vessels (Lacroix et al., 2008). Within the OB, IR kinase is widely distributed across the external plexiform layer (dendrodendritic synapses between granule and mitral cells), the glomerular layer (axodendritic/axosomatic synapses between mitral cells and OSNs), the cell bodies of the mitral cells, and within the granule cell layer (Hill et al., 1986; Werther et al., 1987; Matsumoto and Rhoads, 1990; Marks et al., 1990; Fadool et al., 2000; Marks and Fadool, 2007; Lacroix et al., 2008; Marks et al., 2009; Aimé et al., 2012). Embryonically until birth and developmentally through the early postnatal ages, the levels of IR kinase expression steadily increase within the external plexiform, glomerular, and mitral cell layers, when it plateaus to that of adult levels by postnatal day 10. That expressed in the granule cell layer is independent of developmental changes (Fadool et al., 2000). Within the anterior piriform cortex (aPC), IR kinase immunolabeling is observed in the lateral olfactory tract (LOT) and Layer II where densely-packed glutamatergic principal neurons reside (Al Koborssy et al., 2018). Within Layer II, IR kinase is co-localized with CaM kinase II in pyramidal neurons where the IR kinase immunosignal is found in both the cytoplasm and the nucleus (Zhou et al., 2017). Beyond the PC, immunochemical assays support IR kinase presence in the anterior olfactory nucleus, the olfactory tubercle, the entorhinal cortex, and the limbic structures connected to the olfactory area (Hill et al., 1986; Unger et al., 1989). In total, IR kinase signaling is present from the first step of odorant binding and olfactory signal transduction in the MOE, up through higher-order processing in the OB and the PC, and beyond.

3.35.3.1.2 Glucose

Glucose is the main metabolic substrate for the brain and is essential to fuel the computational demands of action potential generation, synaptic events, and ion concentration gradients (Dienel, 2012; Harris et al., 2012; Howarth et al., 2012). Even though the human brain is only 2% of an individual's total body weight, it consumes 5.6 mg glucose per minute (mg min^{-1}) for every 100 g of brain weight (Erbsloh et al., 1958), or approximately 20% of the body's glucose-derived energy resources (Mergenthaler et al., 2013). The total energy budget to discriminate odorants is quite large. Lecoq et al. (2009) have computed the energetic demands of synaptic transmission in the OB, for example, and have found that odor-evoked oxidative metabolism is energetically demanding and tightly correlated to high capillary density in this olfactory structure (Chaigneau et al., 2007). These authors found that odor-induced mitral/tufted cell activation significantly increased metabolic oxygen consumption and thereby required a strong demand for glucose and related metabolic substrates. Blood-borne metabolic signals or nutrients such as glucose can enter the OB more easily than other brain regions due to the greater permeability of the BBB. Ueno and colleagues (Ueno et al., 1991; Ueno et al., 1996) measured isotopically-labeled albumin uptake as a metric of permeability to generalize that intravascular macromolecules can be transported 2.3x higher into the OB than into the frontal cortex or cerebellum and that this persists throughout adult life. Al Koborssy et al. (2014) used glucose-oxidase biosensors to directly record glucose concentration and reported it higher in the OB over that of the somatosensory cortex.

Because glucose ($C_6H_{12}O_6$) is a polar molecule, its transport across the plasma membrane necessitates integral transport proteins or facilitated diffusion. Glucose transporters were first isolated from hepatic membranes of HepG2 cell lines as reviewed by Baly and Horuk (1988). Once reaching olfactory or chemosensory structures, glucose has been found to bind one of two different families of receptors, one being the family of solute carrier (SLC) transporters (Lin et al., 2015) and the second being the superfamily of seven-transmembrane receptors, or GPCRs (Katritch et al., 2013). Activation of SLC transporters occurs when glucose, or a nutritionally-important molecule, is transported intracellularly across the bilayer using a facilitated protein-mediated process, in which glucose is transported down its concentration gradient, or through secondary active transport, in which glucose is co-transported or coupled with that of another ion, typically Na+, either in the same (symporter) or opposite (antiporter) direction. Regardless of which manner of glucose transport, activation of the SLC transporter causes a modulation of the membrane potential. If the modulation is direct, and glucose is co-transported with ions, the process is called electrogenic transport. If the modulation is indirect, as when glucose activates an intracellular signaling cascade that subsequently activates a down-stream ion channel to alter permeability, the process is called non-electrogenic transport. In the olfactory system, there are examples of both electrogenic solute carrier transporters (SGLT1) and non-electrogenic solute carrier transporters (GLUT). Our discussion of the distribution and then function

(*see section below*) of glucose transporters will be restricted to an example of each of these two subclasses of SLC transport. Readers are directed to Julliard et al. (2017) for an in depth reading of the intricacies of nutrient sensing in the olfactory system driven by glucose, amino acids, and lipids.

3.35.3.1.2.1 Sodium-Glucose Linked Transporters 1 (SGLT1)

The sodium-coupled glucose transporters (SGLT1 and SGLT4) are expressed in a subset of mitral cells (Aimé et al., 2014, Internet 1) and in the internal external plexiform and glomerular layers (Aimé et al., 2014) where they function in an antiport fashion: 1–2 molecules of sodium are transported into the cell in exchange for the export of non-metabolized glucose. Activation of such a co-transporter in the hypothalamus has been demonstrated to hyperpolarize a subset of orexin-expressing neurons (Gonzalez et al., 2008) and could act analogously in the OB. Aimé et al. (2014) reported that the expression of SGLT1, but not GLUT4, was elevated in the genetically-obese and moderately diabetic Zucker fa/fa rat (Aimé et al., 2014). In other areas of the brain, and during pathological states, up-regulation of SGLT1 is proposed to compensate for impairment in GLUTs function (Yu et al., 2013). Interestingly, there has been a report of an odorant receptor, Olfr1393, that is ectopically expressed in the proximal convoluted tubule of the kidney. In the kidney, Olfr1393 regulates glucose handling, and when gene-targeted deleted, SGLT1 also drop in expression, indicating a coordinated function (Shepard et al., 2016).

3.35.3.1.2.2 Glucose Transporters (GLUTs)

Glucose is transported across biological membranes via glucose transporters (GLUTs) according to "an alternating conformer model." According to this model, glucose can bind to one of two mutually-exclusive binding sites of the transporter, either on the extracellular or the intracellular site. The glucose transporter switches from one conformation to another to release its substrate (Carruthers, 1990). GLUTs comprise 14 family members named in the order they were cloned, and divided into three subfamilies, namely: class I (GLUT1-4, and GLUT14), class II (GLUT5, GLUT7, GLUT9, and GLUT11), and class III (GLUT6, 8, 10, 12, and the myoinositol transporter HMIT1 or GLUT13) (Kovach et al., 2016).

At the level of the MOE, there are several members of the class I GLUT subfamily that have been reported. GLUT1 is expressed in endothelial cells of blood vessels of the lamina propria that are positive for the tight junction protein occludin (Hussar et al., 2002). GLUT1 labeling is also observed in the soma, dendrites, and axonal projections of the olfactory sensory neurons (OSNs) and the basolateral side of the sustentacular supporting cells, suggesting a tight morphological and metabolic interrelationship (Nunez-Parra et al., 2011). GLUT3, also a class I member, is found in the Bowman's Glands and the apical side of the sustentacular cells (Villar et al., 2017).

At the level of the OB, the predominate GLUT family member appears to be the class I member, GLUT4 (**Fig. 2**). GLUT4 requires insulin for its translocation to the plasma membrane (Stockli et al., 2011; Leto and Saltiel, 2012) and throughout the brain this transporter is largely neuronal, where it is localized on dendrites or on the membranes of transport vesicles, Golgi apparatus, and the rough endoplasmic reticulum (Kobayashi et al., 1996; Leloup et al., 1996; McCall et al., 1997; El Messari et al., 1998; Choeiri et al., 2002). Accordingly in the OB, GLUT4 is localized on the dendritic terminals of mitral/tufted cells at the level of glomeruli. Glomeruli are sites of synaptic connectivity between the axons of OSNs and mitral cells. GLUT4 is also present on the soma of periglomerular cells (Sharp et al., 1975; Sharp et al., 1977; Aimé et al., 2014; Al Koborssy et al., 2014). *In situ* hybridization has indicated that GLUT4 occurs in the cell bodies of mitral cells and interneurons before being translated and recruited at the synapse for glucose-based modulation of olfactory information (Kovach et al., 2016). Interestingly, Al Koborssy and collaborators also found that GLUT4 protein was co-localized with IR kinase on mitral cells, in line with its insulin-dependent mode of activation. Moreover, the expression and mapping of GLUT4 can be feeding-state dependent (Aimé et al., 2014; Al Koborssy et al., 2014).

Within the PC, GLUT4 is suggested to be the major transporter of glucose (El Messari et al., 2002; Al Koborssy et al., 2019) (**Fig. 2**). Within the aPC, GLUT4 immunolabeling has been reported in the neuronal processes of myelinated mitral and tufted cells of the lateral olfactory tract (LOT), Layer II, and Layer III. In the latter two locations, the GLUT4 signal was localized to principal neurons, was predominately nuclear in appearance, and was excluded from astrocytes (Al Koborssy et al., 2019).

3.35.3.1.3 Ghrelin

The appetite-stimulating, or orexigenic (**Table 1**) hormone, ghrelin, is secreted principally by the stomach during the anticipation of eating, where it is thought to be involved in regulating meal initiation and duration (Kojima et al., 1999). Ghrelin is capable of regulating gastric secretions and helps regulate gastric emptying through controlled contractility of the pyloric gland area of the stomach. Injection of ghrelin potently induces hunger, initiates eating, and enhances fat deposition in both humans and rodents (Tschop et al., 2000; Druce et al., 2005). In fact, sleep helps stabilize our levels of metabolic hormones - a reduction in sleep significantly increases ghrelin while it decreases leptin - leading to an increase in BMI in humans (Taheri et al., 2004). Thus, poor sleep is thought to contribute to obesity!

Within the olfactory system, the receptor for ghrelin, called the growth hormone secretagogue receptor (GHSR; **Fig. 2**), is a G-protein-coupled receptor expressed in the glomerular layer and the mitral and granular cell layers as evidenced by biotinylated ghrelin-binding assays (Tong et al., 2011). Interestingly GHSR is expressed at high density in the facial motor cortex that drives facial muscles governing sniffing movements (Zigman et al., 2006) as explored by Tong and collaborators (see **Ghrelin Increases Olfactory Sniffing Behaviors and Food Searching** section, below). The motivational and rewarding control of food intake is highly

dependent on dopaminergic circuits, upon which ghrelin acts. The reader is referred to a comprehensive review by Al Massadi et al., 2019 for these aspects and potential clinical applications of the hunger hormone.

3.35.3.1.4 Leptin

Leptin is a hormone secreted by fat cells in proportion to their volume and is used as a marker of adiposity and excess energy storage (Getchell et al., 2006). During excess energy abundance, leptin is released from adipocytes that leads to decreased food intake and an increase in energy expenditure (**Table 1**). Obesity is characterized by a leptin-resistant state whereby the hormone signaling pathway exhibits a reduced sensitivity to leptin and its ability to curb food intake (Myers et al., 2010). Leptin is produced by the Obese gene (Ob), which regulates this balance between food intake and energy expenditure (Zhang et al., 1994; Halaas et al., 1995). ob/ob mice that are deficient in the production of leptin, were first discovered in the summer of 1949 through a spontaneous mutation at the Jackson Laboratory. It would be 45 years later that the identification of the leptin hormone was revealed by careful positional cloning and purification of the gene product by the Jeffery Friedman laboratory (Zhang et al., 1994; Halaas et al., 1995). Given the major discovery of this appetitive hormone, the literature (over 30,000 articles to date) can be a bit unwieldy, however, readers are encouraged to read Friedman's Harrington Prize Essay that is a reflection on both the discovery of leptin and the state of clinical applications today (Friedman, 2016).

Although the majority of leptin receptors are found in the hypothalamus, they are also highly expressed in the olfactory bulb (Shioda et al., 1998; Prud'homme et al., 2009) (**Fig. 2**) that is the first location of the brain to perform spatiotemporal coding of odors (Chelminski et al., 2017) and in the MOE (Baly et al., 2007) where it is synthesized locally as opposed to being released from adipocytes into the plasma. Using a combination of light and electron microscopy, RT-PCR, and radioimmunoassay, Baly et al. (2007) probed both isoforms of the leptin receptor (ObR) and mapped the receptors to the sustentacular cells and mature OSNs. In particular, ObRs were densely expressed on the cilia of OSNs; the site of olfactory signal transduction (Baly et al., 2007). Proteins called odorant binding proteins, or OBPs, bind odorant molecules to present them to the ORs (Archunan, 2018). Interestingly, these OBPs are secreted by the Bowman's Glands and are transcriptionally-regulated based upon the state of fasting. Badonnel et al. (2009) were able to tie leptin activation of mucus production by the Bowman's Glands to the level of feeding, thereby making the clever hypothesis that olfactory mucus, and essential odorant binding interactions, is regulated by nutritional cues (Badonnel et al., 2009).

3.35.3.1.5 Endocannabinoids

The more recently discovered family of endocannabinoids exert their effect on the mesolimbic reward circuitry and the lateral hypothalamus to regulate energy expenditure and food-seeking behaviors (Horvath, 2006; Osei-Hyiaman et al., 2006; Matias and Di, 2007). The two major receptors for endocannabinoids, CB1 and CB2, are expressed in all brain regions involved in the control of food intake, but also are expressed peripherally in the pancreas, liver, white adipose tissue, and skeletal muscle. For an in-depth reading of the central and peripheral controls of appetite and food intake by this family of orexigenic molecules, the reader is referred to Matias and Di Marzo (2007) and a recent review by Gatta-Cherifi and Cota (2016).

The olfactory system largely expresses CB1 receptors at many levels (**Fig. 2**) including OSNs and sustentacular cells of the MOE, the periglomerular cells and granule cells of the OB, and in neurons of the anterior olfactory nucleus and olfactory cortices (Egertova and Elphick, 2000; Mackie, 2005; Mailleux and Vanderhaeghen, 1992; Matsuda et al., 1993; Mcpartland et al., 2006; Soria-Gomez, et al., 2014; Tsou et al., 1998). In the MOE, CB1 receptors are concentrated on the dendritic processes of OSNs (Czesnik et al., 2007) where stimulation with antagonists can modulate odor-evoked calcium signaling in the OSNs to alter odor processing.

3.35.3.1.6 Glucagon-like Peptide-1 (GLP-1)

There are two major incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), that are secreted from the small intestine in response to a meal and act to augment insulin release from the pancreatic β-cells (Seino et al., 2010). Like insulin itself, both hormones are capable of reducing food intake and lowering body weight when administered centrally via intracerebroventricular injection (ICV) (Dossat et al., 2011; Kinzig et al., 2002; Tang-Christensen et al., 1996; Turton et al., 1996). GLP-1 signaling has been more widely explored in olfaction and gustation (Takai et al., 2015; Thiebaud et al., 2016) and thus discussion of incretin hormones as modulators of eating and olfaction will be limited to GLP-1. GLP-1 not only regulates central metabolism, it has been reported to reduce water intake, inhibit glucagon secretion, and slow gastric emptying in an effort to regulate glycaemia. Because GLP-1 has a short half-life attributed to the enzymatic breakdown by dipeptidyl peptidase 4 (DPP-4), a number of stable analogs of the peptide have been derived and are effective in the therapeutic treatment of Type 2 Diabetes (Garber, 2011) to lower blood glucose.

In the olfactory system, an advantageous genetic mouse model allowed the exploration of the GLP-1 peptide in the olfactory bulb (Thiebaud et al., 2016, 2019). Reimann et al. (2008) placed a YFP variant called Venus (Nagai et al., 2002) under the control of the mouse preproglucagon (PPG) promotor (mGLU-124 line) to be able to identify proglucagon expressing neurons in the brain. Tracking YFP fluorescence, a population of PPG neurons in the OB were discovered by Thiebaud and collaborators (Thiebaud et al., 2019) that had stellate dendrites covered with spines, which were consistent with deep short axon cells (dSACs) or Cajal cells within the granule cell layer (Ramon y Cajal, 1911; Price and Powell, 1970a, 1970b, 1970c; Eyre et al., 2008, 2009; Nagayama et al., 2014). GLP-1 selectively binds the G-protein-coupled receptor, GLP-1R, to activate adenylate cyclase and cAMP production to increase protein kinase A (PKA) phosphorylation events resulting in the inhibition of a number of different voltage-dependent potassium channels (Gromada et al., 1998a, 1998b, 1998c; MacDonald et al., 2003; Kim et al., 2012, 2013) to ultimately drive depolarization.

Despite GLP-1R immunocytochemical localization to mitral cells and sparse labeling in the granule cell layer (**Fig. 2**), Thiebaud et al. (2016) also used biotinylated GLP-1 peptide as a binding assay in OB slices as well as a fluorescent-conjugated form of a GLP-1 analog (exendin-4; ex4-647) that could be intranasally delivered through the BBB to map the receptor distribution.

Beyond GLP-1 signaling being found in the olfactory system (see **Insulin Changes Feeding Behavior and Dampens Olfactory Sensitivity and Discrimination** section below) a unique reciprocal scenario is that an odorant receptor has been reported in the gut! In human intestinal L-cells that are responsible for releasing GLP-1, there is an expression of the odorant receptor (OR) called OR51E1 (Han et al., 2018). Although it is unusual to find ectopic expression of odorant receptors outside their expression in the MOE, other non-neuronal locations are being reported that have properties of chemoreception, like the spermatocyte, for example (Spehr et al., 2003). The authors found that activation of this intestinal OR with its preferred fatty acid odor ligand stimulated the secretion of GLP-1 from the intestine. The authors could even orally administer this preferred odorant to drive intestinal GLP-1 elevation, which they are currently exploring as an alternative therapeutic for diabetes management.

3.35.3.2 How Does Activation of Neuroendocrine Signaling or Release of Energy Molecules Change Olfactory Behavior and Eating?

Following the discovery of the neuroendocrine hormone and metabolic receptors expressed at high concentrations throughout the MOE, OB, and PC (**Fig. 2**), scientists began pairing the mapped distribution of the receptors with that of function. Olfactory function can be defined broadly in terms of physiology and behavior. Although readers are likely familiar with universal mechanisms to record physiological function, for example, electrophysiological techniques, they may be less familiar with particular behavioral apparatus used to quantify olfactory behaviors. The next section that follows will discuss olfactory functional changes in response to insulin, glucose, ghrelin, leptin, endocannabinoids, and GLP-1 that were captured using either electrophysiological techniques or an array of different olfactory behavioral tests. A comparison of the latter can be found in **Fig. 3** as an introduction to standard olfactory behavioral tests that are largely used with rodents, but some with human patients as well.

3.35.3.2.1 Insulin Changes Feeding Behavior and Dampens Olfactory Sensitivity and Discrimination

The first demonstration that brain insulin was involved in monitoring energy homeostasis and feeding behavior was discovered by Woods and collaborators (Woods et al., 1979) who observed a reduction in eating and loss in body weight of baboons when chronically administered insulin by ICV injection. Readers are referred to Woods and Porte (1983) to further explore insulin as a satiety factor across the CNS. Even when peripheral euglycemia was maintained, insulin or leptin injected into the ventricular system or hypothalamic sites (Brief and Davis, 1984; Flynn et al., 1998; Stockhorst et al., 2000; Porte et al., 2002; Figlewicz, 2003; Woods et al., 2003; Stockhorst et al., 2004) were catabolic in nature; they reduced food intake, decreased body weight, and elevated energy expenditure (Woods et al., 1979; Campfield et al., 1995; Schwartz et al., 2000; Shiraishi et al., 2000).

A less invasive method to deliver insulin as well as other peptides and small molecules was found to be intranasal delivery (Hanson and Frey, 2007; Renner et al., 2012; Chapman et al., 2013) (see also **DpTx-Treated cre-OMP IGF-R Obese Mice** section). Intranasal delivery of insulin afforded a rapid delivery from the MOE to the CNS by using an extracellular route or slits in the cribriform plate without any requirement for axonal transport (Dhanda et al., 2005; Hanson and Frey, 2007; Marks et al., 2009). Frey and collaborators used radioisotopic tracing of insulin to map the rate, distribution, and net concentration received in the OB (first brain region to receive the hormone) and subsequent brain regions (Hanson and Frey, 2007, 2008). Fadool and collaborators have used this route of delivery both acutely and chronically to explore behavioral changes in olfaction following delivery to the OB and further structures. As with humans (Schwartz et al., 2000; Hallschmid et al., 2004), intranasal insulin administration to rodents caused a 5% drop in body weight over the short course of a seven day treatment (Marks et al., 2009). Using a habituation/dishabituation paradigm (Fletcher and Wilson, 2001) (see **Fig. 3**C), the same odor is repeatedly presented to mice using a cotton swab or wooden cube and their exploration time is measured (habituation phase) compared to that of a single presentation of a subsequent novel odor (dishabituation). Mice receiving 7 days of twice-daily intranasal insulin administration significantly increased their ability to discriminate two odors (elevated dishabituation/habituation ratio) over that of mice receiving vehicle or boiled insulin (Marks et al., 2009). Despite intranasal insulin having the ability to enhance odor discrimination there was only a modest change in the threshold for odor detection as determined by a two-choice paradigm (see **Fig. 3**B). Here, the threshold for odor detection is defined based upon decision of the mouse to dig for a hidden, odor-paired food reward across two compartments (Colacicco et al., 2002; Fadool et al., 2004). On average, mice administered a ten-day intranasal insulin treatment were able to detect odorant molecules only one log unit less in concentration than those treated with vehicle (Marks et al., 2009). Interestingly mice administered intranasal insulin took less time to make decisions and also made less transitions across the two compartments before making decisions. Although administration of insulin clearly would impact the time to eating due to these observed variables, these behaviors are likely attributed to insulin perfusing beyond the olfactory bulb and into higher regions of the brain. In fact, Marks et al. (2009) found that intranasal insulin also enhanced memory in the form of object memory and decreased anxiolytic behaviors as determined by light-dark box testing, marble burying behaviors, and enhanced performance in an elevated plus maze. These behavioral changes are likely attributed to enhanced declarative memory tasks governed by the hippocampus and reduction in anxiety governed by higher cortical regions (Benedict et al., 2004). If intranasal insulin administration is extended to a more chronic delivery using twice-daily for 30 to 60 days, which would mimic more of a prediabetic state and hyperinsulinemia rather than postprandial insulin release, then the increase in odorant discrimination and enhanced object memory is no longer observed, suggestive of an insulin resistance.

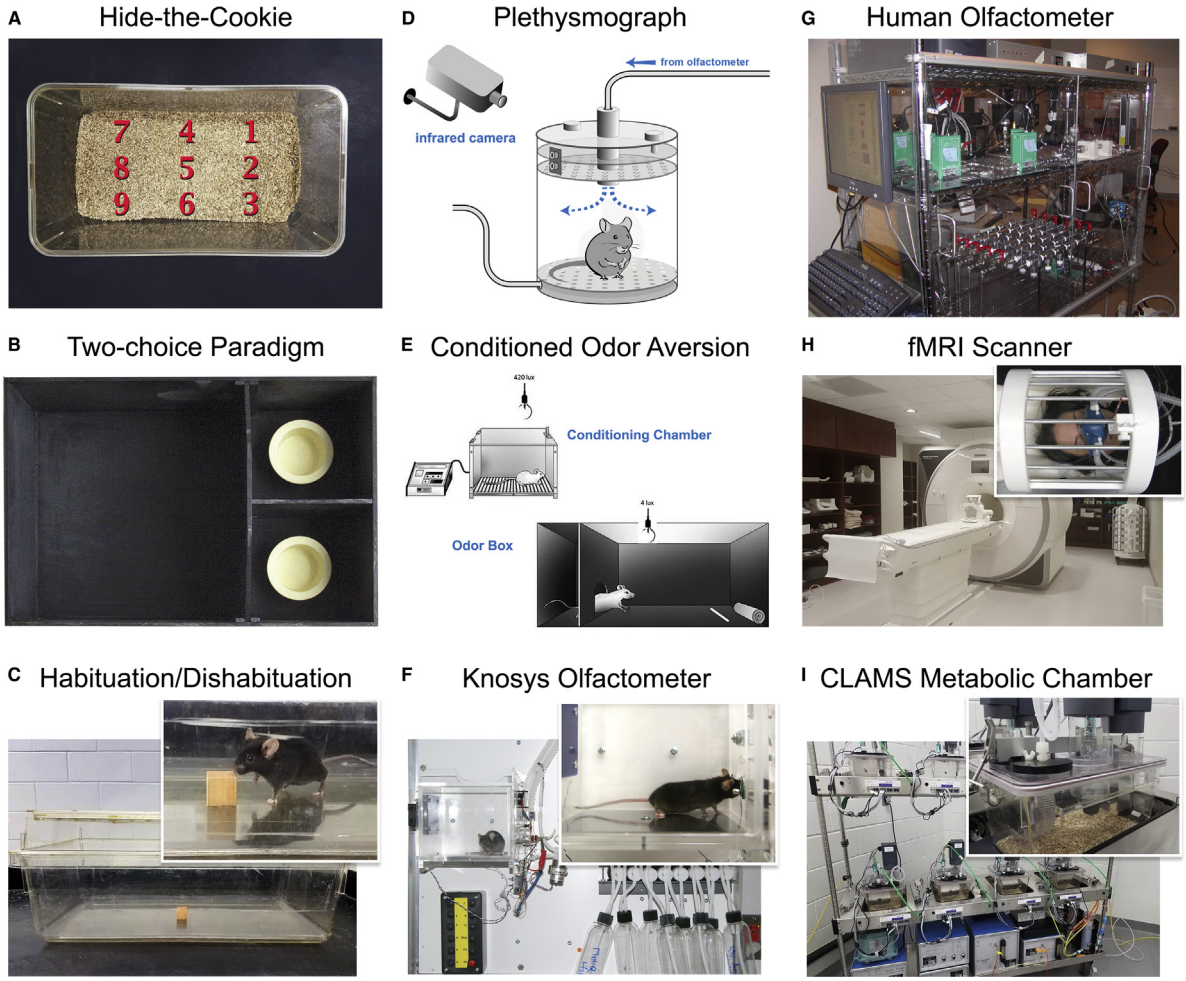

Figure 3 **A Variety of Chambers, Apparatus, and Sophisticated Equipment Are Used to Quantify Olfactory Perception or Correlative Physiology in Rodents and Humans.** (A) **Hide-the-Cookie** - test of general anosmia. A scented (i.e. a cookie) or an unscented object (i.e. marble) is randomly hidden under bedding and the time for retrieval by a rodent is scored. Animals that are anosmic have similar retrieval times between scented and unscented objects. (B) **Two-choice Paradigm** - test of odor threshold. Rodents are placed in the large holding chamber on the left and then the divider is removed. Time to retrieve a buried reward randomly assigned to a compartment is scored. Both dishes have a hidden reward (typically a "cheerio") but one is inaccessible under a wire mesh and one is accessible on top of the mesh, but both are buried under litter. The litter of the accessible hidden reward is scented with an odorant solution, which the animals are trained to associate with the reward. Animals are then presented scented litters over a range of odorant concentrations, until the animal selects the correct compartment based upon chance alone (50% correct), which is the designated threshold of detection. (C) **Habituation/Dishabituation** - test of odorant discrimination. Animal is presented repeatedly with an odorant-scented block (see inset) and exploration time is scored. As the animal habituates to the odor, it explores it less frequently. Lack of dishabituation following the presentation of a new, novel odor, indicates failed discrimination. (D) **Plethysmograph** - test of odorant discrimination. Same paradigm as (C) but uses a customized olfactometer to computerize delivery of the substances and scores breathing frequency rather than exploratory time as the metric of habituation/dishabituation. Schematic drawn from engineered design of this apparatus by the CMO team at the University of Lyon whereby synchronized signals (sniffing and behavioral video records) can be analyzed with software also custom-made by the CMO team. (E) **Conditioned Odor Aversion** - test of odorant discrimination. The test uses a conditioning chamber (top) to pair a shock stimulus to the recognition of an odorant. Animal is then presented with the test odorant and freezing behavior is scored. (F) **Knosys Olfactometer** - test of odorant discrimination and threshold. Animal is trained by operant conditioned (go, no-go) to recognize a test odorant paired with a water reward (inset). Precise control of delivery and concentration can be achieved through computer-operated valves to achieve high throughput quantification of dose-responsivity and reversal learning, for example. (G) **Human Olfactometer** - test of odorant dilution/concentration and threshold. Computerized automation of the delivery of odorants whereby psychophysical tests can analyze hedonics of odors, relative intensities, discrimination from a reference odor/gas, and threshold detection. Typically, these tests are paired with (H) **Functional Magnetic Resonance Imaging (fMRI) Scanner** that detects changes in blood flow associated with brain activation to determine brain activation maps in synchrony with odor presentation. (I) **Comprehensive Laboratory Animal Monitoring System (CLAMS)** - test of metabolism and ingestive behaviors. Computerized monitoring of rodents in a home cage environment for the measurement of indirect calorimetry to assess energy expenditure, locomotor activity, and food and water ingestion. Images in E/F taken with permission from cited sources. Photographs courtesy of D.A. Fadool (A, B, C, F, I), D. Small (G, H), and W. Li (H). Schematic in D drawn by C. Badland from a photograph contributed by A.K. Julliard. Schematic in E modified from Canteras et al. (2015), with permission.

Moreover, mice receiving chronic insulin exhibit an increase in the number of meal bouts, indicative of a smaller meal size because the total caloric food consumption does not change (see **Fig. 3**I) (Bell and Fadool, 2017).

Plasma insulin levels typically follow glycaemia and feeding state (Sitren and Stevenson, 1978) and it is possible to synchronize a daily insulin secretion by habituating animals to a single meal. Aimé and collaborators (Aimé et al., 2012) used this tactic to be able to carefully quantify the change in OB insulin concentration when rats were shifted from fasting to fed state. The determined 2-fold change in insulin could then be administered by ICV injection into fasted rats at low insulin baseline to determine how a physiological bolus of insulin at mealtime might alter behavioral identification to an aversive odor and general sniffing behavior used in food seeking (Wesson et al., 2008). The authors used a modification of the conditioned taste aversion assay (see **Fig. 3**E) originally invented by the psychologist John Garcia (Garcia et al., 1955; Palmerino et al., 1980) and reported that fasted rats infused with this physiological bolus of insulin (14 mU) had a reduced detection of an odor for which they previously acquired an aversion. This paradigm is referred to as a conditioned odor aversion whereby a thirsty and fasted rat learns to avoid consumption of a fluid containing an odor for which it previously suffered malaise attributed to the pairing of the odor with a LiCl injection. With the incorporation of a single ICV injection of insulin, rats reduced their avoidance of the aversive odorant indicating a reduction in odorant detection. Moreover, fasted rats are known to increase the frequency of sniff respirations in response to food odor presentation (Julliard et al., 2007; Kepecs et al., 2007). The authors (Aimé et al., 2012) also used a whole-body plethysmograph in conjunction with an olfactometer (see **Fig. 3**D) to quantify that rats receiving the single ICV insulin treatment no longer increased respiration frequency when presented with a food odorant compared with that of fasted rats injected with only saline. The single ICV insulin injection did not alter body weight or food intake compared to experiments where levels of insulin were more chronically manipulated to simulate that of metabolic dysfunction. The location of ICV injection is an important variable in relation to olfactory behavioral modification. The equivalent injection of insulin into the OB that causes a decrease in olfactory threshold (or olfactory detection) causes a decrease in olfactory discrimination if injected into the aPC (Al Koborssy et al., 2019).

In summary, the administration of insulin, whether acutely or chronically, whether intranasally delivered to mimic transport across the BBB or injected by ICV into the lateral ventricle, causes molecular and physiological changes in the olfactory bulb or across multiple brain regions that evoke changes in weight homeostasis, olfactory discrimination, olfactory detection, meal bouts, aversive learning, object memory, and anxiety. At this time, direct molecular and cellular correlates underlying the noted behavior changes are incompletely known, but much has been uncovered as to the capacity to evoke physiological changes in response to insulin stimulation using *in vitro* and *in vivo* preparations, and heterologous expression systems. The next four sections will discuss what is known regarding insulin stimulation in the MOE, OB, PC, and a heterologous system that adds to our understanding of the underlying basis for behavioral changes observed attributed to insulin.

3.35.3.2.2 Insulin Enhances Olfactory Sensory Neuron Excitability and Reduces the Response to Odors as Determined by Electrophysiology and Electro-olfactogram (EOG) Recordings

Biochemical and physiological studies in the MOE have led us to understand that the response to insulin in the periphery may be dependent upon the nutritional or metabolic status of the animal. When rodents were fasted for 48 hours to evoke a drop in plasma insulin levels, curiously there was an elevation of insulin retention in the MOE and a concomitant enhanced abundance of IR kinase (Lacroix et al., 2008). In slice electrophysiological preparations, the spontaneous action potential firing frequency of OSNs was increased in 91% of sampled OSNs stimulated with insulin, whereas odorant-evoked activity in the presence of insulin resulted in a reduced latency to first spike combined with a decrease in the interspike interval (Savinger et al., 2009). In electro-olfactogram recordings (EOG), addition of insulin caused a decrease in the EOG amplitude in response to general odorants (Lacroix et al., 2008; Savinger et al., 2009), indicating that insulin, while enhancing the spontaneous AP firing frequency of individual OSNs, also decreases the total number of excitable OSNs. A model is presented by which such a dichotomy would elicit a reduced signal-to-noise ratio in the MOE, which would match the behavioral smell ability of an animal in the postprandial period or satiated state (Savinger et al., 2009). It is not clear why the decrease in EOG amplitude was transient, occurring 5 to 10 min after insulin stimulation and demonstrating no reduction or modulation by 15 to 30 min (Lacroix et al., 2008). In humans, insulin levels in the mucus fall below that of the plasma in fasted normal individuals, whereas in fasted thin individuals, insulin levels are doubled, and in diabetic or obese individuals, mucosal insulin level does not change upon fasting (Henkin, 2010). Therefore, it would be interesting to explore a chronic manipulation of insulin's effect on EOG parameters, such as fasting or hyperinsulinemia attributed to weight gain or metabolic disorder to reveal the interaction between peripheral odor sensitivity and metabolic state.

3.35.3.2.3 Insulin Enhances Olfactory Bulb Excitability and Alters Network Activity

At the level of the olfactory bulb, the biophysical effect of insulin has largely been explored in mitral cells, a major projection neuron of the olfactory bulb (see **Fig. 1**), using a cultured neuron preparation and slice electrophysiology (Fadool et al., 2000; Fadool et al., 2011; Kuczewski et al., 2014). Acute insulin stimulation increases the action potential spike firing frequency in the mitral cells by shortening the pause duration between spike clusters or intraburst duration while having less effect on the interspike interval (ISI) (Fadool et al., 2011). Peri-stimulus spike distribution graphs where the number of spikes per bin are plotted across time demonstrate that insulin shortens the first latency pattern of activity. It also dampens spike adaptation so that the neurons can continue to increase frequency of firing output by 2.5x fold in response to higher current stimulation. The underlying Kv1.3 channel exhibits a decreased open probability in response to insulin without affecting the unitary conductance (**Fig. 4**A). The onset of modulation by insulin demonstrates a slow time course of 10–15 minutes following application, which is consistent with insulin-dependent phosphorylation of down-stream substrates and its role as a signalplex, below, involving voltage-dependent potassium channels

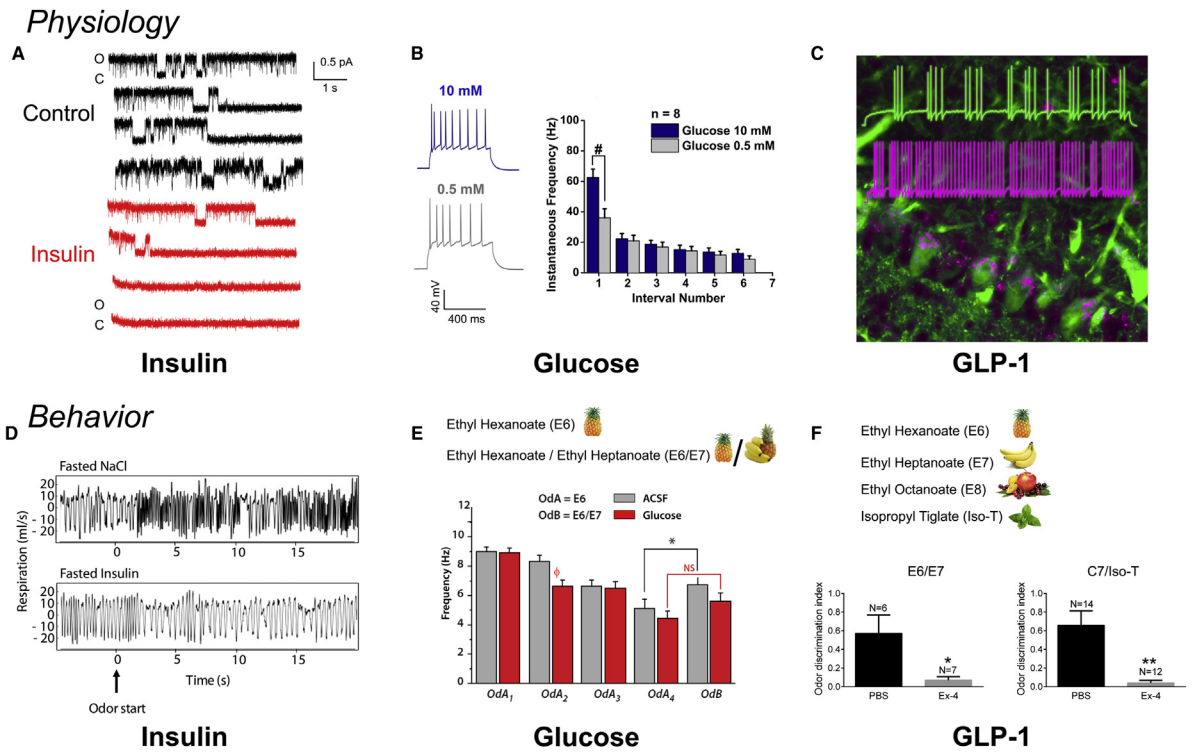

Figure 4 **Physiological and Behavioral Response to Insulin, Glucose, and Glucagon-like Peptide 1 (GLP-1) that Are Elevated Post-prandially (Following a Meal). Physiology:** (A) Change in single channel activity (o = open, c = closed state) of the Kv1.3 ion channel expressed in mitral cells of the olfactory bulb (OB) upon application of insulin. (B) Change in action potential firing frequency (IF = instantaneous frequency) of a superficial pyramidal cell (SP) of the piriform cortex in response to a change in glucose concentration from 10 mM to 0.5 mM. (C) Change in action potential firing frequency of mitral cells of the OB in response to the GLP-1 agonist called Exendin-4 (Ex-4). Top green trace = Control, Bottom purple trace = Ex-4. Ex-4 can be conjugated to a fluorescent molecule so it can be IP injected and mapped to accessible brain regions. Note the purple fluorescent signal tracked to the mitral cell layer of the OB in these mice that have a GFP genetic reporter in the olfactory marker protein expressing olfactory sensory neurons (OMP+ mature OSNs). **Behavior:** (D) Plethysmograph recording (**Fig. 3**D) of the respiratory activity following the ICV administration of insulin to a fasted rat. Note that insulin suppresses the characteristic enhanced breathing frequency observed for a hungry rat (top trace) stimulated with an odor (*arrow*). (E) Habituation/Dishabituation test performed with a Plethysmograph (**Fig. 3**D) demonstrating loss of discrimination following injection of glucose to the anterior piriform cortex. OdA = odor A, habituating odor presented multiple times (OdA1, OdA2, etc), OdB = odor B, dishabituating odor. (F) Same test as in (E) but performed with a wooden block (**Fig. 3**C). A low odor discrimination ratio between novel odor presentation of OdB and the final odor presentation of OdA indicates a reduced discrimination following IP injection of Ex-4 as in (C). Data taken/modified with permission from - Fadool et al. (2000) - Panel A; Al Koborssy et al. (2019) - Panels B, E; Aimé et al. (2012) - Panel D; Thiebaud et al. (2016) - Panel C; Thiebaud et al. (2018) - Panel F.

(see **Insulin Is Part of a Signalplex that Uses Kv1.3 Ion Channel as a Substrate** section; Bowlby et al., 1997; Cook and Fadool, 2002; Tucker and Fadool, 2002; Colley et al., 2004; Marks and Fadool, 2007; Colley et al., 2009; Tucker et al., 2013; Spear et al., 2015; Thiebaud et al., 2016; Velez et al., 2016).

Kuczewski et al. (2014) have recently reported a more complex effect of insulin. The authors report that insulin additionally acts at a second level within the olfactory bulb to indirectly alter GABAergic and glutamatergic synapses onto mitral cells to modulate their network activity (Kuczewski et al., 2014). Interestingly, it was shown that insulin can decrease or increase mitral cell activity evoked by olfactory nerve stimulation, depending upon the initial or basal firing frequency of the cell. A mathematical model is proposed whereby insulin has complex effects within the olfactory bulb that involve excitation and inhibition so that variability to stimulation across cells would be reduced. In this manner, the authors propose that insulin action on the OB network both decreases and increases discrimination of an odor quality dependent upon the nutritional status of the animal.

3.35.3.2.4 Insulin Suppresses Neuronal Activity in the Anterior Piriform Cortex and Decreases the Ability to Discriminate Difficult Odor Tasks

Because the anterior piriform cortex (aPC) is known to process odor objects (Wilson and Sullivan, 2011), govern odor pattern separation (Chapuis and Wilson, 2011; Davison and Ehlers, 2011), and perform many tasks involving odor learning (Morrison et al., 2013; Cohen et al., 2015; Ghosh et al., 2015), it has been a recent challenge to explore how the presence of insulin might affect these higher processing odor functions and ultimately eating behaviors. Zhou and collaborators (Zhou et al., 2017) report that while acute insulin stimulation of pyramidal neurons in the aPC increases action potential firing frequency and synaptic transmission *in vitro*, *in vivo* recordings demonstrate that insulin reduces odor-evoked beta oscillations, underlying gamma oscillations, and

calcium responses. In the *in vitro* recordings, the authors used slice electrophysiology to find that insulin's enhanced excitability was driven by a reduced interspike interval (ISI), a reduced latency to first spike, and it significantly elevated the resting membrane potential by almost 8 mV. Pharmacological block by the potassium channel inhibitors tetraethylammonium (TEA) and margatoxin (MgTx) eliminated the insulin-evoked reduction in ISI, suggesting that the substrate for insulin phosphorylation may be voltage-dependent potassium channels as reported for the olfactory bulb (see **Insulin Is Part of a Signalplex that Uses Kv1.3 Ion Channel as a Substrate** section; Fadool, 1998; Fadool and Levitan, 1998; Fadool et al., 2000; Colley et al., 2004; Marks and Fadool, 2007). Insulin caused an increase in the frequency but not amplitude of observed miniature excitatory post-synaptic potentials (mEPSP) that were spontaneous or evoked by stimulation of the lateral olfactory tract (LOT), which may indicate a presynaptic effect of the hormone exerted from the OB or other interneurons within the aPC. In the awake recordings, a reduction in the odor-evoked local field potentials was observed an hour after ICV administration of insulin and was independent of sniffing rate or odor quality. Fiber photometry approaches were used to demonstrate that the main effect of insulin was to decrease odor-evoked calcium responses. It is likely that the *in vitro* reported effects of insulin are the result of a direct modulation of the pyramidal neurons whereas the *in vivo* reported effects of insulin are driven by indirect synaptic changes of projection neurons connecting to the aPC.

Insulin modulation of the aPC has been found to be dependent upon glucose concentration and glucose metabolism. Al Koborssy and collaborators (Al Koborssy et al., 2018) used a whole-body plethysmograph in conjunction with an olfactometer (see **Fig. 3**D and F, respectively) as a non-invasive manner to record sniffing behaviors in freely moving rats while the animals were intracranially injected with insulin and glucose into the aPC. Rats were challenged with 4 repeated odor trials (habituation) followed by the presentation of a 5th novel odor presentation (dishabituation) to determine their olfactory discrimination ability (**Fig. 3**C). Rats microinjected with insulin could distinguish enantiomer odor pairs using this discrimination paradigm but when presented with ratiometric enantiomer mixtures (considered a difficult discrimination task), only fasted animals could discriminate mixtures, and insulin microinjected (mimicking satiation) animals failed. Mimicking satiation through microinjection of glucose caused rats to not be able to discriminate odors of differing carbon chain length. Injection of voltage-dependent potassium channel blockers increased the rate of habituation and enhanced discrimination. In parallel *in vitro* slice electrophysiology experiments, these authors focused upon the deep half of Layer II (IIb) and measured the instantaneous frequency (IF) of action potential firing to quantify spike adaptation of superficial pyramidal (SP) cells (see **Fig. 2**, anterior piriform cortex) that was first noted by Suzuki and Bekkers (2006). Here they discovered an interplay between insulin and glucose modulation in the SP cells of the aPC. Insulin decreased the IF for SP cells at high levels of glucose (5 to 10 mM) but was ineffective at low glucose concentration (0.5 mM). Moreover, a fraction of SP cells were glucose sensitive (75%), and they lost their sensitivity at high levels of glucose (10 mM) in the presence of insulin, but could regain sensitivity in the presence of insulin if glucose was low (5 mM). A select glucose kinase inhibitor prevented insulin reduction in IF excitability, indicating that the metabolism of glucose was necessary for the modulation by insulin (Al Koborssy et al., 2018). Thus the combined action of glucose and insulin modulates SP cells *in vitro*, and when injected *in vivo*, they decrease olfactory perception requiring high-acuity discrimination.

3.35.3.2.5 Insulin Is Part of a Signalplex that Uses Kv1.3 Ion Channel as a Substrate

It is important to recognize that integral membrane proteins, in particular ion channels and receptors, do not sit in isolation in the plasma membrane, but rather are part of a large signaling complex and molecular scaffold upon which cell signaling pathways are built in regulatory close adjacency. Of interest to that of chemosensory behavior and eating, is the voltage-dependent potassium channel, Kv1.3. This channel is highly expressed in mitral cells of the OB (see **Fig. 1**) where it carries 60%–80% of the voltage-activated, outward currents in these principal output neurons (Fadool and Levitan, 1998; Colley et al., 2004). Gene-targeted deletion of this channel results in a curious phenotype in mice where they are 'Super-smellers' along with maintaining a thin body morphology with resistance to diet-induced obesity attributed to an enhanced total energy expenditure (see **Kv1.3 −/− Super-Smeller Mice** section below) (Xu et al., 2003; Fadool et al., 2004; Upadyay et al., 2013). At the same time, the OB, as previously discussed above, contains the highest density of IR kinase in the CNS (Hill et al., 1986; Banks et al., 1999) and at the level of the mitral cells, it uses Kv1.3 as a substrate for tyrosine kinase phosphorylation (Fadool, 1998; Fadool and Levitan, 1998; Colley et al., 2004; Das et al., 2005) (**Fig. 5**).

Bath perfusion of insulin suppresses outward voltage-gated currents in mitral cells (Fadool et al., 2000), resulting in increased membrane excitability and an increased firing frequency in 91% of recorded neurons (Savinger et al., 2009). When insulin affects the action potential shape in mitral cells, the width at half-maximum is less, the 10%–90% rise time is quicker, and the decay time (1/e) is shortened (Fadool et al., 2011). These biophysical changes are consistent with a modulation of underlying Kv1.3 potassium channel conductances (Fadool et al., 2004). This reduction in outward current flow is mediated by IR kinase and is not elicited by insulin-like growth factor 1 (Fadool et al., 2000). Deletion of the IR kinase catalytic domain (IR−/−) and gene-targeted deletion of the Kv1.3 channel in mice (Kv1.3−/−) each removed insulin-evoked current suppression (Fadool et al., 2004; Das et al., 2005). By mutating key tyrosine phosphorylation recognition motifs on the N- and C-terminal aspects of the Kv1.3 channel (**Fig. 5**), electrophysiological and biochemical evidence supported IR-dependent changes in Kv1. 3 function and thus identified the role of IR kinase as a tyrosine kinase in the olfactory system (Fadool and Levitan, 1998).

Activation of IR kinase recruits a variety of downstream cascades that both directly and indirectly modulate the biophysical properties and targeting of Kv1.3 to the membrane, and thereby influences neuronal excitability. One way to systematically discern the molecular targets for interaction is to use a heterologous expression system to study the cloned components of the interaction partners for which site-directed mutagenesis can be employed to uncover structure/function or loss of function relationships (**Fig. 5**). Tyrosine to phenylalanine conservative point mutations of amino acids 111–113, 449, and 479 in the Kv1.3 channel sequence

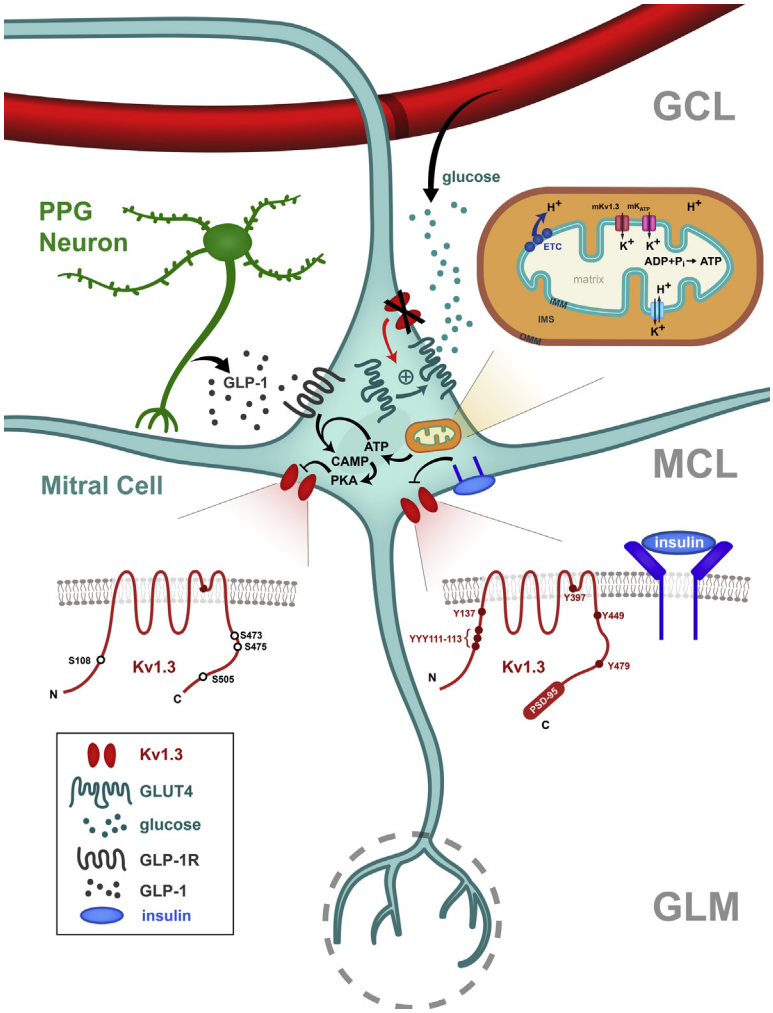

Figure 5 Schematic of the Modulation of Kv1.3 Ion Channel by Glucose, Glucagon-like Peptide 1 (GLP-1), and Insulin within the Mitral Cell of the Olfactory Bulb. Mitral cells (*light blue*) of the olfactory bulb (OB) are sensitive to changes in glucose concentration that generate changes action potential firing frequency, but the molecular signaling mechanism is not well understood. Mice with targeted deletion (X) of the Kv1.3 channel (*red*) are insensitive to glucose modulation and deletion or block of these channels can translocate (*arrow*, plus symbol) glucose transporters (GLUT4, *cyan*) to the membrane to facilitate glucose transport intracellularly, even in the absence of insulin. GLP-1 is produced locally in the OB by preproglucagon (PPG) neurons (*green*) and activation of the receptors for the peptide on mitral cells (*gray*) evokes enhanced firing frequency by shortening the intraburst duration. Because GLP-1 Rs are coupled to cAMP signaling cascades, elevation of PKA is suspected to use Kv1.3 channel as a substrate for serine/threonine phosphorylation to decrease potassium conductances. A schematic of the Kv1.3 secondary structure (left) is presented with targeted serine (S) amino acids (*open circles*) that are being probed by mutagenesis to determine location of modulation by phosphorylation by structure/function analyses. An analogous schematic of the Kv1.3 channel (right) is presented with known tyrosine phosphorylation sites (Y) whereby IR kinase (*blue*) activation uses the channel as a substrate to decrease potassium conductance. Kv1.3 is also expressed in mitochondria (mKv1.3) whose size is smaller in Kv1.3−/− mice and the enlargement of the organelle in response to an obesogenic diet is also prevented in the Kv1.3−/− mice (see **Fig. 9**). GCL = granule cell layer, MCL = mitral cell layer, GLM = glomerular cell layer, dashed circle = glomerulus, ATP = adenosine triphosphate, cAMP = cycle adenosine monophosphate, PKA = protein kinase A, ETC = electron transport chain, H+ = proton, K+ = potassium, IMM = inner mitochondrial membrane, IMS = inner mitochondrial space, OMM = outer mitochondrial membrane, PSD-95 = post-synaptic density 95, N = amino terminus, C = carboxyl terminus, GLP-1 = glucagon-like peptide 1, PPG = preproglucagon, GLUT4 = glucose transporter 4, Kv1.3 = voltage-dependent potassium channel 1.3 (mammalian *Shaker* homolog). Original Art by C. Badland.

results in a loss of IR kinase-induced phosphorylation of Kv1.3, reduction in channel current flow, and ultimately would predict increased mitral cell excitability (Fadool et al., 2000; Fadool et al., 2004). At the unitary level or single channel behavior, insulin causes a decreased open probability of Kv1.3 without a change in conductance (**Fig. 4**A) (Fadool et al., 2000).

Heterologous expression was also the method employed to study how IR kinase interrupts the clustering of Kv1.3 channels by the adaptor protein post-synaptic density 95 (PSD-95) (Marks et al., 2009) and how the insulin-dependent GLUT4 glucose transporter is translocated to the membrane in response to a Kv1.3 conductance decrease (Xu et al., 2004; Kovach et al., 2016). Both these molecular events are tied to metabolic state and correlated neuronal excitability. The first example concerns PSD-95; this is an adaptor protein that has no inherent catalytic activity, but serves to recognize mapped PDZ binding domains of neighboring

proteins. Kv1.3 contains proline-rich sequences that are recognized by SH3 domains in proteins, SH2 domains that are recognized by phosphorylated proteins, and has a PDZ binding domain at its N-terminus (**Fig. 5**) (Cook and Fadool, 2002; Marks and Fadool, 2007; Colley et al., 2009). PSD-95 functions to cluster Kv1.3 channels to post-synaptic locations at the cell membrane and finely regulates membrane excitability. In the presence of IR kinase, the SH3-guanylate kinase domain of PSD-95 uncouples insulin-induced phosphorylation, functionally reversing Kv1.3 current suppression. In this way, Kv1.3 channels serve as a central scaffold upon which insulin signaling can be rapidly modulated by the expression of adapter proteins (Marks and Fadool, 2007; Marks et al., 2009). The second example concerns the GLUT4 transporter, whereby pharmacological block or gene-targeted deletion of Kv1.3 increases translocation of GLUT4 to the membrane, bypassing the requirement for insulin (**Fig. 5**). This process occurs through a Ca2+-dependent mechanism that has yet to be fully described (Li et al., 2006; Li et al., 2007). Utilizing glucose transport for its own signaling pathway, GLP-1 as a G-protein coupled receptor will activate the enzyme adenylate cyclase to produce cAMP from ATP. Glucose uptake of the cell is increased to supply this ATP via glycolysis. Elevated cAMP levels activate protein kinase A (Gromada et al., 1998a, 1998b, 1998c; MacDonald et al., 2003; Kim et al., 2012, 2013), which is believed to modulate the biophysical properties of Kv1.3 by phosphorylation of key serine, rather than tyrosine, residues (Chung and Schlichter, 1997a, 1997b; Kim et al., 2012; Bell, 2018). Similar interactions between GLUT4, Kv1.3 and insulin have been observed in the anterior piriform cortex (see **Endocannabinoids Increase Odor Sensitivity and Link Hunger State to Stronger Odor Processing** section), however, the underlying molecular mechanisms here are not yet known (Al Koborssy et al., 2018).

What we do know about olfactory ion channels, which are important for homeostasis and olfactory behavior in response to metabolic state, is that the relationship between IR kinase and Kv1.3 does not involve just these two players. Rather, many kinases, ligases, and adaptor proteins are expressed in the olfactory system and can impinge on the function of Kv1.3. Readers are encouraged to explore additional sources of regulation of this central olfactory channel that regulates metabolism (Xu et al., 2003; Fadool et al., 2004; Tucker et al., 2012a; Upadyay et al., 2013) and olfactory acuity (Fadool et al., 2004), in detailed works describing its modulation by src kinase (Cook and Fadool, 2002), adaptor proteins Grb10 and Shc (Cook and Fadool, 2002; Colley et al., 2009), TrkB/BDNF signaling (Tucker and Fadool, 2002; Colley et al., 2004; Colley et al., 2007; Mast and Fadool, 2012), trafficking by Sec24a (Spear et al., 2015), and by the ubiquitin ligase Nedd4-2 (Velez et al., 2016).

3.35.3.2.6 Olfactory Neurons are Glucose Sensors

It has been known for decades that the neurochemical signature of fasted and satiated animals in terms of nutritionally-important molecules such as glucose, as well as the release of food-related neuropeptides, causes a change in the olfactory system's reactivity to odors. Satiety and the sense of smell are linked; increased preprandial odor sensitivity is evolutionarily beneficial to enhance both food-seeking behaviors and to avoid predators during such activity (Aimé et al., 2007). While early and more recent experiments clearly demonstrate that fasting drives olfactory acuity (as discussed below, **How Does Fasting Enhance Olfactory Behaviors?** section) (Pager, 1978; Apelbaum et al., 2005; Aimé et al., 2007; Albrecht et al., 2009; Julliard et al., 2007; Stafford and Welbeck, 2011; Rolls, 2015) to what extent do olfactory structures sense glucose? Is glucose, as a byproduct of metabolism, able to modulate physiological processes to drive behavioral changes, and if so, how can olfactory neurons sense glucose? For readers that have a high interest in brain glucose sensing in the control of energy balance, a special topical issue is found on this subject in the *Frontiers in Physiology* edited by Cruciani-Guglielmacci and Fioramonti (Cruciani-Guglielmacci and Fioramonti, 2019).

In the MOE, cilia are the site of odor transduction where a number of enzymes must be catalyzed by ATP hydrolysis, notwithstanding the energetic demands of action potential generation and propagation. Villar and colleagues (Villar et al., 2017) made the curious computation that based upon the number of mitochondria per olfactory cilia and the typical diffusion rate of ATP along the cilium's length, an additional ATP source must be required. Glucose is delivered to the MOE through blood vessels in the lamina propria using GLUT1 transporters. They reported that using GLUT3 transporters, the sustentacular cells are responsible for releasing the needed glucose to mucus in the epithelium (see **Fig. 2**), which in turn metabolizes glucose to yield the ATP required for transduction and the detection of odorants by the olfactory sensory neurons (OSNs). A secondary pool of ATP is provided by localized mitochondria in the dendritic knob of the OSNs. If the authors removed extracellular glucose, incorporated broad spectrum GLUT inhibitors, or inhibited glycolysis or oxidative phosphorylation, then odor transduction was impaired as determined via EOG or loose patch voltage-clamp recordings.

In the OB, the target for glucose sensing appears to be a voltage-dependent potassium channel, Kv1.3. As previously described in **Insulin Is Part of a Signalplex that Uses Kv1.3 Ion Channel as a Substrate** section, Kv1.3 is part of a signalplex serving as a substrate for phosphorylation, a scaffold for protein-protein interactions, and it dampens excitability of olfactory bulb neurons by timing the action potential frequency and allowing stabilization of the resting potential (Yellen, 2002). Although Kv1.3 carries 60%–80% of the outward current in mitral cells in the OB (Fadool and Levitan, 1998; Colley et al., 2004), it was first described as a predominant conductance in T-lymphocytes (Cahalan and Chandy, 2010) to drive the immune response. It was here in the T-lymphocytes where its link to glucose sensing was hinted because reactive oxygen species (ROS) as a byproduct of glucose metabolism were able to suppress Kv1.3 activity (Duprat et al., 1995; Cayabyab et al., 2000) while ATP was found to increase channel activity (Chung and Schlichter, 1997a, 1997b). Studying cloned Kv1.3 channels heterologously expressed in HEK293 cells, Tucker et al. (2013) found that the channels were metabolically sensitive to D-glucose but not L-glucose in a dose-dependent manner using voltage-clamp. Here, the greatest current amplitude was found at 10 mM glucose, mimicking the fed state, and was the lowest at the upper and lower extremes of the dose-response curve where anticipated changes in ATP/ROS production might occur. Hypoglycemic conditions would promote depletion of ATP while hyperglycemic conditions yield high production of ROS due to changes in electron transport coupling. Switching the physiological preparation to an OB slice, the authors then studied glucose sensitivity of

mitral cells in order to be able to target native Kv1.3 in these neurons. The response of mitral cells to changes in glucose concentration was heterogeneous, in that three-fourths of the recorded neurons were inhibited by a change to higher glucose while one-fourth of neurons were excited (Tucker et al., 2013). In contrast to insulin modulation of mitral cells, that is slow and consistent with the timing of a biochemical event, modulation by glucose was rapid. It occurred on the order of minutes and was readily reversible. Neurons that basally were lower in spike firing frequency tended to be glucose excitatory whereas those that were basally higher in spike firing frequency tended to be glucose inhibitory. There are a number of glucose/ATP/ROS sensitive ion channels expressed in mitral cells - namely Kir6.2, KCa1.1, and Na-activated K channels (Slack/Slick) (Zhou et al., 2002; Sausbier et al., 2006; Lu et al., 2010) - that could provide an alternative molecular mechanism for metabolic sensing of glucose by mitral cells following a meal, however, Kv1.3−/− mice were glucose insensitive and incubation of the OB slices in a pore blocker of Kv1.3 also rendered the mitral cells unresponsive to glucose (Tucker et al., 2013).

Despite our knowledge of mitral cells serving as a sensor of glucose and the Kv1.3 ion channels expressed there serving as important contributors, it is not yet confirmed if glucose modulation is triggered by binding to GLUT4 or if glucose metabolism is required to alter mitral cell activity (Al Koborssy et al., 2015) (**Fig. 5**). Outside the olfactory system, Xu et al. (2004) have demonstrated that pharmacological inhibition or gene-targeted deletion of Kv1.3−/− stimulates glucose uptake through translocation of GLUT4 in adipose tissue and skeletal muscle in a calcium-dependent fashion. Despite the GLUT4 transporter being insulin-dependent, site-directed mutagenesis of the channel or blocking the conductance of Kv1.3 is able to translocate the transporter in the absence of insulin (Xu et al., 2004; Kovach et al., 2016) offering a strong therapeutic target for diabetes (Choi and Hahn, 2010; Perez-Verdaguer et al., 2016).

In the aPC, there is an interplay between glucose and insulin modulation of neuronal excitability in superficial pyramidal (SP) cells as described previously (**Insulin Suppresses Neuronal Activity in the Anterior Piriform Cortex and Decreases the Ability to Discriminate Difficult Odor Tasks** section) where insulin modulation requires glucose metabolism. Similar to what is reported in the OB concerning mitral cells, SP cells also exhibit a heterogeneity of glucose sensitivity (Al Koborssy et al., 2019). Roughly three-fourths of SP cells are found to be glucose excited and the remaining one-fourth are glucose insensitive. In response to a depolarizing current step, SP cells fire two APs in rapid succession followed by a rather tonic train of APs (Suzuki and Bekkers, 2006). An elevation in glucose concentration evokes both a reduction in spike firing frequency but also a reduction in the instantaneous frequency (IF) of the rapid successive pair of APs that are postulated to be mediated by an underlying calcium conductance (Suzuki and Bekkers, 2006). Therefore, similar to glucose sensing cells in the pancreas and those centrally in the ventromedial hypothalamus (VMH), activation of a down-stream calcium channel may be involved in glucose sensing in the aPC (Moriyama et al., 2004; Song and Routh, 2006; Marty et al., 2007).

Some brain regions are capable of using fructose as opposed to glucose for energy production (Oppelt et al., 2017). Excessive fructose intake has been linked with adverse health implications as recently reviewed by Johnson and collaborators (Johnson et al., 2010). Although fructose modulation of olfactory physiology and feeding behavior has not been explored in normal weight individuals, Riviere and collaborators have demonstrated strong losses in structure and function of the MOE and olfactory discrimination in mice that have been made obese through maintenance on a high fructose diet (Riviere et al., 2016) (see **Diet-Induced Obesity Mouse Models** section, below).

3.35.3.2.7 Ghrelin Increases Olfactory Sniffing Behaviors and Food Searching

Due to the discovery of ghrelin receptors in olfactory centers and the known appetite-stimulating effects of ghrelin, Tong and colleagues tested the hypothesis that elevation of this hormone might lower olfactory detection thresholds (Tong et al., 2011). Uniquely the investigative team tested the olfactory behavioral outcome of the ICV infusion of the hormone in both rats and humans for parallel comparison purposes. In rats, infusion of ghrelin enhanced sniffing frequency as well as increased odor discrimination using a COA paradigm (see **Fig. 3**E). In parallel for humans, infusion of ghrelin showed a dose-responsive increase in sniffing magnitude for the presentation of food, and non-food odors while there was no change in the pleasantness of the odorants following hormone delivery. The authors conjecture that the observed enhancement in olfactory function is likely attributed to a combination of changes in sniffing behavior and changes in central perception of odors to enhance the efficiency of food-finding behaviors.

3.35.3.2.8 Leptin Decreases Food-seeking Behavior and Decreases Olfactory Bulb Coding and the Activation of Higher Centers

One of the earliest reports concerning the modulation of leptin on olfactory sensitivity came from the Getchells' laboratory where they sought a role for pre-ingestive feeding behavior that was mediated by olfaction (Getchell et al., 2006). Here the investigators took advantage of two mouse lines with targeted deletion of the Obese gene (ob/ob mice) and the leptin receptor (db/db mice). Because both lines have an absence of leptin signaling, the mutant mice become obese attributed to hyperphagia and reduced total energy expenditure (Elmquist et al., 1999; Zigman and Elmquist, 2003). Using a modification of the hidden cookie paradigm (see **Fig. 3**A), the authors measured mean reward retrieval time 5 times per day for 6 days in food-restricted mutant vs. wildtype mice following a daily intraperitoneal (IP) injection of leptin. Both cohorts of uninjected, genetically obese mice retrieved food 10 times as fast as wildtype mice, indicating that leptin signaling slowed food retrieval, and in fact, administering the leptin to the ob/ob mice rescued this phenotype. Trellakis et al. (2011) further explored in humans how odorant perception could be linked with peripheral metabolism. Specifically they measured blood concentrations of leptin and ghrelin to see if there was a correlation with odor pleasantness or odor hedonics (Trellakis et al., 2011). Both leptin and ghrelin concentrations correlated with the odor of black pepper oil.

Leptin concentration was positively associated with the ability for odor identification, which was thought to be the result of both enhanced sensory function and also improved learning and memory reported for leptin elevation in other brain regions.

3.35.3.2.9 Endocannabinoids Increase Odor Sensitivity and Link Hunger State to Stronger Odor Processing

Using a newly available mouse model (CB-1−/− in glutamatergic neurons), Soria-Gómez and colleagues (Soria-Gomez et al., 2014) were not only able to manipulate CB-1 expression in the granule cell layer of the OB (Fig. 1) (and hence eating) but also uncovered the involvement of centrifugal glutamatergic projections back to the OB from the anterior olfactory nucleus and the piriform cortex (AON/PC) (Fig. 1). Fasting induced an elevated production of endocannabinoids that drove hyperphagia, which was mediated by decreased activity of the granule cells and a subsequent reduction in glutamatergic transmission. By using a combination of strategic viral infections to eliminate or rescue CB-1 expression in either the granule cells or centrifugal synapses, the authors were able to demonstrate that the centrifugal feedback was required to induce food intake after fasting elevated endocannabinoid production. Administration of the exogenous cannabinoid, THC (tetrahydrocannabinol), was shown to increase odor discrimination using the habituation/dishabituation paradigm (see Fig. 3C). Finally the authors provided direct evidence for their hypothesis that reduction of centrifugal transmission back to the OB by CB-1 activation in granule cells was driving food intake by devising an awake recording of head-fixed mice where they could optogenetically excite the AON/PC and note postsynaptic currents in the granule cells. The optogenetically-derived postsynaptic currents in the granule cells were indeed reduced upon application of a CB-1 agonist in the OB. This elegant study was able to link internal state or hunger to olfactory central processing in the olfactory bulb/AON/PC to that of the behavioral process of eating.

3.35.3.2.10 Glucagon-like Peptide-1 Defines a Unique Microcircuit within the Olfactory Bulb and Decreases Olfactory Discrimination

Following the discovery of GLP-1 producing neurons in the OB (PPG neurons) Thiebaud and collaborators used a combination of whole-cell electrophysiology and optogenetics to define the molecular action of the peptide on mitral cells and how modulation might alter olfactory discrimination (Thiebaud et al., 2016; Thiebaud and Fadool, 2016; Thiebaud et al., 2018; Thiebaud et al., 2019). GLP-1 and its more stable analog exendin 4 (Ex-4) evoked a dose-dependent increase in AP firing frequency of mitral cells attributed to a reduction in interburst intervals (between spike trains) as opposed to interspike intervals (ISI; spikes within a burst) (Fig. 4C). Overall, GLP-1 was found to decrease the activation threshold for mitral cell firing as observed by changing external K+ concentrations. Because GLP-1 had been shown to inhibit potassium conductances in other cell types (MacDonald et al., 2003; Gaisano et al., 2010; Kim et al., 2012, 2013) and the pattern of spike inhibition in mitral cells in response to a Kv1.3 channel blocker mirrored that of GLP-1 application, the authors tested GLP-1 sensitivity in Kv1.3−/− mice and discovered that they were insensitive (Thiebaud et al., 2016). This group was then able to optogenetically activate channel rhodopsin (ChR) expressed selectively in the PPG neurons and combine this with pharmacological strategies to reveal that the PPG neurons comprised a special excitatory microcircuit containing the PPG neurons/mitral cells/granule cells within the OB. Typically neurons such as the PPG neurons, contained within the granule cell layer, function as inhibitory interneurons, but activation of this microcircuit stimulates an unusual, excitatory glutamatergic pathway (Thiebaud et al., 2019). The PPG neurons are not excitable by 5HT or leptin but are modulated by acetylcholine (ACh) and cholecystokinin (CCK). Intranasal and intraperitoneal (IP) injection of a fluorescent conjugated form of Ex-4 is demonstrated to arrive in the OB and bind strongly to the GLP-1R expressed on mitral cells (see Fig. 4C). Using this approach, Huang et al. (2017) has preliminarily shown that elevation of Ex-4 can cross the BBB and cause a decrease in odor discrimination as measured through a habituation/dishabituation behavioral assay (see Fig. 4F). At this time it is unknown if circulating GLP-1 might be able to arrive at the level of the OB following postprandial activations (i.e. a meal) given known levels of DPP4 enzymatic degradation peripherally (Olivares et al., 2018) or if GLP-1 function is released as a local modulator following excitation of PPG neurons (see Fig. 5).

3.35.4 Fasting, Eating (Satiation), and Excess Nutrition (Obesity) Affects the Structure and Function of the Olfactory System

The nutritional and metabolic state of both animals and humans affects olfactory ability. The influence of satiety and olfaction is actually bidirectional in that informational cues from the olfactory system can alter eating behavior (Rolls, 2005; Yeomans, 2006; Lushchak et al., 2015), and oppositely, whether one is fasted or satiated largely impacts the ability of the olfactory system to discriminate informational or odor cues (Pager, 1978; Julliard et al., 2007; Albrecht et al., 2009; Marks et al., 2009; Stafford and Welbeck, 2011; Rolls, 2015). Readers are referred to a recent review by Soria-Gomez et al. (2014) for a further understanding of feeding behavior, and as authors describe, the "invisible magnet" between olfaction and food intake. Because the body favorably times physiological function across the circadian cycles, it is not unexpected that eating, olfactory sensation, and endocrine secretions could be purposely synchronized across the sleep/wake cycles depending upon the animal or individual. Finally, the ability to train olfactory behaviors or improve your olfactory function can alter brain structure (Al Aïn et al., 2019), while oppositely, we are beginning to understand that excess nutrition or diet-induced obesity (DIO) can drastically damage olfactory structures and circuits. The extent of anatomical changes undergone as a result of fasting is completely unexplored and whether anatomical losses attributed to DIO can be reversed with proper nutrition is an area of current exploration (Thiebaud et al., 2014; Chelette and Fadool, 2019). This

next section therefore describes what is known regarding the influence of metabolic state and olfactory acuity using behavior or eating as an output and then describes structural changes in olfactory structures as a result of changes in metabolism or excess eating.

3.35.4.1 How Does Fasting Enhance Olfactory Behaviors?

In the late 1950s, the link between food odors and their elicited alimentary behavior was first quantified (Le, 1959). Olfactory sensitivity and its control of food intake in humans has been shown to increase with hunger (Ramaekers et al., 2016) (see **How Does Human Olfaction Change with Altered Eating, Disrupted Metabolism, Poor Nutrition, or Sensory Damage?** section, below) yet a decrease in odor sensitivity following a meal remains experimentally controversial. The determination of the palatability of food and the degree of satiation following a meal is more easily controlled using experimental paradigms in animals. Classical experiments by Pager (Pager, 1974a; Pager, 1974b) showed that mitral cell single-unit firing patterns increased in fasted rats and curiously this increase was dampened if he habituated rats to a restricted food pattern for 15 days. This was the first demonstration that the sustained nutritional status of an animal modified its internal state to evoke changes in olfactory neuronal excitability (Pager et al., 1972; Pager, 1974b). Aimé and colleagues carefully studied olfactory detection ability using the conditioned odor avoidance (COA) assay (**Fig. 3**E) because they reasoned it allowed them to determine how nutritional status influenced odorant detection uncoupled from food intake (Aimé et al., 2007). The investigators selected an odorant that had no food significance in rats and then trained mice to recognize it as an aversive odorant by pairing its presentation during training to a LiCl IP injection to cause malaise. When restimulated with the aversive odorant during experimental sessions, rats that had been fasted were shown to have an increased detection of odorized water three orders of magnitude lower in concentration than that of fed rats. Such enhanced odor sensitivity in fasted rats could be mimicked by administering the neuroendocrine signature of fasting, or under nutrition in satiated animals (Julliard et al., 2007; Badonnel et al., 2012), a subject discussed in the next section. Chronically restricting rats to only a single meal per day of a 2-hr duration caused rats to lose 20% of their normal body weight and have lower resting glucose, leptin, insulin, and triglycerides. These animals begin to show an adaptive locomotor response to food seeking behavior without changes in olfactory performance (Badonnel et al., 2012). General hunger has also been demonstrated to increase the synthesis of an endocannabinoid called 2-arachidonoylglycerol, or 2-AG, by the OSNs and supporting sustentacular cells (Breunig et al., 2010). Blockers of 2-AG had been previously demonstrated to decrease odor-evoked calcium responses and delay odor-activated spike frequency in OSNs, so elevation of the endocannabinoid was predicted to elicit the opposite (Czesnik et al., 2007; Breunig et al., 2010). Breunig and colleagues (Breunig et al., 2010) found if they food deprived larval *Xenopus*, the odor threshold for amino acid detection was reduced due to elevated lipase activity to enhance synthesis of 2-AG. The authors propose a cellular model whereby elevation of the ligand concentration increases probability of 2-AG binding with CB-1 receptors on the dendrites of OSNs to increase odorant sensitivity in the hunger state. Another caveat is that chronic fasting during pregnancy (20% caloric restriction) can modify the level of endocannabinoid (2-AG) and related lipids (arachidonic acid and palmitoylethanolamide) in female, low weight offspring, selectively in the olfactory bulb over that of other brain regions (Ramirez-Lopez et al., 2017).

Daumas-Meyer et al. (2018) have recently proposed that astrocytes of the glomerular layer in the OB may provide the plasticity of the olfactory system to adapt to fasting. Because the major glutamatergic synapses between the OSNs and the mitral cells are regulated by a combination of astrocytes and centrifugal inputs, they sought to quantify the activation (expansion of processes) of astrocytes in response to a 17-hr fast in rats. Not only did fasting cause a spreading of glomerular astrocytic processes, the authors were able to reverse this activation through an IP injection of the ghrelin.

3.35.4.2 Olfaction Is Tied to Circadian Physiology, Meal/Hormone Fluctuations, and Satiation

Circadian rhythms that are entrained by light/dark cycles in the master suprachiasmatic nucleus (SCN) can coordinate with other brain clocks and those in the periphery using feeding-related cues such as temperature, nutrient availability, and release of metabolic hormones. It has been demonstrated that delivering rhythmic odor stimulations to voluntary running mice, lengthens the circadian activity rhythms - indicating that odor itself can act as a circadian cue (Abraham et al., 2013). It has been well established that the OB has its own clock that is independent of that of the SCN, and that electrical excitability can be maintained as a circadian rhythm for several days in OB explants (Abraham et al., 2005; Dibner et al., 2010; Ono et al., 2015; Korshunov et al., 2017). While there is experimental agreement as to the presence of a molecular clock and identified gene in the OB (Ono et al., 2015), differences in enhanced odor sensitivity in synchrony with both the dark and light cycle have been reported, which is at odds with meal consumption and activity. Amir and collaborators used odor-evoked, c-fos immediate early gene activation (Sallaz and Jourdan, 1993; Guthrie and Gall, 1995) to demonstrate that greatest odorant sensitivity coincided with the active or dark cycle in rodents (Amir et al., 1999a, 1999b; Funk and Amir, 2000a, 2000b). Granados-Fuentes et al. (2006) also found that c-fos mapped activity could be established in constant darkness to be oscillatory and occurred 4 hours into the normal dark cycle (established by increased locomotor activity). Using strategic lesioning, the authors results support that the OB is a master oscillator that drives forward to the PC and coordinates circadian behaviors with the SCN (Granados-Fuentes et al., 2006). Another study, however, has found the opposite - that there is enhanced protein production of signal transduction machinery in the MOE during the day. Here, Francois and collaborators mapped out the sensitivity of the MOE to odorant stimulation using a combination of EOG recordings and traditional patch-clamp electrophysiology and report that the greatest odorant sensitivity is a few hours after the light phase in rodents (Francois et al., 2017). Regardless of the oscillatory pattern, olfactory sensitivity that will drive food preference is not static over the course of 24 hours. A most interesting recent study has even shown that mice made

anosmic by zinc sulfide lesioning still can demonstrate independent entrainment of the OB to daily meal times, indicating that olfaction and input from the OSNs is not required for the independent circadian clock in the OB (Pavlovski et al., 2018). In humans, olfactory acuity was thought to only vary by individual genetic differences, age, gender, and health, but recently Herz and collaborators (Herz et al., 2017) have reported that male adolescents have the lowest olfactory threshold following melatonin onset in early evening whereas their peak olfactory acuity never occurred in early morning. The authors offer evolutionary adaptation to enhanced acuity with the main meal and need for predatory avoidance when visual cues are poorer.

Certainly the elevation of incretin hormones (such as insulin or GLP-1) or energy availability (glucose) in synchrony with a meal creates a non-stationary effect throughout the 24 hour day of an individual and would anticipate to modulate olfactory physiology and eating behavior as previously described (see **The Olfactory System Is Home to Metabolic Hormones and Energy Important Molecules That Regulate Eating Behaviors** section). As eloquently put by S.C. Woods, "The act of eating, although necessary for the provision of energy, is a particularly disruptive event in a homeostatic sense" (Woods, 1991). To determine if nutritional status could be chemically mimicked to alter olfactory behaviors, a creative behavioral experiment was performed by Prud'homme and colleagues (Prud'homme et al., 2009). The authors administered an anorexogenic hormone (see **Table 1**) to satiated rats while providing an orexigenic hormone to fasted rats and measured c-fos immediate early gene, locomotor activity, and sniffing time as the readout (**Fig. 8**). By using leptin, they were able to elicit decreased sniffing and locomotor activity in response to a familiar odor or food odor in fasted animals that ordinarily would have evoked the opposite. Similarly an injection of orexin into satiated animals was able to increase sniffing time and locomotor activity as if they were fasted. By using hypothalamic and peripheral hormones the researchers could therefore trick the internal chemistry into a perception of an opposite nutritional status and the appropriate OB neural activation and concomitant olfactory behavior could be elicited.

3.35.4.3 Obesity Damages Olfactory Structure and Evokes a Loss of Function

In both taste and olfactory systems, diet-induced obesity or excess nutrition can damage anatomical structures in rodents and ultimately causes a reduction in chemosensory ability (Tucker et al., 2012b; Thiebaud et al., 2014; Lacroix et al., 2015; Kovach et al., 2016; Fardone et al., 2018; Kaufman et al., 2018). Thiebaud et al. (2014) took advantage of mouse models originally derived from the Axel and Mombaerts Laboratories (Mombaerts et al., 1996; Zheng et al., 2000; Potter et al., 2001; Feinstein et al., 2004; Mombaerts, 2006) that had odorant receptors as genetic reporters. Using these transgenic mice, they could identify the axonal projections of specific OSNs as a molecular tool to visualize the effects of DIO. In these mice, an internal ribosome entry site (IRES) that directs the translation of Tau:LacZ fusion protein was positioned immediately downstream of a variety of odorant receptor (OR) stop codons (Mombaerts et al., 1996; Zheng et al., 2000). Thiebaud and collaborators could then place one of a variety of these mice (called M72*TauLacZ*) on modified fatty diets to identify circuitry changes as a result of dietary manipulation. They additionally took mice that were either resistant to DIO (Kv1.3−/− mice) (Xu et al., 2003; Fadool et al., 2004; Xu et al., 2004) or were genetically obese (MC4R−/− mice (Tucker et al., 2008)) and place them also on the M72*TauLacZ* reporter background to see any potential anatomical changes in mice resistant or prone to obesity (Thiebaud et al., 2014). What they discovered was that maintenance on a moderately high-fat (MHF; 32% fat) or a high-fat (HF; 60% fat) diet caused a severe loss of over 50% of the OSNs that positively expressed the M72 odorant receptor (**Fig. 6**A). When they traced the remaining axonal projections to the lateral and medial M72 glomerulus, the cross-sectional area was concomitantly reduced by 50% (**Fig. 6**B). This effect was restricted to this one class of odorant receptors, but they observed a 20% reduction of OMP+ OSNs in endoturbinate IIb of OMP+gfp mice suggesting a global loss of OSNs and their projections centrally to the OB. OMP, or olfactory marker protein, is a protein that is found in all mature OSNs, and thus represents the majority of all OR-expressing OSNs globally (Margolis, 1972). Moreover there was a loss of G-protein olfactory (G_{olf}), the major G-protein involved in olfactory transduction of odor signals (Jones and Reed, 1989), and a loss of an odorant receptor for which there was reliable antibody localization, called MOR28. Interestingly, mice that were resistant to DIO in terms of glucose clearance, less body weight, reduction in adiposity, and reduced circulating levels of leptin and insulin (Fadool et al., 2004; Tucker et al., 2008; Thiebaud et al., 2014) still exhibited loss of OSNs when challenged with MHF diets, and mice that were genetically obese but did not consume fatty diets (MC4R−/− mice) had no anatomical damage attributed to obesity (Thiebaud et al., 2014), suggesting that it was the fat in the diet that was causing the loss of chemosensory structures (see **Fasting, Eating (Satiation), and Excess Nutrition (Obesity) Affects the Structure and Function of the Olfactory System** section below). Along with loss of axonal projections, Fardone et al. (2018) used odor-evoked c-fos immediate gene activation to report a loss of activated juxtaglomerular cells surrounding the medial but not the lateral M72 glomerulus in mice maintained on fatty diets. These data suggest that fat may asymmetrically disturb the glomerular "mirror image" map that may be more sensitive to fat on the medial as opposed to lateral OB glomeruli.

Consistent with a loss of OSNs attributed to DIO, fat-fed mice have a reduced electro-olfactogram (EOG) amplitude without a change in rise time, latency to response, or event recovery, which infers a shear loss of functional OSNs rather than any dysfunction in olfactory transduction or adaptation of the odor response (Thiebaud et al., 2014). Using different models of obesity-prone rodents, both Thiebaud et al. (2014) and Lacroix et al. (2015) observed olfactory behavioral losses in animals challenged on the fatty diets. Lacroix and collaborators report that obesity prone rats maintained on a high fat/high sugar diet have reduced sniffing behaviors, slower times to uncover a hidden cookie odor reward (see **Fig. 3**A), and a significant reduction in performance in the conditioned odor-fear place test (see **Fig. 3**E) (Lacroix et al., 2015). Thiebaud and collaborators report that there is a reduction in the ability of DIO mice to learn operant conditioning paradigms using a go, no-go olfactometer (see **Figs. 3**F and **7**A) and poorer overall ability of the mice to discriminate even simple odor discrimination tasks (odor vs. diluent) (Bodyak and Slotnick,

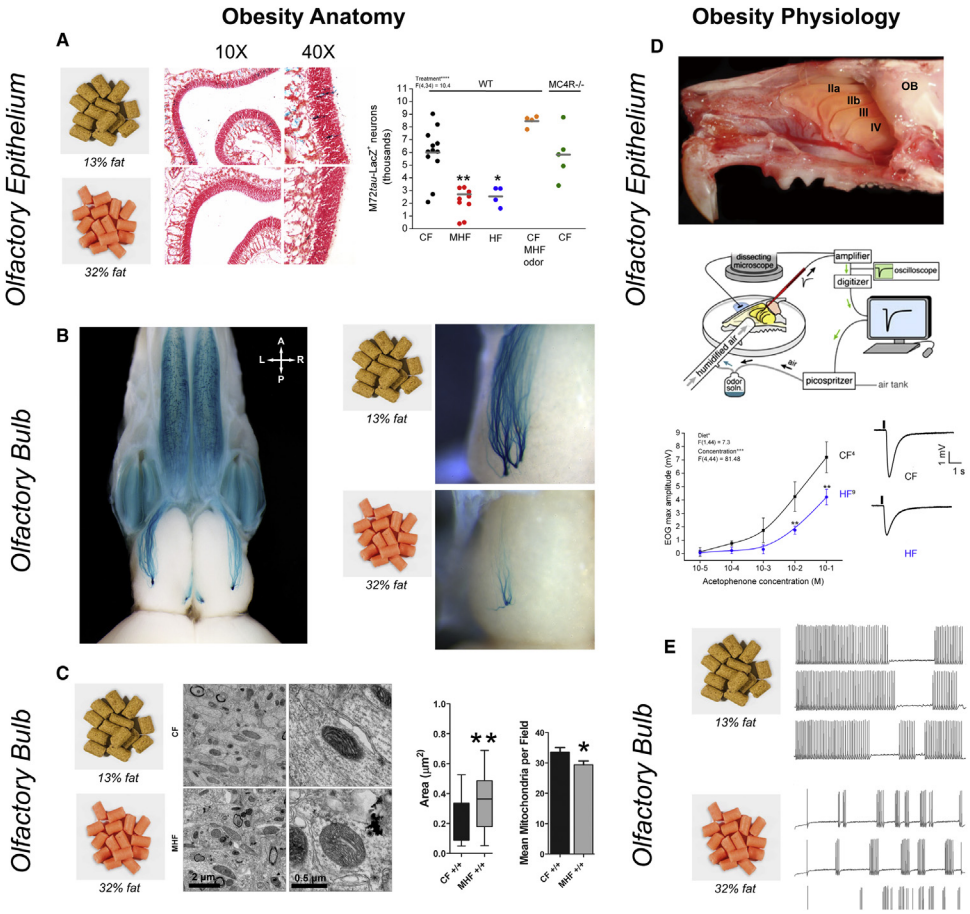

Figure 6 **Anatomical and Physiological Changes in the Olfactory Epithelium and Olfactory Bulb in Response to Diet-induced Obesity.** In this composite panel, mice were maintained on a control diet (CF, 13% fat, brown food picture), moderately high-fat diet (MHF, 32% fat, pink food picture), or high-fat diet (HF, 60% fat). Obesity Anatomy: Structural changes of the (A) olfactory epithelium, (B) axonal targets of the olfactory sensory neurons (OSNs) to defined glomeruli in the olfactory bulb, or mitochondria of the mitral cells in the olfactory bulb in response to fatty diets. (A) Photomicrograph of the olfactory turbinates at 10X and 40X magnification used to count the number of genetically-tagged M72 odorant receptor-expressing OSNs across the entire epithelium. In the adjacent histogram, circles represent individual mice whose number of M72+ OSNs were tabulated following maintenance on an obesogenic diet. Note CF MHF odor = mice that were presented with MHF fatty odor but consumed CF diet did not exhibit loss of OSNs nor did mice that were genetically obese (MC4R−/−) but consumed CF diet. (B) Whole-mount images of the OB showing the B-galactosidase staining (*blue*) of the axons of M72+ OSNs. The left whole-mount was a CF animal and the inset shows CF vs. MHF. (C) Electron micrograph and associated histogram plot demonstrating the increase in size and loss of abundance of mitochondria of the mitral cell in response to MHF diet. Obesity Physiology: (D) An electroolfactogram recording of the IIb turbinate was made in animals maintained on HF diets demonstrates a reduced amplitude in response to the odorant acetophenone whose odorant receptor, M72, lies in this turbinate. (E) Changes in mitral cell action potential firing patterns following maintenance on MHF diets reveals a change in odor information coding. Data taken/modified with permission from - (Thiebaud et al., 2014) - Panel B (inset photographs courtesy of B. Chelette; (Kovach et al., 2016)) - Panel C; (Fadool et al., 2011) - Panel E. Schematic in D from Cygnar et al. (2010), with permission. Photograph in D courtesy of N. Thiebaud.

1999; Restrepo and Slotnick, 2005) with an inability to reversal learn; a test of cognitive flexibility (Izquierdo et al., 2017) (**Fig. 7**B). This is consistent with general learning and memory losses in obese mouse models and humans using a gamut of different behavioral phenotyping or clinical tests (Pager et al., 1972; Greenwood and Winocur, 2005; Winocur and Greenwood, 2005; Tucker et al., 2012b; Lacroix et al., 2015) including object memory recognition, water Morris maze, and conditioned fear paradigms.

Considering the variety of anatomical losses of the olfactory system with regards to DIO, the cellular and molecular basis of these changes are not fully understood. There is some evidence of obesity-related neuroinflammation reported in both taste and olfactory structures in response to over-nutrition. Kaufman et al. (2018) used a 60% HF diet challenge in control and TNFα−/− mice to study taste bud regeneration in response to differential effects of chronic low grade inflammation known to play a central role in neuronal apoptosis and pathogenesis of metabolic dysfunction (Hotamisligil, 2006; Shoelson et al., 2006). Interestingly, while both taste buds and OSNs are fewer following DIO, both show enhanced apoptosis demonstrated by elevated TUNEL labeling, but taste buds exhibited reduced proliferation while OSNs appear to have increased proliferation (Thiebaud et al., 2014; Kaufman et al.,

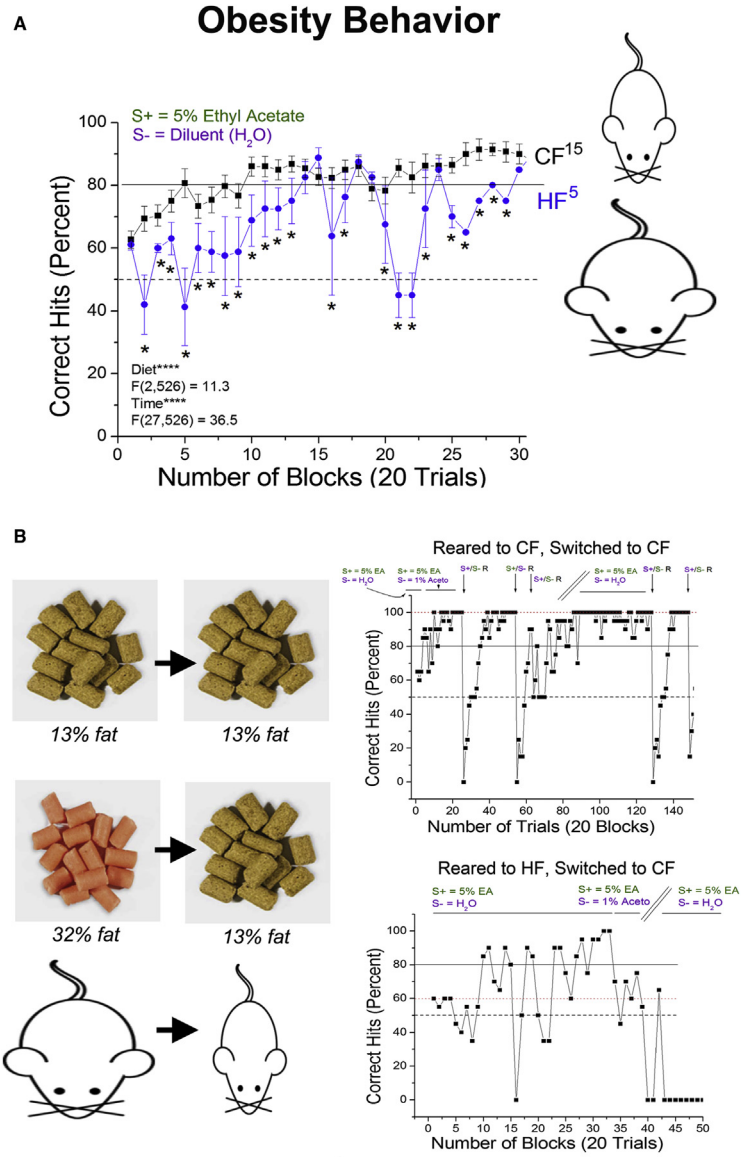

Figure 7 **Olfactory Behavioral Changes in Mice in Response to Maintenance (or 'Dieting') on an Obesogenic Diet of High Fat.** In this composite panel, mice were maintained on a control diet (CF, 13% fat, brown food picture, little mouse), moderately high-fat diet (MHF, 32% fat, pink food picture, fat mouse), or high-fat diet (HF, 60% fat, fat mouse) starting at weaning for a 6-month duration. **Obesity Behavior:** (A) Mice were trained for operate conditioning behavior on a go, no-go Knosys olfactometer (**Fig. 3**F) following maintenance on obesogenic diets. Block = 20 trial presentations of random-ordered S+ and S−, solid line = mouse performance at 80% correct decisions, dashed line = mouse performance by chance alone (50% correct decisions). Note that as mouse blocks progress, CF mice achieve a performance above criteria in less than 10 blocks and retain that learning level. HF mice are slower to learn and then do not continue to perform at criteria (poorer odor discrimination). S+ = Water-providing odor stimulus, S− = Water-depriving odor stimulus (B) Top cohort of mice are (weaned) reared to CF food where they are trained on the Knosys olfactometer, then switched to CF food at six months of age (*double hash bar*). They are transitioned from discriminating Odor vs. Water (5% ethyl acetate, EA vs. water, H_2O), then Odor vs. Odor (5% EA vs. 1% acetophenone (aceto)), and finally an odorant reversal learning paradigm where the S+ (water rewarding) is switched to the S- (water restricted). During the reversal learning paradigm, they fall to 100% incorrect, but then learn the new rules of the game quickly. The bottom cohort of mice are reared to MHF food but then at 6 months of age they are "dieted" to CF food for 6 months *(double hash bar*). Note that they are not able to reversal learn and even after losing the body weight, they cannot successfully perform on the olfactometer to discriminate odor molecules. Data taken/modified with permission from Thiebaud et al. (2014) - Panels A,B. Photographs courtesy of D. Fadool and mouse schematics by clker.com.

2018). In a model of obesity-prone rats, an obesogenic diet was reported to decrease expression of IR kinase and glucocorticoid receptors that are known to enhance proliferation of olfactory basal cells while increasing apoptosis of mature OSNs (Lacroix et al., 2015). An obesogenic diet, therefore, appears to cause inflammation in both olfactory and taste chemosensory cell types and likely perturbation of homeostatic regeneration and renewal.

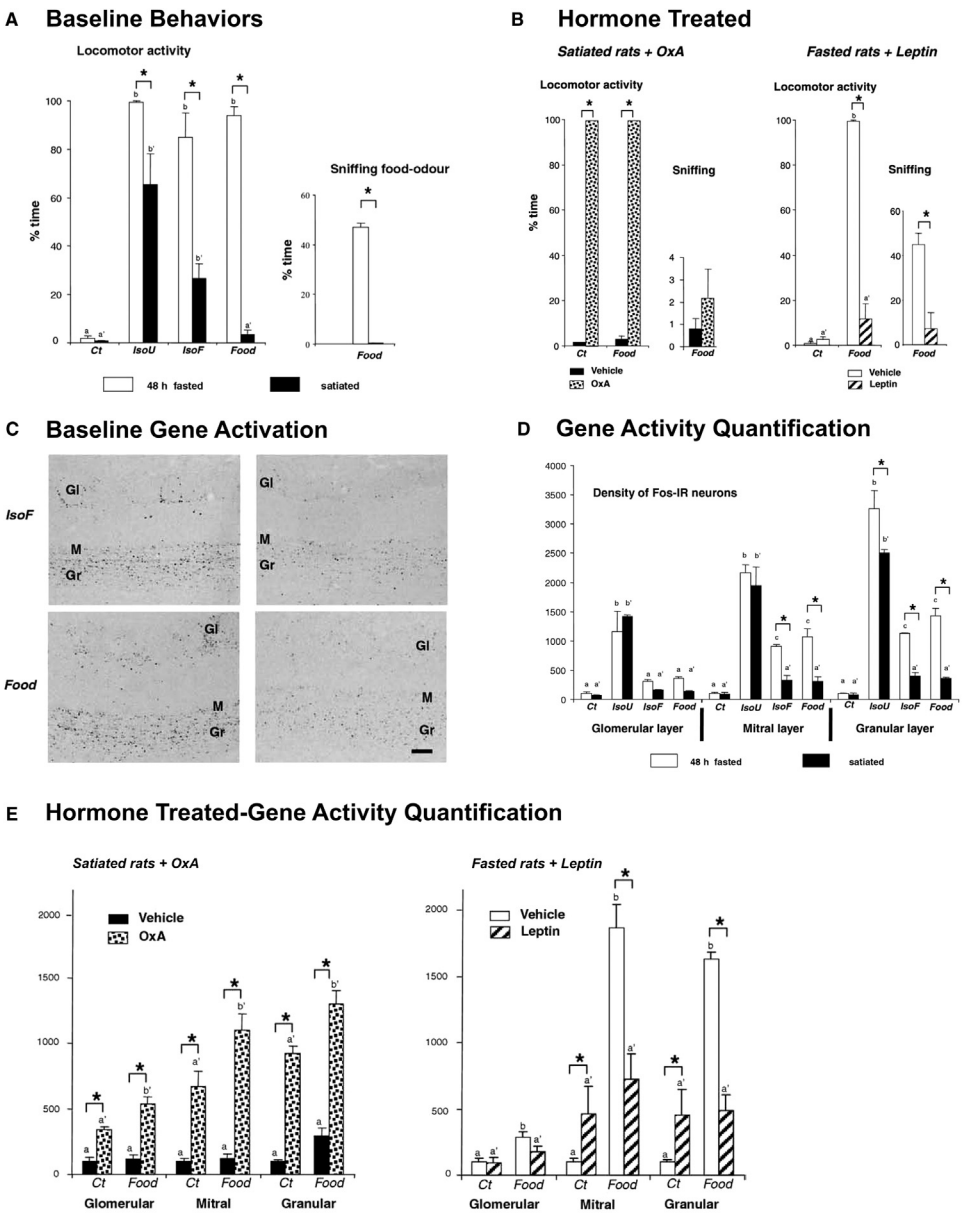

Figure 8 Reversal of a Fasted or Satiated Nutritional State by Administration of Leptin and Orexin, Respectively, as Determined by Immediate Early Gene Activation, Sniffing, and Locomotor Activity in Rats. In this composite panel, rats were cleverly administered an orexigenic hormone (orexin) when they were satiated to mimic the neuroendocrine state of fasting, or oppositely, they were administered an anorexigenic hormone (leptin) when they were fasted to mimic the neuroendocrine state of satiation. (A) Bar graph of the baseline locomotor activity (left) and sniffing behavior (right) of rats that were fasted (*open bars*) or satiated (*closed bars*). Note characteristic behavior of increased locomotor and sniffing behavior of fasted animals. (B) Bar graph of the changed locomotor and sniffing behavior following the hormone treatment. Note that the satiated rats (+orexin, OxA) now have behaviors as if they were fasted (*stippled bars*) and the fasted rats (+Leptin) now have behaviors as if they were satiated (*stripped bars*). (C) Photomicrographs of the immediate-early gene activation (c-fos, neural activity marker) demonstrating the cellular correlates of the behavioral experiment in (A). (D) Bar graph quantifying olfactory bulb neuronal activation following odor stimulation that is significant in the mitral and granular layers. (E) Bar graph of the changed neural activation following the hormone treatment. Note that similar to the behavioral reversals, the satiated rats (+OxA) now have gene activation as if they were fasted (*stippled bars*) and the fasted rats (+Leptin) have gene activation as if they were satiated (*stripped bars*). Ct = control, IsoU = isoamyl acetate unfamiliar odor, IsoF = isoamyl acetate familiar odor, Food = food odor, Vehicle = saline control, Gl = glomerular layer, M = mitral layer, Gr = granule cell layer, different letters (or letter prime) indicate significantly different mean values analyzed within state or drug treatment (ANOVA), * = post-hoc test analyzed across state or drug treatment. Data taken/modified with permission from Prud'homme et al. (2009).

Along with modifying regular renewal of chemosensory neurons, obesity may cause long-term adaptation of the energy required of olfactory neurons. Obesity-prone rats have reduced GLUT3/GLUT4 expression in the MOE, obese Zucker rats have enhanced SCGT receptors in the OB, and monocarboxylate transporter expression is both down- and up-regulated across the MOE and OB, respectively (Aimé et al., 2014; Lacroix et al., 2015). Such changes in glucose/ketone body transport/lactate utilization may be an adaptive response to the hyperglycemic conditions of obesity but may also disrupt the metabolic energy exchange across cell types in olfactory structures needed for odorant transduction and olfactory coding. Interestingly, Kovach et al. (2016) observed ultrastructural changes in mitochondria of obese mice within the mitral cell layer (**Fig. 6**C). The mitochondria were fewer but larger in cross sectional area following an obesogenic diet, an observation that was not found for the Kv1.3−/− 'Super-smeller' and obesity-resistant mice, which had smaller and more numerous mitochondria that were insensitive to changes in dietary fat (Kovach et al., 2016). It is conjectured that chronic maintenance on fatty diets can lead to unhealthy mitochondrial ion transport across the inner mitochondrial membrane, or IMM, leading to mitophagy and drop in organelle density to change energy availability for olfactory processing.

What about the generational impact of excess nutrition on the olfactory system? There is a large body of experimental evidence that maternal high-fat diet can lead to neuronal and brain function changes (Elias et al., 2003; Elias et al., 2005; Schwartz and Porte, Jr., 2005; Janthakhin et al., 2017) and increase the likelihood of obesity as an adult (Lifshiz, 2008). Merle et al. (2019) examined the effect of a high fat and high sucrose (HFHS) diet in pregnant or lactating dams on their progeny's ability to respond to olfactory information. Despite the progeny not demonstrating any change in odor-evoked EOG amplitudes, the male progeny had reduced sniffing behavior in response to a variety of odorants and took longer to find hidden rewards in anosmia tests (hidden cookie test; see **Fig. 3**A). Male progeny did have excess body weight attributed to increased deposition of epididymal adipose tissue. Because the investigators did not find any cellular changes (mRNA) in odorant transduction machinery in the progeny of HFHS maintained dams, they suggest that altered olfactory perception in the subsequent generation could be attributed to changed modulation of central processing in higher olfactory centers.

3.35.4.4 Fat in the Diet Is a Culprit for Olfactory Losses and Is Not Readily Reversible in Animal Models

It has been shown that even though DIO mice and genetically-predisposed (MC4R−/−) obese mice have significant adiposity and similar changes in elevated blood insulin, glucose, and leptin (Huszar et al., 1997), they vary in the degree to which they exhibit behavioral deficits in odor detection, odor discrimination, and long-term memory (Tucker et al., 2012b). As described above, mice maintained on excess nutrition have structural changes in the abundance of OSNs, density of axonal projections, loss in G-protein coupled machinery, reduction in ORs, with losses in EOG amplitude, loss of mitral cell excitability by neurohormones, and poorer odor discrimination using COA or go, no-go operant conditioning paradigms (Aimé et al., 2014; Fadool et al., 2011; Thiebaud et al., 2014; Lacroix et al., 2015; Fardone et al., 2018). With the absence of the melanocortin 4 receptor in the hypothalamus, MC4R−/− mice have late-onset diabetes and associated weight gain, have hyperleptinemia, and are hyperphagic. Noteworthy, the MC4R−/− mice exhibit all these obesogenic phenotypes when maintained on control chow; they are not anosmic nor do they exhibit structural changes in OSN abundance or associated axonal projections despite their obesity (Tucker et al., 2008; Tucker et al., 2012a; Thiebaud et al., 2014) (**Fig. 6**A, right). By comparison, Kv1.3−/− mice that are maintained on MHF diets, remain thin and have low circulating levels of leptin, but are not resistant to either the structural olfactory losses nor reduced go, no-go odorant discrimination tasks when consuming the fatty diet (Tucker et al., 2008; Thiebaud et al., 2014). In fact, these mice have a significant increase in light phase metabolism that makes them resistant to the MHF diet, and when they undergo removal of the olfactory bulb (olfactory bulbectomy), their light phase metabolism fails to be upregulated, their dark phase metabolism and total energy expenditure is decreased - and they become overweight (Tucker et al., 2012a). These data suggest that the resistance of Kv1.3−/− mice to obesity is olfactory bulb dependent and the consumption of excess nutrition or fat, and perhaps not adiposity itself, is causing loss of olfactory structure and function.

To test the idea that fat is the culprit for olfactory losses, Chelette and colleagues established pair-feeding experiments whereby mice would be maintained on isocaloric diets, but be challenged with different fat percentages making up the diet (Chelette et al., 2018; Chelette and Fadool, 2019). Using mice with genetic reporters to visualize circuitry changes in response to fat in the diet (M72*IresTauLacZ* mice mentioned previously (Mombaerts et al., 1996; Zheng et al., 2000)), mice were provided a daily food allotment for 4 months that was isocalorically set to that of a control fed mouse, but contained 32 rather than 13% fat (control fed). Even though the pair-fed, MHF-diet mice did not gain adiposity over that of control fed mice and were able to clear a glucose challenge (glucose tolerance test called IPGTT) the same as controls, they still exhibited loss of OSNs and associated axonal projections. These results suggest that the long-term macronutrient imbalance via fat in the diet is driving anatomical loss in the olfactory system. How permanent is this loss once exposed to the fat in the diet? Given the well characterized regenerative power of the olfactory system that can reestablish connections from basal cells within 30 days (Monti Graziadei and Graziadei, 1979), Thiebaud and colleagues "dieted" fat fed mice for 6 months until their resting blood glucose and body weight were equivalent to age-matched sibling mice that had been alternatively reared to control diets (Thiebaud et al., 2014). Quite markedly, fat-reared mice that were 'slimmed down' did not regain their capacity to discriminate odors in a go, no-go operant conditioning task nor were their axonal projections and olfactory circuitry reestablished following the return to normal body weight (**Fig. 7**B). These findings have repercussions for weight loss interventions in humans (i.e. gradual dieting vs. bariatric surgery) because it is unknown if the deleterious effect of excess nutrition in mouse models is universal across species. Gastric bypass surgery (in both rodents and humans) has been found to reestablish only some taste thresholds back to that measured for normal-weight individuals - other changes in brain function were

noted (Scruggs et al., 1994; Bueter et al., 2011; Berthoud et al., 2012; Pepino et al., 2014; Thanos et al., 2015) while less is known about olfactory function with such acute weight loss intervention (see **Starvation, Restricted-Timed Eating, or Bariatric Surgery** section, below).

3.35.5 How Have Animal Models and Drug Delivery Approaches Uncovered a Link Between Olfaction, Eating, and Metabolism?

The ability to detect and discriminate between various odors is necessary for food choice and for survival. These abilities are shaped by evolutionary pressures in ways that are observable all the way down to the genetic level. To learn more about the ways in which these molecular changes influence whole-animal physiology, a variety of genetic and pharmaceutical approaches have been employed using mouse models. This next section describes a cadre of mouse models that has uncovered a link between olfaction, eating, and metabolism. These include a voltage-dependent potassium channel null (Kv1.3−/−) mouse line, a potassium and sodium/calcium ion channel exchanger (NCKX4−/−) null mouse line, diet- and genetic-obese (MC4R−/−, ob/ob) mouse lines, genetically- and chemically-ablated mouse lines, intranasally-treated mice, mice with ciliary dysfunctions, and studies of pregnant mice with overnutrition.

3.35.5.1 Kv1.3 −/− Super-smeller Mice

3.35.5.1.1 Olfactory Behavioral Ability

The voltage-gated potassium ion channel Kv1.3 plays a prominent role in the excitability of a major output neuron of the OB (mitral cells), and its biophysical properties are modulated via phosphorylation by several identified tyrosine kinase signaling cascades initiated by metabolic molecules (**Fig. 5**). As previously mentioned, Kv1.3 carries 60%–80% of the underlying outward voltage-activated currents in mitral cells (Fadool et al., 1993; Fadool and Levitan, 1998) and accordingly is a major regulator of excitability and timing of the interspike interval (Jan and Jan, 1994). Although Kv1.3-null mice (Kv1.3 −/−) were originally developed to investigate the role of this ion channel in immune responses of thymocytes (Koni et al., 2003), Fadool, Overton, and Kaczmarek collaborated to discover that these mice exhibited enhanced olfactory discrimination and threshold, increased frequency in food events without change in total caloric intake, and increased total energy expenditure (Fadool et al., 2004) (**Fig. 9**).

In testing for general anosmia (**Fig. 3**A), it was found that the retrieval time for Kv1.3-null mice was less than half that of wild-type mice, with both groups performing equally when finding a control item without an associated odor (Fadool et al., 2004). To further explore the olfactory ability of the null mice, the habituation/dishabituation paradigm (**Fig. 3**C) was performed. Kv1.3-null mice habituated slightly faster than wild-type counterparts and showed a 4- to 30-fold increase in mean exploratory time following dishabituation depending upon the tested odorant pair versus wild-type mice (Fadool et al., 2004). Lastly, the odor-detection threshold of the Kv1.3-null mice was characterized using a two-choice paradigm (**Fig. 3**B). After being trained to dig for a food reward, mice were presented with a food reward hidden beneath peppermint-scented bedding. Kv1.3-null mice outperformed wild-type mice, retrieving hidden rewards at odorant concentrations 1000- to 10,000-fold less than those retrieved by wild-type mice (Fadool et al., 2004). This earned Kv1.3-null mice their 'Super-smeller' name (**Fig. 9**), along with their ability to discern odor compounds that were only one carbon atom different.

The link between olfaction and emotion has been well characterized, but the nature of the relationship is not fully understood. Olfaction is the primary sensory modality through which animals are informed of their environment. Mice utilize olfaction to detect food, mates and predators. Bulbectomy leads to anxiety-like behaviors, and bulbectomized rats have long been used as a model for testing antidepressant drugs (Cairncross et al., 1977). Reciprocally, it has been demonstrated that changes in emotional and disease state can modulate olfactory ability (Krusemark and Li, 2012; Krusemark et al., 2013; Takahashi et al., 2015). Olfactory deficits were previously shown to cause anxiety-like behaviors using genetically-ablated mice with functional inactivation of the main olfactory epithelium (Glinka et al., 2012). To further characterize this relationship, Kv1.3-null mice were challenged with marble burying, light-dark box, and elevated-plus maze tests (Bailey and Crawley, 2009). Despite their increased olfactory ability ('Super-smeller' phenotype), Kv1.3-null mice showed increased anxiety levels compared to wild-type mice (Huang et al., 2018). Albeit having no deficits in long- or short-term object memory (Tucker et al., 2012b), Huang et al. (2018) observed that the 'Super-smeller' mice had an ADHD-like phenotype that can be co-morbid with anxiety, which was discovered using an attentional based task (Alkam et al., 2011). Moreover, these deficits could be ameliorated with the administration of Adderall, a well-known ADHD medication. All of the above olfactory, memory, anxiety, and attention tasks rely on measurements of basal locomotor activity. Measurements of locomotor activity determined that Kv1.3-null mice exhibit increased activity during the dark cycle but not during the light cycle (Fadool et al., 2004), not unexpected for a nocturnal rodent. When permitted access to voluntary running wheels, however, Kv1.3-null mice run the same distance and velocity as wild-type mice, however their patterns of activity (less rests or pauses) differ across the dark cycle (Chelette et al., 2019).

3.35.5.1.2 Metabolic Phenotype

The metabolic phenotype of Kv1.3-null mice was determined by housing the mice in a Comprehensive Lab Animal Monitoring System or CLAMS metabolic chamber system (**Fig. 3**I). The CLAMS allows a continual monitoring of system physiology parameters and ingestive behaviors while contained in a home cage environment. The body weight of Kv1.3-null mice was shown to be less than that of their wild-type counterparts, even though total caloric and water intake were not different (Fadool et al., 2004) (**Fig. 9**). How they consumed food and water, however, was modified - they ate many frequent meals in the dark cycle and partook

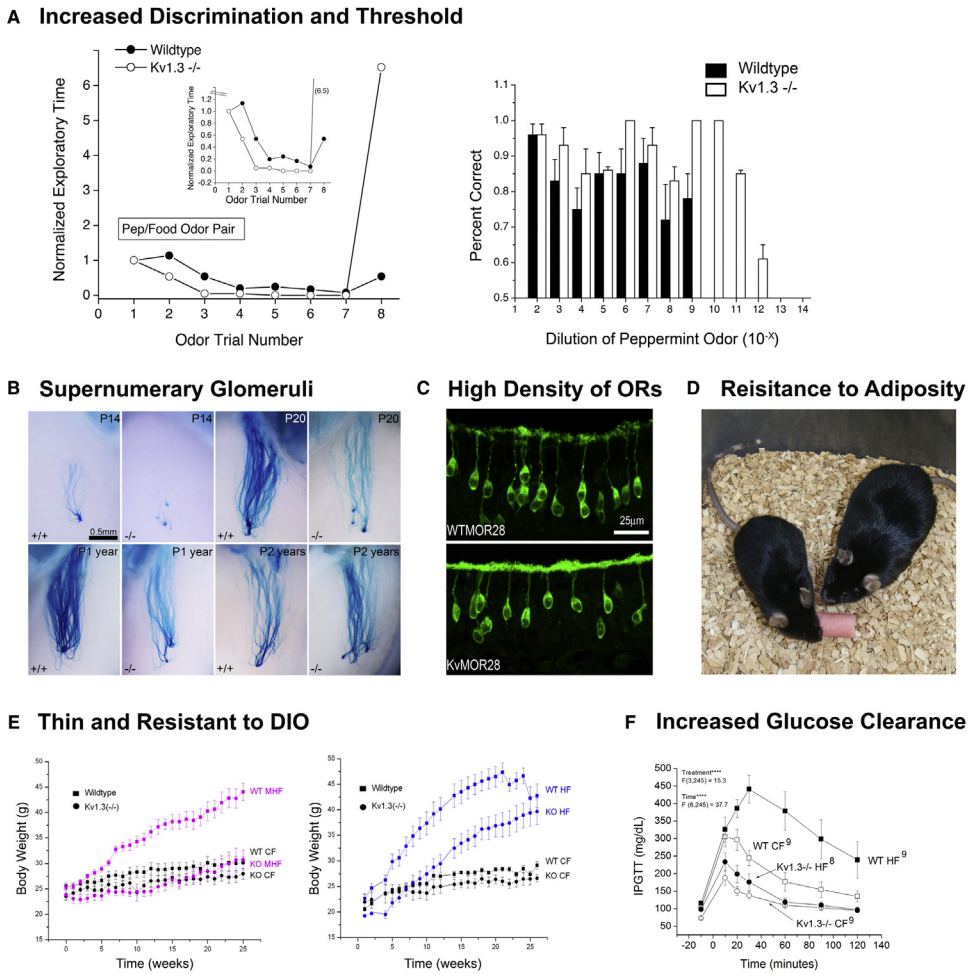

Figure 9 **Super-smeller Mouse Model.** A comparison of olfactory behavior, anatomy, and metabolic function between wildtype (WT, +/+) and Kv1.3−/− mice (−/−). Mice with a targeted deletion (−/−) of the voltage-dependent potassium channel, Kv1.3, have a 'Super-smeller' phenotype and a resistance to diet-induced obesity (DIO). (A) Line-graph (left) of a habituation/dishabituation paradigm (**Fig. 3**C) comparing WT (solid circles) and Kv1.3−/− mice (*open circles*). Note increased discrimination to the novel odorant, enlargement in inset. Bar graph (right) of a two-choice paradigm (**Fig. 3**B) comparing WT (*black bars*) and Kv1.3−/− mice (*open bars*). Note higher threshold for WT mice and increased odor sensitivity of Kv1.3−/− mice. (B) Whole-mount photographs of the M72+ OSN axonal projections displayed as a developmental profile from age postnatal 14 (P14) through 2 years in WT (+/+) vs. Kv1.3−/− (−/−) mice. Note the supernumerary glomeruli in the −/− mice. (C) Photomicrograph of the MOE labeled with an antibody directed against the MOR28 odorant receptor in WT (WTMOR28) vs. Kv1.3−/− mice (KvMOR28). Note the intense increase in cilia labeling in the 'Super-smeller mice'. (D) Photograph of a Kv1.3−/− mouse (left) alongside a WT mouse (right) following maintenance for 6 months on a moderately high-fat diet (pink chow pellet). (E) Line graph of the body weight of wildtype (WT, *squares*) and Kv1.3−/− (KO, *circles*) maintained on control food (CF, *brown*), moderately high-fat (MHF, *pink*), or high-fat (HF, *blue*). (F) Line graph of the clearance of a glucose challenge using an intraperitoneal glucose tolerance test (IPGTT); open symbols CF, and closed symbols HF. Data taken/modified with permission from - Fadool et al. (2004) - Panel A; Biju et al. (2008) - Panels B, C; Thiebaud et al. (2014) - Panels E, F. Photograph in D courtesy of D. Fadool, with permission from Thiebaud et al. (2014).

large boluses of water. Interestingly, metabolic rate as measured by relative oxygen consumption of Kv1.3-null mice, was identical to wild-type (Fadool et al., 2004), but total energy expenditure (TEE) as measured by indirect calorimetry was significantly higher in Kv1.3-null mice (Xu et al., 2003), particularly in the light cycle.

When challenged with an *ad libitum* high-fat diet, wild-type mice become obese and develop insulin resistance. The Desir and Fadool laboratories discovered that the Kv1.3-null mice were resistant to maintenance on fatty diets, where mice did not gain adiposity, maintained normal insulin sensitivity, and retained low glucose-challenged and resting plasma glucose (Xu et al., 2003; Fadool et al., 2004; Tucker et al., 2008; Thiebaud et al., 2014) (**Fig. 9**). This resistance to what typically would result in diet-induced obesity (DIO) with associated increase in TEE for Kv1.3-null mice has been shown to be olfactory bulb-dependent. Tucker and collaborators performed bilateral olfactory bulbectomy in mice and then challenged them with a fatty diet. After removal of the olfactory bulb, Kv1.3-null mice showed equal weight gain and TEE as compared to DIO wild-type controls (Tucker et al., 2012a). They lost their ability to be resistant to obesity. For readers with additional interests in the prevention of DIO by targeting the Kv1.3 channel in the periphery, rather than the olfactory system centrally, please see interesting experiments by Upadhyay and collaborators (Upadhyay et al., 2013) who pharmacologically blocked the Kv1.3 channel with a potent sea anemones

peptide to discover changes in oxidation of fatty acids, glycolysis, oxygen consumption, and energy expenditure contributed by activation of brown fat and liver metabolism in DIO-treated mice to mitigate obesity and insulin resistance.

Because Kv1.3−/− mice were resistant to DIO, Tucker and collaborators explored whether this resistance extended to genetic-, rather than diet-induced obesity (Tucker et al., 2008). The melanocortin-4 receptor is a part of the hypothalamic anorexogenic pathway which controls metabolism and satiety (the brainstem-mediated control of meal size and food preference) (Butler, 2006; Paeger et al., 2017). MC4R-null mice (MC4R −/−) exhibit severe obesity, hyperinsulinemia, hyperphagia, and are often used as a genetic model for Type 2 Diabetes Mellitus (T2DM) (Weide et al., 2003). Therefore, the investigators bred the Kv1.3−/− mice to homozygosity with MC4R-null mice to determine if Kv1.3 deletion could abrogate this genetic model of obesity. Kv/MC4R-null progeny gained significantly less weight and showed increased TEE compared to MC4R-null mice (Tucker et al., 2008). Deletion of the Kv1.3 channel in the MC4R−/− mice reduced body weight by decreasing fat deposition and subsequent fasting leptin levels without changing overall growth. Interestingly, MC4R−/− mice have a much shorter life span (~400 days) and poor reproductive success, both of which were significantly improved by the deletion of Kv1.3.

3.35.5.1.3 Circuitry Glomerular Changes

Axonal projections of OSNs to defined glomerular synaptic centers creates a topographical map of odorant representation across the combined OBs (Mori et al., 1999; Strotmann et al., 2000). Image analyses of the OB in Kv1.3-null mice indicate increased glomerular density without an apparent change in overall brain volume. The glomeruli in these mice are both smaller and more numerous than that of wild-type animals (Fadool et al., 2004). Synaptic refinement is impaired in the Kv1.3-null mice; OSNs expressing P2, M72, and MOR28 odorant receptors fail to undergo neural pruning over development, but the mapped axonal projection or location is not misdirected (**Fig. 9**). Nonetheless, the total population of OSNs in Kv1.3-null mice is seemingly reduced in number (Biju et al., 2008; Tucker et al., 2012a). Despite having fewer OSNs, electron microscopy has revealed that these mice have 2-fold the abundance of cilia per OSN, the site of olfactory signal transduction (Biju et al., 2008). In fact, upon examination of individual OSNs, the Kv1.3−/− 'Super-smeller' mice have enhanced expression of OR proteins and G-protein olfaction, or G_{olf} (Jones and Reed, 1989; Biju et al., 2008), per neuron, which results in an overall overproduction of these transduction proteins (Biju et al., 2008).

3.35.5.2 NCKX4 Mutant Mice

Intracellular calcium ions play a major role in ensuring the proper activation, termination and adaptation of sensory responses. In OSNs, calcium ions assist in amplification of membrane depolarization events by evoking chloride ion currents (Lowe and Gold, 1993; Kleene, 1997; Reisert et al., 2005). Alternatively, calcium ions also mediate a poorly-characterized pathway that desensitizes OSNs to repeated odorant exposure (Zufall et al., 2000). NCKX4 is the primary potassium-dependent sodium/calcium exchanger that governs these properties in OSNs and subsequently influences how odor information is encoded and perceived (Stephan et al., 2011). Olfactory conditional NCKX4-null mice (OMP-NCKX4−/−) show slowed response termination without affecting odorant sensitivity as determined by EOG. Interestingly, NCKX4-null mice over-adapt to repeated odorant exposure by significantly suppressing OSN response even when the time between exposures was lengthened significantly. As a result, NCKX4-null mice perform poorly when tasked with locating a scented treat versus wild-type mice. NCKX4-null mice also weigh significantly less than wild-type controls, though the metabolic phenotype of these mice has not been assessed (Stephan et al., 2011).

3.35.5.3 Diet-Induced Obesity Mouse Models

3.35.5.3.1 Insulin Resistance and EOG Deficiencies

DIO, insulin resistance, and olfactory sensitivity are closely interrelated. In both the olfactory system as well as in other areas of the brain, it has been demonstrated that fat-enriched diets elicit a significant reduction in neuronal excitability (Fadool et al., 2011; Pancani et al., 2013; Underwood and Thompson, 2016; Paeger et al., 2017). In order to investigate this relationship, mice are commonly made obese by diet or by genetic manipulation of hypothalamic or leptin pathways (see **Obesity Damages Olfactory Structure and Evokes a Loss of Function** section as well as **Diet-Induced Obesity Mouse Models** section, below). It turns out that the route of induction of obesity can elicit different changes in olfactory function and structure (Tucker et al., 2012b; Thiebaud et al., 2014) even though each may be characterized by increased body weight, elevated fasting glucose levels, or hyperinsulinemia (Wang and Liao, 2012; DiNicolantonio et al., 2015; Rivière et al., 2016). A good example is that performed by Rivière and collaborators (**Fig. 10**) who selected to examine the deleterious effects of a high-fructose diet to mimic the early stages of prediabetes (4 to 8 weeks) (Riviere et al., 2016) rather than that of high-fat. DIO and associated T2DM can be induced in mice in as little as 4–8 weeks using a high-fructose diet. Unlike mice maintained on fatty diets, those challenged with a high-fructose diet exhibited both a reduction in EOG amplitude, and additionally a slowed kinetics of the response, both onset and decay. Also in contrast to fatty diets, a high fructose diet elicited enhanced density of olfactory marker protein positive (OMP+) OSNs, rather than a reduction in OSN abundance. Experiments by Rivière demonstrated a decrease in programmed cell death or apoptosis that might prevent more mature neurons (OMP+) from entering their regular cell cycle stages. The fact that a high-fructose diet causes a progressive loss of odor-scented hidden rewards in anosmia tests (**Fig. 3**A) and evokes a loss in odorant discrimination as evidence by habituation/dishabituation assays (**Fig. 3**C) (Riviere et al., 2016) but maintenance on fatty diets does not (Tucker et al., 2012b), is quite curious given that both obesogenic diets result in reduced EOG responses (Thiebaud et al., 2014; Riviere et al., 2016) (**Fig. 6**D). Although maintenance of mice on fatty diets does cause olfactory dysfunction when more complex behavioral tasks are performed using traditional olfactometry (go, no-go liquid based Knosys olfactometer; see **Figs. 3**F and **7**), including reversal learning as

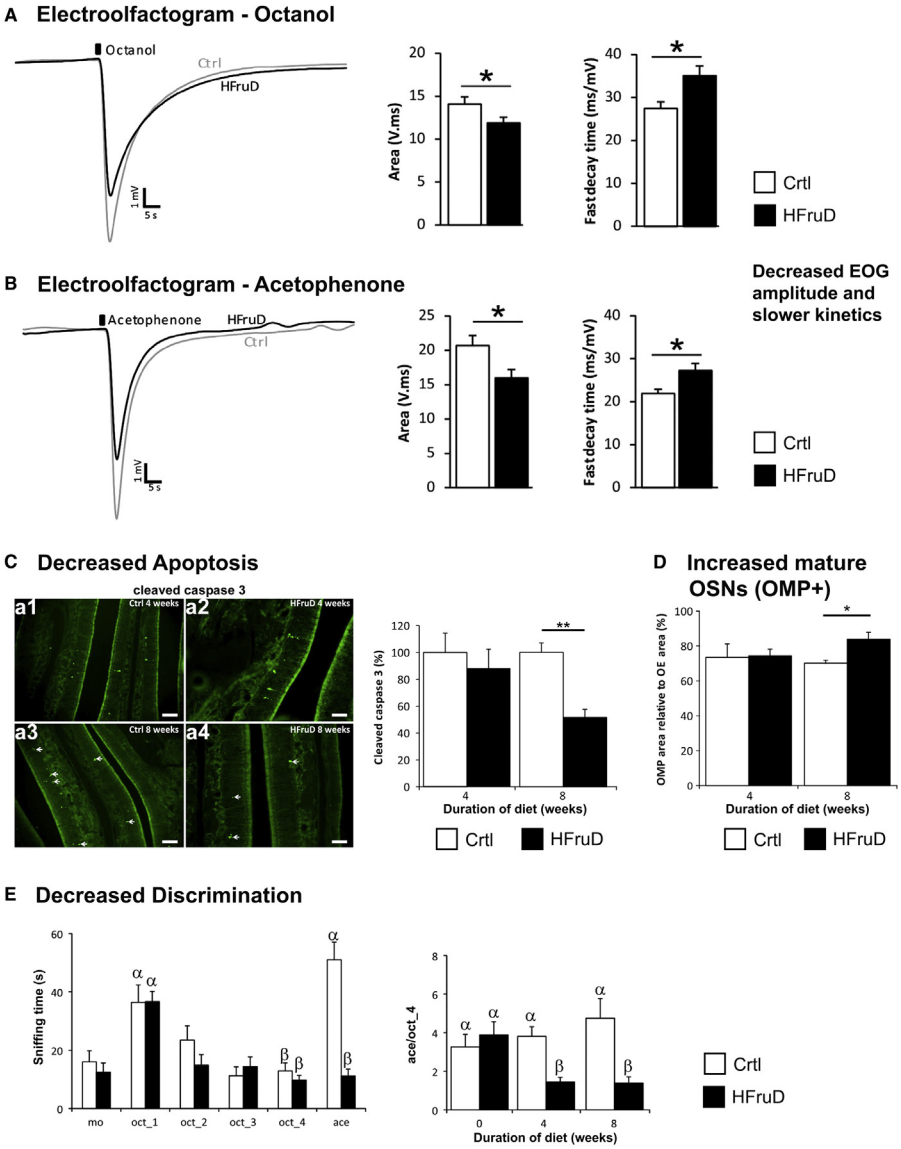

Figure 10 **Changes in Olfactory Physiology and Behavior in Mice in Response to Maintenance on a High-fructose Diet.** In this composite panel, mice were supplemented with 60% fructose (HFruD) for 4 or 8 weeks starting from 5 weeks of age to determine the structural and functional effect of a prediabetic state. In comparison with data contained in **Fig. 6** (high-fat diets), both dietary challenges result in olfactory dysfunction and reduced electroolfactogram (EOG) amplitude, but high-fat diets causes loss of OSNs whereas high-fructose diets result in a changed cell cycle and over-abundance of mature OSNs. (A, B) Example EOG recordings acquired from mice after an 8 week dietary supplement with HFruD compared with that of control diet (Ctrl). Note bar graphs that reflect a reduction in EOG area under the curve but a slower kinetics. (C) Photomicrographs that show an immunochemical label for an apoptotic marker (Caspase 3) in the MOE of mice following 4 vs. 8 week supplementation. Right bar graph quantifies reduction in cell death following 8 weeks HFruD compared with (E) bar graph that reflects increase in percentage of mature olfactory marker protein positive (OMP+) OSNs. (E) Habituation/dishabituation paradigm (as in **Fig. 3**C) indicates that HFruD supplemented mice have failed discrimination over that of control (Crtl) fed mice. mo = mineral oil (control solvent), oct_1 = octanol (first presentation), ace = acetophenone (dishabituating odor). Different Greek letters indicate significantly different mean values (ANOVA), * = significantly different (*t*-test). Data taken/modified with permission from Riviere et al. (2016).

previously described, the fact that these differential nutritional excesses oppositely modify OSN abundance may result in slightly different deficits in olfactory perception.

3.35.5.4 Ob/Ob and MC4R−/− Mice

Previously-described MC4R-null mice (see **Metabolic Phenotype** section, above) are widely used as a genetic model for severe DIO and T2DM (Sutton et al., 2006). MC4R plays a central role in energy homeostasis and insulin resistance, and administration of agonists for the receptor are shown to improve insulin sensitivity independent of food intake, while antagonists are associated

with insulin resistance (Obici et al., 2001). Thus, MC4R-null mice develop hepatic insulin resistance with obesity, independent of diet (Sutton et al., 2006). MC4R-null mice show elevated fasting glucose and insulin levels and have significantly higher body weight at 6 months age as compared to wild-type (Trevaskis et al., 2007; Thiebaud et al., 2014). When challenged with a high-fat diet, these mice demonstrate impaired response to insulin during an insulin tolerance test and diminished glucose clearance during an intraperitoneal glucose tolerance test (Sutton et al., 2006). The mechanisms underlying insulin resistance in obese MC4R-null mice remain unclear; however, it is known that MC4R-null mice show a significant increase in metabolic efficiency (weight gain per kilojoule consumed) (Sutton et al., 2006; Trevaskis et al., 2007). MC4R-null mice are slower in retrieval of a hidden peanut-butter cracker than wild-type mice but perform similarly when retrieving a chocolate whopper (Tucker et al., 2012b). MC4R-null mice perform similarly to wild-type mice in habituation/dishabituation trials that are designed to discriminate fatty food odorants (linoleic acid vs. oleic acid) but demonstrate an inability to discriminate general odorants (peppermint vs. geranyl acetate). Tucker and collaborators were not able to test MC4R−/− mice in more advanced olfactometry paradigms because they exhibited deficits in 24-hr object memory tests (Tucker et al., 2012b).

Using the obese ob/ob mice that are leptin deficient (previously described, see **Leptin Decreases Food-Seeking Behavior and Decreases Olfactory Bulb Coding and the Activation of Higher Centers** section), leptin has been identified to slow retrieval times in the hidden cookie assay (**Fig. 3A**, Getchell et al., 2006). Chelminski et al. (2017) have recently utilized the ob/ob mice to better understand how the spatiotemporal coding of odorant information is modulated by leptin. In the leptin-deficient ob/ob mice, the investigators examined local field potential (LFP) oscillations in unrestrained, freely behaving mice while performing behaviorally in a go, no-go Knosys olfactometer (**Fig. 3**F). This mouse model was found to discriminate more effectively in a two-odor discrimination task than that of wild-type mice. Typically interactions between the mitral and granule cell network produce an oscillatory activity - high frequency (60–150 Hz) gamma oscillations dominate general exploration and are switched to low frequency (15–35 Hz) beta oscillations when an odor is presented and sampled. With learning, the beta oscillations increase, however, in the ob/ob mouse, they were stronger in power and longer duration or frequency (Chelminski et al., 2017). Because oscillations in general help facilitate sensory information across higher cortical regions of the brain, in particular temporal coordination, it appears leptin not only balances energy expenditure and food intake, but must normally regulate learning by altering neural dynamics of rhythmic oscillations of piriform cortex feedback to the OB.

3.35.5.5 DpTx-Treated cre-OMP IGF-R Obese Mice

Using mice that have been genetically engineered to express a diphtheria toxin receptor on OSNs, Riera and collaborators (Riera et al., 2017) delivered diphtheria toxin to genetically ablate OSNs in mature mice. They found that inducing hyposmia through such OSN ablation makes mice resistant to DIO. Genetic ablation after onset of obesity abrogated further weight gain, decreased fat mass, and improved insulin sensitivity. These changes occurred without reduction in food intake, and the lean phenotype was associated with increases in total energy expenditure and metabolism. Genetic ablation produced a significant increase in both beta-adrenergic receptors and activated hormone-sensitive lipase, which directly mediated lipolysis (Riera et al., 2017).

Insulin-like growth factor 1 (IGF1) is known to play a role in peripheral regeneration of OSNs, and ablation of the IGF1 receptor (IGF1R) in neural stem cells leads to enhanced olfactory function (Pixley et al., 1998; Chaker et al., 2015). Utilizing a conditional knockout of IGF1R limited to mature OSNs, these same investigators showed that IGF1R-null mice (IGF1R −/−) showed enhanced olfactory performance in the hidden cookie assay (**Fig. 3**A) as well as increased adiposity and insulin resistance (Riera et al., 2017). In contrast to the Kv1.3-null 'Super-smeller' mice who gain resistance to DIO and increased insulin sensitivity, IGF1R-null mice increase olfactory ability, adiposity, and insulin resistance concurrently (Fadool et al., 2004; Riera et al., 2017).

3.35.5.6 Intranasal Insulin Delivery

Not all glucose transport in the CNS is insulin dependent. This suggests that insulin has uncharacterized regulatory roles within the brain (Bruning et al., 2000; Hallschmid et al., 2004). As mentioned previously, IR kinase is highly expressed in the OB where its activation effects the phosphorylation of several identified insulin receptor substrates (**Fig. 5**). Among these, Kv1.3 is phosphorylated on critical tyrosine residues located within both N- and C-terminal aspects of the protein. This phosphorylation suppresses the ion channel current, altering its biophysical properties and concomitantly altering the electrical activity of the OB (Fadool, 1998; Fadool et al., 2000; Marks and Fadool, 2007). Intranasal delivery of insulin has gained favor as a potential therapeutic route to bypass the defenses of the blood brain barrier, with implications as a therapy for memory degeneration, neuroAIDS, Alzheimer's Disease and Diabetes (Benedict et al., 2004; Gonzalez et al., 2006; Hanson and Frey, 2007; Reagan, 2007). In mice, intranasal delivery of insulin is known to acutely increase memory, recognition, and olfactory discrimination and decrease anxiety (Marks et al., 2009). Long-term intranasal insulin delivery does not provide these benefits, and it is postulated that the total quantity of insulin delivered intranasally may lead to desensitization of the insulin receptors of the OB (Bell and Fadool, 2017). In humans, intranasal delivery of insulin evokes a loss in body fat that appears to be sex-selective. Men receiving daily insulin for eight weeks reduced body fat mass by ~5%, whereas women failed to reduce fat mass and increased body weight due to an increase in extracellular water retention (Schwartzet al., 2000; Hallschmid et al., 2004).

3.35.5.7 MgTx-QD Treated Mice

Margatoxin (MgTx) is a peptide isolated from scorpion venom, and is an inhibitor of Kv1.3 and Kv1.2 channels (Garcia-Calvo et al., 1993; Bednarek et al., 1994; Bartok et al., 2014). Due to the complex population of ion channels *in vivo*, it is often necessary to verify

the delivery and action of ion channel inhibitors. To this end, luminescent quantum dots (QDs) have been covalently conjugated to MgTx peptides. The QD is first encompassed in a shell of dihydrolipoic acid, and MgTx molecules are then coupled to that shell using carbodiimide chemistry. Schwartz and collaborators have showed that coupled MgTx-QD particles affect the biophysical properties of target cells in the same manner as unbound MgTx both *in vitro* and *ex vivo*. Given the olfactory and metabolic benefits instilled upon Kv1.3-null mice, direct cannular delivery of MgTx-QD to the olfactory bulb may be a useful tool to determine the role of the olfactory bulb in these processes (Fadool et al., 2004; Schwartz et al., 2017).

3.35.5.8 Chemically-Induced Anosmia in Mice

In order to further explore the relationship between olfaction and obesity, different approaches to induce anosmia in mice are being explored. Methyl bromide is an odorless colorless gas which is administered to mice as an inhalant and induces lesioning of the olfactory epithelium, killing >90% of OSNs (Iwema et al., 2004; Holbrook et al., 2014). Intraperitoneal injection of methimazole is alternatively used to chemically ablate the olfactory epithelium (Gatlin et al., 2019), but may be less useful in investigating the metabolism-olfaction relationship due to its effect on the production of thyroid hormones (Crescioli et al., 2007; Xie et al., 2011; Tsourdi et al., 2015; Choi et al., 2016). Slotnick and collaborators have explored the use of zinc sulfate irrigation over the years in both rats and mice as a means to chemically ablate the MOE (Slotnick and Gutman, 1977; Slotnick et al., 2000; McBride et al., 2003). Temporary (2–4 day) deficits in the detection of low odorant concentrations were observed in rats (Slotnick et al., 2000) and longer (5–30 day) olfactory discrimination losses were found for mice (McBride et al., 2003). In mice, anterograde transport of a chemical conjugate (WGA-HRP) was used to confirm loss of anatomical connectivity in circuits from the MOE to the OB (McBride et al., 2003). Therefore intranasal delivery of zinc sulfate in mice was found to be effective in complete disruption of olfactory function; inducing temporary anosmia.

3.35.5.9 Other Mouse Models

3.35.5.9.1 Ciliary Dysfunction

Bardet-Biedl syndrome (BBS), a genetic syndrome associated with a defect in cilia, presents with sensory, renal, and limb malformations. Among these, individuals with BBS typically exhibit partial or complete anosmia (Kulaga et al., 2004; Jenkins et al., 2009). Genetic models with targeted deletion of genes associated with BBS have identified olfactory ciliopathy as a diagnostic symptom for BBS and other broad ciliopathies (Kulaga et al., 2004; Iannaccone et al., 2005; Tadenev et al., 2011; McIntyre et al., 2012, 2013). Non-invasive intranasal delivery has been used for delivery of viral particles carrying replacement genes, which could restore olfactory function in these anosmic BBS models (McIntyre et al., 2012, 2013; Boesveldt and de, 2017). Interestingly, these anosmic BBS models have a metabolic phenotype - they are obese - but nothing has been studied in terms of ingestive or eating behaviors.

3.35.5.9.2 Pregnancy

Even before birth, animals begin to learn about their environment. Flavor learning occurs perinatally, and odors encountered by pregnant dams influence preference for these odors by rodent pups after weaning (Smotherman, 1982; Woo and Leon, 1987; Nolte and Mason, 1995; Miller and Spear, 2008; Todrank et al., 2011; Ventura and Worobey, 2013; Liu et al., 2016). When this odor exposure is limited to the perinatal period and removed before birth, mouse pups still show attenuated suckling preference and locomotor activity in response to the odor (Logan et al., 2012; Gaztanaga et al., 2015). These behavioral effects are likely due to enhanced glomerular refinement of ectopic OSNs as well as by changes in glomerular density (Kerr and Belluscio, 2006; Marks et al., 2006; Todrank et al., 2011; Valle-Leija et al., 2012; Valle-Leija, 2015). In addition to changes in offspring olfactory behavior in response to maternal high-fat diets (see **Obesity Damages Olfactory Structure and Evokes a Loss of Function** section, above), Baly and collaborators have recently explored olfactory sensitivity of pups in response to chronic odorant exposure (Dewaele et al., 2018; Bernal-Melendez et al., 2019). In response to perinatal exposure of a particular fruity odorant, heptanal, weaned mice demonstrate an enhanced olfactory sensitivity for the odor. Because the authors examined this chronic odorant exposure in I7Tau*gfp* reporter mice, for which heptanal is the preferred odorant ligand for the I7 OR, they were able to visualize the circuit plasticity surrounding the I7-expressing axonal projections to the I7 glomerulus. Anatomically the glomerular projections were supernumerary and did not developmentally prune to a single glomerulus over the same time course as observed for non-odorant exposed mice. Curiously, the increase in olfactory performance associated with this anatomical change was correlated to a decrease in EOG amplitude (Dewaele et al., 2018). Therefore, as in humans (i.e., Lipchock et al., 2011), prenatal or early postnatal odorant exposure or eating can influence offspring olfactory or eating behavior. This same research group has interestingly reported olfactory anatomical, behavioral, and synaptic alterations in young rabbits whose mothers were exposed to diesel pollutants (Bernal-Melendez et al., 2019).

3.35.5.9.3 Embryonic Development

Using a conditional deletion of *Dicer1*, Kersigo et al. (2011) identified a specific miRNA that may be responsible for early neurosensory development. The disappearance of this miRNA, miR-124, precedes a rapid reduction in growth of the telencephalon, cerebellum, olfactory epithelium, anterior retina, and the ear (Kersigo et al., 2011). As a result, this malformation is fatal. While there are tools to investigate sensory dysfunction in living animals, more specific deletions of *Dicer1* and miR-124 represent a powerful tool to investigate mechanisms underlying sensory malformation such as in congenital anosmia.

3.35.5.9.4 How Does Human Olfaction Change with Altered Eating, Disrupted Metabolism, Poor Nutrition, or Sensory Damage?

Mouse models have provided a foundation of understanding of the factors that can regulate, modify, or disrupt olfactory-based eating behaviors, and while each afford a system where experimental variables can be well controlled, the ultimate goal is to know how olfaction can change in humans in response to altered eating (either over- or under-nutrition), metabolic disease, or sensory damage. Although it can be difficult to draw generalizations from human data due to differences in olfactory stimuli, psychophysical parameters, the satiety state, the age of patients, the experience of the patient, and the level of adiposity, some patterns are emerging. In human olfactory assessments, three common standardized measures involve: 1) olfactory threshold, or the minimum concentration of olfactory stimulus required for a person to smell, 2) identification, or the recognition of the olfactory stimulus, and then finally, 3) discrimination, or the ability to differentiate one odor from another. The first process is largely governed by the MOE and the OB, whereas the last two recruit higher cortical processing including the limbic system. This final section is not meant to be an exhaustive discussion of human olfactory ability correlated with nutrition and metabolism, but rather to provide some examples of interesting studies in human populations that are obese, suffering from diabetes mellitus, exhibit anorexia, have undergone bariatric surgery, or have anosmia (**Table 2**). For greater comparison of human olfactory ability and metabolic state, readers are referred to Palouzier-Paulignan et al. (2012).

3.35.5.10 Obesity

In studies of extreme morbid obesity in adults (body mass index, BMI >45), individuals score lower in general odorant identification tasks and have reduced odorant detection compared to lean, age-matched adults (Obrebowski et al., 2000; Richardson et al., 2004, 2012). Small and colleagues found that individuals with obesity perceived odors, but not flavored solutions, as more intense when hungry than when satiated (Sun et al., 2016). The increased odor intensity in the hungry state was correlated to postprandial suppression of ghrelin and differential fMRI patterns in the cerebellum in response to odor cues, and was not correlated with differences in circulating leptin, insulin, glucose, triglycerides, or sniffing frequency in the patients with obesity compared with that in lean controls. Stafford and Whittle (Stafford and Whittle, 2015) report that individuals with obesity (BMI > 30) rate the odor of chocolate, in particular, as more pleasant and they are more sensitive to this odor than that of lean controls suggesting that there may be a greater attraction to energy dense foods. Certainly the odor of food is a powerful sensory cue, which in humans can alter satiety just from the aroma itself - without consumption of the food item (Rolls and Rolls, 1997). Added to this, is the pleasure derived from eating and the complexity of the food reward generated by the interaction of senses - taste, somatosensory processes in the oral cavity, retronasal olfaction, and the sight of food. Children who are overweight consume more calories than lean individuals following exposure to such multisensory food cues and this may reflect learned associations between the smell and taste of palatable foods (Jansen et al., 2003). An interesting discussion concerning individual differences in reward and obesity is presented by Small (2009) and must be considered in the context of the powerful reinforcing effects of both food and drugs in terms of similar neuroanatomical pathways (Volkow et al., 2012). In consideration of the theory of increased "cue reactiveness" in persons with obesity (Schachter, 1968), Proserpio and colleagues tested for change in appetite and consumption of low energy dense food (vegetable soup) in response to preexposure to bread odor in patients (Proserpio et al., 2019) and report that consumption increased with "scent" exposure. For readers that have interest in olfactory influences on appetite (please see Yeomans, 2006; Ramaekers et al., 2014; Boesveldt and de, 2017). A quite fascinating report is the ability to "image odors", such as fresh chocolate chip cookies

Table 2 Human Diseases That can Change Olfactory Physiology and Eating Behaviors

	Degree of severity	*Odor detection threshold*	*Odor discrimination/ Identification*	*Test*	*References*
Obesity	BMI>45	NA	↑	CC-SIT	Richardson et al., 2004, 2012
	BMI>45	↑	NA	Meta- Analysis	Valladares and Obregon Rivas, 2015
	BMI>30	↓	NA	Sniff Bottle Liquid Dilution	Stafford and Whittle, 2015
Diabetes	Type 1	NA	=	OIT	Naka et al., 2010
	Type 2	NA	↓	OIT	Naka et al., 2010
	Type 1	NA	↓	Sniffin' Sticks	Falkowski et al., 2017
	Type 2	↓	↓	Sniffin' Sticks, Butanol Threshold Test	Yazla et al., 2018
Anorexia nervosa	NA	↑ Preprandial (food odor)	↓	Sniffin' Sticks	Schreder et al., 2008
	Low Bodyweight Females	↑	=	Sniffin' Sticks	Fernandez-Aranda et al., 2016
	Recent- Onset Females	↑	↑	Sniffin' Sticks	Bentz et al., 2017

Metabolic Disorders can Disrupt Normal Olfactory Processes. Not assessed (NA); significantly decreased (down arrow), increased (up arrow), or not different compared with control (=); Cross Cultural Smell Identification Test (CC-SIT); Odor Identification Test (OIT). Cited above Richardson et al., 2004; Schreder et al., 2008; Naka et al., 2010; Richardson et al., 2012; Valladares and Obregon Rivas, 2015; Stafford and Whittle, 2015; Fernandez-Aranda et al., 2016; Falkowski et al., 2017; Bentz et al., 2017; Yazla et al., 2018. For further reading, see Palouzier-Paulignan et al. (2012).

coming out of the oven, the smell of popcorn at the movies, or being hit by the smell of barbeque at a social, is directly correlated to your BMI! - the greater the BMI, the greater the individual's ability to image these olfactory experiences (Patel et al., 2015).

3.35.5.11 Diabetes Mellitus

Because patients with diabetes mellitus can present with other co-morbidities and have continuous drug regiments it is difficult to discern whether olfactory deficits are the result of a secondary complication rather than the result of a purely metabolic dysfunction. Patients tested with "Sniffin' Sticks" (Hummel et al., 2007) have a poorer threshold-discrimination-identification, or TDI score. These patients have a decreased olfactory sensitivity with impaired olfactory discrimination when compared with that of persons without diabetes (Naka et al., 2010; Brady et al., 2013; Gouveri et al., 2014). However, the reduced olfactory acuity may be associated with patients who are referred to as those with 'complicated" diabetes, such as those experiencing neuropathic pain, which would anticipate to affect attention and concentration. Pathophysiological changes with time and long-term drug treatment prevent the interpretation of the cause of olfactory dysfunction from being straight forward. Uncomplicated diabetes patients are reported to have little to no chemosensory deficits (either olfaction or taste) (Naka et al., 2010). Those with uncomplicated, Type II diabetes have a lower TDI score than that of Type I, which may be a factor of either co-morbidity (hypertension, BMI) or increased age on onset that would be predictive of poorer olfactory function.

3.35.5.12 Anorexia Nervosa

Reduced olfactory acuity has been determined for a number of mental health problems (for example, schizophrenia or anxiety) but for eating disorders, a distorted reward system may also contribute to olfactory ability (Berridge, 2009). Despite the complexity of the etiopathology of eating disorders, often with patients having a reduced BMI or disturbed nutritional profile, earlier studies reported no changes in olfactory identification in persons with anorexia or bulimia nervosa (Kopala et al., 1995). Patient populations that included severe weight loss began to detect impairments in odor identification and threshold (Fedoroff et al., 1995), but these deficits were also compounded by smoking in this sample. A recent meta-analysis attempt by Islam et al. (2015), who reviewed the existing literature (1352 articles) on eating disorders, could not draw a firm conclusion regarding olfactory changes. A great heterogeneity in experimental approach, lack of males, low sample power, and lack of age group distinctions made it impossible to accurately correlate olfactory function with eating disorders.

3.35.5.13 Starvation, Restricted-Timed Eating, or Bariatric Surgery

Despite any clear distinction in olfactory changes in anorexia nervosa - a state of chronic food deprivation and nutritional depletion - a 24-h fast in humans generally increases odor discrimination, increases odor identification, improves TDI score, and enhances food palatability (Cameron et al., 2012). Acute negative energy balance and sensory ability was first examined over 50 years ago by Goetzl and Stone (1947) who quantified that olfactory sensitivity increased when individuals skipped a single meal. There are some noted exceptions to an enhanced chemosensory performance in hungry individuals. Stafford and Welbeck (2011) curiously found that fasted individuals showed improved odor threshold and discrimination for neutral odors but not that of food odors. They also measured higher odor acuity to food odors by select individuals that had higher BMI and were satiated over those who were fasted. Because the lower BMI individuals had no changed acuity with changed hunger state, they concluded that BMI, odor relatedness, and internal state make a combined predictive difference in odor sensitivity. This is in contrast with studies reported by Albrecht and collaborators, who found the opposite, that fasting significantly changed odor threshold for food odors without modifying that for non-food odors. Oddly, however, it was the satiated state for which odor sensitivity improved and the threshold was lowered, not the hunger state. But with satiation, the ranked pleasantness of the food was significantly less, purportedly evoking less food intake. Age and hunger state can also intercept, a factor that has been examined in older individuals with poorer nutrition. Elderly individuals have a depressed olfactory ability even following fasting and refeeding in comparison to that of younger subjects whose hunger remains predictive of blood glucose levels (Albrecht et al., 2009; Mulligan et al., 2002).

Starvation or reduced food consumption from an obese state is quite physiologically different in an endocrinological sense than that from a normal body weight. Given that olfactory cues and reward circuits are instrumental in the regulation of food intake and food choice, what happens in individuals with obesity that undergo bariatric surgery and are physically forced to eat less? Typically, these individuals are also less motivated to eat. In a study using 'Sniffin' Sticks' (Kobal et al., 1996) to determine olfactory ability in patients undergoing Roux-en-Y gastric bypass vs. that of sleeve gastrectomy (Peng et al., 2019), the reversal of the negative shifts in olfactory function observed with increase in BMI, was more immediate and pronounced in patients undergoing the sleeve type of bariatric surgery for weight loss. The sleeve gastrectomy therefore is effective in reversing the olfactory decline associated with obesity.

3.35.5.14 Anosmia and Eating Behavior

We have all experienced temporal anosmia or hyposmia attributed to sinus infection or colds, and with reduced retronasal olfaction, the enjoyment of eating is severely dampened. Long-term olfactory impairment (attributed, for example, to head injury,

deviated septum, chemotherapy, neurodegenerative disease, chronic respiratory infections - see risk factors in (Murphy et al., 2002)) can have a major impact on an individual's quality of life, positive and negative emotional memories related to odors, food intake and subsequent health, and can cause depression (Rochet et al., 2018). Patients with olfactory disorders report lower ratings for food, which causes either over-, or predominantly, under-eating (Ferris and Duffy, 1989) and a loss of appetite (Temmel et al., 2002; Blomqvist et al., 2004; Nordin et al., 2011). Persons with anosmia report over-salting, increasing spices (Miwa et al., 2001), and experimenting with texture or colors of food to enhance enjoyment for eating (Internet 2). Although olfactory dysfunction in young adults has not been correlated with increased risk of dementia, neurodegeneration, or mortality as it has been in older adults (Pinto et al., 2014), older adults that are dementia-free can be at risk if they become anosmic. In a study of dementia-free older adults (mean age 78), individuals with hyposmia or anosmia had smaller hippocampal, entorhinal, and middle temporal cortices that might predict faster cognitive decline and neurodegeneration than individuals with normal olfactory function (Dintica et al., 2019).

3.35.5.15 Summary and Future Directions to Uncover Regulation of Olfaction and Eating

The olfactory system is beautifully poised to capture the odor cues surrounding the detection and consumption of food while simultaneously adjusting consumption based upon regulatory detection of metabolic state. Investigators have uncovered metabolic hormones and energy important molecules across the MOE, OB, and aPC that guide eating behaviors. Manipulation of these signaling endocrine factors have led to the understanding that olfactory perception is not static. Future explorations should include a better understanding of how disease perturbs olfactory perception and eating behavior, particularly with the rising incidence of obesity and the performance of bariatric surgery. Better elucidation of the impact of the microbiome and gut communications to the olfactory system need to be probed. With the advent of *in vivo* physiological preparations, the ability to visualize in real-time the changes in physiological activity across the MOE, OB, aPC could be mapped during the course of food ingestion and interweaving the variables of metabolic state and disease. The next time you have a delicious meal, pinch your nose, take a few more bites, and release! Now you can better reflect on the role of olfaction and flavor for your eating behavior! It's best done with jelly beans - an excellent educational outreach activity, we might add.

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