

# Olfaction Under Metabolic Influences

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## Abstract

Recently published work and emerging research efforts have suggested that the olfactory system is intimately linked with the endocrine systems that regulate or modify energy balance. Although much attention has been focused on the parallels between taste transduction and neuroendocrine controls of digestion due to the novel discovery of taste receptors and molecular components shared by the tongue and gut, the equivalent body of knowledge that has accumulated for the olfactory system, has largely been overlooked. During regular cycles of food intake or disorders of endocrine function, olfaction is modulated in response to changing levels of various molecules, such as ghrelin, orexins, neuropeptide Y, insulin, leptin, and cholecystokinin. In view of the worldwide health concern regarding the rising incidence of diabetes, obesity, and related metabolic disorders, we present a comprehensive review that addresses the current knowledge of hormonal modulation of olfactory perception and how disruption of hormonal signaling in the olfactory system can affect energy homeostasis.

**Key words:** endocrine, energy homeostasis, hormone, metabolism, obesity, olfactory

## Introduction

Energy homeostasis is achieved through a coordinated regulation between the peripheral organs and the brain. A variety of hormones and nutrients are released by the gastrointestinal tract and associated glands, and these are carried by the blood to the central nervous system (CNS). Central structures, the hypothalamus in particular, release peptides to stimulate neuronal pathways that modify food intake to match the nutritional needs of the organism. We propose that the olfactory system is intimately linked with the endocrine system: in essence, the olfactory system may serve a secondary function as an internal sensor of chemical state or nutritional balance. Here we summarize the current known distribution of peripherally—and centrally—derived energy-signaling molecules and their receptors in the olfactory system. We then provide a thorough discussion of olfactory function as modulated by hormones and the nutritional state of the animal, which leads to a summary of how these endogenous signals regulate

olfactory-driven behavior in animals. This is followed by a reflection of how feeding state modulates olfactory sensitivity in animals and humans with a bridge to digestive physiology. In view of the rapidly expanding awareness of the correlation between metabolic disorders, body weight, and olfaction, we pull together the current literature in an attempt to elucidate how obesity, diabetes, and eating disorders affect, and are affected by, the physiological workings of the olfactory system.

## Hormones, endogenous modulators, and their receptors are present in the olfactory system

Food intake relies on the interaction between homeostatic regulation and hedonic sensations. Olfaction is one of the major sensory modalities that contributes to hedonic evaluation of a food, resulting in food choice and its possible consumption. Nutritional status is well

	Peripheral	Central
<b>Orexigenic signals</b>	Ghrelin	Neuropeptide Y (NPY)
		Orexins/hypocretins
		Melanin-concentrating hormone (MCH)
		Galanin
		Somatostatin
		Endocannabinoids
		Endogenous opioids
<b>Anorexigenic signals</b>	Insulin	Bombesins
	Leptin	Corticotropin-releasing factor (CRF)
	Cholecystokinin (CCK)	Cocaine- and amphetamine-related transcript (CART)
	Nutrients	Glucagon-like peptide 1 (GLP1)

**Table 1** Main molecules implicated in appetite regulation and expressed in the olfactory system.

known to influence odor detection by individuals. Fasting results in an increased ability to detect odors, some of which are food-related, whereas satiety with one type of food reduces the ability to detect the odor specially associated with that food type (O'Doherty et al. 2000; Mulligan et al. 2002). Metabolic peptides and hormones that govern the cellular processes underlying hunger and satiety are typically classified as either orexigenic or anorexigenic factors, depending upon their stimulatory or inhibitory role in food intake, respectively (Table 1). Since the 1980s, receptors for metabolic hormones and peptides have been known to be expressed in olfactory-related brain areas. The last 10 years have brought in new data demonstrating that the olfactory mucosa (OM) and the olfactory bulb (OB), the first two steps of olfactory signal initiation and transfer to the brain, are targets for these metabolic factors (Figure 1). Consequently, this section will focus primarily upon the OM and OB levels of the olfactory pathway, with a minor discussion of metabolic receptor localization in the olfactory cortices. A comparison of protein and transcript expressions of the principal metabolic factors and their receptors across the OM, OB, and the hypothalamus is provided in Table 2. Figure 1 and Tables 1–2 were designed to be as comprehensive as possible; however, only selective metabolic factors could be described, in parallel, in the text.

## Orexigenic molecules (stimulatory)

### Ghrelin

Ghrelin is produced mainly by the stomach and gastrointestinal tract (Kojima et al. 1999; Date et al. 2000), whereby release of circulating ghrelin increases before a meal and then decreases during eating (Cummings et al. 2001; Tschöp et al. 2001). Ghrelin's pattern of release has led to investigations that support its regulation of meal initiation (Cummings 2006) and food intake (Nakazato et al. 2001; Wren et al. 2001). It has also been implicated in a number of other physiological functions, such as the control of gastric motility, regulation of acid secretion, homeostasis of glycemia, and stimulation of growth-hormone secretion (Bednarek et al. 2000; Kamegai et al. 2000; Masuda et al. 2000; Takaya et al. 2000; Broglio et al. 2001; Date et al. 2001). Recent work by Tong et al. (2011) demonstrated the expression of the GHSR-1a type of ghrelin receptor in the glomerular, mitral, and granule cell layers of the OB and in the piriform cortex.

### Neuropeptide Y

Neuropeptide Y (NPY) is widely expressed in the central and peripheral nervous systems. After a meal, its levels are higher in the hypothalamus, where the peptide acts as an important regulator of body weight through its effects on food intake and energy expenditure (Nguyen et al. 2011). NPY also participates in diverse physiological functions such as sleep, tissue growth, cardiovascular rhythms, and inflammation (Hansel et al. 2001; Groneberg et al. 2004; Doyle et al. 2008; Hodges et al. 2009; Dyzma et al. 2010). NPY is principally synthesized by the hypothalamus, thalamus, amygdala, hippocampus, nucleus of the solitary tract, and the locus coeruleus (Chronwall et al. 1985; Palkovits 1992; Meister 2007). NPY labeling is reported in both the OM and OB. In the OM, NPY is expressed in the sustentacular cells (Hansel et al. 2001), in a subpopulation of microvillar cells (Montani et al. 2006), and in the ensheathing cells of olfactory nerve axon bundles (Ubink et al. 1994). It is observed at low levels in the soma of olfactory sensory neurons (OSNs) (Doyle et al., 2008). At the level of the OB, most of the NPY is reported to be in fibers originating from the brain stem (Sanides-Kohlrausch and Wahle 1990; Bouna et al. 1994). NPY is also localized to neuronal cell bodies and is sparsely observed in the granule cell layer (Gall et al. 1986) or in ensheathing cells of the glomerular layer (Jia and Hegg 2010). Interestingly, the OB contains one of the highest levels of mRNA expression in the brain, which markedly increases with developmental age (Larhammar et al. 1987; Rutkoski et al. 1999; Blakemore et al. 2006).

Of the five NPY receptor subtypes, Y1, Y2, Y4, and Y5 receptors have been reported in the olfactory system (Gall et al. 1986; Scott et al. 1987). The Y1 and Y2 subtypes, together with Y5, are implicated in feeding behavior (Beck 2006). The Y1 receptor is conjectured to mediate most of the NPY-induced effects in the OM (Hansel et al. 2001; Doyle et al. 2008), where it has been detected in a subset of OSNs located in discrete patches (Negroni et al., submitted) and in putative basal cells (Hansel et al. 2001). Recent studies have demonstrated that a selective knockout of the Y1 receptor leads to a moderate, but specific, impairment of olfactory function, probably due to a significant reduction in the number of OSNs (Hansel et al. 2001; Doyle et al. 2008). The authors conclude that NPY may serve as an essential neuroproliferative factor for the OM (Hansel et al. 2001; Doyle et al. 2008). NPY-deficient mice also have a phenotype parallel to that of a human metabolic syndrome (Pedrazzini



In the OB, orexins and OXR immunolabeling has been well resolved. OXA and OXB signals are associated with varicose fibers mainly in the granule cell layer, around glomeruli, and in the mitral cell layer (Caillol et al. 2003; Hardy et al. 2005; Shibata et al. 2008). Here, OXR1 is the predominant player, whereas OXR2 labeling in the OB is quite faint. OXR1 is widely expressed in the cell bodies and processes of mitral/tufted cells, and the periglomerular and granule cells. OXA-induced changes in mitral cell firing are discussed along with modulation of olfactory behavior (Apelbaum et al. 2005; Hardy et al. 2005; Julliard et al. 2007; Prud'Homme et al. 2009) in the following two sections.

### Endocannabinoids

One widely reported effect of cannabinoids is their ability to stimulate appetite. Endocannabinoids are lipid derivatives synthesized after neurotransmitter release or metabolic challenge. They are produced “on demand” at the synaptic cleft by cleavage of the postsynaptic membrane phospholipids. Increase in postsynaptic intracellular calcium during synaptic transmission is the trigger signal for their release (Grotenhermen 2004; Alger and Kim 2011). Two cannabinoid receptors, CB1 and CB2, have been described. The CB1 receptor has been implicated in the regulation of appetite and in the consumption of palatable foods, and forms part of the neural circuitry regulated by leptin (Di Marzo et al. 2001). CB1 receptors are present in the sustentacular cells of the OM, in the periglomerular cells of the OB, and in the anterior olfactory nucleus and olfactory cortices (Mailleux and Vanderhaeghen 1992; Matsuda et al. 1993; Tsou et al. 1998; Hermann and Lutz 2005; Caillol, unpublished data). A recent study in mice by South and Huang (2008) has shown that the level of CB1 expression in various brain regions, including the olfactory nucleus, is modulated by diet-induced obesity (see also penultimate section).

### Endogenous opioids

Numerous studies have reported that animals synthesize opiate-like compounds referred to as endogenous opioids, which are structurally identical to vegetal alkaloids (Bodnar and Klein 2004). Three of them—endorphin, dynorphin, and enkephalin—derived from the prohormones proopiomelanocortin, prodynorphin, and proenkephalin, respectively, have been cloned. They affect a wide range of functions including nociception, memory, gastric motility, cell death, hormone secretion, and food intake (Bodnar and Klein 2004). These peptides increase sugar/fat consumption and influence food reward. For review, see the article by Olszewski et al. (2011). For example, in humans, the overeating induced by opioids and the consumption decrease induced by their antagonists are stronger for sweet or fatty foods (Cooper and Turkish 1989; Drownowski et al. 1992). These neuroregulatory peptides are synthesized in the periphery and the CNS (for review, see Bodnar 2011). In the olfactory system, the peptides are found in the OB, where a strong immunolabeling is described in the glomerular and external plexiform layers, both in cell bodies and processes and in the granule cell layer. They are also present in cells and processes of the anterior nucleus and olfactory tubercle and within fibers in the piriform cortex (Laux et al. 2011).

Endogenous opioids bind to three receptor classes: mu, delta, and kappa (Waldhoer et al. 2004). The receptors are largely distributed within peripheral organs, notably the gastrointestinal tract (Bagnol et al. 1997). The OM expresses mu- and kappa-receptor mRNAs only prenatally (Zhu et al. 1998). In the CNS, opioid receptors are

described in hypothalamic and olfactory areas, and show a very high density in the amygdala, known to modulate reward (Pert et al. 1973). In the adult olfactory system, all receptor types (proteins and mRNAs) are found in the OB, the olfactory tubercle, and the piriform cortex (George et al. 1994; Mansour et al. 1994; Simonin et al. 1994; Bausch et al. 1995; McBride et al. 1998; Neal et al. 1999). Interestingly, the OB expresses the highest density of delta- (Mansour et al. 1988) and mu-opioid receptor isoform 1B (MOR1B)-coded (carboxyl-terminal splice variant) mu receptors (Schulz et al. 1998) in the brain. This opioid system is functional because it modulates olfactory learning as well as the consolidation and expression of early olfactory preferences in rats (Kinsley and Bridges 1990; Shide and Blass 1991; Kinsley et al. 1995; Roth and Sullivan 2001; Roth and Sullivan 2003). Moreover, some studies have described the link between olfaction, food intake, and opioids (see section “Hormones drive olfactory behaviors”).

### Anorexigenic molecules (inhibitory)

#### Insulin

Insulin and leptin are two major metabolic hormones that control food intake by exerting an anorexigenic effect, mainly at the level of the hypothalamus (Williams et al. 2011); but several other targets have been identified, including the olfactory pathway. Insulin is released by the pancreatic beta cells in response to the feeding state in a glucose-dependent manner (Henquin 2011). In the OM, as in other peripheral tissues, insulin must be received from the peripheral circulation (Urayama and Banks 2008). How the hormone is transported from the blood to the OM remains to be fully determined. The transport mechanism to the OM is difficult to envision because the endothelium of the lamina propria vessels display tight junctions that partly isolate the OM from its blood constituents (Hussar et al. 2002). Much debate in the literature suggests that little insulin is produced in the brain (Woods et al. 2003). Early studies by Margolis and Altszuler (1967) and efforts by Woods and Porte, as reviewed by Kahn (1995), accurately demonstrated by radioimmunoassay that peripheral infusions of insulin increased cerebrospinal fluid (CSF) insulin levels by transport across the blood–brain barrier (BBB; Banks 2004). Because the correlation between insulin levels in the serum and those in the CSF were not linear, this result provided strong evidence of a saturable transport system for insulin across the BBB (Banks 2004). Interestingly, the rate of transport into the CNS decreases proportionately with higher serum insulin levels, and although the identity of the transporter is not yet known, many factors influence its operation. For example, researchers have demonstrated that hyperglycemia abolishes insulin transport (Banks et al. 1997), obesity decreases transport (Baskin et al. 1985; Kaiyala et al. 2000), and diabetes increases transport (Banks et al. 1997). Likewise, all regions of the BBB are not equally permeable to insulin. In fact, transport into the OB is two to eight times faster than that into the whole brain (Banks et al. 1999), consistent with findings that the OB is the brain region with the highest concentration of insulin (Baskin et al. 1983) as well as the highest density of insulin receptor (IR) kinase (Hill et al. 1986) and it is most enzymatically active against insulin (Banks et al. 1999). In fact, olfactory bulbectomy results in an increased sensitivity to peripherally administered insulin (Perassi et al. 1975). Curiously, OB insulin has also been found to be low after a meal when the circulating plasma level

of the hormone is increased, and it is elevated in animals fasted for 72h when the circulating plasma insulin is low (Fadool et al. 2000). These types of studies demonstrate that insulin levels in the OB appear to be highly regulated, but the mechanism of such regulation is still unknown.

In addition to the canonical peripheral insulin source described here, recent data strongly suggest the existence of a second, perhaps supplementary, source of insulin originating from the OM. Indeed, transcripts coding for insulin, Pdx1 (an insulin transcription factor), and prohormone convertases (implicated in insulin maturation) are expressed in this tissue (Lacroix et al. 2008). The existence of a local production of insulin in the OB may not be ruled out because transcript coding for this hormone is reported (Baly et al. 2008). In fact, adult neuronal progenitor cells derived from the OB have recently been grafted to the pancreas in diabetic mice, which have then remarkably shown reduction of serum glucose during a glucose tolerance test (Kuwabara et al. 2011). Insulin signaling is also functional *in vivo* in the OM and OB, as various effects of this hormone have been reported on the olfactory behavior and modulation of the electrophysiological responses of OM and OB neurons (Fadool et al. 2000; Lacroix et al. 2008; Marks et al. 2009; Savigner et al., 2009; Palouzier-Paulignan et al., 2010; Fadool et al. 2011; see next section).

Regardless of its route of entry into the olfactory system or the possibility of local production of insulin, the hormone binds with high affinity to the IR kinase to initiate a plethora of downstream signaling cascades. For more than 20 years, the IR has been known to be widespread in brain regions related to olfactory function. High levels of insulin binding or IR immunolocalization are observed in the anterior olfactory nucleus, the olfactory tubercle, the piriform and entorhinal cortices, the limbic structures connected to the olfactory area, and the OB (Hill et al. 1986; Unger et al. 1989). Indeed, the highest insulin-binding affinities, IR density, and IR kinase activity in the brain are localized to the OB (Baskin et al. 1983; Hill et al. 1986; Gupta et al. 1992; Banks et al. 1999; Fadool et al. 2000). More recent studies have shown a high level of insulin binding in the OM (Lacroix et al. 2008). Consequently, IR signaling is present from the first step of odorant binding and olfactory signal transduction, through higher-order processing in the OB and beyond.

In the OM, high IR labeling is observed in the external border (Lacroix et al. 2008; Marks et al. 2009), an area rich in OSNs and their dendritic knobs, which express the odorant receptors and related transduction machinery. IR signal is also observed to a lesser extent in some immature OM neurons and some non-neuronal cells, for example, basal progenitor cells involved in mucosa renewal, sustentacular cells mainly implicated in detoxification, and the endothelium of the lamina propria vessels (Lacroix et al. 2008). IR localization in the compartment of the sustentacular cell microvilli contributes to the intense IR labeling observed in the external border of the OM.

At the level of the OB, IR is expressed in dendritic fields receiving synaptic inputs, such as the external plexiform layer (dendrodendritic synapses between granule and mitral cells) and, to a lesser extent, the glomerular layer (axodendritic/axosomatic synapses between mitral cells and OSNs; Hill et al. 1986; Werther et al. 1987; Matsumoto and Rhoads 1990; Fadool et al. 2000; Marks and Fadool 2007; Lacroix et al. 2008; Marks et al. 2009). Besides neuropil localization, IR is also observed in the mitral cell bodies and in the granule cell layer of the OB (Marks et al. 1990; Marks et al.

2009; Caillol, unpublished data). Fadool et al. (2000) showed that this IR cartography is established progressively during the first 3 weeks of life. Interestingly, the OB expresses mainly the short form of IR (generated by exon 11 skipping) classically described in brain tissues, whereas the OM expresses both the short and the long forms of the receptor (Lacroix et al. 2008). Indeed, both isoforms mediate insulin signaling, but the short isoform is more often implicated in mitogenic and anti-apoptotic signals, whereas the long isoform is associated with cellular differentiation (Sciacca et al. 2003).

Additional elements of the IR-signaling cascade are reported in both the OM and the OB. IRS1 and IRS2, the major downstream targets for this receptor, are expressed in the OM, as is PI3 kinase (Lacroix et al. 2008). In the OB, IRS1 and PI3 kinase expression is weak or absent (Folli et al. 1994); but Fadool et al. (2000) provided evidence that an alternative, multiply-phosphorylated downstream substrate of insulin signaling in the OB is a voltage-gated potassium channel (Kv1.3) (see next section).

### Leptin

Leptin, the second main anorectic circulating hormone, is secreted by peripheral adipocytes, but a discrete production also exists in peripheral tissues, like the placenta, stomach, muscle, and the OM (Zhang et al. 1994; Masuzaki et al. 1997; Bado et al. 1998; Wang et al. 1998; Baly et al. 2007), and in some central structures, like the cortex, cerebellum, hypophysis, hypothalamus, and the OB (Morash et al. 1999). Circulating levels of the hormone are directly correlated with fat mass and fluctuate according to nutritional status (Friedman and Halaas 1998). After meal consumption, circulating leptin starts to increase and reaches a maximum within a few hours (Saladin et al. 1995; Schoeller et al. 1997).

Six isoforms of the leptin receptor (Ob-R) have been reported in rodents. They differ mainly in the length of the cytoplasmic domain that results from alternative splicing of transcripts from a single Ob-R gene (Bjørbaek et al. 1997; Yamashita et al. 1998; Ahima and Osei 2004; Morris and Rui 2009). They are divided into three classes based on the lengths of their cytoplasmic domains: long, short, and secretory isoforms. The long isoform (Ob-Rb) and one of the short isoforms (Ob-Ra) have been reported to transduce the leptin signal (Yamashita et al. 1998; Morris and Rui 2009). Ob-Rb is mainly expressed in the hypothalamus where it takes part in energy homeostasis. Ob-Ra is more abundant in peripheral tissues, where it participates in mitogenic activity (Bjørbaek et al. 1997; Yamashita et al. 1998). Leptin crosses the BBB by a saturable, receptor-mediated mechanism, through binding to Ob-Ra (short form) expressed in blood vessels and the plexus choroids (Banks et al. 1996; Bjørbaek et al. 1998; Kastin et al. 1999) to influence various neural pathways (Elmqvist et al. 1998; Gautron and Elmqvist 2011). The Ob-Rs are largely observed in brain areas related to olfactory pathways, such as the nucleus of the lateral olfactory tract (Elmqvist et al. 1998), the piriform cortex (Huang et al. 1996; Getchell et al. 2006), and the OB (Shioda et al. 1998; Prud'Homme et al. 2009).

Both the Ob-Rb and Ob-Ra transcripts are expressed in the OM and OB (Baly et al. 2007). In the OM, these receptor isoforms are observed in the dendritic knobs of the mature OSNs at the surface of the epithelium and to a lesser extent in immature OSNs (Baly et al. 2007). Ob-Rs are also found in the supranuclear region of the sustentacular cells and duct cells of the Bowman's glands (Getchell et al. 2006; Baly et al. 2007). A faint labeling of basal

progenitor cells is also observed. Finally, a set of discrete leptin-sensitive mucous cells, which secrete odorant-binding proteins involved in odorant–receptor interaction, is also evidenced in the OM (Badonnel et al. 2009).

In the OB, the Ob-Rb isoform, is predominantly observed in the mitral and glomerular cell layers (Shioda et al. 1998; Prud'Homme et al. 2009). Some labeling is also reported for astrocytes contained in the glomerular structures and within the granule cell layer (probably the Ob-Ra isoform; Prud'Homme et al. 2009). Similar to the hormone insulin, leptin reaches the OM originating mainly from the general circulation; but leptin mRNA is also expressed in the OM and in the OB, suggesting a local source for this hormone (Baly et al. 2007). Similar to insulin, leptin is able to modulate olfactory behavior as well as neuronal firing (Julliard et al. 2007; Prud'Homme et al. 2009; Savigner et al., 2009; see the following two sections).

### Cholecystokinin

Cholecystokinin (CCK), a peptide originally discovered in the gastrointestinal tract, is one of the most abundant and widely distributed neuropeptides in the brain. Indeed, CCK was the first gut peptide found to be tandemly expressed in the gut and the CNS (Vanderhaeghen et al. 1975). It is produced when a bolus rich in lipids and protein arrives in the duodenum and jejunum (Larsson and Rehfeld 1978; Liddle et al. 1985; Lin and Chey 2003) and it increases gastric motility, enzymatic release, and gastric acid secretion. It crosses the BBB and is one of the most abundant and widely distributed neuropeptides of the brain stem and hypothalamus (Mercer et al. 2000; Mercer and Beart 2004); but it also enters the OB, the anterior olfactory nucleus, the olfactory tubercles, and the piriform cortex (Beinfeld et al. 1981; Dupont et al. 1982; Ekstrand et al. 2001; Gutierrez-Mecinas et al. 2005). By a central action, it reduces food intake (Blevins et al. 2004; Woods and D'Alessio 2008) but also modulates intrinsic neuronal excitability and synaptic transmission, acting as a key molecular switch to regulate the functional output of neuronal circuits (Lee and Soltesz 2011). In addition to its multiple roles as a neurotransmitter, CCK and its receptors (CCK1R and CCK2R) have been implicated in a diverse array of behaviors, such as learning, memory, nociception, feeding, and satiety (Noble and Roques 2006).

The form of CCK that is predominantly expressed in the brain is an octapeptide referred to as CCK-8S (Beinfeld 1981). In the OB, CCK is localized within all neural lamina except the olfactory nerve layer (Seroogy et al. 1985). Won et al. (1997) suggested that CCK might be involved in modulation of olfactory transmission, given its widespread fiber distribution in the cat. High levels of CCK are also reported in olfactory-related brain regions including the olfactory tubercles (Beinfeld et al. 1981). Both CCK receptors and their transcripts are expressed in higher olfactory cortical regions; mainly, the CCK2R type is expressed in the anterior olfactory nucleus and in the piriform cortex (Honda et al. 1993). The CCK2R type is specifically observed in the internal plexiform layer of the OB (Carlberg et al. 1992; Honda et al. 1993; Mercer et al. 2000) and in the juxtglomerular and mitral cells (Ma et al. 2011). Its physiological action strongly modulates olfactory recognition of distinct odorants (Lemaire et al. 1994). Although no targeted deletions of either receptor have been reported, an interesting, spontaneous CCK1R knockout rat model, called the Otsuka Long-Evans Tokushima Fatty (OLETF) rat, is obese and hyperphagic and displays alteration of olfactory sensitivity (Swartz et al. 2010).

Evaluation of olfactory performance in these rats could reveal how the CCK system operates at the OB/OM level in regulating feeding and satiety.

### Nutrient glucose

Glucose is the main energy source of organisms. A large part of it comes from ingested food, and logically, glucose uptake depends on food quality. Once in the blood, glucose is stored in various peripheral tissues like the heart, adipose tissue, and skeletal muscle to maintain glycemia, which stops food intake and starts insulin secretion (notably; for review, see Thorens 2008). In the CNS, glucose uptake is performed by two main families of membrane-associated carrier proteins: the energy-dependent sodium-glucose-linked transporters (SGLT; Yu et al. 2010) and the facilitative glucose transporters (GLUT; McEwen and Reagan, 2004). Each family is composed of individual isotypes that are differentiated by substrate specificity, kinetic characteristics, expression profile or localization, and specific function (Scheepers et al., 2004).

Although the two gene families are closely related, only reports of GLUT expression in the olfactory system are known. In the OM, GLUT1 and GLUT3 are expressed in the Bowman's glands and sustentacular cells. OSNs only express GLUT1 (Nunez-Parra et al. 2011). To enter the brain, glucose is transported through the BBB by a specific transporter (55-kDa-GLUT1–55) exclusively found in the microvascular endothelial cells of the central capillaries (Pardridge et al. 1990). Note that brain extracellular space contains glucose concentrations lower than those in the blood (Routh 2002), with the exception of the circumventricular organs like the median eminence and hypothalamus, where the BBB is highly permeable. Brain glucose concentrations are therefore probably quite similar to those in the peripheral blood (Norsted et al. 2008). Once in the extracellular space, the nutrient enters astrocytes with the help of GLUT1-45 (45kDa) and neurons with GLUT3 (Pardridge et al. 1990) or GLUT4. This latter transporter is colocalized with IR in the cerebellum, hippocampus, hypothalamus, OB, anterior olfactory nucleus, olfactory tubercle, piriform cortex, and entorhinal cortex (El Messari et al. 1998, 2002).

In the OB, the BBB is highly permeable (Ueno et al. 1996), and the glomerular layer possesses the highest capillary network density (Chaigneau et al. 2007). Several glucose transporters—GLUT1, GLUT3, and GLUT4—have been described, notably in the mitral cell layer and, to a lesser extent, in the nerve and granule cell layers (Leloup et al. 1996; El Messari et al. 1998; Choeiri et al. 2002).

### Further metabolic factors

A few additional metabolic factors or their receptors have been described in the OM and the OB, but their potential regulatory role in olfaction remains to be established. Despite the clear and specific expression of these molecules, further investigation is required and thus we will simply provide a few examples and references for the reader. In the OM, for example, transcript coding for the type-1 adiponectin receptor (AdipoR1) has been reported in the OSNs (Hass et al. 2008). Peptide YY (PYY) expression has been reported to be restricted to the sustentacular cells even though, quite interestingly, a targeted deletion of the peptide results in an increased expression of OSNs where it might play a role in neuronal differentiation (Doyle et al., 2012). In the OB, for example, mitral cells strongly express the melanin-concentrating hormone receptor

(MCHR; Scalera and Tarozzi 1998; Hervieu et al. 2000; Francke et al. 2005; Lepousez et al. 2010), the glucagon-like peptide (GLP-1) receptor (protein plus mRNA; Merchantaler et al. 1999b), and the bombesin neuromedin B (Ohki-Hamazaki, 2000).

### Regulation of expression of peptide hormones and their receptors in OM and OB by nutritional status

Expression of many of the metabolic factors and their receptors discussed thus far are regulated by the nutritional or the metabolic status of the individual. For example, in rats, IR kinase and Ob-R transcript levels in the OM are upregulated by a 48-h fast, which results in an increase of IR number (Baly et al. 2008; Lacroix et al. 2008). Extending the fast to 72 h significantly increases insulin levels in the OB, by 15-fold, compared with that in the plasma, whereas preventing sensory experience by means of unilateral naris occlusion decreases IR-immunoreactive OSNs by 90% (Fadool et al. 2000). A recent study by Negroni et al. (submitted) showed that the NPY receptor Y1 is also selectively overexpressed in the OM of 14-h-fasted rats. This overexpression leads to an increased electrophysiological response of OSNs to NPY, which is specific to the fasted condition. Interestingly, when a local source of metabolic peptide hormone is observed in the olfactory tissue, some regulation of its level by nutritional status is often observed. For example, orexin content in the OB in the form of OXB, but not OXA, is slightly decreased after a 14-h-fasted (Shibata et al. 2008). Finally, nutritional status can change the expression of other molecules related to olfactory functions, such as odorant-binding proteins, which indirectly change OM function (Badonnel et al. 2007).

Taken together, these published data show that even the first levels of olfactory signal processing can, in tandem, acquire chemical nutritional information that can modulate the olfactory message. The large array of metabolic peptide signaling systems, expressed in a variety of neuronal and nonneuronal support cells of the olfactory system, suggests a wide range of biological roles for these factors, which will be addressed in the next section.

### Hormones and endogenous modulators regulate neuronal activity of the olfactory system

#### Neuromodulation in the OM

Not only does expression of hormones and their receptors depend on nutritional state, but changes in nutritional status are also known to alter the expression of olfactory transduction machinery, the induction of feeding- and chemosensory-related genes, the representation of food odors, the selection of food odors, how odors modulate life span, and the activity of the first olfactory synapse in simple animals and invertebrates (Colbert and Bargmann 1997; Hancock and Foster 1997; Davidson et al. 2006; Gorojankina et al. 2007; Jiu et al. 2010; Liu et al. 2010; Root et al. 2011; Farhadian et al. 2012). Although it has not been demonstrated that commonalities in hormone regulation exist across species, it is certainly evident that nutritional status in a variety of organisms impacts their olfaction. Early studies in *Caenorhabditis elegans* used chemotaxis-based experiments to determine that starvation modulated the process of olfactory adaptation and not olfactory sensitivity (Colbert and Bargmann 1997). Because the effect of starvation on olfactory adaptation was perturbed by topically applied serotonin, the neurosecretory molecule that was endogenously produced in

the pharyngeal neurons was speculated to have access to the chemosensory neurons in the head of the worm, thereby linking feeding state to olfactory adaptation.

In more recent work with *Drosophila*, starvation induced an increased expression of the receptor for the short neuropeptide F (sNPF) through reduction in insulin signaling (Root et al. 2011). sNPF is expressed in the *Drosophila* OSNs and mediates a starvation-dependent presynaptic facilitation of olfactory sensory transmission, which fine-tunes olfactory representation for food finding (Root et al. 2011). Because reduced insulin signaling is required to induce the upregulation of expression of the receptor for sNPF, which then triggers the presynaptic facilitation, the authors suggested that the IR represents the metabolic sensor that triggers appetitive behavior in the fly olfactory system.

In lower vertebrates, the functional role of endocannabinoids as a link between olfaction and nutrition has been demonstrated in *Xenopus laevis* larvae by Breunig et al. (2010). In frog larvae, the endocannabinoid 2-arachidonoylglycerol (2-AG) is produced by two different enzymatic pathways in the OSNs rather than the supportive sustentacular cells. Although release of 2-AG can therefore be both paracrine and autocrine, the paracrine mechanism is selectively upregulated by a hungry state. The authors thereby demonstrated that 2-AG release, evoked by hunger, modulates odor-induced calcium transients in the frog to allow recognition of odor stimuli at lower concentrations.

In higher vertebrates, NPY is localized to the olfactory ensheathing cells and is thought to mediate axon guidance of the OSNs to glomerular targets in the OB (Ubink and Hokfelt 2000; Montani et al. 2006; Martin et al. 2009). Although some reports specify its role in apoptosis and regeneration of the OSNs (Montani et al. 2006; Martin et al. 2009), its important role in regulating appetite and hunger has been well studied physiologically in the axolotl (Mousley et al. 2006; Martin et al. 2009). Mousley et al. (2006) cloned the full-length NPY gene from this species to synthesize species-specific hormone for use in electrophysiological studies in the mucosa of this vertebrate. NPY was found to increase the amplitude of electroolfactogram (EOG) responses to a food-related odorant, L-glutamic acid, only under fasting conditions. By means of whole-cell patch electrophysiology, a tetrodotoxin (TTX)-sensitive inward current was identified, which was also modulated by L-glutamic acid and again only under fasting conditions. The authors hypothesized that either the level of the peptide hormone or expression of its receptors depended upon hunger level. Furthermore, very recent data have shown that NPY increased the electrophysiological response of OSNs in the rat, which is specific to a fasted condition (Negroni et al., personal communication).

In mammals, the status of satiety is signaled by blood-circulating peptide hormones, which in turn can modulate olfactory neural activity. Because many of these molecules are synthesized and secreted by hypothalamic neurons (see reviews by Woods et al. 1998; Schwartz et al. 1999; Schwartz et al. 2000; Woods and Seeley 2000; Woods 2005; Woods and D'Alessio 2008; Luquet and Magnan 2009) and then released at the level of the OB through centrifugal fiber connections (see penultimate section), a majority of the research effort has centered on neuromodulation of the OB (see the following section); but other metabolically important hormones have access to the OM through the peripheral circulation and their effects on odorant responses have been well studied. Insulin and leptin are particularly interesting because the receptor expression for these circulating hormones is regulated by the nutritional status of the

animal (Baly et al. 2007; Lacroix et al. 2008), suggesting that metabolic status can control the first level of odorant detection at the OM. Using an *in vitro* slice preparation to patch-clamp the spontaneous activity in rat OSNs, Savigner et al. (2009) found that bath perfusion of insulin or leptin significantly increased the spontaneous firing frequency in 91% and 75% of recorded neurons, respectively. When activity was electrically evoked, both peptides shortened the latency to the first action potential while decreasing the interspike interval (ISI) (Savigner et al., 2009). Quite surprisingly, acute application of insulin or leptin was found to reduce the EOG amplitude in response to general odorants (Lacroix et al. 2008; Savigner et al. 2009). By decreasing the EOG amplitude and increasing the spontaneous activity, insulin and leptin evoked a decreased global signal-to-noise ratio at the level of the mucosa (Savigner et al. 2009). The EOG amplitude, representing the population of responding OSNs, was affected and not the kinetics of the response, suggesting that non-neuronal cells, mucus composition, or airflow were not attributable to the reduced odorant response (Lacroix et al. 2008). 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, given the finding that the decrease in EOG amplitude was transient, occurring 5 to 10 min after insulin stimulation and demonstrated no reduction or modulation by 15 to 30 min (Lacroix et al. 2008). Such transient modulation may be in keeping with putative postprandial levels of insulin concentrations observed at the level of the OM after a meal, which currently are unknown. Sustained levels of insulin after a fast, however, have been reported in humans as measured in the nasal mucus of normal, obese, thin, and diabetic individuals (Henkin 2010). 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 with the fast. Moreover, Lacroix et al. (2008) report strong evidence for the existence of endogenous insulin produced within the OM, which would be supplementary to the peripheral circulating source of insulin, as previously discussed. The concentration of any locally produced insulin was determined by radioimmunoassay to be very low (1:200) in comparison with circulating insulin (Lacroix et al. 2008), and any distinct physiological role of either pool has not been investigated. Also unknown is whether OSNs are sensitive to glucose, as are certain neuronal populations in the hypothalamus (see following section); but glucose transporters have been reported as potential candidate targets (Figure 1), as already reviewed in the previous section.

### Neuromodulation of the OB

In the early 1970s, Pager et al. (1972) and Giachetti et al. (1970) were the first to report that mitral cell activity could be perturbed in hungry, as opposed to satiated, rats in response to food odors. In the Pager laboratory, multi-unit activity in the mitral cell layer was recorded in unanesthetized rats that were chronically and bilaterally implanted with bipolar electrodes. Rats that were fasted for 24 h exhibited an odor-evoked increased firing frequency compared with satiated animals (recorded 2 h after ingestion of a meal). Moreover, mitral cell firing increased in hungry rats in response to a food odor but not in response to a control odor (amyl acetate). In parallel studies, hunger was alternatively induced by injection of insulin to promote hypoglycemia in 24-h fasted animals. Insulin evoked a similar but stronger increase in mitral cell firing specific to the food

odor. Although the identity of the mechanism was unknown at the time, the authors correctly deduced that the varying nutritional status of the animal caused differential response to the same odorant and thereby “provides strong evidence that the mitral cell activity is driven by some factors related to the metabolic state” (Pager et al. 1972). In non-food-deprived rats, Cain (1975) similarly discovered that an injection of insulin changed the response to odors in approximately one-fourth of his OB- or amygdala-recorded units. Although he reported no selective facilitation to food odors, he did report more complex changes in response to insulin—a majority of records showed increased magnitude of response, but others showed reversed response direction and were inhibitory. More recently, Apelbaum and Chaput (2003) made use of a feeding paradigm originally designed by Pager (1974b) to demonstrate that differential access to food can cause a drastic decrease in mitral cell activity. Using single-unit mitral cell recordings, they discovered that the increase in mitral cell firing in response to fasting is smaller if rats are habituated to a daily restricted food pattern for 15 days compared with that in rats fasted for the first time. They concluded that the OB is very plastic to changes of the internal state and can be modified with prolonged environmental changes, and they questioned the stability of odorant coding in light of nutritional status.

These early studies, in which feeding state was demonstrated to affect physiological olfactory sensitivity, led to studies that explored the cross talk between the hypothalamic feeding network and the olfactory system. Both hypothalamic and peripheral circulating hormones had been reported to affect food intake, and therefore, were the first targets for electrophysiological studies. Centrally available insulin or leptin injected into the ventricular system or hypothalamic sites while maintaining peripheral euglycemia (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) was found to be catabolic in nature; they reduced food intake, lowered body weight, and elevated energy expenditure (Woods et al. 1979; Campfield et al. 1995; Schwartz et al. 2000; Shiraiishi et al. 2000). NPY and orexin were reported to be orexigenic in nature; acting antagonistically to insulin (Stockhorst et al. 2004) by stimulating food intake and increasing body weight (Edwards et al. 1999; Ida et al. 1999; Rodgers et al. 2002; Leibowitz and Wortley 2004). Therefore, this group of molecules that regulates energy homeostasis has recently been investigated in terms of physiological function in the OB because interdependency has been reported in the literature for olfactory behavior, metabolism, and food intake.

NPY-like immunoreactivity had been reported in several layers and cell types of the OB as had the localization of four of the five major NPY receptor subtypes (Figure 1). Nonetheless, the role of NPY in neurotransmission or neuromodulation of electrical activity in the OB had not been extensively explored. Using a rat primary OB culture preparation, Blakemore et al. (2006) demonstrated that NPY and NPY<sub>13–36</sub> (ligand for the Y<sub>2</sub> receptor subtype) reduce spontaneous excitatory activity of interneurons. NPY inhibited excitatory postsynaptic potentials as well as reduced action-potential frequency. The authors observed a concomitant reduction in miniature excitatory postsynaptic current frequency but not amplitude and a significant inhibition of voltage-gated calcium currents. Thereby, it was concluded that NPY signaling was acting presynaptically to inhibit release of glutamate as an excitatory transmitter.

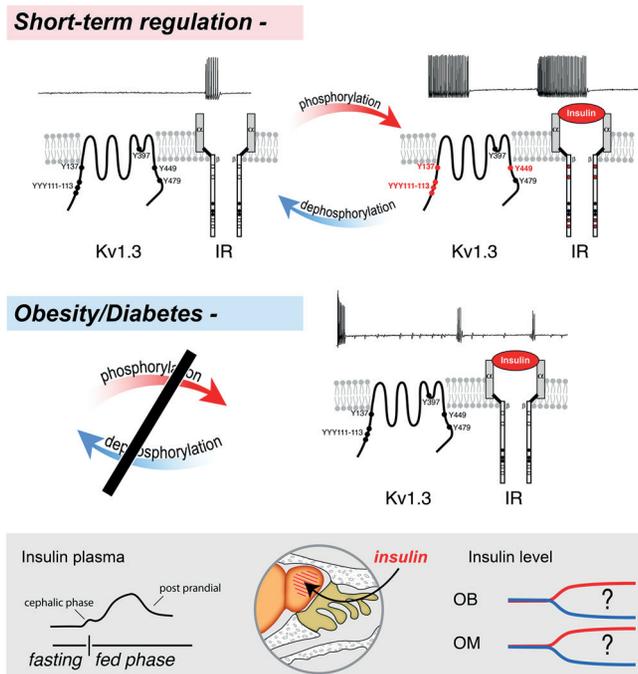
The modulatory effect of orexin A, also known as hypocretin-1, on mitral cell activity has been studied due to its known

immunocytochemical distribution in this lamina (see Figure 1; Shibata et al. 2008; Suzuki et al. 2008). Apfelbaum et al. (2005) determined both the central and local effects of this hormone on the spontaneous firing frequency of mitral cells by using icv injections and topical applications on the OB, respectively, in an anesthetized, awake rat preparation. The mitral cell firing frequency was reduced in 50% of neurons when orexin A was acutely administered to the OB, whereas 14% of neurons exhibited reduced excitability when it was applied centrally. Neither route of administration, however, was found to significantly increase bulb responsiveness to either food or nonfood odors (Apfelbaum et al. 2005). The authors reported that a temporal reorganization of mitral cell discharge, nonetheless, appeared to take place, in that some cells that did not respond to an odorant before orexin stimulation responded with a decrease in firing frequency to that same odorant after orexin treatment. Hardy et al. (2005) present a nice model and electrophysiological evidence that orexin A acts on the bulb network by inducing two types of opposite actions on the spontaneous activity in mitral cells. In the first scenario, orexin A reversibly reduces spontaneous firing and eliminates excitatory postsynaptic potentials. The hyperpolarizing effect of orexin A, which is suspected to mediate the reduction in spontaneous activity, was blocked by bicuculline and suppressed by an OXRT1 antagonist. Therefore, this first action of orexin A is hypothesized to be attributed to the hyperpolarization of mitral cells due to reciprocal depolarization of GABAergic interneurons, periglomerular cells, and granule cells, which would in turn inhibit mitral cells through GABA release; this GABA then acts on GABA<sub>A</sub> receptors of the mitral cells. In the second scenario, orexin A is hypothesized to depolarize mitral cells directly by binding to OXRT receptors that are expressed on a subset of mitral cells. Most recently, Prud'Homme et al. (2009) explored fos immediate-early gene induction in the periglomerular, granule, and mitral cell layers of the OB-fed rats that were administered orexin A by icv injection. Fasted rats demonstrated an elevation in fos immunoreactivity in response to a familiar food odor and this effect could be mimicked in satiated rats that were treated with orexin A. Corroborating results were found in fasted rats treated with an orexin A-receptor antagonist, which then demonstrated a decreased fos immunoreactivity in all lamina of the OB in response to food odors, thereby mimicking the satiated state.

The highest brain insulin-binding affinities, IR density, and IR kinase activity are 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), as described in the previous section (see also Figure 1). Using a dissociated primary cell-culture preparation of the OB, Fadool et al. (2000) reported that the hormone insulin, but not the related insulin-like growth factor I (IGFI), evoked the suppression of outward currents as recorded from mitral cells using a whole-cell patch-clamp configuration. The modulation occurred over the course of 15–20 min and was attributed to a decrease in peak amplitude of the current without any modification of the kinetics of inactivation or deactivation. Unitary currents, elicited by step depolarization in cell-attached patches, responded to insulin with a significant decrease in open probability of the channel without any change in unitary conductance. Insulin-evoked suppression of outward current was eliminated in cultures prepared from naris-occluded rats, which demonstrated a reduction in IR kinase expression in multiple neural lamina of the OB, suggesting that insulin modulation of mitral cells was also dependent upon sensory experience.

Traditional structure–function analyses and pharmacological studies, as well as electrophysiological phenotyping of mice with gene-targeted deletions (Fadool and Levitan 1998; Colley et al. 2004; Fadool et al. 2004; Das et al. 2005), identified a substrate for insulin phosphorylation in the OB as the mammalian homologue of the *Shaker* subfamily member, Kv1.3 (Figure 2). Kv1.3 carries 60–80% of the outward current of mitral cells as calculated from pharmacological voltage-clamp experiments in cultures and slices (Fadool and Levitan 1998; Fadool et al. 2004; Fadool et al. 2011). Tyrosine to phenylalanine mutations in the carboxyl- and amino-terminal cytoplasmic aspects of the channel or deletion of the IR catalytic domain of the receptor blocked insulin-induced modulation and concomitant phosphorylation of the channel. Likewise, gene-targeted deletion of either the Kv1.3 channel or IR kinase resulted in loss of insulin-evoked current suppression of voltage-activated currents of mitral cells (Fadool et al. 2004; Das et al. 2005). Blocking the vestibule of the Kv1.3 channel with the scorpion toxin, margatoxin, mimicked a loss of insulin modulation similar to that observed in the Kv1.3-null mice (Colley et al. 2004; Fadool et al. 2004). Kv1.3 channels contain multiple tyrosine-phosphorylated residues that serve as recognition sites for SH2-containing proteins and they contain proline-rich sequences for protein–protein interactions with SH3-containing protein kinases and adaptor proteins (Cook and Fadool 2002; Colley et al. 2009). As such, they serve as a central scaffold upon which brain insulin signaling can be readily modified (Marks et al. 2009). For example, membrane excitability and synaptic transmission can be finely regulated through the colocalization of Kv1.3, IR kinase, and postsynaptic density (PSD-95; Marks and Fadool 2007). The canonical carboxyl-terminal PDZ recognition motif of the channel is the site of interaction with PSD-95, which serves to cluster the channel in the absence of IR kinase. The SH3-guanylate kinase domain of PSD-95, however, functionally uncouples insulin-induced Kv1.3 current suppression and phosphorylation, which would be predicted to dampen excitability of Kv1.3-expressing neurons in the OB.

In recent investigations of insulin modulation of mitral cell activity, an *in vivo* preparation using postnatal and adult slices of the OB has facilitated a more detailed electrophysiological analysis of insulin's molecular mechanism (Palouzier-Paulignan et al. 2010; Tucker et al. 2010; Fadool et al. 2011). Evoked neural responses elicited by current injection in the current-clamp mode were differentially modulated by the hormone insulin, dependent on the duration of stimulation: acute or chronic (Fadool et al. 2011). Acute stimulation enhanced mitral cell firing frequency and significantly inhibited spike adaptation that is typically elicited at higher current intensities. Acute stimulation was found to decrease the ISI and the pause duration between action potential clusters, which is mediated by intrinsic membrane properties and is thought to regulate odorant coding (Balu et al. 2004). Insulin fails to modulate mitral cell activity in slices derived from Kv1.3-null mice, whose basal spike activity exhibits short pause duration between clusters, greater mean spike length, and shortened latency to first spike. In contrast, chronic stimulation by insulin evoked a decrease in mitral cell spike activity, regardless of the initial pattern of spike firing activity. Chronic stimulation by insulin was achieved via intranasal delivery (Thorne et al. 2004; Marks et al. 2009; Henkin 2010; Lochhead and Thorne 2011) to the OB for a period of 8 days, after which the basal firing activity of mitral cells was also modified. One class of mitral cells had a higher basal firing frequency than control animals, in that very few pause durations



**Figure 2** A schematic representing the identity of a voltage-dependent potassium channel, Kv1.3, which is a substrate for insulin signaling in the OB. Kv1.3 is highly expressed in mitral neurons of the OB, where it carries a large proportion of voltage-gated outward currents (not shown) and mediates dampening of excitability by regulating action-potential timing and interspike interval (top left traces). Short-term regulation by insulin: Kv1.3 has multiple tyrosine (Y) residues (circles) that could serve as recognition motifs for tyrosine phosphorylation. Upon binding of the hormone insulin to the alpha subunits of the insulin receptor (IR) kinase (right side of schematic), multiple sites along the beta subunits (red circles) undergo autophosphorylation and the activated IR subsequently phosphorylates residues 111–113, 137, and 449 in the amino and carboxyl terminals of the Kv1.3 channel (red circles). As measured by recording under voltage-clamp conditions, phosphorylation causes a suppression of Kv1.3 via decreased open probability of the channel and via current clamp, it increases evoked action-potential frequency, spike train duration, and interspike interval while decreasing the pausing between spike clusters (top right traces). Obesity/Diabetes: Following diet-induced obesity (DIO) or chronic hyperglycemia of diabetes, the normal cycles of phosphorylation/dephosphorylation are imbalanced (black bar). Mice challenged with DIO exhibit mitral cell firing with irregular spike firing frequency, prominent spike adaptation, or partial amplitude. Application of acute insulin fails to increase spike frequency and Kv1.3 remains unphosphorylated (black circles)—both signs of insulin resistance. Bottom box: During natural cycles of feeding and fasting, olfactory physiology can be modulated through the rapid transport of insulin across the blood—brain barrier; but measured daily fluctuations in olfactory bulb (OB) and olfactory mucosal (OM) insulin are currently not reported.

between spike clusters were observed. A second class of mitral cells only fired a single spike cluster after chronic intranasal delivery of insulin. The authors hypothesized that the combined data point to the OB as an internal sensor of metabolism by insulin-induced modulation of the potassium channel Kv1.3.

Ma et al. (2011) found that a major brain receptor for CCK, called CCK2R, was expressed in the mitral and juxtglomerular cell layers, but not in the granule cell layer. CCK transiently increased mitral cell spike frequency in a slice preparation of the

OB, which was unmodulated when slices were prepared from CCK2R-null mice. CCK also induced a slow inward current that may be mediated by a suppression of a potassium current based on observed reversal potential. The authors speculate that the amplification of mitral cell outputs by excitation of coactive bulb circuits could promote olfactory coding information of shared olfactory receptor classes (Ma et al. 2011). Liu and Shipley (2010) interestingly reported that the intrabulbar association system exclusively contains CCK. They report that CCK enhanced inhibitory postsynaptic currents in periglomerular and short axon cells and evoked presynaptic inhibition of the olfactory nerve terminals by depolarizing and increasing GABA release in a CCK2R-dependent mechanism. They suggested that CCK therefore enhances intraglomerular inhibition of mitral/tufted cells to thereby regulate sensory processing in glomeruli. They hypothesized that this CCKergic class of neurons would shape the OB output to the olfactory cortex by modulating intraglomerular inhibitory circuits.

Modulation of neural activity in the OB was first explored through fasting paradigms used to elicit changes in nutritional status. Most recently, Fadool et al. (2011) have adopted the opposite tactic and placed mice on enriched fat diets to test whether mitral cell activity would be attenuated. Mice made obese through maintenance on a moderately high-fat diet of 32% fat exhibited prominent changes in mitral cell action potential shape and clustering behavior, whereby subsequent response to acute insulin stimulation was either attenuated or completely absent. Parallel studies demonstrated a degree of insulin resistance attributed to the moderately high-fat diet, whereby insulin-induced phosphorylation of the Kv1.3 channel was inhibited in the OB after diet-induced obesity (Marks et al. 2009).

Beyond promoting a modified response to brain insulin, increased adiposity is predicted to elevate circulating hormones from fat stores, modify satiety hormone release centrifugally back to the level of the OB, and disrupt glucose balance. A complex array of variables could therefore modulate neuronal activity in the OB, specifically at the level of the mitral cell. Insulin and glucose homeostasis, by nature of their signaling mechanisms, are combinatorial and hypoglycemia itself is a potent signal for the brain (Stockhorst et al. 2004). Initial studies by Tucker et al. (2010) suggest that mitral cells sense glucose, like those found in key areas of the brain involved in energy homeostasis, such as the ventromedial hypothalamus. In the ventromedial hypothalamus, a majority of the neurons are excited by physiological concentrations of glucose, become hyperpolarized, and then decrease in firing frequency in response to a decrease in brain glucose (Cotero and Routh 2009). Electrophysiological studies have identified the presence of glucose-sensing neurons (either excited or inhibited by extracellular glucose levels) in the hypothalamus, hippocampus, substantia nigra, septal nucleus, and brain stem (Anand et al. 1964; Oomura and Yoshimatsu 1984; Routh 2002; for review, see Routh et al. 2004), where they participate in the control of glucose homeostasis and several other behaviors including feeding, energy storage, and expenditure. Quite interestingly, mitral cells are also sensitive to changes in glucose concentrations, a response that is quite rapid and lost in Kv1.3-null mice (Tucker et al. 2010). Moreover, the oxidative status of a cell is known to depress Kv currents (Cayabyab et al. 2000; Conforti and Millhorn 2000). Work from the Schlichter laboratory (Cayabyab et al. 2000) has demonstrated that deprivation of oxygen and glucose can cause an increase in phosphorylation of Kv1.3 channels in lymphocytes and that these conditions simultaneously decrease whole-cell currents in voltage-clamp experiments.

The fact that Kv1.3-null animals are resistant to diet- and genetic-induced obesity (Xu et al. 2003; Fadool et al. 2004; Tucker et al. 2008; Tucker et al. 2010; Tucker et al., 2012) via increased basal metabolic rate without altering total caloric consumption presents an interesting link between OB signaling and energy homeostasis. The Desir laboratory has found that blocking of Kv1.3 function in mice, either pharmacologically or by gene-directed deletion, confers higher insulin sensitivity and lower plasma glucose levels (Xu et al. 2004; Tschitter et al., 2006). The investigators attribute this result to increased depolarization, which translocates the glucose receptor, GLUT4, to the plasma membrane, bypassing the requirement for insulin (Li et al., 2006). A recently discovered polymorphism in the human Kv1.3 gene that functionally elicits a gain-in-function has been associated with impaired glucose tolerance, lower insulin sensitivity, and impaired olfactory sensitivity in homozygous carriers (Tschitter et al., 2006; Guthoff et al. 2009). The Kv1.3 channel, as a reported “diabetes risk allele” in humans, may represent an important candidate gene for therapeutic intervention (Choi and Hahn 2010). In support of a potential central target for metabolism (Tucker et al. 2010), Tucker et al. (2012) have recently demonstrated that Kv1.3-null mice are no longer resistant to obesity and display decreased metabolism after bilateral olfactory bulbectomy.

### Neuromodulation of higher olfactory projections

Modulation of the piriform cortex and higher processing centers has been only scantily explored in terms of their physiological response to endocrine-based hormones. One region that has been the focus of study is the orbitofrontal-temporal association cortex, which is the site of convergence of information from olfaction, taste, and visual sensory cues. Neurons from the primate orbitofrontal cortex were reported to decrease their responsiveness to an odor after satiation (Critchley and Rolls 2011).

### Hormones drive olfactory behaviors

Although modulation of olfactory-driven behavior by feeding state is yet to be unequivocally demonstrated in humans, it has been well established in rodents. Fasted animals have greater olfactory sensitivity and exhibit greater food-odor exploration time than do satiated ones (Aimé et al. 2007; Prud’Homme et al. 2009). Strong candidates for involvement in such modulations include hormones originating from the CNS or from the periphery and known to act on receptors located in the olfactory system (Figure 3). An opposite effect on olfactory-driven behavior can be expected from appetite-stimulating (orexigenic) and appetite-suppressing (anorexigenic) hormones. To explore this idea, we will focus principally on two examples for each of these peptide categories (ghrelin and orexin for the first, and insulin and leptin for the second) by combining the results of the available studies performed on humans and animals.

#### Orexigenic signals

Several reports indicate that orexinergic signals act on the olfactory system to increase olfactory abilities. Systemic infusion of ghrelin, another orexigenic peptide, increases human sniffing responses without affecting the hedonic value of the odorants (Tong et al. 2011), consistent with a recent study (Trellakis et al. 2011) in which the hedonic rating was not affected by ghrelin for five of six odors tested (food- and nonfood odors). In satiated rats, an icv injection

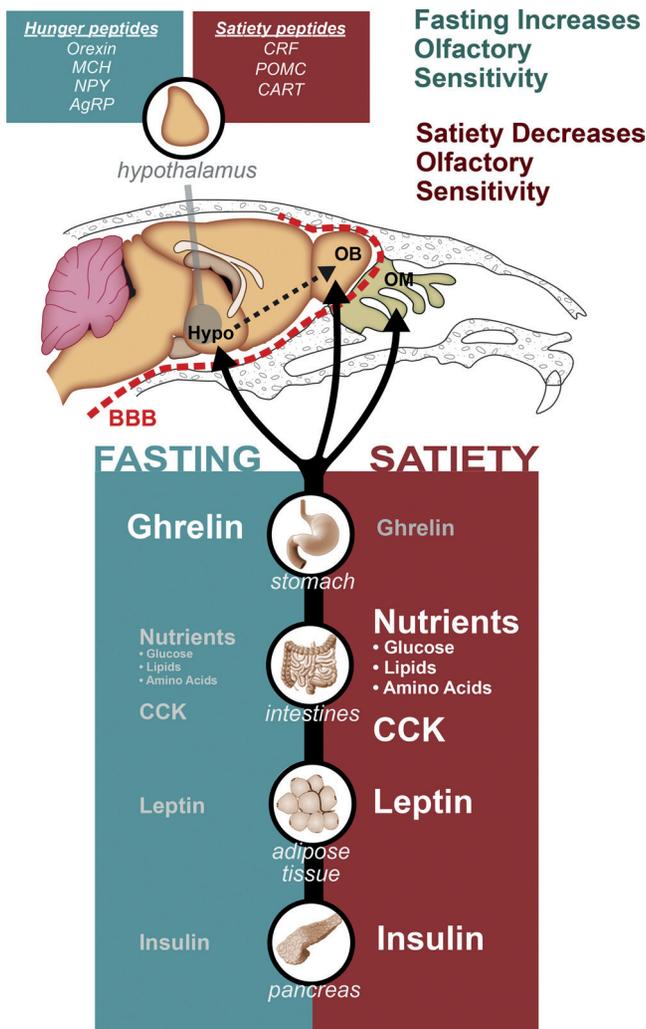
of ghrelin increases olfactory sensitivity and exploratory food-sniffing frequency (Tong et al. 2011).

Similarly, narcoleptic/cataplectic patients, with a specific loss of central orexinergic neurons and virtually no orexin-A detected in the CSF, show a decrease of olfactory detection, discrimination, and identification (Baier et al. 2008; Bayard et al. 2010; Buskova et al. 2010). This effect is reversed by intranasal administration of orexin A (Baier et al. 2008). Specific loss of orexinergic hypothalamic neurons therefore impairs olfaction. Accordingly, in rodents, an icv injection of orexin A increases the olfactory sensitivity of satiated animals (Julliard et al. 2007), which are otherwise known to have low sensitivity (Aimé et al. 2007). In addition, blocking orexin action in fasted rats by oral administration of antagonists to orexin receptors (OXR1 and OXR2) significantly decreases the exploration time for a food odor (Prud’Homme et al. 2009). These data indicate that ghrelin and orexin A, the levels of which are maximal during a fast, act on the olfactory system to increase its performance before the meal and therefore contribute to food localization. For orexin at least, these behavioral effects could partly be mediated by hormone action on OB networks (see previous section).

A recently emerging body of data suggests that the endogenous cannabinoid and opioid systems are involved in the homeostatic and hedonic aspects of eating behavior, thereby representing key circuits that respond to the rewarding value of food (for review see Cota et al. 2006; Cota 2008). Cannabinoids markedly impaired olfactory discrimination reversals without disrupting acquisition of the original discrimination whereby a CB1 antagonist was capable of reversing all cannabinoid effects on olfactory discrimination reversals (Sokolic et al. 2011). Several lines of evidence point to the relationship between opioids and the palatability of food items. In animals, ingestion of palatable food activates  $\beta$ -endorphins in the hypothalamus (Dum et al. 1983). Opioid blockade has been suggested to result in an altered taste perception, making sweetened and salty solutions less palatable (Levine et al. 1982; Fantino et al. 1986; Bertino et al. 1991). Only a few investigations have reported any functional consequence of opioid signaling in olfaction; most have focused on opioid-induced changes in food perception. Icv infusions of morphine have been shown to disrupt, and naloxone shown to restore, olfactory preferences for pup odors by lactating rats (Kinsley et al. 1995). In human test subjects, pharmacological blocking of opioid receptors has been found to attenuate olfactory and gustatory hedonic responses of palatable meals (Yeomans and Wright 1991). Administration of the opioid remifentanyl raised olfactory thresholds while having little or no influence on odor discrimination and odor identification performance (Lotsch et al. 2001).

#### Anorexigenic signals

The aforementioned data lead to the prediction that anorectic hormones should act in opposition to orexigenic peptides. Supporting that assumption, Ketterer et al. (2011) have demonstrated that an acute hyperinsulinemic-euglycemic clamp reduces olfactory abilities in healthy humans. The authors conclude that this process is probably a means “to reduce the pleasantness of eating.” In the rodent OB, Fadool and collaborators identified a Kv1.3 channel to which potassium current is suppressed by insulin through multiple phosphorylation of the *Shaker* ion channel (Fadool and Levitan 1998; Fadool et al. 2000; Figure 2). Moreover, Kv1.3<sup>-/-</sup> mice demonstrate an increase in insulin sensitivity together with an impaired glucose metabolism (Xu et al. 2004) and, interestingly, a “Super-smeller”



**Figure 3** Mechanisms by which regulatory metabolic factors can shift olfactory sensitivity to achieve nutritional homeostasis. Upon fasting or satiety, various peripheral molecules from the stomach, intestines, adipose tissue, and pancreas, among other peripheral localities, are up- or downregulated (bottom box). Through the blood, these signals target the hypothalamus (Hypo), olfactory bulb (OB), and olfactory mucosa (OM), among others. In turn, the hypothalamus releases metabolic factors to adapt food intake, which then maintains nutritional homeostasis. Both central and peripheral factors directly or indirectly target the olfactory system as a means to adapt it to the food foraging and the nutritional needs of the organism. Fasting increases olfactory sensitivity and associated olfactory-driven behaviors, whereas satiety counterbalances to decrease sensitivity and associated behaviors. MCH = melanin-concentrating hormone, NPY = neuropeptide Y, AgRP = agouti-related peptide, CRF = Corticotropin-releasing factor, POMC = proopiomelanocortin, CART = cocaine- and amphetamine-related transcript, OB = olfactory bulb, OM = olfactory mucosa, Hypo = hypothalamus, BBB = blood-brain barrier. Note: Size of font in bottom box reflects up- or down-regulation of the metabolic factor during fasting or satiety.

phenotype (Fadool et al. 2004). Indeed, they have a 1,000- to 10,000-fold lower threshold for olfactory detection and display greater discrimination abilities, as evidenced by habituation/dishabituation (Fadool et al. 2000). Likewise, a reported polymorphism of the human Kv1.3 gene, which presents with a gain in Kv1.3 channel, impairs human olfactory function, particularly in male patients

(Guthoff et al. 2009), suggesting that a decreased IR-signaling pathway found in these patients leads to a decrease in olfactory performance. In a further exploration of the biochemical and behavioral effects of insulin, physiological hormone administrations were performed in wild-type mice (Marks et al. 2009) and rats (Aimé, unpublished data). Twice-daily intranasal insulin deliveries phosphorylate the Kv1.3 channel, notably in the OB and the hippocampus, without damaging the OM (Marks et al. 2009). Functional activation of the IR/Kv1.3 pathway is associated with an increase in odor-discrimination ability, with no change in odor-detection threshold, a decrease in anxiety-related behaviors, and an increase in object memory recognition. In fasted rats, icv administration of an insulin dose equivalent to that found in the satiated state reduces olfactory detection and prevents the rise of respiratory frequency induced in control fasted animals by food odor presentation (Aimé, unpublished data). These data demonstrate that insulin modulates olfactory sensitivity and behaviors linked to food finding and intake.

Leptin, another anorectic hormone, also plays a role in olfactory function. In humans, elevated leptinemia and a high body-mass index (known to be directly correlated with high circulating leptin levels; Considine et al. 1996) are reflected by low ratings of black pepper-odor pleasantness (Trellakis et al. 2011). In addition, blood leptin concentration is correlated, in a gender-specific way, with odor identification (Karlsson et al. 2002). Mutant mice represent convenient models for gaining insight into the role of leptin signaling in olfactory-driven behaviors. Olfactory performances (i.e., time needed to find a cracker hidden under the cage bedding, a task based on olfactory cues only) of wild-type, *ob/ob* (non-leptin-producing), and *db/db* (mutation on the long form of the leptin receptor) mice were therefore compared (Getchell et al. 2006). Mice lacking physiological leptin regulation (*ob/ob* and *db/db*) detected the cracker faster than their wild-type litter mates. Restoring leptin levels by intraperitoneal injection in the *ob/ob* mice decreased their performances to the level of control animals. Accordingly, central administration of leptin in fasted rats induces a dose-dependent decrease of olfactory detection (Julliard et al. 2007) and reduces food-odor exploration time (Prud'Homme et al. 2009). These data, taken together, indicate that anorectic hormones, such as leptin and insulin, decrease olfactory abilities.

Converging evidence demonstrates that the olfactory system is a target for hormones related to metabolism and food-intake regulation; it adapts its function to nutritional needs by promoting or inhibiting food foraging. Metabolism is tightly balanced by the complementary intervention of appetite-regulating peptides, by either stimulating food intake (orexin, ghrelin) or suppressing it (insulin, leptin). As expected, they are also complementary in their effects on olfaction because they increase or decrease olfactory performance, respectively, according to specific metabolic requirements (Figure 3).

## Crosstalk between feeding state and olfactory perception

### Feeding state modulates olfactory sensitivity

Do metabolic status and feeding state modulate olfactory function? The answer to this question is still quite controversial despite many studies performed over the years in humans. At the beginning of the 20th century, prolonged fasting was shown to increase olfactory sensitivity (Langfeld 1914; Glaze 1928a, 1928b). An olfactory diurnal cycle shaped by metabolic status was described, wherein

olfactory perception increases in hungry humans and decreases in satiated ones (Goetzl and Stone 1947, 1948; Goetzl et al. 1950; Hammer 1951; Schneider and Wolf 1955; Guild 1956; Furchtgott and Friedman 1960). This ultradian cycle of olfactory sense can be experimentally reproduced if metabolic variation is mimicked through sucrose intake or stomach distension in fasted subjects (Ahokas and Goetzl 1951; Goetzl et al. 1951). Patients with metabolic disorders (obesity, anorexia nervosa, bulimia nervosa, and morbid obesity) have impaired olfactory detection, recognition, or discrimination (Le Floch et al. 1993; Weinstock et al. 1993; Fedoroff et al. 1995; Obrebowski et al. 2000; Richardson et al. 2004; Roessner et al. 2005; Aschenbrenner et al. 2008; Rapps et al. 2010); but these pathological conditions may not allow identification of the mechanisms responsible for the modifications of olfactory function because of the numerous and complex endocrine disturbances associated with them (see penultimate section).

From these initial human studies, an easy conclusion would be that a tight link exists between olfaction and metabolic status. Unfortunately, the results of Goetzl's team were not replicated (Janowitz and Grossman 1949; Zilstorff-Pederesen 1955; Turner and Patterson 1966); and then Koelega (1994) showed that the diurnal modulation of olfactory perception was not linked to the feeding state. He proposed that strictly controlling some experimental parameters like "size and nutrient composition of the meal, timing of not only lunch but also breakfast" could standardize the metabolic state of the subjects and thus be favorable to appreciation of subtle olfactory modulations. He also suggested using finer gradations of stimuli. In this way, the "Sniffin' sticks" designed by Hummel et al. (1997) allowed measurement of olfactory threshold through an orthonasal delivery (odorant molecules administered through the nostrils) of various odorant concentrations by means of pen-like devices. Controlling odor distribution, however, was not sufficient to standardize results, because two research teams (Albrecht et al. 2009; Stafford and Welbeck 2011) obtained contradictory data with a neutral odor although employing similar stimulation devices (Hummel et al. 1997). However, with food odor, both teams, as reported previously by Berg et al. (1963), showed that satiation increases olfactory sensitivity to food odors and they proposed that this increase regulates intake by ruling out nutrients no longer needed. This interpretation is congruent with reports of a lower pleasantness rating for food odors after a meal (Cabanac 1971; Rolls and Rolls 1997; Jiang et al. 2008; Albrecht et al. 2009), as reviewed by Sorenson et al. (2003) and Yeomans (2006). Another explanation for not observing a strong correlation between satiation and olfactory ability in humans could be attributed to individual differences in sensory acuity, which mask trends driven by satiation state. Therefore, despite an abundance of human studies attempting to correlate metabolic state with olfactory ability, the debate remains open.

Animal studies may prove more pragmatic in attempts to answer this long-standing debate, as they permit study of the cellular mechanisms implicated in olfactory regulation. Moreover, the experimental conditions can be more stringently standardized because qualitative and quantitative features of meals can be normalized over longer periods so that the metabolic status of the animals can be better equalized before testing. Controlling the experimental conditions is essential to revealing the subtle modulation of olfactory sensitivity, and such supervision is almost impossible with human subjects. The consensus that olfactory function is modulated by related food-intake molecules

emerges from studies performed on a variety of species: *C. elegans* (Colbert and Bargmann 1997; Harris et al. 2011), axolotls (Mousley et al. 2006), *Drosophila* (Root et al. 2011), tsetse flies (Liu et al. 2010), and rodents (Fadool et al. 2000; Julliard et al. 2007; Marks et al. 2009; Prud'Homme et al. 2009). Here, we review experiments on rodents, which demonstrate an increase in olfactory performance in hungry, awake animals. Aimé et al. (2007) reported that olfactory sensitivity was higher before a meal than that after a meal. To evaluate odor threshold, these authors induced a conditioned odor aversion in which animals learned to associate isoamyl acetate (dilution:  $10^{-5}$ ) with symptoms of nausea to avoid future poisoning. After this training, animals were given the choice between pure water and water odorized with various concentrations of isoamyl acetate (dilutions ranging from  $10^{-10}$  to  $10^{-7}$ ). Fasted rats detected and avoided the odorized water (dilutions:  $10^{-9}$  to  $10^{-8}$ ) much better than satiated ones, demonstrating that fasting increases olfactory sensitivity. In addition, food-odor exploration time increased before a meal (Prud'Homme et al. 2009) because fasted rats explored a tea ball containing food pellets longer than did satiated rats. Therefore, in the physiological context of rats that are awake, olfactory modulation by nutritional states is associated with odors linked to intake behavior. Such modulation would have particular relevance during food foraging; but note that nutritional meaning of an odor is a dynamic concept because it can be extended by learning. After suitable conditioning, a non-food-related odor can become palatable (Pager 1974a). Similarly, in conditioned odor aversion, animals associate odors with symptoms of nausea (Aimé et al. 2007), thus modifying their repertory of odors related to intake.

### Olfaction is linked with digestive physiology

Although olfaction influences metabolic status, the reverse is also true. In the presence of food, olfactory and visual cues are perceived before any intake. These stimuli, presented alone or in combination, participate in the "cephalic phase" of digestive physiology, notably by increasing, in humans, the flow rates of saliva and gastric acid (Pangborn et al. 1979; Feldman and Richardson 1986; Rogers and Hill 1989; Lee and Linden 1992; Engelen et al. 2003; Epstein et al. 2003). According to their quality, odors evoke different autonomic reactions. Appetizing ones induce a salivary reflex through submandibular gland activation (Lee and Linden 1992) or swallowing reflex (Ebihara et al. 2006; Munakata et al. 2008). Irritating stimuli, like lemon or peppermint, activate preferentially the parotid gland; another, black pepper oil, whose flavor comes from piperine, improves the swallowing reflex by activating the insular cortex and causing an increase in serum substance P (Ebihara et al. 2006). These latter reflexes seem to implicate the trigeminal rather than the olfactory nerve (Lee and Linden 1991, 1992). During activation of the autonomic system, olfaction also modulates hormonal concentrations by increasing gastric secretion of gastrin and ghrelin (Feldman and Richardson 1986; Massolt et al. 2010); but in females fasted for 6 h, smelling chocolate decreases both appetite and total ghrelin levels (Massolt et al. 2010). In this study, odor exposure lasted 5 min, leading to odor habituation and to a concomitant decrease of salivary reflex (Epstein et al. 2003), which, together with ghrelin reduction, is probably responsible for satiation.

Insulin levels are also affected by olfaction, because meal presentation (which activates both olfaction and vision) participates in



	Degree of Severity	Age or Study Group	Hedonic Value	Detection Threshold	Discrimination/ Identification	Test	Reference
Obesity	BMI>45	Human	NA	NA	↑ risk for anosmia	CC-SIT	Richardson et al 2004, 2011
	without diabetes	Human 10-16 yrs	NA	↑	↓	Elsberg & Levy Olfactometry	Obrebowski et al 2000
	without diabetes	Human	= non-food odor	NA	NA	Magnitude estimation Pleasantness rating	Thompson et al 1997
Diabetes	Type 1	Human	NA	NA	=	OIT	Naka et al 2010
	Type 2	Human	NA	NA	↓	OIT	Naka et al 2010
	unspecified	Human Children	NA	↑	↑ identification threshold	ODT,OIT	Prusezewicz et al 1988
	unspecified	Human	NA	↑	NA	Elsberg & Levy Olfactometry	Jorgensen and Buch 1961
	unspecified	Human	NA	↑	NA	Elsberg & Levy Olfactometry	Patterson et al 1966
	unspecified	Human	NA	NA	↑ associated with macrovascular disease, not type or hyperglycemia	Odor Confusion Matrix	Weinstock et al 1993
	unspecified	Human	NA	NA	↓	OIT	Le Floch et al 1993
	unspecified	Human	NA	NA	= risk for hyposmia ↑ risk for anosmia	SOIT	Bramerson et al 2004
Anorexia nervosa		Human	NA	=	↓ identification = discrimination	Sniffin' Sticks	Rapps et al 2010
		Human	↓ Preprandail pleasantness of high caloric food odors	NA	NA	Self-Assessment Manikin Scale of pleasantness	Jaing et al 2010
		Human	↓ (food odor)	↓ Preprandail (food odor)	↓ (food odor)	Sniffin' Sticks	Schreder et al 2008
		Human	NA	=	↓ discrimination	Sniffin' Sticks	Aschenbrenner et al 2008
		Human	NA	↓	↓ discrimination	Sniffin' Sticks	Roessner et al 2005
		Human	NA	NA	=	UPSIT	Kopala et al 1995
	Very low weight	Human	NA	↑	↓ identification	UPSIT	Fedoroff et al 2006
Bulimia nervosa		Human	NA	=	=	Sniffin' Sticks	Aschenbrenner et al 2008
		Human	NA	=	=	UPSIT	Fedoroff et al 2006

**Table 3** Olfactory disruption and metabolic disorders. Not accessed (NA), significantly decreased compared with control (↓), significantly increased compared with control (↑), not significantly different compared with control (=), Cross Cultural Smell Identification Test (CC-SIT), University of Pennsylvania Smell Identification Test (UPSIT), Odor Identification Test (OIT), Odor Detection Test (ODT), and Scandinavian Odor Identification Test (SOIT).

subcutaneous adiposity in adult males was found to be correlated with lower detection thresholds (Hubert et al. 1980). The abilities to detect and identify odors have been found to decrease as body mass index (BMI) increases in subjects less than 65 years old, independent of any linkage to food odor or gender (Simchen et al. 2006). A Swedish population-based odor-identification study, however, found a correlation with serum leptin levels in a gender-dependent manner but not with BMI. This correlation between odor identification and leptin concentration was negative for women and positive for men (Karlsson et al. 2002b). This result is interesting given that BMI should be correlated with circulating leptin levels. Mice made obese through a random mutation in the leptin gene or its receptor actually find food faster than control mice (Getchell et al. 2006); but whether this result arises from increased sensitivity of the olfactory system or from motivation to seek out food as a result of the perception of hunger remains unclear. The ability to correctly identify odors has been both positively (Simchen et al. 2006) and negatively (Hunter-Smith et al. 1996) correlated with BMI in subjects

older than 65. Morbidly obese patients display decreased olfactory acuity (Richardson et al. 2004) and are significantly more likely to have absolute olfactory dysfunction or anosmia (Richardson et al. 2012). In the latter study, the effects of morbid obesity on olfactory function were not reversed by significant weight loss due to gastric bypass surgery, evidence, the authors suggested, that the olfactory dysfunction may have contributed to the obesity rather than the other way around (Richardson et al. 2012). Contributing factors, such as diet, lifestyle, and heredity, are variable across human studies, as are the multitude of complications that result from the excess adiposity. Therefore, it is not surprising that the findings of human olfactory studies are at this time contradictory. Controlled animal studies, in which a variety of obesity models, based on both genetics and diet, are tested for changes in detection threshold and odor discrimination without using food as motivation may be a more direct method to selectively elucidate which aspects of obesity affect olfaction. At this time, human studies collectively appear to indicate that obesity increases the detection threshold of odors, severe obesity

increases the risk for anosmia, and the variations in ability to identify odors with increased adiposity, gender, and age may be due to higher cognitive changes.

### Diabetes

Of the two classical types of diabetes, the correlation of Type-2, the most prevalent form of diabetes, with olfactory dysfunction, has been much more widely studied (Table 3). Type-1 diabetes, also known as insulin-dependent diabetes mellitus, is a result of disrupted insulin production. Type-2, or non-insulin-dependent diabetes mellitus, can be due to a disruption of IR signaling even though circulating insulin levels are high. Type-2 diabetes is associated with insulin resistance and is sometimes a comorbidity of obesity. Regardless of cause, diabetes results in the inability of cells to take up and use glucose properly, leading to high levels of circulating glucose. Diabetes has also been found to decrease odor-identification ability (Le Floch et al. 1993; Weinstock et al. 1993; Naka et al. 2010), increase detection threshold (Jorgensen and Buch 1960; Patterson et al. 1966; Hubert et al. 1980), and increase the risk of anosmia (Bramerson et al. 2004) in humans. In rodent studies, the OB also develops insulin resistance in both genetic and diet-induced obesity models. Obese, insulin-resistant (*fa/fa*) Zucker rats have a decreased level of tyrosine-phosphorylated proteins in the OB and piriform cortex (Livingston et al. 1993). Insulin binding in the OB of obese (*fa/fa*) Wistar Kyoto rats (Figlewicz et al. 1986) and *fa/fa* Zucker rats (Figlewicz et al. 1985) is decreased. Insulin immunoreactivity is more severely decreased in the OB and hypothalamus of *fa/fa* Zucker rats than in other insulin-sensitive parts of the CNS (Baskin et al. 1985). Intranasal delivery of insulin to the OB of lean C57BL/6 mice increases both the autophosphorylation of the IR and tyrosine phosphorylation of one of its known substrates in the OB, Kv1.3 (Marks et al. 2009). Acute application of insulin increases the excitability of mitral cells obtained from lean mice, in a Kv1.3-dependent manner via tyrosine phosphorylation (Fadool et al. 2000; Colley et al. 2004; Fadool et al. 2004; Marks and Fadool 2007; Tucker et al. 2010; Fadool et al. 2011). Diet-induced obesity prevents this autophosphorylation of the receptor and Kv1.3 in response to intranasal delivery of insulin (Marks et al. 2009), modifies baseline firing of mitral cells, and prevents Kv1.3-dependent modulation of activity (Figure 2; Fadool et al. 2011). Chronic intranasal delivery of insulin, designed to mimic hyperinsulemia seen in Type-2 diabetes, also modifies mitral-cell-current-evoked activity and prevents further modulation in response to acute application of insulin (Fadool et al. 2011). How diabetes and obesity affect the sensitivity of the main olfactory epithelium is unknown. Complete anosmia in humans with diabetes can be a result of macrovascular complications (Weinstock et al. 1993); but humans, like rodents, may develop an insulin resistance of the olfactory system, which could disrupt olfactory function.

### Anorexia nervosa

Like olfactory studies of obese patients, studies of anorexia patients are variable. Anorexia nervosa is a psychiatric disease in which the patient has a distorted body perception and a morbid fear of weight gain. The patient uses extreme measures to restrict caloric intake, which result in a dangerously low body weight (Hoek 2006); and as a consequence, they have low levels of serum insulin, leptin (Dostalova et al. 2007), and IGF1 (Misra and Klibanski 2011), and

modified levels of CCK (Tomasik et al. 2005) and BDNF (Lebrun et al. 2006). Odor-detection threshold in anorexic patients has been reported to be both unchanged from (Aschenbrenner et al. 2008; Rapps et al. 2010) and lower than (Roessner et al. 2005; Schreder et al. 2008) that for control patients. One study even reported an increased odor-detection threshold in very-low-weight patients (Fedoroff et al. 1995). Odor discrimination has been found to be both normal (Kopala et al. 1995; Rapps et al. 2010) and reduced (Roessner et al. 2005; Aschenbrenner et al. 2008) in anorexic patients. Odor identification by anorexic patients has been reported to be reduced for a variety of odors (Rapps et al. 2010), only in very-low-weight patients (Fedoroff et al. 1995), and only for food-related odors (Schreder et al. 2008). The hedonic value or pleasantness of food odors has also been found to be reduced in anorexic patients (Schreder et al. 2008); but Jiang and colleagues (2010) found that only the pleasantness of high-calorie food odors presented in the preprandial state was reduced (Jiang et al. 2010; Soussignan et al. 2011). More large-scale studies in humans and with animal models of anorexia are needed to clarify how anorexia and malnutrition modify olfactory function.

### Metabolic disorders and body weight modify the physiological response to odors

Physiological responses to odors are also modified in metabolic disorders. In normal-weight humans, exposure to the sight and smell of food induces salivation. After prolonged exposure, the individual habituates to the food odor, and the salivary response is reduced; but overweight individuals have a higher salivary response (Ferriday and Brunstrom 2010) and anorexic individuals have a lower initial salivary response to the smell of food than control subjects (LeGoff et al. 1988). Obese women do not habituate (Epstein et al. 1996) and have a higher peripheral insulin response (Sjostrom et al. 1980) to the food cue than do lean women. In a functional magnetic-resonance-imaging study in which control and obese patients were fasted overnight and then exposed to a preferred food odor, control and obese patients experienced an increase in brain activity in the reward-related brain regions, including the insular and gustatory cortex, cingulate, and ventral striatum (Bragulat et al. 2010); but obese individuals and lean individuals differed in brain activation to preferred food odors. Obese individuals exhibited higher activation of the hippocampal and parahippocampal regions, whereas lean subjects had higher activation of the posterior insula (Bragulat et al. 2010). This demonstrates a difference in brain activation to preferred food odors between lean and obese individuals.

Olfactory receptor and  $G_{\text{olf}}$  expression are modified in rodent models of metabolic disorders. A recent genome-wide association study of early-onset extreme obesity found a bi-allelic deletion region in chromosome 11q11 encoding three olfactory receptor genes, OR4P4, OR4S2, and OR4C6, in parents and their obese offspring (Jarick et al. 2011). Olfactory receptor 1434 is also expressed in white adipose tissue and is downregulated in Sprague-Dawley rats with diet-induced obesity (Joo et al. 2010). Interestingly, at least 931 olfactory receptors are expressed in the placenta of Swiss mice (Mao et al. 2010). Fifty-two of these were either up- or downregulated at least 2-fold when the mother had been fed either a high-fat or a low-fat diet for 30–35 weeks before pregnancy compared with those of control-fed mothers (Mao et al. 2010). The alpha subunit of the G protein, which is principally used to transduce cAMP-signaling pathways in olfactory transduction,  $G_{\text{olf}}$  is also expressed in

the  $\beta$ -cells of the pancreas and is upregulated in the islets of the GK rat model of insulin-independent diabetes (Frayon et al. 1999). Whether maternal diet, diabetes, or adiposity affects the olfactory receptor or expression of the  $G_{\text{olf}}$  gene in the olfactory system remains unclear and warrants future investigation. These results suggest that expression of olfactory signal-transduction machinery can be modified in response to metabolic disorders and, conversely, that expression of the signal-transduction machinery might in turn contribute to metabolic disorders.

The expression and activity of several proteins found in olfaction-related areas are modified in rodent models of metabolic disorders. As mentioned earlier, insulin and its receptor are expressed in the OM, and insulin is secreted into the OM (Lacroix et al. 2008). Like that in rodents (Lacroix et al. 2008), expression of insulin in the human OM is significantly higher during fasting than after a meal (Henkin 2010), the opposite of that in the plasma. Interestingly, obese, diabetic, and low-weight individuals all have higher levels of insulin in the OM than normal, control-weight individuals (Henkin 2010). Diet-induced obesity in mice increases the expression of serotonin receptor 5-HT<sub>2A</sub> mRNA in the olfactory nucleus, when compared with those of obesity-resistant and control-fed mice and is significantly correlated with adiposity (Huang et al. 2004). Chronic caloric restriction (60% decrease in caloric intake) increases the serotonin metabolite 5-hydroxy-indoleacetic acid (5HIAA) in the OB of male Fisher rats and decreases OB norepinephrine in both male and female Fisher rats (Kolta et al. 1989). In the early stages of diet-induced obesity in C57BL/6 mice, the cannabinoid CB<sub>1</sub> receptor binding is increased in the medial/ventral anterior olfactory nucleus (South and Huang 2008). Leptin receptor mRNA expression is increased (Huang et al. 1997) and NPY subtype-5 receptor mRNA expression is decreased (Xin and Huang 1998) in the piriform cortex of ob/ob obese mice. These are not all of the proteins regulated by diabetes, obesity, and anorexia; but modulation of any of these pathways in olfactory-related brain regions can disrupt normal olfactory processing.

The causes of abnormal body weight and the consequent physiological and endochronological changes are wide ranging (McAllister et al. 2009), resulting in the various changes in olfactory ability mentioned earlier. Moreover, an interesting, growing body of evidence indicates that the olfactory system can in fact modulate energy balance. The OB projects indirectly, through multisynaptic connections, to the suprachiasmatic and paraventricular hypothalamic nuclei and then through either the intermedialateral column of the spinal cord to regulate sympathetic tone or through the dorsal motor nucleus of the vagus to regulate parasympathetic activity (Ruger and Scheer 2009), as summarized in Figure 4. Furthermore, olfactory stimulation has been linked to changes in sympathetic and autonomic activity as well as metabolism. In particular, short-term (10-min) olfactory stimulation with grapefruit oil increases sympathetic neuronal output to epididymal adipose tissue (Nijima and Nagai 2003), intrascapular brown adipose tissue, and the adrenal gland (Shen et al. 2005), whereas it decreases the activity of the parasympathetic gastric (Shen et al. 2005) and renal sympathetic (Tanida et al. 2008) nerves in rodents. Olfactory stimulation with lavender oil, on the other hand, results in opposite effects (Shen et al. 2005; Tanida et al. 2006, 2008). In humans, the smells of pepper, fennel, estragon, and grapefruit oils increases sympathetic activity, whereas those of rose and patchouli oils decrease it, as measured through changes in blood pressure and plasma catecholamine levels (Haze et al. 2002).

Bilateral olfactory bulbectomy studies also reveal evidence of a role for the olfactory system in energy balance and body weight. Olfactory bulbectomy results in energy-balance-related changes, such as weight loss (Hellweg et al. 2007; Primeaux et al. 2007; Tucker et al. 2010) and short-term increases in caloric intake (Meguid et al. 1997; Primeaux et al. 2007), locomotor activity (Hellweg et al. 2007), heart rate, and body temperature (Marcilhac et al. 1997; Vinkers et al. 2009). Evidence also indicates OB-mediated circadian changes with olfactory bulbectomy in several rodent species and at least one primate species (Possidente et al. 1990; Vagell et al. 1991; Possidente et al. 1996; Meguid et al. 1997; Saulea et al. 1998; Perret et al. 2003; Seguy and Perret 2005; Vinkers et al. 2009). Furthermore, olfactory bulbectomy prevents the diet-induced obesity resistance of the “Super-smeller” Kv1.3-null mice (Tucker et al. 2010, 2012). These results suggest that the olfactory system can modulate pathways critical to the regulation of energy balance.

### Future investigations into neuroendocrine drivers of the olfactory system

Research in the last decade has shown that nutritional and metabolic state can modulate olfactory responses at the initial detection stage of olfactory cues in the OM, up through the relay of information and olfactory processing in the OB, and beyond. Inversely, the sense of smell is an important partner of food intake and regulation. One of the future challenges will be to understand the degree of crosstalk between external odor signals and internal metabolic cues and whether such potential regulation is a short- or long-term process.

Because receptors to metabolic signaling pathways are expressed in the same locale as the olfactory signal-transduction machinery, what degree of crosstalk might exist between, for example, ORs activated by inhaled odor and metabolic receptors activated by peptides diffusing from blood vessels or secreted by paracrine/autocrine pathways? The degree of functional interaction is completely unexplored. Ambrosio et al. (2011) and Rediger et al. (2011) propose a physical interaction between hormone receptors and G-protein-coupled receptors (i.e., GHSR, OXR, and NPY receptors) as heterodimer-inducing signaling cascades. Such types of protein–protein interactions have been reported for ORs and the  $\beta$ -adrenergic receptor (Hague et al. 2004) or the mACh receptor (Li and Matsunami 2011), the latter of which was shown to enhance OR signaling *in vitro*. Because there are few details regarding metabolic-receptor-signaling pathways in olfactory tissues as opposed to the wealth of details known for classical and noncanonical olfactory signal-transduction cascades, this is an obvious line of investigation needed to uncover potential crosstalk between pathways leading to fine regulation.

Another promising area for future study is the challenge of the regenerative OM combined with the need for internal metabolic homeostasis. Knowledge of the health and cellular dynamics of the OM are important as we continue to explore the therapeutic use of basal cells for cell therapy targeted against neurodegenerative diseases. The OM is under regulation by neurotrophic factors as well as metabolic peptide hormones; therefore, neuroprotective, apoptotic processes and neuroproliferation of this organ likely involve a delicate balance of endogenous factors and metabolic signaling (e.g., Lacroix et al. 2011). All of these, of course, will affect olfactory perception. The dialogue between OSNs and sustentacular cells is likely an important element of OM homeostasis

and survival, as is the putative role of recently discovered glucose transporters in the OM to mediate proper metabolic demands and interrelationships.

In the OB, metabolic receptors are present on neurons, astrocytes, and fibers originating from the brain stem. The current data set concerning the regulation of OB cell firing by metabolic hormones were recorded at mitral cell bodies. We know little about modulation of other neuronal cell types or their synaptic communications. Moreover, a variety of imaging approaches are available (Pain et al. 2011), and when combined with specific metabolic and transgenically modified mammalian models, could help to understand the cellular regulation taking place at the initial OSN/mitral cell synaptic level and then across the OB network.

At the most integrated level, psychophysical data in patients remain controversial; but they are needed to suggest new indicators in the evaluation of nervous pathologies associated with metabolic disorders and complementary treatments based on intranasal delivery or sensory conditioning. Vertebrate animal models of metabolic dysfunction and diet-induced obesity are predicted to facilitate the discovery of olfactory changes due to chronic imbalance in metabolism. Although current data suggest perturbation of electrical signaling in the OB after diet-induced obesity, the biochemical and anatomical correlates and the potential impact on olfactory behavior has been largely unexplored and necessitates full investigation.

## Conclusion

Energy balance and olfaction are intimately linked. Metabolic disorders that disrupt energy balance perturb olfactory ability by changing protein expression in olfactory-related areas, chronically changing circulating levels of molecules that modify olfactory ability in response to feeding state and changing the pattern of brain activation in response to food odors. The OM and OB express many receptors and peptides that are traditionally considered to be related to feeding and are therefore well positioned to detect changes in both peripheral and central hormone and glucose levels. The projections to and from the OB allow ample opportunity for crosstalk between the olfactory system and the hypothalamus. Furthermore, the olfactory system has been shown to influence energy balance by modulating caloric intake and metabolism. The olfactory system is not simply a sensor of external chemical cues, but a parallel detector of internal chemical cues—the chemistry of metabolism.

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