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# Effects of nicotine on homeostatic and hedonic components of food intake

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## Abstract

Chronic tobacco use leads to nicotine addiction that is characterized by exaggerated urges to use the drug despite the accompanying negative health and socioeconomic burdens. Interestingly, nicotine users are found to be leaner than the general population. Review of the existing literature revealed that nicotine affects energy homeostasis and food consumption via altering the activity of neurons containing orexigenic and anorexigenic peptides in the brain. Hypothalamus is one of the critical brain areas that regulates energy balance via the action of these neuropeptides. The equilibrium between these two groups of peptides can be shifted by nicotine leading to decreased food intake and weight loss. The aim of this article is to review the existing literature on the effect of nicotine on food intake and energy homeostasis and report on the changes that nicotine brings about in the level of these peptides and their receptors that may explain changes in food intake and body weight induced by nicotine. Furthermore, we review the effect of nicotine on the hedonic aspect of food intake. Finally, we discuss the involvement of different subtypes of nicotinic acetylcholine receptors in the regulatory action of nicotine on food intake and energy homeostasis.

## Key Words

- ▶ nicotine
- ▶ food intake
- ▶ obesity
- ▶ orexigenic peptides
- ▶ anorexigenic peptides

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## Introduction

Food intake is a complex physiological process necessary for the survival, and is affected by both homeostatic mechanisms as well as palatability of food. The homeostatic mechanisms involved in the regulation of food intake and energy expenditure include endocrine factors, such as hormones released from the pancreas and gastrointestinal neuroendocrine cells and adipose tissues, as well as gut/brain reflexes activated via the autonomic nervous system by peripheral signals from more than 20 regulatory hormones (Wren & Bloom 2007, Kobeissy *et al.* 2008, Suzuki *et al.* 2010, Harwood 2012). Neural afferents and hormonal signals from the periphery are then

integrated with neuronal circuits located in the central nervous system (CNS) implicated in the control of reward drive and mood to regulate appetite and control energy balance (Sam *et al.* 2012, Murray *et al.* 2014).

The hypothalamus along with the nucleus of the solitary tract (NST) in the brain stem, are the major brain regions responsible for the control of energy homeostasis, whereas the mesolimbic dopaminergic neurons and other brain areas, involved in motivation and emotion, are in charge of the hedonic aspects of food intake (Kelley & Berridge 2002, Naleid *et al.* 2005). Hypothalamic neurons largely project to extrahypothalamic regions such as

amygdala and the bed nucleus of stria terminalis (BNST), establishing connections between metabolism and eating behaviors (Nestler 2005, Rinaman 2010).

There are two major neuronal areas in the hypothalamus identified as regulators of food intake: the ventromedial hypothalamus (VMH), recognized as the appetite-suppressing center, and the lateral hypothalamus (LHA), involved in appetite stimulation (Anand & Brobeck 1951). Subsequent studies have found the arcuate nucleus of hypothalamus (ARC) as another hypothalamic region with relevant functions in the control of food intake, since specific lesions performed in experimental animals at this level were found to promote food intake (Hamilton *et al.* 1976).

The ARC is located in the VMH and is characterized by the presence of two distinct, but intermingled neuronal populations, which have opposite effects on feeding behavior: the anorexigenic proopiomelanocortin (POMC) neurons and the orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons. The localization of these neurons as well as the rich innervations of the area, permit an easy access of the information coming from peripheral organs as well as from multiple parts of the CNS, making the POMC and NPY/AgRP neuronal groups integrating components of peripheral and central inputs to modulate feeding behavior (Gropp *et al.* 2005, Aponte *et al.* 2011).

Earlier studies based on stimulation of specific neuronal populations have demonstrated that direct activation of POMC neurons lead to suppression of food intake (Zhan *et al.* 2013). Later, it was shown that activation of POMC neurons suppresses appetite by causing the release of  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH), the endogenous melanocortin receptor agonist (Smart & Low 2003); whereas, AgRP neurons inhibit POMC neurons possibly by directly blocking melanocortin receptors (Aponte *et al.* 2011).

Tobacco users have been reported to weigh less compared to their same sex- and age-matched non-smokers (Albanes *et al.* 1987). In contrast, cessation of smoking has been associated with increased food intake, decrease in metabolic rate and concomitant weight gain (Stamford *et al.* 1986, Filozof *et al.* 2004). Indeed, in the first year after cigarette cessation, ex-smokers have been shown to gain on average about 10 pounds (Audrain-McGovern & Benowitz 2011). Notably, this weight gain during abstinence represents an obstacle in smoking cessation because it serves as a motivating factor in former addicts to relapse to tobacco use (Donny *et al.* 2011).

The regulation of feeding and energy metabolism involves two interacting brain circuits: a homeostatic

system centered in the hypothalamus and a hedonic system composed of the cortico-limbic-striatal circuits (Zoli & Picciotto 2012). Several studies have demonstrated that nicotine reduces body weight by increasing energy expenditure and inhibiting food intake (Hofstetter *et al.* 1986, Perkins 1992), and that those effects are the result of the modulatory effect of nicotine on both metabolic processes and reward circuits (Blendy *et al.* 2005, Porter 2017). Studies performed in rodents have shown that nicotine exert pleasurable effects, similar, although weaker than cocaine and other addictive drugs (Risner & Goldberg 1983). Furthermore, continuous subcutaneous administration of nicotine in obese rats under high-fat diet reduces food intake and suppresses further weight gain (Seoane-Collazo *et al.* 2014), indicating that these effects of nicotine are the result of the modulatory effects of nicotine on metabolic processes and reward circuits (Blendy *et al.* 2005, Porter 2017).

Nicotine exerts its effects on energy homeostasis via nicotinic acetylcholine receptors (nAChRs). These receptors are widely expressed throughout the central and peripheral nervous systems and particularly well positioned in the hypothalamus to alter the expression, secretion or function of neuropeptides that regulate appetite and food intake, thereby modulating energy homeostasis and feeding behavior. Nicotine has also been shown to change the levels of certain peptides in the periphery, by acting on nAChRs located in taste, visceral and nociceptive vagal afferent pathways, which also play a functional role in the ability of nicotine to alter food intake (Boucher *et al.* 2003, Mao *et al.* 2006, Dani & Bertrand 2007, Oliveira-Maia *et al.* 2009).

Our goal is to describe the effects of nicotine in the functional features of the input, output and central integration systems that regulate the expression of the peptides present in the gastrointestinal tract, adipocytes and hypothalamus to regulate the homeostatic and hedonic aspects of food intake.

## Effects of nicotine on energy homeostasis

Homeostasis in mammals is an intricate process aimed to maintain a delicate balance between food intake, energy expenditure and thermogenic activity. Most of the chemical reactions in the cell are pointed at making the energy in foods available to the various physiologic systems in the cell. All the energy in foods such as carbohydrates, fats and proteins, can be oxidized in the cells, and during this process, large amounts of energy are released with the ultimate goal of producing adenosine

triphosphate (ATP) for the cells (Suzuki *et al.* 2010, Myers & Olson 2012).

ATP is a labile compound with a structure characterized by the presence of two last phosphate radicals with high-energy bonds, consisting of about 12,000 calories under the usual physiologic conditions in the human body. Therefore, the removal of each radical in the body liberates about 12,000 calories of energy. If only one of those high-bond phosphates is lost, ATP is converted to adenosine diphosphate (ADP). When the second phosphate is liberated, ATP becomes adenosine monophosphate (AMP). The energy provided by ATP is not heat, but energy for the conduction of nerve impulses, for the active transport of molecules, to cause mechanical movement in the case of muscle or to concentrate solutes in the case of glandular secretion among others (De la Fuente *et al.* 2014).

Energy homeostasis is also dependent on thermogenic activity. Brown adipose tissue (BAT) is a specialized tissue critical for non-shivering or adaptive thermogenesis producing heat through mitochondrial uncoupling. BAT, and the newly described brite ('brown in white') adipose tissue (Harms & Seale 2013), are crucial organs in facultative thermogenesis (acute response) and have a great plasticity to respond to long-term changes (e.g. cold acclimation (Harms & Seale 2013, Vosselman *et al.* 2013). BAT mitochondria are distinct from their counterparts in other tissues in that ATP production is not their primary physiologic role. The inner mitochondrial membrane of BAT is loaded with the uncoupling protein-1 (UCP1). When activated, UCP1 allows protons in the intermembrane space to re-enter the mitochondrial matrix without generating ATP. As a consequence, heat is generated from the combustion of available substrates and is distributed to the rest of the body through the circulation (Vosselman *et al.* 2013, Contreras *et al.* 2017, Crichton *et al.* 2017, Porter 2017).

Thermogenesis by UCP1 in BAT is triggered by the release of noradrenaline from sympathetic nerve terminals regulated by the hypothalamus (Lowell & Spiegelman 2000, Kelley & Berridge 2002, Cano *et al.* 2003). Interestingly, it has been shown that acute or chronic nicotine exposure upregulates thermogenesis in BAT. Nicotine increases activity of lipoprotein lipase, improving lipid profile in rats by decreasing cholesterol and low-density lipoprotein (Chajek-Shaul *et al.* 1994) and inhibits fatty acid synthase in cell cultures of adipocytes (An *et al.* 2007). Moreover, microinjection of nicotine (0.5 mg/kg) into the preoptic area (POA) or the dorsomedial hypothalamus (DMH), but not the paraventricular nucleus (PVN) of rats, increases

BAT sympathetic nerve activity and BAT temperature through the activation of corticotropin releasing hormone/factor type 1 (CRH1/CRF1) receptors, indicating that one of the mechanisms for nicotine to affect energy homeostasis, is by eliciting the thermogenesis of BAT in the hypothalamus.

In this regard, it is noteworthy to state that nicotine elicits some of its actions via the endogenous opioid enkephalin (Berrendero *et al.* 2005), which has been implicated in being process, where white fat is converted to brown fat (Brestoff *et al.* 2015). Considering that brown fat is metabolically active and leads to greater energy utilization and thus body weight loss, it is possible that nicotine causes an increase in the expression of enkephalins in fat cells, inducing greater proportion of white to brown fat conversion. Indeed, nicotine has been shown to increase thermogenesis in BAT and also increase its mass via the adrenergic nervous system (Wager-Srdar *et al.* 1984, Lupien & Bray 1988, Yoshida *et al.* 1990, 1999). However, as stated above, enkephalin may be involved in this process. Thus, further studies are needed to assess if this action of nicotine is exerted via the endogenous enkephalins, and if this response mediates the ability of nicotine to reduce food intake and alter energy homeostasis. Additionally, it would be essential to explore whether this response is mediated via an action of nicotine on expression of enkephalin locally in white adipocytes. Furthermore, given that enkephalin is implicated in the rewarding action of nicotine, it is crucial to determine if enkephalin plays any functional role in the regulatory action of nicotine on hedonic aspect of food intake.

Adipose tissue plays a critical role in the maintenance of energy homeostasis through the secretion of adipokines, which interact with central as well as peripheral organs such as the brain, liver, pancreas and skeletal muscle to control carbohydrate metabolism, lipid metabolism, energy expenditure and feeding behavior (Scherer *et al.* 1995). Adiponectin, an adipokine secreted by the white adipose tissue (WAT), and present at high concentrations in the circulation, has been shown to be negatively correlated with body weight, body fat mass, degree of insulin resistance and weight reduction in obese individuals (Yamauchi *et al.* 2001, 2007, Kadowaki *et al.* 2006). Studies based on central administration of adiponectin in rodents, found that the animals presented significant weight and fat mass loss than their vehicle-treated counterparts, and that this decrease was a consequence of the increase in energy expenditure (stimulation of lipid oxidation by peripheral action on muscle and liver) independent of

food intake, consistent with centrally mediated effects (Qi *et al.* 2004) (Kubota *et al.* 2007). Likewise, studies based on receptor-binding assays to evaluate the effect of nicotine on the function of adipocytes, revealed the presence of nAChRs in adipose tissues, and that both short- or long-term exposure to nicotine stimulates the secretion of adiponectin into the culture medium, indicating that nicotine modulates food intake and body weight at least in part by an increase in the secretion of adiponectin through the activation of nAChRs (Liu *et al.* 2004). Clinical studies aimed to evaluate the changes of plasma adiponectin levels after smoking cessation, showed that the mean plasma adiponectin levels of the participants, when compared to the baseline, were significantly increased after 4 weeks of nicotine withdrawal (Won *et al.* 2014). Moreover, levels of adiponectin were directly related to weight gain after smoking cessation (Inoue *et al.* 2011), suggesting that nicotine regulates body weight by controlling adipose tissue homeostasis.

Nicotine has been shown to regulate many processes of energy balance by modulating the actions of AMP-activated protein kinase (AMPK). AMPK integrates hormonal and nutritive signals in peripheral organs and hypothalamus, thereby playing a major role in regulation of energy balance (Kahn *et al.* 2005). Activated in state of low energy balance, AMPK stimulates feeding behavior by modulating mitochondrial fatty acid oxidation in the hypothalamus, and its activity is regulated by changes in the expression of neuropeptides in the ARC (Minokoshi *et al.* 2004, Lopez *et al.* 2008). For example, the AgRP increases the activity of AMPK in the hypothalamus, whereas AMPK activity is inhibited by leptin in the ARC and PVN, as well as by insulin in multiple hypothalamic areas (Minokoshi *et al.* 2004). Likewise, changes in the activity of AMPK in the hypothalamus regulate the expression of these neuropeptides (Minokoshi *et al.* 2004).

Studies performed in rats showed that nicotine downregulates AMPK activity in the hypothalamus, and this effect mediates a decrease in food intake and BAT activation, as well as an increase in lipid oxidation. Conversely, genetic overactivation of AMPK in VMH can reverse nicotine-induced weight loss and normalize the mRNA levels of NPY, AgRP and POMC in ARC (Martinez de Morentin *et al.* 2012). Taken together, these data suggest that nicotine, by acting at peripheral and central levels, modulates food intake and energy homeostasis and controls the expression of several neuropeptides in the fat cells and hypothalamus to exert its regulatory action on food intake and energy expenditure.

### Effects of nicotine on central regulatory mechanisms of energy homeostasis

Food intake is a process controlled by the CNS, and it is stimulated by sensations such as hunger, craving, pleasure and reward (Schwartz *et al.* 2000). The hypothalamus is the main brain region responsible for the control of food intake via the actions of certain neuropeptides that are secreted from two groups of neurons in ARC (Cone 2005). One neuronal population secretes orexigenic peptides, such as NPY and AgRP that stimulate appetite, whereas the other set of neurons express anorexigenic peptides, such as  $\alpha$ -MSH, a product of POMC, and the cocaine- and amphetamine-regulated transcript (CART), that suppresses appetite (Meister 2000, Lenard & Berthoud 2008). Activation of NPY/AgRP-secreting neurons results in increased food intake, whereas stimulation of POMC/CART containing neurons leads to decreased food intake. AgRP and  $\alpha$ -MSH act on melanocortin-3 and 4 receptors (MC3R and MC4R) to regulate feeding behavior. The AgRP is an inverse agonist, while  $\alpha$ -MSH acts as an agonist of melanocortin receptors (MCR).

The neurons that secrete orexigenic and anorexigenic peptides predominantly project to other neurons located in the PVN, lateral hypothalamic area (LHA), perifornical area (PFA), ventromedial (VMN) and dorsomedial nuclei (DMN), establishing an anatomical and functional connection between these nuclei where the neuropeptides that they express can modulate eating behaviors (Schwartz *et al.* 2000, Ramos *et al.* 2005).

Smokers are reported to have reduced level of NPY, whereas smoking cessation is linked with increased levels of NPY (Hussain *et al.* 2012). In animal studies, mice chronically exposed to low-dose nicotine showed decreased NPY levels in the PVN (Chen *et al.* 2007) and ARC (Frankish *et al.* 1995), as well as reduced NPY receptor density in the hypothalamus (Kane *et al.* 2001), together with a nicotine-dependent increase in the activity of POMC neurons (Huang *et al.* 2011). This suggests that chronic administration of nicotine, by decreasing the level of NPY and upregulating the activity of POMC neurons, may negatively affect food intake and energy balance. However, further research is needed in this area to establish a causal relationship between weight gain and increased NPY levels in the hypothalamus following nicotine cessation.

Two other neuropeptides involved in regulation of feeding behavior are melanin-concentrating hormone (MCH) (Van Bockstaele *et al.* 2000) and hypocretin (also known as orexin), both of which are produced in the

lateral hypothalamus (Skofitsch *et al.* 1985). It has been shown that the increase in either MCH or hypocretin stimulates food intake (Qu *et al.* 1996, de Lecea *et al.* 1998). Interestingly, self-administration of nicotine in rats has been associated with increased expression of hypocretin receptor mRNA in ARC (LeSage *et al.* 2010). The modulation that nicotine exerts on the expression of peptides in ARC is more significant by considering that ARC also integrates the signal coming from peripheral organs and the rest of the CNS in order to execute the command for feeding behavior. For example, when the level of sugar rises in the blood circulation, it leads to the release of insulin from the pancreas, which not only increases the uptake of sugar by the muscle and liver, but also inhibits NPY/AgRP-containing neurons and stimulates POMC/CART-containing neurons in the ARC, leading to satiety. Similar effect is induced by leptin released from the fat cells (Schwartz *et al.* 2000). Thus, nicotine regulates energy homeostasis by influencing the secretion of insulin and leptin by regulating the expression of neuropeptides in specific hypothalamic nuclei.

Hypothalamic neurons also produce endocannabinoids, which play a critical role in maintaining a precise equilibrium between caloric intake and energy expenditure, storage and transport, factors that keep body weight stable over time (Valassi *et al.* 2008, Cristino *et al.* 2014).

The endocannabinoid system is composed of the cannabinoid receptors (CB1 and CB2), their endogenous ligands, like N-arachidonylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), the enzymes that produce and inactivate endocannabinoids, and endocannabinoid transporters (Piomelli 2003, Gardner 2005). Cannabinoid CB1 receptors are present in the ventral tegmental area (VTA) and the nucleus accumbens (NAc) and in several areas projecting to these two structures, including the prefrontal cortex, central amygdala and hippocampus, and they appear to play an important role in brain reinforcement/reward processes (Maldonado *et al.* 2006, Solinas *et al.* 2008).

Recent studies have implicated endocannabinoids in the pharmacological and behavioral effects of nicotine. For example, chronic nicotine injections increased endocannabinoids levels in the limbic forebrain and brainstem, but decreased levels in the hippocampus, striatum and cerebral cortex (Gonzalez *et al.* 2002), the same areas involved in the reinforcing/rewarding effects of addictive drugs (Koob *et al.* 1998). Moreover, a CB1 receptor antagonist, rimonabant, decreased nicotine self-administration and conditioned place preference

(CPP) in rats (Cohen *et al.* 2004, Le Foll & Goldberg 2004), indicating that endocannabinoid signaling is involved in nicotine reinforcement and reward. Endocannabinoids stimulate appetite through different brain regions, such as limbic system (responsible for hedonic evaluation of food), hypothalamus, hindbrain, but also peripherally, at the level of adipose tissue and intestinal system (Fride *et al.* 2005). Blocking CB1 receptor in mice reduces appetite and lipogenesis in WAT (Cota *et al.* 2003). Chronic nicotine administration was shown to reduce body weight in wild-type, but not in CB1<sup>-/-</sup> mice (Bura *et al.* 2010), suggesting that nicotine-mediated weight loss might be by the endocannabinoid system. More specific genetic approach in mice demonstrated that targeted deletion of CB1 receptor in cortical glutamatergic neurons reduces food intake (Bellocchio *et al.* 2010), suggesting that the decrease level of endocannabinoids in cortex observed with chronic nicotine administration (Gonzalez *et al.* 2002) might represent one of the mechanisms of nicotine-induced weight loss.

Interplay between rewarding effect of food and nicotine was also found in human studies where neuronal circuits activated by food rich in sugar and fat overlapped with those observed by smoking (Volkow *et al.* 2008). Moreover, absence of smoking increases the reward threshold for food (Kenny & Markou 2006), suggesting that greater amount of highly rewarding food is sought in order to satisfy the rewarding effect previously achieved with nicotine (Spring *et al.* 2003). An intriguing proposal is that nicotine may hijack the reward circuit and devalue the motivational valence of food, thereby leading to decrease in food intake. However, further studies are needed to test this possibility.

Additionally, nicotine has been shown to activate the hypothalamic–pituitary–adrenal (HPA) axis, as shown by increases in the level of the stress hormone, i.e., cortisol in human/corticosterone in rodents (Rohleder & Kirschbaum 2006). This process involves the release of CRH/CRF, which is known to exert anorexigenic effect (Glowa & Gold 1991, Uehara *et al.* 1998). Thus, it is possible that nicotine, by activating the HPA axis and causing the release of CRH exerts its inhibitory effects on food intake. However, further studies are needed in this area to test this possibility and related research questions.

### Effects of nicotine on peripheral regulatory mechanisms of energy homeostasis

The metabolic status of the body is also dependent on endocrine signals produced by the gastrointestinal

system. Enteroendocrine cells of the gastrointestinal tract produce and release hormones to promote appetite (such as ghrelin) or satiety (e.g., cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide tyrosine tyrosine (PYY) and serotonin). Administration of serotonin in the PVN, VMH and DMN of rats results in inhibition of food intake (Sleight *et al.* 1995, Leibowitz & Alexander 1998). Ghrelin is an important hormone produced by the enteroendocrine cells of the gastric fundus and is released before a meal and its amount is reduced after a meal. Ghrelin regulates appetite by stimulating the AgRP- and NPY-containing neurons in the ARC as well as the NST, which in turn increases food intake (Gil-Campos *et al.* 2006).

Nicotine has been shown to alter mRNA expression and plasma levels of several gastrointestinal hormones (Chowdhury *et al.* 1990, Gomez *et al.* 1996). For example, smoking in human subjects acutely elevated the plasma level of ghrelin, an orexigenic hormone (Bouros *et al.* 2006). In another study, total plasma ghrelin levels were measured before and after smoking two cigarettes in non-smokers and habitual smokers who underwent overnight fasting and also remained abstinent from smoking. It was found that the total plasma ghrelin level declined progressively in non-smokers, but not in smokers (Kokkinos *et al.* 2007). Given that the fasting plasma ghrelin level was similar between habitual smokers and non-smokers, the authors concluded that the decline in plasma ghrelin induced by acute nicotine may be blunted in smokers due to desensitization as a result of habitual nicotine use (Kokkinos *et al.* 2007). Furthermore, the plasma ghrelin levels decrease following two months of successful abstinence from nicotine (Lee *et al.* 2006), and that systemic elevation of plasma ghrelin occurred in acute but not in chronic smokers (Bouros *et al.* 2006), indicating that the desensitization induced by chronic nicotine exposure is overcome after nicotine cessation. Ghrelin was shown to increase food intake and this response was reduced by systemic administration of mecamylamine, a centrally acting nAChR antagonist, despite the animals were fasted overnight. In contrast, the peripherally acting nAChR antagonist, hexamethonium, failed to alter food intake in these animals, suggesting that the ability of ghrelin to increase food intake is mediated at least in part via the central nAChRs (Dickson *et al.* 2010). Additionally, fasting-induced food intake was reduced by mecamylamine in this study, suggesting that rewarding properties of food is mediated via the nAChRs, and this response might be reduced in smokers due to

desensitization of nAChR as a result of chronic nicotine use, thereby giving a possible explanation for reduced food intake in smokers.

Leptin and insulin have overlapping intracellular signaling mechanisms and exert anorexigenic actions in the hypothalamus. Leptin, which is secreted predominantly from WAT, provides feedback information on the amount of fat stores to the ARC, PVN, LHA and the DMN of the hypothalamus, by acting on the long form of the leptin receptor (OB-Rb) (Meister 2000, Woods & D'Alessio 2008). Leptin binding to OB-Rb in hypothalamus initiates tyrosine phosphorylation by janus tyrosine kinase 2 (JAK2). Phosphorylated JAK2 recruits and phosphorylates signal transducer and activator of transcription 3 (STAT3). The activated STAT3 dimerizes and translocate to the nucleus, stimulating gene transcription (Vaisse *et al.* 1996). Studies aimed to investigate the consequences of nicotine exposure during lactation, showed that offspring of lactating rats infused with nicotine (6 mg/kg per day), a dose that produces serum nicotine levels similar to those observed in typical smokers, results in lower expression of OB-R, JAK2 and phosphorylated STAT3 with higher suppressor of cytoskeleton signaling 3 (SOCS3) expression in the hypothalamus, indicating that nicotine induces leptin resistance via the same intracellular pathways as leptin (de Oliveira *et al.* 2010). Chronic administration of nicotine in rats was shown to increase expression of Ob-Rb and leptin-binding sites within the hypothalamus of rats, while plasma leptin level remained reduced in WAT and BAT (Li & Kane 2003). In a different study, chronic nicotine use in the form of nicotine gum or cigarette smoking caused an increase in circulating leptin level compared to control subjects, which was linked to the low body weight in nicotine users than control (Eliasson & Smith 1999).

Insulin is also a critical regulator of energy homeostasis. As with leptin, insulin receptors are widely distributed in the brain, with higher concentrations in the ARC. *In vivo* and *in vitro* data have demonstrated that both leptin and insulin exert their metabolic functions by activating similar signaling pathways, including those that promote glucose uptake and glycogen storage through activation of JAK2, that in turn phosphorylates insulin receptor substrate 2 (IRS2) to activate phosphoinositide 3-kinase (PI3K), thereby increasing SOCS3 expression (Tanaka *et al.* 2009, Burgos-Ramos *et al.* 2011). Interestingly, there are reports that chronic nicotine administration (3 mg/kg/day/subcutaneously) for 6 weeks enhances insulin sensitivity in normal rats, by activating hypothalamic

$\alpha$ 7-nAChR-STAT3 signaling pathway (Xu *et al.* 2012), the same pathway used by leptin to control appetite and body weight, as well as lipid and energy metabolism. Long-term oral nicotine administration reduces insulin resistance in obese rats (Liu *et al.* 2003). Furthermore, oral administration of  $\alpha$ 7-nAChR-selective agonist in leptin-resistant db/db obese mouse for 7 weeks prevented further weight gain, reduced food intake and improved plasma glucose level (Marrero *et al.* 2010). Likewise, nicotine infusion via osmotic minipumps showed differential effects on leptin levels, a decrease in the levels of leptin was observed after 4 days of nicotine administration, whereas an increase was observed when nicotine infusion was continued for 14 days compared with their respective controls (Arai *et al.* 2001). Interestingly, the increase in leptin levels was also dependent on the type of adipose tissue, being higher in omentum, retroperitoneal and epididymal WAT (Arai *et al.* 2001), suggesting that long-term nicotine administration induces tissue-selective leptin secretion.

With regard to insulin, it has been demonstrated that rats fed with high-fat diet and treated with daily subcutaneous nicotine injections for 8 days, show a significant reduction in body weight, food intake, insulin levels, improved serum lipid profile and reduced hepatic steatosis (Seoane-Collazo *et al.* 2014), indicating an improvement in insulin sensitivity. However, studies with chronic administration of nicotine using minipumps for 4 weeks in mice showed AMPK $\alpha$ -dependent nicotine-induced insulin resistance (Wu *et al.* 2015). Clinical studies aimed to investigate the effects of chronic nicotine on leptin levels showed that leptin secretion was negatively correlated with chronic nicotine consumption and that leptin plasma concentration increases 8 weeks after cessation of smoking, in proportion to the gain in body weight (Eliasson & Smith 1999). Overall, these studies suggest that chronic administration of nicotine may have positive outcome on metabolism in obesity and that the increase of leptin observed after chronic administration of nicotine, may be the result of the increase of plasma insulin concentration as a consequence of the insulin resistance induced by long-term tobacco smoking.

The report of the pathways by which nicotine acts to enhance insulin and leptin sensitivity gives a better perspective on the real effects of nicotine on energy homeostasis, since results from clinical and animal studies are inconsistent. Some clinical studies reported that nicotine infusion acutely impairs insulin sensitivity in type 2 diabetic patients and smokers but not in healthy

subjects (Axelsson *et al.* 2001, Morgan *et al.* 2004). Long-term nicotine gum or nicotine patch replacement in previous smokers is associated with insulin resistance (Assali *et al.* 1999). These discrepancies between clinical and animal studies may be the result of difference in the duration and route of nicotine administration as well as the nutritional status of the subjects.

Leptin exerts its regulatory actions on food intake via homeostatic and reward mechanisms. During fasting, the levels of circulating leptin decreases, resulting in the activation of NPY- and AgRP-containing neurons and the secretion of the orexigenic peptides (NPY and AgRP) (Enriori *et al.* 2006, Ahima 2008), which induces feelings of hunger (Schwartz *et al.* 2000). In a fed state, an increase in leptin level stimulates the secretion of anorexigenic peptides, such as  $\alpha$ -MSH and CART from ARC that projects to the LHA and PFA, resulting in satiety sensation (Stanley *et al.* 1993, Ahima 2008).

Similarly to leptin, insulin acts in the ARC during feeding phase and its action is to inhibit NPY/AgRP- and stimulate POMC-containing neurons to prevent further food intake and contribute to the feeling of satiety (Plum *et al.* 2006). Moreover, it has been shown that intracerebroventricular administration of PI3K inhibitors in rodents, blocks the ability of leptin and insulin, but no other anorexigenic substances, to reduce food intake, indicating that both hormones utilize the same intracellular pathways and confirming the importance of their interaction in the maintenance of metabolic homeostasis (Niswender *et al.* 2003).

As with leptin and insulin, nicotine also regulates metabolic homeostasis at both peripheral and central levels, although the exact mechanisms have not yet been elucidated (Tweed *et al.* 2012). Clinical studies in populations with metabolic syndrome show that, independent of the weight, there are discrepancies in the distribution of adipose tissue. Some studies have reported that chronic smoking actually increased fat accumulation, which was accompanied with central obesity and insulin resistance (Barrett-Connor & Khaw 1989). Similar studies showed that smokers have higher level of plasma triglycerides and lower level of high density lipoprotein cholesterol (HDL) (Facchini *et al.* 1992). Long-term smokers had higher waist-to-hip ratio compared to non-smokers, even though they were not heavier than non-smokers (Kim *et al.* 2012). Moreover, the waist-to-hip ratio correlated with increase in the number of cigarettes consumed (Clair *et al.* 2011). A positive correlation was found between body mass index (BMI) and increase in cigarette smoking in obese



and morbidly obese subjects, suggesting that smoking might be more rewarding in this population (Chiolo *et al.* 2008). Besides, it has been reported that diabetic patients have lower rate of smoking cessation than non-diabetic smokers (Solberg *et al.* 2004, Gill *et al.* 2005). In conclusion, the effects of smoking on specific metabolic outcomes is somewhat complex, as smoking seems to contribute to weight loss in obese populations, while contributing to the development of central obesity and type-2 diabetes in lean smokers. Further research is needed in this area to define the underlying mechanism of this dichotomy.

### Role of nicotinic receptors in regulation of energy homeostasis

Nicotine exerts its effects on energy homeostasis via nAChRs (Benowitz 2010). The nAChRs are widely expressed throughout the brain and particularly well positioned in the hypothalamus (Wada *et al.* 1989, O'Hara *et al.* 1998), to alter the function of neurons containing neuropeptides that regulate appetite and food intake, thereby modulating energy homeostasis and feeding behavior (Mineur *et al.* 2011). Nicotine has also been shown to change the level of certain peptides in the periphery that may also play a functional role in the ability of nicotine to alter food intake. The nAChRs are also found in brain areas involved in motivation and reward (Naude *et al.* 2016) and thus may be involved in the actions of nicotine on hedonic aspect of food intake (Lutter & Nestler 2009).

The nAChRs are ligand-gated ion channels comprising five transmembrane subunits, which may be arranged in a  $\alpha\beta$ -combinations ( $\alpha 2$ – $\alpha 6$  and  $\beta 2$ – $\beta 4$ ; e.g.,  $\alpha 3\beta 4^*$  containing nAChRs; the asterisk refers to one or more additional subunits that could be associated with the receptor), homomeric nAChRs ( $\alpha 7$ – $\alpha 9$ ) and a heteromer  $\alpha$ -combination ( $\alpha 9$  with  $\alpha 10$ ) (McGehee *et al.* 1995, Jones *et al.* 1999, Dani & Bertrand 2007). An earlier *in situ* hybridization study showed that there are moderate-to-high levels of expression of  $\alpha 4$ ,  $\alpha 7$  and  $\beta 2$  mRNA in the hypothalamus (Jo *et al.* 2002), suggesting that these nAChRs subunits might be predominately involved in the regulation of appetite control by nicotine. Depending on the dose and duration of nicotine exposure, nAChRs can either be desensitized or upregulated, thereby leading to different metabolic and behavioral effects by nicotine.

### Control of feeding by nicotinic cholinergic $\alpha 3\beta 4$ subunit-containing receptors

Nicotine has been shown to reduce food intake and weight gain by modulating the function of melanocortin system through  $\alpha 3\beta 4^*$ -containing nAChRs (Mineur *et al.* 2011). In particular, nicotine activates  $\alpha 3\beta 4^*$  nAChRs expressed on POMC neurons in the ARC nucleus of the hypothalamus (Mineur *et al.* 2011) that project to the PVN. Binding of nicotine to  $\alpha 3\beta 4^*$  nAChRs leads to depolarization of POMC-containing neurons in the ARC, which in turn results in the release of  $\alpha$ -MSH (Cone 2005) and activation of MCRs located in PVN, thereby leading to reduced food intake (Mineur *et al.* 2011). Consistent with this notion, POMC knockout mice were shown to be resilient to the inhibitory effect of nicotine on food intake (Mineur *et al.* 2011).

### Control of feeding by nicotinic cholinergic $\beta 2$ subunit-containing receptors

Recent studies have indicated that activation of  $\beta 2^*$ -containing nAChRs similar to  $\alpha 3\beta 4^*$  nAChRs regulate the function of melanocortin system to reduce food intake and body weight gain in mice (Dezfuli *et al.* 2016). A relatively selective ligand of  $\beta 2^*$ -containing nAChRs sazetidine-A (SAZ-A) significantly reduced body weight and food intake in obese mice (Dezfuli *et al.* 2016). Specifically, chronic desensitization of  $\beta 2$  nAChRs with continuous infusion of SAZ-A via subcutaneous osmotic pump resulted in reduction in body weight gain and food intake, and these changes were not observed in  $\beta 2^{-/-}$  and MCR4 $^{-/-}$  mice (Dezfuli *et al.* 2016). These findings suggest that  $\beta 2$  nAChRs might have an important role in regulation of food intake through melanocortin system. However, further studies are needed in this area to determine if the absence of  $\beta 2$  subunit-containing nAChRs would cause alterations in the function of  $\alpha 3\beta 4^*$  containing nAChRs or vice versa and if that these variations could regulate food intake and body weight.

### Control of feeding by nicotinic cholinergic $\alpha 4\beta 2$ subunit-containing receptors

Expression analysis within the hypothalamus has identified  $\alpha 4\beta 2$  subunits of nAChRs in LHA, ARC and PVN (Wada *et al.* 1989). Furthermore,  $\alpha 4\beta 2$  nAChRs are found on axons and cell bodies of dopaminergic neurons (Zoli *et al.* 2002), where it is involved in nicotine-induced dopamine release (Grady *et al.* 1992) and nicotine reward

(McGranahan, 2011 #1592). Activation of these receptors in the LHA appears to reduce food intake. Systemic, as well as local administration of  $\alpha 4\beta 2$  receptor antagonist, di-hydro- $\beta$ -erythroidine (DH $\beta$ E) in LHA of fasted rats led to increased food intake in comparison to saline-treated controls (García *et al.* 2015). It is considered that modulatory action of endogenous ACh is mediated by  $\alpha 4\beta 2$  nAChRs, which was shown previously to affect the release of serotonin and dopamine in LHA (Meguid *et al.* 2000). This may be induced by a direct activation of  $\alpha 4\beta 2$  nAChRs in the LHA, as application of DH $\beta$ E on hypothalamic slices inhibited nicotine-induced depolarization of POMC neurons (Huang *et al.* 2011). In another study, selective agonist of  $\alpha 4\beta 2$  receptor ((R,E)-5-(2-pyrrolidin-3-ylvinyl)-pyrimidine) reduced food intake and body weight without affecting metabolic parameters such as glucose and triglyceride levels (Marrero *et al.* 2010). Replacement of nicotine with chronic administration of SAZ-A, a potent nAChR partial agonist (Xiao *et al.* 2006) that causes desensitization of  $\alpha 4\beta 2$  nAChRs, was shown to reverse the upregulation of the receptor induced by chronic nicotine administration. Besides, this drug, like nicotine, was able to reduce body weight in rats (Hussmann *et al.* 2014). Therefore, it may be that weight-reducing effect of nicotine is mediated, at least in part, by its action on POMC neurons via the  $\alpha 4\beta 2$  nAChRs.

### Control of feeding by nicotinic cholinergic $\alpha 7$ subunit-containing receptors

Despite the relevance of majority of nicotinic receptors being involved in control of feeding behaviors (Jo *et al.* 2002, Mineur *et al.* 2011), it is considered that the most prominent action of nicotine in control of feeding is accomplished through the activation of  $\alpha 7$  nAChRs. Neurons containing  $\alpha 7$  nAChRs are found in the ARC nucleus, VMH and DMN (Seguela *et al.* 1993). Apart from the hypothalamus,  $\alpha 7$  nAChRs are expressed on dopaminergic neurons (Klink *et al.* 2001) and glutamatergic afferents projecting to the VTA (Jones & Wonnacott 2004). Stimulation of  $\alpha 7$  nAChRs was shown to suppress food intake via its actions in the hypothalamus (Jo *et al.* 2002). The  $\alpha 7$  nAChRs are expressed on both POMC and NPY expressing neurons in the ARC nucleus and nicotine exerts its action on feeding behaviors by modulating the activity of these neurons. For example, an *in vitro* study showed that the effect of nicotine was reduced in isolated POMC neurons through the application of the  $\alpha 7$  nAChR non-selective antagonist methyllycaconitine (MLA)

(Huang *et al.* 2011). On the other hand, levels of NPY were shown to be lower in smokers and also to be increased during nicotine cessation, suggesting that NPY has important role in control of food intake and body weight gain following smoking cessation (Hussain *et al.* 2012). In similar fashion,  $\alpha 7$  nAChR antagonist MLA reduced the excitation of NPY by nicotine (Huang *et al.* 2011).

Aside from modulating the activity of neurons in the hypothalamus,  $\alpha 7$  nAChRs have also been implicated in the release of neurotransmitters, such as -aminobutyric acid (GABA), glutamate, serotonin and dopamine. Nicotine administration can facilitate activation of GABA activity (Jo *et al.* 2002) and application of the  $\alpha 7$  nAChR-specific antagonist ( $\alpha$ -bungarotoxin) diminished this effect (Zhang & Berg 2007), suggesting that the increase in GABAergic neuronal activity in the hypothalamus may mediate the anorexigenic effect of nicotine.

The role of  $\alpha 7$  nAChR in modulating the dopamine release in connection to food intake is somewhat intricate. Taking into account that  $\alpha 7$  nAChRs are widely expressed in the VTA, nicotine-induced activation of these receptors contributes to the release of glutamate (Schilstrom *et al.* 1998, 2000), which ultimately leads to increases in dopaminergic activity and release of dopamine in the NAc. In that regard, it is considered that  $\alpha 7$  nAChRs contribute to the increased rewarding aspects of food (Schilstrom *et al.* 1998). On the other hand, elevated release of dopamine from dopaminergic projections to the LHA and VMH by nicotine is correlated with reduction in food intake (Meguid *et al.* 2000).

The  $\alpha 7$  nAChRs are also found on serotonergic neurons (Galindo-Charles *et al.* 2008) and their activation by nicotine leads to the release of serotonin (Summers & Giacobini 1995). Serotonin inhibits food intake (Waldbillig *et al.* 1981) and this is considered to be regulated via the inhibitory action of serotonin on NPY neurons, where it reduces the release of NPY (Dryden *et al.* 1996). Ultimately, nicotine-induced activation of nicotinic receptors increases the release of serotonin from extrinsic projections to the LHA, which contributes to appetite suppression (Jo *et al.* 2002).

### Nicotine and obesity-induce inflammation and insulin resistance

Gene expression analysis studies in adipose tissue have revealed an increased expression of inflammatory markers in obese animals (Weisberg *et al.* 2003). Conversely, after weight loss in obese individuals, decreased expression

(Clement *et al.* 2004) and secretion (Arvidsson *et al.* 2004) of pro-inflammatory components have been reported. The adipose tissue itself in obese individuals is thus a site of production of inflammatory markers (Wisse 2004). As in human and rodent models of obesity, a correlation was observed between the number of macrophages and the total amount of body fat, it was suggested that in obese subjects, the adipose tissue is actually in a pro-inflammatory state (Weisberg *et al.* 2003, Wisse 2004).

The increased accumulation of macrophages in WAT tissue may contribute to the enhanced systemic concentrations of pro-inflammatory cytokines in obesity. Not only tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) but also interleukin-6 (IL-6) (Lehrke *et al.* 2004) are known to interact directly with the insulin signaling cascade (Kershaw & Flier 2004, Trayhurn & Wood 2004, Wisse 2004), leading to the development of insulin resistance usually linked to obesity. Chronic cigarette smoking has been associated with elevated circulating levels of inflammatory cytokines, such as TNF- $\alpha$  and IL6 (Fernandez-Real *et al.* 2003, Ellingsgaard *et al.* 2008).

Aside from its central action, nicotine acting on  $\alpha 7$  nAChRs expressed on immune cells may affect metabolic homeostasis. Recruitment of  $\alpha 7$  nAChRs inhibits activation of pro-inflammatory nuclear factor-B (NF-B) signaling cascade in macrophages, that in turn reduces local inflammation (Pavlov *et al.* 2003). The anti-inflammatory action of nicotine, like that of the endogenous neurotransmitter acetylcholine (ACh), is due to the binding to and activation of  $\alpha 7$  nAChRs on resident macrophages under the control of the 'cholinergic anti-inflammatory pathway' (CAP) (Borovikova *et al.* 2000, Wang *et al.* 2003, Tracey 2007). The  $\alpha 7$  nAChRs activation by ACh released from the efferent vagus nerve may be important in this regard (Borovikova *et al.* 2000). Clinical studies showed that the expression of  $\alpha 7$  nAChR was reduced in fat cells isolated from subcutaneous adipose tissue of obese human subjects (Canello *et al.* 2012). Moreover, oral application of specific  $\alpha 7$  nAChR agonist in leptin-resistant db/db obese mice reduced food intake and weight gain in these mice (Marrero *et al.* 2010).  $\alpha 7$  nAChRs play a major role in the central and peripheral regulation of food intake and energy homeostasis. Furthermore, nicotine, acting on  $\alpha 7$  nAChRs may inhibit the activation of pro-inflammatory cytokines, limiting the inflammatory state of obese smokers, and helping in reducing body weight. Although complex, activation of  $\alpha 7$  nAChRs is critical in suppression of appetite and reduction of body weight gain.

In addition, studies have shown that higher circulating IL-6 promotes a shift in peptide production from glucagon toward glucagon-like peptide 1 (GLP-1), thus promoting functional beta-cell compensation to maintain proper insulin secretion and glucose homeostasis (Ellingsgaard *et al.* 2008). Moreover, knockout of IL-6 in mice or neutralization of IL-6 in wild-type mice fed with high-fat diet caused impairment of glucose homeostasis (Ellingsgaard *et al.* 2011), indicating that an adipose tissue-endocrine-islet loop exists that could be regulated in some extent by nicotine-induced IL-6 secretion, inducing metabolic adaptations that could result in weight loss in obese smokers. It does not explain, however, the presence of insulin resistance observed in chronic smokers. It may be a consequence of the desensitization that chronic nicotine exposure induces on  $\alpha 7$  nAChRs, reducing circulating IL-6, therefore reducing GLP-1 secretion. It is accepted now that apart from its central action, nicotine activation of  $\alpha 7$  nAChRs expressed on certain cells of the immune system may affect metabolic homeostasis. This is a new field that is being explored nowadays.

## Effects of nicotine on hedonic aspects of feeding

Cigarette smoking constitutes a significant public health matter and is associated with increased risk of early morbidity and mortality. This becomes an even greater subject of concern if consider that nicotine, the primary psychoactive substance in tobacco smoke, activates mesolimbic dopaminergic signaling pathways, which are important component of the reward system in the brain and is implicated in the development of addiction (Nestler 2005, Criscitelli & Avena 2016). Nicotine also plays an important role in the modulation of food intake and metabolism. As with nicotine, highly palatable foods are also capable of altering dopamine release within this system, giving place to addictive responses in susceptible individuals (Zoli & Picciotto 2012).

In support of this notion, there is a large body of evidence showing that motivational aspects of certain foods and drugs of abuse share similar reward pathways. For example, nicotine mediates its rewarding effect by directly stimulating dopaminergic transmission from VTA to NAc and food produces similar responses within the mesolimbic system (Nestler 2005).

Preclinical and clinical studies demonstrate that despite strong commitment of smokers to stop smoking,

the addictive properties of nicotine makes cessation from smoking too difficult (Goodman *et al.* 2008). For example, out of 70% smokers who try to quit smoking, only 7% were reported to achieve long-term abstinence from tobacco use (Goodman *et al.* 2008). Furthermore, among human population, nicotine mechanisms of addiction seem to be related with the concentration and distribution of adipose tissue, as individuals with higher BMI smoke more cigarettes per day than non-smokers (Rupprecht *et al.* 2015). Moreover, results obtained from human studies showed that nicotine was less rewarding to obese non-deprived smokers, as measured by percentage of total puffs taken from cigarettes with normal nicotine content (Blendy *et al.* 2005). On the other hand, obese participants were experiencing higher hedonic effect with cigarettes that were containing lower content of nicotine (Rupprecht *et al.* 2015), suggesting that obese people might be more prone to smoking, while increased smoking in obese population might be related to lower rewarding effect of nicotine (Rupprecht *et al.* 2015). Studies performed in rodents displayed similar results. Mice fed a high-fat diet failed to display preference to nicotine in CPP paradigm indicating that, consumption of palatable food can alter normal reward processing (Blendy *et al.* 2005, Kenny 2011), which may explain the difference in smoking habits between lean and obese human population.

Regulation of food intake by dopamine takes place in the hypothalamus through the action of dopamine on its receptors, D1 and D2 receptors (Ramos *et al.* 2005). In the hypothalamus, release of dopamine is associated with increased duration of food intake. Free-feeding rats treated with repeated systemic administration of D1 agonist (SKF 38393) exhibit decrease food intake, while D2 receptor agonist (+)-4-propyl-9-hydroxynaphthoxazine (PHNO) has opposite effects in the same animal population (Rusk & Cooper 1989). Outside the hypothalamus, activation of D1 expressing neurons in the NAc has been reported to stimulate feeding behavior (Zhu *et al.* 2016). Released ACh from the cholinergic interneurons in the NAc binds to nAChRs and influences the release of dopamine and thus reward processing (Mark *et al.* 2011). Both acute and chronic nicotine treatment modulates the hedonic aspects of food intake by increasing the release of dopamine from the ventral and dorsal striatum, through activation of nAChRs, such as  $\alpha 4^*$  and  $\alpha 6^*$  containing nAChRs (Grady *et al.* 2007, De Biasi & Dani 2011). Furthermore, chronic long-term sucrose intake increased  $\alpha 4\beta 2^*$  while decreases  $\alpha 6\beta 2$  nAChRs in the NAc (Shariff *et al.* 2016).

Administration of mecamylamine suppressed sucrose intake (Shariff *et al.* 2016), pavlovian incentive motivation (Ostlund *et al.* 2014) and operant self-administration of sucrose at higher doses (Ford *et al.* 2009).

Projections from the shell of NAc to the lateral hypothalamus and striatopallidal system, which are regulated by opioids, endocannabinoids and dopaminergic input, respond and mediate the sensory properties of palatable food as well as that of drugs of abuse, such as nicotine (Kenny 2011a,b). Consumption of palatable food and drugs of abuse also induces changes in striatal reward circuits through the action of hormones and neuropeptides. Hypocretin and MCH are two neuropeptides that not only regulate food intake, but also mediate the rewarding properties of drugs of abuse by modulating the function of mesolimbic dopaminergic neurons (Zheng *et al.* 2007, Chung *et al.* 2009). The MCH receptors are expressed in the NAc, activation of which stimulates feeding behaviors (Georgescu *et al.* 2005). On the other hand, inhibition of MCH receptors in the NAc diminished cocaine-induced CPP (Chung *et al.* 2009). Likewise, alcohol CPP was decreased in MCH1-R knockout mice (Karlsson *et al.* 2016), suggesting that MCH signaling might also be involved in the rewarding effect of nicotine. Blockade of hypocretin receptor in insula reduces nicotine self-administration in rats (Hollander *et al.* 2008).

Nicotine-induced CPP as well as nicotine withdrawal were attenuated in mice lacking the preproenkephalin gene compared to their wild-type controls (Berrendero *et al.* 2005), suggesting that opioids derived from proenkephalin are involved in the rewarding effect of nicotine as well as nicotine dependence. The significance of POMC signaling on nicotine reward was shown in an earlier study, where mice lacking beta-endorphin displayed reduced nicotine-induced CPP (Trigo *et al.* 2009). Mice lacking beta-endorphin had higher body weight compared to their wild-type controls (Rubinstein *et al.* 1996), suggesting that beta-endorphin may also be involved in energy homeostasis and in the ability of nicotine to reduce body weight. Considering that mice lacking POMC exhibited blunted response to nicotine-induced reduction of food intake (Mineur *et al.* 2011) and that beta-endorphin is derived from POMC, further research is needed to assess the role of beta-endorphin in the ability of nicotine to reduce body weight and energy homeostasis.

Nicotine administration was shown to reduce NPY immunoreactivity in the shell of NAc, PVN and ARC (Kotagale *et al.* 2014). Co-administration of NPY Y1 receptor potentiated the inhibitory effect of agmatine

on nicotine-induced CPP, suggesting that NPY signaling negatively affects nicotine-mediated reward processing (Kotagale *et al.* 2014). However, further research is needed to define the underlying mechanism of the regulatory action of NPY on nicotine reward and whether this is a direct effect of NPY or a combination of agmatine and NPY.

In addition to neuropeptides, hormonal regulator of appetite such as ghrelin increases motivation for food and drug intake by activating cholinergic and dopaminergic systems (Jerlhag *et al.* 2006, Skibicka *et al.* 2011). Ghrelin activates dopaminergic neurons of the VTA via cholinergic input, leading to dopamine overflow in the NAc, suggesting that ghrelin may regulate motivational aspect of feeding behavior (Jerlhag *et al.* 2006).

Leptin receptors are expressed on dopaminergic neurons (Figlewicz *et al.* 2003) and leptin inhibits appetite by regulating the function of the mesolimbic neurons (Fulton *et al.* 2006). More specifically, leptin attenuates activation of striatal reward system, as it was shown that leptin replacement reduces self-reported liking of food in humans (Farooqi *et al.* 2007). Infusion of leptin directly into the VTA inhibits activation of dopamine neurons (Hommel *et al.* 2006) and decreases brain reward function in rats (Bruijnzeel *et al.* 2011). Mice fed a high-fat diet had reduced expression of leptin receptor in the VTA, and also did not exhibit nicotine CPP (Blendy *et al.* 2005), suggesting that increased leptin level in obesity attenuates reward processing in the brain via an action on the activity of dopaminergic neurons.

Insulin is another hormone that regulates energy homeostasis. Insulin receptors are found to be expressed in the VTA and NAc, suggesting that insulin is involved in the regulation of food intake by an action on dopaminergic neurons (Zahniser *et al.* 1984, Figlewicz *et al.* 2003). In particular, insulin administration in the VTA decreases rewarding effect of palatable food (Figlewicz *et al.* 2008) by increasing reuptake of dopamine through the dopamine transporter (Mebel *et al.* 2012). In contrast, inactivation of insulin receptor in dopaminergic neurons leads to hyperphagia and weight gain (Konner *et al.* 2011). Diabetic rats are shown to have reduced level of dopamine in midbrain and striatum (Murzi *et al.* 1996), and streptozotocin-induced hypoinsulinemic rats showed increased nicotine self-administration (O'Dell *et al.* 2014). Similarly, insulin-resistant rats fed a high-fat diet showed enhanced nicotine preference in the CPP paradigm (Richardson *et al.* 2014). This disrupted dopamine-mediated reward transmission induced by impaired insulin signaling, may explain higher preference for nicotine intake in obese smokers. It also suggests that higher self-administration of nicotine in diabetic rats may

be due to reduced nicotine reward in these rats compared to controls. However, further studies are needed to determine whether the differences are as a result of species differences (mouse vs rat), treatment (high fat vs streptozotocin) and/or experimental procedure (CPP vs drug self-administration paradigm).

Nicotine has been shown to serve as a gateway drug to promote the use of other addictive drugs, such as alcohol and cocaine (Huang *et al.* 2013). Nicotine also appears to affect the reward threshold for natural reinforcing agents, suggesting common mechanism for the gateway action of nicotine. However, the effect of nicotine on these reinforcers is different depending on the duration of nicotine administration and whether animals are exposed to sucrose or fat, and even the content of fat in food is important in this regard. Acute nicotine enhances rewarding effect of palatable food. For example, mice with acute exposure to nicotine were found to have higher brake-point for sucrose in the operant conditioning paradigm (Brunzell *et al.* 2006). Similarly, using CPP paradigm, Buffalari and coworkers showed that animals conditioned with cocaine or sucrose and tested for place preference after a single nicotine challenge exhibited greater preference for the sucrose- as well as cocaine-paired compartment, showing that nicotine increased the motivational valence of contextual cue associated with cocaine as well as sucrose (Buffalari *et al.* 2014). Animals fed on high-fat diet and exposed to chronic nicotine tend to maintain or even increase their body weight in comparison to their regular low-fat diet-fed controls (Wellman *et al.* 1986, Mangubat *et al.* 2012). Another similar study showed that chronic peripheral administration of nicotine induces reduction of body weight and increases BAT thermogenesis in groups of rats fed either high or low-fat diet, suggesting that the reinforcing effect of nicotine disappears after chronic exposure, but may be restored after the cessation of nicotine use (Parker & Doucet 1995).

## Summary and conclusions

The regulation of feeding and metabolism by nicotine appears somewhat complex, mainly because it acts at different levels, both centrally and peripherally, to regulate multiple hormones and neuropeptides and their receptors to modify energy expenditure and feeding behavior.

Adipose tissue has a crucial role in metabolic homeostasis and is one of the targets of nicotine's action. On the one hand, nicotine increases energy expenditure

and thermogenesis by enhancing the expression of the mitochondrial carrier proteins UCP1 mRNA in BAT (Chen *et al.* 2006, Zoli & Picciotto 2012). On the other hand, nicotine stimulates the secretion of adiponectin and leptin (hormones with autocrine, paracrine and endocrine functions) from WAT, which lead to reduced food intake and increased metabolism, both effects observed in tobacco smokers. Interestingly, experimental studies in rodents suggest that adiponectin increases insulin sensitivity in peripheral tissues (Matsuzawa 2006), whereas human studies report that long-term exposure to nicotine induces changes in fat distribution associated with insulin resistance (Wu *et al.* 2015). Further studies show that resident macrophages located in WAT express 7 $\alpha$ nAChR, and that once activated by nicotine, they inhibit the secretion of pro-inflammatory cytokines. This could be the cause of the weight loss observed in obese smokers, who present a mild state of chronic inflammation. However, it has also been shown that long-term exposure to nicotine desensitizes its receptor, increasing the secretion of cytokines, a situation that may lead to fat redistribution, insulin resistance and worsening of the metabolic state.

Nicotine exerts its modulatory effects by binding to the nAChRs, which are widely distributed in the ARC nucleus of hypothalamus, allowing the regulation of the signals that arrive from the periphery to the brain, leading to reduced food intake and increase energy output. At central levels, nicotine has been shown to stimulate the orexigenic neurons NPY/AgRP and inhibit the anorexigenic POMC-containing neurons, probably through the activation of  $\alpha$ -7 and  $\alpha$ 3 $\beta$ 4 containing nicotinic receptors which in turn activate the AMPK signaling pathways. Hence nicotine, by affecting feeding behavior, could affect the storage of energy, which in turn modulates the secretion of hormones, peptides and neurotransmitters that ultimately would induce changes in energy expenditure and metabolic homeostasis.

Finally, nicotine, by stimulating dopaminergic transmission within the mesolimbic system, stimulates the reward system in the same way that recreational drugs such as cocaine does, making it difficult for smokers to quit using tobacco. Nicotine exerts this effect by acting upon different subtypes of nAChRs, like  $\alpha$ 4 $\beta$ 2\* and  $\alpha$ 6 $\beta$ 2 nAChRs, opening a new field of study about addiction and smoking tobacco and other nicotine-containing products.

In spite of the evidence accumulated with regard to the action of nicotine, further studies are needed to delineate the exact mechanism of nicotine-induced changes in energy expenditure and feeding behavior. The

results of these studies are expected to provide useful basic science information that may lay the foundation for the development of novel pharmacotherapy to treat nicotine as well as food addiction and obesity.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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**References**

Ahima RS 2008 Revisiting leptin's role in obesity and weight loss. *Journal of Clinical Investigation* **118** 2380–2383. (doi:10.1172/JCI36284)

Albanes D, Jones DY, Micozzi MS & Mattson ME 1987 Associations between smoking and body weight in the US population: analysis of NHANES II. *American Journal of Public Health* **77** 439–444. (doi:10.2105/ajph.77.4.439)

An Z, Wang H, Song P, Zhang M, Geng X & Zou MH 2007 Nicotine-induced activation of AMP-activated protein kinase inhibits fatty acid synthase in 3T3L1 adipocytes: a role for oxidant stress. *Journal of Biological Chemistry* **282** 26793–26801. (doi:10.1074/jbc.M703701200)

Anand BK & Brobeck JR 1951 Localization of a feeding center in the hypothalamus of the rat. *Proceedings of the Society for Experimental Biology and Medicine* **77** 323–324. (doi:10.3181/00379727-77-18766)

Aponte Y, Atasoy D & Sternson SM 2011 AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. *Nature Neuroscience* **14** 351–355. (doi:10.1038/nn.2739)

Arai K, Kim K, Kaneko K, Iketani M, Otagiri A, Yamauchi N & Shibasaki T 2001 Nicotine infusion alters leptin and uncoupling protein 1 mRNA expression in adipose tissues of rats. *American Journal of Physiology – Endocrinology and Metabolism* **280** E867.

Arvidsson E, Viguierie N, Andersson I, Verdich C, Langin D & Arner P 2004 Effects of different hypocaloric diets on protein secretion from adipose tissue of obese women. *Diabetes* **53** 1966–1971. (doi:10.2337/diabetes.53.8.1966)

Assali AR, Beigel Y, Schreiberman R, Shafer Z & Fainaru M 1999 Weight gain and insulin resistance during nicotine replacement therapy. *Clinical Cardiology* **22** 357–360. (doi:10.1002/clc.4960220512)

Audrain-McGovern J & Benowitz NL 2011 Cigarette smoking, nicotine, and body weight. *Clinical Pharmacology and Therapeutics* **90** 164–168. (doi:10.1038/clpt.2011.105)

Axelsson T, Jansson PA, Smith U & Eliasson B 2001 Nicotine infusion acutely impairs insulin sensitivity in type 2 diabetic patients but not in healthy subjects. *Journal of Internal Medicine* **249** 539–544. (doi:10.1046/j.1365-2796.2001.00840.x)

Barrett-Connor E & Khaw KT 1989 Cigarette smoking and increased central adiposity. *Annals of Internal Medicine* **111** 783–787. (doi:10.7326/0003-4819-111-10-783)

Bellocchio L, Lafenetre P, Cannich A, Cota D, Puente N, Grandes P, Chaouloff F, Piazza PV & Marsicano G 2010 Bimodal control of stimulated food intake by the endocannabinoid system. *Nature Neuroscience* **13** 281–283. (doi:10.1038/nn.2494)

- Benowitz NL 2010 Nicotine addiction. *New England Journal of Medicine* **362** 2295–2303. (doi:10.1056/NEJMra0809890)
- Berrendero F, Mendizabal V, Robledo P, Galeote L, Bilkei-Gorzo A, Zimmer A & Maldonado R 2005 Nicotine-induced antinociception, rewarding effects, and physical dependence are decreased in mice lacking the preproenkephalin gene. *Journal of Neuroscience* **25** 1103–1112. (doi:10.1523/JNEUROSCI.3008-04.2005)
- Blendy JA, Strasser A, Walters CL, Perkins KA, Patterson F, Berkowitz R & Lerman C 2005 Reduced nicotine reward in obesity: cross-comparison in human and mouse. *Psychopharmacology* **180** 306–315. (doi:10.1007/s00213-005-2167-9)
- Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, Wang H, Abumrad N, Eaton JW & Tracey KJ 2000 Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* **405** 458–462. (doi:10.1038/35013070)
- Boucher Y, Simons C, Cuellar J, Jung S-W, Carstens M & Carstens E 2003 Activation of brain stem neurons by irritant chemical stimulation of the throat assessed by c-fos immunohistochemistry. *Experimental Brain Research* **148** 211–218. (doi:10.1007/s00221-002-1308-1)
- Bouros D, Tzouveleakis A, Anevlavis S, Doris M, Tryfon S, Froudarakis M, Journatzi V & Kukulitis A 2006 Smoking acutely increases plasma ghrelin concentrations. *Clinical Chemistry* **52** 777–778. (doi:10.1373/clinchem.2005.065243)
- Brestoff JR, Kim BS, Saenz SA, Stine RR, Monticelli LA, Sonnenberg GF, Thome JJ, Farber DL, Lutfy K, Seale P, et al. 2015 Group 2 innate lymphoid cells promote being of white adipose tissue and limit obesity. *Nature* **519** 242–246. (doi:10.1038/nature14115)
- Bruijnzeel AW, Corrie LW, Rogers JA & Yamada H 2011 Effects of insulin and leptin in the ventral tegmental area and arcuate hypothalamic nucleus on food intake and brain reward function in female rats. *Behavioural Brain Research* **219** 254–264. (doi:10.1016/j.bbr.2011.01.020)
- Brunzell DH, Chang JR, Schneider B, Olausson P, Taylor JR & Picciotto MR 2006 Beta2-Subunit-containing nicotinic acetylcholine receptors are involved in nicotine-induced increases in conditioned reinforcement but not progressive ratio responding for food in C57BL/6 mice. *Psychopharmacology* **184** 328–338. (doi:10.1007/s00213-005-0099-z)
- Buffalari DM, Marfo NY, Smith TT, Levin ME, Weaver MT, Thiels E, Sved AF & Donny EC 2014 Nicotine enhances the expression of a sucrose or cocaine conditioned place preference in adult male rats. *Pharmacology Biochemistry and Behavior* **124** 320–325. (doi:10.1016/j.pbb.2014.06.013)
- Bura SA, Burokas A, Martin-Garcia E & Maldonado R 2010 Effects of chronic nicotine on food intake and anxiety-like behaviour in CB(1) knockout mice. *European Neuropsychopharmacology* **20** 369–378. (doi:10.1016/j.euroneuro.2010.02.003)
- Burgos-Ramos E, Chowen JA, Arilla-Ferreiro E, Canelles S, Argente J & Barrios V 2011 Chronic central leptin infusion modifies the response to acute central insulin injection by reducing the interaction of the insulin receptor with IRS2 and increasing its association with SOCS3. *Journal of Neurochemistry* **117** 175–185. (doi:10.1111/j.1471-4159.2011.07191.x)
- Cancello R, Zulian A, Maestrini S, Mencarelli M, Della Barba A, Invitti C, Liuzzi A & Di Blasio AM 2012 The nicotinic acetylcholine receptor alpha7 in subcutaneous mature adipocytes: downregulation in human obesity and modulation by diet-induced weight loss. *International Journal of Obesity* **36** 1552–1557. (doi:10.1038/ijo.2011.275)
- Cano G, Passerin AM, Schiltz JC, Card JP, Morrison SF & Sved AF 2003 Anatomical substrates for the central control of sympathetic outflow to interscapular adipose tissue during cold exposure. *Journal of Comparative Neurology* **460** 303–326. (doi:10.1002/cne.10643)
- Chajek-Shaul T, Scherer G, Barash V, Shiloni E, Caine Y, Stein O & Stein Y 1994 Metabolic effects of nicotine on human adipose tissue in organ culture. *Clinical Investigation* **72** 94–99. (doi:10.1007/BF00184583)
- Chen H, Hansen MJ, Jones JE, Vlahos R, Bozinovski S, Anderson GP & Morris MJ 2006 Cigarette smoke exposure reprograms the hypothalamic neuropeptide Y axis to promote weight loss. *American Journal of Respiratory and Critical Care Medicine* **173** 1248–1254. (doi:10.1164/rccm.200506-9770C)
- Chen H, Hansen MJ, Jones JE, Vlahos R, Bozinovski S, Anderson GP & Morris MJ 2007 Regulation of hypothalamic NPY by diet and smoking. *Peptides* **28** 384–389. (doi:10.1016/j.peptides.2006.07.034)
- Chiolero A, Faeh D, Paccaud F & Cornuz J 2008 Consequences of smoking for body weight, body fat distribution, and insulin resistance. *American Journal of Clinical Nutrition* **87** 801–809.
- Chowdhury P, Hosotani R, Chang L & Rayford PL 1990 Metabolic and pathologic effects of nicotine on gastrointestinal tract and pancreas of rats. *Pancreas* **5** 222–229. (doi:10.1097/0000676-199003000-00016)
- Chung S, Hopf FW, Nagasaki H, Li CY, Belluzzi JD, Bonci A & Civelli O 2009 The melanin-concentrating hormone system modulates cocaine reward. *PNAS* **106** 6772–6777. (doi:10.1073/pnas.0811331106)
- Clair C, Chiolero A, Faeh D, Cornuz J, Marques-Vidal P, Paccaud F, Mooser V, Waeber G & Vollenweider P 2011 Dose-dependent positive association between cigarette smoking, abdominal obesity and body fat: cross-sectional data from a population-based survey. *BMC Public Health* **11** 23. (doi:10.1186/1471-2458-11-23)
- Clement K, Viguierie N, Poitou C, Carette C, Pelloux V, Curat CA, Sicard A, Rome S, Benis A, Zucker JD, et al. 2004 Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. *FASEB Journal* **18** 1657–1669. (doi:10.1096/fj.04-2204com)
- Cohen C, Perrault G, Griebel G & Soubrie P 2004 Nicotine-associated cues maintain nicotine-seeking behavior in rats several weeks after nicotine withdrawal: reversal by the cannabinoid (CB1) receptor antagonist, rimonabant (SR141716). *Neuropsychopharmacology* **30** 145–155. (doi:10.1038/sj.npp.1300541)
- Cone RD 2005 Anatomy and regulation of the central melanocortin system. *Nature Neuroscience* **8** 571–578. (doi:10.1038/nn1455)
- Contreras C, Nogueiras R, Diéguez C, Rahmouni K & López M 2017 Traveling from the hypothalamus to the adipose tissue: the thermogenic pathway. *Redox Biology* **12** 854–863. (doi:10.1016/j.redox.2017.04.019)
- Cota D, Marsicano G, Tschop M, Grubler Y, Flachskamm C, Schubert M, Auer D, Yassouridis A, Thone-Reineke C, Ortman S, et al. 2003 The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *Journal of Clinical Investigation* **112** 423–431. (doi:10.1172/JCI17725)
- Crichton PG, Lee Y & Kunji ERS 2017 The molecular features of uncoupling protein 1 support a conventional mitochondrial carrier-like mechanism. *Biochimie* **134** 35–50. (doi:10.1016/j.biochi.2016.12.016)
- Criscitelli K & Avena NM 2016 The neurobiological and behavioral overlaps of nicotine and food addiction. *Preventive Medicine* **92** 82–89. (doi:10.1016/j.ypmed.2016.08.009)
- Cristino L, Becker T, Becker T & Di Marzo V 2014 Endocannabinoids and energy homeostasis: an update. *BioFactors* **40** 389–397. (doi:10.1002/biof.1168)
- Dani JA & Bertrand D 2007 Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system. *Annual Review of Pharmacology and Toxicology* **47** 699–729. (doi:10.1146/annurev.pharmtox.47.120505.105214)
- De Biasi M & Dani JA 2011 Reward, addiction, withdrawal to nicotine. *Annual Review of Neuroscience* **34** 105–130. (doi:10.1146/annurev-neuro-061010-113734)
- De la Fuente IM, Cortés JM, Valero E, Desroches M, Rodrigues S, Malina I & Martínez L 2014 On the dynamics of the adenylate energy system: homeorhesis vs homeostasis. *PLoS ONE* **9** e108676. (doi:10.1371/journal.pone.0108676)
- de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, Fukuhara C, Battenberg EL, Gautvik VT, Bartlett FS 2nd, et al. 1998 The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *PNAS* **95** 322–327. (doi:10.1073/pnas.95.1.322)
- de Oliveira E, Moura EG, Santos-Silva AP, Pinheiro CR, Lima NS, Nogueira-Neto JE, Nunes-Freitas AL, Abreu-Villaca Y, Passos MC & Lisboa PC

- 2010 Neonatal nicotine exposure causes insulin and leptin resistance and inhibits hypothalamic leptin signaling in adult rat offspring. *Journal of Endocrinology* **206** 55–63. (doi:10.1677/JOE-10-0104)
- Dezfuli G, Kellar KJ, Dretchen KL, Tizabi Y, Sahibzada N & Gillis RA 2016 Evidence for the role of beta2\* nAChR desensitization in regulating body weight in obese mice. *Neuropharmacology* **110** 165–174. (doi:10.1016/j.neuropharm.2016.07.020)
- Dickson SL, Hrabovszky E, Hansson C, Jerlhag E, Alvarez-Crespo M, Skibicka KP, Molnar CS, Liposits Z, Engel JA & Egecioglu E 2010 Blockade of central nicotine acetylcholine receptor signaling attenuate ghrelin-induced food intake in rodents. *Neuroscience* **171** 1180–1186. (doi:10.1016/j.neuroscience.2010.10.005)
- Donny EC, Caggiula AR, Weaver MT, Levin ME & Sved AF 2011 The reinforcement-enhancing effects of nicotine: implications for the relationship between smoking, eating and weight. *Physiology and Behavior* **104** 143–148. (doi:10.1016/j.physbeh.2011.04.043)
- Dryden S, Frankish HM, Wang Q, Pickavance L & Williams G 1996 The serotonergic agent fluoxetine reduces neuropeptide Y levels and neuropeptide Y secretion in the hypothalamus of lean and obese rats. *Neuroscience* **72** 557–566. (doi:10.1016/0306-4522(95)00566-8)
- Eliasson B & Smith U 1999 Leptin levels in smokers and long-term users of nicotine gum. *European Journal of Clinical Investigation* **29** 145–152. (doi:10.1046/j.1365-2362.1999.00420.x)
- Ellingsgaard H, Ehses JA, Hammar EB, Van Lommel L, Quintens R, Martens G, Kerr-Conte J, Pattou F, Berney T, Pipeleers D, et al. 2008 Interleukin-6 regulates pancreatic  $\alpha$ -cell mass expansion. *PNAS* **105** 13163–13168. (doi:10.1073/pnas.0801059105)
- Ellingsgaard H, Hauselmann I, Schuler B, Habib AM, Baggio LL, Meier DT, Eppler E, Bouzakri K, Wueest S, Muller YD, et al. 2011 Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. *Nature Medicine* **17** 1481–1489. (doi:10.1038/nm.2513)
- Enriori PJ, Evans AE, Sinnayah P & Cowley MA 2006 Leptin resistance and obesity. *Obesity* **14** (Supplement 5) 254s–258s. (doi:10.1038/oby.2006.319)
- Facchini FS, Hollenbeck CB, Jeppesen J, Chen YD & Reaven GM 1992 Insulin resistance and cigarette smoking. *Lancet* **339** 1128–1130. (doi:10.1016/0140-6736(92)90730-Q)
- Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S & Fletcher PC 2007 Leptin regulates striatal regions and human eating behavior. *Science* **317** 1355. (doi:10.1126/science.1144599)
- Fernandez-Real JM, Broch M, Vendrell J & Ricart W 2003 Smoking, fat mass and activation of the tumor necrosis factor-alpha pathway. *International Journal of Obesity and Related Metabolic Disorders* **27** 1552–1556. (doi:10.1038/sj.ijo.0802472)
- Figlewicz DP, Evans SB, Murphy J, Hoen M & Baskin DG 2003 Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat. *Brain Research* **964** 107–115. (doi:10.1016/S0006-8993(02)04087-8)
- Figlewicz DP, Bennett JL, Aliakbari S, Zavosh A & Sipols AJ 2008 Insulin acts at different CNS sites to decrease acute sucrose intake and sucrose self-administration in rats. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology* **295** R388–R394. (doi:10.1152/ajpregu.90334.2008)
- Filozof C, Fernández Pinilla MC & Fernandez-Cruz A 2004 Smoking cessation and weight gain. *Obesity Reviews* **5** 95–103. (doi:10.1111/j.1467-789X.2004.00131.x)
- Ford MM, Fretwell AM, Nickel JD, Mark GP, Strong MN, Yoneyama N & Finn DA 2009 The influence of mecamylamine on ethanol and sucrose self-administration. *Neuropharmacology* **57** 250–258. (doi:10.1016/j.neuropharm.2009.05.012)
- Frankish HM, Dryden S, Wang Q, Bing C, MacFarlane IA & Williams G 1995 Nicotine administration reduces neuropeptide Y and neuropeptide Y mRNA concentrations in the rat hypothalamus: NPY may mediate nicotine's effects on energy balance. *Brain Research* **694** 139–146. (doi:10.1016/0006-8993(95)00834-D)
- Fride E, Bregman T & Kirkham TC 2005 Endocannabinoids and food intake: newborn suckling and appetite regulation in adulthood. *Experimental Biology and Medicine* **230** 225–234. (doi:10.1177/153537020523000401)
- Fulton S, Pissios P, Manchon RP, Stiles L, Frank L, Pothos EN, Maratos-Flier E & Flier JS 2006 Leptin regulation of the mesoaccumbens dopamine pathway. *Neuron* **51** 811–822. (doi:10.1016/j.neuron.2006.09.006)
- Galindo-Charles L, Hernandez-Lopez S, Galarraga E, Tapia D, Bargas J, Garduno J, Frias-Dominguez C, Drucker-Colin R & Mihailescu S 2008 Serotonergic dorsal raphe neurons possess functional postsynaptic nicotinic acetylcholine receptors. *Synapse* **62** 601–615. (doi:10.1002/syn.20526)
- García AP, Aitta-aho T, Schaaf L, Heeley N, Heuschmid L, Bai Y, Barrantes FJ & Apergis-Schoute J 2015 Nicotinic  $\alpha$ 4 receptor-mediated cholinergic influences on food intake and activity patterns in hypothalamic circuits. *PLoS ONE* **10** e0133327. (doi:10.1371/journal.pone.0133327)
- Gardner EL 2005 Endocannabinoid signaling system and brain reward: emphasis on dopamine. *Pharmacology Biochemistry and Behavior* **81** 263–284. (doi:10.1016/j.pbb.2005.01.032)
- Georgescu D, Sears RM, Hommel JD, Barrot M, Bolanos CA, Marsh DJ, Bednarek MA, Bibb JA, Maratos-Flier E, Nestler EJ, et al. 2005 The hypothalamic neuropeptide melanin-concentrating hormone acts in the nucleus accumbens to modulate feeding behavior and forced-swim performance. *Journal of Neuroscience* **25** 2933–2940. (doi:10.1523/JNEUROSCI.1714-04.2005)
- Gil-Campos M, Aguilera CM, Canete R & Gil A 2006 Ghrelin: a hormone regulating food intake and energy homeostasis. *British Journal of Nutrition* **96** 201–226. (doi:10.1079/BJN20061787)
- Gill GV, Morgan C & MacFarlane IA 2005 Awareness and use of smoking cessation treatments among diabetic patients. *Diabetic Medicine* **22** 658–660. (doi:10.1111/j.1464-5491.2005.01471.x)
- Glowa JR & Gold PW 1991 Corticotropin releasing hormone produces profound anorexigenic effects in the rhesus monkey. *Neuropeptides* **18** 55–61. (doi:10.1016/0143-4179(91)90164-E)
- Gomez G, Lambert I, Udipi V, Qi X, Thompson JC & Greeley GH Jr 1996 Influence of nicotine on gastrin and peptide YY in the rat. *Regulatory Peptides* **67** 55–61. (doi:10.1016/S0167-0115(96)00107-3)
- Gonzalez S, Cascio MG, Fernandez-Ruiz J, Fezza F, Di Marzo V & Ramos JA 2002 Changes in endocannabinoid contents in the brain of rats chronically exposed to nicotine, ethanol or cocaine. *Brain Research* **954** 73–81. (doi:10.1016/S0006-8993(02)03344-9)
- Goodman T, Ferro A & Sharma P 2008 Pharmacogenetics of aspirin resistance: a comprehensive systematic review. *British Journal of Clinical Pharmacology* **66** 222–232. (doi:10.1111/j.1365-2125.2008.03183.x)
- Grady S, Marks MJ, Wonnacott S & Collins AC 1992 Characterization of nicotinic receptor-mediated [3H]dopamine release from synaptosomes prepared from mouse striatum. *Journal of Neurochemistry* **59** 848–856. (doi:10.1111/j.1471-4159.1992.tb08322.x)
- Grady SR, Salminen O, Lavery DC, Whiteaker P, McIntosh JM, Collins AC & Marks MJ 2007 The subtypes of nicotinic acetylcholine receptors on dopaminergic terminals of mouse striatum. *Biochemical Pharmacology* **74** 1235–1246. (doi:10.1016/j.bcp.2007.07.032)
- Gropp E, Shanabrough M, Borok E, Xu AW, Janoschek R, Buch T, Plum L, Balthasar N, Hampel B, Waisman A, et al. 2005 Agouti-related peptide-expressing neurons are mandatory for feeding. *Nature Neuroscience* **8** 1289–1291. (doi:10.1038/nn1548)
- Hamilton CL, Ciaccia PJ & Lewis DO 1976 Feeding behavior in monkeys with and without lesions of the hypothalamus. *American Journal of Physiology* **230** 818–830.
- Harms M & Seale P 2013 Brown and beige fat: development, function and therapeutic potential. *Nature Medicine* **19** 1252–1263. (doi:10.1038/nm.3361)
- Harwood HJ Jr 2012 The adipocyte as an endocrine organ in the regulation of metabolic homeostasis. *Neuropharmacology* **63** 57–75. (doi:10.1016/j.neuropharm.2011.12.010)



- Hofstetter A, Schutz Y, Jéquier E & Wahren J 1986 Increased 24-hour energy expenditure in cigarette smokers. *New England Journal of Medicine* **314** 79–82. (doi:10.1056/NEJM198601093140204)
- Hollander JA, Lu Q, Cameron MD, Kamenecka TM & Kenny PJ 2008 Insular hypocretin transmission regulates nicotine reward. *PNAS* **105** 19480–19485. (doi:10.1073/pnas.0808023105)
- Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, Gao XB, Thurmon JJ, Marinelli M & DiLeone RJ 2006 Leptin receptor signaling in midbrain dopamine neurons regulates feeding. *Neuron* **51** 801–810. (doi:10.1016/j.neuron.2006.08.023)
- Huang H, Xu Y & van den Pol AN 2011 Nicotine excites hypothalamic arcuate anorexigenic proopiomelanocortin neurons and orexigenic neuropeptide Y neurons: similarities and differences. *Journal of Neurophysiology* **106** 1191–1202. (doi:10.1152/jn.00740.2010)
- Huang YY, Kandel DB, Kandel ER & Levine A 2013 Nicotine primes the effect of cocaine on the induction of LTP in the amygdala. *Neuropharmacology* **74** 126–134. (doi:10.1016/j.neuropharm.2013.03.031)
- Hussain T, Al-Daghri NM, Al-Attas OS, Draz HM, Abd Al-Rahman SH & Yakout SM 2012 Plasma neuropeptide Y levels relate cigarette smoking and smoking cessation to body weight regulation. *Regulatory Peptides* **176** 22–27. (doi:10.1016/j.regpep.2012.02.005)
- Hussmann GP, DeDominicis KE, Turner JR, Yasuda RP, Klehm J, Forcelli PA, Xiao Y, Richardson JR, Sahibzada N, Wolfe BB, et al. 2014 Chronic sazetidine-A maintains anxiolytic effects and slower weight gain following chronic nicotine without maintaining increased density of nicotinic receptors in rodent brain. *Journal of Neurochemistry* **129** 721–731. (doi:10.1111/jnc.12653)
- Inoue K, Takeshima F, Kadota K, Yoda A, Tatsuta Y, Nagaura Y, Yoshioka S, Nakamichi S, Nakao K & Ozono Y 2011 Early effects of smoking cessation and weight gain on plasma adiponectin levels and insulin resistance. *Internal Medicine* **50** 707–712. (doi:10.2169/internalmedicine.50.4600)
- Jerlhag E, Egecioglu E, Dickson SL, Andersson M, Svensson L & Engel JA 2006 Ghrelin stimulates locomotor activity and accumbal dopamine-overflow via central cholinergic systems in mice: implications for its involvement in brain reward. *Addiction Biology* **11** 45–54. (doi:10.1111/j.1369-1600.2006.00002.x)
- Jo YH, Talmage DA & Role LW 2002 Nicotinic receptor-mediated effects on appetite and food intake. *Journal of Neurobiology* **53** 618–632. (doi:10.1002/neu.10147)
- Jones IW & Wonnacott S 2004 Precise localization of alpha7 nicotinic acetylcholine receptors on glutamatergic axon terminals in the rat ventral tegmental area. *Journal of Neuroscience* **24** 11244–11252. (doi:10.1523/JNEUROSCI.3009-04.2004)
- Jones S, Sudweeks S, & Yakel JL 1999 Nicotinic receptors in the brain: correlating physiology with function. *Trends in Neuroscience* **22** 555–561. (doi:10.1016/S0166-2236(99)01471-X)
- Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K & Tobe K 2006 Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *Journal of Clinical Investigation* **116** 1784–1792. (doi:10.1172/JCI29126)
- Kahn BB, Alquier T, Carling D & Hardie DG 2005 AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metabolism* **1** 15–25. (doi:10.1016/j.cmet.2004.12.003)
- Kane JK, Parker SL & Li MD 2001 Hypothalamic orexin-A binding sites are downregulated by chronic nicotine treatment in the rat. *Neuroscience Letters* **298** 1–4. (doi:10.1016/S0304-3940(00)01730-4)
- Karlsson C, Rehman F, Damdzic R, Atkins AL, Schank JR, Gehlert DR, Steensland P, Thorsell A & Heilig M 2016 The melanin-concentrating hormone-1 receptor modulates alcohol-induced reward and DARPP-32 phosphorylation. *Psychopharmacology* **233** 2355–2363. (doi:10.1007/s00213-016-4285-y)
- Kelley AE & Berridge KC 2002 The neuroscience of natural rewards: relevance to addictive drugs. *Journal of Neuroscience* **22** 3306–3311.
- Kenny PJ 2011a Common cellular and molecular mechanisms in obesity and drug addiction. *Nature Reviews Neuroscience* **12** 638–651. (doi:10.1038/nrn3105)
- Kenny PJ 2011b Reward mechanisms in obesity: new insights and future directions. *Neuron* **69** 664–679. (doi:10.1016/j.neuron.2011.02.016)
- Kenny PJ & Markou A 2006 Nicotine self-administration acutely activates brain reward systems and induces a long-lasting increase in reward sensitivity. *Neuropsychopharmacology* **31** 1203–1211.
- Kershaw EE & Flier JS 2004 Adipose tissue as an endocrine organ. *Journal of Clinical Endocrinology and Metabolism* **89** 2548–2556.
- Kim JH, Shim KW, Yoon YS, Lee SY, Kim SS & Oh SW 2012 Cigarette smoking increases abdominal and visceral obesity but not overall fatness: an observational study. *PLoS ONE* **7** e45815. (doi:10.1371/journal.pone.0045815)
- Klink R, de Kerchove d'Exaerde A, Zoli M & Changeux JP 2001 Molecular and physiological diversity of nicotinic acetylcholine receptors in the midbrain dopaminergic nuclei. *Journal of Neuroscience* **21** 1452–1463.
- Kobeissy FH, Jeung JA, Warren MW, Geier JE & Gold MS 2008 Changes in leptin, ghrelin, growth hormone and neuropeptide-Y after an acute model of MDMA and methamphetamine exposure in rats. *Addiction Biology* **13** 15–25. (doi:10.1111/j.1369-1600.2007.00083.x)
- Kokkinos A, Tentolouris N, Kyriakaki E, Argyrakopoulou G, Doupiis J, Psallas M, Kyriaki D & Katsilambros N 2007 Differentiation in the short- and long-term effects of smoking on plasma total ghrelin concentrations between male nonsmokers and habitual smokers. *Metabolism* **56** 523–527. (doi:10.1016/j.metabol.2006.11.012)
- Konner AC, Hess S, Tovar S, Mesaros A, Sanchez-Lasheras C, Evers N, Verhagen LA, Bronneke HS, Kleinriders A, Hampel B, et al. 2011 Role for insulin signaling in catecholaminergic neurons in control of energy homeostasis. *Cell Metabolism* **13** 720–728. (doi:10.1016/j.cmet.2011.03.021)
- Koob GF, Sanna PP & Bloom FE 1998 Neuroscience of addiction. *Neuron* **21** 467–476. (doi:10.1016/S0896-6273(00)80557-7)
- Kotagale NR, Walke S, Shelkar GP, Kokare DM, Umekar MJ & Taksande BG 2014 Agmatine attenuates nicotine induced conditioned place preference in mice through modulation of neuropeptide Y system. *Behavioural Brain Research* **262** 118–124. (doi:10.1016/j.bbr.2014.01.004)
- Kubota N, Yano W, Kubota T, Yamauchi T, Itoh S, Kumagai H, Kozono H, Takamoto I, Okamoto S, Shiuchi T, et al. 2007 Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. *Cell Metabolism* **6** 55–68. (doi:10.1016/j.cmet.2007.06.003)
- Le Foll B & Goldberg SR 2004 Rimobant, a CB1 antagonist, blocks nicotine-conditioned place preferences. *Neuroreport* **15** 2139–2143. (doi:10.1097/00001756-200409150-00028)
- Lee H, Joe KH, Kim W, Park J, Lee DH, Sung KW & Kim DJ 2006 Increased leptin and decreased ghrelin level after smoking cessation. *Neuroscience Letters* **409** 47–51. (doi:10.1016/j.neulet.2006.09.013)
- Lehrke M, Reilly MP, Millington SC, Iqbal N, Rader DJ & Lazar MA 2004 An inflammatory cascade leading to hyperresistemia in humans. *PLoS Medicine* **1** e45. (doi:10.1371/journal.pmed.0010045)
- Leibowitz SF & Alexander JT 1998 Hypothalamic serotonin in control of eating behavior, meal size, and body weight. *Biological Psychiatry* **44** 851–864. (doi:10.1016/S0006-3223(98)00186-3)
- Lenard NR & Berthoud HR 2008 Central and peripheral regulation of food intake and physical activity: pathways and genes. *Obesity* **16** (Supplement 3) S11–S22. (doi:10.1038/oby.2008.511)
- LeSage MG, Perry JL, Kotz CM, Shelley D & Corrigan WA 2010 Nicotine self-administration in the rat: effects of hypocretin antagonists and changes in hypocretin mRNA. *Psychopharmacology* **209** 203–212. (doi:10.1007/s00213-010-1792-0)
- Li MD & Kane JK 2003 Effect of nicotine on the expression of leptin and forebrain leptin receptors in the rat. *Brain Research* **991** 222–231. (doi:10.1016/j.brainres.2003.08.024)

- Liu R-H, Mizuta M & Matsukura S 2003 Long-term oral nicotine administration reduces insulin resistance in obese rats. *European Journal of Pharmacology* **458** 227–234. (doi:10.1016/S0014-2999(02)02726-7)
- Liu R-H, Mizuta M & Matsukura S 2004 The expression and functional role of nicotinic acetylcholine receptors in rat adipocytes. *Journal of Pharmacology and Experimental Therapeutics* **310** 52–58. (doi:10.1124/jpet.103.065037)
- Lopez M, Lage R, Saha AK, Perez-Tilve D, Vazquez MJ, Varela L, Sangiao-Alvarellos S, Tovar S, Raghay K, Rodriguez-Cuenca S, et al. 2008 Hypothalamic fatty acid metabolism mediates the orexigenic action of ghrelin. *Cell Metabolism* **7** 389–399. (doi:10.1016/j.cmet.2008.03.006)
- Lowell BB & Spiegelman BM 2000 Towards a molecular understanding of adaptive thermogenesis. *Nature* **404** 652–660.
- Lupien JR & Bray GA 1988 Nicotine increases thermogenesis in brown adipose tissue in rats. *Pharmacology Biochemistry and Behavior* **29** 33–37. (doi:10.1016/0091-3057(88)90269-9)
- Lutter M & Nestler EJ 2009 Homeostatic and hedonic signals interact in the regulation of food intake. *Journal of Nutrition* **139** 629–632. (doi:10.3945/jn.108.097618)
- Maldonado R, Valverde O & Berrendero F 2006 Involvement of the endocannabinoid system in drug addiction. *Trends in Neurosciences* **29** 225–232. (doi:10.1016/j.tins.2006.01.008)
- Mangubat M, Lutfy K, Lee ML, Pulido L, Stout D, Davis R, Shin CS, Shahbazian M, Seaholtz S, Sinha-Hikim A, et al. 2012 Effect of nicotine on body composition in mice. *Journal of Endocrinology* **212** 317–326. (doi:10.1530/JOE-11-0350)
- Mao D, Yasuda RP, Fan H, Wolfe BB & Kellar KJ 2006 Heterogeneity of nicotinic cholinergic receptors in rat superior cervical and nodose ganglia. *Molecular Pharmacology* **70** 1693–1699. (doi:10.1124/mol.106.027458)
- Mark GP, Shabani S, Dobbs LK & Hansen ST 2011 Cholinergic modulation of mesolimbic dopamine function and reward. *Physiology and Behavior* **104** 76–81. (doi:10.1016/j.physbeh.2011.04.052)
- Marrero MB, Lucas R, Salet C, Hauser TA, Mazurov A, Lippello PM & Bencherif M 2010 An alpha7 nicotinic acetylcholine receptor-selective agonist reduces weight gain and metabolic changes in a mouse model of diabetes. *Journal of Pharmacology and Experimental Therapeutics* **332** 173–180. (doi:10.1124/jpet.109.154633)
- Martinez de Morentin PB, Whittle AJ, Ferno J, Nogueiras R, Dieguez C, Vidal-Puig A & Lopez M 2012 Nicotine induces negative energy balance through hypothalamic AMP-activated protein kinase. *Diabetes* **61** 807–817. (doi:10.2337/db11-1079)
- Matsuzawa Y 2006 The metabolic syndrome and adipocytokines. *FEBS Letters* **580** 2917–2921. (doi:10.1016/j.febslet.2006.04.028)
- McGehee DS, Heath MJ, Gelber S, Devay P & Role LW 1995 Nicotine enhancement of fast excitatory synaptic transmission in CNS by presynaptic receptors. *Science* **269** 1692–1696. (doi:10.1126/science.7569895)
- Mebel DM, Wong JC, Dong YJ & Borgland SL 2012 Insulin in the ventral tegmental area reduces hedonic feeding and suppresses dopamine concentration via increased reuptake. *European Journal of Neuroscience* **36** 2336–2346. (doi:10.1111/j.1460-9568.2012.08168.x)
- Meguid MM, Fetissov SO, Varma M, Sato T, Zhang L, Laviano A & Rossi-Fanelli F 2000 Hypothalamic dopamine and serotonin in the regulation of food intake. *Nutrition* **16** 843–857. (doi:10.1016/S0899-9007(00)00449-4)
- Meister B 2000 Control of food intake via leptin receptors in the hypothalamus. *Vitamins and Hormones* **59** 265–304. (doi:10.1016/S0083-6729(00)S9010-4)
- Mineur YS, Abizaid A, Rao Y, Salas R, DiLeone RJ, Gündisch D, Diano S, De Biasi M, Horvath TL, Gao XB, et al. 2011 Nicotine decreases food intake through activation of POMC neurons. *Science* **332** 1330–1332. (doi:10.1126/science.1201889)
- Minokoshi Y, Alquier T, Furukawa N, Kim YB, Lee A, Xue B, Mu J, Fougelle F, Ferre P, Birnbaum MJ, et al. 2004 AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature* **428** 569–574. (doi:10.1038/nature02440)
- Morgan TM, Crawford L, Stoller A, Toth D, Yeo K-TJ & Baron JA 2004 Acute effects of nicotine on serum glucose insulin growth hormone and cortisol in healthy smokers. *Metabolism* **53** 578–582. (doi:10.1016/j.metabol.2003.12.006)
- Murray S, Tulloch A, Gold MS & Avena NM 2014 Hormonal and neural mechanisms of food reward, eating behaviour and obesity. *Nature Reviews Endocrinology* **10** 540–552. (doi:10.1038/nrendo.2014.91)
- Murzi E, Contreras Q, Teneud L, Valecillos B, Parada MA, De Parada MP & Hernandez L 1996 Diabetes decreases limbic extracellular dopamine in rats. *Neuroscience Letters* **202** 141–144. (doi:10.1016/0304-3940(95)12232-X)
- Myers MG & Olson DP 2012 Central nervous system control of metabolism. *Nature* **491** 357–363. (doi:10.1038/nature11705)
- Naleid AM, Grace MK, Cummings DE & Levine AS 2005 Ghrelin induces feeding in the mesolimbic reward pathway between the ventral tegmental area and the nucleus accumbens. *Peptides* **26** 2274–2279. (doi:10.1016/j.peptides.2005.04.025)
- Naude J, Tolu S, Dongelmans M, Torquet N, Valverde S, Rodriguez G, Pons S, Maskos U, Mouro T, Marti F, et al. 2016 Nicotinic receptors in the ventral tegmental area promote uncertainty-seeking. *Nature Neuroscience* **19** 471–478. (doi:10.1038/nn.4223)
- Nestler EJ 2005 Is there a common molecular pathway for addiction? *Nature Neuroscience* **8** 1445–1449. (doi:10.1038/nn1578)
- Niswender KD, Morrison CD, Clegg DJ, Olson R, Baskin DG, Myers MG, Seeley RJ & Schwartz MW 2003 Insulin activation of phosphatidylinositol 3-Kinase in the hypothalamic arcuate nucleus. *A Key Mediator of Insulin-Induced Anorexia* **52** 227–231. (doi:10.2337/diabetes.52.2.227)
- O'Dell LE, Natividad LA, Pipkin JA, Roman F, Torres I, Jurado J, Torres OV, Friedman TC, Tenayuca JM & Nazarian A 2014 Enhanced nicotine self-administration and suppressed dopaminergic systems in a rat model of diabetes. *Addiction Biology* **19** 1006–1019. (doi:10.1111/adb.12074)
- O'Hara BF, Edgar DM, Cao VH, Wiler SW, Heller HC, Kilduff TS & Miller JD 1998 Nicotine and nicotinic receptors in the circadian system. *Psychoneuroendocrinology* **23** 161–173. (doi:10.1016/S0306-4530(97)00077-2)
- Oliveira-Maia AJ, Stapleton-Kotloski JR, Lyall V, Phan T-HT, Mummalaneni S, Melone P, DeSimone JA, Nicoletti MAL & Simon SA 2009 Nicotine activates TRPM5-dependent and independent taste pathways. *PNAS* **106** 1596–1601. (doi:10.1073/pnas.0810184106)
- Ostlund SB, Koshelev AR & Maidment NT 2014 Differential effects of systemic cholinergic receptor blockade on Pavlovian incentive motivation and goal-directed action selection. *Neuropsychopharmacology* **39** 1490–1497. (doi:10.1038/npp.2013.348)
- Parker LA & Doucet K 1995 The effects of nicotine and nicotine withdrawal on taste reactivity. *Pharmacology Biochemistry and Behavior* **52** 125–129. (doi:10.1016/0091-3057(95)00060-A)
- Pavlov VA, Wang H, Czura CJ, Friedman SG & Tracey KJ 2003 The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation. *Molecular Medicine* **9** 125–134.
- Perkins KA 1992 Metabolic effects of cigarette smoking. *Journal of Applied Physiology* **72** 401–409.
- Piomelli D 2003 The molecular logic of endocannabinoid signalling. *Nature Reviews Neuroscience* **4** 873–884. (doi:10.1038/nrn1247)
- Plum L, Belgardt BF & Bruning JC 2006 Central insulin action in energy and glucose homeostasis. *Journal of Clinical Investigation* **116** 1761–1766. (doi:10.1172/JCI29063)
- Porter C 2017 Quantification of UCP1 function in human brown adipose tissue. *Adipocyte* 1–8.

- Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, Scherer PE & Ahima RS 2004 Adiponectin acts in the brain to decrease body weight. *Nature Medicine* **10** 524–529. (doi:10.1038/nm1029)
- Qu D, Ludwig DS, Gammeltoft S, Piper M, Pellemounter MA, Cullen MJ, Mathes WF, Przypek R, Kanarek R & Maratos-Flier E 1996 A role for melanin-concentrating hormone in the central regulation of feeding behaviour. *Nature* **380** 243–247. (doi:10.1038/380243a0)
- Ramos EJ, Meguid MM, Campos AC & Coelho JC 2005 Neuropeptide Y, alpha-melanocyte-stimulating hormone, and monoamines in food intake regulation. *Nutrition* **21** 269–279. (doi:10.1016/j.nut.2004.06.021)
- Richardson JR, Pipkin JA, O'Dell LE & Nazarian A 2014 Insulin resistant rats display enhanced rewarding effects of nicotine. *Drug Alcohol Depend* **140** 205–207. (doi:10.1016/j.drugalcdep.2014.03.028)
- Rinaman L 2010 Ascending projections from the caudal visceral nucleus of the solitary tract to brain regions involved in food intake and energy expenditure. *Brain Research* **1350** 18–34. (doi:10.1016/j.brainres.2010.03.059)
- Risner ME & Goldberg SR 1983 A comparison of nicotine and cocaine self-administration in the dog: fixed-ratio and progressive-ratio schedules of intravenous drug infusion. *Journal of Pharmacology and Experimental Therapeutics* **224** 319–326.
- Rohleder N & Kirschbaum C 2006 The hypothalamic-pituitary-adrenal (HPA) axis in habitual smokers. *International Journal of Psychophysiology* **59** 236–243. (doi:10.1016/j.ijpsycho.2005.10.012)
- Rubinstein M, Mogil JS, Japon M, Chan EC, Allen RG & Low MJ 1996 Absence of opioid stress-induced analgesia in mice lacking beta-endorphin by site-directed mutagenesis. *PNAS* **93** 3995–4000. (doi:10.1073/pnas.93.9.3995)
- Rupprecht LE, Donny EC & Sved AF 2015 Obese smokers as a potential subpopulation of risk in tobacco reduction policy. *Yale Journal of Biology and Medicine* **88** 289–294.
- Rusk IN & Cooper SJ 1989 The selective dopamine D1 receptor agonist SKF 38393: its effects on palatability- and deprivation-induced feeding, and operant responding for food. *Pharmacology Biochemistry and Behavior* **34** 17–22. (doi:10.1016/0091-3057(89)90346-8)
- Sam AH, Troke RC, Tan TM & Bewick GA 2012 The role of the gut/brain axis in modulating food intake. *Neuropharmacology* **63** 46–56. (doi:10.1016/j.neuropharm.2011.10.008)
- Scherer PE, Williams S, Fogliano M, Baldini G & Lodish HF 1995 A novel serum protein similar to C1q, produced exclusively in adipocytes. *Journal of Biological Chemistry* **270** 26746–26749. (doi:10.1074/jbc.270.45.26746)
- Schilström B, Svensson HM, Svensson TH & Nomikos GG 1998 Nicotine and food induced dopamine release in the nucleus accumbens of the rat: putative role of alpha7 nicotinic receptors in the ventral tegmental area. *Neuroscience* **85** 1005–1009. (doi:10.1016/S0306-4522(98)00114-6)
- Schilström B, Fagerquist MV, Zhang X, Hertel P, Panagis G, Nomikos GG & Svensson TH 2000 Putative role of presynaptic alpha7\* nicotinic receptors in nicotine stimulated increases of extracellular levels of glutamate and aspartate in the ventral tegmental area. *Synapse* **38** 375–383. (doi:10.1002/1098-2396(20001215)38:4<375::AID-SYN2>3.0.CO;2-Y)
- Schwartz MW, Woods SC, Porte D Jr, Seeley RJ & Baskin DG 2000 Central nervous system control of food intake. *Nature* **404** 661–671. (doi:10.1038/35007534)
- Seguela P, Wadiche J, Dineley-Miller K, Dani JA & Patrick JW 1993 Molecular cloning, functional properties, and distribution of rat brain alpha 7: a nicotinic cation channel highly permeable to calcium. *Journal of Neuroscience* **13** 596–604.
- Seoane-Collazo P, Martínez de Morentin PB, Ferno J, Dieguez C, Nogueiras R & Lopez M 2014 Nicotine improves obesity and hepatic steatosis and ER stress in diet-induced obese male rats. *Endocrinology* **155** 1679–1689. (doi:10.1210/en.2013-1839)
- Shariff M, Quik M, Holgate J, Morgan M, Patkar OL, Tam V, Belmer A & Bartlett SE 2016 Neuronal nicotinic acetylcholine receptor modulators reduce sugar intake. *PLoS ONE* **11** e0150270. (doi:10.1371/journal.pone.0150270)
- Skibicka KP, Hansson C, Alvarez-Crespo M, Friberg PA & Dickson SL 2011 Ghrelin directly targets the ventral tegmental area to increase food motivation. *Neuroscience* **180** 129–137. (doi:10.1016/j.neuroscience.2011.02.016)
- Skofitsch G, Jacobowitz DM & Zamir N 1985 Immunohistochemical localization of a melanin concentrating hormone-like peptide in the rat brain. *Brain Research Bulletin* **15** 635–649. (doi:10.1016/0361-9230(85)90213-8)
- Sleight AJ, Carolo C, Petit N, Zwingelstein C & Bourson A 1995 Identification of 5-hydroxytryptamine7 receptor binding sites in rat hypothalamus: sensitivity to chronic antidepressant treatment. *Molecular Pharmacology* **47** 99–103.
- Smart JL & Low MJ 2003 Lack of proopiomelanocortin peptides results in obesity and defective adrenal function but normal melanocyte pigmentation in the murine C57BL/6 genetic background. *Annals of the New York Academy of Sciences* **994** 202–210. (doi:10.1111/j.1749-6632.2003.tb03181.x)
- Solberg LI, Desai JR, O'Connor PJ, Bishop DB & Devlin HM 2004 Diabetic patients who smoke: are they different? *Annals of Family Medicine* **2** 26–32. (doi:10.1370/afm.36)
- Solinas M, Goldberg SR & Piomelli D 2008 The endocannabinoid system in brain reward processes. *British Journal of Pharmacology* **154** 369–383. (doi:10.1038/bjp.2008.130)
- Spring B, Pagoto S, McChargue D, Hedeker D & Werth J 2003 Altered reward value of carbohydrate snacks for female smokers withdrawn from nicotine. *Pharmacology Biochemistry and Behavior* **76** 351–360. (doi:10.1016/j.pbb.2003.08.008)
- Stamford BA, Matter S, Fell RD & Papanek P 1986 Effects of smoking cessation on weight gain, metabolic rate, caloric consumption, and blood lipids. *American Journal of Clinical Nutrition* **43** 486–494.
- Stanley BG, Willett VL 3rd, Donias HW, Ha LH & Spears LC 1993 The lateral hypothalamus: a primary site mediating excitatory amino acid-elicited eating. *Brain Research* **630** 41–49. (doi:10.1016/0006-8993(93)90640-9)
- Summers KL & Giacobini E 1995 Effects of local and repeated systemic administration of (-)nicotine on extracellular levels of acetylcholine, norepinephrine, dopamine, and serotonin in rat cortex. *Neurochemical Research* **20** 753–759. (doi:10.1007/BF01705545)
- Suzuki K, Simpson KA, Minnion JS, Shillito JC & Bloom SR 2010 The role of gut hormones and the hypothalamus in appetite regulation. *Endocrine Journal* **57** 359–372. (doi:10.1507/endocrj.K10E-077)
- Tanaka C, Asakawa A, Ushikai M, Sakoguchi T, Amitani H, Terashi M, Cheng K, Chaolu H, Nakamura N & Inui A 2009 Comparison of the anorexigenic activity of CRF family peptides. *Biochemical and Biophysical Research Communications* **390** 887–891. (doi:10.1016/j.bbrc.2009.10.069)
- Tracey KJ 2007 Physiology and immunology of the cholinergic anti-inflammatory pathway. *Journal of Clinical Investigation* **117** 289–296. (doi:10.1172/JCI30555)
- Trayhurn P & Wood IS 2004 Adipokines: inflammation and the pleiotropic role of white adipose tissue. *British Journal of Nutrition* **92** 347–355. (doi:10.1079/BJN20041213)
- Trigo JM, Zimmer A & Maldonado R 2009 Nicotine anxiogenic and rewarding effects are decreased in mice lacking beta-endorphin. *Neuropharmacology* **56** 1147–1153. (doi:10.1016/j.neuropharm.2009.03.013)
- Tweed JO, Hsia SH, Lutfy K & Friedman TC 2012 The endocrine effects of nicotine and cigarette smoke. *Trends in Endocrinology and Metabolism* **23** 334–342. (doi:10.1016/j.tem.2012.03.006)
- Uehara Y, Shimizu H, Ohtani K, Sato N & Mori M 1998 Hypothalamic corticotropin-releasing hormone is a mediator of the anorexigenic effect of leptin. *Diabetes* **47** 890–893. (doi:10.2337/diabetes.47.6.890)

Vaisse C, Halaas JL, Horvath CM, Darnell JE, Stoffel M & Friedman JM 1996 Leptin activation of Stat3 in the hypothalamus of wild-type and ob/ob mice but not db/db mice. *Nature Genetics* **14** 95–97. (doi:10.1038/ng0996-95)

Valassi E, Scacchi M & Cavagnini F 2008 Neuroendocrine control of food intake. *Nutrition, Metabolism and Cardiovascular Diseases* **18** 158–168. (doi:10.1016/j.numecd.2007.06.004)

Van Bockstaele EJ, Peoples J, Menko AS, McHugh K & Drolet G 2000 Decreases in endogenous opioid peptides in the rat medullo-coerulear pathway after chronic morphine treatment. *Journal of Neuroscience* **20** 8659–8666.

Volkow ND, Wang GJ, Fowler JS & Telang F 2008 Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. *Philosophical Transactions of the Royal Society of London* **363** 3191–3200. (doi:10.1098/rstb.2008.0107)

Vosselman MJ, van Marken Lichtenbelt WD & Schrauwen P 2013 Energy dissipation in brown adipose tissue: from mice to men. *Molecular and Cellular Endocrinology* **379** 43–50. (doi:10.1016/j.mce.2013.04.017)

Wada E, Wada K, Boulter J, Deneris E, Heinemann S, Patrick J & Swanson LW 1989 Distribution of alpha 2, alpha 3, alpha 4, and beta 2 neuronal nicotinic receptor subunit mRNAs in the central nervous system: a hybridization histochemical study in the rat. *Journal of Comparative Neurology* **284** 314–335. (doi:10.1002/cne.902840212)

Wager-Srdar SA, Levine AS, Morley JE, Hoidal JR & Niewoehner DE 1984 Effects of cigarette smoke and nicotine on feeding and energy. *Physiology and Behavior* **32** 389–395. (doi:10.1016/0031-9384(84)90252-X)

Waldbillig RJ, Bartness TJ & Stanley BG 1981 Increased food intake, body weight, and adiposity in rats after regional neurochemical depletion of serotonin. *Journal of Comparative and Physiological Psychology* **95** 391–405. (doi:10.1037/h0077790)

Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, Li JH, Wang H, Yang H, Ulloa L, et al. 2003 Nicotinic acetylcholine receptor [alpha]7 subunit is an essential regulator of inflammation. *Nature* **421** 384–388. (doi:10.1038/nature01339)

Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL & Ferrante AW 2003 Obesity is associated with macrophage accumulation in adipose tissue. *Journal of Clinical Investigation* **112** 1796–1808. (doi:10.1172/JCI200319246)

Wellman PJ, Marmon MM, Reich S & Ruddle J 1986 Effects of nicotine on body weight, food intake and brown adipose tissue thermogenesis. *Pharmacology Biochemistry and Behavior* **24** 1605–1609. (doi:10.1016/0091-3057(86)90493-4)

Wisse BE 2004 The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *Journal of the American Society of Nephrology* **15** 2792–2800. (doi:10.1097/01.ASN.0000141966.69934.21)

Won W-Y, Lee C-U, Chae J-H, Kim J-J, Lee C & Kim D-J 2014 Changes of plasma adiponectin levels after smoking cessation. *Psychiatry Investigation* **11** 173–178. (doi:10.4306/pi.2014.11.2.173)

Woods SC & D'Alessio DA 2008 Central control of body weight and appetite. *Journal of Clinical Endocrinology and Metabolism* **93** s37–s50. (doi:10.1210/jc.2008-1630)

Wren AM & Bloom SR 2007 Gut hormones and appetite control. *Gastroenterology* **132** 2116–2130. (doi:10.1053/j.gastro.2007.03.048)

Wu Y, Song P, Zhang W, Liu J, Dai X, Liu Z, Lu Q, Ouyang C, Xie Z, Zhao Z, et al. 2015 Activation of AMPK $\alpha$ 2 in adipocytes is essential for nicotine-induced insulin resistance in vivo. *Nature Medicine* **21** 373–382. (doi:10.1038/nm.3826)

Xiao Y, Fan H, Musachio JL, Wei ZL, Chellappan SK, Kozikowski AP & Kellar KJ 2006 Sazetidine-A, a novel ligand that desensitizes alpha4beta2 nicotinic acetylcholine receptors without activating them. *Molecular Pharmacology* **70** 1454–1460. (doi:10.1124/mol.106.027318)

Xu T-Y, Guo L-L, Wang P, Song J, Le Y-Y, Viollet B & Miao C-Y 2012 Chronic exposure to nicotine enhances insulin sensitivity through  $\alpha$ 7 nicotinic acetylcholine receptor-STAT3 pathway. *PLoS ONE* **7** e51217. (doi:10.1371/journal.pone.0051217)

Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, et al. 2001 The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity. *Nature Medicine* **7** 941–946. (doi:10.1038/90984)

Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, Okada-Iwabu M, Kawamoto S, Kubota N, Kubota T, et al. 2007 Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nature Medicine* **13** 332–339. (doi:10.1038/nm1557)

Yoshida T, Yoshioka K, Hiraoka N & Kondo M 1990 Effect of nicotine on norepinephrine turnover and thermogenesis in brown adipose tissue and metabolic rate in MSG obese mice. *Journal of Nutritional Science and Vitaminology* **36** 123–130. (doi:10.3177/jnsv.36.123)

Yoshida T, Sakane N, Umekawa T, Kogure A, Kondo M, Kumamoto K, Kawada T, Nagase I & Saito M 1999 Nicotine induces uncoupling protein 1 in white adipose tissue of obese mice. *International Journal of Obesity and Related Metabolic Disorders* **23** 570–575. (doi:10.1038/sj.ijo.0800870)

Zahniser NR, Goens MB, Hanaway PJ & Vinych JV 1984 Characterization and regulation of insulin receptors in rat brain. *Journal of Neurochemistry* **42** 1354–1362. (doi:10.1111/j.1471-4159.1984.tb02795.x)

Zhan C, Zhou J, Feng Q, Zhang J-e, Lin S, Bao J, Wu P & Luo M 2013 Acute and long-term suppression of feeding behavior by POMC neurons in the brainstem and hypothalamus, respectively. *Journal of Neuroscience* **33** 3624–3632. (doi:10.1523/JNEUROSCI.2742-12.2013)

Zhang J & Berg DK 2007 Reversible inhibition of GABA(A) receptors by  $\alpha$ 7-containing nicotinic receptors on the vertebrate postsynaptic neurons. *Journal of Physiology* **579** 753–763. (doi:10.1113/jphysiol.2006.124578)

Zheng H, Patterson LM & Berthoud HR 2007 Orexin signaling in the ventral tegmental area is required for high-fat appetite induced by opioid stimulation of the nucleus accumbens. *Journal of Neuroscience* **27** 11075–11082. (doi:10.1523/JNEUROSCI.3542-07.2007)

Zhu X, Ottenheimer D & DiLeone RJ 2016 Activity of D1/2 receptor expressing neurons in the nucleus accumbens regulates running, locomotion, and food intake. *Frontiers in Behavioral Neuroscience* **10** 66. (doi:10.3389/fnbeh.2016.00066)

Zoli M & Picciotto MR 2012 Nicotinic regulation of energy homeostasis. *Nicotine and Tobacco Research* **14** 1270–1290. (doi:10.1093/ntr/nts159)

Zoli M, Moretti M, Zanardi A, McIntosh JM, Clementi F & Gotti C 2002 Identification of the nicotinic receptor subtypes expressed on dopaminergic terminals in the rat striatum. *Journal of Neuroscience* **22** 8785–8789.

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