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

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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 α-melanocyte stimulating hormone (α-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

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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 corticotropic 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 beiging 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

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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 α-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 α-MSH act on melanocortin-3 and 4 receptors (MC3R and MC4R) to regulate feeding behavior. The AgRP is an inverse agonist, while α-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

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lateral hypothalamus (Skofitsch *et al*. 1985). It has been showed 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-arachidonoylethanolamine (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 $CB1^{-/-}$ 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

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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

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α7-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 α7-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 AMPKα-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 α-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

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and morbidly obese subjects, suggesting that smoking might be more rewarding in this population (Chiolero *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 αβ-combinations (α2–α6 and β2–β4; e.g., α3β4* containing nAChRs; the asterisk refers to one or more additional subunits that could be associated with the receptor), homomeric nAChRs (α7–α9) and a heteromer α-combination (α9 with α10) (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 α4, α7 and β2 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 α3β4 subunit-containing receptors

Nicotine has been shown to reduce food intake and weight gain by modulating the function of melanocortin system through α3β4*-containing nAChRs (Mineur *et al.* 2011). In particular, nicotine activates α3β4* 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 α3β4* nAChRs leads to depolarization of POMC-containing neurons in the ARC, which in turn results in the release of α-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 β2 subunit-containing receptors

Recent studies have indicated that activation of β2*-containing nAChRs similar to α3β4* 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 β2*-containing nAChRs sazetidine-A (SAZ-A) significantly reduced body weight and food intake in obese mice (Dezfuli *et al.* 2016). Specifically, chronic desensitization of β2 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 $\beta2^{-/-}$ and $MCR4^{-/-}$ mice (Dezfuli *et al.* 2016). These findings suggest that β2 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 β2 subunit-containing nAChRs would cause alterations in the function of α3β4* containing nAChRs or vice versa and if that these variations could regulate food intake and body weight.

Control of feeding by nicotinic cholinergic α4β2 subunit-containing receptors

Expression analysis within the hypothalamus has identified α4β2 subunits of nAChRs in LHA, ARC and PVN (Wada *et al.* 1989). Furthermore, α4β2 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

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(McGranahan, 2011 #1592). Activation of these receptors in the LHA appears to reduce food intake. Systemic, as well as local administration of α4β2 receptor antagonist, di-hydro-β-erythroidine (DHβE) 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 α4β2 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 α4β2 nAChRs in the LHA, as application of DHβE on hypothalamic slices inhibited nicotine-induced depolarization of POMC neurons (Huang *et al*. 2011). In another study, selective agonist of α4β2 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 α4β2 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 α4β2 nAChRs.

Control of feeding by nicotinic cholinergic α7 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 α7 nAChRs. Neurons containing α7 nAChRs are found in the ARC nucleus, VMH and DMN (Seguela *et al*. 1993). Apart from the hypothalamus, α7 nAChRs are expressed on dopaminergic neurons (Klink *et al*. 2001) and glutamatergic afferents projecting to the VTA (Jones & Wonnacott 2004). Stimulation of α7 nAChRs was shown to suppress food intake via its actions in the hypothalamus (Jo *et al*. 2002). The α7 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 α7 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, α7 nAChR antagonist MLA reduced the excitation of NPY by nicotine (Huang *et al*. 2011).

Aside from modulating the activity of neurons in the hypothalamus, α7 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 α7 nAChR-specific antagonist (α-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 α7 nAChR in modulating the dopamine release in connection to food intake is somewhat intricate. Taking into account that α7 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 α7 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 α7 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

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(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-α 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-α and IL6 (Fernandez-Real *et al*. 2003, Ellingsgaard *et al*. 2008).

Aside from its central action, nicotine acting on α7 nAChRs expressed on immune cells may affect metabolic homeostasis. Recruitment of α7 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 α7 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 α7 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 α7 nAChR was reduced in fat cells isolated from subcutaneous adipose tissue of obese human subjects (Cancello *et al*. 2012). Moreover, oral application of specific α7 nAChR agonist in leptin-resistant db/db obese mice reduced food intake and weight gain in these mice (Marrero *et al*. 2010). α7 nAChRs play a major role in the central and peripheral regulation of food intake and energy homeostasis. Furthermore, nicotine, acting on α7 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 α7 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 α7 nAChRs, reducing circulating IL-6, therefore reducing GLP-1 secretion. It is accepted now that apart from its central action, nicotine activation of α7 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,

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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 α4* and α6* containing nAChRs (Grady *et al*. 2007, De Biasi & Dani 2011). Furthermore, chronic long-term sucrose intake increased α4β2* while decreases α6β2 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 2011*a*,*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

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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

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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 7αnAChR, 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 α-7 and α3β4 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 α4β2* and α6β2 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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