Pharmacology & Therapeutics 219 (2021) 107693

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Nicotine' actions on energy balance: Friend or foe?

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ARTICLE INFO

Available online 26 September 2020

Keywords:
Nicotine
Nicotinic acetylcholine receptors
Food intake
Energy expenditure
Glucose homeostasis
Hypothalamus
Adipose tissue
Obesity

ABSTRACT

Obesity has reached pandemic proportions and is associated with severe comorbidities, such as type 2 diabetes mellitus, hepatic and cardiovascular diseases, and certain cancer types. However, the therapeutic options to treat obesity are limited. Extensive epidemiological studies have shown a strong relationship between smoking and body weight, with non-smokers weighing more than smokers at any age. Increased body weight after smoking cessation is a major factor that interferes with their attempts to quit smoking. Numerous controlled studies in both humans and rodents have reported that nicotine, the main bioactive component of tobacco, exerts a marked anorectic action. Furthermore, nicotine is also known to modulate energy expenditure, by regulating the thermogenic activity of brown adipose tissue (BAT) and the browning of white adipose tissue (WAT), as well as glucose homeostasis. Many of these actions occur at central level, by controlling the activity of hypothalamic neuropeptide systems such as proopiomelanocortin (POMC), or energy sensors such as AMP-activated protein kinase (AMPK). However, direct impact of nicotine on metabolic tissues, such as BAT, WAT, liver and pancreas has also been described. Here, we review the actions of nicotine on energy balance. The relevance of this interaction is interesting, because considering the restricted efficiency of obesity treatments, a possible complementary approach may focus on compounds with known pharmacokinetic profile and pharmacological actions, such as nicotine or nicotinic acetylcholine receptors signaling.

Contents

Abbreviations: α-MSH, alpha melanocyte-stimulating hormone; Ach, acetylcholine; AgRP, agouti-related protein; AKT, protein kinase B; AMPK, AMP-activated protein kinase; ARC, arcuate nucleus of the hypothalamus; BAT, brown adipose tissue; BF, basal forebrain; CART, cocaine- and amphetamine-regulated transcript; CNS, central nervous system; CVD, cardiovascular disease; DA, dopamine; DMH, dorsomedial nucleus of the hypothalamus; DMPP, dimethylphenylpiperazinium; GLP-1, glucagon-like peptide 1; IR, insulin resistance; IRS, insulin receptor substrate; HGP, hepatic glucose production; KOR, kappa opioid receptor; LHA, lateral hypothalamic area; nAChR, nicotinic acetylcholine receptor; MCH, melanin-concentrating hormone; MC4R, melanocortin receptor 4; NAc, nucleus accumbens; NPY, neuropeptide Y; NRT, nicotine replacement therapy; mHb, medial habenula; OX, orexin; PFA, perifornical area; POMC, proopiomelanocortin; PVH, paraventricular nucleus of the hypothalamus; SNS, sympathetic nervous system; STAT3, signal transducer and activator of transcription 3; UCP1, uncoupling protein 1; VMH, ventromedial nucleus of the hypothalamus; VTA, ventral tegmental area; WAT, white adipose tissue.

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https://doi.org/10.1016/j.pharmthera.2020.107693

1. Introduction

Currently, obesity rates have reached pandemic proportions (Al-Massadi, Ferno, Dieguez, Nogueiras, & Quinones, 2019; Dragano, Ferno, Dieguez, Lopez, & Milbank, 2020; Muller, Clemmensen, Finan, DiMarchi, & Tschop, 2018; Srivastava & Apovian, 2018; Williams, Nawaz, & Evans, 2020). The challenge of obesity resides in the premature disability and death due to its comorbidities, namely cardiovascular diseases (CVD), type 2 diabetes, metabolic-associated hepatic steatosis, osteoarthritis, depression and some types of cancers, among others (Al-Massadi, Ferno, et al., 2019; Bluher, 2019; Dragano et al., 2020). Up to now, neither obesity prevention by behavioral interventions to reduce food intake and increase energy expenditure, nor most of the approved drugs and treatments (3–7% net weight loss) have provided convincing results against obesity. This lack of success is mainly due to the inherent difficulty to maintain life-style changes that lead to a lower body weight, the presence of unwanted side effects, and the unavailability of effective and safe treatments for the affected population. Furthermore, most of the factors known to promote a negative energy balance have not been translated to successful pharmacological treatments due to the development of drug resistance (Al-Massadi, Ferno, et al., 2019; Dragano et al., 2020; Muller et al., 2018; Srivastava & Apovian, 2018; Williams et al., 2020). With this in mind, expanding our knowledge on the mechanism of action of compounds already used for other purposes, but known to influence body weight, may facilitate our search to identify and design clear-cut treatments against obesity and associated pathologies.

Over the past 50 years, there has been an increasing amount of literature on the inverse relationship between cigarette smoking and body weight. Individuals who smoke are commonly thinner than nonsmokers of the same age and sex, due to the reduced caloric intake and higher resting energy expenditure in the smokers (Albanes, Jones, Micozzi, & Mattson, 1987; Blauw et al., 2015; Collins, Walker, & Stamford, 1996; Dallosso & James, 1984; Hofstetter, Schutz, Jequier, & Wahren, 1986; Perkins, 1992). On average, smokers gain 4.5 kg in the first year after quitting smoking (Audrain-Mcgovern & Benowitz, 2011). Post-cessation increase in appetite and weight gain are the principal causes that discourage smokers from quitting (Hsieh et al., 2019; Stamford, Matter, Fell, & Papanek, 1986; Williamson et al., 1991; Zoli & Picciotto, 2012). However, heavy and/or long-term smokers are more likely to be overweight or obese (Dare, Mackay, & Pell, 2015; Mackay, Gray, & Pell, 2013), associated with tendency to develop central adiposity and insulin resistance (IR) (Houston et al., 2006). So, the paradoxical scenario is that while smoking reduces body weight, obese subjects are more likely to smoke and show a higher smoking intensity (Carreras-Torres et al., 2018; Filozof, Fernandez Pinilla, & Fernandez-Cruz, 2004). Body weight control might be the explanation to this as, especially in adolescent women (Fang, 2019), higher body mass index causally influences several aspects of smoking, including lifetime smoking habits, the likelihood of smoking initiation, and the number of cigarettes smoked per day (Taylor et al., 2019). In addition, smoking is associated with lower exercise levels and lower physical endurance (Conway & Cronan, 1992; Furlanetto et al., 2014; Hirsch, Sue, Wasserman, Robinson, & Hansen, 1985; Sandvik, Erikssen, & Thaulow, 1995) while smoking cessation improves physical performance (Feinberg et al., 2015; Hashizume, Yamaji, Kusaka, & Kawahara, 2000). This is especially important, as the co-occurrence of obesity and smoking may increase the risk of CVD.

Because of the clear-cut effects of smoking on body weight, uncovering the mechanism of action has for long been in the spotlight to develop a treatment for obesity, without the detrimental effects of long-term smoking. Both peripheral and central actions of nicotine, the main bioactive component of tobacco, have been focused on due to its capacity to modulate feeding, energy expenditure, and glucose homeostasis (Eliasson, 2003; Martinez de Morentin et al., 2012; Mineur et al., 2011; Nogueiras, Dieguez, & Lopez, 2015; Picciotto & Mineur, 2013; Seoane-Collazo et al., 2014; Seoane-Collazo et al., 2019). Based on these, the functional and pharmacological properties of nicotinic acetylcholine receptors (nAChR) have been largely studied. So far, evidence suggests that 16 genes encode nAChR subunits in mammalian genomes, including humans (Schaaf, 2014). The nAChRs are ligand-gated ion channels comprising five transmembrane α and β-subunits (Bertrand, Lee, Flood, Marger, & Donnelly-Roberts, 2015; Gotti, Zoli, & Clementi, 2006; Leonard & Bertrand, 2001; Stojakovic, Espinosa, Farhad, & Lutfy, 2017; Terry & Callahan, 2019; Tregellas & Wylie, 2019). In response to binding acetylcholine (ACh) or nicotine, the cation channel opens to permit influx of Na^+ or Ca^{2+} into the cell. Two types of receptor conformations exist, varying in their constituent subunits and pharmacology. Heteromeric nAChRs comprise three α subunits combined with two β subunits, normally alpha4beta2 in the brain. Homomeric nAChRs assemble from a single subunit type, typically α7 in the human brain. Homomeric α7 nAChRs are highly permeable to Ca^{2+}. Both receptor types are expressed both pre- and postsynaptically. Presynaptic nAChRs, positioned to allow Ca^{2+} influx into the synaptic bouton, play a major role in modulating the release of many neurotransmitters. Physiologically, the two types of nAChRs differ in their affinity for nicotine. One essential characteristic of nAChRs is that in response to endogenous ACh or other cholinergic ligands, like nicotine, depending on the dose and duration of exposure, can either be desensitized or upregulated (Bertrand et al., 2015; Gotti, Zoli, & Clementi, 2006; Leonard & Bertrand, 2001; Stojakovic et al., 2017; Terry & Callahan, 2019; Tregellas & Wylie, 2019). For example, α2β4 binds nicotine with high affinity, and produce a continuous response. On the other hand, α7 nAChRs are less responsive to nicotine, produce a rapid effect, and desensitize quickly following ligand binding (Hurst, Rollema, & Bertrand, 2013; Olale, Gerzanich, Kuryatov, Wang, & Lindstrom, 1997; Tregellas & Wylie, 2019). This together with ability to form homomeric or heteromeric receptors and their ubiquitous expression in the central nervous system (CNS) and peripheral tissues (Changeux, 2010; Gotti et al., 2009; Hurst et al., 2013), enable nicotine to exert broad actions in the regulation of energy homeostasis. Published data indicate that nicotine prevents weight gain through reduction in appetite and an increase in metabolic rate (Audrain-Mcgovern & Benowitz, 2011; Jo, Talmage, & Role, 2002). First, nicotine modulates energy intake by acting on the feeding-related hypothalamic neuropeptide system (Fornari et al., 2007; Frankish et al., 1995; Martinez de Morentin et al., 2012; Mineur et al., 2011). Second, nicotine promotes energy expenditure by activating brown adipose tissue (BAT) thermogenesis and, importantly, the browning of white adipose tissue (WAT) (Arai et al., 2001; Mano-Otagiri, Iwasaki-Sekino, Ohata, Arai, & Shibasaki, 2009; Martinez de Morentin et al., 2012; Seoane-Collazo et al., 2019; Shelton, Gayerie De Abreu, Hunter, Parkinson, & Lamming, 1990). Third, nicotine's ability to promote adipocyte lipolysis leads to decreased fat cell size and lower overall adiposity (Andersson & Arner, 2001; Sztalryd, Hamilton, Horwitz, Johnson, & Kraemer, 1996; Wu

et al., 2015). Fourth, nicotine regulates glycemia through bi-directional actions on insulin sensitivity and glucose production in a time-dependent manner (Nogueiras et al., 2015; Vu et al., 2014; Wu, Song, et al., 2015). Of note, taste perception (Perkins et al., 1990; Stojakovic et al., 2017), gastrointestinal exocrine and endocrine secretion and gastrointestinal motility (Hajek, Gillison, & McRobbie, 2003; Konturek, Solomon, McCreight, Johnson, & Jacobson, 1971; Lindell et al., 1993; Wu & Cho, 2004) are also among the described effects associated with smoking and/or nicotine administration. The impact of nicotine in gastrointestinal hormone secretion such as ghrelin or insulin (Ejiri, Taniguchi, Ishihara, Hara, & Baba, 1990; Kokkinos et al., 2007; Konturek et al., 1971; Koopmann et al., 2015; Stadler et al., 2014; Stojakovic et al., 2017), provides another mechanism of action for nicotine, given the influence of these signals on energy and metabolic homeostasis (Al Massadi, Lopez, Tschop, Dieguez, & Nogueiras, 2017; Cui, Lopez, & Rahmouni, 2017; Lopez et al., 2008; Muller et al., 2015; Tschop, Smiley, & Heiman, 2000). Smoking and/or nicotine exposure might also influence on these hormones by altering the microbiome in different areas of the gastrointestinal tract (Ganesan et al., 2017; Shanahan et al., 2018). Changes in the intestinal microbiota and the fecal metabolome, are well documented to influence energy homeostasis (Chevalier et al., 2015; Moreno-Navarrete et al., 2018; Rosenbaum, Knight, & Leibel, 2015; Suarez-Zamorano et al., 2015; Wang et al., 2019; Zarrinpar et al., 2018) and nicotine could thus modulate energy balance and the ingestion of palatable food, while its effects in intestinal secretions and intestinal motility, could impact nutrient absorption. Therefore, understanding the mechanisms underlying the actions exerted by nicotine might be a promising approach to explore suitable pharmacological targets for the treatment of obesity and its associated metabolic disorders. In this work, we will review the current knowledge of nicotine's actions on energy balance, trying to address whether nicotine and/or nAChRs could be a reasonable target for anti-obesity therapies.

2. Nicotine's effects of food intake

Food intake is regulated by two overlapping circuits involving hypothalamic and mesocorticolimbic structures among others (Dragano et al., 2020; Muller et al., 2018; Stojakovic et al., 2017; Zoli & Picciotto, 2012). Within the hypothalamus, the arcuate nucleus (ARC) has a privileged anatomical position and acts as a gate for the brain to sense peripheral signals, thereby sensing energy status. In the ARC, feeding is regulated by two sets of neurons expressing anorexigenic and orexigenic neuropeptides. One set of neurons expresses the orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP), while another set of neurons expresses the anorectic proopiomelanocortin (POMC) and cocaine and amphetamine-related peptide (CART) (Al Massadi et al., 2017; Seoane-Collazo et al., 2015). ARC neurons project to various brain regions including two major areas enabling a coordinated behavioral response: the lateral hypothalamic area (LHA), that acts as a critical link between homeostatic and hedonic feeding (Rossi & Stuber, 2018), and the cortico-limbic-striatal circuit, a key player in reward and motivated behavior in rodents and humans. Palatable food and drugs of abuse influence consummatory behavior (Richard, Castro, Difeliceantonio, Robinson, & Berridge, 2013; Stojakovic et al., 2017; Zoli & Picciotto, 2012) by increasing dopaminergic signaling from the ventral tegmental area (VTA) to the prefrontal cortex and the nucleus accumbens (NAc), two central components of the circuitry underlying reward and memory of reward (Pignatelli & Bonci, 2015; Stice, Burger, & Yokum, 2013). Given that this mechanism accounts for overeating associated with obesity (Nummenmaa et al., 2012; Simon et al., 2014), targeting both components of feeding could be an appealing approach for the development of therapeutics against obesity. The presence of several nAChR subunits and the rich cholinergic afferents in both circuits (Britto et al., 1992; Calarco et al., 2018; de Kloet, Mansvelder, & De Vries, 2015; Goldman, Simmons, Swanson, Patrick, & Heinemann, 1986; Harfstrand et al., 1988; Jo, Wiedl, & Role, 2005; Okuda et al., 1993; Shioda et al., 1997), together with nicotine's capacity to regulate both homeostatic and hedonic processes (Fig. 1) (Berrendero, Robledo, Trigo, Martin-Garcia, & Maldonado, 2010; Kroemer, Guevara, Vollstadt-Klein, & Smolka, 2013; Martinez de Morentin et al., 2012; Mineur et al., 2011; Seoane-Collazo et al., 2014; Seoane-Collazo et al., 2019; Zoli & Picciotto, 2012) points to nicotine signaling as an attractive therapeutic target.

2.1. POMC/CART and AgRP/NPY systems

Although POMC neurons are specifically located in the ARC, POMC/CART fibers spread widely in the CNS, including energy homeostasis related areas, such the paraventricular nucleus of the hypothalamus (PVH), the dorsomedial nucleus of the hypothalamus (DMH), the LHA and the perifornical area (PFA). Another large set of neurons in the ventromedial ARC expresses NPY and AgRP, and projects their axons mainly to the same regions innervated by POMC; with especially dense innervation in the PVH, the DMH and the posterior hypothalamus (Cone, 2005). AgRP/NPY and POMC express receptors for circulating signals regulating energy balance such as leptin and ghrelin (Cowley et al., 2001; Cowley et al., 2003; Cui et al., 2017; Waterson & Horvath, 2015). POMC and NPY/AgRP neurons constitute a functional unit in which neural orexigenic inputs, such as ghrelin, rapidly activates NPY/AgRP neurons and, subsequently inhibits POMC neurons by increasing the GABAergic tone in NPY/AgRP neurons (Al Massadi et al., 2017; Cowley et al., 2003) leading to increased appetite. Conversely, anorexigenic inputs, such as leptin and nicotine, directly activate POMC neurons and inhibit the NPY/AgRP GABAergic tone to POMC neurons (Cowley et al., 2001; Martinez de Morentin et al., 2012). In this regard, both AgRP and POMC neurons show enriched expression of α3, α6, β2 or β4 nAChR subunits to a similar extend, whereas α4 and α7 mRNA levels were found to differ between the two neuronal subsets (Calarco et al., 2018; Henry, Sugino, Tozer, Branco, & Sternson, 2015). α7nAChR also co-localize with α-melanocyte-stimulating hormone (α -MSH, a product of POMC processing) and NPY in hypothalamic cells (Souza et al., 2019). In fact, several studies have showed that nicotine modulates energy intake by altering the expression of orexigenic and anorexigenic peptides in the ARC (Bishop, Parker, & Coscina, 2002; Fornari et al., 2007; Frankish et al., 1995; Hur, Hong, Choi, Shin, & Chun, 2010; Jang et al., 2003; Martinez de Morentin et al., 2012; Mineur et al., 2011).

Activation of POMC neurons increases the release of melanocortin peptides, including, α-MSH, and β-endorphin. These peptides are known to play pivotal roles in energy homeostasis via the brain-expressed melanocortin receptor (MCR) (Cone, 2005; Harno, Gali Ramamoorthy, Coll, & White, 2018). Several pieces of evidence suggest that nicotine exerts its anorectic effect via the hypothalamic-melanocortin system. Systemic nicotine treatment or activation of hypothalamic nAChR increase POMC mRNA levels (Martinez de Morentin et al., 2012) and activate POMC neurons in the ARC with the subsequent stimulation of MC4R in the PVH (Mineur et al., 2011) (Fig. 1). POMC appears to be indispensable in nicotine's anorexigenic effect since POMC null mice show no difference in food intake after treatment with nicotine or cytisine, a full agonist at α3β4nAChR (Mineur et al., 2011). The critical role of β4 subunit-containing nAChRs in the regulation of appetite by nicotine is confirmed by the negative energy balance (including reduced food intake) observed in diet-induced obese mice after treatment with dimethylphenylpiperazinium (DMPP, a human α3β4 agonist) (Clemmensen et al., 2018). Results from α3β4nAChR antagonism provide additional evidence, by showing blunted nicotine anorectic action in rats after mecamylamine treatment (Martinez de Morentin et al., 2012). However, α3β4nAChR are abundantly expressed in peripheral ganglia, where its activation is associated with adverse effects such as emesis and nausea (Ji et al., 2007), thus hindering the design of therapeutics targeting this receptor. Other reports have also supported the intervention of α4β2 and α7nAChR in the

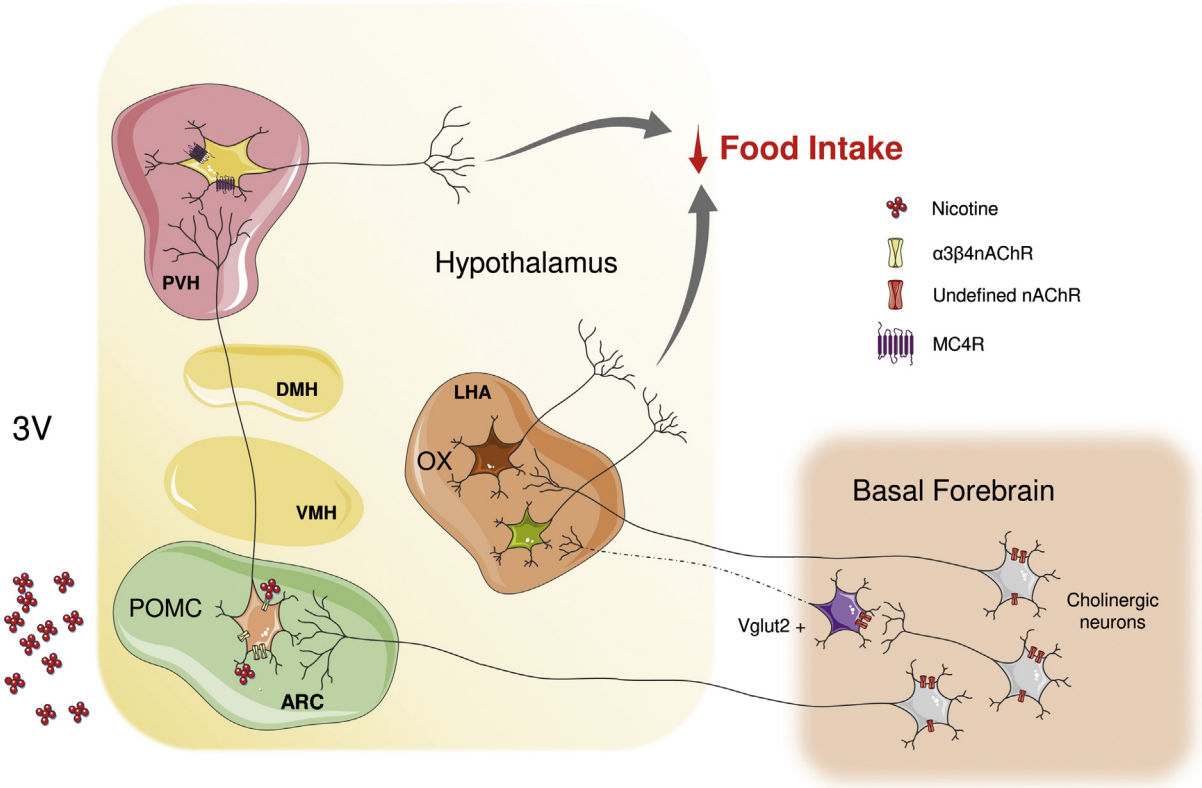

Fig. 1. Nicotine's regulation of food intake. Stimulation of hypothalamic α3β4nAChR by nicotine stimulate POMC neurons in the ARC and subsequently activates MC4R in second order neurons in the PVH leading to decrease in food intake. A new potential target for nicotine-mediated appetite suppression has been identified in extra-hypothalamic areas. A subset of GABAergic cholinergic neurons in the basal forebrain, projecting to downstream neurons in the hypothalamus, such OX and POMC neurons, have been found to suppress appetite. In the same area, vGlut2 positive odor-responsive neurons expressing functional acetylcholine nicotinic receptors, receive projections from neighboring cholinergic neurons. These neurons decrease food intake and promote food avoidance, presumably through neurons in the LHA. 3V: third ventricle; ARC: arcuate nucleus of the hypothalamus; DMH: dorsomedial nucleus of the hypothalamus; LHA: lateral hypothalamic area; MC4R: melanocortin 4 receptor; nAChR: nicotinic acetylcholine receptor; OX: orexin; POMC: proopiomelanocortin neurons; PVH: paraventricular nucleus of the hypothalamus; vGlut2+: vesicular Glutamate transporter 2 positive neurons.

activation of POMC neurons (Huang, Xu, & van den Pol, 2011). Nevertheless, the role of nAChRs containing β2 subunit seems to be critical for the nicotine reinforcing properties but not for the regulation of energy balance (Picciotto et al., 1998; Picciotto & Mineur, 2013). The clinical use of varenicline, a derivate of cytisine that acts as a partial agonist for α4β2 and α3β4 nAChRs and as a total agonist for α7nAChR (Mihalak, Carroll, & Luetje, 2006) for smoking cessation treatment, shows only modest attenuation of post-cessation weight (Sun, Duan, Meng, Li, & Jia, 2018; Yang et al., 2016), but with larger effect than nicotine patch for nicotine replacement therapy (NRT) (Taniguchi et al., 2014). Nevertheless, chronic varenicline increases the risk of nausea and, presumably, has cardiovascular side effects based on studies in patients and in animal models (Chelladurai & Singh, 2014; Gibbons & Mann, 2013; Selcuk et al., 2015). Although approaches targeting α3β4nAChRs in POMC neurons seem promising to reduce food intake, current implementation is not possible due to the lack of specific drugs, highlighting the need for more work in this area.

Nicotine and CART share several overlapping actions on the stress response, anxiety, and reward behaviors as well as on the regulation of feeding (Rogge, Jones, Hubert, Lin, & Kuhar, 2008). The presence of α7nAChR in CART neurons in the hippocampus (Borkar, Sagarkar, Sakharkar, Subhedar, & Kokare, 2019) suggests that nicotine directly regulates CART expression; but since CART is highly co-expressed with POMC in hypothalamic neurons (Elias et al., 1998), an indirect regulation cannot be overruled. In this regard, although nicotine regulates CART expression in discrete brain regions, including the hypothalamus (Kramer et al., 2007) and the mesocorticolimbic system (Hurd & Fagergren, 2000; Kaya et al., 2016), several studies showed absence of effect or inconsistent changes in CART expression (especially in the ARC) after nicotine administration (Calarco, Lee, & Picciotto, 2017; Fornari et al., 2007 ; Martinez de Morentin et al., 2012). While acute anorexigenic effect of nicotine could be related to an increase in hypothalamic CART expression (Dandekar, Nakhate, Kokare, & Subhedar, 2011; Kramer et al., 2007), chronic nicotine exposure reinstate feeding (Bellinger et al., 2005; Kamdi, Nakhate, Dandekar, Kokare, & Subhedar, 2009; Levin, Morgan, Galvez, & Ellison, 1987) and is associated with restored or even decreased CART hypothalamic levels (Kramer et al., 2007). This suggests that the nicotine effect on food intake because of CART modulation could be dependent on the length of the treatment. However, quite the opposite to these findings, *Hur* et al. found increased hypothalamic CART mRNA levels after two weeks of nicotine treatment (Hur et al., 2010). The reason for this discrepancy is unclear but can be related to differences in injection frequency or administration route (four intraperitoneal injections during dark phase (Kramer et al., 2007) vs. one subcutaneous injection every 12 h (Hur et al., 2010). These are relevant issues as repeated intraperitoneal administration would sustain higher nicotine levels leading to nAChR desensitization and the subsequent unresponsiveness to nicotine anorexigenic effect. CART levels are reduced after nicotine withdrawal (Dandekar et al., 2011; Hur et al., 2010). The existence of tolerance to the anorectic effects of nicotine after chronic treatment (Bellinger et al., 2005; Kamdi et al., 2009; Levin et al., 1987) suggests that CART might mediate both acute and chronic nicotine effects, as well as the consequences of nicotine withdrawal due to its potential role in desensitization to nicotine treatment (Dandekar et al., 2011). This is particularly important and

needs to be validated in the future to avoid interferences with possible druggable agents derived from nicotine.

In animal studies, both tobacco smoke and nicotine administration chronically or acutely (at high doses) reduce NPY in the PVH (Chen et al., 2005; Chen et al., 2006) and the ARC (Frankish et al., 1995; Martinez de Morentin et al., 2012), in which was associated with reduced food intake in a dose-dependent manner given that low dosages of nicotine affect NPY levels only in animals that were previously fasted (Jang et al., 2003). However, the effect of nicotine on NPY is highly controversial, as some studies reported opposite results. Chronic exposure to nicotine at doses inducing anorexia increases NPY levels in the PVH, in the ARC, and in the DMH (Li et al., 2000). Of note, nicotine doses higher than those observed in smokers increase NPY mRNA to a lesser extent than physiological doses (Li et al., 2000). Also, NPY neurons show increased firing in ex vivo hypothalamic slices exposed to nicotine (Huang et al., 2011). These contradictory results could be explained by: i) reduced NPY receptor density in the hypothalamus after chronic nicotine treatment (Kane, Parker, & Li, 2001; Li et al., 2000); ii) the activation of NPY neurons by nicotine may occur to a lesser extent than POMC neurons and iii) after nicotine's treatment an inhibition of glutamate release is observed in NPY neurons, but not in POMC neurons (Huang et al., 2011). Therefore, regardless of NPY levels, nicotine could exert its anorectic effects through complementary pathways, such as inhibition of AgRP expression in the same set of neurons of the ARC (Fornari et al., 2007; Martinez de Morentin et al., 2012). Also, given that nicotine treatment increases NPY mRNA in the rat adrenal gland when injected subcutaneously but not when delivered by osmotic minipumps (Hiremagalur & Sabban, 1995), inconsistencies in NPY results may be attributable to dosage, duration of nicotine exposure and inoculation method. To our knowledge, only one clinical trial has shown changes in plasma NPY levels with respect to smoking status. In this study, smokers were leaner and showed lower levels of NPY, while cigarette cessation increased NPY levels together with body weight and waist circumference (Hussain et al., 2012). However, no data of food consumption or appetite were included in the study, thus preventing from drawing conclusions about the role of serum NPY in nicotine-induced anorexia. In addition, circulating NPY levels should be interpreted with caution as major concerns exist on whether plasma NPY accurately reflects NPY central levels (Lundberg, Franco-Cereceda, Hemsen, Lacroix, & Pernow, 1990; Lundberg, Rudehill, Sollevi, Theodorsson-Norheim, & Hamberger, 1986). Furthermore, NPY release is modulated by stress hormones such as catecholamines and steroids in response to different stressors, such as psychosocial stressors (Meng et al., 2011) or aggression (Kuo et al., 2007) in humans and rodents. NPY also plays a critical role in the activation of the hypothalamus-pituitary-adrenal axis (Reichmann & Holzer, 2016). To what degree these features could act as confounding events is unclear. Therefore, more research on this topic is needed to improve our understanding of the association between the anorectic effects of nicotine and NPY.

2.2. Orexin and melanin-concentrating hormone systems

Based on the literature reviewed above, one may assume that nicotine effects on food intake are mainly elicited through its action on hypothalamic neurons of the ARC. Far from being the case, nicotine modulates intricate signaling networks, including those involving orexin (OX)-producing neurons (Fig. 1). This small group of neurons is located mainly in the LHA and surrounding regions, including the PFA and dorsomedial and posterior hypothalamus (Nambu et al., 1999; Peyron et al., 1998; Sakurai et al., 1998). The widespread extension of OX network in the CNS includes hypothalamic POMC, NPY,α-MSH, and melanin-concentrating hormone (MCH) neurons, GABAergic neurons of the preoptic area, ventromedial nucleus of the hypothalamus (VMH), DMH, PVH nuclei; as well as extrahypothalamic areas such as the basal forebrain (BF), VTA and NAc of the mesolimbic system and monoaminergic and cholinergic nuclei in the brainstem (Chen, Dun, Kwok, Dun, & Chang, 1999; Date et al., 1999; Elias et al., 1998; Gonzalez, Iordanidou, Strom, Adamantidis, & Burdakov, 2016; Peyron et al., 1998; Sakurai et al., 2005; Yoshida, McCormack, Espana, Crocker, & Scammell, 2006). This network lends support to the diverse physiological roles of OX peptides, including the regulation of wakefulness and sleep states, emotion and reward system, autonomic/neuroendocrine modulation, and feeding behavior (Ferno, Senaris, Dieguez, Tena-Sempere, & Lopez, 2015; Lopez, de Lecea, & Dieguez, 2020; Lopez, Tena-Sempere, & Dieguez, 2010; Milbank & Lopez, 2019; Sakurai, 2014; Sakurai et al., 1998; Soya & Sakurai, 2020; Yamanaka et al., 2003). A plethora of signals of energy status such as glucose, triglycerides, amino acids, and circulating hormones modulate OX neuronal activity (Burdakov, Gerasimenko, & Verkhratsky, 2005; Chang, Karatayev, Davydova, & Leibowitz, 2004; Karnani et al., 2011; Lopez et al., 2000). Leptin and ghrelin respectively inhibit and activate OX neurons directly (Lopez et al., 2000; Yamanaka et al., 2003), although the effect of ghrelin on OX expression in unclear (Seoane et al., 2003). Afferents from ARC neurons responsive to these signals can also indirectly activate OX neurons (Elias, Saper, et al., 1998) suggesting a critical role of the OX system in the regulation of energy homeostasis (Ferno et al., 2015; Lopez, Tena-Sempere, & Dieguez, 2010; Milbank & Lopez, 2019). OX neurons respond to low energy levels primarily by releasing OX peptides (OX-A and OX-B) (Fujiki et al., 2001; Lopez et al., 2000; Moriguchi, Sakurai, Nambu, Yanagisawa, & Goto, 1999; Sakurai et al., 1998). When OX-A is increased at central level food intake is elevated in a dose-dependent manner, predominantly through OX receptor 1 signaling (Ferno et al., 2015; Haynes et al., 2000; Lopez, Seoane, Garcia Mdel, Dieguez, & Senaris, 2002; Lopez, Tena-Sempere, & Dieguez, 2010; Milbank & Lopez, 2019; Sakurai et al., 1998; Sweet, Levine, Billington, & Kotz, 1999) leading to the regulation of sleep/wakefulness states to support food-seeking behavior (de Lecea et al., 1998; Dube, Kalra, & Kalra, 1999; Haynes et al., 2000; Lopez et al., 2000; Sakurai et al., 1998; Yamanaka et al., 2003).

Chronic nicotine treatment at doses that induce anorexia activates OX neurons and upregulates OX peptides and their receptors in hypothalamic regions receiving projections from the LHA, such as the DMH and the PVH (Kane et al., 2000). Both nuclei are a target of OX-A orexigenic effect and are deeply involved in the regulation of energy balance (Dube et al., 1999). Of note, OX-B has a lower impact on food intake (Dube et al., 1999; Sweet et al., 1999), indicating that the effect of nicotine on this neuropeptide may not be related to feeding. The theoretical inconsistency in nicotine-induced anorexia in the context of elevated OX levels could be explained by a decrease in the affinity of OX-A binding after chronic nicotine treatment, suggesting reduced neural orexin signaling (Kane et al., 2001). In line with this, although nicotine increases the firing of OX neurons, the response is smaller than in NPY or POMC cells (Huang et al., 2011).

Limited data is available on the specific nAChR subunits expressed in OX neurons, however cholinergic regulation of OX neurons activity is only partially mediated by muscarinic receptors (Henny & Jones, 2006; Ohno, Hondo, & Sakurai, 2008), suggesting a direct role of nAChRs in OX neurons. Data gathered so far reveal the expression of the α4nAChR subunit in about 30% of these neurons (Garcia et al., 2015). In this regard, OX neurons increase firing after nicotine exposure presumably through postsynaptic α4β2- containing nAChRs (Zhou, Gao, & Picciotto, 2015), as suggested by the attenuated activation of OX neurons in response to the nicotinic antagonists' mecamylamine and dihydro-beta-erythroidine (Garcia et al., 2015; Pasumarthi, Reznikov, & Fadel, 2006). α7nAChRs also contribute to OX neuronal responses to nicotine treatment, but to a lesser extent (Zhou et al., 2015). In addition, desensitization of presynaptic nAChRs has been found to reduce the efficacy of glutamatergic transmission, thus leading to the reduced firing of OX neurons to a similar degree as the antagonist mecamylamine (Zhou et al., 2015). In summary, nicotine regulates the OX system by a mechanism involving nAChRs that opposes presynaptic and postsynaptic processes.

OX neurons in the PFA and the DMH can be activated by low or high doses of nicotine, while OX neurons in the LHA only respond to high doses (Kane et al., 2000; Pasumarthi et al., 2006; Pasumarthi & Fadel, 2008; Plaza-Zabala, Martin-Garcia, de Lecea, Maldonado, & Berrendero, 2010), suggesting a distinct regional sensitivity to cholinergic signaling. This dose-dependent activation could explain the different roles observed in these subsets of neurons. OX neurons located in the PFA and DMH modulate processes regulated by daily rhythms, such as production or maintenance of arousal, stress responses (Estabrooke et al., 2001; Korim, Bou Farah, McMullan, & Verberne, 2014), blood pressure (Zhang, Sakurai, Fukuda, & Kuwaki, 2006) or glucose homeostasis through the sympathetic nervous system (SNS) (Otlivanchik, Le Foll, & Levin, 2015; Yi et al., 2009). Particularly significant is the contribution of PFA OX neurons to feeding during glucoprivation in response to the input of catecholamine neurons in the hindbrain (Li, Wang, Elsarelli, Brown, & Ritter, 2015), suggesting a role in arousal and motivation to forage for food under low energy status. Conversely, OX neurons in the LHA are independent of daily changes and, together with the midbrain dopaminergic system, participate in the regulation of reward processing (Estabrooke et al., 2001; Harris, Wimmer, & Aston-Jones, 2005). Indeed, OX-A is critical for the induction of synaptic plasticity in the VTA (Borgland, Taha, Sarti, Fields, & Bonci, 2006) leading to long-term effects of chronic drug use and motivated behaviors related to food and drug reward. One of the consequences of prenatal nicotine exposure is the increase of OX expression in LHA and VTA terminals of OX neurons leading to changes in motivated behaviors associated with food and drug reward in the offspring (Morgan, Harrod, Lacy, Stanley, & Fadel, 2013). Overall, the current evidence suggests that OX mediates nicotine effects through both homeostatic and hedonic circuits, but its role in the rewarding and addictive behavior (Hollander, Lu, Cameron, Kamenecka, & Kenny, 2008; Huang et al., 2011; Kane et al., 2000; Plaza-Zabala et al., 2010), in the regulation of thermogenesis-induced energy expenditure (Ferno et al., 2015; Folgueira et al., 2019; Martins et al., 2016; Milbank & Lopez, 2019; Sellayah, Bharaj, & Sikder, 2011) (will be addressed in the following section) or glucose homeostasis (Otlivanchik et al., 2015; Tsuneki et al., 2016; Yi et al., 2009) seems to be more critical. All the above suggests that targeting nicotinic signaling in the OX system for feeding control could have an impact on the rewarding and addictive properties of drugs of abuse.

MCH is a relevant regulator of food intake, glucose metabolism, and adiposity; and is predominantly expressed the LHA subzona incerta and the PFA (Skofitsch, Jacobowitz, & Zamir, 1985) where its distribution overlaps with OX neurons (Bayer et al., 2005). MCH system also partakes in the regulation of arousal by modulation of the activity of the locus coeruleus (Monti, Lagos, Jantos, & Torterolo, 2015), learning and memory in the amygdala and hippocampus (Adamantidis & De Lecea, 2009), motivated food behavior by enhancing the hedonic value of food after stimulating MCH receptor 1 (MCHR1) activity in the shell of NAc and VTA (Georgescu et al., 2005; Saito, Cheng, Leslie, & Civelli, 2001) and hepatic function through kappa opioid receptor (κOR) in the LHA (Imbernon et al., 2016). MCH induces hyperphagia and body weight gain (Ludwig et al., 2001; Qu et al., 1996; Romero-Pico et al., 2018). Of note, MCH system deficiency not only causes hypophagia (Chen et al., 2002; Ito et al., 2009; Marsh et al., 2002; Mashiko et al., 2005; Shearman et al., 2003; Shimada, Tritos, Lowell, Flier, & Maratos-Flier, 1998) it also reduces body weight and mitigates obesity induced by leptin deficiency (Alon & Friedman, 2006; Segal-Lieberman et al., 2003)) or high caloric diet (Chen et al., 2002; Marsh et al., 2002) by increasing energy expenditure and locomotor activity (Kokkotou et al., 2005). The role of MCH neurons and MCHR1 in neuroendocrine regulation is supported by extensive networks within hypothalamic nuclei such as the PVH, the LHA, the VMH, and the ARC, including the leptin-sensitive POMC neurons (Chee, Pissios, & Maratos-Flier, 2013; Saito et al., 2001) highlighting the important role of MCH in orexigenic processes (Al-Massadi et al., 2019). Several anorexigenic factors such as leptin, α-MSH, glucagon-like peptide 1 (GLP-1), neurotensin (Ludwig et al., 1998; Sahu, 1998; Tritos et al., 1998), and NPY receptor antagonism (Chaffer & Morris, 2002) inhibit MCH-induced feeding. In this sense, nicotine administration or activation of presynaptic nAChR suppress appetite by the potentiation of LHA GABAergic transmission and the subsequent inhibition of PFA MCH neurons in both adult mice or pups exposed to prenatal nicotine (Jo et al., 2005; Jo & Role, 2002). Presynaptic activation of α7 containing-nAChRs on GABAergic terminals might mediate this mechanism, as suggested by pharmacological and genetic studies (Jo et al., 2005), although the role of this mechanism in vivo is yet to be demonstrated.

2.3. Extrahypothalamic areas and food motivated behavior

In terms of drug dependence, nicotine-addiction is present in a higher number of people than for any other drug (Polosa & Benowitz, 2011). Apart from caffeine and tea, nicotine and alcohol are considered the most widely used drugs (Crocq, 2003). A frequent issue related to substance dependence is the existence of many cross-addictions, meaning shifting from one addiction to another. Recently, food addiction, as defined by the *Yale Food Addiction Scale*, has also emerged as one of high prevalence, diagnosed in 19.9% of subjects (Pursey, Stanwell, Gearhardt, Collins, & Burrows, 2014). Interestingly, the prevalence of food dependence among subjects with other addictions, including smokers, is higher than in the general population (Tinghino et al., 2020). This is significant as almost every addiction share common neurochemical characteristics in the CNS, such as altering dopamine (DA) release in the mesolimbic system, as reported for both high palatable food or nicotine (Balfour, 2009; Criscitelli & Avena, 2016; Rice & Cragg, 2004; Stice et al., 2013). In fact, in subjects with obesity there is an increase in functional connectivity between the hypothalamus and the NAc and orbitofrontal areas, as well as decreases in functional connectivity of the hypothalamus with middle prefrontal areas. The higher functional connectivity in the former network is thought to have implications in the inability to cut down food intake and the presence of symptoms related to food addiction (Contreras-Rodriguez, Martin-Perez, Vilar-Lopez, & Verdejo-Garcia, 2017; Martin-Perez, Contreras-Rodriguez, Vilar-Lopez, & Verdejo-Garcia, 2019).

Neuronal communication between the shell of NAc, the LHA and the striatopallidal system in the BF modulate various neuronal and peptide systems, among them opioid peptides and OX and MCH neurons, involved in the hedonic response to palatable food and drugs of abuse like nicotine (Berrendero et al., 2010; Bruijnzeel, 2012; Kenny, 2011). The BF comprises a heterogeneous mixture of cell types, including glutamatergic and GABAergic neurons; many of the latter co-expressing ACh and somatostatin (Gritti et al., 2006; Saunders, Granger, & Sabatini, 2015; Zhu et al., 2017). Several of these neuronal populations play specific roles in regulating feeding behavior via an intricate network. Specifically, vesicular GABA transporter positive neurons in the BF induce general food intake, while somatostatin positive neurons motivate fat and sucrose intake associated with anxiety-like behaviors (Zhu et al., 2017). Projections from the somatostatin neurons to LHA regulate the preference for high-fat diet consumption; however, their projections to NAc motivate sucrose-seeking (Labouebe, Boutrel, Tarussio, & Thorens, 2016; Zhu et al., 2017). Here, nicotinic signaling might play a critical role given that administration of nicotinic antagonists such mecamylamine or varenicline inhibits sucrose intake and other motivated behaviors (Ford et al., 2009; Ostlund, Kosheleff, & Maidment, 2014; Shariff et al., 2016). Also, nicotinic signaling in the NAc appears to be modulated by high palatable food as observed by upregulation and downregulation of α4β2 and α6β2 nAChRs, respectively, in the NAc after chronic sucrose intake (Shariff et al., 2016). Both these receptors, together with α7nAChRs, have been found to mediate nicotine-induced dopaminergic firing and DA release in mesolimbic regions that regulate motivation and emotion (de Kloet et al., 2015; Ferrari, Le Novere, Picciotto, Changeux, & Zoli, 2002; Picciotto et al., 1998; Tolu et al., 2013), suggesting a link between

nicotinic signaling and the rewarding properties of palatable food. Given that presynaptic α7nAChRs stimulate glutamatergic transmission in the VTA, and subsequently DA output to the NAc, blockade of α7nAChRs in the VTA has been proposed as a druggable target to decrease food-seeking (Schilstrom, Svensson, Svensson, & Nomikos, 1998). It remains to be established the contribution of α7nAChRs in neurons and astrocytes of the VTA to this effect, as well as what it will be the effect of selective blockade in the VTA in terms of cognitive function (Garzon et al., 2013).

Impairment of a subset of BF GABAergic cholinergic neurons in the diagonal band of Broca leads to hyperphagia and severe obesity, independently of energy expenditure (Herman et al., 2016). This suggests a role in suppressing food intake partially through projections to downstream feeding-related neurons in the hypothalamus, such as orexin neurons in the LHA (Sakurai et al., 2005) and POMC neurons in the ARC (Wang et al., 2015). Although the anorectic effect of this subset of neurons is partially blunted by mecamylamine, suggesting direct involvement of nicotinic receptors in ARC neurons, muscarinic signaling cannot be ruled out (Herman et al., 2016). In addition, a vGlut2 positive neuronal population that expresses functional nAChR and receives projections from neighboring cholinergic neurons (Fig. 1) (Patel et al., 2019) responds to food-odor related stimuli in the BF, diminishing food intake and causing food avoidance (Patel et al., 2019) probably through a mechanism that involves LHA neurons (Do et al., 2016). The physiological role of BF in regulating feeding is unknown but might be an intermediary between anxiety, evaluation of food palatability, and food consumption (Cassidy et al., 2019).

In summary, besides the modulation of appetite through POMC neuron signaling, nicotine could also influence the motivation for food-seeking and the hedonic value of palatable foods via different nAChR subtypes in the mesolimbic system. These findings point to potential new targets for nicotine-mediated appetite suppression in extra-hypothalamic neurons.

3. Nicotine's effects on energy expenditure

A considerable amount of literature exists regarding nicotine's action on energy expenditure. These studies have reported increased energy expenditure in humans and rodents after exposure to cigarette smoke or nicotine (Grunberg et al., 1988; Hofstetter et al., 1986; Martinez de Morentin et al., 2012; Perkins, 1992; Seoane-Collazo et al., 2019). Energy expenditure encompasses obligatory (basal metabolic rate) and facultative (physical activity and thermogenesis) aspects (Cannon & Nedergaard, 2004; Cannon & Nedergaard, 2017; Contreras et al., 2015; Silva, 2006). The latter is a fundamental process in homeothermic organisms that produces the energy needed for the body to function and for maintaining temperature and involves the muscle in avian and BAT in mammals (Cannon & Nedergaard, 2004; Cannon & Nedergaard, 2017; Contreras et al., 2015; Foster & Frydman, 1978; Silva, 2006). Classical activation of thermogenesis is regulated by increases in the activity of the SNS to BAT. This increases noradrenaline (NA) release at nerve endings and the subsequent activation of β adrenergic receptors in brown adipocytes, mainly via the β3-adrenergic receptor, which triggers the uncoupling of the respiratory chain by uncoupling protein 1 (UCP1) and, eventually, the generation of heat (Cannon & Nedergaard, 2004; Cannon & Nedergaard, 2017; Contreras et al., 2015; Foster & Frydman, 1978; Harlan & Rahmouni, 2013; Silva, 2006). Remarkably, beige adipocytes showing characteristics of brown fat-like exist in white adipose tissue (Nedergaard & Cannon, 2014; Wu et al., 2012). Importantly, UCP1-positive adipocytes in humans partially resemble rodent beige adipocytes (Jespersen et al., 2013; Nedergaard & Cannon, 2014; Shinoda et al., 2015; Zingaretti et al., 2009). The ability of both brown and beige adipocytes to catabolize the surplus of energy has been recognized as a potential therapy for obesity and metabolic illnesses (Contreras et al., 2017; Cypess & Kahn, 2010; Linares-Pose et al., 2018; Nedergaard & Cannon, 2014; Tran & Kahn, 2010; Tseng, Cypess, & Kahn, 2010; Villarroya & Vidal-Puig, 2013). The effect of nicotine on BAT was first reported in a study where chronic exposure to cigarette smoke or nicotine injection increased BAT mass in hamsters (Wager-Srdar, Levine, Morley, Hoidal, & Niewoehner, 1984) and posteriorly confirmed by the analysis of NA turnover and guanosine 5′-diphosphate binding (a marker of thermogenesis) in BAT mitochondria suggesting increased SNS activity and BAT thermogenic capacity in response to nicotine treatment (Lupien & Bray, 1988; Yoshida, Sakane, Umekawa, & Kondo, 1994). The effect of nicotine treatment in UCP1 mRNA expression in BAT is maintained even in conditions of low energy status, such as decreased energy intake (Arai et al., 2001). Interestingly, obese mice also show increased UCP1 mRNA in both BAT and WAT and higher metabolic rate after chronic nicotine treatment (Seoane-Collazo et al., 2014; Yoshida et al., 1999; Yoshida, Yoshioka, Hiraoka, & Kondo, 1990). This is an important finding as it rules out possible resistance in obesity to the ability of nicotine to induce negative energy balance, as previously reported for other factors such as leptin or GLP-1 (Caro et al., 1996; Considine et al., 1996; Cui et al., 2017; Nogueiras et al., 2009).

Although available data clearly demonstrate the ability of nicotine to increase energy expenditure, the underlying mechanisms remain to be elucidated. Reports on the regulation of SNS tone by central mechanisms (Egawa, Yoshimatsu, & Bray, 1990; Morrison, 1999; Sakaguchi, Arase, & Bray, 1988) and the presence of nicotinic receptors in the CNS (Goldman et al., 1986; Gotti et al., 2009; Harfstrand et al., 1988) suggest a potential role of hypothalamic circuits in mediating nicotine action on energy expenditure. Initial work in this regard showed that intracerebroventricular administration of a corticotropin-releasing hormone-binding protein inhibitor overturns the body weight gain and hyperphagia induced by nicotine withdrawal in an animal model of obesity (Heinrichs et al., 1996). Interestingly, chronic treatment with the inhibitor failed to reduce food intake, suggesting that changes in body weight were due to a rise in energy expenditure via lipolysis and/or thermogenesis (Heinrichs et al., 1996). This was later demonstrated by the inhibition of nicotine-induced NA release in BAT after the antagonism of corticotropin-releasing hormone type 1 receptor (Mano-Otagiri et al., 2009).

Some of the actions of nicotine on energy expenditure take place in the VMH. The VMH is involved in the regulation of many homeostatic and behavioral functions, such as regulation of sexual behavior, fear response, cardiovascular function, and satiety (Choi, Fujikawa, Lee, Reuter, & Kim, 2013). Specifically, the VMH establishes multiple connections with other areas related to energy homeostasis, including the ARC, DMH, LHA, brainstem, and amygdala (Lindberg, Chen, & Li, 2013; Seoane-Collazo et al., 2015). Given its neuronal heterogeneity, the VMH responds to several signals regulating energy homeostasis, such as glucose, leptin, insulin, and ghrelin (Dhillon et al., 2006; Ruud, Steculorum, & Bruning, 2017). The VMH was the first hypothalamic region associated with thermoregulation based on the evidence of increased temperature in the interscapular BAT after the electrical stimulation of this nucleus and the inhibition of this effect after β-adrenergic blockade (Holt, Wheal, & York, 1987; Hugie, Halvorson, & Thornhill, 1992; Kelly & Bielajew, 1991; Perkins, Rothwell, Stock, & Stone, 1981; Saito, Minokoshi, & Shimazu, 1987; Yoshida & Bray, 1984). VMH-specific injections of glutamate, (NA) , hydroxybutyrate, serotonin, and tryptophan also stimulate BAT thermogenesis (Contreras et al., 2015). Genetic evidence has also supported the role of VMH in the modulation of BAT thermogenesis. Mice lacking steroidogenic factor-1 (Jo, 2012; Kim et al., 2011) and estrogen receptor α (Musatov et al., 2007; Xu et al., 2011) in the VMH show reduced energy expenditure and thermogenesis in BAT, demonstrating that the VMH is an essential modulator of BAT function. Our group has extensively characterized the mechanisms within the VMH that regulate BAT activity, pointing toward the VMH-SNS-BAT axis as a canonical pathway controlling energy expenditure. In this sense, AMP-activated protein kinase (AMPK) in the VMH has emerged as an essential regulator of this axis

by acting as an integrator of peripheral signals such as thyroid hormones (Lopez et al., 2010; Martinez-Sanchez et al., 2017), estradiol (Martinez de Morentin et al., 2014; Martinez de Morentin et al., 2015), GLP-1 (Beiroa et al., 2014), leptin (Tanida, Yamamoto, Shibamoto, & Rahmouni, 2013) and bone morphogenic protein 8b (Martins et al., 2016; Whittle et al., 2012). In the same way, nicotine-induced weight loss is associated with inhibition of hypothalamic AMPK activity (decreased the phosphorylated levels of AMPKα, pAMPKα), leading to decreased orexigenic hypothalamic signaling and increased energy expenditure by activation of BAT thermogenesis through augmented SNS tone (Fig. 2) (Martinez de Morentin et al., 2012). Several reports point to the critical role of hypothalamic nAChR in thermoregulatory pathways (Hall & Myers, 1971; Sack et al., 2005). Data from our group showed that nicotine's effects on body weight and BAT thermogenesis were blunted by co-treatment with mecamylamine, which points to α3β4nAChR in mediating nicotine-induced negative energy balance (Martinez de Morentin et al., 2012). This is in accordance with BAT activation and increased lipolysis observed after pharmacological stimulation of α3β4nAChR (Batt & Topping, 1979; Clemmensen et al., 2018; Steiner & Evans, 1972). These results identify hypothalamic α3β4nAChR as the mediator of nicotine effects and a key modulator of the hypothalamus-SNS-BAT pathway leading to weight loss.

So far, there has been little evidence about how nicotine could regulate the browning of WAT. The presence of nAChRs in autonomic ganglia, macrophages, or in adipocytes implies regulation of WAT by cholinergic signaling (Andersson & Arner, 2001; Ji et al., 2007). Recently, a significant contribution showed α2nAChR as a mediator of thermogenic status in activated beige adipocytes, via a cAMP- and protein kinase A-dependent pathway (Jun et al., 2018). This process mediates the activation of essential thermogenic genes such as *Ucp1* and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (Fig. 2) (Jun et al., 2018). The specificity for beige adipocytes was confirmed by the absence of impact in white adipocytes within the same subcutaneous fat cell culture or in brown adipocytes (Jun et al., 2018). This process is mediated by paracrine mechanisms involving the stimulation of α2nAChR through ACh produced by immune cells in WAT (Jun et al., 2018). This is in accordance with other reports of paracrine thermogenic activation by immune cells (Brestoff et al., 2015; Cereijo et al., 2018; Finlin et al., 2017; Lee, Kim, Kwon, Maddipati, & Granneman, 2016; Lee, Petkova, & Granneman, 2013; Pirzgalska et al., 2017; Sato et al., 2020). Of note, human mesenchymal progenitors of beige adipocyte express a unique set of cytokines and transcriptional regulators involved in the recruitment of neighboring immune and stromal cells, which in turn could affect browning of adipose tissue (Min et al., 2019). Given that signaling via α2nAChR is conserved in human subcutaneous fat, the value of this novel, potentially druggable pathway, is of significance. Current evidence points to a pivotal role of nicotine signaling in the direct modulation of browning inside the WAT depots. However, considering that: i) nicotine levels are higher in the brain and fluctuate less than peripheral and circulating levels (Brody et al., 2006), ii) the brain is the main target for nicotine's action (Benowitz, Hukkanen, & Jacob 3rd., 2009; Brody et al., 2006; Hukkanen, Jacob 3rd, & Benowitz, 2005) and iii) browning is a

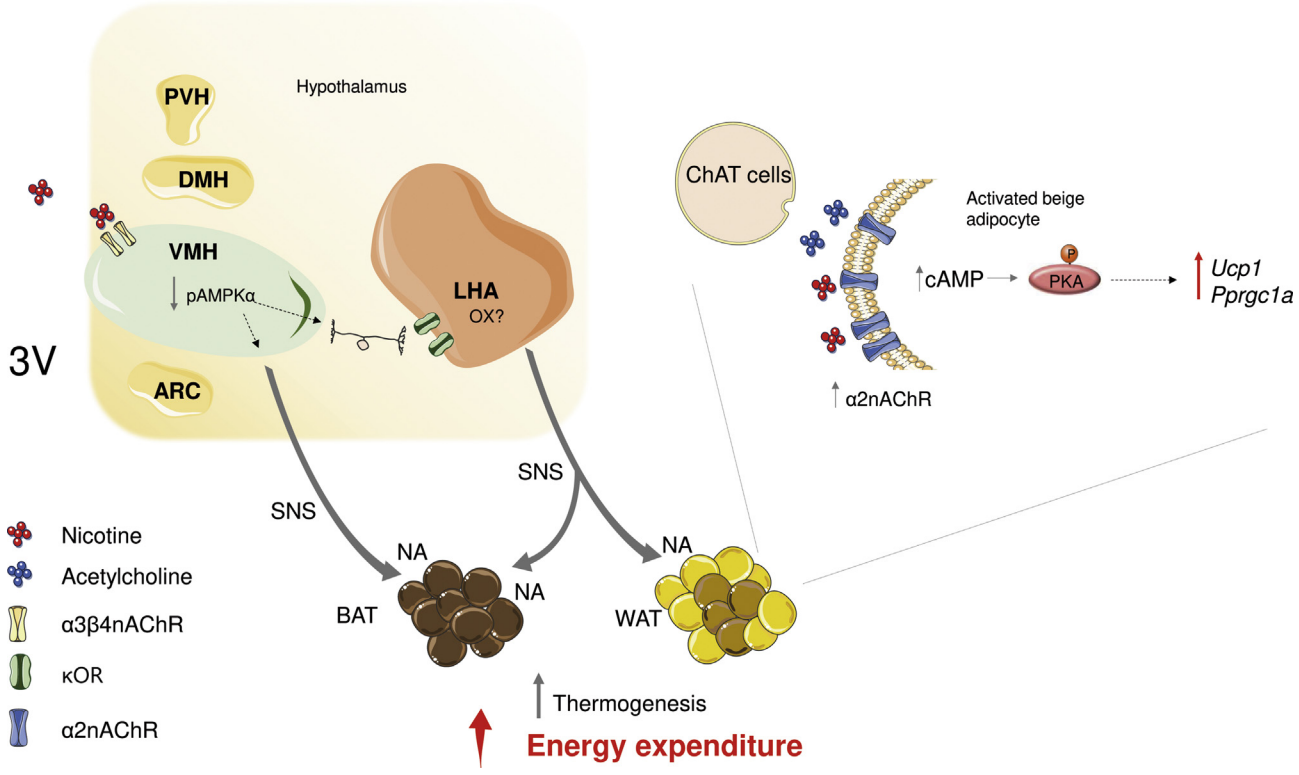

Fig. 2. Nicotine's regulation of energy expenditure. Nicotine-induced weight loss through α3β4nAChR is associated with inactivation of hypothalamic AMPK (decreasing the phosphorylated levels of AMPKα, pAMPKα) leading to an increase in energy expenditure by activating BAT thermogenesis through increase in SNS firing, likely through OX neurons in the LHA, although this requires still experimental demonstration. Central administration of nicotine induces browning of WAT by eliciting sympathetic activation to WAT, increasing the thermogenic capacity of beige adipocytes, and inducing trophic effects. Nicotine-induced activation of BAT thermogenesis and browning of WAT is modulated by the KOR in the LHA. Browning of WAT can be also modulated by increased density of α2nAChR in activated beige adipocytes leading to increase thermogenic markers in a PKA-mediated pathway. Stimulation of this receptor by acetylcholine released by acetylcholine-producing immune cells regulates this process by paracrine mechanisms. 3V: third ventricle; ARC: arcuate nucleus of the hypothalamus; BAT: brown adipose tissue; cAMP: cyclic adenosine monophosphate; ChAT: choline acetyltransferase; DMH: dorsomedial nucleus of the hypothalamus; κOR: kappa opioid receptor; LHA: lateral hypothalamic area; NA: noradrenaline; nAChR: nicotinic acetylcholine receptor; OX: orexin; pAMPKα: phosphorylated AMP-activated protein kinase alpha; PKA: protein kinase A; *Ppargc1a*: PPARG coactivator 1 alpha gene; PVH: paraventricular nucleus of the hypothalamus; SNS: sympathetic nervous system; *Ucp1*: uncoupling protein 1 gene; WAT: white adipose tissue.

hypothalamic regulated event (Contreras et al., 2017; Linares-Pose et al., 2018; Martinez-Sanchez et al., 2017), the central regulation of browning of WAT by nicotine cannot be ruled out. To address this possibility, we have thoroughly investigated whether nicotine may modulate the browning of white fat via the SNS. Our data showed that intracerebroventricular treatment with nicotine induces browning of subcutaneous, visceral, and gonadal WAT depots (Seoane-Collazo et al., 2019). In addition, central nicotine treatment elicits sympathetic nerve activation to WAT, leading to NA release. Remarkably, nicotine also has trophic actions on sympathetic nerves, as demonstrated by increases in dendrite density in gonadal WAT (Seoane-Collazo et al., 2019). The clinical relevance of these findings is supported by the fact that smokers showed higher *Ucp1* mRNA levels in WAT, which correlated with smoking status, an important finding taking into account the high rate of failure in clinical trials related to nicotine receptors related compounds in neuropsychiatric disorders (Terry & Callahan, 2019). This failure was probable due to the lack of adequate preclinical models assessing cognitive function in contrast to data obtained on the effects of nicotine on diet-induced obesity (Terry & Callahan, 2019). To further address the molecular mechanism involved in nicotine's central effect, we focused on opioid signaling. As stated before, nicotine modulates hedonic/reward pathways, including the endogenous opioid system (Kishioka, Kiguchi, Kobayashi, & Saika, 2014) that apart from its role in these processes, (Bruijnzeel, 2009; Darcq & Kieffer, 2018), acts as a homeostatic modulator of energy balance and BAT function (Burghardt, Rothberg, Dykhuis, Burant, & Zubieta, 2015; Nogueiras et al., 2012; Panigrahi, Meece, & Wardlaw, 2019). Notably, our data showed that nicotine-induced weight loss, BAT thermogenesis, and browning of WAT are modulated by the KOR within the LHA (Seoane-Collazo et al., 2019). These data unveiled a previously unknown role of hypothalamic κOR signaling in mediating nicotine actions on energy expenditure (Fig. 2). Several observations provide a functional and anatomical mechanism by which this is compatible with previous reports of VMH AMPK regulating nicotine negative energy balance (Martinez de Morentin et al., 2012); i) bone morphogenic protein 8B B (BMP8B) regulates energy homeostasis by a functional link between AMPK in the VMH and LHA (through a glutamatergic-dependent mechanism and OX neurons) (Fig. 2) (Martins et al., 2016), ii) OX and dynorphin, the endogenous ligand of κOR, highly colocalize in the LHA (Chou et al., 2001) and, iii) OX signaling regulates SNS tone to BAT (Ferno et al., 2015; Milbank & Lopez, 2019; Morrison, Madden, & Tupone, 2012; Yasuda et al., 2005) and is essential for BAT tissue development, differentiation, and function (Sellayah et al., 2011), primarily by OX1R (Sellayah & Sikder, 2012). In this sense, OX deficiency in humans and mice is associated with obesity and diabetes (Hara et al., 2001; Hara, Yanagisawa, & Sakurai, 2005; Honda, Doi, Ninomiya, & Ninomiya, 1986; Nishino, 2007), likely via an impaired response to leptin and deficient energy regulation (Dahmen, Tonn, Messroghli, Ghezel-Ahmadi, & Engel, 2009; Funato et al., 2009; Kakizaki et al., 2019; Milbank & Lopez, 2019). Overall, these data suggest that both central circuits and peripheral cholinergic signaling modulate the activity of white adipocytes and subsequently browning of WAT (Jun et al., 2018; Seoane-Collazo et al., 2019). Nevertheless, more research is needed to fully understand the role of the peripheral and central mechanisms modulating nicotine actions on energy expenditure.

4. Nicotine's effects on glucose homeostasis

IR is a condition in which cells from the target tissues are less able to produce a glucose-lowering response. Therefore, high levels of insulin are needed to sustain its physiological function (Biddinger & Kahn, 2006; Nandi, Kitamura, Kahn, & Accili, 2004; Petersen & Shulman, 2018). IR is often associated with low physical activity and increased body weight. Surprisingly, even though smokers tend to have lower body weight, they often show IR, dependent on the dosage of cigarette smoking (Albanes et al., 1987; Eliasson, Attvall, Taskinen, & Smith, 1994; Eliasson, Taskinen, & Smith, 1996; Facchini, Hollenbeck, Jeppesen, Chen, & Reaven, 1992) and associated impaired glucose tolerance (Eliasson et al., 1996; Frati, Iniestra, & Ariza, 1996). Smoking increases plasma endothelin levels, promoting vasoconstriction and subsequent tissue hypoxemia that could account for reduced glucose utilization by peripheral tissues and thus may elevate plasma glucose levels (Borissova, Tankova, Kirilov, Dakovska, & Krivoshiev, 2004). In this way, smokers show high fasting glucose, dyslipidemia, postprandial lipid intolerance, among other features of the IR syndrome (Chiolero, Faeh, Paccaud, & Cornuz, 2008; Filozof et al., 2004). Accordingly, smoking increases the risk of type 2 diabetes and leads to a worst prognosis of comorbidities associated with this illness, while smoke cessation decreases the rate of diabetes to that of nonsmokers (Chase et al., 1991; Eliasson, 2003; Will, Galuska, Ford, Mokdad, & Calle, 2001). Within diabetic patients, smokers had higher insulin requirement and serum triglyceride levels. These seem to be dependent on the smoking status as heavy smokers showed a 30% increase in these parameters (Madsbad et al., 1980). In addition, it is necessary to note that the association of smoking with increased pro-inflammatory factors (Fernandez-Real, Broch, Vendrell, & Ricart, 2003) and fasting glucagon levels, especially in heavy smokers, may play a role in the elevated risk of type 2 diabetes in these subjects (Grondahl et al., 2018).

NRT in the form of nicotine gum (Eliasson et al., 1996; Filozof et al., 2004) has become a popular therapy to combat the substantial postcessation weight gain in ex-smokers (Aubin, Farley, Lycett, Lahmek, & Aveyard, 2012; Audrain-Mcgovern & Benowitz, 2011). However, nicotine gum has also been associated with IR and other metabolic disorders (Eliasson et al., 1996). Similarly, the use of e-cigarettes, also called vaping, show comparable effects to smoking cigarettes on weight and metabolic parameters, such as IR and cardiovascular risk (Lanza, Pittman, & Batshoun, 2017; Mayyas et al., 2020; Pokhrel, Bennett, & Boushey, 2020; Verhaegen & Van Gaal, 2017). Therefore, the use of these therapies should be strictly controlled to avoid IR aggravation. In fact, type 2 diabetic patients and smokers, but not healthy subjects, show impaired insulin sensitivity (to a variable extent) after nicotine infusion (Axelsson, Jansson, Smith, & Eliasson, 2001; Morgan et al., 2004). Overall, these data imply a deleterious effect of nicotine on glycemic control (Fig. 3). It is of great importance to uncover the underlying mechanisms when designing a drug or treatment for obesity and related metabolic disturbances based on specific nicotine actions. Despite the numerous reports of nicotine's adverse impact on insulin sensitivity, studies addressing its effect on insulin secretion have shown different outcomes depending on treatment administration route, duration, and dosage (Benowitz & Henningfield, 1994). Hormonal secretion from the pancreatic cell sdepends on nutritional, hormonal, and paracrine regulatory mechanisms, as well as on autonomic neural control involving cholinergic signaling. The finding of functional nAChR subunits α2, α3, α4, α5, α7, β2 and β4 in rat islets as well as in INS-1, a rat β-cells line suggests a possible direct effect of nicotine to modulate insulin release (Yoshikawa, Hellstrom-Lindahl, & Grill, 2005). Almost all the data about physiological insulin release are originated from studies of rodent islets or cloned cell lines, but significant differences exist in the morphological organization of human and rodent islets, implying a distinct regulatory mechanism. In human islets, the proportion of β-cells is lower than α-cells, and cells are randomly scattered throughout the islet opposing the mantle-core pattern of α and βcells in rodents (Cabrera et al., 2006). Distinct mechanisms of cholinergic input to β-cells appear to underlie the regulation of β-cell function in humans and rodent islets. Thus, ACh release from α-cells in human islets and parasympathetic nerves in both mouse and human appears to stimulate the pre-absorptive phase of insulin secretion (Ahren & Holst, 2001; Rodriguez-Diaz et al., 2011; Rodriguez-Diaz et al., 2011). Abundant evidence establish a role for muscarinic ACh receptors in this process in both human and animal studies (Gautam et al., 2006; Noguchi & Huising, 2019; Zhu et al., 2019). Some evidence links nicotinic receptor activity to the regulation of pre-absorptive insulin secretion. First,

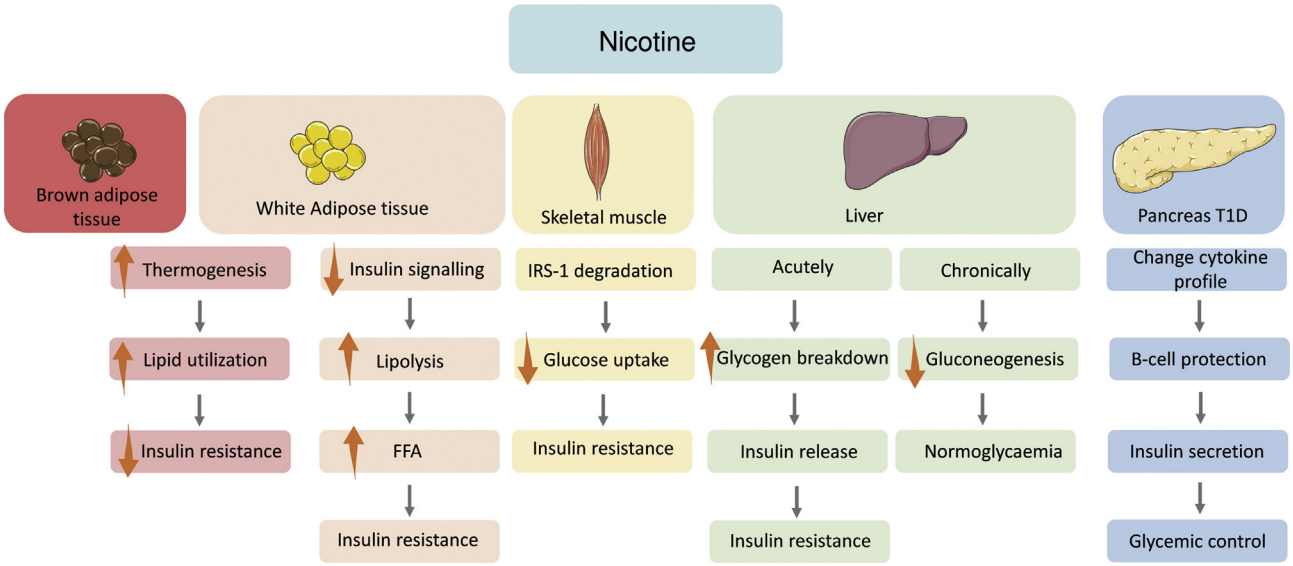

Fig. 3. Nicotine's regulation of glucose homeostasis. The actions of nicotine on glucose homeostasis are complex and tissue dependent. Nicotine can induce insulin resistance by affecting insulin action at target organs. In adipocytes, activation of α7nAchR has been proposed to mediate nicotine-induced insulin resistance triggering a signaling cascade that eventually induce the degradation of IRS-1 and subsequently suppressing insulin signaling and upregulating lipolysis. Nevertheless, in activated brown and beige adipocytes, increased thermogenesis engages lipid utilization which reduces circulating FFA and improve insulin resistance. In muscle, nicotine induces insulin resistance by inducing the degradation of insulin receptor substrate-1 (IRS-1) leading to reduced glucose uptake. In liver, acute nicotine treatment induces hyperinsulinemia by glycogen breakdown upon activation of nAChR. However, chronic nicotine treatment blunts these effects by gluconeogenesis. In animal models of Type 1 Diabetes, nicotine exerts a protective role against β-cells destruction by changing the cytokine profile expressed in the pancreas. In addition, cholinergic receptors in β-cells has been found to regulate insulin secretion, thus facilitating glycemic control.

blocking nicotinic ganglionic receptors inhibits insulin release, which is only partially impaired by muscarinic antagonists (Ahren & Holst, 2001). Second, nicotinic receptor signaling, probably involving β2 and β4 subunits, is required for ACh-mediated insulin secretion (Ganic et al., 2016). The sustained elevated nicotine levels experienced by chronic smokers may impact desensitization, and its maintenance, of nAChR (Brody et al., 2006). Receptor desensitization by chronic stimulation in pancreatic islets may interrupt the transmission of endogenous ACh and impair insulin secretion, as seen in type 2 diabetic subjects (Ganic et al., 2016). The rate of desensitization is dependent on the specific subunit composition of the nAChR (Giniatullin, Nistri, & Yakel, 2005). The α7nAChRs respond to lower nicotine concentrations and are particularly susceptible to desensitization, as opposed to α3β4nAChR receptors that are activated by higher concentrations of nicotine and slowly desensitize (Hurst et al., 2013; Olale et al., 1997).

4.1. Acute effect of nicotine on glucose homeostasis

Evidence from in vivo and in vitro acute nicotine treatment studies recapitulates the effect of smoking on glucose homeostasis. Acute nicotine treatment promotes hyperinsulinemia, presumably by glycogen breakdown, induced by an increase in catecholamine plasma levels upon activation of nAChR (Scholze, Orr-Urtreger, Changeux, McIntosh, & Huck, 2007; Vu et al., 2014). Similar effects were found after treatment with DMPP. The acute hyperglycemic effect of DMPP is mediated by β4nAChR-elicited release of adrenaline in diet-induce obese mice, showing elevated gluconeogenic gene expression, and depleted hepatic glycogen stores (Jall et al., 2020). Although both nicotine and DMPP cause hyperglycemia, their mechanisms seem to be different since DMPP's effect is independent of increased insulin levels. The most likely explanation for this difference is that nicotine releases adrenaline and NA, while DMPP only releases adrenaline (Jall et al., 2020).

In human muscle cells, both smoking and nicotine stimulate insulin receptor substrate-1 (IRS) Ser^{636} phosphorylation (Bergman et al., 2009), likely in a mechanistic target of rapamycin-dependent manner (Bergman et al., 2012). Subsequently, this blunts insulin-stimulated IRS1 tyrosine phosphorylation, phosphatidylinositol 3-kinase activity, and glucose uptake leading to IR (Copps & White, 2012; Petersen & Shulman, 2018).

4.2. Chronic effect of nicotine on glucose homeostasis

Although nicotine causes acute hyperglycemia, its chronic administration enhances glucose tolerance (Seoane-Collazo et al., 2014) and insulin sensitivity by activating hepatic AKT (protein kinase B) and glycogen synthase 3β phosphorylation and subsequently suppressing gluconeogenesis (Vu et al., 2014). Additional studies showed that chronic nicotine exposure enhances insulin sensitivity via the activation of α7nAChR and the signal transducer activator of transcription 3 (STAT3) pathway in skeletal muscle, adipose tissue, and liver of mice in an inflammation-independent manner (Xu et al., 2012). Activation of STAT3 after the stimulation of α7nAChR is also observed in 3T3-L1 cells (Wang et al., 2015). Consistent with these reports, the use of DMPP for 7 days also shows an improvement in glucose tolerance, via mechanisms independent from body weight reduction (Clemmensen et al., 2018). Current data demonstrate that DMPP promotes insulin-stimulated glucose uptake by peripheral tissues including, muscle, heart, and BAT, but not subcutaneous or visceral WAT (Jall et al., 2020). Specifically, agonism of α3β4nAChR decreased glycogen synthase phosphorylation in skeletal muscle, which in turn activates the enzyme, leading to increased glycogen stores, in an AKT independent pathway (Jall et al., 2020). However, contradictory effects were shown after chronic activation of α7nAChR in adipocytes which were proposed to mediate nicotine-induced IR by a pathway involving the activation of AMPKα2 that leads to the degradation of mitogen-activated protein phosphatase-1. This triggers a signaling cascade that eventually induces the degradation of IRS1 and subsequently AKT inhibition, leading to suppressed insulin signaling and upregulating of lipolysis in WAT (Wu et al., 2015). Through this process, nicotine treatment increases free fatty acids, causing whole-body glucose intolerance and IR in muscle and liver (Fig. 3) (Nogueiras et al., 2015; Wu, Jiao, et al., 2015). The inconsistency with previous studies could be attributed to differences in nicotine dosage and desensitization of nAChRs, given that treatment with low doses nicotine evoke moderate weight loss and IR, whereas

at high doses it induces body weight reduction and glucose tolerance (Wu, Song, et al., 2015).

The beneficial effect of chronic nicotine exposure on insulin sensitivity is maintained in obese rats (Liu, Kurose, & Matsukura, 2001; Liu, Mizuta, & Matsukura, 2003; Seoane-Collazo et al., 2014) and genetically obese mice (*db*/*db*) (Tsuneki et al., 2016). Presumably, these effects involve a reduction of cytokine milieu and free fatty acid levels through cholinergic anti-inflammatory pathways via α7nAChR (Wang, Yang, Xue, & Shi, 2011) and janus kinase 2-signal transducer and STAT3 signaling (Marrero et al., 2010). Finally, chronic nicotine was found to have a protective role against β-cells destruction by changing the cytokine profile expressed in the pancreas, probably via the anti-inflammatory pathway mediated by α7nAChR and phosphatidylinositol 3-kinase signaling (Gupta, Lacayo, Greene, Leahy, & Jetton, 2018), thus reducing the incidence of diabetes in two animal models of Type I diabetes (Mabley, Pacher, Southan, Salzman, & Szabo, 2002).

4.3. Central vs. peripheral nicotinic signaling in the regulation of glucose homeostasis

As stated above, plausible explanations for the discrepancies related to the effect of nicotine on insulin sensitivity might be nicotine's dosage and treatment extent and/or tissue-specific actions. In this sense, while nicotine activates AMPKα2 in WAT, liver, and muscle (Nogueiras et al., 2015; Wu, Jiao, et al., 2015), it inhibits this kinase at hypothalamic level (Martinez de Morentin et al., 2012), reduces insulin circulating levels, and shows a diet-dependent effect on AMPK in the liver, where it decreases insulin signaling and hepatic inflammatory markers (Seoane-Collazo et al., 2014).

Given that that nicotine modulates other features of energy homeostasis, such as food intake or energy expenditure via CNS, several studies have also attempted to determine whether nicotine uses brain circuits to regulate glucose metabolism. In fact, *Claude Bernard* proposed in the XIXth century that type 2 diabetes was a brain's disease (Tups, Benzler, Sergi, Ladyman, & Williams, 2017). Hepatic glucose production (HGP) is tightly regulated by the CNS through the autonomous nervous systems (Inoue et al., 2006; Schwartz et al., 2013; Wunderlich et al., 2010). In this regard, chronic oral treatment with nicotine reduces hyperglycemia in *db*/*db* type 2 diabetic mice. This effect is independent of changes in body weight, body fat or insulin levels, but associated with decreased hepatic levels of glucose-6-phosphatase (Tsuneki et al., 2016). Hepatic vagotomy or deficiency in orexin abolishes nicotine-induced hyperglycemia, suggesting the suppression of hepatic gluconeogenesis after nicotine-induced activation of the hypothalamic orexin-parasympathetic nervous system (Tsuneki et al., 2016). Activation of OX neurons in the PFA could partially explain nicotine-induced acute hyperglycemia. The PFA is sensitive to catecholamines injection and is one of the most sensitive areas in the hypothalamus for elicitation of feeding by exogenous NPY (Stanley, Magdalin, Seirafi, Thomas, & Leibowitz, 1993; Stanley & Thomas, 1993), which is a known co-mediator of glucoprivic feeding (Li, Wang, Dinh, & Ritter, 2009). In response to glucoprivation, catecholamine co-expressing NPY neurons in the hindbrain (Li et al., 2015; Li & Ritter, 2004; Li, Wang, & Ritter, 2006; Sawchenko et al., 1985) mediate the activation of OX neurons in the PFA and the subsequent regulation of plasmatic glucose levels by increasing the HGP (Yi et al., 2009) and facilitate the counterregulatory response (Otlivanchik et al., 2015). Additional regulation of glucose levels by the hypothalamic cholinergic system rapidly induces hyperglycemia by enhancing HGP (Brito, Brito, Kettelhut, & Migliorini, 1993; Takahashi, Kishi, Ishimaru, Ikarashi, & Maruyama, 1998). In accordance with this, stimulation of the cholinergic anti-inflammatory pathway by nicotine leads to inhibition of the secretion by macrophages of inflammatory molecules (Jamal Uddin et al., 2013). In addition, direct nicotine action in the brain promotes peripheral interleukin-6 production (Song et al., 1999). Peripheral nicotine treatment also increases STAT3 phosphorylation in the liver of healthy rodents (Vu et al., 2014; Xu et al., 2012), as well as in *db*/*db* mice (Tsuneki et al., 2016). This is of importance, as the increase in hepatic interleukin-6 induced by the brain-insulin action is essential for the activation of STAT3 and the suppression of HGP (Inoue et al., 2006). Finally, a group of neurons activated by nicotine is located in the medial habenula (mHb) of the rodent brain. Here, the diabetes-associated gene *Tcf7l2* (encoding transcription factor 7-like 2, TCF7L2), facilitates the recovery of nAChR from its desensitization, promoting aversion to nicotine (Duncan et al., 2019). Notably, nicotine seems to increase blood glucose levels by TCF7L2-dependent stimulation of the mHb through a mechanism involving polysynaptic connections from the mHb to the pancreas (Duncan et al., 2019). The physiological relevance of these findings is demonstrated by the fact that mutant Tcf7l2 rats are resistant to nicotine-induced impairment in glucose homeostasis (Duncan et al., 2019). This evidence points to the existence of a habenula-pancreas axis that links nicotine to its diabetes-promoting actions (Bruschetta & Diano, 2019; Duncan et al., 2019; Morris, 2020). In summary, several lines of evidence suggest that nicotine regulation of glycemic status by both insulin-dependent and -independent mechanisms (Fig. 3), that could involve a CNS-parasympathetic glucoregulatory system to suppress hepatic glucose production.

5. Conclusions. Nicotine as a therapeutic agent

In 2012 more than 1.6 million premature fatalities were attributable to hyperglycemia and diabetes (Roglic & World Health Organization, 2016). Based on present trends, by 2030, more than 3 billion adults could be either overweight or obese (Kelly, Yang, Chen, Reynolds, & He, 2008). The *International Diabetes Federation* predicts that nearly 600 million people could be diabetic by 2035 (Guariguata et al., 2014). For these reasons, the development of pharmacotherapies to treat obesity is of vital importance. Firsts attempts to induce weight loss by targeting the CNS have failed due to the occurrence of adverse effects such as dependence, CVD, and neuropsychiatric events, including suicide (Al-Massadi, Ferno, et al., 2019; Christensen, Kristensen, Bartels, Bliddal, & Astrup, 2007; Dragano et al., 2020; Krentz, Fujioka, & Hompesch, 2016; Muller et al., 2018; Nathan, O'Neill, Napolitano, & Bullmore, 2011; Srivastava & Apovian, 2018; Williams et al., 2020), resulting in drugs being withdrawn from the market. Recently, lorcaserin, a drug use for weight control, has been withdrawn from the market after a study showing increased occurrence of certain types of cancer (Aschenbrenner, 2020). Currently, pharmacologic agents include selective ligands like liraglutide and new approaches as polypharmacological agents acting synergistically in multiple neural pathways, have been proven effective in the long run with less side effects (Dragano et al., 2020; Muller et al., 2018). In fact, interventions to increase energy expenditure trigger counter-regulatory responses by orexigenic feeding circuits to increase food intake or vice-versa, which is consistent with the well-established relationship between feeding and energy expenditure (Bluher, 2019; Clemmensen et al., 2018; Cottle & Carlson, 1954; Dragano et al., 2020; Muller et al., 2018; Ravussin, Xiao, Gavrilova, & Reitman, 2014). Naltrexone, an opioid receptor antagonist, in combination with bupropion, has been approved for the treatment of obesity (Bluher, 2019; Dragano et al., 2020; Fujioka et al., 2016; Halseth, Shan, Walsh, Gilder, & Fujioka, 2017; Khera et al., 2016; Muller et al., 2018). These medications impact eating behavior, presumably via their impact on food reward. However, the recently described role of κOR in the LHA in mediating the catabolic effect of nicotine on WAT (Seoane-Collazo et al., 2019) suggests a possible impact of the drugs targeting the opioid system in the regulation of energy expenditure. Thus, new approaches to combat obesity should aim to achieve a synergistic effect by identifying compounds that target both sides of the energy balance equation (namely feeding and energy expenditure). Indeed, such actions are relevant for nicotine, which is in a privileged position due to its well-known pharmacokinetic profile and pharmacological actions, including anorectic and catabolic effects

(Audrain-Mcgovern & Benowitz, 2011; Jo et al., 2002; Martinez de Morentin et al., 2012; Mineur et al., 2011; Picciotto & Mineur, 2013; Seoane-Collazo et al., 2014; Seoane-Collazo et al., 2019). In this sense, NRT is a widely used method in humans against smoking addiction and to a lesser extent to improved cognitive function. NRT provides lower and slower-rising plasma nicotine concentrations than do cigarettes, reducing the reinforcing effect of smoking. All forms of NRT appeared to have comparable efficacy (Hajek et al., 1999). A meta-analysis of 133 clinical trials found the Risk Ratio for any form of NRT versus control was 1.55 [95% confidence interval 1.49–1.61], and specifically Risk Ratio = 1.49 (1.40–1.60) for nicotine gum, 1.64 (1.53–1.75) for the patch, 1.52 (1.32–1.74) for nicotine lozenges, 1.90 (1.36–2.67) for the inhaler, and 2.02 (1.49–2.73) for the nasal spray (Hartmann-Boyce, Chepkin, Ye, Bullen, & Lancaster, 2018). Evidence suggests that chronic nicotine use by vaping is associated with increased odds of myocardial infarction, stroke, and circulatory problems, as seen in cigarette smokers (Mayyas et al., 2020; Moheimani et al., 2017). However, it appears that short-term nicotine use, as seen in NRT, might be reasonable safe given the little cardiovascular risk (Hatsukami et al., 2007; Joseph et al., 1996; Lindson et al., 2019; Mills, Thorlund, Eapen, Wu, & Prochaska, 2014), even to patients with known CVD (1994; Joseph et al., 1996), and other mild secondary effects such as the increased risk of heart palpitations and chest pains, nausea and vomiting, gastrointestinal complaints, and insomnia (Mills et al., 2014). It should be taken into consideration that, the adverse effects of NRT are usually assessed after short periods in trials designed to investigate the impact on cessation rates. In addition, some of the NRT methods partially maintain part of the deleterious effects of nicotine, such as IR (Eliasson et al., 1996; Lanza et al., 2017; Mayyas et al., 2020; Pokhrel et al., 2020; Verhaegen & Van Gaal, 2017), thus investigating of the safety of longer use of NRT is necessary.

Despite that nicotine actions on feeding, BAT thermogenesis, and browning makes it an attractive target against obesity, there are gaps in knowledge regarding nicotine's impact on glycemic control, which seem to be variable, and may promote some detrimental undesired side effects (Fig. 3). Although nicotine and smoking seem to increase the risk of IR (Albanes et al., 1987; Eliasson et al., 1994; Eliasson et al., 1996; Wu, Jiao, et al., 2015), several studies have shown opposite effects (Liu et al., 2001; Liu et al., 2003; Petersen & Shulman, 2018; Vu et al., 2014). For instance, nicotine can suppress HGP through an anti-inflammatory signaling pathway involving α7nAChRs (Marrero et al., 2010; Tsuneki et al., 2016; Wang et al., 2011). In preclinical studies, protein tyrosine-kinase inhibitors such as genistein (an isoflavone present in many edible plants) reduce body weight gain and adiposity and improve insulin sensitivity by enhancing insulin signaling in retroperitoneal WAT (Shen et al., 2019). In addition, genistein supplementation significantly reduces fasting blood glucose in postmenopausal women (Braxas, Rafraf, Karimi Hasanabad, & Asghari Jafarabadi, 2019). Evidence that obese subjects exhibit significantly reduced expression of α7nAChR (Cancello et al., 2012) and that genistein could potentially upregulate these receptors (Cho et al., 2005), support further the feasibility of a nicotine-agonist based therapy.

The regulation of nAChRs depends on the number of agonist binding sites, determined by the proportion of α- and non-α -type subunits within the receptor, and the binding sites for allosteric modulators (Gotti et al., 2007). The assembly and stoichiometry of the receptors have a significant impact on the response to allosteric ligands binding and subsequent receptor activity (Bondarenko et al., 2014; da Costa & Sine, 2013; Hamouda, Kimm, & Cohen, 2013). For instance, simultaneous binding at two allosteric sites with different affinities for agonists and antagonists within a receptor could either show additive (Olsen et al., 2013), or even opposite (Spurny et al., 2012) effects. Allosteric modulators with the ability to increase receptor activity in response to the endogenous cholinergic tone, avoiding the usual desensitization observed by agonist stimulation, are promising therapeutics with reduced side effects. Thus, the design of drugs aimed to act at specific allosteric sites in nAChRs, expressing particular subunit compositions, will help to acquire higher pharmacological specificity allowing treatment for a wide range of mild-to-severe symptoms associated with obesity (Iturriaga-Vasquez, Alzate-Morales, Bermudez, Varas, & Reyes-Parada, 2015). However, the diverse range of heteromeric nAChRs and the undefined in vivo functional roles of some AChR subtypes create substantial challenges for subtype-selective targeted drug design (Gotti, Riganti, Vailati, & Clementi, 2006; Taly, Corringer, Guedin, Lestage, & Changeux, 2009).

The development of polyagonists is one of the most promising, elegant, and smart strategies for weight management and metabolic disease (Clemmensen et al., 2019; Clemmensen, Muller, Finan, Tschop, & DiMarchi, 2016; Muller et al., 2018; Tschop et al., 2000). The fact that nicotine or nicotinic receptor agonism can simultaneously modulate food intake, in terms of both homeostatic and hedonic components (Mineur et al., 2011; Picciotto & Mineur, 2013), BAT thermogenesis/browning or WAT (Martinez de Morentin et al., 2012; Seoane-Collazo et al., 2014; Seoane-Collazo et al., 2019) and glucose homeostasis (Eliasson, 2003; Nogueiras et al., 2015) makes nicotine signaling an exciting candidate for drug development, alone or as conjugated polyagonists (Clemmensen et al., 2018; Jall et al., 2020). Supporting the role of nicotine for obesity treatment using such strategy is the elegant work of *Clemmensen and colleagues* demonstrating that DMPP, apart from suppressing appetite, improves glycemic status (Clemmensen et al., 2018; Jall et al., 2020). Given that this effect is due to specific α3β4nAChR agonism, the possible deleterious effect of nicotine treatment, which would target all the nicotinic receptors, would support the use of DMPPs like ligands as a potential drugs for glycemic control (Clemmensen et al., 2018; Jall et al., 2020).

In the context of obesity, for which there is a chronic unmet clinical need, the development of an optimal therapeutic nicotine-based strategy will need to take into consideration several issues, such as testing of new selective nAChR subtype receptor agonists and/or allosteric compounds, as well as targeting specific neuronal populations in the hypothalamus. From a conceptual point of view, this will allow a safer pharmacological profile with a drastic decrease in side effects. Further work will be necessary to gain a thorough understanding of the pleiotropic actions of nicotine on energy homeostasis and to address whether new formulations of this molecule, or other nicotinic receptor agonists, may be suitable to combine the beneficial and desired anorectic, thermogenic and glycemic effects, an exciting adventure for the times to come.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

We thank *Dr. Johan Fernø* (University of Bergen, Norway) for his comments. The research leading to these results has received funding from the Xunta de Galicia (RN: 2016-PG057; ML: 2016-PG068); Ministerio de Economía y Competitividad (MINECO) co-funded by the FEDER Program of EU (RN: RTI2018-099413-B-I00; CD: BFU2017-87721-P; ML: RTI2018-101840-B-I00; JMF-R and ML: BFU2017-90578-REDT/Adipoplast); Instituto de Salud Carlos III (JMF-R: PI15–01934); Atresmedia Corporación (RN and ML); Fundación BBVA (RN); "la Caixa" Foundation (ID 100010434), under the agreement LCF/PR/HR19/52160022 (ML); European Foundation for the Study of Diabetes (RN); ERC Synergy Grant-2019-WATCH- 810331 (RN); US National Institutes of Health (KR: HL084207); the US Department of Veterans Affairs (KR: I01BX004249); The University of Iowa Fraternal Order of Eagles Diabetes Research Center (KR). PS-C is recipient of a fellowship from Xunta de Galicia (ED481B 2018/050). The CiMUS is supported by the Xunta de Galicia (2016-2019, ED431G/05). *CIBER* de Fisiopatología de la Obesidad y Nutrición is an initiative of ISCIII. The

funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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