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REVIEW

Nicotinic Cholinergic Signaling in Adipose Tissue and Pancreatic Islets Biology: Revisited Function and Therapeutic Perspectives

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Abstract Nicotinic acetylcholine receptors (nAChRs) are membrane ligand-gated cation channels whose activation is triggered by the binding of the endogenous neurotransmitter acetylcholine or other biologic compounds including nicotine. Their roles in synaptic transmission in the central and peripheral nervous system as well as in the neuromuscular junction have been extensively studied. Recent implications of nAChRs in intracellular signaling and their detection in peripheral nonneural cells (including epithelial cells and immune cells) have renewed the interest for this class of ionotropic receptors. In the present review, we focus our attention on the potential use of nicotinic cholinergic signaling in the treatment of metabolic diseases (such as obesity and diabetes) in browsing functions of nAChRs in adipose tissue and pancreatic islet biology. In fact, different nAChR subunits can be detected in these metabolic tissues, as well as in immune cells interacting with them. Various rodent models of obesity and diabetes benefit from stimulation of the nicotinic cholinergic pathway, whereas mice deficient for some nAChRs, in particular the α7 nAChR subunit, harbor a worsened metabolic phenotype. In contrast to potential therapeutic applications in metabolic diseases, an overstimulation of this signaling pathway during the early stage of development (typically through nicotine exposure during fetal life) presents deleterious consequences on ontogeny and functionality of adipose tissue and the endocrine pancreas which persist throughout life.

Keywords Nicotine · nAChR · Islet · Adipocyte · Obesity · Diabetes

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Abbreviations

ACh	Acetylcholine
AChE	Acetylcholinesterase
AKT	Protein kinase B
AMPK	AMP-activated protein kinase
BAT	Brown adipose tissue
ChAT	Choline acetyltransferase
CREB	cAMP response element-binding protein
DIO	Diet-induced obesity
DOHaD	Developmental Origins of Health and Disease
FFA	Free fatty acid
F-FDG	Fluorodeoxyglucose
GDP	Guanosine-5′-diphosphate
IL	Interleukin
JAK2/STAT3	Janus kinase 2 and signal transducer and activator of transcription 3
MCP-1	Monocyte chemoattractant protein-1
nAChR	Nicotinic acetylcholine receptor
NPY	Neuropeptide Y
PI3-kinase	Phosphatidylinositide 3-kinase
POMC	Proopiomelanocortin
PPAR-γ	Peroxisome proliferator-activated receptor gamma
SNP	Single nucleotide polymorphism
T1D	Type 1 diabetes
TNF-α	Tumor necrosis factor alpha
UCP-1	Uncoupling protein 1
WAT	White adipose tissue

Sum-up of Nicotinic Cholinergic Signaling Biology

Acetylcholine (ACh) is a small organic molecule initially discovered by H.H. Dale and later identified by O. Loewi as the first neurotransmitter. Dale and Loewi jointly

received in 1936 the Nobel Prize in physiology or medicine for their discoveries "relating to chemical transmission of nerve impulses" (Raju 1999). ACh is synthesized intracellularly by the enzyme choline acetyltransferase (ChAT) from choline and acetyl-coenzyme A before being released into the extracellular space to act on synaptic-adjacent cells. In contrast, the enzyme acetylcholinesterase (AChE) can rapidly clear the extracellular ACh pool into its inactive metabolites choline and acetate. This signaling system is targeted by various biological modulators which can, for example, inhibit ACh release or AChE activity. Sensitivity to natural ACh mimetics has allowed deciphering between two different cholinergic signaling pathways. Muscarine, a poisonous molecule found in mushrooms, induces a strong activation of the peripheral parasympathetic nervous system (muscarinic syndrome) that can end in convulsions and death. Nicotine, a natural alkaloid produced by the tobacco plant, is one of the most widely consumed psychostimulants, inducing strong behavioral dependence. These two molecules act via distinct types of cholinergic receptors. The muscarinic ACh receptors (AChRs M1–5) consist of a family of five metabotropic or second messenger-coupled receptors (Eglen 2012; Ishii and Kurachi 2006). On the other hand, the nicotinic AChRs (nAChRs) consist of a family of ligand-gated cation channels (Albuquerque et al. 2009; Changeux 2012). Purification of protein extracts and electronic microscopy have revealed amino acid sequence and size of nAChR (Changeux et al. 1970; Changeux 1990) before later cloning revealed the chromosomal location of a total of 16 genes coding for different nAChR subunits in mammalian genomes: 9 α subunits (CHRNA 1–7, CHRNA 9–10), 4 β subunits (CHRNB 1–4) and 3 atypical γ, δ, ε subunits (CHRNG, CHRND, CHRNE) (Albuquerque et al. 2009). These genes are probably from a common ancestor through a duplication and mutation process, since they are highly conserved throughout evolution (Le Novere and Changeux 1995). The pentameric structure initially described (Hucho and Changeux 1973) and confirmed by refined modeling at 4A resolution (Unwin 2005) consists of a symmetrical arrangement of the five subunits around a central pore. Each subunit possesses four transmembrane domains with their N- and C-terminus located extracellularly. nAChRs can be classically subclassed as muscular or neuronal. The muscular nAChR is a heteropentameric protein composed of $(\alpha 1)_2$, β1, δ, γ subunits in the fetus and $(\alpha 1)_2$, β1, δ, ε subunits in the adult. The neuronal nAChRs can be heteropentamerics, resulting from the assembly of different subunits with at least one of them being α, or homopentameric when composed of five identical α subunits (typically the α7 nAChR). The subunit composition of nAChRs determines their expression pattern, function and pharmacologic properties (such as agonist sensitivity or desensitizing period) (Hogg et al. 2003; Hurst et al. 2013; Lindstrom 1996). Functionally, non-muscular nAChRs are generally categorized as high-affinity nicotine binding receptors (integrating α4 subunits), α-bungarotoxin-sensitive neuronal nAChRs (composed of an α7 subunit) and ganglionic receptors (composed of α3 and β4 subunits) (Hogg et al. 2003; Hurst et al. 2013; Lindstrom 1996). Mechanistically, α7 nAChRs are opened by relatively low nicotine concentrations, but then rapidly desensitized contrary to α3/β4 nAChR receptors, insensitive to low nicotine concentrations and slow to desensitize (Hogg et al. 2003; Hurst et al. 2013; Lindstrom 1996). Ionic selectivity also differentiates nAChRs, since α7 nAChR specifically presents high permeability to Ca^{2+} exceeding that of other nAChRs (Hogg et al. 2003; Lindstrom 1996; Uteshev 2012). These features and advances in understanding the structural/functional properties of α7 nAChRs through new techniques have recently suggested its use as a new pharmacotherapeutic target (Palma et al. 2012; Taly and Charon 2012).

Beyond their channeling activity, nAChRs can be involved in other intracellular events involving signaling through PI3-kinase (Huang et al. 2012; Kihara et al. 2001), ERK1/2 (Dajas-Bailador et al. 2002), AKT (Nakayama et al. 2002; West et al. 2003) and CREB (Brunzell et al. 2003) pathways. Other regulatory roles for nAChRs have also been described in proteolysis (Meyer et al. 2002; Minana et al. 1998) and mitochondrial permeability (Gergalova et al. 2012). In addition to their classic roles of neurotransmitter in the central nervous system, neuromuscular junction and autonomic nervous fibers, several studies have detected nAChR expression in many different non-neuronal cell types throughout the body (for review see Conti-Fine et al. 2000; Gahring and Rogers 2005; Sharma and Vijayaraghavan 2002). These observations have led to reconsidering the role of ACh not only as a neurotransmitter, but also as a paracrine messenger able to interact with peripheral nAChRs. In this context, the interaction between ACh released by the vagus nerve and α7 nAChR expressed on macrophages/immune cells (Wang et al. 2003) represents a "cholinergic anti-inflammatory pathway" (Tracey 2007) of particular clinical interest. There is increasing evidence that smokers have a lower incidence of certain bowel inflammations (Lakhan and Kirchgessner 2011) and that use of the cholinergic anti-inflammatory pathway can present valuable therapeutic perspectives in a wide range of pathologies including sepsis, endotoxemia, ischemia/reperfusion injury, hemorrhagic shock, rheumatoid arthritis and other conditions of excessive cytokine release (Oke and Tracey 2009; Tracey 2007).

The present review aims to evaluate the function and the potential therapeutic perspectives of peripheral cholinergic signaling through nAChRs with special focus on adipose

and pancreatic islet biology, two tissues involved in metabolic diseases. To this purpose, we then summarize and discuss: (1) peripheral detection of different subunits composing nAChRs, (2) experimental results from animal/cell models exposed to nAChR agonists/antagonists and (3) basal or challenged phenotypes of animals deficient in some nAChR subunits, in the context of adipose tissue and pancreatic islet physiology and their commonly associated pathologies: obesity and diabetes.

Nicotinic Cholinergic Signaling in Brown and White Adipose Tissue Biology and Therapeutic Perspectives in the Treatment of Obesity

White adipose tissue (WAT) functions as a reservoir of energy stored as triglycerides after a meal and released into the bloodstream as fatty acids and glycerol between meals. WAT also acts as a thermal insulator and possesses endocrine functions, secreting many adipokines (cytokines produced by adipose tissue) involved in the regulation of body weight homeostasis and insulin sensitivity (Harwood 2012).

Brown adipose tissue (BAT) is especially abundant in newborns and in hibernating mammals, but recent studies have revealed its persistence in human adults (Cypess et al. 2009; van Marken Lichtenbelt et al. 2009). BAT, which is more innervated and vascularized than WAT, is the main site of adaptative thermogenesis, a process of heat production independent of muscular shivering (Lowell and Spiegelman 2000).

White and brown adipocytes present morphologic and molecular features corresponding to their distinct functional roles. In white adipocytes, triglyceride storage is unilocular (a single lipid droplet is present in the cytosol) and mitochondria are small and elongated, with randomly oriented cristae. In contrast, in brown adipocytes, triglyceride storage is multilocular (numerous intracellular small lipid droplets) and mitochondria are large, numerous, endowed with laminar cristae and specifically express the uncoupling protein 1 (UCP-1) responsible for uncoupling of the oxidative phosphorylation that in turn is responsible for heat production (Cinti 2005, 2012; Frontini and Cinti 2010).

Peripheral nicotinic cholinergic signaling could be involved in adipose tissue biology through localization of nAChRs at various levels, such as in autonomic ganglia, macrophages, or directly in adipocytes. Studies on knockout mice have demonstrated that combinations of α3 with β2 or β4 subunits compose most nAChRs in autonomic ganglia of the sympathetic nervous system (Wang et al. 2002) which control adipose tissue activity. Macrophages, mediating the cholinergic anti-inflammatory pathway through the α7 nAChR (Wang et al. 2003), are responsible for the inflammatory response in WAT during obesity (Weisberg et al. 2003; Xu et al. 2003) and also secrete local catecholamines during adaptative thermogenesis in BAT (Nguyen et al. 2011). Adipose tissue possesses functional cholinergic signaling machinery as shown by its regulated expression of butyrylcholinesterase (Wang et al. 2011). Moreover, various nAChR subunits can be detected in isolated adipocytes (Liu et al. 2004), as well as in BAT and WAT from rodents (Gochberg-Sarver et al. 2012) and humans (Cancello et al. 2012).

Nicotine Exposure Effects

In Humans

Epidemiological studies dealing with the metabolic action of tobacco consumption represent an extensive source of information, nevertheless difficult to interpret in the context of nicotinic cholinergic action on the adipose metabolism due to both the simultaneous central and peripheral action of nicotine and the large panel of bioactive compounds accompanying nicotine in tobacco (Borgerding and Klus 2005). Selective and focal nicotine exposure through microdialysis is an interesting technique used to directly study in vivo nicotinic cholinergic signaling on the human adipose metabolism. In healthy subjects, this route of nicotine administration causes a concentration-dependent and reversible increase in the levels of glycerol release, whereas the opposite effect is induced by carbachol, demonstrating a dual effect of the nicotinic/muscarinic cholinergic system on lipolysis (Andersson and Arner 1995). In healthy male smokers, acute nicotine infusion increases free fatty acid (FFA) release in adipose tissue consecutively to an oral glucose tolerance test (Eliasson et al. 1997). This technique also shows that nicotine-induced increase in venous, arterial and adipose glycerol occurs with no change in blood flow (Andersson and Arner 2001), suggesting an induction of lipolysis through activation of the classical adrenergic mechanism and by activation of a nicotinic cholinergic lipolytic receptor located in the adipose tissue (Andersson and Arner 2001).

In Control Animals

In basal physiologic conditions, changes in body fat proportion parallels changes in body weight in response to nicotine exposure in rats, suggesting that nicotine administration decreases body weight by lowering fat stores in the body (Winders and Grunberg 1990). Central anorexigenic features of nicotine (for review see Jo et al. 2002; Li et al. 2000b; Zoli and Picciotto 2012) can in part explain

dampening of adipose storage. In fact, numerous hypothalamic neuropeptides involved in the control of food intake are regulated by nicotinic cholinergic signaling. Nicotine increases neuropeptide Y (NPY) in different hypothalamic areas (Jang et al. 2003; Li et al. 2000a), but limits elevation of NPY during food restriction (Jang et al. 2003). Ex vivo, nicotine directly induces depolarization of NPY neurons and reduces their glutamatergic input (Huang et al. 2011). Nicotine also increases expression of orexin and its receptor in the hypothalamus (Kane et al. 2000), but decreases orexin binding (Kane et al. 2001) and induces fos expression in some orexin neuron subpopulations (Pasumarthi et al. 2006), linked with the release of glutamate and ACh in the lateral hypothalamus (Pasumarthi and Fadel 2010). Nicotine also induces release of hypothalamic monoamines (Fu et al. 2001; Meguid et al. 2000; Sharp and Matta 1993; Yang et al. 1999), indirect inhibition of melanin-concentrating hormone neurons (through activation of GABAergic transmission) (Jo et al. 2005), direct stimulation of proopiomelanocortin (POMC) neurons (Huang et al. 2011; Mineur et al. 2011) and inactivation of hypothalamic AMP-activated protein kinase (AMPK) (Martinez de Morentin et al. 2012). Different nAChRs seem to mediate nicotine inhibition of food intake. In the lateral hypothalamus, neuronal webs receive cholinergic afferents and express α4/β2 and α7 nAChRs (Jo et al. 2002; Seguela et al. 1993; Wada et al. 1989). α3/β4 nAChRs seem rather implicated in both nicotinic cholinergic stimulation of POMC neurons (Mineur et al. 2011) and inactivation of hypothalamic AMPK (Martinez de Morentin et al. 2012). Interestingly, despite that leptin receptor isoform b and α7 nAChRs share the same JAK2/STAT3 downstream effectors (de Jonge et al. 2005; Hakansson and Meister 1998; Kloek et al. 2002; Vaisse et al. 1996), and despite the known effects of nicotine on feeding behavior, the relationship between α7 nAChRs and leptin sensitivity remains unexplored. The JAK2/STAT3 activation by α7 nAChR stimulation (by nicotine or more specific agonists) in situations of leptin resistance, as seen in obesity, may represent a new approach to control feeding behavior.

Beyond these central effects indirectly impacting adipose tissue through limitation of energy intake, nicotine also directly impacts WAT and BAT metabolism. Nicotine does not seem to alter the composition of the major fatty acids in adipose triglycerides (Brindis et al. 1973), but induces a fall in the respiratory quotient (Bishop et al. 2004; Martinez de Morentin et al. 2012) reflecting a rise in lipid use. Nicotine induces a fall in circulating triglyceride levels associated with decreased adipose tissue lipoprotein lipase activity (Chajek-Shaul et al. 1987; Sztalryd et al. 1996). By increasing basal lipolysis, but blunting the lipolytic response to sympathomimetic β-receptor stimulant isoproterenol, nicotine appears to divert fat storage from adipose tissue toward utilization by the muscle (Sztalryd et al. 1996). Nicotine administration also interferes with the endocrine function of adipose tissue by decreasing circulating leptin levels (Arai et al. 2001) and gene expression in the perirenal and epididymal WAT (Li and Kane 2003). Nicotine-induced weight loss is associated with increased BAT thermogenesis and increased energy expenditure (Martinez de Morentin et al. 2012). Acute and chronic exposure to nicotine increases both the turnover of norepinephrine and the binding of the guanosine-5′-diphosphate (GDP) to BAT mitochondria (Lupien and Bray 1988). Decreased vacuolation, elevated UCP-1 and norepinephrine contents are also observed in BAT in a depot-specific manner following nicotine administration (Arai et al. 2001; Brees et al. 2008). Nicotine induces uptake of ^{18}F-FDG in BAT (blockable by a prior injection of β-adrenergic antagonists) (Baba et al. 2007) and a reversible noradrenaline release from BAT (blockable by antagonism of corticotrophin-releasing factor receptor type 1) (Mano-Otagiri et al. 2009).

In Obesity Models

Lipolytic and thermogenic features of nicotinic cholinergic signaling previously described in the basal state led to evaluate its potential weight loss promoting action in different rodent models of obesity. Genetically obese ob/ob mice subcutaneously injected with nicotine present a rise in plasma FFA with no change in basal body temperature or cold-induced hypothermia (Batt and Topping 1979). In monosodium-L-glutamate obese mice, nicotine treatment attenuates obesity in the absence of food intake modification by significantly increasing norepinephrine turnover, GDP binding/oxygen consumption in BAT and the resting metabolic rate (Yoshida et al. 1990). Obese yellow KK mice chronically treated with nicotine present decreased weight, smaller subcutaneous and retroperitoneal WAT depot harboring multilocular cells and ectopic UCP-1 gene expression leading to the mitigation of obesity (Yoshida et al. 1999). In Zucker fatty rats, the tumor necrosis factor (TNF)-α level is specifically lowered in visceral fat pads (Liu et al. 2001) in response to nicotine administration. In genetically obese mice with a defective leptin receptor (db/db) as well as in diet-induced obese (DIO) mice, nicotine does not change body weight or appetite, but reduces the inflammation of adipose tissue depots through activation of the cholinergic anti-inflammatory pathway (Wang et al. 2011). In DIO mice, treatment with galantamine (an AChE inhibitor enhancing cholinergic signaling and also acting as a positive allosteric modulator of α7 nAChR) (Albuquerque et al. 2001) significantly reduces body weight, food intake, abdominal adiposity, plasma cytokine and adipokine levels, and significantly improves blood glucose,

insulin resistance and hepatic steatosis (Satapathy et al. 2011). These results suggest that galantamine has both a central and a peripheral anti-inflammatory effect (Satapathy et al. 2011). In conclusion, various rodent models of obesity can benefit from activation of the nicotinic cholinergic signaling pathway (Table 1).

nAChR Subunits Involved and Genetic Models

Quantification of nAChR subunits in adipose tissue or adipose cells from rodents and humans (summarized in Table 2) as well as metabolic phenotyping of animal models harboring a deficiency in nAChR subunits also contribute to deeper understanding of the role of the nicotinic cholinergic pathway in adipose tissue development and function. Gene expression of α1–7, α9, α10, β1–4, δ and ε nAChR subunits can be detected in rat adipocytes, in line with immunocytochemical labeling of α7 and β2 subunits (Liu et al. 2004). Functional binding of labeled nicotine directly on adipocytes corroborate functionality of these adipose nAChRs (Liu et al. 2004). In mice, the expression pattern of nAChR subunits in WAT ($\alpha2 > \alpha5 > \beta2 > \alpha4$) diverges from that of BAT ($\alpha2 > \beta2 > \beta4 > \alpha5$) (Gochberg-Sarver et al. 2012) suggesting depot-specific functional roles. In link with these basic observations, single nucleotide polymorphism (SNP) in the α2 nAChR subunit appears as a risk factor for overweight/obesity in a human cohort (Kim 2008). Genetic deletion of AChE (as well as administration of AChE pharmacological inhibitors) induces hypothermia associated with reduced nicotinic receptor currents in isolated sympathetic ganglia neurons mediating the activation of BAT (Sun et al. 2007). Chronic nicotine treatment decreases gene expression of TNF-α, adiponectin and monocyte chemoattractant protein-1 (MCP-1) in WAT and those of TNF-α and adiponectin in BAT (Gochberg-Sarver et al. 2012). β2 nAChR subunit deficiency (β2 $nAChR^{-/-}$ mice) affects gene expression of cyclooxygenase 2 and nerve growth factor β in WAT and those of leptin, cyclooxygenase 2, adiponectin and haptoglobin in BAT suggesting a role for this subunit in regulation of gene transcription in adipose tissue (Gochberg-Sarver et al. 2012). The cholinergic anti-inflammatory pathway also seems to play an important role in obesity-induced inflammation of adipose tissue. In fact, metabolic phenotype of α7 $nAChR^{-/-}$ mice shows that their macrophages present elevated proinflammatory cytokine production in response to FFAs (Wang et al. 2011). Nicotine significantly suppresses FFA- and TNF-α-induced cytokine production in wild-type but not in α7 $nAChR^{-/-}$ macrophages, suggesting that α7 nAChR mediates the anti-inflammatory effect of nicotine (Wang et al. 2011). Inactivation of the cholinergic anti-inflammatory pathway in the α7 $nAChR^{-/-}$ mouse model results in increased adipose tissue infiltration of classically activated M1 macrophages and inflammation leading to impaired insulin sensitivity independent of any change in body weight (Wang et al. 2011). These experimental observations in rodents are strikingly highlighted by the recent investigations on α7 nAChR subunits in human WAT. α7 nAChR expression appears lowered in the subcutaneous adipose tissue of obese humans compared with that of control subjects (Cancello et al. 2012). In isolated mature adipocytes from highly obese subjects, α7 nAChR expression and protein content are 75 % lower compared with control subjects, whereas weight loss induces an increase in α7 nAChR expression (Cancello et al. 2012).

Cell Culture

Some molecular mechanisms involved in nicotinic cholinergic signaling in fat cells are more thoroughly elucidated through in vitro experiments using adipocyte cell lines or primary cultures. Exposure of 3T3L1 adipocytes to nicotine increases lipolysis and inhibits fatty acid synthase activity, phosphorylating both AMPK and acetyl-CoA carboxylase (An et al. 2007). These effects appear to be mediated through induction of reactive oxygen species (An et al. 2007). In rat adipocyte primary culture, nicotine induces a dose-responsive release of TNF-α, adiponectin and FFA into the medium (Liu et al. 2004). In contrast, TNF-α protein levels decrease in adipocytes, suggesting that nicotine regulates time dependently the production and secretion of adipokines (Liu et al. 2004). In mice adipocyte primary cultures, application of nicotine after silencing the β2 nAChR subunit significantly elevates the expression level of cyclooxygenase-2 gene, corroborating a molecular link between the β2 nAChR subunit and the expression levels of specific adipokines also affected by nicotine (Gochberg-Sarver et al. 2012). In vitro stimulation of human adipocytes with the specific α7 nAChR agonist PNU282987 induces a significant anti-inflammatory effect, decreasing the pro-inflammatory up-regulation of interleukin (IL)-6, MCP-1 and TNF-α genes induced by lipopolysaccharide (Cancello et al. 2012). Likewise, a genistein treatment inducing an increase in α7 nAChR protein content results in a significantly decreased expression of IL-6 and MCP-1 genes in adipocyte culture (Cancello et al. 2012).

Early Deleterious Programming Action

The programming phenomenon [also known as the Barker's Hypothesis or Developmental Origins of Health and Disease (DOHaD) theory] is a biological process underlying developmental plasticity. This concept of "fetal

Table 1 Effects of nicotinic cholinergic signaling modulation in animal models of obesity and diabetes

Animal model	Nicotinic cholinergic agonist	Dose of exposure	Route of exposure	Main observations	References
ob/ob mice	Nicotine	0.5 mg/kg	s.c.	Acute treatment raises plasma FFAs, but does not alter body temperature at ambient temperature or cold-induced hypothermia in contrast to observations performed in control mice	Batt and Topping (1979)
MSG obese mice	Nicotine	0.4 mg/kg	s.c.	Two-week treatment increases norepinephrine turnover, GDP binding, BAT oxygen consumption, resting metabolic rate, and significantly reduces b.w. in MSG obese mice, as well as in control mice, without affecting food intake	Yoshida et al. (1990)
Obese yellow KK mice	Nicotine	1–1.2 mg/kg	s.c.	Six-month treatment reduces b.w., s.c. and retroperitoneal WAT pads, food intake. Brown-like phenotype (UCP-1 presence, multilocular cells) is observed in s.c. and retroperitoneal WAT	Yoshida et al. (1999)
Zucker fatty rats	Nicotine	4.6 mg/kg/day	Oral	Eight-week nicotine administration lowers glycemia (before and after GTT), islet size and TNF-α levels in visceral fat compared to control pair-fed group	Liu et al. (2001)
Zucker fatty rats	Nicotine	4.6 mg/kg/day	Oral	Eight-week nicotine administration enhances insulin sensitivity, and decreases gluconeogenesis in the liver and hepatic glucose output	Liu et al. (2003)
db/db mice	Nicotine	400 μg/kg	i.p. twice daily	Three-week nicotine administration improves glucose homeostasis and insulin sensitivity (without changes in b.w. but through down-regulation of adipose tissue inflammation)	Wang et al. (2011)
DIO mice	Nicotine	400 μg/kg	i.p. twice daily	Three-week nicotine administration improves glucose homeostasis and insulin sensitivity (without changes in b.w. but through down-regulation of adipose tissue inflammation)	Wang et al. (2011)
db/db mice	TC-7020 (α7 nAChR-selective agonist)	1 mg/kg daily	Oral gavage	Seven-week TC-7020 administration reduces weight gain, food intake, glucose and glycated hemoglobin levels, and lowers elevated plasma levels of triglycerides and the proinflammatory cytokine TNF-α. These changes are reversed by an α7-selective antagonist or by a Janus kinase 2 inhibitor	Marrero et al. (2010)
DIO C57BL/6 J obese mice	Galantamine	4 mg/kg	i.p. once daily	Four-week galantamine treatment reduces b.w., food intake, abdominal adiposity, plasma cytokine and adipokine levels, and improves blood glucose, insulin resistance and hepatic steatosis	Satapathy et al. (2011)
BALB/c streptozotocin-treated mice NOD mice	Nicotine	0.4 mg/kg	s.c.	21-day (for STZ) or 13–20-week (for NOD) nicotine treatment reduces hyperglycemia and incidence of disease and preserves pancreatic insulin content. Diabetes-induced elevation of pancreatic levels of Th1 cytokines (IL-12, IL-1, TNF-α, IFN-γ) is prevented by nicotine treatment, which increased the pancreatic levels of Th2 cytokines (IL-4 and IL-10)	Mabley et al. (2002)

Table 1 completed

Animal model	Nicotinic cholinergic agonist	Dose of exposure	Route of exposure	Main observations	References
β2 nAChR$^{-/-}$ mice	Nicotine	8.0 mg/kg daily	s.c. infusion	In β2 nAChR$^{-/-}$ mice, gene expression is specifically altered in WAT and BAT (see Table 2). Interactions between β2 nAChR subunit and nicotine treatment also affects the adipokine expression in both adipose tissues, suggesting that β2 nAChR is involved in control of specific adipokine expression, which is also affected by nicotine	Gochberg-Sarver et al. (2012)
α7 nAChR$^{-/-}$ mice	–	–	–	No difference in b.w., epididymal fat mass or food intake in α7 nAChR$^{-/-}$ mice on either chow or high-fat diet. α7 nAChR$^{-/-}$ mice have increased adipose tissue macrophage infiltration and inflammation on both diets. α7 nAChR$^{-/-}$ mice develop insulin resistance on high-fat diet	Wang et al. (2011)
α7 nAChR$^{-/-}$ mice	Nicotine	3 mg/kg/day	s.c.	α7 nAChR deficiency abrogates insulin-sensitizing effect of nicotine observed in control animals	Xu et al. (2012)
AMPKα2$^{-/-}$ mice	PNU-282987 (α7 nAChR-selective agonist)	0.53 mg/kg/d	s.c.	Six-week treatment improves insulin sensitivity in AMPKα2$^{-/-}$ mice	Xu et al. (2012)

GTT glucose tolerance test, *i.p.* intraperitoneal, *s.c.* subcutaneous, *b.w.* body weight, *STZ* streptozotocin, *IFN-γ* interferon gamma

origin of adult diseases" suggests that a mismatch between fetal expectation of the postnatal environment and actual postnatal environment could contribute to later adult disease risk (Gluckman and Hanson 2004). For example, maternal inadequate nutrition, which limits fetal growth leading to low birth weight, predisposes to obesity in adulthood, especially when postnatal nutrition is highly caloric (Hales and Barker 1992). Voluntary or passive exposure to chemical pollutants also contribute to inadequate intrauterine environment, and despite medical advice more than 10 % women continue smoking during pregnancy (for review see Somm et al. 2009). In contrast to the direct lipolytic and anti-inflammatory action of nicotinic cholinergic signaling previously discussed, fetal nicotinic exposure seems to present an opposite effect by programming excessive adipose tissue development later in life. Epidemiological studies have correlated maternal smoking during pregnancy with increased risk of obesity in children at different ages (Al Mamun et al. 2006; Koupil and Toivanen 2008; Mizutani et al. 2007; Ong et al. 2002; Power and Jefferis 2002; Sowan and Stember 2000; Toschke et al. 2002a, b). Animal studies show that nicotine exposure mimics the effect of maternal tobacco consumption on obesity occurrence in the offspring (for review see Somm et al. 2009). Initial observations showing elevation in body fat proportion by one-third just before birth in rat fetuses prenatally exposed to nicotine (Williams and Kanagasabai 1984) are corroborated by more recent studies. Epididymal, mesenteric and perirenal fat pad weights are increased in adulthood in Wistar rats perinatally exposed to nicotine (Gao et al. 2005). Epididymal fat pad weight is also heavier at weaning in Sprague–Dawley rats exposed to nicotine during their uterine life, mainly due to enhanced differentiation of their adipocytes (Somm et al. 2008). Prenatal nicotine exposure also exacerbates post-weaning weight gain and fat deposition caused by high-fat diet consumption (Somm et al. 2008). Maternal nicotine exposure restricted to the lactating period also leads to early and late metabolic defects. Higher levels of HDL-C, leptin, corticosterone and adrenal catecholamine content are observed at PND15, (Oliveira et al. 2010) and overweight (with increased fat mass and hypertrophy of adipocyte), hyperleptinemia (with impaired hypothalamic leptin signaling), hyperinsulinemia and hypothyroidism are reported in adult rat offspring exposed to nicotine through maternal milk (de Oliveira et al. 2010). Different mechanisms could explain the enhanced adipose storage due to early nicotine exposure during the early stage of development such as (1) increased release and transport of fatty acids from maternal adipose tissue to the fetal circulation (Williams and Kanagasabai 1984), (2) a nicotine-mediated stimulatory effect on PPAR-γ gene expression in the adipocyte (Somm et al. 2008), as previously observed in monocytes (Amoruso

Table 2 Detection of nAChR subunits in adipose or pancreatic islet cells and tissues

Tissue/cell line	Specie	nAChR subunits	Method of detection	Remarks	References
Adipose tissue					
Epididymal WAT	Mice	α2 > α5 > β2 > α4	qPCR	In β2 nAChR$^{-/-}$ mice, the expression levels of Cox2 and Ngfβ genes are significantly altered in WAT	Gochberg-Sarver et al. (2012)
Interscapular BAT	Mice	α2 > β2 > β4 > α5	qPCR	In β2 nAChR$^{-/-}$ mice, the expression levels of Leptin, Cox2, AdipoQ and haptoglobin are significantly altered in BAT	Gochberg-Sarver et al. (2012)
Subcutaneous WAT	Human	α7	qPCR	Gene expression of α7 nAChR is reduced in obese subjects	Cancello et al. (2012)
Isolated mature adipocyte	Human	α7	qPCR/WB	α7 nAChR expression is higher in mature adipocytes than in whole adipose tissue. α7 nAChR in adipocytes of obese subjects is significantly lowered (mRNA and protein). In obese subjects, weight loss increases α7 nAChR expression	Cancello et al. (2012)
Epididymal WAT	Mice	α7	qPCR	The expression of α7 nAChR tends to be higher in adipose macrophages than in isolated adipocytes. Butyrylcholinesterase is the major cholinesterase in adipose tissue (up-regulated with chronic nicotine treatment, down-regulated in DIO and in db/db mice)	Wang et al. (2011)
In vitro differentiated adipocyte	Rat	α1–7, 9, 10, β1–4, δ, ε	PCR/IHC	Functionality of nAChRs expression is also substantiated by a dose-dependent binding of labeled nicotine	Liu et al. (2004)
Pancreatic islet cell					
Islet (β cell)	Rat	α7	IHC	α7 nAChR subunit is expressed in the central part of the islets and co-localizes with insulin, ChAT, VAChT while AChE expression is stronger in the surrounding, exocrine tissue and in the mantle region of the islet	Delbro (2012)
INS-1 (β cell line)	Rat	α2, α3, α4, α5, α7, β2	PCR	Binding of α-bungarotoxin and cytisine indicates functionality of these subunits in INS-1 cells and rat islets	Yoshikawa et al. (2005)
TC6 insulinoma cells (β cell line)	Mice	α3, α4, β2, β4	PCR	α5 nAChR subunit mRNA is also detected, whereas mRNAs for α2, α6, and α7 nAChR subunits are not detected. Nicotinic agonists (epibatidine > nicotine ≈ cytisine, A-83850, and DMPP) also elicit increases in intracellular calcium. Binding results with [^{3}H]epibatidine demonstrate high levels of nicotinic receptors with high affinity	Ohtani et al. (2006)

AdipoQ adiponectin, *Cox2* cyclooxygenase-2, *DMPP* dimethylphenylpiperazinium

et al. 2007); (3) decreased physical activity [linked to alterations in motor behavior related to disruptions in the mesoaccumbens dopaminergic pathway (Oliff and Gallardo 1999)]; and (4) decreased cold-induced thermogenesis [in accordance with alterations in adrenergic responsiveness of sympathetic target tissues (Navarro et al. 1990) and blunted sympathetic responsiveness leading to hypoactivity of the noradrenergic system (Levin 2005)].

Nicotinic Cholinergic Signaling in Pancreatic Islet Biology and Therapeutic Perspectives in the Treatment of Diabetes

Pancreatic islets (also named Langerhans islets) are clusters of endocrine cells which represent approximately 1–2 % of the mass of the whole pancreatic tissue. These endocrine structures play a central role in metabolism through direct secretion into the blood flow of key hormones involved in the regulation of nutrient uptake or transformation. β Cells (producing insulin, c-peptide and amylin) and α cells (producing glucagon) are the major cell types present in pancreatic islets; other cell types include δ cells (producing somatostatin), PP cells (producing pancreatic polypeptide) and ε cells (producing ghrelin). In addition to nutritional, hormonal and paracrine regulatory mechanisms, the secretory activity of pancreatic islets is under tight control of the autonomic nervous system involving cholinergic signaling, as demonstrated by the tenfold higher activity of CHAT and AChE in the islets compared to the surrounding exocrine tissue (Godfrey and Matschinsky 1975). At the sympathetic level, the preganglionic fibers release ACh that acts on nicotinic receptors on intraganglionic neurons, whereas the postganglionic fibers release several neurotransmitters including norepinephrine (Ahren 2000; Cerf 2011; Gilon and Henquin 2001; Woods and Porte 1974). Sympathetic islet innervation lowers insulin and stimulates glucagon release to maintain or increase glycemia in stress conditions such as neuroglycopenia or physical exercise (Ahren 2000; Cerf 2011; Gilon and Henquin 2001; Woods and Porte 1974). At the parasympathetic level, the preganglionic fibers reach

intrapancreatic ganglia dispersed in the exocrine tissue and unmyelinated postganglionic fibers leave the ganglia toward the islets (Ahren 2000; Cerf 2011; Gilon and Henquin 2001; Woods and Porte 1974). Preganglionic vagal fibers release ACh that binds to nicotinic receptors on intraganglionic neurons and postganglionic vagal fibers release several neurotransmitters including ACh. Parasympathetic islet innervation stimulates insulin, glucagon and PP release (Ahren 2000; Cerf 2011; Gilon and Henquin 2001; Woods and Porte 1974).

The muscarinic receptor is classically described as the terminal effector of cholinergic signaling in pancreatic β cells (Gilon and Henquin 2001; Lundquist 1982; Ruiz de Azua et al. 2012), and the function of nicotinic cholinergic receptors in the context of pancreatic islets has long been limited to their role in ganglionic autonomic neurotransmission. Nicotinic cholinergic signaling stimulates vagal transmission in ganglionic neurons, and nAChR agonists, including nicotine, mimic this vagal signaling (Ahren et al. 1986; Ahren and Taborsky 1986; Kirchgessner and Liu 1998; Nishi et al. 1987; Sha et al. 1997; Stagner and Samols 1986).

More recent direct detection of nAChRs in immune and islet cells leads to revise the potential role of the nicotinic cholinergic pathway in endocrine pancreas physiology and diseases. Species differences in morphological organization of pancreatic islets need to be considered in this context. In contrast to rodent islets, harboring a central core of β cells surrounded by peripheral α cells in the mantle position, the cytoarchitecture of human islets does not show such distinct anatomical subdivisions with α, β and δ cells scattered throughout the islet, complicating a precise order of paracrine interactions (Cabrera et al. 2006). The innervation pattern of islets also seems to be different between rodents and humans. Visualization of axons in three dimensions and quantification of axonal densities and contacts within pancreatic islets show that human endocrine cells are sparsely contacted by autonomic axons (Rodriguez-Diaz et al. 2011a). Few parasympathetic cholinergic axons penetrate the human islet, and the invading sympathetic fibers preferentially innervate smooth muscle cells of blood vessels located within the islet, suggesting a role in the control of local blood flow (Rodriguez-Diaz et al. 2011a). Poor cholinergic innervation of human islets appears to be substituted by the α cells which provide paracrine cholinergic input to surrounding endocrine cells (Rodriguez-Diaz et al. 2011b). ACh secretion by α cells seems to sensitize the β cell response to increase in glucose concentration (Rodriguez-Diaz et al. 2011b), making the paracrine cholinergic signaling within islets a potential therapeutic target in diabetes. In rodents, the expression of ChAT, VAChT, CHT-1 and α7 nAChR is identified in the core of islets (β cells), and expression of AChE is stronger in the surrounding exocrine tissue and in the mantle region of the islet (Delbro 2012), suggesting that rat β cells produce ACh which could in an autocrine/paracrine mechanism participate in insulin secretion via α7 nAChR receptors. Some previous functional experiments substantiate this histologically based hypothesis and attribute a primary role to nicotinic cholinergic signaling in pancreatic islet secretion. In islets isolated from rats, exposure to the muscarinic receptor blocker, atropine, suppresses insulin release, whereas α-bungarotoxin (antagonist of the α7 nAChR) increases insulin and glucagon release (Ejiri et al. 1989, 1990), suggesting that not only muscarinic but also nicotinic cholinergic receptors influence insulin release in isolated islets. In rat and human islets, nicotine moderately inhibits insulin release, both in the presence of basal and elevated glucose levels (Yoshikawa et al. 2005). Specific binding of labeled nicotine is demonstrated in rat islets as well as in INS-1, a rat β cell line expressing α2, α3, α4, α5, α7 and β2 nAChR subunits (Yoshikawa et al. 2005). Cytisine (a partial agonist of α4/β2*nAChRs and a full agonist of α3/β4*nAChRs) partially inhibits tolbutamide-induced insulin release (by direct closure of K^+-ATP channels) in INS-1 cells (Yoshikawa et al. 2005). In contrast, specific binding of α-bungarotoxin slightly increases insulin release in INS-1 cells (Yoshikawa et al. 2005). In mice β-TC6 insulinoma cells harboring α3, α4, β2, β4 nAChR subunits, nicotine elicits membrane depolarization, elevation of intracellular calcium and release of insulin (Ohtani et al. 2006). In these β-TC6 insulinoma cells, the maximal elevation of cytoplasmic [Ca^{2+}] induced by carbamylcholine (a mixed muscarinic/nicotinic receptor agonist) is greater than that of oxotremorine M (a selective muscarinic agonist) or nicotine alone (Ohtani et al. 2009). Nevertheless, carbamylcholine induces a smaller extent of insulin secretion than oxotremorine M, suggesting a negative type of interaction between nicotinic and muscarinic cholinergic receptors (Ohtani et al. 2009). Together, these observations suggest the presence of a functional nicotinic cholinergic system in isolated rodent and human pancreatic islets, as well as in available endocrine β cell lines (Table 2). In contrast to muscarinic cholinergic signaling, nicotinic cholinergic signaling in islets seems rather to dampen insulin secretion through presently unknown mechanisms. Nevertheless, several studies have successfully investigated the therapeutic perspectives proposed by nicotinic cholinergic pathways in the pathological context of diabetes.

Type 1 Diabetes

Type 1 diabetes (T1D) is a juvenile disease due to immune destruction of the insulin-producing pancreatic β cells (Noorchashm et al. 1997). Experimentally, rodent models

of the disease range from animals with spontaneously developing autoimmune diabetes (NOD mice, BB rats) to chemical ablation of the pancreatic beta cells (with streptozotocin or alloxan) (King 2012).

In vitro, stimulation of the muscarinic receptor by carbachol protects islets from the apoptotic/necrotic action of cytokines characteristic of T1D (Laychock et al. 2006). Interestingly, nicotinic cholinergic signaling could also present protective effects. In fact, nicotine administration reduces hyperglycemia and preserves pancreatic insulin content, reducing the incidence of T1D in both streptozotocin-treated and NOD mice (Mabley et al. 2002). Mechanistically, the elevated levels of pro-inflammatory cytokines (IL-12, IL-1, TNF-α, and interferon γ) are downregulated in pancreas of both diabetic models by nicotine administration (Mabley et al. 2002). In contrast, nicotine increases the pancreatic levels of anti-inflammatory cytokines (IL-4 and IL-10), suggesting that nicotinic cholinergic signaling reduces the incidence of T1D in rodent models by shifting the profile of pancreatic cytokine expression from helper T cells type1 to type2 (Mabley et al. 2002).

Type 2 Diabetes

Type 2 diabetes (T2D also known as noninsulin-dependent diabetes or adult-onset diabetes) is primarily due to increased peripheral insulin resistance which challenges the capacity of the β cells to produce a compensative amount of insulin. The pathology is generally linked to increased fat mass and animal models mimicking the disease involve for example genetic mutation in leptin gene (ob/ob mice), in leptin receptor gene (db/db mice or Zucker fatty rats) or diet-induced obesity (DIO) (King 2012).

Clinically, a genetic study involving multiple SNP analysis reveals significant associations between variants in the α5/α3/β4 nAChR gene cluster with both insulin resistance and T2D (Yang et al. 2012). In control rats, nicotine administration reduces insulinemia and globally improves insulin sensitivity (Xu et al. 2012). In Zucker fatty rats chronically exposed to nicotine, both basal and post-glucose tolerance test glycaemia are reduced (Liu et al. 2001). In this model, nicotine administration reduces pancreatic islet size (without change in α/β cell mass proportion) (Liu et al. 2001). Further investigations reveal that chronic nicotine treatment in Zucker fatty rats does not impact body weight and food intake, but improves insulin sensitivity in link with a liver-specific attenuation of glycogenogenesis and gluconeogenesis (Liu et al. 2003). In db/db and in DIO mice, nicotine administration improves glucose homeostasis and insulin sensitivity also independently of any change in body weight (Wang et al. 2011), but in connection with an α7 nAChR role on glucose metabolism. α7 nAChR$^{-/-}$ mice are gluco-intolerant and resistant to insulin without change in body weight or insulin secretion (Wang et al. 2011). Likewise, nicotine-induced insulin-sensitizing action is abrogated in α7 nAChR$^{-/-}$ mice (Xu et al. 2012). α7 nAChR deficiency seems to elevate adipose tissue infiltration by classically activated macrophages and leads to an inflammatory-prone status which induces insulin resistance. In contrast, pharmacological administration of the α7 nAChR agonist TC-7020 to db/db obese mice reduces their elevated glucose levels and lowers their elevated plasma levels of triglycerides and TNF-α (Marrero et al. 2010). These benefits are abolished by both the α7-selective antagonist methyllycaconitine and a Janus kinase 2 inhibitor, confirming the involvement of α7 nAChRs and the downstream JAK2/STAT3 signaling pathway (Marrero et al. 2010). Chronic treatment with the selective α7 nAChR agonist PNU-282987 significantly enhances insulin sensitivity in normal mice as well as in insulin-resistant AMP-activated kinase-α2$^{-/-}$ mice, also in link with enhanced phosphorylation of STAT3 (Xu et al. 2012).

Together, these preclinical observations in animals suggest that peripheral nicotinic cholinergic signaling could represent a potential therapeutic target for the different forms of diabetes (Table 1).

Early Deleterious Programming Action

In contrast to the insulin-sensitizing and anti-inflammatory action of nicotinic cholinergic signaling previously discussed, fetal nicotinic oversignaling seems to present a deleterious action in programming altered glucose homeostasis later in life. Recent data suggest that insulin resistance and T2D could be "programmed" during intrauterine life by diverse insults to the growing fetus (Berends and Ozanne 2012), including exposure to endocrine disruptors (Alonso-Magdalena et al. 2011). In this context, developing fetuses can be widely exposed to tobacco and nicotine (Althabe et al. 2008; Martin et al. 2005; Nabet et al. 2005) and epidemiological studies have demonstrated an increased prevalence of diabetes in children born to smoking women (Montgomery and Ekbom 2002). This clinical observation is corroborated by several animal studies investigating the impact of early life exposure to nicotine on endocrine pancreas development and later control of glucose homeostasis. α2–α4, α6, α7 and β2–β4 nAChR subunits can be detected early in the developing rat pancreas (Bruin et al. 2008b), suggesting a primary deleterious effect of prenatal nicotine exposure on the development of this organ. Rat offspring exposed to nicotine during fetal and neonatal life present increased β cell apoptosis at birth (Holloway et al. 2005) and reduced β cell mass in adulthood, indicating a permanent β cell loss

(Bruin et al. 2007). Islet size, number and transcriptional activity are reduced on postnatal day 7 due to prenatal nicotine exposure in rats (Somm et al. 2008). Underlying molecular mechanisms involved in nicotine-induced β cell apoptosis during development include (1) the death receptor pathway [with elevated Fas and soluble FasL levels (Bruin et al. 2008a)], (2) the mitochondrial pathway [with increases in the ratio of Bcl2/Bax, Bax translocation to the mitochondria and cytochrome *c* release to the cytosol (Bruin et al. 2008a)], (3) oxidative stress [with increased pancreatic glutathione peroxidase and manganese superoxide dismutase protein expression consecutive to induction of reactive oxygen species production (Bruin et al. 2008b)]. These early morphological and molecular alterations lead to later defect in control of glucose homeostasis. Animal models exposed early to nicotine show glucose intolerance (Holloway et al. 2005; Somm et al. 2008) associated with insulin resistance (Somm et al. 2008). Impairment in glucose homeostasis caused by perinatal nicotine exposure also seems to be transgenerational (Holloway et al. 2007), suggesting nicotine-induced epigenetic modifications persisting throughout generations.

Conclusion

nAChRs represent a large and complex family of ligand-gated ion channels that are widely expressed in the synapse of the central and peripheral nervous system and the neuromuscular junction. More recently, new functions in intracellular signaling and detection in the peripheral non-neuronal cell have renewed the interest for this class of receptors in various fields of investigation.

In the present review, we focus our attention on the role of nAChRs in adipose tissues and pancreatic islet biology, as well as on the potential therapeutic perspectives for nicotinic cholinergic signaling through these nAChRs in metabolic diseases such as obesity and diabetes. In fact, various nAChR subunits are expressed in pancreatic islet cells, adipocytes and, also importantly, in immune cells interacting with them. Independently of its well-known central anorexigenic action, experimental exposure to nicotine or other nAChR agonists activates lipolytic activity in WAT and thermogenic activity in BAT through both nervous and non-nervous mechanisms. Moreover, moderate doses of nicotine seem to be effective in reducing the inflammation process linked to obesity. These actions allow dampening metabolic defects in various rodent models of genetic and nutritional obesity. Anti-inflammatory and insulin-sensitizing properties of the nicotinic cholinergic signaling pathway also show therapeutic benefit for the treatment of T1D and T2D in preclinical studies. Metabolic phenotyping of mice deficient in some nAChR subunits (in particular, α7 nAChR) confirms this rationale considering nicotinic cholinergic signaling as a treatment for metabolic syndrome. Keeping in view that nicotine stimulates non-specifically all types of nAChRs, leading to toxic effects at high doses, and that the α7 nAChR seems to be the subtype most involved in inflammation and insulin sensitivity improvement, development and testing of new specific α7 nAChR agonists represent a rather promising new pharmacotherapeutic approach.

In contrast to potential therapeutic use in metabolic diseases, an overstimulation of this signaling pathway during the early stage of development (typically through nicotine exposure during fetal life) presents deleterious consequences in the ontogeny and functionality of adipose tissue and the endocrine pancreas which persist throughout life.

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