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The endocrine effects of nicotine and cigarette smoke

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Abstract

With a current prevalence of approximately 20%, smoking continues to impact negatively upon health. Tobacco or nicotine use influences the endocrine system, with important clinical implications. In this review we critically evaluate the literature concerning the impact of nicotine as well as tobacco use on several parameters of the endocrine system and on glucose and lipid homeostasis. Emphasis is on the effect of smoking on diabetes mellitus and obesity and the consequences of smoking cessation on these disorders. Understanding the effects of nicotine and cigarettes on the endocrine system and how these changes contribute to the pathogenesis of various endocrine diseases will allow for targeted therapies and more effective approaches for smoking cessation.

Keywords

nicotine; cigarettes; pituitary; hormones; hypogonadism; addiction

Epidemiology of nicotine use

Cigarette smoking is a major public health issue in both the US and worldwide placing an enormous burden on the US economy. Approximately 20% (~60 million) of Americans smoke [1]. In addition, in 2008 in the US, approximately 88 million nonsmokers aged 3 years were exposed to second-hand smoke [2]. Previous declines in rates of tobacco use have stalled over the past 5 years [3]. Cigarette smoking (first- and second-hand) and exposure to nicotine are associated with premature death from chronic diseases, economic losses to society, and a substantial public health burden [4]. The Centers for Disease Control (CDC) estimate that, between the years 2000 and 2004, the average annual productivity losses attributable to smoking were approximately \$96.8 billion [4]. Tobacco use has remained a particular burden for those below the poverty line [5], thus contributing to some of the health disparities in the US.

Even though notable progress has been made in raising awareness of cigarettes in relation to cardiovascular and lung diseases, much less is known about the endocrine effects of nicotine and smoking. The goal of this article is therefore to review the effects of nicotine (Box 1) and cigarette smoking on the endocrine system, by critically evaluating studies in both humans and animal models, and to address areas in need of further research. Gaining a better understanding of the effects of nicotine on the endocrine system and its subsequent impact upon the pathogenesis of various endocrine diseases will allow targeted therapies and

provide useful information for the development of more effective approaches for smoking cessation.

Box 1

Pharmacology and Physiology of Nicotine

Nicotine sources and pharmacokinetics

Nicotine is a naturally occurring alkaloid found in the tobacco plant, *Nicotiana tabacum* [100]. In humans, when nicotine is inhaled, it rapidly enters the blood stream, crosses the blood–brain barrier and reaches the central nervous system (CNS) where it acts as a stimulant [100,101]. Nicotine is metabolized in the liver by the cytochrome P450 enzymes CYP2A6 and CYP2B6 to form a variety of metabolites, 70 to 80% of which are converted to cotinine that is then excreted in the urine [102].

Tobacco and cigarette smoke also contain other compounds such as tar, arsenic, 1,3-butadiene and carbon monoxide [103]. In addition, several nitrosamines, aldehydes, and small organics are found in cigarette smoke which may contribute to the cancer risk associated with smoking [103]. The effect of these components on the endocrine system is not known.

Pharmacodynamics

In the brain, nicotine acts by binding to and activating the nicotinic acetylcholine receptors (nAChRs), members of a superfamily of transmembrane ligand-gated ion-channel proteins [104], found in both the CNS, peripheral nervous system (PNS) as well as in some peripheral tissues [105]. Some of the addictive properties of nicotine are attributable to its ability to increase synaptic neurotransmission in the CNS, particularly of dopamine, from the mesolimbic dopaminergic neurons; the neurotransmitter dopamine is involved in the rewarding and reinforcing effects of nicotine and plays a key role in the addictive properties of tobacco [106]. The effects of nicotine on the PNS include skeletal muscle contraction due to activation of nAChRs at the neuromuscular junction and neurotransmission along the autonomic ganglia, which leads to activation of postganglionic adrenergic and cholinergic fibers. Activation of nAChRs in the adrenal medulla leads to increased catecholamine levels with corresponding cardiovascular and metabolic responses.

The predominant effects of nicotine in humans include increased release of catecholamines into the bloodstream that increase pulse rate and blood pressure, the release of plasma free fatty acids, and the mobilization of blood glucose [107]. Decreases in skin temperatures, arousal and relaxation are also noted following nicotine administration [107]. At the cellular level, the effects of nicotine include increased synthesis and release of neurotransmitters and hormones, induction of oxidative stress, activation of transcription factors and the catecholamine-synthesizing enzyme tyrosine hydroxylase, as well as prevention of apoptosis [107]. Serving as the fundamental mediator of neurotransmission in the CNS and PNS, the activation of nAChRs has important physiological consequences for multiple organs, including the endocrine system.

The effects of smoking and nicotine on pituitary/ end-organ endocrine systems (Figure 1 and Table 1)

Brief overview of the endocrine system

The endocrine system is a group of glands that maintain body homeostasis via the secretion of different hormones. Many of these hormones are regulated via various regulatory axes including the hypothalamic–pituitary–adrenal axis (HPA), the hypothalamic–pituitary–gonadal axis (HPG), and the hypothalamic–pituitary–thyroid axis (HPT).

The HPA axis is activated with the release of corticotropin-releasing hormone (CRH) from the hypothalamus, typically in response to psychological or physical stress. CRH then stimulates the anterior pituitary to produce adrenocorticotropic hormone (ACTH), which activates the production of cortisol by the adrenal gland. Cortisol mediates the physiological effects of this axis which include effects on the cardiovascular system, control of metabolic homeostasis, effect on connective tissue, modulation of the immune system, and effects on behavior and cognition. The HPG axis is activated by gonadotropin-releasing hormone (GnRH), which is released from the hypothalamus and then stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. FSH and LH stimulate the testes and ovaries to release sex hormones, estradiol in females and testosterone in males. The HPT axis is activated by thyrotropin-releasing hormone (TRH) that is secreted from the hypothalamus which then stimulates the release of thyroid-stimulating hormone (TSH) from the anterior pituitary. TSH induces the production and release of triiodothyronine (T3) and thyroxine (T4) from the thyroid gland.

Two additional anterior pituitary hormones are prolactin (PRL), which is regulated by dopamine, and growth hormone (GH), which is in part is regulated by growth hormone releasing hormone (GHRH) secreted from the hypothalamus. PRL regulates lactation. GH has many physiological functions including stimulating growth, cell regeneration and promoting gluconeogenesis. Vasopressin and oxytocin (OT) are hormones released from the posterior pituitary gland.

Cigarettes and prolactin

PRL secretion from the anterior pituitary is primarily inhibited by dopamine. Acute cigarette smoke significantly increased PRL secretion and the increase in PRL levels correlated with increased plasma nicotine levels [6]. When subjects smoked nicotine-free cigarettes, PRL levels were unchanged [6]. Significant increases in PRL levels in response to opioid blockade have also been observed [7]. However, the response is significantly diminished in smokers, relative to nonsmokers [7]. Because dopamine inhibits PRL secretion, opioids increase dopamine secretion that results in an inhibition of PRL secretion. Therefore, these data suggest that smokers may have blunted opioid-mediated dopamine release or dysregulated interactions between dopamine and PRL [7]. Considering the importance of dopamine levels in nicotine addiction, dysregulation of dopamine-release may play a role in the mechanism of addiction associated with nicotine. In light of the stimulatory effects of nicotine on dopamine levels one would expect a decrease in PRL secretion, given the inverse relation between dopamine and PRL. Decreased PRL levels are observed in long-term, but not acute smoking, possibly due to desensitization of the nAChRs [8].

Cigarettes and the HPT axis

The HPT axis maintains thyroid hormone production and disruption of this axis can result in either hypothyroidism or hyperthyroidism. Serum TSH levels are lower, whereas T3 and T4 levels are higher, in smokers versus non-smokers [9] and in both active smokers and passive smokers [10,11]. This suggests that there is a stimulatory effect of cigarette smoke exposure

on thyroid hormone release, with resultant suppression of TSH. This may have important clinical relevance when making the already difficult evaluation and management of smokers with subclinical hyperthyroidism. Multiple studies have shown that there is a lower prevalence of thyroid auto-antibodies in smokers compared with nonsmokers [11,12] and smokers have lower rates of hypothyroidism [13]. However, these studies only offer evidence of an association between smoking and lower rates of hypothyroidism, and do not provide confirmation on causality or potential mechanisms behind the association between smoking and decreased rates of hypothyroidism. One recent study showed that discontinuation of smoking might increase the risk of developing thyroid peroxidase (TPO) antibodies [14]. In patients with Graves' disease, smoking clearly worsens thyroid-associated ophthalmopathy (TAO) [15]. The pathogenesis of TAO involves inflammation, excess production of glycosaminoglycans, and adipogenesis resulting in an increase in the volume of both the orbital fatty connective tissues and the extraocular muscle bodies [16]. Interestingly, in an *in vitro* model, cigarette smoke extract increased both glycosaminoglycan production and adipogenesis, presenting a possible mechanism by which cigarette smoke worsens TAO [16].

Nicotine and cigarettes and the HPA axis

Studies conducted in rats illustrate that nicotine and smoking stimulate the HPA axis and proceed via a central mechanism to stimulate CRH and/or arginine-vasopressin (AVP) which then leads to the release of ACTH from the anterior pituitary [17]. Smoking acutely activates the HPA axis resulting in increased cortisol levels [6,18], and nicotine is the principal component of tobacco responsible for the stimulation of the HPA axis [19]. Some of the effects of smoking on the HPA axis are given in Box 2.

Box 2

Smoking and the HPA axis

- In nicotine-dependent male smokers, smoking cigarettes containing higher but not lower nicotine content leads to increased peak nicotine levels followed by an increase of HPA axis hormones (ACTH and cortisol), suggesting a dose-dependent effect of nicotine or a threshold response to nicotine in activating the HPA axis [108].
- Nicotine levels increase significantly after smoking each of three high-nicotine cigarettes at 1 h intervals, attributable to the cumulative effect of the three consecutive cigarettes smoked [108]. The cumulative increase in nicotine levels seen after second and third smoked cigarettes is not accompanied by progressive increases in peak positive subjective effects ratings, or peak heart rate, ACTH, cortisol, or DHEA levels, suggesting tolerance to the effects of nicotine despite increased nicotine levels [108].
- In over 150 adolescents followed from 6 months to 5 years, higher basal cortisol levels (measured using nocturnal free urinary cortisol and salivary cortisol levels) correlated with an increased risk of smoking initiation and smoking persistence [109]. In addition, exposure to stressful life-events had an additive effect on smoking [109].
- In a recent study of 106 healthy smokers, a significant increase in cortisol concentrations was found following exposure to the stressor in daily smokers, occasional smokers, and nonsmokers, and the magnitude of the cortisol increase in the daily smoker group was lower than in the occasional smokers and nonsmoker groups [110].

- A positive correlation has been identified between stress-induced changes in salivary cortisol concentrations and increased cigarette-craving, but not with the quantity of cigarettes smoked [111].

The role of stress in affecting the HPA axis and how this pertains to smoking habits is important. Smokers cite stress-relief as one of the major reasons for smoking [20]. Grunberg and Shafer postulated the mechanisms on why stress is associated with increased smoking as follows: (a) smoking decreases stress levels because nicotine or some other chemical in tobacco relieves some aspects of stress; (b) stress decreases the action of nicotine, thereby resulting in increased nicotine self-administration to reach the levels of activity that occur in non-stressful circumstances; (c) stress decreases the availability of nicotine, precipitating withdrawal and resulting in subsequent increased tobacco use; (d) tobacco smoking (and nicotine) enhance cognitive functions which overcome the deleterious effects of stress on cognition [21]. Stress is one of the leading causes of smoking relapse [22,23]. Stress also potentiates the rewarding and reinforcing actions of smoking [22,24]. Alternatively, nicotine deprivation between cigarettes involves withdrawal symptoms including irritability, frustration, poor concentration, insomnia, and restlessness, all of which may exacerbate stress [25] and lead to craving for continued nicotine use. Use of nicotine lozenges reduces affective withdrawal symptoms in dependent smokers who recently quit [26]. Interestingly, in dependent smokers who report that smoking helps cope with stress, smoking cessation is associated with lowering of stress [27]. Despite the acute effects smoking may have on perceived stress, overall it appears that smoking may worsen negative emotional states [27]. It is likely that this overall state of elevated stress in smokers, as measured by elevated resting cortisol, is a reflection of a dysregulated HPA axis.

Cigarette use and the reproductive axis

Cigarette smoking is associated with decreased fertility in both males and females [28,29]. Cigarette smoking also has a significant negative effect on the clinical outcome of assisted reproduction treatment (ART) [30].

The data on the effects of cigarette smoking on testosterone levels in men are conflicting. A cross-sectional study including a total of 255 men failed to show any significant association between cigarette smoking and several markers of male reproductive hormones, including total, free and bioavailable testosterone, sex-hormone-binding globulin (SHBG), LH and FSH [31]. By contrast, in a cross-sectional population-based study of 3427 men, Svartberg and Jorde found that men who smoked had significantly higher levels of total and free testosterone, compared with men who never smoked, and that testosterone levels were correlated with the number of cigarettes smoked daily [32]. Furthermore, Wu and colleagues found that the total but not free testosterone, SHBG, and LH were also significantly higher in current smokers compared with nonsmokers [33]. The conflicting data on the effects of smoking on testosterone may make the evaluation of testosterone levels in smokers difficult. It may skew the clinical evaluation of hypogonadism in men, and make the diagnosis and management of hypogonadism in older men more difficult. Cigarette smoking is also associated with erectile dysfunction and it was estimated that 23% of cases of erectile dysfunction can be attributed to smoking [34].

A cross-sectional study conducted in postmenopausal women revealed that testosterone levels were higher in current smokers, compared with nonsmokers, and testosterone, estradiol and SHBG levels increased as the extent of cigarette exposure increased [35]. After women stopped smoking for one year, levels of estradiol and total and free testosterone returned to those of nonsmokers [35]. Because high testosterone is part of the polycystic ovarian syndrome (PCOS) that is associated with infertility, lack of ovulation, menstrual

irregularities and insulin resistance, the resolution of hormonal changes following smoking cessation suggests that smoking cessation could help ameliorate some of the PCOS-related complications.

Cord-blood levels of LH and FSH in maternal smokers were not significantly different between smokers and non-smokers [36]. However, placental estriol, human placental lactogen (HPL) and β -human chorionic gonadotropin (β -HCG) negatively correlated with the number of cigarettes smoked per day [36]. These changes may be significant because these placental hormones may affect fetal brain development.

Cigarettes and the GH/insulin-like growth factor (IGF-1) axis—Cigarette use in pregnancy is associated with intrauterine growth restriction (IUGR) [37]. Cord plasma concentrations of IGF-I and IGF binding protein-3 were lower in the babies of mothers who had smoked, and this may contribute to fetal IUGR [38]. This suggests that smoking might have some attenuating effects on growth in babies as a result of lower IGF-1. IGF-1 was decreased in female but not male fetuses of asthmatic mothers who smoked cigarettes [39]. A lower birth-weight of female but not male neonates of mothers with asthma who smoked during pregnancy correlated with lower IGF-1 levels [39]. Unfortunately few data are available regarding the effects of smoking on IGF-1 levels in men or women, although older data show that smoking acutely raises GH levels [8]. Based on the available literature on how smoking affects IGF-1 and GH *in utero* we conclude that smoking cessation during pregnancy is a prudent measure and beneficial to the health and growth of the fetus.

Cigarettes, nicotine, AVP and OT—Tobacco smoke and nicotine interact with the hormones AVP and OT secreted from the posterior pituitary (neurohypophysis). Direct application of nicotine to rodent hypothalamic tissue was shown to increase AVP levels [40]. In humans, cigarette smoking increased plasma AVP [8] and OT [41] levels. Most interestingly, the responses of AVP and cortisol to smoking are highly correlated, suggesting that the cortisol response to smoking may be attributable to the AVP increase [42]. Significantly higher levels of OT receptor mRNA were found in preterm myometrial strips in human and rats receiving cigarette-smoke extract compared to control groups that did not receive the extract [43]. These results, in both rats and humans, suggest that smoking may be related to increased contractile sensitivity of preterm myometrium in response to OT, which leads to increased risk of preterm delivery in women who smoke during pregnancy [43].

Cigarette smoking and osteoporosis

The association between smoking and osteoporosis is well established [44] with increased hip fractures seen in smokers [45]. Calcium absorption and vitamin D levels are lower in smokers [46], with variable reports on PTH levels [47,48]. In addition, cigarette smoking may reduce the efficacy of estradiol therapy in increasing bone mass [49]. The literature in humans clearly shows a relation between smoking and osteoporosis, and smoking cessation efforts should help decrease the rate of osteoporosis in smokers.

Metabolic homeostasis and cigarettes/nicotine

Obesity

It has long been recognized that smokers generally have reduced body-weight compared to nonsmokers [50], that smoking cessation leads to weight gain [50], and that weight loss recurs when cigarette smoking is resumed [51]. Studies have reported a U-shaped relation between body mass index (BMI) and number of cigarettes smoked [52], with weight gain in the heavy smokers that correlates positively with number of cigarettes smoked [53], possibly influenced by poorer lifestyle habits among heavy smokers [54].

The mechanisms that underlie this weight phenomenon are complex and involve multiple neurochemical pathways that govern hunger and satiety. Recent studies in rodents have shown that nicotine suppresses appetite ultimately via the activation of melanocortin-4 receptors (MC4R) expressed on hypothalamic pro-opiomelanocortin (POMC) neurons [55,56] that signals satiety. However, animal studies found that hypothalamic neuropeptide Y (NPY), a potent orexigenic neuropeptide that increases food intake, may be enhanced (either acutely [56] or after 7 weeks of nicotine exposure [57]) or, conversely, suppressed after 12 weeks of exposure [58]. Orexins, a family of hypothalamic hormones which also enhance feeding, were found to increase following nicotine exposure, in rodents [56]. Data with regards to the gut peptide ghrelin that induces satiety are unclear, and it has been reported that ghrelin may [59] or may not [60] be affected acutely by cigarette exposure in habituated smokers. However, it may fall with smoking cessation [61], and it may also be acutely reduced by cigarette exposure of nonsmokers [60]. The levels of the fat-derived hormone, leptin, and its hypothalamic receptor OBRb [62] may be reduced with nicotine exposure [62] and increased with cessation in humans [61], and this might be related to the changes observed in weight following nicotine exposure. Nicotine exposure also increases energy expenditure [50], which is reversible with nicotine withdrawal [63].

Prenatal smoking exposure studies have found an association with subsequent childhood obesity [64,65] and have also suggested additional ‘imprinting’ mechanisms [66] that contribute to obesity in the child, occurring dose-dependently and even in association with paternal smoking (i.e. passive exposure) [67]. Animal models have shown that nicotine-exposed neonates which have experienced growth retardation *in utero* display ‘catch-up’ growth and an expansion of adipose stores when provided with calorie excess, and this contributes to insulin resistance and glucose intolerance later in life [68]. An observed association between maternal smoking and short stature in the child [67] might be consistent with this theory, but the role of low birth-weight in the pathogenesis of this phenomenon has been questioned [66].

In practice, fear of weight gain may attenuate the adherence of patients to smoking cessation programs, particularly among female smokers [69]. Greater abstinence may be achieved with smoking cessation programs that are combined with a variety of weight loss interventions, at least in the short-term [70,71]; long-term efficacy is less certain [70,71], and adjunctive pharmacotherapies for smoking cessation that also attenuate weight gain appear to be more effective than behavioral interventions alone [71]. Another related, troubling phenomenon in clinical practice is the use of cigarette smoking as an intentional means to lose weight [72].

Cigarette smoking/nicotine and insulin resistance and diabetes mellitus

Despite weight loss, cigarette exposure worsens insulin resistance [73], even with passive exposure, in a dose-dependent manner [74], predisposing to the metabolic syndrome as a consequence [73]; alternatively, smoking cessation may also lead to changes that favor the development of insulin resistance, depending on the resulting variations in body weight [75]. Smoking is also associated with worsening visceral adiposity independently of changes in BMI [76], which helps explain the paradox of increased metabolic risk associated with visceral adiposity, despite overall weight loss. However, the incidence of metabolic syndrome may not be increased if weight loss is associated with a net loss of central adiposity [77]. Other potential mechanisms of nicotine-induced insulin resistance, born out of cell culture, rodent and human studies, are listed in Box 3.

Box 3**Potential mechanisms of nicotine-induced insulin resistance**

- Increased expression of tumor necrosis factor- α leading to increased reactive oxygen species and impairment of Akt phosphorylation and GLUT4 translocation (seen in myocytes when in the presence of palmitate [112]).
- Increased saturation of intramyocellular triglyceride and diacylglycerol associated with increased serine-phosphorylation of the insulin-receptor substrate-1 (IRS-1) [113].
- Adiponectin levels that fall with smoking [114] and rise with smoking cessation [115], but may also fall with smoking cessation in the presence of post-cessation weight gain [75].
- Maternal cigarette exposure during pregnancy and breastfeeding, 'imprinting' on the child, leading to insulin resistance later in childhood [66,74].
- Nicotine activates an innate, anti-inflammatory pathway via the macrophage $\alpha 7$ -nicotinic acetylcholine receptor, and interruption of this pathway exacerbates nicotine-associated inflammation and insulin resistance in mice [116], which would be consistent with a co-existing anti-inflammatory effect of nicotine on obesity-related inflammation [117].

Studies have found that nicotine can dose-dependently reduce body-weight gain in mice that consume either a high-fat diet (HFD) or a normal chow diet, but this effect is significantly greater in mice in the HFD group. Computed tomography analysis for fat distribution demonstrated that nicotine effectively reduced abdominal fat in mice that consumed the HFD, resulting in lower visceral fat [78]. The effect of nicotine on weight loss in mice on a HFD was completely blocked by mecamylamine, a nonselective nAChR antagonist, but was only partially blocked by the $\alpha 4\beta 2$ nAChR partial agonist/antagonist, varenicline, a drug known as Chantix that is currently used in the clinic for smoking cessation [78].

Consistent with the adverse effects of nicotine on insulin sensitivity, there is a clear, dose-dependent relation between diabetes or glucose intolerance and both active and passive cigarette exposure [79]. However, in keeping with the paradox of smoking-associated weight loss and greater insulin-resistance, some studies found that the amount of smoking interacts with BMI to produce either adverse or favorable effects on diabetes [80]. The incidence of diabetes may be lower with smoking if the weight loss leads to a net improvement in central adiposity [77]. With smoking cessation, the risk of diabetes decreases over time [81], but it may also paradoxically increase in association with the weight gain that occurs during the first 3–5 years following smoking cessation [82].

Development of glucose intolerance requires impairment of β cell function. Recent animal studies have shown that prenatal nicotine exposure, which is toxic to β cell mitochondria and leads to apoptosis, impairs pancreatic islet development [66,68], thus limiting β cell reserve; however, in one rat study, if nicotine exposure was not continued through both gestation and lactation, β cell recovery was still possible [83]. Maternal smoking during pregnancy has also been implicated in diabetes secondary to nonselective damage to the pancreas [84], and in association with β cell auto-antibodies, in young children [85].

In patients with established diabetes, nicotine exposure may paradoxically increase the incidence of severe hypoglycemia in insulin-treated patients [86], possibly via reduced clearance of subcutaneous insulin and enhancement of insulin action [87]. In addition, the

kinetics of pulmonary absorption of inhaled insulin increase substantially in the smoking versus the nonsmoking state [88]. In diabetes care, smoking cessation is crucial to facilitating glycemic control and limiting the development of complications [23].

Smoking and fatty liver

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steato-hepatitis (NASH) have emerged as important complications of insulin resistance. In humans, cigarette exposure is independently associated with ultrasound-defined NAFLD [89] as well as with advanced hepatic fibrosis [90], and fatty liver synergizes with smoking in its association with metabolic derangements [91]. In obese rats, the severity of NAFLD is worsened with long-term cigarette exposure, in association with increased oxidative stress and apoptosis [92]. In a mouse model of diet-induced obesity, increased abdominal lipolysis coupled with exacerbation of hepatic steatosis [93] and increased skeletal muscle [94] fat accumulation was observed following nicotine treatment. This is of potentially serious clinical relevance because the clinical consequences of further progression of NASH and NAFLD to hepatic cirrhosis can be life-threatening.

Smoking and dyslipidemia

The dyslipidemia observed with cigarette smoking mirrors the classic dyslipidemia of insulin-resistance that is characterized by elevated triglycerides (TG) and reduced high-density lipoprotein cholesterol (HDL-C) [95], with lesser effects on total and low-density lipoprotein cholesterol (LDL-C). Enzymes that modulate this dyslipidemic profile, such as hepatic lipase and cholesterol ester transfer protein, are involved in mediating these effects [95]. Favorable changes are seen with smoking cessation, particularly increased HDL-C [96]. These effects are closely associated with changes in insulin resistance, and probably contribute to the overall cardiovascular risks of smoking.

Concluding remarks

We have examined how nicotine exposure from smoking affects hormonal levels and metabolic homeostasis, using information from both humans and animal studies. The effect of smoking in thyroid disease, osteoporosis, and lipid levels has also been discussed. With the high prevalence of smoking throughout the world and the growing burden of diabetes, smoking cessation of patients should be actively pursued as part of prevention and management of diabetes regimens. However, the challenge of weight gain following smoking cessation remains, and this current review points out the impact of underlying hormonal changes, as well as the psychological factors that are associated with this weight gain. Furthermore, as smoking by pregnant women continues, hormonal changes in response to nicotine exposure might gravely impact upon fetal health, and thus smoking cessation is highly recommended.

Additional research is needed to tease out the differences between the effects of nicotine and cigarettes on the endocrine system and to decipher the physiological and clinical relevance of these hormonal changes; this information is lacking in the current literature. In addition, the effects of second-hand smoke and of other forms of nicotine (nicotine replacement therapies such as gums and patches, as well as chewless tobacco, Hookah, and electronic cigarettes) on the endocrine and metabolic systems also need to be explored. Future studies should focus on providing useful information on the mechanisms of smoking-associated endocrine and metabolic diseases and give additional credence to smoking cessation.

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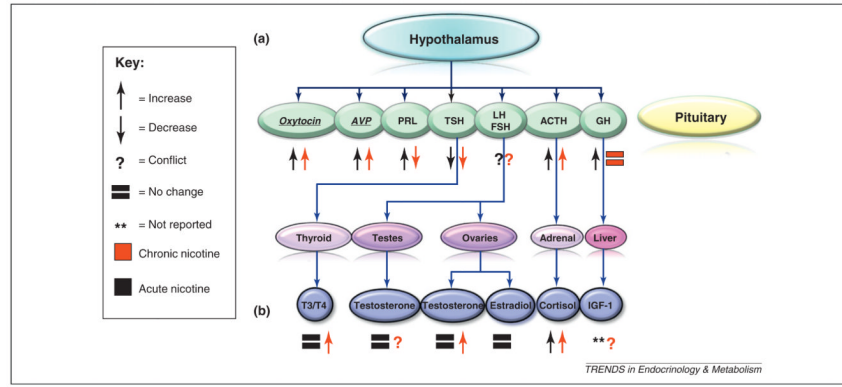


Figure 1. Effects of nicotine on hypothalamic–pituitary–end organ axes. Schematic demonstrating the effects of acute and chronic nicotine /cigarette use on hypothalamic–pituitary–end organ axes. (a) Nicotine mediates its effects on the hormonal levels of cortisol and AVP at the level of the hypothalamus or in other brain regions. (b) Nicotine mediates its effects on hormonal levels T3/T4 via direct activation of its end-organ target, the thyroid. Most acute information is from nicotine administration studies whereas chronic information is predominantly from studies on cigarette smokers. The level of regulation of other hormones is either at the pituitary or unknown. It is important to note that many of the effects of nicotine on hormones are not well-understood, and often we can only assess the end result of observed changes in circulating hormone levels. Underlined text in italics indicates hormones originating from the posterior pituitary.

Table 1

Summary of the effects of acute and chronic nicotine use on the endocrine systems of rodents and humans

Hormone	Acute	Chronic	Potential physiological outcome	Refs
Prolactin (PRL)	↑	↓	Fertility, sexual behavior, lactation	[6,7]
Thyroid hormones (T4/T3)	=	↑	Increased metabolism	[9–11]
ACTH/cortisol	↑	↑	Increased catabolism (breakdown of protein), increased ability to handle stress, altered immune response	[17,19]
Estradiol	=	↑	Endometrial build-up	[35]
Testosterone	=	↑ or ↓	In women: irregular periods and problems with ovulation. In men: increased aggression	[32,33,35]
Growth hormone (GH)/IGF-1	↑	↓	Changes in anabolism (build-up of protein) and cell proliferation, low birth-weight neonates	[8,39]
Vasopressin (AVP)	↑	=	Changes in blood pressure, serum sodium levels and cognition	[8,42]
β-Endorphin	↑	↑↓	Pain threshold, immune responses	[97–99]
POMC		↑	Suppressed appetite	[55,56]
NPY	↑	↑↓	Increased appetite	[56,57]
Orexins		↑	Increased appetite	[56]
Ghrelin	↑↓		Suppressed appetite	[59,60]
Leptin		↓	Weight gain	[62]
Insulin		↓	Increased energy expenditure, weight loss	[62]

Most acute data are from nicotine administration whereas chronic data are predominantly from studies on cigarette smokers. Note: the effects of nicotine on the endocrine system are complex and the expected physiological outcomes may or may not be manifested depending on the dose and duration of exposure, as well on changes in other known and unknown hormone systems. Symbols: ↑, stimulation; ↓, inhibition; ↑↓, conflicting; =, no change; no symbol, not reported.