Review

# The endocrine effects of nicotine and cigarette smoke

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**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.**

## 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.

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*Keywords:* nicotine; cigarettes; pituitary; hormones; hypogonadism; addiction.

## 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 thyrotopin-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

 1043-2760/$ – see front matter © 2012 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.tem.2012.03.006 Trends in Endocrinology and Metabolism, July 2012, Vol. 23, No. 7

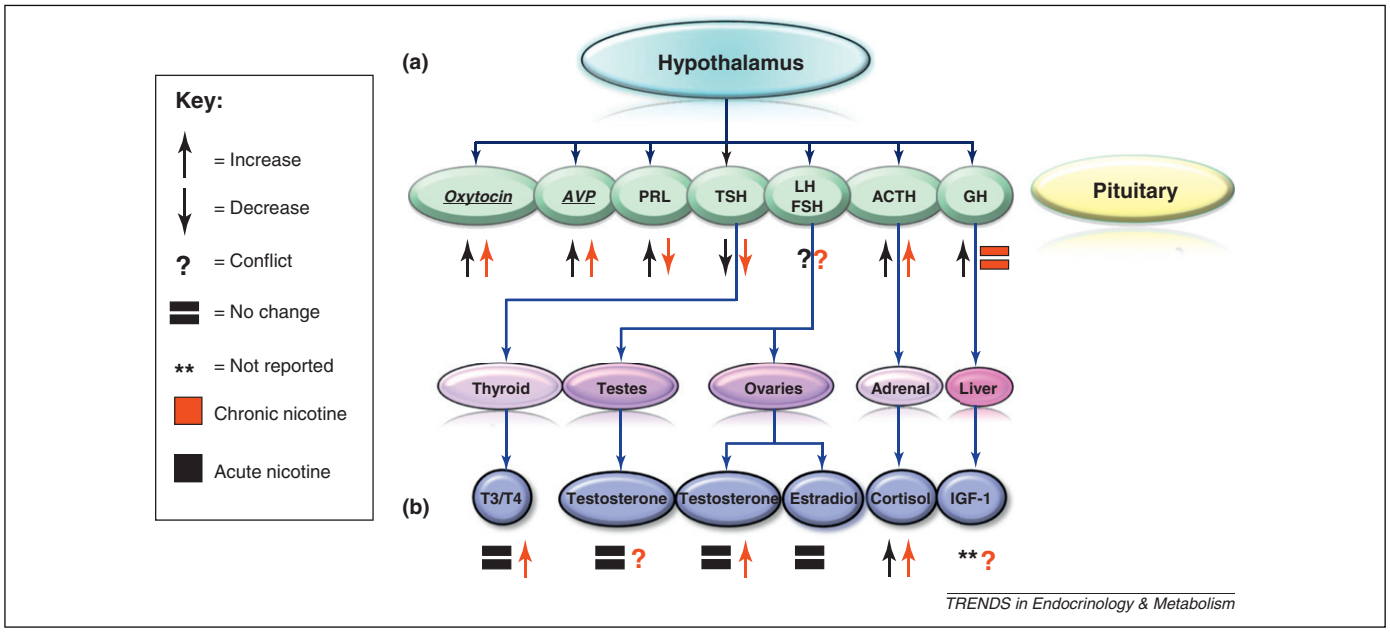


**Figure 1.** Effects of nicotine on hypothalamic–pituitary–end organ axes. Schematic demonstrating the effects of acute and chronic nicotine /cigarette use on hypothalamic–pituitary–end organ axes. (a) Nicotine mediates its effects on the hormonal levels of cortisol and AVP at the level of the hypothalamus 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.

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

**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.

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