The smoking gun: many conditions associated with tobacco exposure may be attributable to paradoxical compensatory autonomic responses to nicotine

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Summary Tobacco exposure is implicated in many illnesses such as cardiovascular disease and cancer, but the mechanisms underlying these associations are poorly understood. The mechanisms by which tobacco induces pro-sympathetic and pro-inflammatory changes also remain elusive. Some studies have attributed these changes to the direct effects of nicotine, but such findings run counter to the pro-vagal, anti-inflammatory nature of the nicotinic pathway. We hypothesize that the illnesses associated with smoking may be partly attributable to autonomic dysfunction, sympathetic bias, and T helper (Th)\textsubscript{2} inflammation induced by a paradoxical compensatory response to intermittent nicotinic exposure. The confusion of interpreting the adrenergia and inflammation associated with nicotine as a primary response instead of a secondary compensation may be explained by the unusually rapid absorption, action, and serum elimination of nicotine. Given the fast action and clearance of nicotine, even heavy smokers spend large portions of the day and the entire night in nicotine withdrawal, at which time rebound sympathetic bias may manifest as a result of desensitization of nicotinic receptors. This may help reconcile why the features observed in smokers such as tachycardia, hypertension, inflammation, insomnia, and anxiety, which are perhaps mistakenly attributed to the direct action of nicotine, are identical to those seen during acute nicotine withdrawal after smoking cessation. On the other hand, delayed responses to cessation of smoking such as weight gain and increased heart rate variability are compatible with reduced sympathovagal ratio and resensitization of nicotinic receptors. Sympathetic bias and the associated Th\textsubscript{2} inflammation underlie many systemic diseases. Tobacco-related cancers may be partly attributable to immunomodulatory properties of chronic nicotine exposure by dampening Th1
immunity and enabling tumoral evasion of immune surveillance. Other conditions associated with tobacco exposure may also operate through similar autonomic and immune dysfunctions. Therapeutic implications are discussed. © 2004 Elsevier Ltd. All rights reserved.

Hypothesis

Tobacco, smoked or chewed, is a major cause of cardiovascular disease and has been implicated in many aspects of atherosclerosis including endothelial dysfunction, inflammation, and acute thrombotic events [1,2]. Recent reviews examining the link between tobacco use and cardiovascular disease report that the toxic component of tobacco and the pathophysiologic mechanism involved in tobacco-related cardiovascular dysfunction remain largely unknown [1,3]. Oxidant gases, polycyclic aromatic hydrocarbons, and carbon monoxide are among the many putative causal agents that have been proposed but none have been validated to date [3,4]. Nicotine is generally not suspected as the culprit since parasympathetic function, which is activated in part by nicotinic acetylcholine receptors, is generally cardio-protective while sympathetic function is increasingly being implicated in cardiovascular dysfunction and inflammation [5,6]. We hypothesize that the host compensatory response to chronic, intermittent nicotinic exposure associated with tobacco may paradoxically elevate the baseline sympathovagal ratio, leading to a compendium of conditions associated with tobacco use.

Evidence

Nicotine is a component of smoked and chewed tobacco and represents a key part of tobacco dependence. When attempting to understand the biological consequences of nicotine exposure, it is also helpful to consider the tissue distribution of neuronal and non-neuronal receptors that are agonized by nicotine. Neuronal nicotinic receptors, which are associated with nerves in numerous tissues, mediate transmission of neural signals by acetylcholine. Non-neuronal nicotinic receptors, which do not participate in nerve transmission but respond to acetylcholine, are present in a variety of tissues including the thymus, the bronchi, endothelial cells, and keratinocytes [7]. The high density of nicotinic acetylcholine receptors in bronchial and endothelial surfaces has led to previous speculations about their pathogenic role in lung cancer and cardiovascular disease [7]. Nevertheless, the mechanistic link has not been found, leading many authors to dismiss nicotine as the causative agent of tobacco-related dysfunctions other than addiction [8,9]. Given that nicotine is a potent agonist of the α7 receptors associated with vagal function and antagonizes inflammation [5], it might appear unseemly that nicotine could be the culprit in tobacco-related dysfunctions, which are generally conditions linked to sympathetic over-activity such as cardiovascular disease and inflammation [1,10–12].

Viewed differently, however, we are intrigued by the possibility that the host compensatory response to chronic nicotine exposure may paradoxically induce sympathetic over-activity and thereby contribute to tobacco-related diseases. There are well-known examples where exposing biologic equilibria to intermittent short-acting challenges produces paradoxical responses in the long run by eliciting opposing compensatory mechanisms [13]. Parathyroid hormone, which induces osteoporosis when chronically released, increases bone mass if pulsed in high doses [14]. Similarly, pulsed growth-hormone releasing-hormone, which is thought to promote growth, counter-intuitively reduces the growth rate in chickens [15].

The prototypical autonomic example of this phenomenon is the reduction of sympathovagal ratio that can be achieved by periodic sympathetic surge associated with exercise [13]. The deleterious effects of smoking may operate through a similar mechanism, except in reciprocal fashion. That is, intermittent exposure to nicotine, which generally promotes vagal function [16], may induce reflex compensatory adrenergic upregulation that leads to the compendium of dysfunctions associated with smoking. The differential responses of the autonomic system to intermittent exercise during the acute phase (pro-sympathetic) and the baseline chronic phase (pro-parasympathetic) reveal the importance of chronobiologic considerations in studying the behavior of the autonomic system. Therefore, it is imperative that empirical evidence surrounding biologic effects of nicotine be segregated into four distinct categories: (1) acute exposure; (2) chronic exposure; (3) acute withdrawal; and (4) chronic withdrawal.
Acute nicotine exposure

The acute effects of nicotine on autonomic balance are complex, and the empiric evidence is confounded by a lack of standardization in reporting primary and secondary responses to nicotine exposure as well as differential effects of nicotine in different parts of the body [17]. Numerous studies have suggested that nicotine has a direct pro-sympathetic effect as evidenced by acute increases in blood pressure, heart rate, ventilation, and norepinephrine levels [3,17–25]. However, other studies have shown acute bradycardia, hypotension, and apnea [17,24,26,27]. It is possible, then, that the pro-sympathetic effects of nicotine may represent a secondary compensatory response to nicotine exposure rather than its primary direct response. Notably, the seminal study which suggested that nicotine acutely stimulates the sinoatrial node to cause tachycardia acknowledged that the first effect of nicotine exposure is a decrease in heart rate, which is more consistent with a cholinergic, anti-sympathetic effect [24]. Similarly, the hypertension associated with nicotine is preceded by an initial period of hypotension [26,28], which suggests more of a reflex hypertensive response rather than a primary response. A recent report confirmed that the hypertension associated with nicotine may be a reflex phenomenon secondary to activation of carotid and aortic chemoreceptors [17].

The difficulty in distinguishing the primary and secondary responses to nicotine may be related to its pharmacokinetic and pharmacodynamic properties: rapid absorption and action as well as rapid clearance from serum. Acute spikes of serum nicotine are observed after cigarette exposure [29], and the primary effect of nicotine is thought to last only 1 min due to rapid uptake from the blood into tissues. Nicotine has an elimination half-life of about 2 h [30], but only 1% of an intravenously injected nicotine dose is observed after 5 min due to rapid tissue uptake [17,31].

Chronic nicotine exposure

Numerous studies have shown that chronic exposure to tobacco and nicotine is associated with sympathetic over-activity, which can contribute to a wide variety of cardiovascular dysfunctions including atherogenesis, thrombogenesis, vasoconstriction, lipid abnormalities, insulin resistance, and endothelial dysfunction [3,32]. Based on our discussion in the previous section, it is possible that the sympathetic bias is a compensatory reflex phenomenon reflecting a series of “mini-withdrawal” states between exposures to nicotine. While trough nicotine levels can be raised with repetitive exposures [33], it is plausible given its rapid serum clearance that smokers may experience a relative “mini-withdrawal” during large portions of the day and the entirety of the night [12], at which times rebound sympathetic bias may manifest [34]. Indeed, insomnia, which is a marker for nighttime sympathetic over-activity, is common among smokers and occurs in a dose dependent fashion [35].

When interpreting studies reporting physiologic measurements among smokers, one must keep in mind the likelihood that most of these empiric studies are reporting measurements during “mini-withdrawal” states between tobacco exposures. Thus, reports that heart rate is elevated and heart rate variability (HRV) is reduced among chronic smokers [36] and users of smokeless tobacco [37] support the assertion that the sympathovagal ratio may elevate as a compensatory response. Perhaps tellingly, there is an anecdotal tendency among smokers to seek tobacco during stress, after meals, and after coitus, which are behaviors suggestive of a vagal craving that may be satisfied acutely by smoking.

The autonomic dysfunction related to chronic nicotine exposure may operate through the biologic remodeling of nicotinic acetylcholine receptors. Over-exposure of these receptors to stimulation has been shown to result in their down-regulation and desensitization as adaptive responses [38,39]. The concentration of nicotine absorption [40] is felt to be sufficient to induce a receptor desensitization response [7]. Local dysfunctions can in turn enhance global efferent adrenergic output through pathways including adrenal modulation such that systemic autonomic dysfunctions may arise at sites remote from original nicotine exposure. Other reports have suggested that chronic nicotine exposure may induce systemic autonomic dysfunctions by precipitating baroreceptor and chemoreceptor dysfunctions [41,42].

Smoking is associated with an immune shift to T helper (Th)2-biased inflammation [43,44], but a recent review suggests that the mechanism by which smoking induces inflammation is unknown [3]. More specifically, nicotine exposure has been linked to the shift from Th1 to Th2 bias through an unknown mechanism [45]. The observation runs counter to the recently reported anti-inflammatory properties of nicotinic acetylcholine receptor activation [5]. Our current hypothetical construct may reconcile this apparent contradiction. Intermittent nicotine exposure may lead to receptor desensitization
and paradoxical antagonism of vagal function. Increased sympathetic bias produces shift of Th balance to Th2 bias [6]. Thus, the rebound sympathetic bias from chronic nicotine exposure culminating in a Th2 shift represents a plausible mechanism of tobacco-related inflammatory changes.

**Acute nicotine withdrawal**

The "mini-withdrawal" effect seen between nicotine exposures of chronic smokers may be transformed into full-blown hyperadrenergia and nicotine-hunger after total cessation of tobacco. The typical symptoms seen acutely after smoking cessation include anxiety, insomnia, an increased stress response, and irritability [46,47]. Among components of tobacco, nicotine may be the most likely culprit of rebound hyperadrenergia because patients who quit smoking with the aid of a nicotine patch return to a lower heart rate and a higher HRV after the nicotine is withdrawn [36]. In animal vascular models, if nicotine is withdrawn after a period of exposure, rebound vasoconstriction has been observed suggesting rebound sympathetic activity [48]. Labetalol, an α- and β-receptor blocker, may blunt acute symptoms of nicotine withdrawal [49].

**Chronic changes after nicotine withdrawal**

The long-term response to the cessation of smoking appears to be the reduction of sympathetic bias. HRV elevation [36] and bradycardia [50] have been observed after cessation of smoking, suggesting a re-emergence of vagal strength. Smoking cessation 6–8 weeks prior to surgery may reduce peri-operative complications [51], many of which may be associated with the hyperadrenergic state [6].

Weight gain after the cessation of smoking has been attributed to various putative causes including a transference of addictive behavior [52] or an alteration of metabolism [53]. Alternatively, the phenomenon may operate through a reversal of anorexia and cachexia typically seen in states of hyperadrenergia [54], a phenomenon which may be mediated through tumor necrosis factor (TNF)-α [55]. Anorexia and cachexia are commonly observed in heart failure, AIDS, and cancer, which are associated with hyperadrenergia and elevated TNF-α [54]. The reduction of adrenergia after smoking cessation may reverse anorexia and induce rebound hyperphagia. Indeed, chronic nicotine withdrawal has been shown to promote feeding behavior and weight gain [56]. Administration of an adrenergic stimulant has been shown to blunt the weight gain during nicotine withdrawal [57].

**Implications**

It is apparent that the compendium of cardiovascular dysfunctions associated with tobacco use could be attributed to sympathetic bias. Evidence suggests that sympathetic bias may play a role in lipid dysfunction, insulin resistance, thrombogenesis, Th2 inflammation, endothelial dysfunction, vasoconstriction, and arrhythmogenesis [6,58]. While the direct effects of nicotine could account for tobacco-related sympathetic bias, we are intrigued by the possibility that a reflex compensatory host response to intermittent nicotine challenge may represent the paradoxical source of sympathetic bias. The extension of our proposed framework offers alternative explanations for many observed clinical effects associated with tobacco use.

Smoking has a well-known association with various cancers. This association has generally been attributed to the carcinogenic effects of tobacco smoke, though the actual carcinogen has not been conclusively isolated nor identified. We are curious about the possibility that intermittent nicotine exposure engenders sympathetic bias participates in the emergence of cancer, independent of any carcinogenic substance or any direct pro-tumor effects of nicotine [59]. More specifically, tobacco-induced cancer may be partly attributable to decreased rates of tumor clearance by the immune system, independent of an increase in the background rate of neoplasia. A sympathetic signal shifts lymphoid function to Th2 bias while a parasympathetic signal promotes Th1 bias [6]. Th1 immunity is characterized by cell-mediated immunity and is the primary host defense against cancer [60]. Empirical evidence suggests that sympathetic bias and the associated shift to Th2 immunity is the preferred environment for tumoral evasion of host immunity [54]. Clinical states associated with Th1 depletion and shift to Th2 bias such as aging, HIV infection, and exposure to immunosuppressive therapy are associated with an excess incidence of cancers [54]. Perhaps intermittent mucosal exposure to nicotine may induce local and systemic Th2 bias as a rebound phenomenon that permits greater tumoral evasion of Th1 surveillance. The probability of local neuroimmunomodulation has increased with the recent discovery of the autonomic innervation of the bronchus-associated lymphoid tissue [61]. In cases such as lung cancer and head and neck cancer, there may be profound
mucosal exposure to nicotine which can contribute to the excess cancer rates by inducing shift to Th2 function in the mucosa-associated lymphoid tissue (MALT). The high concentrations of nicotine, cotinine, and other nicotine metabolites in the urine of smokers [62] may similarly account for the excess incidence of bladder cancers by shifting MALT function to Th2 bias. For other cancers associated with tobacco such as breast, pancreatic, and lymphoma, the immunomodulatory effects of nicotine and its metabolites may be systemic.

Many other clinical conditions influenced by smoking possibly owe their associations to nicotine-related sympathetic bias and Th2 bias. Smoking appears to protect against sarcoid and hypersensitivity pneumonitis [16]. There has been speculation that the anti-inflammatory effects of nicotine may offer protection against these diseases by inhibiting pro-inflammatory cytokines such as TNF-α [16], however, this view is not consistent with the observation that TNF-α is substantially elevated in smokers and is promoted by sympathetic bias [63]. Instead, we postulate that the ultimate effect of chronic exposure to nicotine is Th2-biased inflammation accompanied by elevated TNF-α. The shift to Th2 bias may protect against sarcoid and hypersensitivity pneumonitis, which are conditions associated with Th1-biased environments [64].

Other diseases associated with smoking such as type-II diabetes [1], pancreatitis [10], erectile dysfunction [11], and insomnia [12] are mutually linked by their association with sympathetic bias [6,34,65,66]. Additional conditions associated with smoking such as tuberculosis [67] and pulmonary fibrosis [68] share a common feature that they are predominantly associated with Th2 bias [64,69]. Emphysema, the condition most commonly associated with smoking, is generally attributed to elastase dysfunction [70], but the evidence also increasingly implicates inflammation [71], which could arise due to pulmonary sympathetic and Th2 activation. Hypercoagulability associated with smoking is generally attributed to platelet activation and endothelial dysfunction [72], but these processes themselves may occur as a function of sympathetic- and Th2-biased states [58]. The association of smoking with low birth weight has been attributed to various factors such as fetal hypoxia and placental dysfunction [73,74]. Alternatively, given the association of decreased HRV and low birth weight [75], it is also possible that nicotine-related sympathetic bias may play a contributing role in low birth weight. Skin wrinkling, which is associated with smoking [76], may also operate through sympathetic dysfunction [77].

Our hypothesis requires further empiric validation. An assessment of Th balance through cytokine measurements and an assessment of lung sympathetic innervation through meta-iodobenzylguanidine (MIBG) scanning would help establish the proposed biologic changes that may be associated with tobacco smoking. Animal studies involving nicotine exposure without tobacco may isolate nicotine as the agent involved in the pathogenesis of various diseases. One could also perform array experiments from mRNA of cells with nicotine receptors from smokers to determine if gene expression patterns reflect sympathetic simulation and Th2-biased inflammation. Various nicotine pulsing schemes can be studied to better elucidate the primary response and secondary reflex compensation associated with nicotine exposure. Numerous therapeutic implications are apparent. The health impact of nicotine replacement employed in smoking cessation programs may need further evaluation. Controlled administration of nicotine may offer therapeutic benefit in certain diseases, either through the direct effects of nicotine or the compensatory secondary effects of nicotine. The paradoxical effects associated with pulsed, short-acting exposure to nicotine that occurs with smoking may generalize to many other pharmacologic and therapeutic applications. Short-acting formulations of many drugs may be pulsed with sufficient frequency to elicit a paradoxical chronic response for the purpose of treating diseases.

References


[58] Yun AJ, Lee PY, Bazar KA. Can thromboembolism be the result, rather than the inciting cause, of acute vascular events such as stroke, pulmonary embolism, mesenteric ischemia, and venous thrombosis?: a maladaptation of the prehistoric trauma response. Med Hypotheses 2005, doi: 10.1016/j.mehy.2004.08.023.

