

Review

Nicotine and inflammatory neurological disorders

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Cigarette smoke is a major health risk factor which significantly increases the incidence of diseases including lung cancer and respiratory infections. However, there is increasing evidence that smokers have a lower incidence of some inflammatory and neurodegenerative diseases. Nicotine is the main immunosuppressive constituent of cigarette smoke, which inhibits both the innate and adaptive immune responses. Unlike cigarette smoke, nicotine is not yet considered to be a carcinogen and may, in fact, have therapeutic potential as a neuroprotective and anti-inflammatory agent. This review provides a synopsis summarizing the effects of nicotine on the immune system and its (nicotine) influences on various neurological diseases.

Keywords: nicotine; cigarette smoke; immune system

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Introduction

Cigarette smoke is the leading cause of preventable diseases worldwide and, in the USA alone, smoking causes approximately 400 000 deaths annually^[1, 2]. Smoking is associated with an increased incidence of acute respiratory infections^[3], periodontitis^[4], bacterial meningitis^[5], rheumatoid arthritis^[6], Crohn's disease^[7], systemic lupus erythematosus^[8], atherosclerosis^[9], chronic obstructive pulmonary diseases^[10], lung cancer^[11] and coronary heart disease^[12]. While increasing data indicate that smoking might decrease the incidence and/or severity of several diseases, including ulcerative colitis^[13, 14], Parkinson's disease (PD)^[15–18], some forms of Alzheimer's disease (AD)^[19–21], hypersensitivity pneumonitis (HP)^[22] and type I diabetes^[23]; nicotine also protects the kidneys from renal ischemia/reperfusion injury^[24].

A multitude of studies suggest that nicotine, a psychoactive component of tobacco products, acts in a similar fashion as the naturally occurring neurotransmitter, acetylcholine, on nicotinic acetylcholine receptors (nAChRs) found in many organ systems and has profound immunological effects^[25, 26].

During ontogeny, nicotine exposure can modulate T cell and B cell development and activation^[27]. Nicotine exposure also suppresses the T cell response and alters the differentiation, phenotype and functions of antigen-presenting cells (APCs), including dendritic cells^[28, 29] and macrophages^[30]. Exposure to nicotine and/or related agents appears to dampen inflammatory responses and reduce mortality in a mouse model of sepsis^[31] and to protect against induction of type 1 diabetes in mice^[23]. In addition, cigarette smoke inhalation produces sustained suppression of humoral autoimmunity in a murine model of systemic lupus erythematosus (SLE)^[32]. Moreover, several epidemiological studies reveal a strong inverse correlation between smoking and human autoimmune responses manifesting as SLE and ulcerative colitis^[32, 33]. By contrast, other studies suggest that smoking behavior in humans might exacerbate multiple sclerosis (MS) and Crohn's disease^[34–39]. Our recent results show that nicotine exposure significantly delays and attenuates inflammatory and autoimmune responses to myelin antigens in the mouse experimental autoimmune encephalomyelitis (EAE) model^[40]. These apparently conflicting observations suggest that the impact of nicotine on immune responses *in vivo* is complex, being potentially influenced by drug dosage and duration of exposure, the specific organ systems involved in the immune response, the stage and type of disease and by the level of involvement of autoimmune and inflammatory mechanisms.

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Nicotine and immunity

It has long been contemplated that many of the health consequences of chronic cigarette smoking may reflect its adverse effects on the immune system^[41]. Nicotine is a major psychoactive compound in tobacco product. Accumulating evidence suggests that nicotine, a drug that stimulates nicotinic acetylcholine receptors, has profound immunological effects^[41].

Nicotine effects on the immune system *in vitro* There is some evidence that nicotine exposure *in vitro* can produce changes in immunocytes by reportedly affecting the lyses of target cells^[42, 43], decreasing PHA-induced proliferation in human peripheral blood lymphocytes^[44], inducing suppressor cell activity in human T lymphocytes and exhibiting a biphasic effect on the mitogenic responses of peripheral blood lymphocytes^[45]. Aside from its direct effect on peripheral T cells, nicotine also influences T cell development^[27, 46] and alters the expression of certain surface proteins on T cells^[47]. During the primary immune response, exposure of nicotine to T-cells results in altered IL-2, IL-10, and IFN- γ expression in mice^[48]. Furthermore, nicotine inhibits the IL-12 and IL-18 production of ICAM-1, B7.2 and CD40 on monocytes through the up-regulation of cyclooxygenase (COX-2) expression^[49]. Pretreatment with low-dose nicotine causes inhibition of the production of IL-12, IFN- γ , prostaglandin E2, macrophage inflammatory protein (MIP)-1 and TNF- α . In addition, nicotine suppresses the phosphorylation of I- κ B thereby inhibiting the transcriptional activity of NF- κ B and suppressing HMGB1 release^[31, 49–51]. These suppressive effects of nicotine occur at the transcriptional level and are mediated through α 7nAChR.

While macrophages initiate many inflammatory and innate immune functions, dendritic cells (DCs) are the principal antigen-presenting cells. In previous years, several reports documented the biological effect of nicotine on DCs and macrophages^[29, 52–56]. Nicotine has been reported to decrease levels of proinflammatory cytokines and reduce the ability of T-cell priming^[54, 57], but has also been described to enhance the costimulatory molecular expression in DCs and facilitate T-cell priming^[53]. In a recent study, it has also been reported that nicotine could up-regulate expression of nicotinic acetylcholine receptors, costimulatory molecules (such as CD80, CD86), CD40, CD11b, and chemokine receptor, CCR7^[28, 29]. Nicotine could also enhance the endocytotic ability of imDCs in addition to possibly promoting imDC dependent CTL priming and IL-12 secretion *in vitro*^[28, 29, 58].

Nicotine effects on the immune system *in vivo* Increasing evidence has shown that nicotine exerts its effects on

the immune system *in vivo*. Nicotine affects both humoral and cell-mediated branches of the immune system^[2, 40, 59–61] and produces an altered immune response that is characterized by a decrease in inflammation^[62], a decreased antibody response and a reduction in T cell-receptor-mediated signaling^[60]. These effects probably stem from the direct impact that nicotine acts on T lymphocytes. It has been reported that treatment of T lymphocytes with nicotine provides signals that mimic TCR-mediated cell activation signals, thus leading to partial activation of T cells, resulting in anergy^[60, 63, 64]. Chronic administration of nicotine causes T cell anergy, which are primarily mediated via the activation of the hypothalamus-pituitary-adrenal axis^[65]. Nicotine exposure has been associated with the induction of regulatory T cells^[45]. Nicotine also affects B lymphocyte development and controls B lymphocyte survival via nicotinic acetylcholine receptors^[66–69].

Nicotine treatment of a mouse alveolar macrophage cell line (expressing α 4 and β 2, but not α 7 nAChR subunits) results in enhanced intracellular replication of Legionella pneumophila^[70]. Further, the production of the inflammatory cytokines IL-6, TNF- α , and IL-12 are down-regulated in these cells. In our EAE model, we also observed similar results^[40]. Nicotine-induced inhibition of macrophage function may protect against inflammatory lung processes, such as HP, by decreasing the number of alveolar macrophages in the lungs of experimental animals and decreasing inflammatory cytokine production^[22]. Furthermore, chronic nicotine exposure results in a reduction of lung S-adenosylmethionine (AdoMet), which is required for growth of Pneumocystis carinii^[71].

Spectrum of neurological diseases

Nicotine and Parkinson's disease (PD) PD is a debilitating neurodegenerative movement disorder occurring in ~1% of the population over the age of 55. It is the second most common neurodegenerative disease and is characterized by relatively selective damage to dopaminergic nigrostriatal neurons that leads to motor deficits including tremor, rigidity, bradykinesia and postural instability^[72, 73]. Although the entire pathogenesis of PD is still unclear, both environmental and genetic factors contribute to neurodegeneration.

Epidemiological studies have shown an association of smoking with a lower occurrence of PD (Table 1). While several studies were conflicting in regard to worsening of motor performance^[74–77] and the effects of smoking being dose dependent^[78, 79], this negative association between smoking and PD is reproducible, dose related and not a

Table 1. Summary of the effectiveness of nicotine in the neurological diseases patients.

Disease	Clinical effect	References
PD	Protect	[15–18]
	No effect	[74–77]
AD	Protect	[19–21]
	No effect	[111, 112]
MS	High risk	[35, 37–39]

result of selective mortality. Although the component in cigarette smoke that confers this apparent neuroprotective action remains to be identified, numerous studies using experimental animal models suggest that nicotine protects against PD through receptor-mediated and non-receptor-mediated pathways as well (Table 2). Nicotine activates the striatal or mesolimbic dopaminergic system^[80], and protects against glutamate-induced neurotoxicity in striatal, cortical and mesencephalic neurons, as well as nigrostriatal degeneration in MPTP-treated animals^[18, 81, 82]. Nicotine protects against PD by non-receptor-mediated and receptor-mediated pathways. Nicotine could suppress the formation of toxin by directly influencing enzyme activities, such as monoamine oxidases (MAO)^[83]. Nicotine might also modulate the members of the cytochrome P450 (CYP) fam-

Table 2. Summary of neuroprotective effects of nicotine in animal models.

Model	Clinical effect	Mechanisms	References
PD	Protect	Non-receptor-mediated:	
		MAO	[83]
		cytochrome P450 (CYP) family	[84–87]
		mitochondrial complex I activity	[88–90]
		antioxidant	[83, 89]
		Receptor-mediated:	
		$\alpha 4\beta 2$	[15, 95, 97]
$\alpha 7$	[16, 51, 98]		
$\alpha 6\alpha 4\beta 2$	[95]		
$\alpha 6\beta 2$	[15, 95, 99]		
AD	Protect	Reduce A β accumulation and aggregation via $\alpha 7$ nAChR	[113, 114]
		Inhibit NO production	[114]
		Prevent MAPK, NF- κ B, and c-Myc pathways via $\alpha 7$ nAChR	[114]
			[114]
EAE	Protect		[40]

ily^[84–87]. Furthermore, nicotine could act by modulating mitochondrial complex I activity to preserve mitochondrial function and consequently reduce neuronal damage^[88–90], or through a direct chemical action as an antioxidant^[83, 89]. Nicotinic effects could be mediated by stimulating different nAChR subtypes, such as $\alpha 4\beta 2$, $\alpha 7$, $\alpha 6\alpha 4\beta 2$, $\alpha 6\beta 2$, *etc.*^[51, 91–99]. Numerous signaling pathways are altered in response to nACh receptor activation, including presynaptic pathways involved in control of neurotransmitter release (dopamine, ACh, GABA, and glutamate)^[100] and postsynaptic pathways involved in apoptosis (phospholipase C, arachidonic acid, reactive oxygen species, neuronal nitric oxide synthase, and cGMP) and necrosis (phospholipase C, protein kinase C, MAPK, ERK, and Bcl2)^[101–104], immune modulation (IL-1, IL-6, and TNF α)^[16, 105] and neurotrophic factor production (brain derived neurotrophic factor, fibroblast growth factor 2)^[106, 107]. Activation of these pathways might subsequently lead to neuroprotection through inhibition of toxin-induced apoptosis, and increased expression of neurotrophic factors, which are crucial for neuronal maintenance, survival and regeneration.

Nicotine and Alzheimer's disease AD is the most common neurodegenerative disorder that is characterized by impairment of learning and memory. It affects ~2% of the population in industrialized countries. Loss of recent memory is one of the earliest clinical manifestations, but as the disease progresses, patients suffer additional memory losses and experience other cognitive impairments as well. Ultimately, AD patients deteriorate and eventually are no longer able to maintain their own personal independence^[108]. Neuropathological and neurochemical hallmarks of this disease include the presence of extracellular neuritic plaques composed of β -amyloid peptide (A β), neurofibrillary tangles composed of tau protein and a loss of cholinergic neurons of the basal forebrain^[109, 110].

One way for humans to modulate their own cholinergic system is through smoking tobacco. It is fairly well-established that smoking cigarettes can have a protective effect against PD mentioned previously. However, the situation is less clear for AD. Several epidemiological studies have explored the relationship between cigarette smoking and AD, with many of these studies reaching contradictory conclusions (Table 1). These epidemiological studies have been, broadly speaking, either case-control or cohort studies. In general, the case-control studies show that smoking is associated with a decreased risk for developing AD. In contrast, cohort studies tend to show a higher risk of developing AD in smokers compared to non-smokers^[111, 112].

Nicotine protects against AD through $\alpha 7$ nAChR-

mediated and non-receptor-mediated pathways as well (Table 2). Nicotine reduces accumulation of A β in the cortex and hippocampus of amyloid precursor protein (V7171) transgenic mice via $\alpha 7$ nAChR^[113]. Nicotine prevents activation of NF- κ B and c-Myc by inhibiting the activation of MAPKs, resulting in the activation of inducible NOS and the down-regulated production of NO. Further investigation shows that nicotine decreases A β via the activation of $\alpha 7$ nAChRs through MAPK, NF- κ B, and c-Myc pathways^[114]. Nicotine could also inhibit apoptosis and cell cycle progression in this mouse line^[114].

Nicotine and multiple sclerosis MS is an immune-mediated, chronic inflammatory autoimmune disease of the central nervous system (CNS) that is characterized by inflammation, demyelination and axonal damage. Its onset usually starts between 20 and 40 years of age. The prevalence of MS is estimated to be around 400 000 persons in the United States and 2 million people worldwide^[115, 116]. MS leads to substantial disability through deficits of sensation, motor, autonomic and neurocognitive function. Current theories concerning the pathogenesis of MS involve genetic and environmental factors as well as immune dysregulation.

Epidemiological studies have shown an association of smoking with a higher occurrence of MS^[35, 37, 39], while our results show that nicotine exposure significantly delays and attenuates inflammatory and autoimmune responses to myelin antigens in the mouse experimental autoimmune encephalomyelitis (EAE) model^[40]. This occurs whether nicotine treatment begins prior to, at the time of, or after immunization with myelin antigens to induce EAE. Moreover, nicotine exposure also suppresses disease development on adoptive transfer of autoimmune T cells. First, we demonstrated that the expansion of MOG-reactive T cells from the spleen in nicotine-treated mice was significantly dampened. In these animals, MOG-reactive Th cells produced less IFN- γ and IL-2 than cells from PBS-treated controls, whereas the production of IL-10, and particularly TGF- β , was augmented. A marginal, but not significant, reduction of IL-17 was observed in mice received nicotine. Our observation is somewhat surprising given the augmentation of TGF- β in nicotine exposed mice. Nicotine also did not appear to induce apoptosis in autoreactive T cells. This outcome invites the prediction that the immunological effects induced by nicotine may have contributed to the decreased T cell proliferation and altered cytokine profile. We also observed that, although the absolute numbers of CD4⁺CD25⁺ regulatory T cells were not dramatically altered by nicotine exposure, expression of FoxP3 was significantly upregulated. These regulatory T cells with enhanced FoxP3

expression may contribute to the suppression of T effector/autoreactive cells. Furthermore, we found that nicotine significantly reduced levels of MHC class II, CD80, and CD86 expression on peripheral CD11c⁺ and CD11b⁺ cells. Notably, these changes were more dramatic for CD11b⁺ cells. It is likely that the altered APC phenotype in nicotine-treated animals may, at least in part, reduce the encephalitogenic capacity of MOG-reactive T cells in the EAE model.

In the CNS, in sharp contrast with control EAE mice, nicotine-treated animals had relatively few cellular infiltrates in CNS. Further, flow cytometry analysis of the cellular infiltrates showed that a significant reduction of CD4⁺, CD8⁺, CD19⁺, CD11c⁺, CD11b⁺, and CD11b⁺CD45⁺ cell populations; and the reductions in CD19⁺ B cells and CD11c⁺ dendritic cells seem to reflect diminished migration into the CNS from the periphery. It is presently unclear whether the reduction of CD4⁺ and CD8⁺ cells in the CNS stems from reduced influx from the periphery, impaired expansion in the CNS after migration, or both. Whatever the mechanism may be, it is clear that there is significantly reduced expression of antigen presentation machinery by resident or infiltrating CD11c⁺ and CD11b⁺ cells.

There are several possibilities as to how nicotine attenuates the disease even after EAE has been initiated after concurrence of CNS symptoms (Table 2). Nicotine may inhibit myelin-reactive T cell determinant spreading when T cells migrating from the periphery encounter CNS antigens.

Conclusion

Nicotine, the psychoactive component of tobacco smoke, has profound immunological effects. Nicotine has been shown to alter immune responses by decreasing inflammation, decreasing the antibody-forming cell response of splenocytes, decreasing proliferation of peripheral blood mononuclear cells, regulating lymphocytes, macrophages, DC, and affecting the secretion of cytokines of lymphocytes. Nicotine is an agonist at nAChRs, which causes it to interfere with immune responses in a receptor-mediated manner. Nicotine is being considered as an anti-inflammatory agent for the treatment of some diseases such as AD, PD, and Crohn's disease. The effect of nicotine on immune cells, however, is incompletely characterized and controversial. Differences in gender, animal species, age, and disease manifestations may alter the effects of nicotine. The dosage, routes of administration and time may also greatly influence its effects on immunity. Further studies are needed to elucidate the effects of nicotine on the immune system and its effects on various kinds of diseases, including MS.

Epidemiological studies have identified a negative correlation between smoking and the development of neurodegenerative disorders such as PD, and in some studies, AD. These findings have been attributed to the ability of nicotine to act as a neuroprotective agent. Despite the compelling evidence that nicotine is neuroprotective, it is clear that nicotine can be toxic under some circumstances. The balance between nicotine neuroprotection and toxicity depends on dose, developmental stage and regimen of administration. Therefore, a full understanding of the molecular and cellular effects of nicotine on signaling pathways relevant to neuronal survival is critical for informed drug discovery of nicotinic compounds to combat human neurodegeneration.

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Abbreviations

AD, Alzheimer's disease; APCs, antigen-presenting cells; DC, dendritic cell; EAE, experimental autoimmune encephalomyelitis model; MS, multiple sclerosis; nAChRs, nicotinic acetylcholine receptors; PBL, peripheral blood lymphocytes; PD, Parkinson's disease; SLE, systemic lupus erythematosus.

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