1. INTRODUCTION

Nicotine, a small organic alkaloid synthesized by tobacco plants, is the addictive component of cigarettes. Its basic properties permit easy transport across the small intestine and lung tissues into the blood. Nicotine’s size and lipophilic characteristics allow for a small amount to cross cell membranes directly, without interception by a receptor, although its primary effects are via receptor mediation. This small alkaloid acts as an agonist at the nicotinic acetylcholine receptors (nAChRs), found mainly in the central (CNS) and peripheral nervous system, as well as on many other tissue cells throughout the body. The distribution of these receptors on a large variety of cells helps to explain why nicotine has been associated with a wide range of biological actions. These actions of nicotine account, in part, for alterations in the cardiovascular, pulmonary, gastrointestinal, urogenital, hepatic, and nervous systems caused by smoking tobacco.

The most frequent way to acquire nicotine is via tobacco products. Cigarettes contain approximately 1.5–2.5 mg nicotine per cigarette, with the highest level of nicotine reported in the plasma of heavy smokers being about 700 ng/ml. Interestingly, different areas of the body accumulate nicotine at different rates. For example, nicotine is retained at a higher level in the cervix, kidneys, gastrointestinal tract, heart, and muscles than in blood. In terms of distribution in the blood, smoking one cigarette results in about 50 ng nicotine/ml in arterial blood contrasted with the 20 ng nicotine/ml in venous blood. This type of differential distribution of nicotine is important to keep in mind when comparing results of nicotinic action from different experimental protocols.
It is nicotine, just one of the thousands of components of tobacco, that is most strongly related to the addictive consequences of smoking. This addictive characteristic is best explained by the intermittent acquisition of nicotine, which can travel within 8 s to the brain, and the subsequent intermittent release of dopamine in the brain.\(^{13}\) Importantly, chewing tobacco, or smokeless tobacco, also delivers a similar amount of nicotine to the blood; however, the distribution is slower and the timing continuous.\(^{14,15}\) Since high concentrations of nicotine have been reported in the saliva of snuff users (up to 5 \(\mu g/ml\)), it has been suggested that nicotine may be important in the induction of oral cancers in people using smokeless tobacco.\(^{16}\)

At one time, the use of tobacco products was the most direct way of being exposed to nicotine. However, since it is becoming more common for people to use nicotine gums, inhalers, or patches as substitutes for tobacco, nicotine can therefore be acquired independent of the other chemicals in cigarette smoke or chewing tobacco. This use of nicotine is potentially important since nicotine engages many organ systems. It is well supported that nicotine’s action \textit{in vivo} impinges on the hypothalamic–pituitary–adrenal (HPA) axis,\(^{17}\) and thus its effects are broadbased throughout the body. Specifically, it is known that nicotine enhances the release of neurotransmitters and hormones, including acetylcholine, serotonin, dopamine, norepinephrine, prolactin, vasopressin, and corticosteroids.\(^{18}\) These components have their own modulatory actions on the body, extending the potential impact of nicotine. Further, nicotine has been reported to act both via receptor and nonreceptor-mediated mechanisms, again extending the range of its potential effects.

This broad action of nicotine is important to consider since it is used by such a large number of people. In this regard, in addition to its use in facilitating the stopping of smoking, nicotine has been given to people with a variety of diseases since it has been shown to have some measurable clinical benefits.\(^{13}\) For example, in the CNS, nicotine can increase short-term attention, cognition and memory, increase brain energy metabolism, and decrease hunger resulting in decreased body weight. It is used with some success to treat Alzheimer’s disease,\(^{19}\) to enhance cognitive function, to facilitate dopamine release from neurons thus relieving symptoms of Parkinson’s disease, to reduce the severity of involuntary tics in Tourette’s syndrome, and to aid patients with inflammatory bowel disease or attention deficit disorder.

There are many reports demonstrating modulation of immune parameters by nicotine in laboratory experiments; however, there have been no confirming data about the long-term effects of nicotine on immunity in clinical cases. Although the mechanisms of action of nicotine in immune cells are still unclear, data suggest that binding to the nAChR brings about changes in intracellular calcium levels, resulting in alterations of cell signaling pathways. These alterations would then be expected to promote modulations in immune cell activity such as increasing cytotoxicity\(^{20}\) and inducing T-cell anergy \textit{in vivo}.\(^{21,22}\) Although much of the literature supports that the mechanism of action of nicotine is through the nAChR, some reports suggest that the mechanism of action of nicotine may in some cases be independent of the nAChR. In fact, recent work reported that nicotine contributed to neutrophil accumulation in smoke-associated lung diseases by enhancing the survival of these cells, and that the mechanism of action of nicotine was through noncholinergic receptor binding, without activation of protein kinases.\(^{23}\) The interaction of nicotine and the nAChR is described below.