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Volume 2 • Issue 3 • 2018

Review Article

Chronicles of Pharmaceutical Science

ISSN: 2572-7761

Nicotinic Receptor Up regulation and Nicotine Addiction: A Review of Mechanisms

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Received: April 17, 2018; **Published:** May 07, 2018

Abstract

Nicotine has been shown to be the primary component of tobacco that promotes the smoking act through its addictive nature. The adaptive changes of nicotinic acetylcholine receptors that occur through repeated exposure to nicotine play an important role in the establishment of nicotine dependence with its associated behavior. However, one of the major drawbacks of pinpointing the exact etiology of nicotine addiction is the limited understanding of how the various nicotinic receptors in the brain interact with nicotine to promote addiction. In this review the authors attempt relate the nature of nicotine addiction through emphasis on the nicotine-nicotinic receptor relationship.

Keywords: *Nicotine Smoking; Addiction; Nicotinic Receptors; Nicotine Receptor Up-regulation; Acetyl cholinergic Receptors*

Volume 2 Issue 3 May 2018

Introduction

Tobacco use remains the single largest preventable cause of death and disease in the United States. In 2014 roughly 16.8% of the U.S. population, representing 40 million adults, were daily smokers. [1] The World Health Organization estimates that in 2015 over 1.1 billion individuals smoked some form of tobacco. [2] The various reasons that individuals begin to smoke are highly subjective and include peer pressure, social reward, culture, parental influence, media advertising, and stress relief. Even though these factors are highly influential it can hardly be argued that the reason individuals continue to smoke or fail at quitting smoking is due to simple addiction. Addiction to tobacco is synonymous with addiction to nicotine, a normal component of tobacco that exerts a powerful effect on the central nervous system through its interaction with nicotinic acetylcholine receptors.

While it is known that nicotine use results in dependence, the exact mechanism of nicotine dependence has been difficult to elucidate and several theories exist, both old and new, as to which nicotinic receptor subtypes are most implicated in development of dependence and how their upregulation in response to the presence of nicotine leads to sensitization. [3] This article attempts to shed further light on the molecular, pharmacological, and physical aspects of nicotine addiction and its secondary effects on physical and mental health. Specifically, this article describes one of the characteristic properties of nicotine use that results in addiction - the nicotine induced upregulation of the nicotinic acetylcholine receptor. [21]

The Nicotinic Receptor

Acetylcholine Receptors

Acetylcholine (ACh) receptors, also known as cholinergic receptors, are membrane bound proteins that function to modulate nervous system transmission through the binding of the neurotransmitter acetylcholine. Cholinergic receptors are found throughout the central nervous system (CNS) and peripheral nervous system (PNS) and are expressed both in neuronal and non-neuronal tissues. Two main types of cholinergic receptors exist: the metabotropic muscarinic acetylcholine receptors and the ionotropic nicotinic acetylcholine receptors which are both activated by acetylcholine and either muscarine or nicotine individually. Metabotropic receptors are G-Protein Coupled Receptors (GPCR) that activate second messenger systems after binding a suitable ligand. Ionotropic receptors are gated transmembrane channels that facilitate ionic flow after undergoing a shape conformation secondary to ligand binding.

Muscarinic acetylcholine receptors

The muscarinic acetylcholine receptor (mAChR) family is a group of rhodopsin like G-protein coupled receptors consisting of five distinct subtypes M1-M5. [6] The term "muscarinic" is derived from Amanita muscaria, the mushroom species from which the compound muscarine was derived. Muscarine is not normally found in the body but is a selective agonist of a particular acetylcholine receptor. The ability of muscarine to activate certain acetylcholine receptors distinguishes it from nicotine, another type of acetylcholine receptor agonist. Activation of all five receptor subtypes, M1-M5, by either acetylcholine or muscarine results in the promotion of various signaling and regulatory pathways that ultimately lead to intercellular chemical communication and biological function necessary for neurologic transmission. Muscarinic ACh receptors are widely distributed throughout the human body being found in the target organs of postganglionic parasympathetic neurons and this wide distribution of muscarinic receptors is largely facilitated by the ability of GPCRs to adopt a range of conformational states that can lead to distinct functional outcomes. [4] Further, the broad distribution of muscarinic receptors throughout the body is indicative of the critical role they play in a diverse range of biological functions including central and peripheral disease processes. The M1 mAChR is predominantly expressed post-synaptically in the brain, particularly in regions of the hippocampus, prefrontal cortex, and striatum. The M2 and M3 mAChRs are expressed both pre and post-synaptically in different regions of the brain, most notably in the basal forebrain, thalamus, and the hippocampus. Expression of M2 and M3 subtypes in peripheral tissues is mostly restricted to cardiac and smooth muscle.

The M4 and M5 mAChRs are almost exclusively expressed in the CNS, the former pre-synaptically in the striatum and the hippocampus, and the latter in the substantia nigra. Activation of M1, M3 and M5 receptor subtypes primarily results in coupling with the Gq/11 family of G-proteins, activation of phospholipase C, release of inositol-1,4,5- triphosphate (IP3), and subsequent mobilization of intracellular calcium. [6] Activation of the M2 and M4 receptor subtypes results in coupling to the Gi/o family of G-proteins, inhibition of adenylate cyclase, reduction in cyclic AMP (cAMP), and a decrease in neurotransmitter release via the blockage of voltage-gated calcium channels. [6] Muscarinic receptor activation results in the modulation of processes such as learning, memory formation, sleep-wake patterns, attention, endocrine and exocrine secretion, heart rate control, and vasodilation.

Nicotinic Acetylcholine Receptors

Nicotinic Acetylcholine receptors (nAChRs) are a second subtype of Acetylcholine receptor belonging to a family of pentameric cys-loop ligand gated ion channels with acetylcholine being the major ligand and nicotine an alternative ligand for receptor activation.

Every receptor subunit carries an extracellular, hydrophilic sequence of 200 amino that forms a loop and functions as a site for Ach binding. A sagittal section through the receptor reveals four transmembrane domains, M1-M4. [5] Arrangement of the four domains is such that M1 and M3 shield the M2 domain from the lipid component of the cellular bilayer, and the M4 domain is in the close proximity to the lipid component of the bilayer. Arrangement of the receptors polypeptide chains ensures that both the amino and carboxy-terminal of each subunit are present extracellularly and the subunits surround the central pore in which the M2 domain lining the ion channel plays a vital role in ion specificity. [7]

nACHRs are further described based whether they represent a muscular-type receptor or a neuronal-type receptor. Muscular-type nicotinic receptors are found at the neuromuscular junction and are composed of α1, β1, γ, δ, and ε subunits while neuronal-type nicotinic receptors are predominantly located in the CNS and are composed of different combinations of subunits including α2-α10 and β2-β4. However, neuronal-type receptors are not restricted to the CNS as recent studies have discovered that they are present throughout the body as it is postulated that dysfunction in these channels is the base of various neuropsychiatric disorders including Alzheimer's, Parkinson's, and drug (nicotine) addiction.

Variation in the structure, availability, and presence throughout the body either in the form of homopentamers or heteropentamers is indicative of system based specialization. The functional properties of each receptor are unique secondary to extensive variation in individual subunit composition and various stoichiometric combinations of receptors are possible such as (α4)2(β2)3 and (α4)3(β2)2 which exhibit two different efficacies toward nicotinic ligand. This principle of stoichiometric combinations is demonstrated as receptors with two α4 subunits are activated by very low concentrations of Ach while receptors with three α4 subunits require high concentrations of Ach for activity.

α4β2 receptors account for roughly 90% of the high affinity neuronal nAChRs in the mammalian brain along with α7 homopentamers consisting of five ligand binding sites. Other compositions of subunits such as α3β4 receptors are the major subtype found in the autonomic ganglia, adrenal medulla, as well as in CNS neurons of the medial habenula, dorsal medulla, pineal gland and retina. [22]

Neuronal nAChRs are further classified into two classes based on their sensitivity to α-bungarotoxin a neurotoxin that irreversibly binds nicotinic receptors. α-bungarotoxin sensitive receptors are either homopentameric or heteropentameric and are made up of α7, α9, and α10 subunits whereas α-bungarotoxin insensitive receptors which are heteropentameric which are made up of α2-6 subunits and β2-4 subunits.

Acetylcholine binding

Acetylcholine binding sites are generally located at the interface of extracellular subunits depending on the subunit composition. Homopentamers have five identical Ach binding sites while heteropentamers have either two or three binding sites. These binding sites can either interact with endogenous Ach or exogenous nicotine. Further, in order to elicit a receptor response ligands must bind with two orthosteric Ach binding sites in the case of a heteropentamer and three Ach binding sites in the case of a homopentamer.

When acetylcholine is released from the presynaptic nerve terminal into the synaptic cleft, or nicotine is present, it binds to the acetylcholine binding site on its respective receptor and brings about a conformational change causing a twist in the transmembrane domains of the receptor. Immediately after this twisting conformational change has taken place the receptor behaves as a gated channel allowing cations to flow along their concentration gradient through the receptors hydrophilic core which leads to depolarization of the membrane; once the membrane threshold potential is reached an action potential is generated. [10] Of note though, and pertaining to this paper, is that the repeated binding of nicotine with subsequent receptor activation induces spontaneous receptor upregulation and is postulated to be the major cause of nicotine addiction.

Finally, in addition to acetylcholine and nicotine there exist other compounds which can either positively or negatively modulate the activity receptor activity and may provide treatment options for disorders such as Alzheimer's dementia, Parkinson's disease, and nicotine addiction. [11]

Pharmacological Aspects

It has been previously mentioned that nicotine acts as an agonist for nAChRs and induces upregulation of its own receptor and therefore further explanation is warranted. Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring, is a potent parasympathomimetic, and is one of the most commonly used psychostimulants in the world today. [12] Absorption of nicotine occurs through the oral mucosa, lungs, skin, or gastrointestinal mucosa and the absorption rate is dependent on pH with increases in pH promoting an higher absorptions through increased concentration of uncharged lipophilic nicotine which can easily pass through membranes. [15] Nicotine metabolism is highly influenced by both modifiable and non-modifiable factors such as diet, exercise, environment, age, sex, and ethnicity. [14] Nicotine it is metabolized by the liver cytochrome P450 enzyme (CYP2A6) system and its half-life is approximately 2 hrs. [12] Further, metabolism of nicotinic occurs in two phases. Phase one consists of microsomal oxidation which leads to formation of various metabolites including cotinine and nornicotine. The most common way to monitor nicotine intake is via measurement of its major metabolite, cotinine which can be found in blood, urine, nails or saliva. [14] Phase 2 N'- and O'-glucuronidation of metabolites occurs before excretion via urine and feces. [15]

Nicotine exerts both acute and chronic effects on the body via three major mechanisms of action:

1. Ganglionic transmission.
2. Nicotinic acetylcholine receptor activation in chromaffin cells via catecholamines.
3. Central Nervous System stimulation of nAChRs.

When nicotine stimulation exists in a chronic manor craving for nicotine is induced. Brain imaging studies indicate that nicotine use increases activity in the prefrontal cortex, thalamus, and visual system, and is associated with activation of corticobasal ganglia-thalamic circuits, all of which are key brain structures strongly associated with memory formation. When nicotine induced nicotine craving occurs GABAnergic neurons become desensitized and lose their ability to exert an inhibitory effect on dopamine release. When this occurs dopamine stimulation becomes disinhibited leading to the calming effect of nicotine seen in chronic users and this calming effect has been shown to be habit forming.15 It is thus that when chronic nicotine exposure occurs neuroadaptation develops leading to the upregulation of nicotinic acetylcholine receptors in the CNS with subsequent addiction. [13]

Effects on health and metabolism

Along with its addictive properties nicotine imparts significant health risks to users through its ability to induce cellular damage in multiple body systems. One of the most common adverse effects of nicotine use is addiction which can be see through high rates of nicotine use and low rates of successful nicotine discontinuance. While the most intricate details of nicotine dependence have not been fully elucidated, several studies which have focused on the genetic aspect of nicotine dependence or addiction seem to indicate that dependence or addiction to nicotine may be related to an epigenetic inheritance which is transmitted maternally while other studies seem to indicate that nicotine addiction is dependent on duration and frequency of use.

Nicotine use leads to increased risk of cardiovascular, respiratory, and gastrointestinal dysfunction as well as decreased immune response, hypercoagulable state, and infertility. Users may experience a burning sensation in the oral cavity and trachea, increased salivation, headache, nausea, vomiting, diarrhea, abdominal pain, and visual changes. In cases of nicotine toxicity cyanosis, dyspnea, seizure, and coma may be present. [15]

Nicotine use has been shown to convey a substantial risk during pregnancy to the both mother and baby in the form of increased incidence of intrauterine growth restriction, mental retardation, miscarriage, and stillbirth. [15] Nicotine has been shown to be a potent regulator of appetite and body weight as it interacts with the homeostatic system centered in the hypothalamus and hedonic system centered in the cortical-limbic-striatal circuits. Nicotine use has been linked to increased risk of diabetes and insulin resistance and a decreased beta cell population.

Nicotine is a precursor of tobacco specific nitrosamines (TSNAs). The presence of nicotine in the oral cavity leads to the formation, through nitrosation, of N'-nitrosonornicotine and 4-methylnitrosamino)-1-(3-pyridyl)-1-butanone both of which are highly carcinogenic. Other tumorigenic inflammatory markers have been identified by treating normal human lung epithelial cells with tobacco carcinogen nicotine derived nitrosamine (NNK). Results showed that chemokine CCL20 was significantly increased by NNK in 45% of patients and the amount of CCL20 was significantly elevated in tumor cells when compared to their normal cells. CCL20 was found to be up regulated in 52.2% smokers and 37%in non-smokers indicating that there was a link between smoking and cancer.

This effect is significant as most of the nicotine taken into the body occurs orally via use of cigarettes or smokeless tobacco. Previously mentioned was the ability of nicotine to induce cellular DNA damage leading to the survival and proliferation of genetically altered or damaged cells with tumor formation. Nicotine associated tumor formation has been shown to be linked to nicotine's propensity to attenuate arachidonic acid caspase activation and to increase the stability of the Bcl-2 protein thus reducing cellular apoptosis. Nicotine can also modulate VEGF, COX-2, PGE2 and NF-kB causing abnormal cell growth, proliferation, and promotion of various cancers.15 Further studies showed that the glucocorticoid dexamethasone could be used for inhibiting NNK which reduced CCL20 production and lead to a decrease in lung cancer in vitro and in vivo.[19]

Nicotine, through its sympathomimetic action, increases heart rate, blood pressure and contractility through increased release of catecholamine with hemodynamic instability. Not only does the heart respond to increases catecholamines via increased nodal activity but the response to hemodynamic instability is to attempt to increase cardiac output via the Frank Starling Mechanism. Further, nicotine alters the characteristics of the vasculature in a pro-atherosclerotic way by stimulating the release of fibroblast growth factor which inhibits the production of transforming growth factor-1 leading to increased formation of plaques the can occlude arteries, especially the coronary arteries, with resultant cardiac ischemia or infarction. [15]

Nicotine has profound effects on the respiratory system the majority of which are directly attributable to smoking. Oxidation of methionine 358 (Met 358) residues secondary to smoking results in reduced affinity of the alpha-1-antitrypsin protein with its target elastase which results in increased activity of elastase leading to destruction of lung tissue and COPD. Further, nicotine stimulates parasympathetic ganglia inducing bronchoconstriction thereby increasing airway resistance. [15]

Nicotine is associated with Gastroesophageal Reflux Disorder (GERD) and peptic ulcer formation. Increased rates of GERD are thought to be secondary to nicotine's ability to induce smooth muscle relaxation (i.e. gastroesophageal sphincter laxity) via stimulation of nitric oxide production. Due to the decreased tone of the lower esophageal sphincter stomach contents or acid can reflux into the lower esophagus inducing GERD, Barret's esophagus, and adenocarcinoma. Peptic ulcer disease in nicotine users is believed to be secondary to nicotine's action on the cyclooxygenase pathway and cyclooxygenase dysregulation is a known cause of peptic ulceration. Cigarette smoking has also been found to be prevalent in those individuals suffering from Crohn's disease although a significant link has not been established. It is also prudent to mention that cigarette smoke components other than nicotine are known to be gastrointestinal tract irritants which may induce cellular changes on their own.

Nicotine use is known to blunt the body's immunological response in multiple ways. Smoking directly damages epithelial surfaces thereby increasing the risk of infection. For example, IgA secretion through mucosal surfaces can be disrupted by smoking and this disruption can lead to increased rates of infection with antigens that specifically target mucosal surfaces. Further, antigens that have penetrated a mucosal surface have a higher propensity to induce infection in nicotine users due to the effect that nicotine has to interrupt the T-cell signaling cascade through impairment of signal transduction. Indeed, due to impaired T-cell signaling levels of all immunoglobulins are decreased systemically predisposing chronic nicotine users to infection. Nicotine induces alveolar macrophages to produce and release decreased levels of pro-inflammatory cytokines and show an attenuated ability to phagocytize harmful bacteria. Studies have also shown that antigen presenting cells such as dendritic cells show reduced ability to interact with T-cells in order mount an immune response. Migration of inflammatory response cells and fibroblasts is suppressed secondary to chronic nicotine use and there is slow or prolonged wound healing due to reduced cell adhesion and epithelization.

Nicotine promotes pathologic angiogenesis and retinal neovascularization and studies suggest that there is a positive relationship between nicotine and glucose metabolism which increases the risk of cataract formation. Research in mice has shown that chronic nicotine exposure results in increased rates of age-related macular degeneration. [15]

The kidneys are especially susceptible to damage from extended nicotine use. Long term nicotine users often present with renal artery stenosis and chronic kidney disease that progresses to end stage kidney disease requiring dialysis. Chronic nicotine use has been shown to induce albuminuria secondary to glomerular basement membrane damage as well as decreased glomerular filtration rate. The glomerular basement membrane damage experienced in nicotine addiction is likely due to the ability of nicotine to induce cyclo-oxygenase-2 resulting in widespread inflammation. Because the kidneys normally require a substantial percentage of cardiac output to function, nicotine induced heart and vascular damage that decreases organ perfusion is especially harmful to the kidney. [15]

Nicotine induces erectile dysfunction through disruption of nitric oxide synthesis and this is due to the fact that nitric oxide is a necessary component of penile erection. Studies have shown that nicotine has an ability to directly damage seminiferous tubules, affect spermatogenesis, and impair testosterone. Nicotine inhibits 21 hydroxylase causing hypo-estrogenic state which can result in chronic anovulation and oligomenorrhea in females. Nicotine affects the ovaries and alters the production and function of oocytes. Fertilization is impaired due to reduced blood flow to the oviduct. [15]

Nicotine Induced Receptor Up-Regulation, Sensitization, Addiction, Behavior Change, and Withdrawal

Nicotine-induced up regulation of nicotinic receptors occurs subsequent to long term nicotine exposure. The up regulation of nicotine receptors relates to an increased number of functional nicotinic receptors present on neurons in in the mesocorticolimbic reward pathway and is believed to be the root of nicotine dependence and addiction itself. [21]

Prior to assembly into transmembrane protein channels the new nicotinic receptor protein subunits are translated at ribosomal complexes similar to other cellular receptor proteins. Nicotinic receptors are structurally pentamers, hence, after translation, the protein subunits are arranged in pentameric form in the endoplasmic reticulum for assembly by chaperone proteins and further modification. Post translational assembly of the subunits into functional receptors is an inefficient process and only 30% of the receptors produced will have a structure sufficient for function on the cellular membrane. These assembled pentamers are then taken up by Coat Protein Complex II (COPII) vesicles and transported to the Golgi body and undergo further modification before being distributed to the cellular plasma membrane. The older receptors are endocytosed and degraded or re-exposed to the surface. [22]

Nicotine is a lipophilic compound; a psychoactive component found in tobacco which when absorbed in blood stream can easily permeate the blood brain barrier. The action of acetyl cholinesterase disfavors hydrolysis of nicotine which leads to an accumulation of nicotine in the brain with and prolonged exposure to nicotine results in receptor sensitization of the $\alpha4\beta2$ or the homopentameric $\alpha7$ nicotine receptors.

Previously mentioned was that the assembly of the nicotine receptors is low, only 30% of the subunits adopt the appropriate post-translational topography and structural composition required to function on the plasma membrane. In the endoplasmic reticulum, lack of chronic nicotine stimulation causes improperly folded subunits, roughly 70% of subunits, to undergo ubiquitination and degradation by proteasomes and this along with cellular receptor recycling results in the reduced expression of cell surface receptors. [23]

However, studies suggest that the presence of long term nicotine use enhances the up-regulation of receptors on the plasma membrane through increasing the efficiency of post-translational receptor folding and modification by chaperone proteins which increases receptor production. [23] Further, nicotine induces the formation of pentameric subunits of a more stable stoichiometry. This intracellular action of nicotine to up-regulate or increase the total output of stabilized, functional receptors which may be expressed on the plasma membrane is directly responsible for nicotine dependence and addiction.

Further research has shown that upregulation of nicotinic receptors can be attributed to multiple pathways. For example, upregulation of α4β2 nicotinic receptors has been demonstrated through manipulation of a ligand independent PI3K beta mechanism that is enhanced by tumor necrosis factor alpha and also via Jak2 and p38MAPK pathways. [24]

Major factors that contribute to nicotine addiction are neuroadaptation with long term use, calming effects that reinforce dependence, and negative effects when withdrawal occurs. It has been previously stated that nicotine induces upregulation of its own receptor leading to addiction and the subject deserves further discussion. The addiction process is complex however it is believed that nicotine activates midbrain dopaminergic neurons both directly and indirectly and results in in global dopamine release throughout the brain with subsequent release of norepinephrine and serotonin that affects cortical areas which are involved in memory, habit formation, and reward which include the nucleus acumbens, amygdala, and hippocampus. In individual neurons nicotinic receptors are widely distributed and located at the preterminal, presynaptic, axonal, dendritic, and soma areas and because of this distribution even small amounts of nicotine can exert a profound effect. Hence, the influence of nicotine on brain function is determined, at least in part, by the receptors subtype, location, density, and duration of exposure.[20] At physiological pH, nicotine exists in two forms: charged and uncharged. The uncharged form can enter the cell through the lipid membrane and it directly alters intracellular signaling processes while the charged form binds with extracellular nicotine receptors. Because nicotine use, such as smoking, exerts a paradoxical stimulant-relaxant effect it is a highly reinforced behavior. [20]

Nicotine, apart from being an addictive substance itself, is a known gateway drug. The ideology of gateway drugs is simply that they represent legal substances which users become familiar with at a young age before progressing in stages to the use other illegal addictive substances. For example, multiple studies have shown that nicotine use, as in smoking, is a gateway to the use of marijuana and cocaine. In 2012, among U.S. adults 18 to 34 years of age who had ever used cocaine, 87.9% had smoked cigarettes before using cocaine, 5.7% began using cigarettes and cocaine at the same time, 3.5% used cocaine first, and 2.9% had never smoked cigarettes. [25] It has also been shown that nicotine use results in a so-called nicotine induced behavioral changes. In essence individuals who are addicted to nicotine often show behavioral patterns that are contrary to those they would normally choose to exhibit.

Examples of behavioral changes reported by long-term smokers are the avoidance of smoke-free restaurants or social areas or avoidance of socializing with friends and even family members because those individuals do not smoke. The American Cancer Society states that cigarette smoking is the number one cause of preventable death in the United States and that half of all smokers will die from smoking-related illnesses. Even in light of the Surgeon General's warning on smoking those who smoke often attempt to rationalize the effect smoking has on their health through statements such as: "My grandfather smoked his whole life and was healthy" or "I limit my smoking to one pack per week". Finally, although smoking has declined, chronic smoking places a financial burden on an individual or a household as the average smoker reports smoking one pack-per-day and in the United States the cost of the tax-only portion of a pack of cigarettes is as much as $4.35.

In those who are addicted to nicotine, especially smokers, signs of withdrawal may include irritability, anger, anxiety, depression, restlessness, sleep disturbances, and increased appetite and are some of the key reasons that smokers fail to quit. The symptoms of nicotine withdrawal can be grouped according to pattern, intensity, time course, relationship to relapse, neurobiological factors, and even sex. For example, studies have shown that women experience a greater difficulty abstaining from smoking after quitting than men even though the severity of withdrawal symptoms has been shown to be equal in the sexes under most circumstances. However, among women the severity of nicotine withdrawal can fluctuate with symptoms being worse during the luteal phase of the menstrual period and women who attempt to quit cold-turkey during this period can experience severe withdrawal and even depression. [18] Because both positive and negative reinforcement is associated with smoking or smoking cessation those individuals who wish to discontinue smoking face a very difficult task and due to this difficulty management of withdrawal symptoms is a mainstay of any regimen designed to help stop smoking. Withdrawal symptoms typically emerge within a few hours of smoking the last cigarette and gradually decrease with the individual reaching baseline over the course of several weeks, however the time required to quit can vary among individuals.

Concerning the cause of somatic symptoms of withdrawal it has been shown that direct infusion of the non-specific nicotinic antagonist, mecamylamine, into the interpeduncular nucleus can precipitate withdrawal in nicotine-dependent mice, suggesting that the habenular-interpeduncular axis may be important for the expression of somatic signs of nicotine withdrawal. Using mouse models Rubing et al suggested that withdrawal from chronic nicotine activates GABAnergic neurons in the interpeduncular nucleus precipitating the somatic symptoms experienced during withdrawal.

During chronic nicotine exposure, nicotinic acetylcholine receptors containing the β4 subunit were upregulated in somatostatin interneurons clustered in the dorsal region of the interpeduncular nucleus. It is known that that the medial habenula, part of the diencephalon that together with the pineal gland makes up the epithalmus, is a source of glutamate and that GABAnergic projections from the medial habenula to the interpeduncular nucleus exist. When nicotine withdrawal was precipitated GABAergic neurons were found to be activated through the release of glutamate from the medial habernula, the opposite of the process discussed earlier when GABAnergic activity was low and dopamine release was disinhibited through nicotine use leading to a calming effect. [17] It was also shown that that blocking neurotransmission from the medial habenula via the use of lidocaine inhibited activation of interpeduncular nucleus GABAnergic neurons and reduced the symptoms of mecamylamine-induced nicotine withdrawal. [17]

Further, cessation of nicotine independent of mecamylamine infusion contributed to decreased activity of nicotinic receptors and increased glutamate stimulation of GABAnergic pathways projecting to the interpeduncular nucleus from the medial habenula suggesting the pathway is similar for both. It is thus that NMDA receptor antagonists may play a part in reducing neuronal excitability of the habenular-interpeduncluar pathway and increasing success rates of smoking cessation due to reduced somatic withdrawal symptoms. [17]

Conclusion

This review article has attempted to collectively explain the role of nicotine in the addiction process via examination of its molecular propensity to control the upregulation of its own receptor as well as its adverse effects on health and behavior. Although much more is known today about the role nicotine plays in addiction further studies are indicated to elucidate the entire addiction mechanism and to formulate routs for possible treatment of nicotine addiction or reduction in withdrawal symptoms.

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