Nicotine an Efficient Tool of the Neurobiological Research Today, the Tool of Treatment Tomorrow?

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Abstract: Nicotine is a very widely used drug of abuse, which has many neurovegetative behavioural and psychological effects by interacting with neuronal nicotinic acetylcholine receptor. Cholinergic receptors can be divided into two types, muscarinic and nicotinic, based on the pharmacological action of various agonists and antagonists. This review summarises the major recent findings of nicotine effects in order to show the use of this drug in the neurophysiological research and namely as a potential tool for the treatment of some brain disorders.

Introduction

Cigarette smoke (CS) represents the source of nicotine, which can influence the activity of the central nervous system (CNS) [1, 2]. The pharmacological effects induced by CS are mediated mainly by (-)-nicotine [1]. Nicotine is a very widely used drug of abuse, which exerts a number of neurovegetative behavioural and psychological effects by interacting with neuronal nicotinic acetylcholine receptors (NAChR). Smoking and pharmacological doses of nicotine accelerate heart rate, elevated blood pressure and constrict the blood vessels in the skin. At the same time, nicotine can lead to a sensation of relaxation. Nicotine activates reward mechanism in the CNS [3], which is presumed to be the reason why the people smoke, but the mechanism responsible for smoking addiction is more complex.

Cigarette smoke contains approximately 3800 chemicals that include many oxidants and free radicals [4, 5, 6]. Free radicals and other reactive species have been implicated in the progression of at least 100 different diseases [7] thus the interest in free radicals and oxidative stress has grown. However, it is still dubious whether nicotine, the main pharmacological active substance in tobacco, is responsible for deleterious effects due to the production of free radicals, because evidence has shown nicotine to have both antioxidant and prooxidant effects [8].

Nicotine has recently been recognised to have therapeutic effects in some neurodegenerative disorders such as Alzheimer's and Parkinson's diseases [9] where the oxidative stress has been related to the progression of the disease [7]. The crucial question, which has to be answered, is how nicotine is involved in CNS damage or how it can protect it from the damage. The description and understanding of these mechanisms is essential for the future use of the high potential therapeutic capacity of nicotine in CNS disorders and for elimination of its possible side effects.

This review summarises the major recent findings of nicotine effects in order to show the use of this drug in the neurophysiological research and namely as a potential tool for the prevention and treatment of some brain disorders.

The major use of nicotine by humans is in the form of various tobacco products. Another possibility is to use nicotine as an insecticide, where it acts by an over-stimulation and thereby blockade of cholinergic synapses associated with motor nerves. Cigarette smoking is a significant health hazard all over of the world. People who smoke are twice as likely to die earlier when compared with non-

smokers (US Department of Health and Human Services, 1994). People smoke for a variety of reasons. Social, economic, and political factors play an important role in the determination of patterns of smoking prevalence and cessation. More specifically also the personal, family and wider social factors are often critical in determining who starts smoking, who gives up, and who continues [11].

Some people self-administer nicotine in order to achieve analgesia. Nicotine's analgesic properties may help attenuate chronic or acute psychological or somatic pains. There are a number of chronic diseases with concomitant painful symptoms (e.g., fibromyalgia, rheumatoid arthritis, degenerative joint disease) that may induce people to smoke to relieve the pain. If this is true, then nicotine self-administration will increase to soothe the unpleasant experience of pain. This negative reinforcement model may play a role in the nicotine reward. Therefore, nicotine's ability to produce analgesia may partially account for its addictive liability. By studying nicotine-induced analgesia, it would be possible to resolve additional mechanisms of nicotine's addictive properties [12].

The cholinergic system

The opinion that most drugs, hormones and neurotransmitters produce their biological effects by interacting with receptors in cells was introduced by Langley in 1905. Langley's concept was based on the observation of the extraordinary power and specificity with which some drugs were able to mimic a biological response while others prevented it. One of the major transmitter systems in the brain is the cholinergic system. It is associated with many physiological processes such as consciousness, memory, learning, hearing and vision [12, 13, 14].

Two major diffuse cholinergic systems were identified in the brain (Figure 1): The ponto-mesencephalo-tegmental cholinergic complex and the basal forebrain complex. It is mainly the latter that is involved in learning and memory formation.

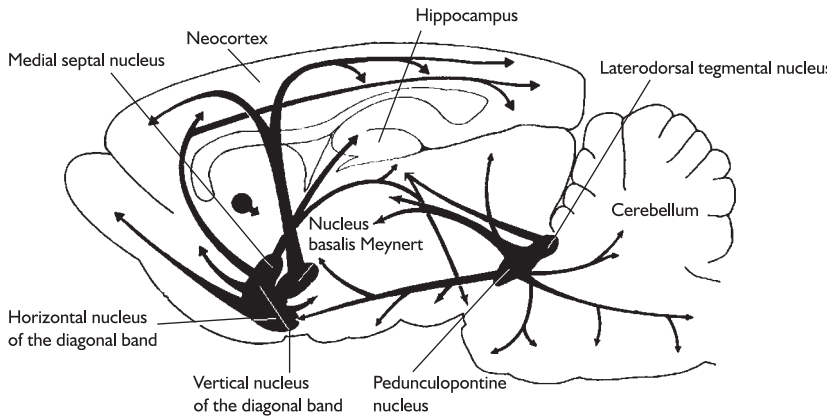

Figure 1 – Distribution of cholinergic cell groups and projections in the rat brain.

Acetylcholine is synthesised in the neuronal axon terminals trough a reaction between acetyl-coenzyme-A and choline, catalysed by cholinacetyltransferase (ChAT). In the synaptic cleft, the enzyme acetylcholine esterase (AChE) regulates the amount of acetylcholine. AChE splits the acetylcholine via hydrolysis, into choline and acetate, which are then transported back into the presynaptic terminal for reuse in the synthesis of acetylcholine [15, 16, 17, 18, 19].

Muscarinic cholinergic receptors

Cholinergic receptors can be divided into two types, muscarinic and nicotinic, based on the pharmacological action of various agonists and antagonists.

Muscarinic receptors are G-protein coupled receptors. Their response is mediated by activating a cascade of intracellular pathways. Muscarine is the prototypical muscarinic agonist and derives from the agaric mushroom Amanita muscaria. Muscarinic receptors are found in the parasympathetic nervous system. Muscarinic receptors in smooth muscle regulate cardiac contraction, gastrointestinal motility and bronchial constriction.

In the 1980's several selective muscarinic antagonists were identified and in this year molecular cloning techniques identified five different subtypes of muscarinic receptors [20, 21]. Each receptor shares common features including specify of binding for the agonists acetylcholine and carbamylcholine and the classical antagonists atropine and quinuclidinyl benzilate. Each receptor subtype couples to a second messenger system trough an intervening G-protein. M1, M3 and M5 receptors stimulate phosphoinositide metabolism while M2 and M4 receptors inhibit adenylatcyclase. The tissue distribution differs for each subtype. M1 receptors are found in the forebrain, especially in the hippocampus and cerebral cortex. M2 receptors are found in the heart and brainstem while M3 receptors are found in the smooth muscle, exocrine glands and the cerebral cortex. M4 receptors are found in the neostriatum and M5 receptors mRNA is found in the substantia nigra, suggesting that M5 receptors may regulate dopamine release at terminals within the striatum. The structural requirements for activation of each subtype remain to be elucidated [22, 23, 24, 25]

Nicotinic cholinergic receptors

Nicotinic receptors produce pharmacologically distinct responses from muscarinic receptors, although acetylcholine stimulates both types of response. Nicotinic response are fast onset, short duration and excitatory in nature. The pharmacology of nicotinic receptors has been studied in great details and our understanding of how ion channel-coupled neurotransmitter receptors work is based largely on the study of this class proteins. Nicotinic receptors are found in variety of tissues, including the autonomic nervous system, the neuromuscular junction and the brain in vertebrates. They are also found in high quantities in the electric organs of various electric eels and rays. The high quantities of receptors in these tissues and

the use of neurotoxins from snake venom (cobra venom) that bind specifically to the nicotinic receptor aided the purification of the receptor protein.

Agonists such as acetylcholine and nicotine produce physiological responses associated with nicotinic cholinergic activation. Acetylcholine produces an influx of sodium trough a ligand – gated ion channel. Acetylcholine also stimulates muscarinic receptors and therefore it should be considered as a mixed cholinergic agonist. The amino acid sequence for the nicotinic receptor was determined after solubilisation of receptors from the electric organ of Torpedo Californica using anionic detergents such as sodium dodecyl sulfate, passing receptor trough an affinity column [26, 27]. Subsequetently, molecular biological techniques were used to clone additional receptor subunits. Any given nicotinic receptor is comprised of five subunits forming an ionophoric channel. Nicotine may also affect more than one of the receptor subtypes and act on more than one binding site in the brain. Nicotinic receptors are involved in the development and ongoing maintenance of the mammalian nervous system and are widely distributed in the human brain. NAChR belong to a super family of ligand gated ion channels (ionotropic neurotransmitter receptors) that includes gamma-amino butyric acid (GABA), glycine, and serotonin receptors. At present, a total of seventeen nicotinic receptor subunit genes have been identified and cloned (a1 to a10, h1 to h4, g, q, and y) [28, 29, 30, 31].

The amino acid sequence for the alpha subunits consists of glycolipid region (which contains the ACh binding site and a sulfhydryl groups) with four hydrofobic regions that span the membrane (Figure 2). Nine alpha subunits have been cloned along with four beta subunits. In the neuromuscular junction, delta and gamma subunits have been identified. The gamma subunit is replaced by an epsilon subunit in the adult muscle. Alfa-bungarotoxin binds to the alpha and beta subunits and probably blocks both the channelled and the acetylcholine (ACh) binding site. Local anaesthetics and other compounds such as phencyclidine bind to the receptor, apparently at the site of the sodium channel and modulate the binding of acetylcholine to the active site.

Local anaesthetics also prevent ion conductance trough a direct action at the channel. The sodium channel and the channel for the nicotinic cholinergic receptor have some similar properties (in both structure and sensitivity to drug action) and may have a common genetic origin. In general terms, acetylcholine binds to the alpha-subunits of the receptor making the membrane more permeable to cations and causing a local depolarization. When summed with the action of other receptors the local depolarization can bring an action potential and lead to muscle contraction. At rest nicotinic receptors posses relatively low affinity for acetylcholine. The affinity for acetylcholine is increased during activation (trough an allosteric mechanism which increased the likelihood of another molecule of acetylcholine binding to other alpha subunit). At high concentration of acetylcholine, the affinity for acetylcholine becomes higher and the receptor

subsequently becomes desensitized. The ionophore (ion channel) is opened during the active state and local anaesthetics may bind to the open channel. The subunit composition of nicotinic receptors differs in skeletal muscle, autonomic ganglia and brain. Note that multiple subunit compositions are possible, which may permit the development of compounds selective for a particular combination. Within the CNS, the alfa4beta2 combination predominates. [15, 16]

Chemistry of nicotine and nicotinic agonist

The chemical formula for nicotine is $C_{10}H_{14}N_2$, for a molecular mass of 162.23 kDa. In the proper nomenclature, nicotine is 3-(1-methyl-2-pyrrolidinyl) pyridine. It is a levorotatory free base [32]. There are four possible conformations for nicotine, and the most likely configuration of nicotine is a rotation between conformations I and II based on dipole moment calculations of nicotine and nicotine-N-oxide in benzene solutions [33]. It is most stable when the pyridine ring is approximately orthogonal to the pyrrolidine ring. In conformation I, the hydrogen on C3 of the pyrrolidine ring is behind H4 of the pyridine ring while in confirmation II, it is behind H2 of the pyridine ring. Using the quantum mechanical method, Pullman calculated that conformer I is 4 kcal/mole more stable than

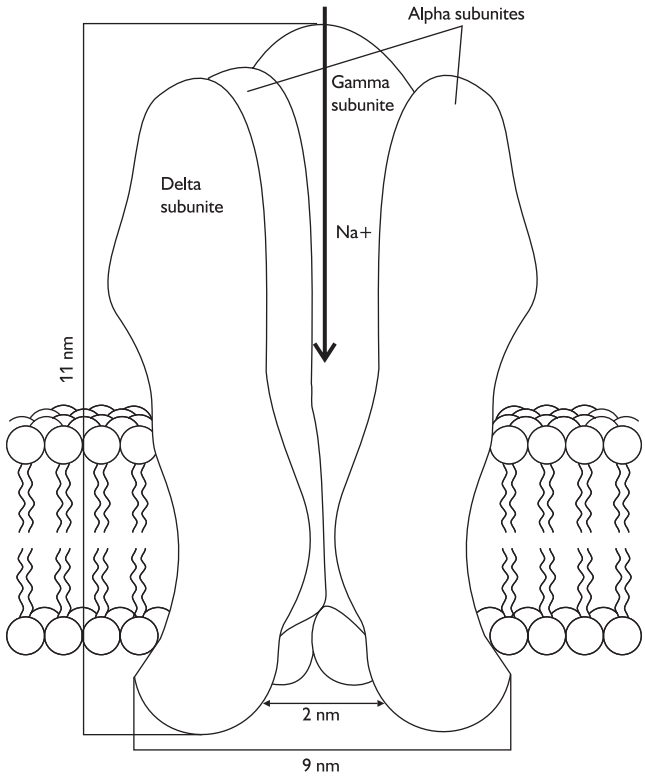

Figure 2 – A schematic representation of the nicotinic acetylcholine receptor.

conformer II. In dilute solutions, however, the preferred conformation is conformer II [32]. Over the past several years, a variety of research groups have focused on the development of selective nicotinic agonists, with the hypothesis that nicotinic agonists could be useful in the treatment of variety of neurological disorders including Alzheimer's disease and chronic pain. [8]. Epibatidine is a nicotinic agonist isolated from the skin of an Ecuadoran frog Epipedobates tricolour that displays potent analgesic properties. Another nicotinic agonist, ABT-418, exhibit some cognition enhancing properties. Note its similarity to nicotine, with an ixoxazole moiety replacing the pyridyl group of nicotine. Epiboxidine is a structural analogue that combines elements of both epibatidine and ABT-418. It also is a potent nicotinic agonist. Two other derivates are worth nothing. The azetidine analogue of epibatidine ABT-594 is a potent analgesic with significantly fewer side effects than epibatidine. SIB-1508 is another nicotinic agonist with potential utility in the treatment of Parkinson's disease. [15, 16]

Chemistry of nicotinic antagonists

Antagonists for nicotinic receptors include such diverse compounds as curare, alfa-bungarotoxin and gallamine. Nicotinic receptors found at the neuromuscular junction differ from the receptors found in autonomic ganglia and can be distinguished both pharmacology and biochemically. Gallamine (mixed muscarinic and nicotinic antagonists) and decamethonium are more effective antagonists at the neuromuscular junction than at the autonomic ganglia. Gallamine and succinylcholine are used during surgery to block neuromuscular junction receptors and produce paralysis. Decamethonium is another nicotinic antagonist with some selectivity for the neuromuscular junction. Ganglionic blockers include the quaternary compounds hexamethonium and tetraethylammonium as well as the tertiary and secondary amines mecamylamine and pempidine. While quaternary amines competitively inhibit cholinergic responses in autonomic ganglia, tertiary and secondary amines also have non-competitive component. [15, 16]

Nicotine and general oxidative stress

Although, the phrase "oxidative stress" is now commonly used, it has been only loosely defined. Sie [34], who originally introduced the phrase, defines it as "a disturbance in the pro-oxidant-antioxidant balance in favour of the former, leading to potential damage". This imbalance is the result of either a decrease in antioxidant levels or an increase reactive oxygen species (ROS) or reactive nitrogen species (RNS) [35]. There have only been a few studies that examined the oxidative stress effects of nicotine per se and without association to a disease or in regard to smoking, tobacco products or smokeless tobacco extract. Typically these studies have been performed in vitro using different cells or cell lines. Two studies used Chinese hamster ovary (CHO) cells in an in vitro model. In the first study, Yildize, Ercal and Armstrong [36], showed that (-)-nicotine and both of its

enantiomers induced cell toxicity (between 4 and 6mM) and inhibited the colony formation of CHO cells at 10mM. Additionally, Yildiz et al. [37] conducted a second study using equivalent methodology, which compared equal levels of pure nicotine [38] with nicotine from smokeless tobacco extract (0.08, 0.8 and 4 mg per 5 ml of media). The results indicated that nicotine decreased glutathione (GSH) levels significantly more than the smokeless tobacco extract of nicotine. In the presence of superoxide dismutase (SOD) and superoxide catalase CAT, the decrease in GSH levels was inhibited in the nicotine condition, but not in the smokeless tobacco extracts condition. This suggests a different mechanism of action by nicotine and the smokeless tobacco extract for the depletion of GSH. These studies provide strong evidence that nicotine produces oxidative stress in the CHO cells in culture. However, it should be noted that the first study employed very high concentrations of nicotine. The concentration of nicotine in the venous blood after smoking several cigarettes ranges from 60nM to 300nM [39], and in the arterial blood, which better represents the level of nicotine in the brain, is 600nM [40]. Similarly, intermittent or continuous administration of nicotine in rats, producing plasma levels of nicotine in the range found in average human smokers, results in brain nicotine concentrations ranging from 75nM to 2μM [41, 42]. Thus, it is very unlikely the nicotine concentrations would ever reach mM concentrations in average human smokers.

Antioxidant effects of nicotine

Interestingly, iron (Fe^{2+}) has been implicated in the progression of both Parkinson's and Alzheimer's disease by the production of oxidative stress through the conversion of hydrogen peroxide (H_2O_2) to hydroxyl radical (OH) [43, 44]. Also, free Fe^{2+} ions and H_2O_2 induces dopamine oxidation, resulting in the formation of 6-hydroxydopamine (6-OHDA) in Parkinson's [45]. A study by Linert et al. [45], examined the possible antioxidant properties of nicotine in relation to Alzheimer's and Parkinson's diseases. The investigators proposed that nicotine may have antioxidant properties, due to its characteristic of binding Fe^{2+} and its reduction of transferrin-mediated Fe uptake. The in vitro results from neocortical tissue of 5 month old rats treated with varying doses of nicotine showed no difference in the thiobarbituric acid reactive material (TBARS) assay (a measurement of the peroxidation of fatty acids, membranes and foods) when compare to controls. In the in vivo experiment, 2 month old rats were intraperitonealy treated with 0.8 mg/kg of nicotine twice daily for 4 days. Results showed that nicotine had no effect on reactive oxygen species of selected tissue (neocortex, hippocampus and neostriatum) as determined by 2'7'-dichlorofluorescein (DCF) fluorescence assay (detection of ROS, primarily levels of hydrogen peroxide, superoxide radical and hydroxyl radical), nor did nicotine affect TBARS formation, although, the nicotine treated rats did show enhanced cognitive performance in the water maze test when compared to controls. The authors concluded that in both the in vitro and in

vivo experiments, nicotine did not show antioxidant properties as determined by DCF and TBARS. They suggested that the use of different oxidative markers would be useful in determining if nicotine has antioxidant properties. Nicotinic receptors have been proposed to mediate the neuroprotective effects of nicotine in vitro. The in vivo studies while few, have also indicated that nicotine could be neuroprotective. In a study by Shytle [46], nicotine given acutely (0.5 mg/kg s.c.) was shown to block kainic acid-induced wet dog shakes in rats when tested in their home-cage and compared to saline/kainic acid control group. Interestingly, nicotine has a lesser effect in blocking kainic acid-induced wet dog shakes in rats that are tested in a novel environment. Kainic acid is a neurotoxin (glutamate analogue) and behaviourally produces motoric seizures, excessive salivation and whole body tremors. N-methyl-D-aspartate (NMDA) receptor activation is involved in both the behavioural and neurotoxic effects of kainic acid and in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) animal model of Parkinson's [46, 47]. In an in vitro study by Dajas-Bailador [108], NMDA-induced cell toxicity was shown to have a significant rise in intracellular Ca^{2+}, while nicotine did not induce intracellular rise in Ca^{2+} when Ca^{2+} was already present in the media. When Ca^{2+} was removed from the incubation media nicotine did induce a rise of intracellular Ca^{2+}. This is important since excess glutamate stimulation has been proposed to be a component of neurodegenerative diseases by inducing intracellular rise in Ca^{2+}. Together these finding may suggest that nicotine act as a neuroprotective agent by calcium dependent mechanism.

Nicotine and neurodegeneration in ageing

Activation of NAChRs has been shown to improve memory performance and learning in rodents and non-human primates and vigilance and rapid information processing in humans [48]. Accordingly, NAChRs blockers (e.g. mecamylamine) impair performance in spatial memory and other cognitive tasks. Notably, nicotine is particularly effective in recovering cognitive deficits caused by lesions of the cholinergic system in animals and ameliorating cognitive functions in both aged humans and animals. Since cognitive decline is a well known correlate of ageing, it has been hypothesized that a deficit in NAChR contributes to the development of cognitive deficits observed in humans during physiological ageing.

First indirect evidence that linked NAChR to ageing comes from epidemiological studies on smoking, Parkinson's disease (PD) and Alzheimer's disease (AD). Several studies have shown that a negative association exists between cigarette smoking and PD or AD, so that non-smokers have about twice PD or AD risk than smokers [49]. However, this association is more consistently found for PD than for AD, especially when possible biases, such as survival bias, are taken into account. Overall, epidemiological data suggest that smoking, and therefore possibly nicotine, may be protective for some forms of PD. The evidence is less convincing for AD. This may be due to the fact that AD is not always distinguished from

mixed forms of AD with multi-infarctual dementia, whose positive association with smoking is well known [49]. That smoking may exert a neuroprotective effect on AD development has been, indeed, suggested by a recent post-mortem neuropathological study [50], which reported that the density of senile plaques is significantly lower in the hippocampus, entorhinal cortex and neocortex of normal aged smokers than of age matched non-smokers.

Smoking, nicotine and Parkinson's disease

Parkinson's disease (PD) is a movement disorder occurring in 1% of the population over the age of 55. It is characterized by selective damage to dopaminergic nigrostriatal neurons that leads to motor deficits including rigidity, tremor, bradykinesia and possibly dementia [51, 52]. The aetiology of PD is unknown, although the disease appears multifactorial in origin, possibly arising from a complex interaction between genetics and environment. The most commonly used treatment is dopamine replacement therapy. Although initially very effective, L-dopa provides only symptomatic relief with an inevitable disease progression. Moreover, it loses efficacy with time and is also plagued by the development of drug-induced side effects [51, 52]. In fact, studies to identify relevant pharmacological compounds are currently in progress [53, 54]. Candidate agents for testing exhibit a broad spectrum of biological actions and include nicotine. Although cigarette smoke contains thousands of chemicals, nicotine represents the possible candidate for two reasons. First, nicotine stimulates striatal dopamine neurons that are selectively damaged in PD. Second, nicotine exposure protects against neuronal insults in experimental models. In PD there is a loss of nigrostriatal dopaminergic neurons. Thus, a crucial question is whether NAChRs are affected by denervation, as this would have an impact on subsequent actions of administered nicotine. Results from animal models with selective lesion of nigrostriatal dopaminergic neurons and in PD demonstrate significant declines in select NAChRs populations [55, 56, 57, 58, 59, 60, 61, 62]. One important action of nicotine is modulation of dopamine release from nigrostriatal dopaminergic terminals [63, 64, 65]. The finding that NAChRs are decreased with nigrostriatal damage suggests that nicotine-evoked dopamine release might also be reduced. Indeed, studies in mice [60] show that there is a decrease in nicotine-evoked dopamine release with nigrostriatal damage that parallels the NAChRs decline. Drugs that target the subtypes of NAChRs that decline with nigrostriatal damage might therefore be useful in treating PD, assuming that the remaining receptors are coupled to their effectors mechanisms and not saturated with Ache. Nicotine itself might not be ideal because it interacts with numerous NAChRs subtypes in both the central and the peripheral nervous systems, and it could result in harmful side effects and/or counteract positive actions at other sites. Drugs that target a subpopulation of NAChRs could provide a superior effect. The modulatory effect of nicotine on nigrostriatal dopamine release [63, 64, 65] is most likely of direct

relevance to PD because there are major deficits in nigrostriatal function in this disorder. Conceivably, enhanced nicotine evoked dopamine release could benefit PD: (i) from an immediate symptomatic standpoint, by alleviating the motor symptoms, and (ii) by protecting against nigrostriatal damage in the long term.

Nicotine as an adjunct therapy with L-dihydroxyphenylalanine (L-dopa) to relieve PD symptoms

Although L-dopa is one of the best treatments for PD, its use is limited because of the development of unwanted side effects. One approach to circumvent these difficulties is to reduce L-dopa dose; however, this strategy results in a worsening of Parkinsonism [66, 67]. Studies in nonhuman primates show that co-administration of a nicotinic agonist with a lower L-dopa dosage resulted in an improvement in Parkinsonism similar to that seen with higher L-dopa dosage, although it led to a decline in motor complications such as dyskinesias [68]. These data suggest that combined treatment with nicotine, or preferably nicotinic agonists that selectively stimulate NAChRs subtypes, could improve PD treatment. Extensive literature suggests that nicotine protects against different toxic insults in culture systems [75, 69], including against MPTP-induced toxicity in nigral neurons [70]. Activation of these signalling mechanisms might subsequently lead to neuroprotection through inhibition of toxin-induced apoptosis, and/or increased expression of neurotrophic factors crucial for neuronal maintenance, survival and regeneration [71, 72]. Although a major focus is on receptor-mediated protection, nicotine might also play a more direct role that bypasses NAChRs. For instance, nicotine could enhance elimination [73] or suppress the formation of toxins by altering monoamine oxidase activity [74, 75]. Nicotine might also act as an antioxidant [74, 75] and/or inhibit complex I of the electron transport chain, with a consequent reduction in the levels of reactive oxygen species [76]. Furthermore, nicotine could act by stimulating drug-metabolizing enzymes in the cytochrome P450 (CYP) family. CYP2E1, CYP2B6 and CYP2B1 are present in dopaminergic regions in the brain and are induced by nicotine at relatively low doses [77, 78, 79]. Enzyme activation can enhance the metabolism of toxic agents, thus lowering their levels and reducing neuronal damage. If nicotine functions through a non-receptor mechanism, nicotinic agonists with low potency, for example D-nicotine, could be very useful because they would exert a minimum of receptor-mediated side effects. The finding that smoking protects against PD raises the question whether nicotine treatment is beneficial either to relieve PD symptoms or for neuroprotection. With regard to use of nicotine in symptomatic treatment, initial reports had suggested that smoking, nicotine patches or nicotine gum alleviate some movement disabilities [80, 81]. To conclude, the therapeutic efficacy of nicotine as an adjunct therapy in the symptomatic treatment of PD requires further study, and its long-term neuroprotective potential has yet to be evaluated.

Neuroprotective effect of nicotine on experimental Huntington's disease in a rat's model Huntington's disease (HD) is a chronic progressive autosomal dominant neurodegenerative disorder that is characterized by a striatal-specific degeneration [82]. The pathological changes manifest clinically in midlife as a triad of cognitive decline, psychiatric disturbance and impairment of motor function. Several attempts have been made to develop experimental model of HD. In the most widely used animal models of HD, excitotoxic amino acids, such as kainic, quinolinic and ibotenic acids, are stereotactically injected into specific region of the brain. Besides being difficult, there is always a chance of error to inject the drugs into the target cells. The most recent model of HD is based on systemic injections of 3-nitropropionic acid (3-NP), a mitochondrial toxin that causes striatal neuropathy similar to that seen in clinical HD [83, 84]. A major advantage of 3-NP model over other model of HD is that the lesions produced are bilateral, striatal specific and develop spontaneously after systemic administration of 3-NP. In spite of extensive research this devastating hereditary disease remains incurable, warranting further studies to determine the causes and cure of HD. Involvement of NAChR in nicotine-induced neuroprotection against quinolinic acid [85] and MPTP [86] induced neurodegeneration has been reported , suggesting a definite role of cholinergic neurotransmission in neuroprotective effect of nicotine [87, 88]. Furthermore, recent studies have shown that neurotrophic factors play a critical role in neuronal survival following exposure to neurotoxins or neurotrauma [89, 90]. Nicotine stimulates the production and release of neurotrophic factors, such as brain derived neurotrophic factor (BDNF), basic fibroblast growth factor (FGF-2) and nerve growth factor (NGF) [90]. Treatment with nicotine has also been shown to up regulate NGF receptor in a variety of neuronal cells [91] and to protect against apoptosis-induced by NGF deprivation [92]. Thus, nicotine may exert its neuroprotective effect at least in part by stimulating neurotrophic factors. Maksimovic et al. [93] also observed a significant reduction in striatal GSH in quinolinic acid-induced model of HD in rats. Nicotine significantly and dose-dependently protected striatum against 3-NP-induced GSH depletion. Recent studies clearly demonstrate that increased oxidative stress can be one of the major deleterious events in clinical [94] and experimentally induced Huntington's disease [93]. Antioxidants, on the other hand, have been shown to protect nervous system against variety of toxins [95, 96]. Nicotine exerts its antioxidant effect due to its free radical chain breaking properties and/or preventing the initiation of free radical generation [97]. Nicotine can bind to complex I of respiratory chain and inhibit the NADH-ubiquinone reductase activity and generation of superoxide (O^{-}) anion radical [98, 99]. Nicotine can also act as a scavenger of hydrogen peroxide and block the Fenton reaction through binding to Fe^{2+} [100]. Nicotine significantly and dose-dependently attenuated 3-NP-induced striatal lesions and behavioural deficits in rats. The protective effect of nicotine may be attributed to its ability of restoring striatal dopamine levels in 3- NP intoxicated rats.

Neuroprotection by nicotine against hypoxia

Brain neurons are highly sensitive to changes in oxygen availability. Any transient incidences of hypoxia/ischemia induce pathophysiological changes such as disturbances in energy metabolism [101] and modifications in synaptic communication [102]. Hypoxia/ischemia, resulting from stroke or head trauma, is a potential risk factor for neurodegenerative disorders such as Parkinson's and Alzheimer's diseases [103, 104]. One therapeutic approach to treating neurodegenerative conditions has been directed at protecting vulnerable neurons, and agonists of neuronal nicotinic acetylcholine receptors are among the growing list of compounds purported to be neuroprotective [105, 106, 107]. Hejmadi [108] demonstrated two novel aspects of NAChRs-mediated neuroprotection. First, that apoptosis induced by hypoxia in primary cortical cultures is suppressed by activation of NAChRs. Second, activation of at least two NAChR subtypes, 7 and 2 NAChR, mediates this neuroprotective effect of nicotine. NAChR may exert a trophic role in the survival of susceptible neurons during transient incidences of hypoxia/ischemia, adding to the therapeutic potential of nicotinic acetylcholine receptor agonists against neurodegenerative diseases.

Nicotine protective potential against excitatory amino acids induced neurodegeneration. In adult rats, systemic or intraventricular administration of the glutamate analogue, kainic acid (KA), results in the expression of a syndrome characterized by behavioural automatisms such as wet dog shakes (WDS), motoric seizures, excessive salivation, whole body tremor, aggression, hyperactivity, and brain neurotoxicity [109]. Although many brain areas are affected by KA administration, the hippocampus is the most affected [110]. The neurodegeneration of cells in the CA3 region results in epileptiform activity displayed by CA1 pyramidal cells, which is characterized by an enhanced NMDA-mediated excitatory phase with an apparent loss of GABA-mediated postsynaptic inhibition [111]. Because of both the behavioural and neurological similarities, this KA-induced syndrome has been proposed as an animal model for human temporal lobe epilepsy [110, 112]. In the experiments of Shytle et al. [114], KA-induced WDS were less prevalent in rats pre-treated with nicotine than in those pre-treated with saline. Authors speculate that while, GABA agonists strongly inhibit both the behavioural and neurotoxic consequences of KA administration [109, 113], it is possible that nicotine blocked KA-induced WDS through a GABA-mediated process.

Whether this ability of nicotine to block the WDS produced by KA is pharmacokinetic or pharmacodynamic remains to be determined; however, WDS are observed after withdrawal from chronic nicotine exposure [114] suggesting that central nicotinic mechanisms may be involved with the expression of WDS. More studies, especially electrophysiological and behavioural studies are needed for the precise understanding of mechanism how nicotine decreases the incidence of WDS (which usually arise in animals exposed to kainic acid), how it modulates

the symptoms of kainic syndrome and by which mechanisms nicotine eventually attenuates this syndrome.

Conclusion

Nicotine is one of the most widespread and most addictive drugs of abuse. Its taking is usually connected with inhalation of tobacco smoke, which contains a whole range of toxic substances. The abuse of tobacco products negatively influences the health of world population in this consequence.

Experiments conducted in recent years point to an interesting fact that (-)-nicotine has or could have positive effect on a variety of diseases, mainly on central nervous system disorders (currently especially PD, AD). This review attempts to summarize, that nicotine could be used therapeutically. If nicotine would not lead to a complete termination of progression of CNS disorders, it could at least slow down the progression and eventually attenuate the symptoms of the disease. Animal experimental models further show, that in the future nicotine could be used for treatment (even if only symptomatic) of variety of other CNS disorders, for example Huntington chorea, consequences or prevention of hypoxia, schizophrenia, etc. The implementation of this therapeutic modality demands series of experiments. First of all it has to be solved the reproducibility and accuracy of results obtained from an animal model to a human population in order to find out the optimal dose and dosage of nicotine and to eliminate its side effects. Only that can assure the maximal security of patients, perhaps treated with nicotine in the future.

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