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Review

Nicotine and brain disorders

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ABSTRACT

During the last decade，brain nicotinic acetylcholine receptors were extensively characterized from electrophysiological and pharmacological points of view. These receptors play important roles in memory and cognition and participate in the pathogenesis of several brain disorders (Parkinson's and Alzheimer's diseases，Tourette's syndrome，schizophrenia，depression，attention deficit disorder). In the same diseases，clinical studies showed that nicotine had beneficial effects，both as therapeutic and prophylactic agent. This review presents recent data concerning the structure and properties of neuronal nicotinic receptors，their involvement in the pathogenesis of various brain disorders and the beneficial effects of nicotine as therapeutic agent.

INTRODUCTION

Brain nicotinic acetylcholine receptors have particular characteristics as a high structural diversity，predominant presynaptic location，upregulation and long-lasting desensitization upon chronical exposure to agonists. Nicotinic receptors play an important role in complex brain functions like attention，memory and cognition but are also involved in the pathogenesis of several brain disorders like Alzheimer's and Parkinson's diseases，Tourette's syndrome，schizophrenia，depression，attention deficit/hyperactivity disorder，autosomal dominant nocturnal frontal lobe epilepsy. In several diseases，nicotine has therapeutic and/or prophylactic properties，but the mechanisms are not fully understood. The present work summarized recent advances concerning the structure and functions of brain nicotinic receptors，as well as the pathogenesis of various brain diseases involving these receptors.

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NEURAL NICOTINIC ACETYLCHOLINE RECEPTORS (nAChRs)

nAChRs are ligand-gated cation channels similar to $GABA_A$，$5\text{-}HT_3$，and glycine receptors[1]. They have a pentameric structure，containing α and β subunits with a stoichiometry $(\alpha x)_2(\beta x)_3$[2]. One of the main characteristics of nAChRs is their structural diversity. Genetic studies revealed the existence of 11 genes (α2-α9 and β2-β4) encoding for nAChRs' subunits[3]，which led to an amazing about 1000 possible types of nAChRs. However，the studies of Whiting and Lindstrom[4] showed that the $(\alpha 4)_2(\beta 2)_3$ type of nAChRs，which bound with high affinity nicotine and acetylcholine，accounted for more than 90 % of brain nAChRs. Another type of nAChRs encoutered in the brain is the α7 subunit-containing one，which can form functional homooligomers and bind with high affinity alpha-bungarotoxin[5]. In autonomic ganglia the predominant types of nAChRs are the $(\alpha 3)_2(\beta 4)_3$ and $(\alpha 5)_2(\beta 4)_3$[6].

Although the existence of pre-terminal[7] and postsynaptic[8] brain nAChRs has been proved，it is believed that most brain nAChRs are presynaptic，and that their role is to modulate the release of various neurotransmitters like GABA，ACh，serotonin，noradrenaline[9].

The pharmacological and electrophysiological properties of the various types of nAChRs were extensively studied by expressing them in *Xenopus* oocytes or in transfected cultured cells. These studies revealed three particular properties of nAChRs：high calcium permeability，rapid and long-lasting de-

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sensitization, and upregulation upon chronic exposure to agonists.

nAChRs have a much higher permeability for calcium than the muscular nicotine acetylcholine receptor (mAChRs). Thus the pCa^{2+}/pNa^{+} ratio has a value of 0.2 for mAChRs, 15 − 20 for α7/α8 homooligomers and 0.5 − 2 for heterooligomers formed of α2-α6 and of β2-β4 subunits[10].

nAChRs desensitize rapidly upon exposure to agonists. If the exposition lasts for more than 5 min, nAChRs acquire a stable desensitized state, presumably due to binding of additional molecule of agonist[10]. The recovery of nAChRs from this stable desensitized state is very slow (hours or days)[11-13].

In contrast to other receptors, both hetero- and homooligomeric nAChRs[14,15] undergo upregulation upon chronical exposure to agonists. The upregulating process had different intensities in various brain areas[16] and was observed in humans, rats and cell cultures[10,14,15]. It was initially believed that nAChRs' upregulation represented an adaptative response to their desensitization and that most nAChRs belonging to the upregulated population were in an inactive state. Indeed, Marks *et al*[14] described tolerance towards certain nicotine effects, associated with an increased density of nAChRs upon chronical exposure to the agonist. However, other studies performed in whole animals[17] and cell cultures[18], indicated a sensitization towards nicotine effects associated with upregulation of nAChRs.

NICOTINE AND ALZHEIMER'S DISEASE (AD)

Senile dementia of Alzheimer type is produced by the degeneration of basal forebrain cholinergic neurons which innervate the cortex, amygdala and hippocampus[19,20].

AD is associated with a loss of high affinity [^{3}H]nicotine receptors (especially in the subicular complex, parahippocampal gyrus, entorhinal cortex and temporal neocortex), but not with a loss of α-bungarotoxin receptors[21,22]. Spontaneously hypertensive rats (SHR), known to have a reduced number of both high affinity [^{3}H]-cytisine binding sites and low affinity [^{125}I] α-bungarotoxin binding sites, have impaired abilities of learning and memory-related tasks[23,24]. It is worthwhile mentioning that patients with uncontrolled elevated blood pressure frequently develop deficits in learning and memory[25].

Several clinical studies revealed that nicotine might improve cognitive function in AD patients. Thus, nicotine, administered subcutaneously or intravenously to patients with AD, improves sustained visual attention, reaction time and perception but does not improve auditory and visual short-term memory[26-28]. Nicotine-induced long-term memory improvement seems to be due to a better aquisition and/or encoding of information and not to improving consolidation[27]. Nicotine has also been shown to antagonize the deleterious effects of anticholinergic drugs as scopolamine on rapid information processing tasks in humans[29]. Nicotine enhances cognitive performance in normal animals[30] but also in animals with lesions of forebrain cholinergic nuclei[31-33] or with age-induced memory deficits[34].

The mechanisms through which nicotine improves memory and attention in AD are yet unknown but may be related to an increase in dopamine release[35], to nicotinic stimulation of the remaining population of cholinergic receptors or to modulation of the activity of ascending catecholaminergic systems such as the coerulo-cortical noradrenergic and mesolimbic dopaminergic projections[36-38].

NICOTINE AND PARKINSON'S DISEASE

Parkinson's disease (PD) is characterized by muscular rigidity, tremor and bradykinesia. It is produced by a destruction of substantia nigra's dopaminergic neurons which project in the striatum[39]. This leads to dopamine depletion in the basal ganglia and especially in the striatum, which releases cholinergic striatal neurons from dopaminergic inhibition[40].

The involvement of nAChRs in the pathogenesis of PD was suggested by the decrease in high affinity nAChRs density in humans with PD, by 70 % in the pars compacta of substantia nigra and by 40 % − 50 % in the laterodorsal tegmental nucleus[22].

The exposure to nicotine seems to protect against PD. Follow-up studies showed that parkinsonism was 20 % − 70 % less frequent in smokers than in non-smokers, whereas case-control studies indicated that smoking subjects had one-half the risk of non-smoking patients in developing PD[41]. Chronic nicotine administration protected against degeneration of central dopamine neurons induced by mechanical lesions[42].

Moll[43] was the first to describe benefic effects of nicotine in PD treatment. In his study, patients with post-encephalitic PD showed marked improvements when treated with progressively increasing concentra-

tions of nicotine. More recently, Fagerström *et al*[44] showed that nicotine, administered as a combination of patch and gum, significantly reduced rigidity, tremor, disorganized thinking and depression in non-smoking patients with PD.

The mechanism of these benefic actions of nicotine seems to be related to an increase in dopamine release. Thus, it was shown that nicotine released dopamine in substantia nigra, potentiated mesolimbic dopamine secretion, and enhanced locomotor responsitivity in animals[45,46].

NICOTINE AND TOURETTE'S SYNDROME

Tourette's syndrome (TS) commonly appears before the age of 18 a and is characterized by sudden, rapid and brief motor and vocal tics, which occur irresistibley, daily or intermitently throughout a period of one year, and commonly associate with obsesive compulsive behavior, attention deficit disorder and visual motor deficits[47].

The brain area involved in the pathogenesis of the TS is basal ganglia, which explains the involuntary movements present in this disorder[48,49].

The pathogenesis of TS is still unknown. It was proposed that TS is produced by excessive striatal dopamine and/or dopamine receptor sensitivity[50], an imbalanced interaction of the mesencephalic-mesolimbic dopaminergic pathways resulting in limbic disinhibition[51] or by streptococcal infection which could induce antineuronal antibodies against cellular components in the basal ganglia[52].

Relatively recent reports suggest that stimulation of brain nAChRs reduces tics. Sanberg *et al*[53] and McConville *et al*[54] showed that the association of nicotine (Nicorette gum, 2 mg) and haloperidol rapidly decreased the tics and other symptoms associated with TS, which were not optimally controlled by haloperidol alone. Similar results were obtained by Silver *et al*[55] using patches with nicotine (7 mg/24 h) as additional treatment in patients with TS receiving neuroleptic treatment. Unexpectedly, in this last study, the effects of nicotine persisted 3 wk to 4 months after interrupting nicotine administration. Shytle *et al*[56] showed that a single transdermal application of nicotine (7 mg/24 h) reduced tics' severity in patients with TS also receiving haloperidol, for 1 - 2 wk. The second administration of nicotine after this interval produced a new remission, longer than the first one, which may illustrate a sensitizing process. The same study revealed that nicotine improved the TS symptomatology in absence of neuroleptics, with similar potency and duration of the effects.

Shytle[56] hypothesized that these benefic actions of nicotine in TS were due to desensitization of nicotinic presynaptic receptors in the striatum which were responsible for dopamine release. Therefore, nicotine, administered chronically in low doses, would act like an antagonist of nAChRs by desensitizing them.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

ADHD is characterized by impaired attentiveness, increased impulsivity and hyperactivity. ADHD is relatively common in children affecting 5 % - 8 % of boys and 2 % - 4 % of girls[57]. It was proposed that ADHD resulted from a genetically transmitted tendency toward dopamine depletion or underactivity in prefrontal, striatal and limbic brain regions[57].

40 % of the adults with ADHD smoke cigarettes as compared to 26 % of the general population[58]. Cigarette smoking and nicotine administration have been found to improve attentiveness, while smoking-withdrawal produces an obvious decrease in attentiveness[30,59,60].

In the study of Levin *et al*[61] nicotine patches applied to patients with ADHD significantly improved their symptomatology as measured by the Clinical Global Impression, the Conner's Continuous Performance Task and the Time Estimation Task.

The positive influence of nicotine in ADHD may be explained by its dopamine-release-promoting action[62]. High concentrations of nAChRs were found in the substantia nigra, ventral tegmental area and striatum[63-65] and nicotine was shown to stimulate dopaminergic neurons in the substantia nigra and ventral tegmental area[66-68]. It is worthwhile mentioning that dopamine-releasing actions similar to the ones of nicotine are shared by methylphenidate, dextroamphetamine, and pemoline, used in the treatment of ADHD[61].

NICOTINE AND SCHIZOPHRENIA

Schizophrenic patients were shown to present abnormalities in sensory physiology like the absence of decrease in the evoked response to the second of closely paired auditory stimuli. Adler *et al*[69] showed that nicotine, self-administered through smoking, can transiently improve this deffect. Nicotine was also shown to improve the deffects in smooth pursuit eye movement[70] controlled by cholinergic neurons of the pedunculopon-

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tine nucleus[71-73]. Recent studies by Freedman *et al*[74,75] indicate a decreased number of hippocampal nAChRs α7 subunit-containing nAChRs in schizophrenic patients and a linkage of the inheritance of the deficit in suppression of P50 to a chromosome 15 locus.

The incidence of smoking among schizophrenic patients is higher than in normal population[76-78]. and smoking withdrawal in these patients results in worsening of schizophrenic symptoms[79]. Also, the cholinergic agonist arecholine is frequently used by schizophrenic patients who do not receive neuroleptic treatment[80]. It was therefore suggested that tabacco used in schizophrenic patients may represent a form of self-medication and that nicotine may partly correct a neuronal deficit involved in the pathophysiology of schizophrenia itself[76].

NICOTINE AND DEPRESSION

According to the monoaminergic theory[81], depression is due to a deficit of dopamine and/or serotonin release in the brain, which induce characteristic affective, cognitive and behavioral deficits. Lesions of the dopaminergic system induce anhedonia (incapacity of experiencing pleasure) or a failure to seek out pleasurable events[81,82].

There is an important body of evidence suggesting that smoking represents a form of self-medication for patients with depression. Thus, smoking is more prevalent in depressed people (46 %) than in the general population (26 %)[77]. Teenagers with depressive disorders are 4-5 times more prone to smoking than teenagers without a depressive disorder[84]. People with major depression have more problems in stopping smoking, most likely due to occurrence of severe withdrawal symptoms or depressing episodes[85,86].

Chronic smoking has been shown to inhibit monoamine oxidase B, enzyme involved in the breakdown of dopamine[87], and of monoamine oxidase A[88] and these actions explain, at least in part, the antidepressant actions of nicotine.

In a recent study, Salín-Pascual and Drucker-Colín[89] showed that nicotine patches, improved mood in non-smoking patients with major depression. Experimental studies performed by the same group[90] showed that transdermal nicotine suppressed ponto-geniculo-occipital waves of Rapid Eye Movement (REM) sleep in cats and increased the incidence and duration of REM sleep. Certain of these nicotine's actions are shared by serotonin. Thus, the inhibitors of serotonin re-uptake have antidepressant actions[91], whereas electrical stimulation of the dorsal raphe nucleus, largest pool of serotonergic neurons in the brain, suppresses the PGO waves of REM sleep[92]. In a subsequent study, performed in rat midbrain slices, we showed that nicotine increased the firing rate of DRN serotonergic neurons and induced serotonin release, in a dose-dependent manner[93]. Overall, the above-described studies provide an additional explanation for the antidepressive effects of nicotine, ie an increased serotonin release from the DRN.

AUTOSOMAL DOMINANT NOCTURNAL FRONTAL LOBE EPILEPSY (ADNFLE)

This disease is characterized by brief partial seizures occurring during light sleep and often misdiagnosed as nightmares[94]. ADNFLE is the first type of epilepsy in which specific mutations have been identified[94-96]. The first type of mutation is located in the α4 subunit of nAChRs, where serine is replaced by phenylalanine at position 247 (S247F)[96], whereas the second one involves insertion of a leucine (776ins3) near the extracellular end of M2 with ADNFLE[97]. Studies with recombinant $(\alpha4)_2(\beta2)_3$ nAChRs[98] showed that both types of mutations decreased the calcium permeability and increased the desensitization rate of $(\alpha4)_2(\beta2)_3$ nAChRs, which may explain how two different genetical alterations may induce the same clinical form of ADNFLE.

SUBTYPE SPECIFIC nAChRs AGONISTS: A VERY PROMISING TREND

Nicotine is a non-selective agonist of nAChRs. Its therapeutical use in humans is strongly limited due to its association with various diseases, especially cardiovascular ones (arterial hypertension and coronary artery disease). Several nAChRs agonists recently synthesized, like SIB-1553A and SIB-1508Y, exhibited a marked selectivity for certain types of nAChRs expressed in transfected human cell lines. Thus, SIB-1508Y has the greatest selectivity for α4β2 subunit containing nAChRs, whereas SIB-1553A shows the greatest activity at α2β4 subunit containing nAChRs[99,100]. Moreover, both these compounds do not show appreciable activities at α7 and α3β4 subunit-containing nAChRs expressed in *Xenopus* oocytes, which limits their secondary effects and especially the cardiovascular ones (the α3β4 nAChRs are the predominant

type in autonomic ganglia)[100].

Microdyalisis and brain slices studies showed that SIB-1553A, SIB-1508Y, and nicotine exhibited marked differences as concerns the release of various neurotransmitters, which strongly suggested the existence of distinct subtypes of nAChRs in various brain areas. Thus, SIB-1553A is about 10 times more active than nicotine and about 2 times more active than SIB-1508Y as concerns hippocampal acetylcholine release[100], whereas SIB-1533A and SIB-1508Y are more powerful stimulators of dopamine release from rat striatal slices than nicotine[99,100]. Both SIB-1553A and SIB-1508Y are relatively ineffective in inducing norepinephrine release from the hippocampus but significantly increase the release of norepinepheine from the cortex[99-101].

Behavioral studies showed that SIB-1553A stimulated cognitive properties (spatial and non-spatial working and reference memory) in animal models of Alzheimer's disease[100], whereas SIB-1508Y (or its racemate SIB-1765F) improved the deficits of the cortex-striatal loop which were associated with the Parkinson's disease[100,102-104]. These last findings may represent, if further confirmed by clinical studies, the beginning of a new era in the treatment of degenerative brain diseases.

CONCLUSIONS

Important progresses in the knowledge of the structure and properties of brain nAChRs were achieved in the last decade. However, the mechanisms of their participation in the pathogenesis of various neuro-psychiatric disorders remains, excepting the autosomal dominant nocturnal frontal lobe epilepsy, largely unknown. Nicotine and related compounds have beneficial effects in the treatment and prophylaxis of Parkinson's disease, Alzheimer's disease, Tourette's syndrome, attention deficit disorder, schizophrenia and depression. Although in all these diseases the positive effects of nicotine are very likely related to dopamine release, other mechanisms (noradrenaline, serotonin or GABA release) may also be involved. Uncovering the exact pathogenesis of these diseases, as well as the mechanisms of nicotine's beneficial actions (sensitization or desensitization of brain nAChRs) remain important challenges for future studies.

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烟碱和大脑功能障碍

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关键词 烟碱；烟碱受体；帕金森病；阿尔采末病；多动秽语综合征；轻微脑损伤综合征；抑郁症；精神分裂症

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