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 chronic 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.

NEURAL NICOTINIC ACETYLCHOLINE RECEPTORS nACHRs

nACHRs are ligand-gated cation channels similar to GABAa 5-HT3 and glycine receptors. They have a pentameric structure containing a and b subunits with a stoichiometry of axbx. One of the main characteristics of nACHRs is their structural diversity. Genetic studies revealed the existence of 11 genes a2-a9 and b2-b4 encoding for nACHRs subunits which led to an amazing about 1000 possible types of nACHRs. However the studies of Whiting and Lindstrom showed that thd a4 b2 type of nACHRs which bound with high affinity nicotine and acetylcholine accounted for more than 90% of brain nACHRs. Another type of nACHRs encountered in the brain is the a7 subunit-containing one which can form functional homooligomers and bind with high affinity alpha-bungarotoxin. In autonomic ganglia the predominant types of nACHRs are thd a3 b4 and a5 b4.

Although the existence of pre-terminal and postsynaptic 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.

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-
sensitization\textsuperscript{[1]} and upregulation upon chronic exposure to agonists.

nAChRs have a much higher permeability for calcium than the muscular nicotinic acetylcholine receptor\textsuperscript{[2]} mAChRs\textsuperscript{[3]}. Thus the pCa\textsuperscript{2+}/pNa\textsuperscript{+} ratio has a value of 0.2 for mAChRs\textsuperscript{[4]} 15 – 20 for a7/a8 homooligomers and 0.5 – 2 for heterooligomers formed of a2-a6 and of \(\beta2-\beta4\) subunits\textsuperscript{[5]}\textsuperscript{[10]}.

nAChRs desensitize rapidly upon exposure to agonists. If the exposition lasts for more than 5 min\textsuperscript{[6]} nAChRs acquire a stable desensitized state\textsuperscript{[7]} presumably due to binding of additional molecule of agonist\textsuperscript{[8]}. The recovery of nAChRs from this stable desensitized state is very slow\textsuperscript{[9]} hours or days\textsuperscript{[10]}\textsuperscript{[11-13]}.

In contrast to other receptors\textsuperscript{[11]} both hetero- and homooligomeric nAChRs\textsuperscript{[12]} undergo upregulation upon chronic exposure to agonists. The upregulating process had different intensities in various brain areas\textsuperscript{[13]} and was observed in humans\textsuperscript{[14]} rats and cell cultures\textsuperscript{[15]}\textsuperscript{[16]}\textsuperscript{[17]}. It was initially believed that nAChRs’ upregulation represented an adaptive response to their desensitization and that most nAChRs belonging to the upregulated population were in an inactive state. Indeed\textsuperscript{[18]} Marks et al\textsuperscript{[19]} described tolerance towards certain nicotine effects\textsuperscript{[20]} associated with an increased density of nAChRs upon chronic exposure to the agonist. However\textsuperscript{[21]} other studies performed in whole animals\textsuperscript{[22]} and cell cultures\textsuperscript{[23]}\textsuperscript{[24]} indicated a sensitization towards nicotine effects associated with upregulation of nAChRs.

**NICOTINE AND PARKINSON’S DISEASE**

Parkinson’s disease\textsuperscript{[2]} PD\textsuperscript{[3]} is characterized by muscular rigidity\textsuperscript{[4]} tremor and bradykinesia. It is produced by a destruction of substantia nigra’s dopaminergic neurons which project in the striatum\textsuperscript{[5]}. This leads to dopamine depletion in the basal ganglia and especially in the striatum\textsuperscript{[6]} which releases cholinergic striatal neurons from dopaminergic inhibition\textsuperscript{[7]}.

The involvement of nAChRs in the pathogenesis of PD was suggested by the decrease in high affinity nAChRs density in humans with PD\textsuperscript{[8]} by 70 % in the pars compacta of substantia nigra and by 40 % – 50 % in the laterodorsal tegmental nucleus\textsuperscript{[9]}.

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\textsuperscript{[10]} whereas case-control studies indicated that smoking subjects had one-half the risk of non-smoking patients in developing PD\textsuperscript{[11]}. Chronic nicotine administration protected against degeneration of central dopaminergic neurons induced by mechanical lesions\textsuperscript{[12]}.

Moff\textsuperscript{[13]} was the first to describe benefic effects of nicotine in PD treatment. In his study\textsuperscript{[14]} 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 beneficial 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 responsivity in animals.43,45

**NICOTINE AND TOURETTE’S SYNDROME**

Tourette’s syndrome TS commonly appears before the age of 18 and is characterized by sudden rapid and brief motor and vocal tics which occur irresistible-ly daily or intermittently throughout a period of one year and commonly associate with obsessive compulsive behavior attention deficit disorder and visual motor deficits.46

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 an imbalanced interaction of the mesencephalic-mesolimbic dopaminergic pathways resulting in limbic disinhibition 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. Sunberg 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 to 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 neurolep-

tics with similar potency and duration of the effects. Shytle56 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.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 striatum63-65 and nicotine was shown to stimulate dopaminergic neurons in the substantia nigra and ventral tegmental area66-68. 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 defect. Nicotine was also shown to improve the deﬁcits in smooth pursuit eye movement controlled by cholinergic neurons of the pedunculopon-
nicotine nucleus. Recent studies by Freedman et al. indicate a decreased number of hippocampal nAChRs a7 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 and smoking withdrawal in these patients results in worsening of schizophrenic symptoms. Also, the cholinergic agonist arecoline is frequently used by schizophrenic patients who do not receive neuroleptic treatment. It was therefore suggested that tobacco 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.

NICOTINE AND DEPRESSION

According to the monoaminergic theory of depression it 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.

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 than in the general population. Teenagers with depressive disorders are 4 – 5 times more prone to smoking than teenagers without a depressive disorder. People with major depression have more problems in stopping smoking most likely due to occurrence of severe withdrawal symptoms or depression episodes.

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

In a recent study Salin-Pascual and Drucker-Colin showed that nicotine patches improved mood in non-smoking patients with major depression. Experimental studies performed by the same group 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 whereas electrical stimulation of the dorsal raphe nucleus largest pool of serotonergic neurons in the brain suppresses the PGO waves of REM sleep. In a subsequent study performed in rat midbrain slices we showed that nicotine increased the firing rate of DRN serotonin neurons and induced serotonin release in a dose-dependent manner. Overall, the above-described studies provide an additional explanation for the antidepressive effects of nicotine i.e. 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. ADNFLE is the first type of epilepsy in which specific mutations have been identified. The first type of mutation is located in the a4 subunit of nAChRs where serine is replaced by phenylalanine at position 247 S247F whereas the second one involves insertion of a leucine 776ins3 near the extracellular end of M2 with ADNFLE. Studies with recombinant a4b2nAChRs showed that both types of mutations decreased the calcium permeability and increased the desensitization rate of a4b2nAChRs which may explain how two different genetic alterations may induce the same clinical form of ADNFLE.

SUBTYPE SPECIFIC nAChRs AGONISTS

A VERY PROMISING TEND

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 a4b2 subunit containing nAChRs whereas SIB-1553A shows the greatest activity at a2b4 subunit containing nAChRs. Moreover, both these compounds do not show appreciable activities at a7 and a3b4 subunit-containing nAChRs expressed in Xenopus oocytes which limits their secondary effects and especially the cardiovascular ones. a3b4 nAChRs are the predominant
type in autonomic ganglia\textsuperscript{100}.

Microdialysis and brain slices studies showed that SIB-1553A$\square$ SIB-1508Y\textsuperscript{101}$\square$ and nicotine exhibited marked differences as concerns the release of various neurotransmitters\textsuperscript{[1]} which strongly suggested the existence of distinct subtypes of nAChRs in various brain areas. Thus\textsuperscript{102}$\square$ SIB-1553A is about 10 times more active than nicotine and about 2 times more active than SIB-1508Y as concerns hippocampal acetylcholine release\textsuperscript{100}$\square$ whereas SIB-1533A and SIB-1508Y are more powerful stimulators of dopamine release from rat striatal slices than nicotine\textsuperscript{99}$\square$. Both SIB-1553A and SIB-1508Y are relatively ineffective in inducing norepinephrine release from the hippocampus but significantly increase the release of norepinephrine from the cortex\textsuperscript{99 - 101}$\square$.

Behavioral studies showed that SIB-1553A stimulated cognitive properties\textsuperscript{[1]} spatial and non-spatial working and reference memory\textsuperscript{[1]} in animal models of Alzheimer’s disease\textsuperscript{100}$\square$ whereas SIB-1508Y or its racemate SIB-1765F\textsuperscript{101}$\square$ improved the deficits of the cortex-striatal loop which were associated with the Parkinson’s disease\textsuperscript{100}$\square$. These last findings may represent\textsuperscript{[1]} if further confirmed by clinical studies\textsuperscript{[1]} 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\textsuperscript{101}$\square$ the mechanisms of their participation in the pathogenesis of various neuro-psychiatric disorders remains\textsuperscript{[1]} excepting the autosomal dominant nocturnal frontal lobe epilepsy\textsuperscript{[1]} largely unknown. Nicotine and related compounds have beneficial effects in the treatment and prophylaxis of Parkinson’s disease\textsuperscript{[1]} Alzheimer’s disease\textsuperscript{[1]} Tourette’s syndrome\textsuperscript{[1]} attention deficit disorder\textsuperscript{[1]} schizophrenia and depression. Although in all these diseases the positive effects of nicotine are very likely related to dopamine release\textsuperscript{[1]} other mechanisms\textsuperscript{[1]} noradrenaline\textsuperscript{[1]} serotonin or GABA release\textsuperscript{[1]} may also be involved. Uncovering the exact pathogenesis of these diseases\textsuperscript{[1]} as well as the mechanisms of nicotine’s beneficial actions\textsuperscript{[1]} sensitization or desensitization of brain nAChRs\textsuperscript{[1]} remain important challenges for future studies.

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