Neuroprotective and Neurotoxic Effects of Nicotine

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Abstract

The interest in the action of nicotine in the central nervous system (CNS) has significantly increased during the past 15 years. This is due in part to the growing importance of nicotine addiction and its consequences in terms of life quality and costs for public health systems in industrialized countries and, on the other hand, to the significantly higher prevalence of tobacco consumption in patients with psychiatric disorders. The actual data indicate opposite effects of nicotine in the CNS. Nicotine seems to have, at the same time, positive, neuroprotective as well as negative, neurotoxic effects. This suggests that nicotine's action is complex, probably involving different neuronal circuits influencing each other through complicated interactions. In the present review we summarize the most important results of experiments about nicotinic neuroprotection and neurotoxicity in humans and animals. Initially, we illustrate well known modifications of cholinergic transmission during physiological (normal aging) and pathological neurodegeneration. In the second part of the paper we describe neuroprotective and neurotoxic effects of nicotine also mentioning the underlying molecular mechanisms.

Introduction

Tobacco is the most abused legal drug in industrialized countries and the incidence of nicotine addiction has been found to be much higher in persons affected from psychiatric disorders, in particular schizophrenia, compared to healthy people. The pathophysiological mechanisms underlying nicotine addiction have not yet been fully elucidated. A central role is surely played by the brain reward system [43]. Also the reasons for the high incidence of tobacco consumption in schizophrenic persons is not well known. Recently, an influence of cholinergic transmission on cognitive symptoms of schizophrenia has been postulated [98].

In contrast to the well known negative consequences of tobacco consumption, there is general agreement that nicotine may have also beneficial effects in the CNS. Nicotine positively influences different aspects of cognition including learning, memory, and attention. Also, it improves mood, stress regulation, and anxiety.

By improving cognition, in particular attention, learning and memory, nicotine has also a neuroprotective function during adulthood and senescence preventing, according to some authors, the onset of degenerative neurological disorders such as Alzheimer's dementia and Parkinson's syndrome or ameliorating symptoms of these diseases.

In cell culture experiments it has been demonstrated that nicotine has neurotrophic properties and nicotinic acetylcholine receptors (nAChRs) play important roles in the control of neurodevelopment and maturation of the CNS already before birth [19, 53, 76, 77].

On the other hand there are reports of neurotoxic properties of nicotine (e.g., learning problems, behavioural anomalies or higher incidence of attention deficit hyperactivity disorder and nicotine addiction in adolescence) after exposure during neurodevelopment.

In animal models, the exposition of developing neurons to nicotine leads to a decrease of the DNA quantity and higher concentrations of apoptotic markers, results, according some authors, in altered synaptic organisation and aberrant synaptic plasticity and causes a remarkable loss of neurons in the midbrain and cortex.

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The discussion about neuroprotection vs. neurotoxicity seems to be complex and to involve regulation mechanisms of nAChRs as well as interactions between nicotine and other neurotransmitters in the CNS.

Cholinergic Transmission, Nicotine and nAChRs

In normal aging

The most cholinergic markers seem, in general, to be unaffected or only slightly altered in both human subjects and rodents during normal aging [7, 30, 39, 171, 204], although stimulation-induced ACh-release is consistently impaired in the aged brain [30].

Human studies

In some brain areas a decrease in nicotinic binding seems to be evident [88, 109]. In the entorhinal cortex and the presubiculum, for instance, a loss of high-affinity nicotine binding has been found in healthy persons after the fourth decade. Additionally, a slight decrease in α-bungarotoxin (an α7-nAChR agonist) binding in the entorhinal cortex already after the second decade has been observed. In the hippocampus only little or no decrease in high-affinity nicotine binding has been reported [28]. The nAChRs-subunits mostly involved in these alterations seem to be α7, α3, α4 and β2. Although no clear age-related variation in α-bungarotoxin binding has been found [28], α7-subunit mRNA seems to be significantly decreased with age in the frontal cortex [189]. Some authors pointed at a significantly decreased β2-subunit mRNA in the cortex and hippocampus in aged persons, while in subjects with status lacunaris both α4- and β2-subunit mRNA were lower than in controls [183, 184]. α3-subunit mRNA was found to be reduced in the entorhinal cortex of subjects between 70 and 90 years age [179]. Other authors described a progressive decrease in binding ligands selective for *hetero*-pentameric nAChRs (being larger in some neocortical and hippocampal areas and less marked or absent in other brain regions, such as the thalamus) but no significant changes in α-bungarotoxin (a marker of *homo*-pentameric nAChRs) binding in human brains [55, 126].

Animal studies

In rats, neurochemical studies of nicotinic function in aged brain suggested an impairment following normal aging with a decreased sensitivity to nicotine, a greatly reduced maximal effect of nicotine on the ability to increase cortical cerebral blood flow [187], and a decreased nicotine-elicited dopamine release in the striatum both *in vivo* and *in vitro* [117, 155], whereas ACh release after stimulation with the nicotinic agonist methyl-carbamylcholine is reduced in frontal cortical and hippocampal slices [5]. A reduction of α4- and β2-encoding mRNAs and a decrease of α4 protein in several brain regions were found during normal aging in rodents. The mRNA for α3- and α6-subunits was slight decreased in the substantia nigra, α5-subunit mRNA seemed, on the contrary, not to be affected [15, 39, 145]. A more recent study described a strain-specific variability in the expression of α7- and β4-mRNA [42].

In pathological neurodegeneration

Most studies about the role of cholinergic transmission and nicotine in degenerating brains have been conducted, however, in people with neurodegenerative diseases, aiming at a possible therapeutic application of nicotine in the treatment of dementia.

Interestingly, a loss of nicotine binding sites has been reported in Alzheimer's dementia (AD), Parkinson's disease (PD) and Lewy body dementia (LBD), as well as in the progressive supranuclear palsy and Down's syndrome [126], thus reflecting the findings in normal aging. The brain regions involved seem to be different, depending on the specific underlying disorder [202]. A common peculiarity of all these disorders is that the loss of nAChRs can be more pronounced than the loss of neurons. Therefore, some authors supposed that the diminution in the quantity of nAChRs could be a first step which precedes neuronal death (127).

Alzheimer's dementia

The decrease of high-affinity nicotine binding sites in brains of patients with AD has been found in post-mortem studies as well as in PET scans [68, 110, 111, 151] and in animal models of AD [147]. However, no change in α-bungarotoxin binding sites has been observed in the cortex of AD patients, suggesting that α7-subunit containing nAChRs are preserved [176]. In patients with LBD, on the contrary, a decrease of α-bungarotoxin binding in comparison to AD patients and aged-matched controls has been described in the frontal cortex, supporting the hypothesis of a different impairment of nAChRs isotypes in different forms of senile dementia [139]. Other studies in humans with AD showed a loss of binding sites also for other nicotinic agonists, such as acetylcholine in the presence of atropine, methyl-carbamylcholine, cytosine epibatidine and ABT418 [45, 68, 196].

Parkinson's disease

Cholinergic deficits have also been observed in the basal forebrain and cortex of patients with Parkinson's disease, particularly those with dementia. The extent of nAChR loss seemed to be related to the progredience of the cognitive impairment [136].

nAChRs

In order to explain the loss of nicotine binding, the quantity of mRNA encoding for specific nAChR subunits and the related protein expression have been measured. Whereas no significant changes in α3 nAChR *mRNA* levels were found, in one study [179] decreases in α3-, α4- and α7-subunit *protein* levels were observed in some brain regions of AD affected persons [48].

A further question is to determine the normal subcellular localization of nAChR subtypes that are lost in patients with AD.

In addition to being localized to cell bodies of cortical neurons, animal studies have demonstrated that nAChRs are present on terminals of neurons projecting from many other brain regions [44]. Based on rat studies showing that neuronal bungarotoxin partially inhibits acetylcholine release from cortical synaptosomes, the decrease in neuronal bungarotoxin binding (β2/α? nAChRs) and the preservation of α-bungarotoxin binding (α7 nAChRs) in the cortex of patients with AD might suggest that nAChRs located on cholinergic afferents from the basal forebrain are lost selectively in AD [176].

Neurotoxicity

Developing neurons

Several studies have shown that nicotine can be neurotoxic, particularly for developing neurons when exposed through mater-

nal smoking, environmental sidestream smoke or use of nicotine replacement therapy [23,53,59–61,73,102,124,159,186,197].
After nicotine administration with an osmotic minipump during the pregnancy, a decrease of dopamine metabolism in the frontal cortex and a reduced serotonin metabolism in the medulla, pons, midbrain, frontal regions, and cerebellum were seen in rats [103]. In the same animal model, the activity of the enzyme acetylcholintransferase was strongly decreased in embryonic brains [107]. Nicotine exposure via placental transfer increases oxidative stress in rats as manifested by an increase in malondialdehyde level [48]. Some authors measured a decreased DNA quantity in brain cells of the rat fetus, an irreversible neuronal damage through an increase of c-fos activity after over-expression of the proto-oncogene c-fos after nicotinic stimulation and an up-regulation of nAChRs after fetal nicotine exposure [165–170]. Cytoplasmatic vacuoles, wider intercellular spaces and increasing pycnotic, apoptotic and mitotic cells as a sign of cytotoxicity have been found in embryonic neuroepithelial cultures from rats after nicotine incubation [148–150]. Developmental exposure to nicotine increases nicotine binding (particularly in α4β2 and α7 nAChRs), acts on the regulation of transmitter release and gene expression, and alters GABAergic signalling. The latter plays a central role in the modulation of neuronal precursor proliferation and migration and, at later stages, dendritic structure, neurite outgrowth, cell survival, and synapse formation and maturation. An altered GABAergic signalling could result in altered synaptic organization and aberrant synaptic plasticity. These detrimental effects may contribute to some of the clinically characterized deficits that result from maternal smoking, such as sudden infant death syndrome and auditory cognitive dysfunction in animal models [14,35,37,53,134] as well as in humans [34,74].
Not only prenatal neurotoxic effects lead to damage of developing neurons. Also in the case of nicotine exposure shortly after birth, a decrease of DNA synthesis with reduced cell replication and differentiation has been described. Furthermore, a higher concentration of apoptosis marker and a decrease of nAChR have been measured [84,92,170]. The ratio between high- and low-affinity binding sites in the cortex seems to be altered after postnatal (17 days after birth) nicotine administration in rats. High- and low-affinity binding sites are initially equable, after 4 months the low-affinity binding sites are, however, significantly decreased [113].
In adolescent rodent, nicotine administration leads to a reduction of DNA as a trait of cell death as well as to an increase of the apoptotic marker p53 [186]. Abreu-Villaca found, moreover, a remarkable loss of neurons in the midbrain and cortex [1,2]. Acute nicotine induces the expression of the dendritically targeted, corticolimbic dendrin in the prefrontal cortex of adolescent rats. Nicotine treatment in parallel enhances dendrin immunoreactivity. As dendrin is an important component of cytoskeletal modifications at the synapse, these results suggest that nicotine influences unique plasticity-related changes in the adolescent forebrain that differ from those in the adult [154].

Molecular mechanisms

In developing neurons nicotine-mediated neurotoxicity may be due to an increased calcium load in immature cells, because transfection of undifferentiated hippocampal cells with calbindin D28K (a calcium-buffering protein not yet expressed in progenitor cells) protects against the cytotoxic effects of activating α7-type nAChRs [13]. High doses of nicotine (more than 2–3 mg/day) are either ineffective or toxic also in developed neurons, suggesting that too much influx through nAChRs might exacerbate calcium overload in adult cells as well. For example, high dose nicotine (≥ 5 mg/kg/day) results in degeneration of the cholinergic habenulo-interpeduncular pathway of the adult rat [21].
A few studies described the possibility that nicotine could act as toxin inducing oxidative stress by depleting glutathione [198,199].
Some authors reported that while nicotine treatment *in vivo* counteracts neuronal death due to excitotoxic lesion of the cerebral cortex in the early postnatal period, the partial α7-type nAChR agonist GTS-21 increases neuronal death due to this lesion. Pro-apoptotic effects of α7 nAChR stimulation have been observed in several populations of developing neurons, including spinal and cranial nerve motoneurons [57,141,206] and hippocampal progenitor cells both *in vitro* [13] and *in vivo* [3]. A role of α7 nAChRs in nicotine-induced neurotoxicity has also been postulated in studies with knock-out mice lacking this subunit. These animals do not show developmental neurotoxicity to nicotine and knock-in of a hyperactive α7 subunit resulted in wide-spread neuronal death [121]. The activation of α7 subunits is also related to an increase of apoptotic markers in developing neurons and adult hippocampal progenitor cells.

Neuroprotection

Compounds interacting with nAChRs of developed neurons are reported to exert neuroprotective actions *in vivo* and *in vitro* and treatment with nAChR agonists elicits long-lasting neurotrophic effects, e.g., improvement of cognitive performance in a variety of behavioural tests in rats, monkeys and humans [100].

Nicotine and Alzheimer's disease

One of the first and major indicators for the neuroprotective effect of nicotine were statistically significant lower rates of dementia in smokers. So, many authors have focused their interest on the study of nicotinic effects in neurodegenerative diseases.
A well known trait of Alzheimer's dementia is the aggregation and precipitation of amyloid precursor proteins (APP) in the CNS in the form of plaques. Senile plaques are formed by an amyloid core, mainly composed of ß-amyloid (Aß, the amyloidogenic fragment of the APP), encircled by degenerating neuritis and reactive astro- and microgliosis. α7-containing nAChRs are present in the plaques and can be co-immunoprecipitated with the amyloidogenic APP fragment Aß(1–42), suggesting a tight association α7-Aß(1–42) [194]. APP exists in an α-helix conformation (APPα), which does not aggregate, and a β-sheet variant (Aß), which, on the contrary, tends to aggregate and precipitate, thus forming the typical senile plaques and fibrils found in AD patients [153]. Nicotine prevents the conversion of APPα to APPβ and modulates [50] and lowers [190] the secretion of APPβ. A recent paper underlined the central role of the α4β2 and α7 nAChRs in enhancing the release of neuroprotective APPα and lowering Aß production [99]. The described neuroprotective effects of nicotine have been observed particularly in the hippocampus, entorhinal cortex and neocortex [126].
Nicotine has an additional protective effect against Aß, also decreasing its toxic action once the senile plaques have already developed [71,72,83,201,203]. Furthermore, nicotine seems to

antagonize Aβ-induced cognitive deficits in delayed alternation, passive avoidance and Morris maze learning in mice [91]. Nicotine can act directly by binding to Aß, inhibiting the formation of new fibrils (119) or, finally, disrupting already formed ones [120]. In addition, nicotine effectively inhibits apoptosis caused by Aß in hippocampal cultures.

The described findings relating nicotine-induced neuroprotection against Aß have been reported both in patients with AD as well as in healthy elderly persons [27], particularly in the hippocampus [201] and cortical neurons [160].

The exact subcellular mechanisms of nicotinic neuroprotection are, however, not yet fully elucidated. In an *in vivo* study of rats, self-administering nicotine showed an increase of transthyretin levels [126] in the brainstem and hippocampus. Transthyretin binds to Aβ protein and prevents its aggregation [78]. In more recent papers the abnormal interactions of Aß with metal ions such as copper and zinc in the process of Aß deposition in AD brains were pointed out. A significant reduction in the metal contents of copper and zinc in senile plaques and neuropil has been observed in APPV717I transgenic mice and SH-SY5Y cells over-expressing the Swedish mutant form of human APP after nicotine treatment. The Swedish mutation is typical for leading to the development of brain Aß deposits [110]. The densities of copper and zinc distributions in a subfield of the hippocampus CA1 region were also reduced after treatment with nicotine. In sum, nicotine decreases the intracellular copper concentration and attenuates Aß-mediated neurotoxicity. This effect seems to be independent of nAChRs binding [82,203,205].

The marked reduction in the accumulation of Aß in the cortex and hippocampus of mice carrying the Swedish mutation of human APP after chronic nicotine administration happens through inhibition of the activation of MAP kinases (MAPKs), thus preventing the activation of the transcription factor NF-κB and the proto-oncogene c-myc. As a result, the activity of iNOS (inducible nitric oxide synthase) and the production of NO (nitric oxide) are down-regulated. In this cell line nicotine also inhibited apoptosis and cell cycle progression [82,203]. Measurements of cellular oxidation and intracellular free Ca^{++} showed that nicotine suppresses the Aß-induced accumulation of free radicals and increase of intracellular free Ca^{++} [205].

The protective effects of nicotine against Aß are suppressed, in primary cultures of cortical neurons, by a α7-nAChR-antagonist, a phosphatidylinositol 3-kinase (PI3 K) inhibitor or an Src inhibitor [70], suggesting that binding to α7-nAChRs may activate intracellular signalling pathways mediated by the PI3 K cascade which act neuroprotectively. The neuroprotective effect of α7-nAChR stimulation is mediated by the Janus kinase 2 (JAK2) [157]. The block of α7 nAChRs leads then to increased internalization and accumulation of Aß(1–42) [104]. A relationship between nAChRs and Aß has also been seen studying the effects of Aß on nAChRs. Although some authors found a reactive up-regulation of α7-nAChR following an increase of Aß in the mouse hippocampus [32], the application of Aß seems, in general, to block different subtypes of nAChRs on rat hippocampal neurons in culture [81,128], to reduce the number of binding sites for nicotinic agonists (epibatidine and α-bungarotoxin) and to decrease both mRNA and protein quantity of the nAChRs subunits α3, α7 and β2 [46].

Not only nAChRs but also the muscarinic acetylcholine receptors M1 and M3 augment, via the activation of protein kinase C (PKC), the production of non-amyloidogenic fragments of APP and inhibit Aβ production [202]. Conversely, a deficit in muscarinic receptors may lead to an increased formation of Aß and amyloid deposition [143]. Hence, it is probably that cholinergic transmission influences APP metabolism via both muscarinic and nicotinic receptors.

In contrast to the described AD-preventing benefits by reducing the accumulation of amyloid plaques, nicotine promotes also the development of the neurofibrillary tangles induced in patients with AD by aberrant tau phosphorylation [188]. In transgenic mice with a copy of the Swedish mutation of the APP and a human tau transgene (tau_{P301L}) chronic oral administration of nicotine led to an increase of aggregation and phosphorylation of tau [115].

Thus, the effects of nicotinic stimulation seem not to be only protective against onset and progression of AD.

Nicotine and Parkinson's disease

Both acute and chronic nicotine treatment *in vivo* can protect the nigrostriatal system from lesions by the selective neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), methamphetamine, 6-hydroxydopamine (6-OHDA) or rotenone [26,62,85,123,152,178]. These agents are commonly used to produce experimental parkinsonism.

Nicotine has shown a protective, antitoxic effect against MPTP [17,65,163]. The underlying neuroprotective mechanisms are probably due either to an inhibition of apoptosis or an increase in the expression of neurotrophic factors [90,144]. Chronic infusion of high-dose nicotine seems, however, to increase MPTP-mediated toxicity [8,51,62].

MPTP is a precursor of *N*-methyl-4-phenylpyridine (MPP^+). By using isolated brain mitochondria, some authors found recently that nicotine inhibited MPP^+- and calcium-induced mitochondria high-amplitude swelling as well as cytochrome C release from intact mitochondria. The intra-mitochondria redox state was also maintained by nicotine, which could be attributed to an attenuation of mitochondria permeability transition. Further investigations revealed that nicotine did not prevent MPP^+- or calcium-induced mitochondria membrane potential loss, but instead decreased the electron leak at the site of respiratory chain complex I. The nicotine-mediated neuroprotective effect has been suggested to be independent on nAChRs-activation [205].

Nicotine pre-treatment attenuated the methamphetamine-induced neurodegeneration in wild-type mice, but not α4 nAChR knockout mice, indicating that α4 stimulation may be crucial for nicotine-mediated neuroprotection [125].

Subcutaneous administration of nicotine was also neuroprotective in rotenone-induced Parkinson's disease models reducing dopaminergic neuronal cell loss in the substantia nigra of treated mice [178].

Exposure to pesticides is considered a positive risk factor for Parkinson's disease. Nicotine treatment partially protects against the pesticide paraquat, which induces declines in nigrostriatal dopaminergic neurons via α6β2 nAChRs [69].

Nicotinic neuroprotection in Parkinson's disease has been postulated, moreover, through the prevention of alpha-synuclein fibril formation. The aggregated form of this small presynaptic protein, that is abundantly distributed in the brain and whose function is unknown, is a pathological hallmark of several neurodegenerative diseases, including Parkinson's disease. Nicotine inhibits alpha-synuclein fibrillation and stabilizes soluble oligomeric forms [56].

Nicotine-induced neuroprotection against excitotoxicity, ischemia and mechanical lesions

Nicotine is also effective in protecting cortical neurons from cell death *in vivo* as a result of excitotoxic, ischemic or mechanical lesions [18, 118, 159].

For instance, nicotine and nicotinic agonists decrease glutamate-, kainic acid-, NMDA- (*N*-methyl-d-aspartate), and quinolinic acid-induced neuronal death in cortical and hippocampal neurons in culture [4, 17, 22, 33, 67, 87, 118, 132, 133, 156, 193].

Nicotine-mediated effects against glutamate-induced neurotoxicity have been found in PC12 cells and are probably due to an increased buffering action on Ca^{++} and modulation of apoptotic processes by inhibiting NO formation [177, 205].

It has been demonstrated that nicotine given acutely also blocks neurotoxicity by kainic acid, a glutamate analogue neurotoxin inducing motoric seizures, excessive salivation and whole body tremors [161, 162].

Nicotine also prevents NMDA receptor activation, which is involved in the neurotoxic effects of kainic acid.

In vitro models of alcohol-induced neurodegeneration have been employed to demonstrate neuroprotective actions of icotinic agonists. Nicotine might act by stabilizing mitochondrial function, attenuating cytochrome c release, and reducing apoptotic cell death [79, 180–182].

Moreover, nicotine can act directly on the metabolism of toxins suppressing, for example, their production or accelerating their elimination by involving enzymes like monoamine oxidase [114, 135, 174]. Some studies suggest that nicotine could act neuroprotective as an antioxidant due to its free radical chain-breaking properties and/or preventing the initiation of free radical generation [47], decreasing the levels of reactive oxygen species by inhibiting complex I of the electron transport chain [24, 25] or functioning as a scavenger of hydrogen peroxide and blocking the Fenton reaction through binding to Fe^{++} [80]. The scavenging effect of nicotine on hydroxyl radicals and superoxide free radicals has been found to be higher than that of vitamin C [205]. An additional nicotine property is the influence of the enzymes of cytochrome P450 (CYP) family. Via inducing CYP2E1, CYP2B6 or CYP2B1 nicotine could accelerate the catabolism of several toxins, thus indirectly acting neuroprotectively [58, 95, 96, 108].

A further series of neuroprotective effects of nicotine has been detected in neurons after ischemia [36, 106]. Although one study showed increased neuronal loss due to middle cerebral artery occlusion following chronic administration of nicotine through an osmotic minipump [195], nicotinic stimulation protects neurons from apoptosis induced by an acute ischemia. This effect seems to be mediated in particular by α7- and β2-subunit containing nAChRs [36, 54]. Nicotine may also exert a trophic function in the survival of susceptible neurons during transient incidences of hypoxia/ischemia [142].

Finally, nicotinic agonists can, *in vivo*, rescue dopaminergic cell bodies the in substantia nigra [64] and nerve terminals in the striatum [41] and nucleus basalis from mechanical lesion, attenuates iNOS expression in spinal cord injury acting neuroprotectively [75], restore glucose utilization in lesioned areas [122, 146], counteract lesion-induced dopamine receptor up-regulation [63] and increase dopamine turnover rate [94, 105, 164, 172].

nAChRs-dependent and -independent neuroprotection

The neurotoxic and neuroprotective effects of nicotine and nicotinic agonists may be induced independently on stimulation of nAChRs or through binding to these receptors. In the latter case, activation of nAChRs may lead either directly to a neuroprotective effect or, alternatively, induce release of other neurotransmitters or neurotrophic factors, thus acting indirectly as an anti-apoptotic or anti-toxic agent.

Nicotine is a lipophilic substance that may enter neurons also without interacting with nAChRs. Some authors reported on neuroprotective effects of nicotine also after nAChRs blockade by nicotinic antagonists, thus suggesting that nicotine enters cells through the cytoplasmic membrane and directly activates intracellular second messenger cascades via nAChRs-independent signalling pathways [120].

The most neuroprotective effects of nicotinic agents are, however, mediated by nAChRs. nAChR binding may result either in direct entry of calcium in the cell from the extracellular compartment or in cell membrane depolarization, the latter leading to calcium entry through voltage-gated Ca^{++} channels or from intracellular stores. The activation of nAChRs may also decrease the levels and/or the activity of pro-apoptotic factors (e.g., caspases, jnk-kinase and cytochrome c) and/or enhance the function of anti-apoptotic agents such as Bcl-2 [129]. The increased production of the survival factor Bcl-2 is induced through the α7 nAChR-JAK2 pro-survival cascade and the transcriptional activation of NF-κB, AP-1, STAT1, STAT3 and STAT5. The increased production of Bcl-2 appears to fully counteract the Aß(1–42)-induced apoptosis of PC12 cells by blocking Aß(1–42)-induced mitochondrial release of cytosolic cytochrome c [88, 173].

Regarding the question as to whether particular nAChRs subtypes are involved in the nAChRs-mediated neuroprotective action of nicotinic agonists, the most studies indicated a central role of α7-subtypes [22, 29, 33, 36, 66, 67, 71, 146, 159] and, in some brain areas, α4β2. In a study investigating the effects of nicotine against 1-methyl-4-phenylpyridinium-induced toxicity in dopaminergic ventral mesencephalic cultures the partial protective effects of nicotine on nigral dopaminergic neurons seemed to occur through an interaction at non-α7-containing receptors [65]. α4β2-nAChRs seem to play a major role in cortical and striatal regions [73, 152], whereas nicotine-induced neuroprotection in the hippocampus and spinal cord may be mediated rather by the α7-subtype [29, 93].

The role of high affinity nAChRs seems to be essential not only in neuroprotection from toxic insults but also in normal aging for neuronal health. Animal experiments with knock-out mice have demonstrated that subjects lacking nAChR subunits (in particular β2) showed neocortical hypotrophy, loss of pyramidal neurons in the CA3 field in the hippocampus, and astro- and microgliosis in the neocortex and CA1-3 hippocampal fields [20, 131, 202, 207, 208].

Effects of nicotine and nicotinic agonists on neurotrophic factors and immune response

Through activation and release of neurotrophic factors and/or augmentation of their signalling as well as through modulation of the immune response nicotine may act indirectly as a neurotrophic agent.

Nicotinic stimulation of α4β2 nAChRs induces an increased release of fibroblast growth factor (FGF-2) in the striatum and enhances its concentration in several other brain regions such as the neocortex, hippocampus and substantia nigra of rats [9–12, 85, 86]. Nicotinic stimulation via local injection of nicotine in the hippocampus has been shown to up-regulate NGF and its receptor trkB, thus preventing cell death [40, 138]. NGF,

on the other hand, increases the mRNA level of PACAP (pituitary adenylate cyclase-activating polypeptide), another neurotrophic factor in CNS [185]. A depletion of nerve growth factor (NGF) induces, on the contrary, apoptosis.

Recently, attention has been focused on inflammatory and immunological effects of nicotine in CNS.

Actual results show that nicotine plays a role in the control of neuroinflammatory reactivity in astrocytes and indicate a connection between a dysfunction of nicotine Ca^{++} signalling in inflammatory reactive astrocytes and up-regulation of IL-1beta and the rearrangements of actin filaments in the cells [31].

A recent paper demonstrated that nicotine exposure selectively reduces numbers of CD11c(+) dendritic and CD11b(+) infiltrating monocytes and resident microglial cells in the CNS and down-regulates the expression of MHC class II, CD80 and CD 86 molecules on these cells. These results underscore the roles of nAChRs and nicotinic cholinergic signalling in inflammatory and immune responses [158]. Inflammatory and immunological pathways are involved in the protective action of nicotine on neural cells after intracerebral hemorrhage. Particularly the thrombin-induced pathological changes in cortico-striatal slice cultures are partially prevented by long-term treatment with nicotine. Nicotine acts neuroprotectively as well in reducing thrombin-induced neuron loss in the cortical region and tissue shrinkage in the striatal region, as well as in suppressing cytotoxic properties of activated microglia [116].

Role of intracellular Ca^{++} in nicotinic-induced neuroprotection

Once a nicotinic agonist has bound to an nAChR, a series of intracellular molecular cascades is activated. This leads, as final result, to an increase in cytoplasmic calcium levels. This cation can enter the cell through the activated nAChRs, which are mostly calcium channels (particularly α7-subtypes seem to have a high calcium conductance) [101, 137, 191] or via intracellular activation of voltage-gated calcium channels. A third mechanism is the nAChRs-induced release of calcium ions from intracellular stores (e.g., endoplasmic reticulum) in the cytosol [29, 93, 140, 175]. In any case, higher intracellular calcium concentrations have been measured in many studies after nicotine stimulation [6, 33, 38, 67, 175].

The dynamics of the intracellular calcium concentration seems, however, to be more complex. The cited studies present just some possibilities as to how intracellular calcium concentration can be increased by nicotine. A more complete analysis of the whole signalling cascades following nicotinic stimulation also considering nicotine's long-term effects, is necessary to better understand the calcium effects in target cells. High calcium levels are neurotoxic and lead to neurons' death. Neurons must, therefore, prevent excessively high intracellular calcium concentrations. The binding of nicotinic agonists to nAChRs causes, at least in the hippocampus, only a modest increase of intracellular calcium via the mechanisms described above. In order to maintain the calcium quantity in the "neuroprotective" range and avoid toxic calcium levels, a series of control mechanisms is in parallel activated. For instance, calcium buffering and expression of calcium-binding proteins are enhanced and reduce calcium levels in the cytosol.

It has been demonstrated that in hippocampal and cerebellar neurons nicotine does not regulate calcium entry through the classical stimulation of glutamate [29, 97], but decreases influx through L-type calcium channels in cortical neurons [175] and increases expression of the calcium-binding protein calbindin in the hippocampus [132, 192].

In sum, neurons stimulated with nicotine have, apparently, efficient regulation mechanisms which ensure optimal intracellular calcium levels for neuroprotection. High doses of nicotine may overstretch the regulatory possibilities of these systems and cause neuronal death.

The balance between protective low intracellular calcium concentration and toxic effects of large calcium signals could explain the different effects of low and high nicotine doses [129].

Neuroprotection or Neurotoxicity?

There is evidence that nicotine administration does not result always in neuroprotection. There is an amount of variables which determine the final (neurotrophic or neurotoxic) molecular effect in the target neurons. One of these factors may be the regimen of nicotine administration. It has been suggested that continuous treatment with nicotine is more likely to be neurotoxic for dopaminergic cells in the substantia nigra, whereas chronic intermittent treatment, which is more similar to nicotine intake from smoking, is more likely to be neuroprotective [8, 62]. Furthermore, continuous infusion of nicotine has been shown to decrease levels of FGF-2 in VTA [16], thus acting as a cytotoxic agent, whereas chronic intermittent nicotine injection increases levels of FGF-2 in the striatum and prevents neuronal death [9, 86].

In addition, the time course and route of administration of nicotine, as well as the nAChR subtypes expressed, may be critical in determining whether neuroprotection or neurotoxicity will occur in a particular cell population after nicotinic stimulation [129].

A still unsolved question is the apparently contradictory involvement of α7-nAChRs in nicotine-mediated neuroprotection and, at the same time, in excitotoxic cell death (see above). A possible interpretation of this finding is that α7-nAChRs-mediated neuronal effects are dose-dependent and follow an inverted U-shaped dose-response curve, with higher doses of nicotine resulting in either no effect or neurotoxicity and lower concentrations causing protection against cell loss [130].

Another unclear aspect is the neuroprotective action of nAChR antagonists. Although this matter has received little attention, numerous studies have shown that NMDA receptor blockers, such as MK-801, are neuroprotective against a wide variety of neurotoxic insults. Furthermore, the nAChR antagonist methyllycaconatine (a selective α7 blocker) shows neuroprotective properties in neonatal neurotoxicity [52, 73].

Final Considerations about Neuroprotective and Neurotoxic Effects of Nicotine

In the past 15 years the attention to the action and the roles of nicotine in CNS has constantly grown. Beyond the comprehension of the general physiology of cholinergic transmission and nAChRs in the brain, the interest has focused more and more on neuroprotection and neurotoxicity induced by nicotine with the aim to better understand the physiopathology of neurodegenerative diseases and develop new therapeutic approaches to AD and PD. Many studies have been conducted to date and some principles of the mechanisms underlying nicotinic neuroprotec-

tion and neurotoxicity are by now quite well known. In general, exposure to nicotine during neurodevelopment induces toxic, detrimental effects while nicotinic stimulation of developed neurons acts neurotrophic, anti-apoptotic, and cytoprotective. High doses of nicotine are, however, either ineffective or toxic also in adult neurons. Several experiments show nicotine-mediated protection with pre-exposure, rather than co-exposure or treatment after the toxic insult. This suggests that nicotine exposure may induce transcription of target molecules (potentially these could be calcium binding proteins, trophic factors, or their receptors), or alters the biochemical machinery of the target cell (potentially through phosphorylation of anti-apoptotic molecules or alteration of other signalling cascades). In the hippocampus and cerebellum, nicotine does not affect calcium entry into neurons, although this may not be the case in other cell types. However, the neuroprotective effect of nicotine is calcium-dependent also in these areas, suggesting that calcium entry is important for downstream signalling events mediated by nicotine. The most neuroprotective effects have been shown to be dependent on the α7 and/or α4/β2 nAChRs, although other receptors subunits may also play a minor role in particular brain areas. Some nAChRs (in particular α7) seem to have, according to the circumstances, neuroprotective as well as neurotoxical effects. The most actual studies about nicotinic action mechanisms in CNS postulate a central role of the mitochondrial oxidative metabolism and intracellular Ca^{++} in nicotine-induced neuroprotection and neurotoxicity. A new approach to nicotinic action in CNS considers the involvement of cholinergic transmission in neuroinflammatory and immunological mechanisms.

In contrast with the important knowledge already acquired, many questions are still unsolved. For instance, the role of α7 nAChRs stimulation both in neuroprotection and neurotoxicity and the effects of nAChR antagonists remain unclear.

Because of the importance of nicotine in the pathophysiology of neurodegenerative diseases and the growing incidence of these disorders due to the increasing average age in industrialized countries it seems important to intensify research in the field of nicotine-induced neuroprotection and neurotoxicity.

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