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Majdi, Alireza; Kamari, Farzin; Vafaei, Manouchehr Seyedi; Sadigh-Eteghad, Saeed

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Alireza Majdi, Farzin Kamari, Manouchehr Seyedi Vafae and Saeed Sadigh-Eteghad*

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Abstract: Brain ageing is a complex process which in its pathologic form is associated with learning and memory dysfunction or cognitive impairment. During ageing, changes in cholinergic innervations and reduced acetylcholinergic tonus may trigger a series of molecular pathways participating in oxidative stress, excitotoxicity, amyloid- β toxicity, apoptosis, neuroinflammation, and perturb neurotrophic factors in the brain. Nicotine is an exogenous agonist of nicotinic acetylcholine receptors (nAChRs) and acts as a pharmacological chaperone in the regulation of nAChR expression, potentially intervening in age-related changes in diverse molecular pathways leading to pathology. Although nicotine has therapeutic potential, paradoxical effects have been reported, possibly due to its inverted U-shape dose-response effects or pharmacokinetic factors. Additionally, nicotine administration should result in optimum therapeutic effects without imparting abuse potential or toxicity. Overall, this review aims to compile the previous and most recent data on nicotine and its effects on cognition-related mechanisms and age-related cognitive impairment.

Keywords: ageing; cognition; nicotine; therapy; toxicity.

Introduction

The population is ageing in many countries and brain ageing and age-related cognitive decline emerge as a major health care issue (Ferreira and Busatto, 2013). Brain ageing is a complex process involving numerous pathways and is associated with declining cognitive and

sensorimotor function (Mora, 2013). Grey matter volume declines with healthy ageing in association with specific molecular changes (Mora et al., 2007), yet unique features distinguish ageing of the brain from that of other tissues (Sibille, 2013). Some hypotheses have been put forward to explain the brain age-related cognitive decline in healthy elderly individuals. However, the detailed biological and neuronal bases of these changes are unclear and should, therefore, be better clarified (Whalley et al., 2004; Craik and Rose, 2012).

Despite the traditional view that assumes that brain ageing is accompanied by substantial loss of cortical neurons, recent studies have proposed that cognitive ageing could rather result from reduced plasticity of synaptic connections (Trachtenberg et al., 2002; Whalley et al., 2004). Besides, age-related changes may rise due to cumulative effects of reactive oxygen species (ROS) and free radicals derived from oxidative glycolysis. The consequent oxidative stress propagates alterations in lipids, proteins, and DNA structure, and disruption of calcium and mitochondrial function in association with neuroinflammation, which together contribute to age-related cognitive decline (Whalley et al., 2004; Sibille, 2013). Progressive accumulation of amyloid- β (A β) plaques in the ageing mammalian brain can also contribute to learning and memory deficits (Zahs and Ashe, 2013), even in the absence of Alzheimer's dementia. Other factors contributing to age-related cognitive decline include changes in neuroprotective peptide levels and neurotransmitter signalling, gliosis, and dendritic shrinkage (Glorioso and Sibille, 2011). Last but not least among proposed mechanisms for age-related cognitive decline is degenerative changes in cholinergic neurones resulting in cholinergic hypofunction and progressive memory loss (Schliebs and Arendt, 2011).

Nicotine is an alkaloid which is extracted from the tobacco plant. It binds to the nicotinic acetylcholine receptors (nAChRs) which are members of a pentameric ligand-gated ion channels activated by nicotine and endogenous acetylcholine (Powledge, 2004). Nicotine by actions at nAChRs evokes plasticity alterations in the cortico-limbic circuits and long-term synapse changes (Mansvelder et al., 2009). In addition to the main pharmacological effects, low doses of nicotine have a number of potentially nAChRs-mediated procognitive effects, as summarised in Table 1. Nicotine acts as an antioxidant reducing oxidative

*Corresponding author: Saeed Sadigh-Eteghad, Neurosciences Research Center, Tabriz University of Medical Sciences, 5166614756 Tabriz, Iran, e-mail: Saeed.sadigetegad@gmail.com

Alireza Majdi and Farzin Kamari: Neurosciences Research Center, Tabriz University of Medical Sciences, 5166614756 Tabriz, Iran

Manouchehr Seyedi Vafae: Neurosciences Research Center, Tabriz University of Medical Sciences, 5166614756 Tabriz, Iran; Department of Psychiatry, Clinical Institute, University of Southern Denmark, 5000 Odense, Denmark; and Department of Nuclear Medicine, Odense University Hospital, 5000 Odense, Denmark

Table 1: Clinical and preclinical studies of effects of nicotine on cognitive impairment in various neurological disorders.

Study type	Disease and/or model type	Outcome	Proposed mechanism(s)	Nicotine dose	Duration	Administration route	Reference
Clinical trials	AD patients	Cognitive improvement	Effects on synaptic plasticity within cortical regions	0.4–0.8 mg	3 sessions	Subcutaneous	Sahakian et al., 1989
	AD patients	Cognitive improvement	Only the middle dose improved the cognition through an undetermined mechanism	Three doses: 0.25 (low), 0.25 (mid), and 0.5 (high) µg/kg/min	3 sessions	Intravenous	Newhouse et al., 1988
Animal studies	MCI patients	Cognitive improvement	NM	15 mg/day	6 months	Transdermal	Newhouse et al., 2012
	AD patients	Cognitive improvement	NM	5–10 mg/day	1 month	Transdermal	White and Levin, 2004
	AD patients	Cognitive improvement	NM	5–10 mg/day	1 month	Transdermal	White and Levin, 1999
	AD patients	Cognitive improvement	NM	22 mg/day	22 days	Transdermal	Wilson et al., 1995
	Schizophrenic patients	Cognitive improvement	NM	Up to 4 nasal sprays	2–4 weeks	Nasal spray	Smith et al., 2006
	Schizophrenic patients	Cognitive improvement	Enhancing deficient nAChR function and dopaminergic activity	14 mg/day	2 days	Transdermal	Barr et al., 2008
	PD patients	No effect on cognitive deficits	Nicotine might not be specific in targeting nicotinic receptors involved in PD	7–21 mg/day	25 days	Transdermal	Lemay et al., 2004
	ADHD patients	Recognition memory improvement	Cholinergic and dopaminergic systems mediate nicotine's effects	7 mg for 45 min	2 days	Transdermal	Potter and Newhouse, 2008
	Rats with septal lesions	Spatial learning and memory improvement	Modulation of post- and presynaptic nAChRs in the hippocampus and enhancing dopamine, serotonin and norepinephrine release	0.1–0.3 mg/kg	15 days	Intraperitoneal	Decker et al., 1992
	Aged rats	Memory improvement	Involvement of nicotinic pathways in memory in aged rats	5 mg/kg per day	28 days	Subcutaneous	Levin and Torry, 1996
AD rat model	Spatial learning and memory improvement	Inhibition of the Aβ-induced prevention of basal synaptic transmission and the reduction of α7 and α4 nAChR upregulation of BDNF	2 mg/kg/twice a Day	6 weeks	Subcutaneous	Srivareerat et al., 2011	
Young and aged normal rats	Spatial learning and memory improvement	nAChRs mediated enhancement of alertness and/or integrative function	0.2 mg/kg/day	3 days	Intraperitoneal	Socci et al., 1995	
Depression model in rat	Cognitive improvement	NM	0.4 mg/kg/day	6 weeks	Intraperitoneal	Andreasen et al., 2011	
Normal NMRI mice	Spatial learning impairment	Especially features of NMRI strain and short duration of treatment	0.35 and 0.175 mg/kg	5 days	Subcutaneous	Moragrega et al., 2003	

The listed studies show that nicotine by enhancing effects on synaptic plasticity as well as deficient nAChR function, upregulation of BDNF, and prevention of Aβ-induced prevention of basal forebrain synaptic transmission could improve cognitive function in various neurological disorders as well as normal ageing. However, some studies failed to show the mentioned procognitive effects.

Aβ, amyloid-beta; AD, Alzheimer's disease; ADHD, attention deficit hyperactivity disorder; BDNF, brain-derived neurotrophic factor; MCI, mild cognitive impairment; nAChRs, nicotinic acetylcholine receptors; NM, not mentioned; NMRI, naval medical research institute; PD, Parkinson's disease.

stress (Guan et al., 2003). Furthermore, nicotine has anti-inflammatory effects and suppresses neuroinflammation (Nizri et al., 2009). Also, nicotine has neuroprotective properties through reducing A β aggregation in the brain (Nordberg et al., 2002).

In contrast to these various neuroprotective and pro-cognitive effects, some studies have reported that high doses of nicotine can induce cognitive, behavioural, and intellectual impairments (Matta et al., 2007; Ortega et al., 2013) emphasising the dose dependence of beneficial actions of nicotine.

Dependence and health risks are the two main issues connected with nicotine use. One of the issues about nicotine may be its influences on health. Nicotine is addictive, but cancer and other health problems of tobacco abuse mostly result from other components of the cigarette smoke such as carbon monoxide and tar (Russell, 1991; Le Houezec, 2003). It is these components as opposed to nicotine itself that eventually impair cerebral blood flow and oxygen metabolism of smokers (Vafae et al., 2015).

Although nicotine has direct toxic effects such as inducing fibrosis in various organ systems and cardiovascular abnormalities (Balakumar and Kaur, 2009; Jensen et al., 2012), these effects might be avoided by a more selective route of administration, i.e. intranasal. Moreover, the reinforcing and addictive properties of nicotine are mainly dependent upon the rate of absorption into circulation, as well as the dosage of administered nicotine. Indeed nicotine, when delivered through routes other than smoking, does not result in high plasma concentrations and is believed not to have high abuse potential (Hughes, 1998; Le Houezec, 2003).

This review aims to gather the previous and most recent data on nicotine and its effects on cognition-related mechanisms and age-related cognitive impairment.

Nicotine-receptor kinetics and dynamics

Nicotine is an alkaloid with both sympathetic and parasympathomimetic features that was first isolated from *Nicotiana tabacum* by Wilhelm Heinrich Posselt and Karl Ludwig Reimann in 1828 (Haass and Kübler, 1997; Dietz, 2016). Composed of pyridine and a pyrrolidine ring, nicotine has two enantiomeric forms. Its natural form is levorotatory ([−]-nicotine), and the other type is dextrorotatory ([+]-nicotine) which is physiologically less active but more toxic (Gause, 1941). Upon delivery by tobacco smoke, nicotine is quickly and extensively distributed

throughout the body by the bloodstream and crosses the blood-brain barrier within 10–20 seconds after inhalation. Due to first pass metabolism and distribution, the arterial plasma concentration declines rapidly to very low levels within minutes of smoking (Le Houezec, 2003). As distinct from smoking, nicotine administration by oral, transdermal, intravenous, and intraperitoneal routes evokes very gradual increases in the cerebral nicotine concentrations, with a lower brain-to-blood ratio (Henningfield, 1995). Nicotine is mainly metabolised by the liver to cotinine (70%) and nicotine-N'-oxide (4%) with an average elimination half-life of 2 h (Benowitz et al., 2002). Its minor metabolites are nicotine glucuronide, *trans*-3'-hydroxycotinine glucuronide, nicotine-N'-oxide, cotinine glucuronide, and *trans*-3'-hydroxycotinine which are less prevalent.

Nicotine, like acetylcholine, acts via nAChRs, which are a family of ligand-gated ion channels with permeability for Na⁺, K⁺, and Ca²⁺ ions. These nAChRs have a pentameric structure composed of α and β subunits, with specific neuronal forms predominating in the brain (Govind et al., 2009; Zouridakis et al., 2009). Clinical trials and animal studies have proved that administration of nicotine could improve cognitive functions through the activation of nAChRs (Table 1) (Barr et al., 2008). The primary forms of nAChRs in the brain are $\alpha_4\beta_2$ heteromers and α_7 homomers. The former has higher affinity to nicotine than the latter (Sadigh-Eteghad et al., 2015a, 2016b) and has the highest expression in the thalamus. In contrast, the α_7 nAChR is relatively common throughout the cerebral cortex, where it is poised to mediate pro-cognitive effects of nicotine and other agonists (Sadigh-Eteghad et al., 2015b). Therefore, selective α_7 nAChR agonists are considerably interesting targets in the treatment of cognitive impairment and Alzheimer's disease (AD) (Faghieh et al., 2007).

In addition to the direct pharmacological activation of nAChRs, nicotine also acts as a pharmacological chaperone of nAChRs, favouring their assembly, and this increases the expression level of functional pentamers in the brain which may subsequently mediate nicotine neuroprotective effects in the brain (Sadigh-Eteghad et al., 2015a).

Cholinergic degeneration

It has been accepted that cholinergic neurones participate in memory, learning, and attention (Levin et al., 2006; Arroyo et al., 2014), especially those in

the nucleus of Meynert of the basal forebrain, which innervate the hippocampus and cerebral cortex. This cholinergic nucleus undergoes degenerative alterations in the course of ageing, and the resulting hypofunction contributes to age-related cognitive deficits and memory loss (Dumas and Newhouse, 2011; Schliebs and Arendt, 2011; Bañuelos et al., 2013). Age-related cognitive impairments are caused not simply by the loss of cholinergic neurones of the basal forebrain, but also by the hypofunction of the remaining neurones and their associated synapses (Ypsilanti et al., 2008; Bañuelos et al., 2013).

Nicotine treatment has been shown to improve memory, learning, and attention through its facilitating effects on cholinergic neurotransmission both in clinical trials and animal studies (Table 1) (Potter and Newhouse, 2008; Arroyo et al., 2014; Logemann et al., 2014). These effects are mainly mediated through the α_7 and $\alpha_4\beta_2$ subtypes of nAChRs (Ortega et al., 2013; Arroyo et al., 2014). Post-mortem studies in smokers and also animal studies have shown that chronic nicotine administration upregulates high-affinity nAChRs in the brain (Fasoli et al., 2016). Evidence suggests that the nicotine-induced increase in the nAChRs is a two-phase process entailing fast (rapid and reversible) and long-lasting (slowed proteasomal degradation of subunits) phases (Govind et al., 2012). The activation-dependent increase in the receptor density is thought to be post-transcriptional (Sadigh-Eteghad et al., 2015b) where nicotine is considered to be a pharmacological chaperone, since the expression of mRNA encoding subunits is altered by nicotine administration in experimental animals (Marks et al., 1992; Sadigh-Eteghad et al., 2015a). It has been proposed that nicotine enhances the receptor transportation to the cell surface (Darsow et al., 2005), reduces their turnover in the cell membrane (Peng et al., 1994), decreases their endoplasmic reticulum (ER)-mediated degradation, and improves the assembly of subunits in the ER (Salette et al., 2005; Rezvani et al., 2007; Sadigh-Eteghad et al., 2016a) all via chaperone-mediated mechanisms.

Nicotine, by the activation of α_7 and non- α_7 nAChRs, causes an increase in the response of N-methyl-D-aspartate receptors to glutamate and consequent long-term potentiation (LTP), which is an essential substrate of memory (Yamazaki et al., 2002; Nakauchi and Sumikawa, 2012). Nicotine-induced enhancement of LTP seems to involve the NMDA-mediated activation of protein kinase A and extracellular signal-regulated kinase 1/2 (ERK1/2) signalling pathways that together mediate plasticity-related alterations of long-term memory (Sweatt, 2004; Gould et al., 2014).

Potentialiation of cholinergic signalling by nicotine and other nAChR agonists has been implicated in the treatment of various neurodegenerative and non-neurodegenerative disorders that primarily or secondarily affect this system (Mufson et al., 2008; Quik et al., 2008; Liepelt et al., 2010; Oz et al., 2016). Thus, it seems that the cholinergic properties of nicotine may favour its use in the treatment of age-related cognitive deficits and memory loss.

Oxidative stress

Oxidative stress is a phenomenon resulting from an imbalance between ROS production and antioxidant as well as free radical scavenging systems (Majdi et al., 2016b). Oxidative stress, in particular, the iron-mediated oxidative brain damage, seems to be a crucial factor in provoking neuronal death and is thus implicated in many age-related neurodegenerative disorders including AD and Parkinson's diseases (PD) (Padurariu et al., 2010; Vaya, 2013; Ward et al., 2014). Furthermore, due to the brain's higher oxygen metabolism and limited capacity of regeneration, oxidative stress (Ward et al., 2014; Daugherty and Raz, 2015) is considered an important role player in the brain ageing and its associated cognitive and functional impairment (Haddadi et al., 2014). Although nicotine properties regarding oxidative stress and neuroprotection are controversial, and may be complicated by inverted U-shaped dose-response curves (Guan et al., 2003; Matta et al., 2007), several studies have reported antioxidant effects of nicotine on neurodegenerative disorders such as AD and PD (Ferber et al., 1998; Linert et al., 1999; Pachauri and Flora, 2013). It has been shown that nicotine administration under certain circumstances can reduce ROS-mediated lipid peroxidation *in vivo* and *in vitro* (Soto-Otero et al., 2002; Guan et al., 2003). This may result from nicotine ability to chelate Fe^{2+} via the pyridine nitrogen and thus inhibit the Fenton reaction which is involved in the formation of hydroxyl free radicals (Ferber et al., 1998; Soto-Otero et al., 2002). Other studies have confirmed the ability of nicotine to chelate iron and prevent the Fenton reaction, and also suggest that nicotine may bind to Fe^{2+} on the proinflammatory thromboxane synthase enzyme and prevent it from functioning (Goerig et al., 1992; Linert et al., 1999).

On the other hand, some studies failed to show the negative effect of nicotine on ROS formation and lipid peroxidation (Bhagwat et al., 1998; Yildiz et al., 1998; Linert et al., 1999; Guan et al., 2003). Indeed, in some circumstances, nicotine administration interferes with

the respiratory chain in mitochondria which subsequently escalates ROS production resulting in oxidative stress (Guan et al., 2003). Nicotine has also been shown to increase malondialdehyde and lactate dehydrogenase activity, which can trigger lipid peroxidation (Song et al., 2016). Furthermore, nicotine is a substrate for cytochrome P-450 enzymes which might provoke intracellular oxidative stress (Yildiz et al., 1998; Guan et al., 2003).

These discrepant reports may reflect many contributing factors including nicotine dose (high or low), and choice of enantiomer as well as brain region-specific effects (Yildiz et al., 1998; Guan et al., 2003; Song et al., 2016). It has been claimed that nicotine effect on oxidative stress is dose dependent prompting antioxidant effects at low doses while exacerbating oxidative stress at a high dose (Guan et al., 2003). Moreover, it has been reported that nicotine-induced changes in antioxidant-system-related gene expression differ between brain regions (Song et al., 2016). It has been claimed that differences in the metabolism rate and major metabolites of nicotine enantiomers, i.e. (-)- and (+)-nicotine, result in enantiomer-specific differences in the amounts of free radical generation, which might explain why nicotine shows opposing effects on oxidative stress in various studies (Yildiz et al., 1998). However, the main findings presented above generally support a beneficial effect of nicotine on oxidative stress, which may favour its potential use as a treatment for age-related cognitive impairment.

Neuroinflammation

Ageing is associated with alterations in the immune system that generally promote proinflammatory cytokines and neuroinflammation process in the brain (Godbout and Johnson, 2009). Neuroinflammation has been implicated in the pathophysiology of many age-related neurodegenerative disorders such as AD and PD (Blasko et al., 2004; Shytle et al., 2004). Neuroinflammation associated with ageing decreases neuronal plasticity and neuronal regenerative capacity, with long-term effects on cognitive function (Godbout and Johnson, 2009; Russo et al., 2011).

Preclinical studies have shown that administration of nicotine reduces neuroinflammation in the brain (Hao et al., 2011). This action may be mediated by the effects of systemic nicotine administration in preventing T-cell proliferation in peripheral tissue and their infiltration to the brain. In addition, nicotine changes the production profile of TNF- α , IL-1 β , IL-6, MIP-2/CXCL2, MIP 1 α /CCL3, and eotaxin/CCL11 in T-helper cells; all of these factors

may disfavour inflammation (Shi et al., 2009; Hao et al., 2011; Han and Lau, 2014; Wei et al., 2015).

Microglia are the resident macrophages of the brain and serve to mediate innate immunity of the nervous system. There is evidence that nicotine administration decreases microglial activation to a remarkable extent. Given that cholinergic neurone degeneration with age is accompanied by enhanced microglial activation, this suggests a mechanism for neuroprotection (Shytle et al., 2004). Furthermore, nicotine reduces the production of certain inflammatory cytokines (such as IL-6 and TNF- α) production in astrocytes, which also disfavours neuroinflammation in the brain (Sadigh-Eteghad et al., 2016b).

The nicotine-induced decrease in CNS neuroinflammation is thought to be mediated by nAChRs (Wei et al., 2015). Among the nAChRs mediating anti-inflammatory features of nicotine, the α_7 subtype of these receptors merits special attention (Pavlov and Tracey, 2006; Bencherif et al., 2011; Han and Lau, 2014). Activation of α_7 nAChRs expressed by microglia and T cells temporarily upregulates Ca²⁺ levels inside these cells, which subsequently decreases the phosphorylation of the mitogen-activated protein kinases (MAPKs) p38 and p44 with the consequent reduction in the expression of proinflammatory cytokine protein expression (Shytle et al., 2004; Suzuki et al., 2006; Razani-Boroujerdi et al., 2007). Additionally, the activation of α_7 nAChRs in monocytes or macrophages has a number of effects disfavoring neuroinflammation: (1) prevention of the phosphorylation of I κ B, an NF- κ B inhibitor, (2) activation of adenylate cyclase 6, and (3) recruitment of Janus kinase 2 (JAK2), all of which initiate cascades of interactions that finally downregulate the NF- κ B signalling pathway and reduce proinflammatory cytokine expression (Figure 1) (Yoshikawa et al., 2006; Marrero and Bencherif, 2009; Nizri et al., 2009; Han and Lau, 2014). In addition, α_7 nAChRs also mediate the nicotine-induced decrease in inflammatory cytokine production in astrocytes (Liu et al., 2012).

In summary, the anti-inflammatory characteristics of the nicotine molecule make it a promising agent to prevent or attenuate age-induced neuroinflammation in the brain.

Amyloid- β

Considerable evidence shows that A β and its aggregates are factors in brain ageing (Fukumoto et al., 1996; Rodriguez et al., 2012). In particular, experimental senescence-accelerated animals have higher amyloid precursor protein (APP) and A β levels that are in association with

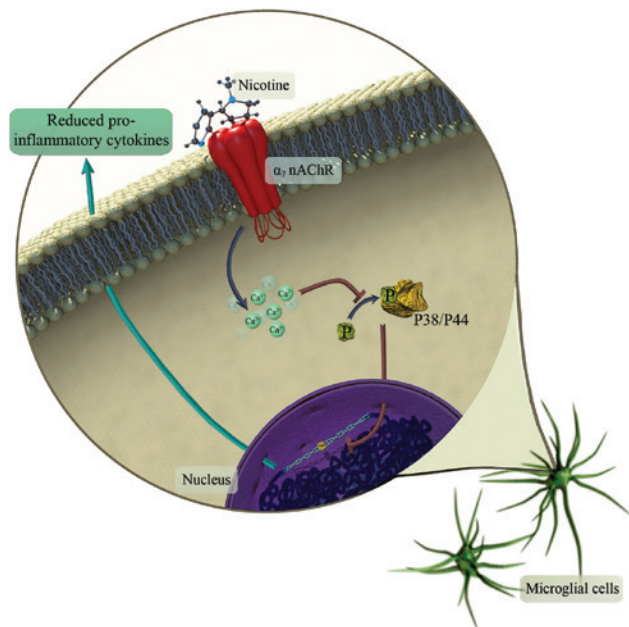


Figure 1: α_7 nAChRs mediate anti-inflammatory features of nicotine. The activation of α_7 nAChRs in microglia temporarily upregulates calcium levels inside these cells, thus decreasing the phosphorylation of mitogen-activated protein kinases (MAPKs) p38 and p44 which subsequently reduces expression of proinflammatory cytokines.

learning as well as memory impairments at younger ages (Morley et al., 2000; Zahs and Ashe, 2013). Promising pre-clinical studies have shown that administration of anti-A β antibody injection reduces cognitive impairments in these animals (Kumar et al., 2000; Banks et al., 2001), although recent clinical trials with similar antibodies have failed to show disease-modifying benefits in patients with AD (Holmes et al., 2008).

Accumulating evidence shows that nicotine treatment both in the short and long run significantly reduces A β depositions and plaque burden in transgenic mouse brain (Nordberg et al., 2002; Court et al., 2004). This reduction in the A β plaque density includes both parenchymal and vascular depositions. Several mechanisms have been reported to be responsible for this phenomenon. In particular, nicotine administration increases the total amount of APP in the cerebrospinal fluid which presumably disfavours amyloidogenesis due to enhanced clearance. However, it is not clear whether nicotine effects on A β clearance are direct (Utsuki et al., 2002), or related to increased overflow to the cerebrospinal fluid. Nicotine may also favour the decomposition of amyloid fibrils, thus interfering in the accumulation of A β plaques (Nordberg et al., 2002; Ono et al., 2002). Improved cholinergic function by nicotine agonism at AChRs might also contribute

to reduced A β depositions with a particular involvement of the α_7 receptor subtype. It has been suggested that a direct interaction between A β and α_7 AChRs results in increased A β -induced MAPK activation and subsequently cAMP-regulatory element-binding protein phosphorylation with the downstream effect of attenuating A β depositions (Beach et al., 2001; Dineley et al., 2001; Nordberg et al., 2002).

Chronic nicotine treatment might also exert neuroprotective influence against pre- and postsynaptic injuries caused by A β oligomers or amyloidosis at the pre-plaque stage. This potential effect is thought to be mediated by the interaction between α_7 nAChRs and the PI3-K/Akt signalling pathway in the pre- and postsynaptic elements (Inestrosa et al., 2013; Sadigh-Eteghad et al., 2014). Also, the activation of α_7 nAChRs through nicotine administration activates the Wnt/b-catenin signalling pathway that is thought to have a major role in protection against A β aggregates in the brain (Inestrosa et al., 2012, 2013).

Overall, it is highly possible that nicotine may diminish the A β plaque load and oligomer concentration in the ageing brain and thus exert neuroprotective effects against A β -induced injury and cognitive impairment.

Neurotrophic factors and neuroprotection

The neurotrophic factors are members of a family of proteins which includes, but is not limited to, brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell line-derived neurotrophic factor (GDNF). These factors together play a significant role in the development, differentiation, survival, and function of neurones (Skaper, 2012; de Azevedo Cardoso et al., 2014; Harada and Harada, 2014). The production of neurotrophic factors normally declines through time in the ageing brain (Erraji-Benchekroun et al., 2005). Evidence suggests that these factors, notably BDNF and related downstream pathways, may present novel and exciting therapeutic interventions for treating age-related brain changes and cognitive deficits (Glorioso and Sibille, 2011; Lu et al., 2014; Pourmemar et al., 2017).

Accumulating evidence shows that nicotine can itself exert neurotrophic effects and together with nAChRs may have a crucial role in the development and maturation of neurones (Ferrea and Winterer, 2009). As noted above, nicotine activates α_7 nAChRs and can increase NGF expression through NF- κ B-dependent pathways

(Martínez-Rodríguez et al., 2003; Hernandez and Terry, 2005; Wongtrakool et al., 2014). Indeed, nicotine increases the nuclear translocation and transcriptional activity of NF- κ B and enhances p65 attachment to the promoter region of the NGF gene which ultimately increases NGF expression (Wongtrakool et al., 2014). Additionally, nicotine increases expression of mRNA for tyrosine receptor kinase A mRNA expression which mediates effects of NGF in the neurones (Garrido et al., 2003). NGF then exerts neuroprotective effects by promoting synaptic plasticity while attenuating glutamate-induced excitotoxicity (Figure 2) (Martínez-Rodríguez et al., 2003). Studies have also shown positive effects of NGF on learning and memory that further substantiate its neuroprotective properties (Fischer et al., 1991; De Rosa et al., 2005).

In addition to these aforementioned effects, there is evidence that certain doses of nicotine can increase BDNF levels in both the hippocampus and the neocortex (Czubak et al., 2009). Administration of an α_7 nAChRs selective antagonist (α -bungarotoxin) reduces BDNF mRNA expression in the brain which strongly suggests that the nicotine-induced increase in the BDNF level might be mediated through α_7 nAChRs (Freedman et al., 1993). Other lines of evidence show that BDNF is an important role player in the formation of memory traces

in the hippocampus and can affect LTP (Tyler et al., 2002; Yamada et al., 2002; Czubak et al., 2007). Similar effects of nicotine have been reported for GDNF levels, a cytokine which has been shown to enhance memory in animal models (Xiaolin et al., 2002; LI et al., 2005).

Accordingly, it appears that nicotine in a time-dependent manner through its positive effects on neurotrophins can improve memory and learning impairments which can arise as part of brain ageing.

Apoptosis

Apoptosis or programmed cell death is an energy-dependent cell suicide program in which the targeted cell is eliminated without the inflammation that usually occurs in necrotic degeneration (Kiss, 2010; Majdi et al., 2016b). While apoptosis is an essential element of brain development, aberrant or pathologic apoptosis has been linked to many neurodegenerative disorders (Majdi et al., 2016b). Furthermore, it has been shown that brain ageing makes the brain more vulnerable to apoptosis-induced neuronal damage (Adams et al., 1996; Chen et al., 2013) which may involve in age-induced cognitive impairment (Wozniak et al., 2004; Chen et al., 2013).

Since nicotine prevents apoptosis, it has been called the 'survival agonist' (Mai et al., 2003; Tizabi et al., 2005). Mounting evidence indicates that nicotine protects neurones against apoptosis through both caspase-dependent and -independent pathways (Yu et al., 2011). Nicotine administration inhibits caspase-3, -8, and -9 activation, and hence blocks the caspase-dependent pathway (Liu and Zhao, 2004; Tizabi et al., 2005). It also blocks the release of apoptosis-inducing factors released from mitochondria and their translocation to the nucleus which may be mediated through α_7 nAChRs activation (Garrido et al., 2001; Yu et al., 2011). Evidence suggests that the α_7 nAChRs are not the only subtype involved in anti-apoptotic effects of nicotine; the $\alpha_4\beta_2$ subtype, which has a wider distribution in the brain and higher affinity to nicotine, may similarly mediate these anti-apoptotic effects (Hejmadi et al., 2003).

Nicotine-mediated anti-apoptotic effects may also be rendered by MAPK and ERK-2 cascade activation which has an important role in regulating cell growth and apoptosis (Heusch and Maneckjee, 1998; Garrido et al., 2001). Even though one study had proposed that changes in the anti-apoptotic Bcl-2 protein levels may not be involved in the anti-apoptotic effects of nicotine (Garrido et al., 2001), a more recent survey showed that

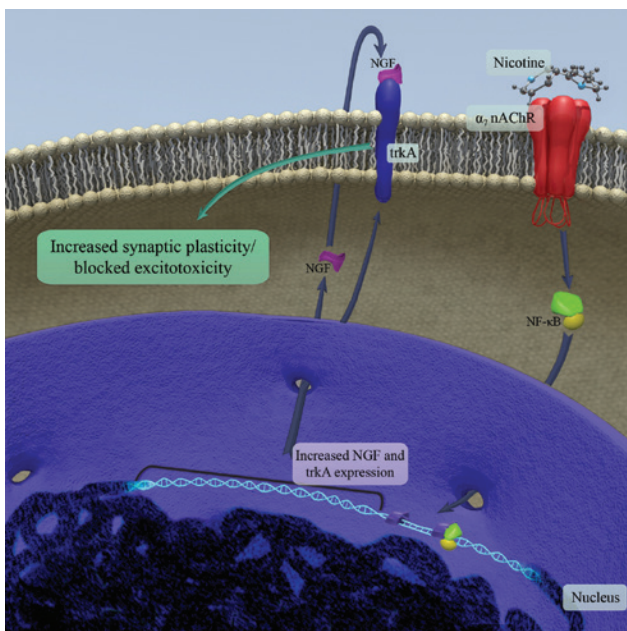


Figure 2: α_7 nAChRs mediate neuroprotective features of nicotine. Nicotine activates α_7 nAChRs and increases the nuclear translocation and transcriptional activity of NF- κ B, which ultimately increases NGF expression. Also, nicotine increases tyrosine receptor kinase A (trkA) mRNA expression, which mediates NGF effects in the neurones.

Bcl-2 participate in nicotine-mediated anti-apoptotic effects via the α_7 nAChR/JAK2/STAT3/NF- κ B/Bcl-2 signalling pathway in neurones (Marrero and Bencherif, 2009). Furthermore, nicotine reduces neuronal nitric oxide synthase activity and nitric oxide production, which may contribute to its anti-apoptotic effects, in addition to less specific ROS-mediated effects (Figure 3) (Garrido et al., 2001).

It seems that nicotine, when administered at appropriate certain doses to a developed brain, may halt age-induced neuronal apoptosis and accordingly may reduce its consequent cognitive impairments.

Excitotoxicity

Excitotoxicity is a glutamate-mediated neuronal injury resulting in excessive neuronal signalling, and an increase in the intracellular Ca^{2+} and neurotoxic effects (Majdi et al., 2016a). It has been demonstrated that brain ageing is accompanied with dysregulation of calcium homeostasis (Toescu et al., 2004), which leads to an increase in the susceptibility of hippocampal neurones to excitotoxicity (McEwen, 2000). This dysregulation may eventually lead

to structural changes in hippocampal neurones resulting in cognitive impairment and memory loss (Toescu et al., 2004; Esposito et al., 2013).

Nicotine has shown anti-excitotoxic effects through a calcium-dependent pathway that is mediated via α_7 nAChRs (Shimohama et al., 1998; Dajas-Bailador et al., 2000; Corsini et al., 2016). This may result from the modulatory effects of α_7 nAChRs on the glutamate-induced prevention of the PI3-K/Akt pathway (Cui et al., 2013). Disinhibition of the PI3-K/Akt pathway then upregulates Bcl-2 and Bcl-x levels and subsequently inhibits neuronal death (Shimohama, 2009). The activation of α_7 nAChRs also results in NMDA receptor internalisation, bringing about a reduction of their numbers presented on the cell surface. This may itself be responsible for the decrease in glutamate-induced Ca^{2+} influx and following caspase-3 activation and neuronal damage (Figure 4) (Shen et al., 2010).

Hence, anti-excitotoxic effects of nicotine seem to mediate neuroprotective effects against ageing, again indicating nicotine as a treatment strategy in cognitive impairment due to ageing.

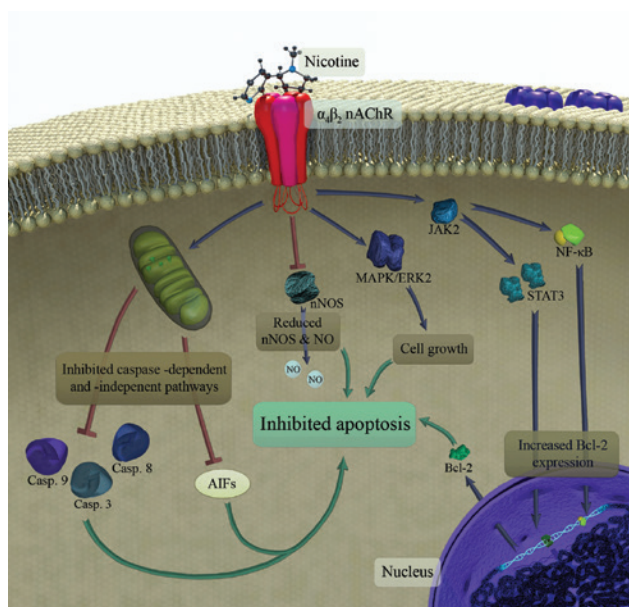


Figure 3: $\alpha_4\beta_2/\alpha_7$ nAChRs mediate anti-apoptotic features of nicotine. Nicotine administration inhibits caspase-3, -8 and -9 activation, and hence blocks the caspase-dependent pathway, activates MAPK and ERK-2 and α_7 nAChR/JAK2/STAT3/NF- κ B/Bcl-2 signalling pathways and reduces neuronal nitric oxide synthase (nNOS) expression and nitric oxide (NO) production which together may contribute to its anti-apoptotic effects.

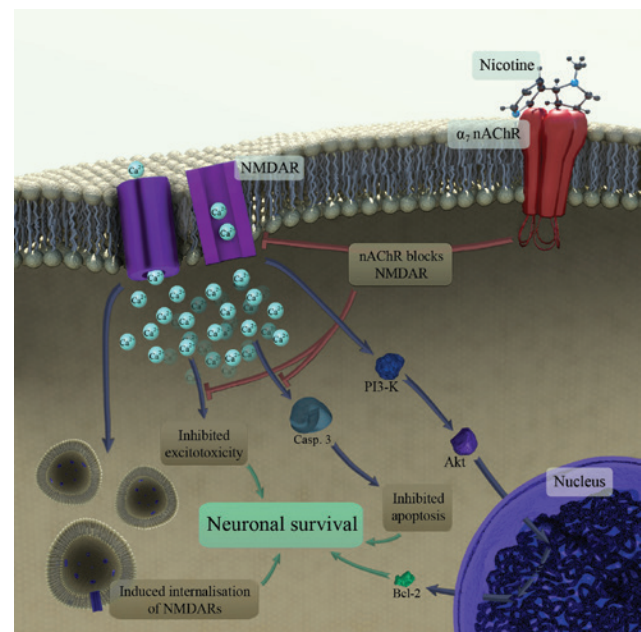


Figure 4: α_7 nAChRs mediate anti-excitotoxic features of nicotine. Nicotine activates α_7 nAChRs, which then exert modulatory effects on the glutamate-induced inhibition of activation of the PI3-K/Akt pathway. Net activation of the PI3-K/Akt pathway then upregulates Bcl-2 and Bcl-x levels and, subsequently, inhibits neuronal death. α_7 nAChR activation also results in increased internalisation of NMDA receptors, thus reducing their numbers presented on the cell surface. This effect may be responsible for the decrease in glutamate-induced Ca^{2+} influx and following caspase-3 activation and neuronal damage.

Nicotine and addiction

One of the biggest obstacles in using nicotine therapeutically in the age-induced cognitive impairments is the risk of nicotine dependence (ND). It has been shown that ND is mediated through particular nAChRs. When nicotine binds to nAChRs, it exerts a dual effect; binding initially induces a series of transient conformational changes that rapidly opens the receptor which is soon followed by the desensitisation phase, during which the receptor closes and becomes unresponsive to nicotine (Govind et al., 2009; Papke et al., 2009). This state is also transient unless there is chronic exposure to nicotine in which event the nAChRs undergo long-term expression changes (Eilers et al., 1997). Accumulating evidence shows that after the withdrawal of nicotine after chronic exposure, high-affinity nAChRs are functionally upregulated, which may be a long-term consequence of the desensitisation described above (Buisson and Bertrand, 2002). It has been proposed that the number of nAChRs and also their sensitivity to nicotine both increase and decrease due to factors such as receptor degradation in the ER, changes in the stoichiometry of receptors' subunits, and slowing of the surface turnover of the receptors (Wonnacott, 1990; Dani and Heinemann, 1996). These observations are not contradictory and may signify the importance of nicotine dosage, duration of exposure, and the type of receptor (Govind et al., 2009).

The α_4 , α_6 , and β_2 subunits-containing nAChRs are expressed on the soma and presynaptic terminals of dopamine neurons of the ventral tegmental area, which provide an innervation of the ventral striatum, where dopamine signalling mediates aspects of reward and reinforcement. The $\alpha_4\beta_2$ nAChRs regulate dopamine release and α_4/β_2 -knocked-out mice do not self-administer nicotine during experiments (Maskos et al., 2005; Pons et al., 2008). Although the α_7 nAChRs are involved in the rewarding effects of nicotine, this is distinct from ND, which is mediated by other factors (Markou and Paterson, 2001) including classical conditioning.

Upon the activation of these receptors by nicotine, the release of many neurotransmitters such as acetylcholine, glutamate, noradrenaline, and dopamine is enhanced in the brain which results in behavioural consequences such as the long-term dependence (Berrendero et al., 2010). Dopamine, glutamate, and type 1 cannabinoid receptors are involved in the rewarding effects of nicotine (Liechti and Markou, 2008; Scherma et al., 2008; Benowitz, 2010; Berrendero et al., 2010).

It has been shown that the rate and route of nicotine administration both play a significant role in the degree of

dependence that develops (Matta et al., 2007); the faster nicotine administered, the greater the risk for dependence it causes, which explains why inhalation of nicotine in tobacco smoke is more addictive than other routes of delivery. This phenomenon may result from the activation of various neuronal circuits and cell types according to the different routes of nicotine delivery (Samaha and Robinson, 2005). Furthermore, the target concentration of nicotine achieved in the brain may also affect nicotine-induced dependence (Matta et al., 2007). Studies support the concept of 'inverted U dose-response relationship' for nicotine, in which low and suboptimal doses of nicotine do not produce effective molecular and behavioural influences on the subject, whereas excessively high doses result in attenuated or adverse effects. Thus, the therapeutic window for pharmacological effects of nicotine is very narrow (Picciotto, 2003), which may explain the contradictory results of studies that have assessed ND and therapeutic benefits. This, in addition to ND, may explain why nicotine with so many positive effects on cognition has not become a therapeutic agent in the treatment of age-related cognitive decline.

Conclusions

It can be concluded that although nicotine's procognitive and therapeutic effects have been investigated in various animal and clinical studies in healthy or diseased conditions, their true nature remains controversial. It seems that under optimal circumstances nicotine treatment can ameliorate age-related cognitive impairment through a combination of nAChR-dependent and -independent mechanisms. Nicotine has a direct effect in modulating oxidative stress, excitotoxicity, A β toxicity, apoptotic pathways, and neuroinflammation, as well as the expression of neurotrophic factors. Moreover, some paradoxical effects of nicotine may arise from its inverted U-shaped dose-response effects, and form complex pharmacodynamical factors. As such, sustained release delivery routes of nicotine at tightly controlled doses may result in optimum therapeutic effects and plasma concentrations without high abuse potential or the toxicity associated with tobacco consumption. The optimum treatment parameters furnishing the best efficacy and safety should be determined in the future pre-clinical studies leading eventually to the design of clinical trials.

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