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Nicotinic receptor agonists as neuroprotective/neurotrophic drugs. Progress in molecular mechanisms

G. Mudo[1], N. Belluardo[1], K. Fuxe[2]

[1] Department of Experimental Medicine, Section of Human Physiology, University of Palermo, Palermo, Italy
[2] Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden

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Summary In the present work we reviewed recent advances concerning neuroprotective/neurotrophic effects of acute or chronic nicotine exposure, and the signalling pathways mediating these effects, including mechanisms implicated in nicotine addiction and nAChR desensitization. Experimental and clinical data largely indicate long-lasting effects of nicotine and nicotinic agonists that imply a neuroprotective/neurotrophic role of nAChR activation, involving mainly α7 and α4β2 nAChR subtypes, as evidenced using selective nAChR agonists. Compounds interacting with neuronal nAChRs have the potential to be neuroprotective 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. Nicotine addiction, which is mediated by interaction with nACh receptors, is believed to involve the modification of signalling cascades that modulate synaptic plasticity and gene expression. Desensitization, in addition to protecting cells from uncontrolled excitation, is recently considered as a form of signal plasticity. nAChR can generate these longe-lasting effects by elaboration of complex intracellular signals that mediate medium to long-term events crucial for neuronal maintenance, survival and regeneration. Although a comprehensive survey of the gene-based molecular mechanisms that underlie nicotine effects has yet not been performed a growing amount of data is beginning to improve our understanding of signalling mechanisms that lead to neurotrophic/neuroprotective responses. Evidence for an involvement of the fibroblast growth factor-2 gene in nAChR mechanisms mediating neuronal survival, trophism and plasticity has been obtained. However, more work is needed to establish the mechanisms involved in the effects of nicotinic receptor subtype activation from cognition-enhancing and neurotrophic effects to smoking behaviour and to determine more precisely the therapeutic objectives in potential nicotinic drug treatments of neurodegenerative diseases.

Keywords: nAChR, nicotinic agonists, neurotrophic factors, FGF-2, neuroprotection, neurotrophism, addiction, desensitization, neuroplasticity

Nicotinic acetylcholine receptors

Neuronal nicotinic acetylcholine receptors (nAChRs) belong to the superfamily of ligand-gated ion channels and are located in both the peripheral and central nervous systems. They are composed of five subunits and at present nine nicotinic receptor α subunits (α2–α10) and three β subunits (β2–β4) have been identified, each encoded by a different gene (Picciotto et al., 2001). In heterologous expression nAChR can contain more than one of the α2, α3, α4 or α6 subunits and/or both β2 and β4 subunits as well (Couturier et al., 1990). Accordingly, several different combinations of nAChR subunit mRNA and/or proteins have been identified in the central and peripheral nervous structures (Le Novere et al., 2002). The subunits α7, α8, α9, and α10 subunits can form homomeric receptors (Le Novere and Changeux, 1995). These multiple combinations of nAChR subunits possess distinct pharmacological and physiological properties. Thus nAChRs show different affinity for ligands, variability of permeability for cations and rate of desensitization (Changeux et al., 1998).

The distribution of neuronal nAChR in the CNS differs for the different subunits and the most common subunit arrangements within the central nervous system include the α4/β2 type receptor and the α7 type receptor. The α4 and β2 are present in the entire nervous system (Wada et al., 1989). By contrast the distribution of α7 subunit mRNA is restricted to certain layers of cerebral cortex, to the hypothalamus, hippocampus and to some brain stem nuclei (Seguela et al., 1993). nAChR containing other subunits are localized in important brain regions, but they are less abundant. The α2 subunit is expressed at very low levels in restricted brain regions (Wada et al., 1989). The α5 subunit mRNA is expressed at high levels in neurons of the subiculum, pre- and parasubiculum, substantia nigra, ventral tegmental area, and weakly expressed in the cerebral

Correspondence: Giuseppa Mudo, Department of Experimental Medicine, Section of Human Physiology, University of Palermo, 90127 Palermo, Italy
e-mail: g.mudo@unipa.it

cortex (Wada et al., 1990). The α3 and β4 subunits, which form the main nAChR responsible for nicotinic synaptic transmission in autonomic ganglia, are highly enriched in the medial habenula (Le Novere and Changeux, 1995). The α6 and β3 subunits are highly and selectively enriched in catecolaminergic nuclei, such as the dopaminergic neurons of the substantia nigra, and the noradrenergic neurons of the locus coeruleus (Le Novere and Changeux, 1995). It has therefore been proposed that they can form, together with other subunits, the nAChR responsible for catecholamine release in the basal ganglia and hippocampus (Le Novere and Changeux, 1995). nAChRs located presynaptically regulate the release of serotonin, dopamine, norepinephrine (Summers and Giacobini, 1995), glutamate (Gray et al., 1996), gamma-aminobutyric acid (Ji and Dani, 2000) and acetylcholine (Tani et al., 1998). The α4/β2 nicotinic receptor binds nicotine with high affinity, while the α7 nicotinic receptor binds nicotine with a low affinity (Lena and Changeux, 1998). When agonists bind to the nAChR, the receptor complex undergoes a conformational change in its structure, which allows the channel gate to open, permitting the passage of cations through the channel pore. However functionally, the nAChR complex can exist in three conformational states, which are dynamically regulated by exposure to the agonist: closed, open and desensitized states.

Neuroprotective/neurotrophic effects of nAChR activation

Recently an increasing number of potent nAChR agonists have been used in experimental research and clinical trials, and have been found displaying efficacy and/or a more selective affinity than nicotine for neuronal nAChR subtypes, some of which are considered potential candidates not only for the treatment of neurodegenerative disease such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Bannon et al., 1998), but also, as discussed below, for cognitive disorders associated with Schizophrenia (Kem, 2000).

A growing number of *in vivo* and *in vitro* findings have shown that nAChRs activation have the potential to be neuroprotective/neurotrophic.

Evidence in vivo

nAChRs have important roles in development and synaptic plasticity (Broide and Leslie, 1999; Levin et al., 1999). α7 nAChRs are expressed early in development and have been shown to be important for the control of neurite outgrowth, and are involved in events of synaptic remodelling in the adult nervous system (Pugh and Berg, 1994). The high concentration of α7 receptors in the hippocampus, a region of the brain that is critical for memory, also supports a role for α7 receptors in the modulation of synaptic plasticity and in memory formation (Small et al., 2001). Nicotinic receptors can modulate the rhythmic activity important for synaptic plasticity, the basis for learning and memory (Huerta and Lisman, 1993).

Many studies have analysed the effect of nAChR agonists and antagonists on cognitive performance in a variety of behavioural tests in rats, monkeys and humans, and their specific involvement in cognitive function, such as attention, learning, sensory perception, memory consolidation and arousal has been reported (Levin and Simon, 1998). The nAChR agonist nicotine improves cognition for prolonged periods in non-human primates and in rodents even after nicotine discontinuation (Gould and Stephen, 2003; Buccafusco et al., 2005). By contrast, a blockade of nicotinic receptors by a nicotinic receptor antagonist impairs memory function (Levin and Rezvani, 2000).

Performance in attention and working memory tasks is improved by nicotine (Gioanni et al., 1999; Levin et al., 2002), and involves multiple brain areas, such as hippocampus, amygdala, and particularly the prefrontal cortex that has been implicated in attention and working memory and goal-directed behaviour (Groenewegen and Uylings, 2000). Epibatidine has been found to induce Long-term potentiation (LTP), improve memory and learning in human and experimental animal models and to be neuroprotective in several *in vitro* models (Jonnala et al., 2002) and both α7 and α4β2 nAChRs are essential for these effects. The GTS-21 nicotinic agonist with potent functional selectivity for the α7 nAChR subtype improves memory performance in several tests, such as one-way active avoidance, Lashley III maze testing, and 17 arm radial maze test performance in aged rats, and improve cognitive and perceptual disturbances in schizophrenia (Arendash et al., 1995). The nicotinic agonist SIB-1508Y, selective for α4β2, and the nicotinic agonist SIB-1553A, active at β4 nAChRs, exhibit ability to improve cognitive activity and learning in a variety of models and to promote locomotor activity (Vernier et al., 1999), with long-lasting effects, in chronic low-dose MPTP-treated monkeys (Schneider et al., 2003). In addition, functional magnetic resonance imaging studies have shown increased activation of frontal networks by nicotine administration during attention tasks (Lawrence et al., 2002). Nicotinic receptor function may also be critical for maintenance of cognitive function during aging. Increased neurodegeneration is seen in aged

β2 subunit knockout mice and is associated with learning deficits as shown during different conditioning tasks (Picciotto et al., 2001).

The mechanism of the persisting effects of nAChR activation is currently unknown, although the involvement of an alteration in nAChR expression or of interactions with other transmitter systems has been suggested (Levin and Simon, 1998). Recently we have taken into consideration the possibility that this persistence of nicotine effects could also be related to the increased levels of neurotrophic factors observed following nAChR agonist treatment in different experimental models (Belluardo et al., 1998, 1999b, 2000).

Neuroprotective effects of nAChR activation have been shown in different models with lesions of septohippocampal or nigrostriatal systems. Nicotinic agonists protect against neocortical neuronal cell loss induced by nucleus magnocellularis lesions in the rats and delayed hippocampal CA1 subregion neuronal death by ischemia (Nanri et al., 1998) and against septal cholinergic neurons death following fimbrial transaction (Martin et al., 2004), and septohippocampal lesion with induced deficits in spatial memory (Decker et al., 1994b, 1995) or working memory (Levin et al., 1993). Prenatal nicotine exposure resulted in a trophic influence on cerebral cortex development characterized by premature increases in cholinergic projections based on analysis of choline acetyltransferase (Navarro et al., 1989).

Chronic nicotine treatment counteracts the disappearance of tyrosine-hydroxylase-immunoreactive or eliminates asymmetry in striatal glucose utilization in the mesostriatal dopamine system after partial hemitransection in the rat (Janson et al., 1988a, 1989; Janson and Moller, 1993; Jeyarasasingam et al., 2002), and protects against neurodegeneration of dopaminergic neurons in the MPTP model (Janson et al., 1988b) and the meth-amphetamine mice model of Parkinson's disease (Maggio et al., 1998).

Evidence in vitro

There exist numerous model systems in which nicotine has shown protective effects on neurons, including exposure to cytotoxic insults of glutamate, β-amyloid or 6-OHDA (Ryan et al., 2001). Nicotine induces protection of cultured cortical and striatal neurons against cytotoxicity mediated by NMDA and AMPA receptors (Kaneko et al., 1997), and of cultured hippocampal and cerebellar neurons against kainic acid induced neurotoxicity (Semba et al., 1996). This nAChR neuroprotection against glutamate cytotoxicity seems to be mediated by their inhibitory action on NO-formation (Shimohama et al., 1996). Other studies have shown that nicotine rescues PC12 cells from death induced by NGF deprivation (Jonnala et al., 2002). Nicotine has recently been shown to inhibit Aβ aggregation by preventing the conversion from α- helix to β-sheet conformations (Salomon et al., 1996). Nicotine was found to prevent Aβ toxicity in hippocampal neurons (Zamani and Allen, 2001) and in cortical neurons (Shimohama and Kihara, 2001), and it has been suggested that nicotine-induced protection from Aβ toxicity is mediated by the phosphatidylinositol 3-kinase cascade (Kihara et al., 2001). Nicotine also inhibits Aβ induced phospholipase A2 activation (Singh et al., 1998). Taken together the results of nicotine inhibition of Aβ toxicity in cell culture suggested the possibility that the nAChR may be a therapeutic target in AD.

Clinical evidence

Parkinson's disease and Alzheimer disease – Epidemiological and clinical studies have for a long time suggested a potential neuroprotective/neurotrophic role of nicotine in neurodegenerative disease, such as AD and PD (Quik, 2004; Newhouse et al., 2004). During the progression of AD, cholinergic inputs degenerate and the number of nAChRs in some areas decreases (Gotti and Clementi, 2004) and high affinity nAChR of the α4β2 subtype, are significantly lost in AD (Court et al., 2001). This loss likely occurs early in the disease and is probably not true for α7-nAChR (Martin-Ruiz et al., 1999) although a loss of α7-nAChRs in AD has been reported (Banerjee et al., 2000). This loss of nicotinic mechanisms, which modulates the gain and accuracy of synapses and modulates the excitability of circuits, is likely to contribute to the overall cognitive deficits associated with AD. Therefore cognitive changes in AD, including memory loss, are also likely to be caused by changes in synaptic plasticity in addition to non-specific neurotoxicity and/or cell loss (Small et al., 2001).

Clinical studies have revealed that nicotine is effective in ameliorating memory and attention deficits in AD patients (Newhouse et al., 2001), and to improve learning and memory in normal humans (Warburton et al., 1986). Numerous studies now demonstrate that chronic nicotine exposure induces increased numbers of CNS nAChR in animals and in human smokers *in vivo* (Wonnacott, 1990) and this up-regulation of receptor number has been proposed to be responsible for nicotine's neuroprotective action (Jonnala and Buccafusco, 2001). ABT-594 and ABT-418, potent and selective agonists for the α4β2 subtype (Bannon et al.,

1998) are 3–10-fold more potent than nicotine as to memory-enhancing actions (Decker et al., 1994a) and improve in subjects with moderate AD deficits in total recall in a verbal learning task, in a selective reminding task, and in non-verbal tasks such as spatial learning and memory and repeated acquisition.

Treatments with cholinesterase inhibitors, such as physostigmine, have shown cognitive improvements (De La Garza, 2003). Recently galantamine, a modest acetylcholinesterase inhibitor and allosteric potentiating ligand at nAChRs, has shown neuroprotective effects against a variety of cytotoxic agents, such as β-amyloid, glutamate and sustained cholinergic stress *in vivo* (Geerts, 2005) and effects on memory, hippocampal plasticity, and elevates the number of nicotinic receptors within the hippocampus and neocortex (Barnes et al., 2000). In patients with AD, galantamine improves cognitive functional and behavioural symptoms (Maelicke et al., 2001). There is ample evidence that these effects of galantamine are mediated through allosteric potentiation of the α7 subunits with the additional benefit of a lower degree of receptor desensitization (Maelicke et al., 2001). Taken together, the loss of nAChRs associated with AD, with the ability of nicotine to upregulate its receptors and the epidemological data showing smokers to be at less risk of AD than non smokers, are consistent with the hypothesis of nicotine receptor involvement in neuroprotective/neurotrophic functions (Perry et al., 1999).

Like for AD an inverse association between cigarette smoking and PD has been reported (Baron, 1986). According to epidemiological studies, it has been shown that cigarette smoking may have therapeutic implications in PD (Baron, 1986) with substantial improvement of the PD symptoms (Kelton et al., 2000), and acute i.v. nicotine improved reaction time, speed of processing and tracking errors, but not selective attention and semantic retrieval (Fratiglioni and Wang, 2000). Based on the epidemiological studies and the neuroprotective actions of nicotine in animal models of PD (Janson et al., 1988a, b; Fuxe et al., 1990) the potential role of nAChRs as targets for treatment of this disease has been raised (Belluardo et al., 2000; Burghaus et al., 2003), including the specific treatment of cognitive dysfunction associated with PD (Forgacs and Bodis-Wollner, 2004). Some of these effects on learning and memory may not only be caused by neurotrophic actions by nicotine and other nicotinic receptor agonists, but may also be mediated by the enhancement of dopaminergic and noradrenergic function via the ability of nicotinic receptor agonists to enhance the release of dopamine and norepinephrine in the brain including the striatum (Summers et al., 1997; Andersson et al., 1981; Fuxe et al., 1989), as well as to increases in tyrosine hydroxylase and dopamine β-hydroxylase mRNA levels (Gueorguiev et al., 2000). Therefore, treatment with nicotine, or preferably selective nicotinic agonists, could attenuate nigrostriatal damage and reduce PD progression and thus provide neuroprotective effects by selectively stimulating nAChR subtypes as well as improve PD symptoms by increasing dopamine release and synthesis (Kelton et al., 2000; Lichtensteiger et al., 1982; Kita et al., 1992; Andersson et al., 1981; Fuxe et al., 1986).

Schizophrenia – Over the last twenty years, a high incidence of smoking has been observed in subjects suffering from schizophrenia (Sacco et al., 2004) and clinical data suggested that nicotine improves certain cognitive and sensory abnormalities associated with schizophrenia such as deficits in sensory gating (Ripoll et al., 2004; Tanabe et al., 2005). Data available suggested that nicotine improves attention and inhibitory functions in hippocampus and cingulate gyrus with involvement of GABAergic mechanisms (Tanabe et al., 2005). Furthermore, a partial α7 agonist improves auditory P50 suppression in schizophrenia (Koike et al., 2005) and it has been indicated to be reasonable candidates for the treatment of cognitive and perceptual disturbances in schizophrenia (Koike et al., 2005; Deutsch et al., 2005), since *inter alia* α7 nicotinic receptor activation may create a glutamatergically mediated increase in dopamine release in the prefrontal cortex, and in area implicated in the development of negative symptoms in patients with schizophrenia (Nomikos et al., 2000). Recent studies have shown that also galantamine improves the cognitive performances of patients with refractory schizophrenia having auditory hallucinations and a disorganized form of schizophrenia (Allen and McEvoy, 2002). Therefore, the alleviation of certain symptoms of some forms of schizophrenia induced by nicotine could explain the high incidence of smoking among schizophrenic patients and suggests that nicotine intake by cigarette consumption may be a form of self-medication. It is of substantial interest that there exists a differential modulation of gene expression in NMDA postsynaptic densities in schizophrenic smokers vs. control smokers (Mexal et al., 2005). It is also possible to conceive that neurotrophic actions of nicotinic agonists can be involved in antischizophrenic actions in view of the neurodevelopmental theory of schizophrenia (Lipska, 2004; Freedman, 2005), since nicotinic receptors and FGF-2 exist in the subependymal layer rich in neuronal progenitor cells (Mudo' et al., 2005).

Taken together the available experimental and clinical data largely indicate long-lasting beneficial effects of nico-

tine and nicotinic agonists that imply a neuroprotective/neurotrophic role of nAChR activation, giving these receptors a therapeutic role in PD and AD. In addition, α7 agonists may have a therapeutic potential in schizophrenia.

Nicotine addiction and neuroplasticity

Brain nAChRs distribute to postsynaptic, as well as to pre-, peri- and other, sites, where they may modulate the neurotransmitter release, synapse action and neuronal activity, playing important roles in many physiological processes including neuron development, learning and memory, and reward responses as well as in addiction development (Dani et al., 2001). Addictive drugs produce forms of structural plasticity similar to those associated with other forms of experience-dependent plasticity. Nicotine addiction, which is mediated by interaction with nAChRs, is believed to involve the modification of signalling cascades that modulate synaptic plasticity and gene expression, as proposed for other drugs of abuse (Dani et al., 2001; Nestler, 2002).

A growing body of evidence has shown that drugs of abuse can activate memory mechanisms in the circuits of the mesolimbic reward center (Nestler, 2001; Samaha and Robinson, 2005). It has been reported that nicotine in the ventral midbrain (VTA), via MLA-sensitive nAChR, stimulates both glutamatergic terminals and DA neurons directly, potentiating excitatory transmission in the VTA and replace presynaptic stimulation completely in LTP induction, generating synaptic plasticity (Mansvelder and McGehee, 2000). The glutamatergic input to the DA neurons can undergo LTP in response to pairing of pre- and postsynaptic stimulation, and this process is dependent on NMDA receptor activation (Bonci and Malenka, 1999).

A limited exposure to nicotine is sufficient to induce lasting changes in the circuitry of the mesolimbic DA reward system as shown in human adolescents expressing behaviours that support the observations of lasting changes in synaptic activity by a single exposure to nicotine (Mansvelder and McGehee, 2000), or initial symptoms of nicotine dependence after smoking of only a few cigarettes (DiFranza and Wellman, 2003). Early on acute nicotine injections and acute intermittent exposure to cigarette smoke was found to increase DA turnover and release in certain limbic DA nerve terminal systems of the nucleus accumbens and the olfactory tubercle (Andersson et al., 1981; Fuxe et al., 1986). With continued nicotine exposure, plastic molecular alterations in central DA systems might underlie the continued propensity to consume nicotine by inducing craving, the aversive effects of withdrawal, and aberrant incentive-salience attribution to environmental stimuli that are associated with nicotine. The synaptic mechanisms that nicotine activates within the DA reward system are likely to underlie the early steps of nicotine dependence and it is one of the critical areas for future research on the physiological basis of nicotine addiction (Pulvirenti and Diana, 2001).

Desensitization: neuroprotection and plastic changes

Work from several laboratories show that when ACh, nicotine or related agonists are continuously applied nAChRs become 'desensitized' or temporarily inactive (Giniatullin et al., 2005). Desensitization in addition to protecting cells from uncontrolled excitation is recently considered as a form of signal plasticity that might modify synaptic efficacy in various brain regions (Dani et al., 2001; Mansvelder and McGehee, 2002). In fact, the most obvious neuroprotective action of desensitized nAChRs is to inhibit excessive excitation dependent on high permeability to Ca^{++} of activated nAChRs. In line with this, mutation at the position leucine 247 of the α7 subunit significantly inhibits desensitization and inserting this mutation into mice can induce animal death (Wang and Sun, 2005). Recently, a reasonable working hypothesis has been developed stating that the phenomena of desensitization beyond simply nicotinic receptor inactivation may contribute to the array of potential effects associated with chronic nicotine exposure. Numerous studies have demonstrated that chronic nicotine exposure induces increased numbers of CNS nAChRs both *in vivo* in animals and in human smokers, caused by post-translational mechanisms (Benwell et al., 1988), and *in vitro* (Bencherif et al., 1995), although other investigations support a change not in the number of receptors but in their state of binding and response to ligands (Vallejo et al., 2005). This nicotine up-regulation of receptor number is viewed as responses to desensitization thereby also implying that the desensitized nAChRs may be responsible for the nicotine's neuroprotective action (Jonnala and Buccafusco, 2001). The mechanism may also involve an enhanced intracellular maturation of the nicotinic receptors (Sallette et al., 2005). Pretreatment with nicotine for 24 h has been shown to alleviate the toxic actions of MPTP, indicating a neuroprotective effect of desensitized nAChRs, and the neuroprotective action of nicotine in cultured PC12 cells has been suggested to be due to upregulation of α7-containing nAChRs following their persistent desensitization (Jonnala and Buccafusco, 2001). According to this finding, it has been reported that desensitized α7 nAChRs have a neuroprotective function through modulating signal

transduction pathways (Dajas-Bailador et al., 2000; Dani, 2001).

A consistent number of reports suggested that the desensitized nAChRs induced by chronic nicotine may be important for learning and memory (Lindstrom et al., 1987). In this context, acute or prolonged chronic nicotine treatment can decrease the threshold for LTP induction in the hippocampus CA1 and can reverse the age-dependent decrease in LTP-induction (Fujii and Sumikawa, 2001). Because a decreased threshold for LTP may be mimicked by MLA and prevented by a non α7 nAChR blocker, it has been suggested that α7 nAChR desensitization are mainly responsible for the effects (Fujii and Sumikawa, 2001). Furthermore, in view of the negative association between cigarette smoking and PD or AD, it has also been suggested that desensitized nAChRs may be responsible for their neuroprotective actions (Baron, 1996). The use of allosteric modulator drugs that do not act as agonists on nAChRs, and therefore cannot generate their widespread desensitization (Maelicke et al., 2000) may be important tools for understanding the role of receptor desensitization in neuroprotection.

Molecular mechanisms mediating neuroprotective effects of nAChR activation

Nicotine and other nAChR agonists as above described have neuroprotective/neurotrophic effects in several *in vivo* and *in vitro* models of neuronal death (O'Neill et al., 2002). Nevertheless, intracellular steps that mediate these effects of nAChR ligands are not fully solved.

Concerning neuroprotective effects, nAChR activation evoking Ca^{++} influx is likely to represent a first step in the intracellular signalling cascades (Dajas-Bailador et al., 2000) followed by diverse downstream pathways and processes that are subsequently activated. Thus, this activation of downstream signalling pathways appears necessary for the prevention of neuronal death. Consistent with this suggestion, block of Ca^{++} influx following activation of α7 nAChR promotes survival of spinal cord motoneurons from programmed cell death (Messi et al., 1997). In hippocampal slices nicotine-induced protection against acute NMDA damage is mediated by the activation of phosphatidylinositol 3-kinase and ERK/MAPK (Ferchmin et al., 2003) or protein kinase C (Li et al., 1999) and regulation of Bcl-2 and Bcl-x expression, which may be involved in prevention of neuronal death (Toborek et al., 2000; Mai et al., 2003). Other results suggested that nAChR stimulation induces neuroprotection against glutamate cytotoxicity by its inhibitory action on NO-formation (Shimohama et al., 1996). Stimulation of nAChR can also lead to the increased expression of neurotrophic factors (Belluardo et al., 2000). Therefore, activation of diverse signalling mechanisms might subsequently lead to neuroprotection through inhibition of apoptosis and/or increased expression of neurotrophic factors crucial for neuronal maintenance, survival (Belluardo et al., 2000; Roceri et al., 2001).

Molecular mechanisms mediating neurotrophic effects of nAChR activation

Regulation of gene expression by synaptic activity is essential both for normal development in the nervous system and for long-term components of synaptic plasticity (Dajas-Bailador et al., 2000). The chain of events connecting synaptic activity and gene expression is often initiated by calcium influx (Hardingham et al., 2001), and nAChRs, and particularly the α7 nAChR, are permeable to Ca^{++}. In neurons, nAChRs activation can play a relevant role in Ca^{++} signalling not only because of the Ca^{++} entry through different nAChR subtypes, but also because nAChR depolarization of the plasma membrane can activate voltage operated calcium channels and may also increase intracellular Ca^{++} by inducing Ca^{++} mobilization from intracellular stores. The absolute quantity and strategic localization of Ca^{++} entry through nAChRs is likely to be relevant for the regulation of calcium-mediated downstream intracellular events, including transmitter release, cell excitability, activation of protein kinases, gene expression, cell differentiation and survival and new protein synthesis, ultimately leading to changes in synaptic plasticity and neuronal remodelling (Dajas-Bailador et al., 2000). Therefore, in addition to rapid changes in membrane potential, activation of nAChR can also generate longer-lasting effects in the receptive neuron, which contribute to the elaboration of complex intracellular signals that mediate medium-to long-term events (Role and Berg, 1996).

nAChRs have been implicated in a wide variety of neurotrophic events, including learning and memory, which involve mechanisms for calcium-dependent synaptic regulation (Dajas-Bailador et al., 2000). nAChR agonists activate mechanisms of synaptic plasticity and long-term enhancement of memory, which involve an increase in the number and efficiency of synaptic connections between neurons. Long-lasting cognitive effects of nAChR ligands may be attributed to the cellular changes that result in synaptic plasticity and LTP is a model of the synaptic plasticity of learning and memory (Buccafusco et al., 2005).

During the past few decades, the pathways that are involved in synaptic plasticity have been elucidated (Kandel,

2001), particularly the phenomenon of LTP, which is an increase in synaptic strength that can persist for extended periods of time (Bliss and Lomo, 1973). The phases of LTP correlate with the stages of memory, and impairment of the mechanisms of LTP leads to memory deficits (Kandel, 2001). In the early phase of LTP, which lasts only hours, Ca^{++} dependent second messenger systems modify existing proteins to enhance neurotransmitter release from presynaptic neurons and support short-term memory. Late phases of LTP require protein synthesis, lasting at least a day, and require prolonged elevation of the intracellular Ca^{++} concentration. The latter activates a cascade that involves adenylyl cyclase, cAMP and second messengers such as protein kinase A and mitogen-activated protein kinase (MAPK) (Impey et al., 1999). In turn, these events may enhance the activity of transcription factors, e.g. the cAMP response element-binding protein-1 (CREB-1), which increases the expression of immediate early genes and stimulates the synthesis of growth factors and other proteins that potentiate cell excitability and support the formation of new synaptic connections. The growth and maintenance of new synaptic connections enables the persistence of long-term memory (Kandel, 2001). Much evidence indicate that activation of nAChRs may initiate a cascade of cellular signals that produces long-term molecular changes involved in the molecular mechanisms of memory. Repeated exposure to nAChR agonists enhances LTP more than a single dose administration, whereas a persistent activation of nAChRs is not required for the maintenance phase of LTP. These effects of nAChR agonists have been characterized most extensively in the hippocampus, where $\alpha 7$ nAChR activation enhance the probability of LTP and might contribute to the mechanisms that underlie the effects of nicotine on cognition (Ji et al., 2001).

nAChR agonists may activate several mechanisms which may induce long-term changes leading to more complex neurotrophic response in addition to increased number and efficiency of synaptic connections between neurons.

Nicotine treatment by increasing permeability of nAChR to Ca^{++} can induce PKC activity (Fenster et al., 1999), and Ca^{++}CaM-dependent protein kinase II, and both effects can be reversed by nAChR antagonists (Damaj, 2000). The mitogen-activated protein kinase (MAPK or Erk1/2) pathway can also be activated by nicotine-dependent increases in Ca^{++} levels (Cox et al., 1996) or alternatively, changes in MAPK activity might be regulated by nicotine-dependent alterations in the levels of fibroblast growth factors that would activate tyrosine kinase receptor-mediated pathways (Blum et al., 1996). Similarly, Nicotine-dependent changes in phospholipase C (Pandey, 1996) and PKA signalling pathways might also be mediated by upstream effects of nicotine on neurotrophic factors or neurotransmitter release.

Previous studies have demonstrated that nicotine administration modulated the expression of a variety of genes, and transcriptional activation (Shim et al., 2000). Exposure to nAChR agonists elevates the expression of the immediate early genes c-Fos and JunB in several brain areas (Harlan and Garcia, 1998). The immediate early genes regulate the transcription of downstream targets that have diverse roles in signalling, cell growth and cell maintenance. Recently, Gene-array technology indicates that nicotine administration might affect numerous genes, including those involved in intracellular signalling, transcription, translation, CREB phosphorylation (Gueorguiev et al., 2004), transmitter receptors, ion channel signalling pathways (Sun et al., 2004) and proteins associated with RNA binding and the plasma membrane (Dunckley and Lukas, 2003). We used Rat Genome U34A Affymetrix GeneChip arrays to find in the rat parietal cortex new genes responsive to acute intermittent nicotine treatment and linked to neuroprotection (Belluardo et al., 2005). In this study 25 modified genes were selected and among them five genes encoding transcription factors were found up regulated (Nr4a1, Cebpg, Egr-1, Egr-2, JunB). All these transcription factors show special significance in view of their known role in regulation of several genes, some of which are involved in neurotrophic and/or neuroprotective actions.

Among the intracellular events regulated by nAChR activation, the CREB and ERK/MAPK signalling cascades have attracted particular attention because their activities are central to long-term plasticity in the nervous system (Sweatt, 2001). In fact, activation of ERK/MAPK is required for the formation of contextual and spatial memories in mammals (Sweatt, 2001) and nAChR mediate the Ca^{++}-dependent activation of ERK/MAPK and sustained phosphorylation of CREB in several neuronal models (Chang and Berg, 2001). Nicotine can alter gene expression in rat hippocampal neurons, as reflected by activation of the transcription factor CREB and appearance of the immediate early gene product c-Fos. The process depends on both CaM and MAP kinases and on calcium release from internal stores (Hu et al., 2002). These findings in addition to having directly physiological relevance in learning and memory, may also have pathological relevance in addiction (Nestler, 2002). Nicotine dependence, which is mediated by interaction with nAChR, is likely to involve the modification of signalling cascades that modulate synaptic plasticity and gene expression, as proposed for other drugs of abuse (Nestler, 2001; Dani et al., 2001). Although there are

few reports on the contributions of signalling pathways in models of nicotine addiction, several studies have focused on the modulation of CREB following chronic treatment with nicotine. CREB activation is required for nicotine reward (Walters et al., 2005) and nicotine withdrawal significantly reduced the concentrations of CREB and phosphorylated CREB in rat cortex and amygdala (Pandey et al., 2001). Phosphorylated CREB appears also to be decreased in the nucleus accumbens in mice following chronic consumption of nicotine in their drinking water (Brunzell et al., 2003). Overall, these results support a role for ERK and CREB activity in neural plasticity associated with nicotine dependence.

nAChRs activation is involved on neurotrophic factor gene expression

The mechanisms by which nicotinic signalling may regulates gene expression are poorly understood, and it is not known how such mechanisms interact with other calcium dependent pathways controlling transcription. Therefore, a comprehensive survey of the gene-based molecular mechanisms that underlie nicotine effects is yet to be performed. During the last years we have begun a study aimed to identify genes encoding neurotrophic factors targeted by nAChR activation and to elucidate the signalling pathways through which nAChR regulate their expression.

Several neuronal populations within the adult CNS require the presence of neurotrophic factors to maintain neuronal function (Sofroniew et al., 1990) and survival (Barde, 1989). Long-term changes in synaptic plasticity are associated with neurotrophic factors (Pang et al., 2004) and the reduction in neurotrophic factor expression may result in the neuronal atrophy seen in normal ageing or the neuronal loss observed in neurodegenerative disorders such as AD and PD (Connor and Dragunow, 1998). Therefore a neurotrophic factor gene regulation by nAChR signalling has been also taken into consideration as a possible mechanism involved in neuroprotective/neurotrophic effects by nAChR activation.

We have analysed the effects of acute intermittent nicotine treatment on FGF-2 expression and the results obtained (Belluardo et al., 1998) showed that treatment with acute intermittent nicotine (four i.p. injections at intervals of 30 min; 1 mg/kg), or with other nicotinic agonists such as epibatidine and ABT-594, lead to a substantial upregulation of FGF-2 mRNA and protein levels in the cerebral cortex, the hippocampal formation, the striatum and the ventral midbrain. An extension of this model to the study of aged rats (24 months old) showed that the nicotine-induced increases of FGF-2 mRNA levels is preserved during aging (Belluardo et al., 1999a, 2000). In cultured chromaffin cells from bovine adrenal medullae stimulation of nAChR increases FGF-2 gene expression (Stachowiak et al., 1994). This nAChR-mediated increase in expression of FGF-2 gene was mediated by adenylate cyclase or protein kinase C and dependent on nuclear interaction of transactivating factors with a novel cis-acting element (Moffett et al., 1998). In order to elucidate the signalling pathways through which nAChR regulate FGF-2 expression we focus on transcription factors identifying a potential role of CREB. We could verify the presence in the promoter of the FGF-2 gene a CRE-site which is able to bind CREB (unpublished data). This involvement of CREB is also supported by the ability of acute nicotine treatment to induce phosphorylation of CREB, without a change in CREB levels, and to increase activation of ERK-1 (unpublished data), which suggests an involvement of Ras/mitogen-activated protein kinase (MAPK) pathways.

This regulation of FGF-2 gene in turn can exert neurotrophic functions involving neuronal survival, trophism and plasticity. FGF-2 exerts its pleiotropic effect through specific high- and low-affinity receptors named FGFR-1-4 (Belluardo et al., 1997). FGF-2 has been implicated to be the potent neurotrophic factor that promotes mitosis and differentiation of neuroblasts (Mayer et al., 1993), and neuronal survival and neurite extension (Ferrari et al., 1989) and protects cultured central neurons from different insults (Cheng and Mattson, 1991). An *in vivo* protective role for FGF-2 has been indicated by studies showing that FGF-2 can support the survival of cholinergic basal forebrain neurons following fimbria transaction (Anderson et al., 1988), dopaminergic neurons following MPTP toxicity (Chadi et al., 1993) and hippocampal neurons following cerebral ischemia (Nakata et al., 1993) or hippocampal damage after excytotoxic injury (Mattson et al., 1989). Endogenous expression of FGF-2 blocked by neutralizing antibodies following unilateral suction lesions of the motor cortex retards recovery from injury in rats (Rowntree and Kolb, 1997). A loss of FGF-2 in the substantia nigra in PD has been reported (Tooyama et al., 1993). Transgenic mice lacking FGF-2 showed a reduction in the neuronal density in the motor cortex, with layer V more greatly affected (Ortega et al., 1998), suggesting that FGF-2 controls migration, differentiation and survival especially of cortical neurons (Dono et al., 1998). Recently FGF-2 has been implicated in neurogenesis in adult rat brain (Kuhn et al., 1997). In this context we revealed in the neuroepithelium of the subventricular zone of the lateral ventricle in the adult rat brain the existence of a trophic mechanism mediated by FGF-2 and its receptor and regulated by nAChR, activation

of which by acute intermittent nicotine treatment enhances neuronal precursor proliferation (Mudo' et al., 2005) Other pieces of evidence that nAChRs may play a direct role in the regulation of neurogenesis come from the reported decline of hippocampal cell proliferation in mice lacking the β2 subunit (Harrist et al., 2004), and a decrease of neurogenesis in the adult hippocampal formation following chronic nicotine self-administration (Abrous et al., 2002). These findings suggest the possibility of *in vivo* regulation of neurogenesis in the adult brain by nicotine agonists and may help to develop treatment stimulating neurogenesis with important therapeutic implication.

Several reports have showed that other neurotrophic factors may be under regulation of nAChR activation. Intra-hippocampal administration of nicotine increases transiently NGF in the CA1 and dentate gyrus of the hippocampus and PC12 neuronal cells exposed to nicotine increase NGF receptor expression (Jonnala et al., 2002). Acute intermittent nicotine treatment increase levels of BDNF in the rat striatum (Maggio et al., 1998), although other reports in similar experimental models have indicated as unchanged the BDNF levels (Belluardo et al., 1999a). NGF itself enhances ACh release (Lapchak et al., 1994), increases mRNA that encodes nAChR subunits (Henderson et al., 1994) and promotes sprouting of ACh-containing fibers in the septum (Heisenberg et al., 1994). Nevertheless, in contrast to NGF, which is expressed only in restricted regions of brain and does not give account for the large effects of nicotine in several brain regions, FGF-2 is widely distributed in the adult CNS both in neuronal and non neuronal cells (Fuxe et al., 1996) and the potent and widespread activation of FGF-2 in several brain regions following nicotine treatment suggested that the cholinergic activation of the FGF-2 gene via nAChR may be better suited to participate in the plasticity changes and improved neuronal survival in the brain found after nicotine agonist treatment. Therefore, this FGF-2 nicotine activation supports the suggestion that the previously observed neuroprotective effects of nicotine and the potential beneficial effects of nicotine agonists in the treatment of AD and PD, may at least in part involve an activation of the neuronal and glial FGF-2 signalling.

Conclusions

Although the large amount of data acquired in the last years have added new important insight in our understanding the molecular mechanisms that underlie nicotine effects, more work is needed to establish the mechanisms involved in any nicotinic receptor activation effects, from cognition-enhancing effects to smoking behaviour, and to determine more precisely the therapeutic objectives in potential nicotinic drug treatment of neurodegenerative diseases. In addition, it will be also important to determine how the diverse nAChR subtypes are integrated in such actions and the impact of their changes for pathology, and to define whether neuroprotective/neurotrophic and cognitive enhancements are mediated via acute activation, repetitive activation, or more chronic inactivation of nAChR function or by some combination of these actions. Such knowledge is important for the development of targeted drug therapies acting on nAChRs to delay the onset and progression of chronic age related brain neurodegenerative pathologies, as seen in PD and AD, leading to improvement of cognitive abilities.

References

Abrous DN, Adriani W, Montaron MF, Aurousseau C, Rougon G, Le MM, Piazza PV (2002) Nicotine self-administration impairs hippocampal plasticity. J Neurosci 22: 3656–3662

Allen TB, McEvoy JP (2002) Galantamine for treatment-resistant schizophrenia. Am J Psychiatry 159: 1244–1245

Anderson KJ, Dam D, Lee S, Cotman CW (1988) Basic fibroblast growth factor prevents death of lesioned cholinergic neurons in vivo. Nature 332: 360–361

Andersson K, Fuxe K, Agnati LF (1981) Effects of single injections of nicotine on the ascending dopamine pathways in the rat. Evidence for increases of dopamine turnover in the mesostriatal and mesolimbic dopamine neurons. Acta Physiol Scand 112: 345–347

Arendash GW, Sengstock GJ, Sanberg PR, Kem WR (1995) Improved learning and memory in aged rats with chronic administration of the nicotinic receptor agonist GTS-21. Brain Res 674: 252–259

Banerjee C, Nyengaard JR, Wevers A, de Vos RA, Jansen Steur EN, Lindstrom J, Pilz K, Nowacki S, Bloch W, Schroder H (2000) Cellular expression of alpha7 nicotinic acetylcholine receptor protein in the temporal cortex in Alzheimer's and Parkinson's disease – a stereological approach. Neurobiol Dis 7: 666–672

Bannon AW, Decker MW, Holladay MW, Curzon P, Donnelly-Roberts D, Puttfarcken PS, Bitner RS, Diaz A, Dickenson AH, Porsolt RD, Williams M, Arneric SP (1998) Broad-spectrum, non-opioid analgesic activity by selective modulation of neuronal nicotinic acetylcholine receptors. Science 279: 77–81

Barde YA (1989) Trophic factors and neuronal survival. Neuron 2: 1525–1534

Barnes CA, Meltzer J, Houston F, Orr G, McGann K, Wenk GL (2000) Chronic treatment of old rats with donepezil or galantamine: effects on memory, hippocampal plasticity and nicotinic receptors. Neuroscience 99: 17–23

Baron JA (1986) Cigarette smoking and Parkinson's disease. Neurology 36: 1490–1496

Baron JA (1996) Beneficial effects of nicotine and cigarette smoking: the real, the possible and the spurious. Br Med Bull 52: 58–73

Belluardo N, Blum M, Mudo G, Andbjer B, Fuxe K (1998) Acute intermittent nicotine treatment produces regional increases of basic fibroblast growth factor messenger RNA and protein in the tel- and diencephalon of the rat. Neuroscience 83: 723–740

Belluardo N, Mudo G, Blum M, Cheng Q, Caniglia G, Dell'Albani P, Fuxe K (1999a) The nicotinic acetylcholine receptor agonist (+/−)-epibatidine increases FGF-2 mRNA and protein levels in the rat brain. Brain Res Mol Brain Res 74: 98–110

Belluardo N, Mudo G, Blum M, Fuxe K (2000) Central nicotinic receptors, neurotrophic factors and neuroprotection. Behav Brain Res 113: 21–34

Belluardo N, Mudo G, Caniglia G, Cheng Q, Blum M, Fuxe K (1999b) The nicotinic acetylcholine receptor agonist ABT-594 increases FGF-2 expression in various rat brain regions. Neuroreport 10: 3909–3913

Belluardo N, Olsson PA, Mudo' G, Sommer WH, Amato G, Fuxe K (2005) Transcription factor gene expression profiling after acute intermittent nicotine treatment in the rat cerebral cortex. Neuroscience 133: 787–796

Belluardo N, Wu G, Mudo G, Hansson AC, Pettersson R, Fuxe K (1997) Comparative localization of fibroblast growth factor receptor-1, -2, and -3 mRNAs in the rat brain: in situ hybridization analysis. J Comp Neurol 379: 226–246

Bencherif M, Fowler K, Lukas RJ, Lippiello PM (1995) Mechanisms of up-regulation of neuronal nicotinic acetylcholine receptors in clonal cell lines and primary cultures of fetal rat brain. J Pharmacol Exp Ther 275: 987–994

Benwell ME, Balfour DJ, Anderson JM (1988) Evidence that tobacco smoking increases the density of (–)-[^{3}H]nicotine binding sites in human brain. J Neurochem 50: 1243–1247

Bliss TV, Lomo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232: 331–356

Blum M, Wu G, Mudo G, Belluardo N, Andersson K, Agnati LF, Fuxe K (1996) Chronic continuous infusion of (–)nicotine reduces basic fibroblast growth factor messenger RNA levels in the ventral midbrain of the intact but not of the 6-hydroxydopamine-lesioned rat. Neuroscience 70: 169–177

Bonci A, Malenka RC (1999) Properties and plasticity of excitatory synapses on dopaminergic and GABAergic cells in the ventral tegmental area. J Neurosci 19: 3723–3730

Broide RS, Leslie FM (1999) The alpha7 nicotinic acetylcholine receptor in neuronal plasticity. Mol Neurobiol 20: 1–16

Brunzell DH, Russell DS, Picciotto MR (2003) In vivo nicotine treatment regulates mesocorticolimbic CREB and ERK signaling in C57Bl/6J mice. J Neurochem 84: 1431–1441

Buccafusco JJ, Letchworth SR, Bencherif M, Lippiello PM (2005) Long-lasting cognitive improvement with nicotinic receptor agonists: mechanisms of pharmacokinetic-pharmacodynamic discordance. Trends Pharmacol Sci 26: 352–360

Burghaus L, Schutz U, Krempel U, Lindstrom J, Schroder H (2003) Loss of nicotinic acetylcholine receptor subunits alpha4 and alpha7 in the cerebral cortex of Parkinson patients. Parkinsonism Relat Disord 9: 243–246

Chadi G, Moller A, Rosen L, Janson AM, Agnati LA, Goldstein M, Ogren SO, Pettersson RF, Fuxe K (1993) Protective actions of human recombinant basic fibroblast growth factor on MPTP-lesioned nigrostriatal dopamine neurons after intraventricular infusion. Exp Brain Res 97: 145–158

Chang KT, Berg DK (2001) Voltage-gated channels block nicotinic regulation of CREB phosphorylation and gene expression in neurons. Neuron 32: 855–865

Changeux JP, Bertrand D, Corringer PJ, Dehaene S, Edelstein S, Lena C, Le NN, Marubio L, Picciotto M, Zoli M (1998) Brain nicotinic receptors: structure and regulation, role in learning and reinforcement. Brain Res Rev 26: 198–216

Cheng B, Mattson MP (1991) NGF and bFGF protect rat hippocampal and human cortical neurons against hypoglycemic damage by stabilizing calcium homeostasis. Neuron 7: 1031–1041

Connor B, Dragunow M (1998) The role of neuronal growth factors in neurodegenerative disorders of the human brain. Brain Res Rev 27: 1–39

Court J, Martin-Ruiz C, Piggott M, Spurden D, Griffiths M, Perry E (2001) Nicotinic receptor abnormalities in Alzheimer's disease. Biol Psychiatry 49: 175–184

Couturier S, Bertrand D, Matter JM, Hernandez MC, Bertrand S, Millar N, Valera S, Barkas T, Ballivet M (1990) A neuronal nicotinic acetylcholine receptor subunit (alpha 7) is developmentally regulated and forms a homo-oligomeric channel blocked by alpha-BTX. Neuron 5: 847–856

Cox ME, Ely CM, Catling AD, Weber MJ, Parsons SJ (1996) Tyrosine kinases are required for catecholamine secretion and mitogen-activated protein kinase activation in bovine adrenal chromaffin cells. J Neurochem 66: 1103–1112

Dajas-Bailador FA, Lima PA, Wonnacott S (2000) The alpha7 nicotinic acetylcholine receptor subtype mediates nicotine protection against NMDA excitotoxicity in primary hippocampal cultures through a Ca(2+) dependent mechanism. Neuropharmacology 39: 2799–2807

Damaj MI (2000) The involvement of spinal Ca(2+)/calmodulin-protein kinase II in nicotine-induced antinociception in mice. Eur J Pharmacol 404: 103–110

Dani JA (2001) Overview of nicotinic receptors and their roles in the central nervous system. Biol Psychiatry 49: 166–174

Dani JA, Ji D, Zhou FM (2001) Synaptic plasticity and nicotine addiction. Neuron 31: 349–352

De La Garza VW (2003) Pharmacologic treatment of Alzheimer's disease: an update. Am Fam Physician 68: 1365–1372

Decker MW, Brioni JD, Bannon AW, Arneric SP (1995) Diversity of neuronal nicotinic acetylcholine receptors: lessons from behavior and implications for CNS therapeutics. Life Sci 56: 545–570

Decker MW, Brioni JD, Sullivan JP, Buckley MJ, Radek RJ, Raszkiewicz JL, Kang CH, Kim DJ, Giardina WJ, Wasicak JT (1994a) (S)-3-methyl-5-(1-methyl-2-pyrrolidinyl)isoxazole (ABT 418): a novel cholinergic ligand with cognition-enhancing and anxiolytic activities: II. In vivo characterization. J Pharmacol Exp Ther 270: 319–328

Decker MW, Curzon P, Brioni JD, Arneric SP (1994b) Effects of ABT-418, a novel cholinergic channel ligand, on place learning in septal-lesioned rats. Eur J Pharmacol 261: 217–222

Deutsch SI, Rosse RB, Schwartz BL, Weizman A, Chilton M, Arnold DS, Mastropaolo J (2005) Therapeutic implications of a selective alpha7 nicotinic receptor abnormality in schizophrenia. Isr. J Psychiatry Relat Sci 42: 33–44

DiFranza JR, Wellman RJ (2003) Preventing cancer by controlling youth tobacco use. Semin Oncol Nurs 19: 261–267

Dono R, Texido G, Dussel R, Ehmke H, Zeller R (1998) Impaired cerebral cortex development and blood pressure regulation in FGF-2-deficient mice. EMBO J 17: 4213–4225

Dunckley T, Lukas RJ (2003) Nicotine modulates the expression of a diverse set of genes in the neuronal SH-SY5Y cell line. J Biol Chem 278: 15633–15640

Fenster CP, Beckman ML, Parker JC, Sheffield EB, Whitworth TL, Quick MW, Lester RA (1999) Regulation of alpha4beta2 nicotinic receptor desensitization by calcium and protein kinase C. Mol Pharmacol 55: 432–443

Ferchmin PA, Perez D, Eterovic VA, de VJ (2003) Nicotinic receptors differentially regulate N-methyl-D-aspartate damage in acute hippocampal slices. J Pharmacol Exp Ther 305: 1071–1078

Ferrari G, Minozzi MC, Toffano G, Leon A, Skaper SD (1989) Basic fibroblast growth factor promotes the survival and development of mesencephalic neurons in culture. Dev Biol 133: 140–147

Forgacs PB, Bodis-Wollner I (2004) Nicotinic receptors and cognition in Parkinson's Disease: the importance of neuronal synchrony. J Neural Transm 111: 1317–1331

Fratiglioni L, Wang HX (2000) Smoking and Parkinson's and Alzheimer's disease: review of the epidemiological studies. Behav Brain Res 113: 117–120

Freedman R (2005) The choice of antipsychotic drugs for schizophrenia. N Engl J Med 353: 1286–1288

Fujii S, Sumikawa K (2001) Acute and chronic nicotine exposure reverse age-related declines in the induction of long-term potentiation in the rat hippocampus. Brain Res 894: 347–353

Fuxe K, Andersson K, Eneroth P, Harfstrand A, Agnati LF (1989) Neuroendocrine actions of nicotine and of exposure to cigarette smoke: medical implications. Psychoneuroendocrinology 14: 19–41

Fuxe K, Andersson K, Harfstrand A, Agnati LF (1986) Increases in dopamine utilization in certain limbic dopamine terminal populations after a short period of intermittent exposure of male rats to cigarette smoke. J Neural Transm 67: 15–29

Fuxe K, Janson AM, Jansson A, Andersson K, Eneroth P, Agnati LF (1990) Chronic nicotine treatment increases dopamine levels and reduces dopamine utilization in substantia nigra and in surviving forebrain dopamine nerve terminal systems after a partial di-mesencephalic hemitransection. Naunyn Schmiedebergs Arch Pharmacol 341: 171–181

Fuxe K, Tinner B, Zoli M, Pettersson RF, Baird A, Biagini G, Chadi G, Agnati LF (1996) Computer-assisted mapping of basic fibroblast growth factor immunoreactive nerve cell populations in the rat brain. J Chem Neuroanat 11: 13–35

Geerts H (2005) Indicators of neuroprotection with galantamine. Brain Res Bull 64: 519–524

Giniatullin R, Nistri A, Yakel JL (2005) Desensitization of nicotinic ACh receptors: shaping cholinergic signaling. Trends Neurosci 28: 371–378

Gioanni Y, Rougeot C, Clarke PB, Lepouse C, Thierry AM, Vidal C (1999) Nicotinic receptors in the rat prefrontal cortex: increase in glutamate release and facilitation of mediodorsal thalamo-cortical transmission. Eur J Neurosci 11: 18–30

Gotti C, Clementi F (2004) Neuronal nicotinic receptors: from structure to pathology. Prog Neurobiol 74: 363–396

Gould TJ, Stephen HJ (2003) Nicotine enhances contextual fear conditioning in C57BL/6J mice at 1 and 7 days post-training. Neurobiol Learn Mem 80: 147–157

Gray R, Rajan AS, Radcliffe KA, Yakehiro M, Dani JA (1996) Hippocampal synaptic transmission enhanced by low concentrations of nicotine. Nature 383: 713–716

Groenewegen HJ, Uylings HB (2000) The prefrontal cortex and the integration of sensory, limbic and autonomic information. Prog Brain Res 126: 3–28

Gueorguiev VD, Frenz CM, Ronald KM, Sabban EL (2004) Nicotine and epibatidine triggered prolonged rise in calcium and TH gene transcription in PC12 cells. Eur J Pharmacol 506: 37–46

Gueorguiev VD, Zeman RJ, Meyer EM, Sabban EL (2000) Involvement of alpha7 nicotinic acetylcholine receptors in activation of tyrosine hydroxylase and dopamine beta-hydroxylase gene expression in PC12 cells. J Neurochem 75: 1997–2005

Hardingham GE, Arnold FJ, Bading H (2001) Nuclear calcium signaling controls CREB-mediated gene expression triggered by synaptic activity. Nat Neurosci 4: 261–267

Harlan RE, Garcia MM (1998) Drugs of abuse and immediate-early genes in the forebrain. Mol Neurobiol 16: 221–267

Harrist A, Beech RD, King SL, Zanardi A, Cleary MA, Caldarone BJ, Eisch A, Zoli M, Picciotto MR (2004) Alteration of hippocampal cell proliferation in mice lacking the beta 2 subunit of the neuronal nicotinic acetylcholine receptor. Synapse 54: 200–206

Heisenberg CP, Cooper JD, Berke J, Sofroniew MV (1994) NMDA potentiates NGF-induced sprouting of septal cholinergic fibres. Neuroreport 5: 413–416

Henderson LP, Gdovin MJ, Liu C, Gardner PD, Maue RA (1994) Nerve growth factor increases nicotinic ACh receptor gene expression and current density in wild-type and protein kinase A-deficient PC12 cells. J Neurosci 14: 1153–1163

Hu M, Liu QS, Chang KT, Berg DK (2002) Nicotinic regulation of CREB activation in hippocampal neurons by glutamatergic and nonglutamatergic pathways. Mol Cell Neurosci 21: 616–625

Huerta PT, Lisman JE (1993) Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. Nature 364: 723–725

Impey S, Obrietan K, Storm DR (1999) Making new connections: role of ERK/MAP kinase signaling in neuronal plasticity. Neuron 23: 11–14

Janson AM, Fuxe K, Agnati LF, Jansson A, Bjelke B, Sundstrom E, Andersson K, Harfstrand A, Goldstein M, Owman C (1989) Protective effects of chronic nicotine treatment on lesioned nigrostriatal dopamine neurons in the male rat. Prog Brain Res 79: 257–265

Janson AM, Fuxe K, Agnati LF, Kitayama I, Harfstrand A, Andersson K, Goldstein M (1988a) Chronic nicotine treatment counteracts the disappearance of tyrosine-hydroxylase-immunoreactive nerve cell bodies, dendrites and terminals in the mesostriatal dopamine system of the male rat after partial hemitransection. Brain Res 455: 332–345

Janson AM, Fuxe K, Sundstrom E, Agnati LF, Goldstein M (1988b) Chronic nicotine treatment partly protects against the 1-methyl-4-phenyl-2,3,6-tetrahydropyridine-induced degeneration of nigrostriatal dopamine neurons in the black mouse. Acta Physiol Scand 132: 589–591

Janson AM, Moller A (1993) Chronic nicotine treatment counteracts nigral cell loss induced by a partial mesodiencephalic hemitransection: an analysis of the total number and mean volume of neurons and glia in substantia nigra of the male rat. Neuroscience 57: 931–941

Jeyarasasingam G, Tompkins L, Quik M (2002) Stimulation of non-alpha7 nicotinic receptors partially protects dopaminergic neurons from 1-methyl-4-phenylpyridinium-induced toxicity in culture. Neuroscience 109: 275–285

Ji D, Dani JA (2000) Inhibition and disinhibition of pyramidal neurons by activation of nicotinic receptors on hippocampal interneurons. J Neurophysiol 83: 2682–2690

Ji D, Lape R, Dani JA (2001) Timing and location of nicotinic activity enhances or depresses hippocampal synaptic plasticity. Neuron 31: 131–141

Jonnala RR, Buccafusco JJ (2001) Relationship between the increased cell surface alpha7 nicotinic receptor expression and neuroprotection induced by several nicotinic receptor agonists. J Neurosci Res 66: 565–572

Jonnala RR, Terry AV Jr, Buccafusco JJ (2002) Nicotine increases the expression of high affinity nerve growth factor receptors in both in vitro and in vivo. Life Sci 70: 1543–1554

Kandel ER (2001) The molecular biology of memory storage: a dialogue between genes and synapses. Science 294: 1030–1038

Kaneko S, Maeda T, Kume T, Kochiyama H, Akaike A, Shimohama S, Kimura J (1997) Nicotine protects cultured cortical neurons against glutamate-induced cytotoxicity via alpha7-neuronal receptors and neuronal CNS receptors. Brain Res 765: 135–140

Kelton MC, Kahn HJ, Conrath CL, Newhouse PA (2000) The effects of nicotine on Parkinson's disease. Brain Cogn 43: 274–282

Kem WR (2000) The brain alpha7 nicotinic receptor may be an important therapeutic target for the treatment of Alzheimer's disease: studies with DMXBA (GTS-21). Behav Brain Res 113: 169–181

Kihara T, Shimohama S, Sawada H, Honda K, Nakamizo T, Shibasaki H, Kume T, Akaike A (2001) alpha 7 nicotinic receptor transduces signals to phosphatidylinositol 3-kinase to block A beta-amyloid-induced neurotoxicity. J Biol Chem 276: 13541–13546

Kita T, Okamoto M, Nakashima T (1992) Nicotine-induced sensitization to ambulatory stimulant effect produced by daily administration into the ventral tegmental area and the nucleus accumbens in rats. Life Sci 50: 583–590

Koike K, Hashimoto K, Takai N, Shimizu E, Komatsu N, Watanabe H, Nakazato M, Okamura N, Stevens KE, Freedman R, Iyo M (2005) Tropisetron improves deficits in auditory P50 suppression in schizophrenia. Schizophr Res 76: 67–72

Kuhn HG, Winkler J, Kempermann G, Thal LJ, Gage FH (1997) Epidermal growth factor and fibroblast growth factor-2 have different effects on neural progenitors in the adult rat brain. J Neurosci 17: 5820–5829

Lapchak PA, Araujo DM, Hefti F (1994) Effects of chronic nerve growth factor treatment on hippocampal [^{3}H]cytisine/nicotinic binding sites

and presynaptic nicotinic receptor function following fimbrial transections. Neuroscience 60: 293–298
Lawrence NS, Ross TJ, Stein EA (2002) Cognitive mechanisms of nicotine on visual attention. Neuron 36: 539–548
Le Novere N, Changeux JP (1995) Molecular evolution of the nicotinic acetylcholine receptor: an example of multigene family in excitable cells. J Mol Evol 40: 155–172
Le Novere N, Corringer PJ, Changeux JP (2002) The diversity of subunit composition in nAChRs: evolutionary origins, physiologic and pharmacologic consequences. J Neurobiol 53: 447–456
Lena C, Changeux JP (1998) Allosteric nicotinic receptors, human pathologies. J Physiol Paris 92: 63–74
Levin ED, Bettegowda C, Blosser J, Gordon J (1999) AR-R17779, and alpha7 nicotinic agonist, improves learning and memory in rats. Behav Pharmacol 10: 675–680
Levin ED, Bradley A, Addy N, Sigurani N (2002) Hippocampal alpha 7 and alpha 4 beta 2 nicotinic receptors and working memory. Neuroscience 109: 757–765
Levin ED, Christopher NC, Briggs SJ, Rose JE (1993) Chronic nicotine reverses working memory deficits caused by lesions of the fimbria or medial basalocortical projection. Brain Res Cogn Brain Res 1: 137–143
Levin ED, Rezvani AH (2000) Development of nicotinic drug therapy for cognitive disorders. Eur J Pharmacol 393: 141–146
Levin ED, Simon BB (1998) Nicotinic acetylcholine involvement in cognitive function in animals. Psychopharmacology (Berl) 138: 217–230
Li Y, Papke RL, He YJ, Millard WJ, Meyer EM (1999) Characterization of the neuroprotective and toxic effects of alpha7 nicotinic receptor activation in PC12 cells. Brain Res 830: 218–225
Lichtensteiger W, Hefti F, Felix D, Huwyler T, Melamed E, Schlumpf M (1982) Stimulation of nigrostriatal dopamine neurones by nicotine. Neuropharmacology 21: 963–968
Lindstrom J, Schoepfer R, Whiting P (1987) Molecular studies of the neuronal nicotinic acetylcholine receptor family. Mol Neurobiol 1: 281–337
Lipska BK (2004) Using animal models to test a neurodevelopmental hypothesis of schizophrenia. J Psychiatry Neurosci 29: 282–286
Maelicke A, Samochocki M, Jostock R, Fehrenbacher A, Ludwig J, Albuquerque EX, Zerlin M (2001) Allosteric sensitization of nicotinic receptors by galantamine, a new treatment strategy for Alzheimer's disease. Biol Psychiatry 49: 279–288
Maelicke A, Schrattenholz A, Samochocki M, Radina M, Albuquerque EX (2000) Allosterically potentiating ligands of nicotinic receptors as a treatment strategy for Alzheimer's disease. Behav Brain Res 113: 199–206
Maggio R, Riva M, Vaglini F, Fornai F, Molteni R, Armogida M, Racagni G, Corsini GU (1998) Nicotine prevents experimental parkinsonism in rodents and induces striatal increase of neurotrophic factors. J Neurochem 71: 2439–2446
Mai H, May WS, Gao F, Jin Z, Deng X (2003) A functional role for nicotine in Bcl2 phosphorylation and suppression of apoptosis. J Biol Chem 278: 1886–1891
Mansvelder HD, McGehee DS (2000) Long-term potentiation of excitatory inputs to brain reward areas by nicotine. Neuron 27: 349–357
Mansvelder HD, McGehee DS (2002) Cellular and synaptic mechanisms of nicotine addiction. J Neurobiol 53: 606–617
Martin LF, Kem WR, Freedman R (2004) Alpha-7 nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. Psychopharmacology (Berl) 174: 54–64
Martin-Ruiz CM, Court JA, Molnar E, Lee M, Gotti C, Mamalaki A, Tsouloufis T, Tzartos S, Ballard C, Perry RH, Perry EK (1999) Alpha4 but not alpha3 and alpha7 nicotinic acetylcholine receptor subunits are lost from the temporal cortex in Alzheimer's disease. J Neurochem 73: 1635–1640
Mattson MP, Murrain M, Guthrie PB, Kater SB (1989) Fibroblast growth factor and glutamate: opposing roles in the generation and degeneration of hippocampal neuroarchitecture. J Neurosci 9: 3728–3740
Mayer E, Dunnett SB, Fawcett JW (1993) Mitogenic effect of basic fibroblast growth factor on embryonic ventral mesencephalic dopaminergic neurone precursors. Brain Res Dev Brain Res 72: 253–258
Messi ML, Renganathan M, Grigorenko E, Delbono O (1997) Activation of alpha7 nicotinic acetylcholine receptor promotes survival of spinal cord motoneurons. FEBS Lett 411: 32–38
Mexal S, Frank M, Berger R, Adams CE, Ross RG, Freedman R, Leonard S (2005) Differential modulation of gene expression in the NMDA postsynaptic density of schizophrenic and control smokers. Brain Res Mol Brain Res 139: 317–332
Moffett J, Kratz E, Stachowiak MK (1998) Increased tyrosine phosphorylation and novel cis-acting element mediate activation of the fibroblast growth factor-2 (FGF-2) gene by nicotinic acetylcholine receptor. New mechanism for trans-synaptic regulation of cellular development and plasticity. Brain Res Mol Brain Res 55: 293–305
Mudo G, Mauro A, Trentuno D, Curcio E, Belluardo N, Fuxe K (2005) Acute intermittent nicotine treatment enhances proliferation of neuronal precursor cells in the subventricular zone (svz) of adult rat brain. National Congress of the Italian Society for Neuroscience and Joint Italian-Swedish Neuroscience Meeting, 1–4 Ottobre, Lacco Ameno, Ischia (Naples): P 19_02
Nakata N, Kato H, Kogure K (1993) Protective effects of basic fibroblast growth factor against hippocampal neuronal damage following cerebral ischemia in the gerbil. Brain Res 605: 354–356
Nanri M, Yamamoto J, Miyake H, Watanabe H (1998) Protective effect of GTS-21, a novel nicotinic receptor agonist, on delayed neuronal death induced by ischemia in gerbils. Jpn J Pharmacol 76: 23–29
Navarro HA, Seidler FJ, Eylers JP, Baker FE, Dobbins SS, Lappi SE, Slotkin TA (1989) Effects of prenatal nicotine exposure on development of central and peripheral cholinergic neurotransmitter systems. Evidence for cholinergic trophic influences in developing brain. J Pharmacol Exp Ther 251: 894–900
Nestler EJ (2001) Molecular basis of long-term plasticity underlying addiction. Nat Rev Neurosci 2: 119–128
Nestler EJ (2002) Common molecular and cellular substrates of addiction and memory. Neurobiol Learn Mem 78: 637–647
Newhouse PA, Potter A, Kelton M, Corwin J (2001) Nicotinic treatment of Alzheimer's disease. Biol Psychiatry 49: 268–278
Newhouse PA, Potter A, Singh A (2004) Effects of nicotinic stimulation on cognitive performance. Curr Opin Pharmacol 4: 36–46
Nomikos GG, Schilstrom B, Hildebrand BE, Panagis G, Grenhoff J, Svensson TH (2000) Role of alpha7 nicotinic receptors in nicotine dependence and implications for psychiatric illness. Behav Brain Res 113: 97–103
O'Neill MJ, Murray TK, Lakics V, Visanji NP, Duty S (2002) The role of neuronal nicotinic acetylcholine receptors in acute and chronic neurodegeneration. Curr Drug Targets CNS Neurol Disord 1: 399–411
Ortega S, Ittmann M, Tsang SH, Ehrlich M, Basilico C (1998) Neuronal defects and delayed wound healing in mice lacking fibroblast growth factor 2. Proc Natl Acad Sci USA 95: 5672–5677
Pandey SC (1996) Effects of chronic nicotine treatment on the expression of phospholipase C isozymes and the alpha subunit of Gq/11 protein in the rat brain. Neurosci Lett 212: 127–130
Pandey SC, Roy A, Xu T, Mittal N (2001) Effects of protracted nicotine exposure and withdrawal on the expression and phosphorylation of the CREB gene transcription factor in rat brain. J Neurochem 77: 943–952
Pang PT, Teng HK, Zaitsev E, Woo NT, Sakata K, Zhen S, Teng KK, Yung WH, Hempstead BL, Lu B (2004) Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. Science 306: 487–491
Perry DC, vila-Garcia MI, Stockmeier CA, Kellar KJ (1999) Increased nicotinic receptors in brains from smokers: membrane binding and autoradiography studies. J Pharmacol Exp Ther 289: 1545–1552

Picciotto MR, Caldarone BJ, Brunzell DH, Zachariou V, Stevens TR, King SL (2001) Neuronal nicotinic acetylcholine receptor subunit knockout mice: physiological and behavioral phenotypes and possible clinical implications. Pharmacol Ther 92: 89–108

Pugh PC, Berg DK (1994) Neuronal acetylcholine receptors that bind alpha-bungarotoxin mediate neurite retraction in a calcium-dependent manner. J Neurosci 14: 889–896

Pulvirenti L, Diana M (2001) Drug dependence as a disorder of neural plasticity: focus on dopamine and glutamate. Rev Neurosci 12: 141–158

Quik M (2004) Smoking, nicotine and Parkinson's disease. Trends Neurosci 27: 561–568

Ripoll N, Bronnec M, Bourin M (2004) Nicotinic receptors and schizophrenia. Curr Med Res Opin 20: 1057–1074

Roceri M, Molteni R, Fumagalli F, Racagni G, Gennarelli M, Corsini G, Maggio R, Riva M (2001) Stimulatory role of dopamine on fibroblast growth factor-2 expression in rat striatum. J Neurochem 76: 990–997

Role LW, Berg DK (1996) Nicotinic receptors in the development and modulation of CNS synapses. Neuron 16: 1077–1085

Rowntree S, Kolb B (1997) Blockade of basic fibroblast growth factor retards recovery from motor cortex injury in rats. Eur J Neurosci 9: 2432–2441

Ryan RE, Ross SA, Drago J, Loiacono RE (2001) Dose-related neuroprotective effects of chronic nicotine in 6-hydroxydopamine treated rats, and loss of neuroprotection in alpha4 nicotinic receptor subunit knockout mice. Br J Pharmacol 132: 1650–1656

Sacco KA, Bannon KL, George TP (2004) Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders. J Psychopharmacol 18: 457–474

Sallette J, Pons S, villers-Thiery A, Soudant M, Prado de CL, Changeux JP, Corringer PJ (2005) Nicotine upregulates its own receptors through enhanced intracellular maturation. Neuron 46: 595–607

Salomon AR, Marcinowski KJ, Friedland RP, Zagorski MG (1996) Nicotine inhibits amyloid formation by the beta-peptide. Biochemistry 35: 13568–13578

Samaha AN, Robinson TE (2005) Why does the rapid delivery of drugs to the brain promote addiction? Trends Pharmacol Sci 26: 82–87

Schneider JS, Tinker JP, Menzaghi F, Lloyd GK (2003) The subtype-selective nicotinic acetylcholine receptor agonist SIB-1553A improves both attention and memory components of a spatial working memory task in chronic low dose 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys. J Pharmacol Exp Ther 306: 401–406

Seguela P, Wadiche J, neley-Miller K, Dani JA, Patrick JW (1993) Molecular cloning, functional properties, and distribution of rat brain alpha 7: a nicotinic cation channel highly permeable to calcium. J Neurosci 13: 596–604

Semba J, Miyoshi R, Kito S (1996) Nicotine protects against the dexamethasone potentiation of kainic acid-induced neurotoxicity in cultured hippocampal neurons. Brain Res 735: 335–338

Shim IS, Won JS, Lee JK, Song DK, Kim SE, Huh SO, Kim YH, Suh HW (2000) Modulatory effect of ginseng total saponin on dopamine release and tyrosine hydroxylase gene expression induced by nicotine in the rat. J Ethnopharmacol 70: 161–169

Shimohama S, Akaike A, Kimura J (1996) Nicotine-induced protection against glutamate cytotoxicity. Nicotinic cholinergic receptor-mediated inhibition of nitric oxide formation. Ann NY Acad Sci 777: 356–361

Shimohama S, Kihara T (2001) Nicotinic receptor-mediated protection against beta-amyloid neurotoxicity. Biol Psychiatry 49: 233–239

Singh IN, Sorrentino G, Sitar DS, Kanfer JN (1998) (–)Nicotine inhibits the activations of phospholipases A2 and D by amyloid beta peptide. Brain Res 800: 275–281

Small DH, Mok SS, Bornstein JC (2001) Alzheimer's disease and Abeta toxicity: from top to bottom. Nat Rev Neurosci 2: 595–598

Sofroniew MV, Galletly NP, Isacson O, Svendsen CN (1990) Survival of adult basal forebrain cholinergic neurons after loss of target neurons. Science 247: 338–342

Stachowiak MK, Moffett J, Joy A, Puchacz E, Florkiewicz R, Stachowiak EK (1994) Regulation of bFGF gene expression and subcellular distribution of bFGF protein in adrenal medullary cells. J Cell Biol 127: 203–223

Summers KL, Giacobini E (1995) Effects of local and repeated systemic administration of (–)nicotine on extracellular levels of acetylcholine, norepinephrine, dopamine, and serotonin in rat cortex. Neurochem Res 20: 753–759

Summers KL, Kem WR, Giacobini E (1997) Nicotinic agonist modulation of neurotransmitter levels in the rat frontoparietal cortex. Jpn J Pharmacol 74: 139–146

Sun X, Liu Y, Hu G, Wang H (2004) Protective effects of nicotine against glutamate-induced neurotoxicity in PC12 cells. Cell Mol Biol Lett 9: 409–422

Sweatt JD (2001) The neuronal MAP kinase cascade: a biochemical signal integration system subserving synaptic plasticity and memory. J Neurochem 76: 1–10

Tanabe J, Tregellas JR, Martin LF, Freedman R (2005) Effects of Nicotine on Hippocampal and Cingulate Activity During Smooth Pursuit Eye Movement in Schizophrenia. Biol. Psychiatry: PM: 16259965

Tani Y, Saito K, Imoto M, Ohno T (1998) Pharmacological characterization of nicotinic receptor-mediated acetylcholine release in rat brain-an in vivo microdialysis study. Eur J Pharmacol 351: 181–188

Toborek M, Garrido R, Malecki A, Kaiser S, Mattson MP, Hennig B, Young B (2000) Nicotine attenuates arachidonic acid-induced overexpression of nitric oxide synthase in cultured spinal cord neurons. Exp Neurol 161: 609–620

Tooyama I, Kawamata T, Walker D, Yamada T, Hanai K, Kimura H, Iwane M, Igarashi K, McGeer EG, McGeer PL (1993) Loss of basic fibroblast growth factor in substantia nigra neurons in Parkinson's disease. Neurology 43: 372–376

Vallejo YF, Buisson B, Bertrand D, Green WN (2005) Chronic nicotine exposure upregulates nicotinic receptors by a novel mechanism. J Neurosci 25: 5563–5572

Vernier JM, El-Abdellaoui H, Holsenback H, Cosford ND, Bleicher L, Barker G, Bontempi B, Chavez-Noriega L, Menzaghi F, Rao TS, Reid R, Sacaan AI, Suto C, Washburn M, Lloyd GK, McDonald IA (1999) 4-[[2-(1-Methyl-2-pyrrolidinyl)ethyl]thio]phenol hydrochloride (SIB-1553A): a novel cognitive enhancer with selectivity for neuronal nicotinic acetylcholine receptors. J Med Chem 42: 1684–1686

Wada E, McKinnon D, Heinemann S, Patrick J, Swanson LW (1990) The distribution of mRNA encoded by a new member of the neuronal nicotinic acetylcholine receptor gene family (alpha 5) in the rat central nervous system. Brain Res 526: 45–53

Wada E, Wada K, Boulter J, Deneris E, Heinemann S, Patrick J, Swanson LW (1989) Distribution of alpha 2, alpha 3, alpha 4, and beta 2 neuronal nicotinic receptor subunit mRNAs in the central nervous system: a hybridization histochemical study in the rat. J Comp Neurol 284: 314–335

Walters CL, Cleck JN, Kuo YC, Blendy JA (2005) Mu-opioid receptor and CREB activation are required for nicotine reward. Neuron 46: 933–943

Wang H, Sun X (2005) Desensitized nicotinic receptors in brain. Brain Res Rev 48: 420–437

Warburton DM, Wesnes K, Shergold K, James M (1986) Facilitation of learning and state dependency with nicotine. Psychopharmacology (Berl) 89: 55–59

Wonnacott S (1990) The paradox of nicotinic acetylcholine receptor upregulation by nicotine. Trends Pharmacol Sci 11: 216–219

Zamani MR, Allen YS (2001) Nicotine and its interaction with beta-amyloid protein: a short review. Biol Psychiatry 49: 221–232