Nicotine: Pharmacology and Therapeutic Implications in Neurodegenerative and Psychiatric Disorders

Charles Scerri

Abstract

The pathophysiology of tobacco-related diseases is complex and multifactorial. Among the various compounds in tobacco smoke are carcinogens such as nitrosamines, irritants such as a variety of phenolic compounds, volatiles such as carbon monoxide, and of course nicotine. Nicotine itself has quite complex actions, mediated in part by nicotinic cholinergic receptors that may have extraneuronal, as well as neuronal distribution. Its actions have also been implicated in a variety of neurodegenerative and psychiatric disorders. This short review discusses the recent pharmacology of nicotine and recent progress on its possible therapeutic benefits.

Keywords

Nicotine, smoking, withdrawal, Parkinson's disease, Alzheimer's disease, depression, schizophrenia, anxiety, psychiatric disorders

Charles Scerri PhD, CBiol MIBiol Department of Clinical Pharmacology and Therapeutics University of Malta, Msida, Malta E-mail: charles.scerri@um.edu.mt

Introduction

There is little doubt that the majority of people who smoke tobacco do so in order to experience the psychopharmacological properties of nicotine present in smoke and that a significant proportion of habitual tobacco users become addicted to the drug.¹ As a result, nicotine itself has been used increasingly by many smokers wanting to stop smoking highlighting its important therapeutic role. However, nicotine has also been found to influence neural systems in the brain that are thought to be involved in a range of neurological disorders. The rate of smoking is much higher in schizophrenics (up to 90%), depressed patients (up to 65%) and alcoholics (up to 90%) than in the general population.² It appears that these effects of nicotine are mediated through selective activation of different subtypes of the neuronal nicotinic acetylcholine receptor (nAChR). Nicotine interacts with a variety of pre-synaptic nAChRs to facilitate the release of a number of neurotransmitters including acetylcholine (ACh), dopamine (DA), noradrenaline (NA), serotonin (5-HT), gammaaminobutyric acid (GABA) and glutamate, many of which play an important role in mediating a number of cognitive functions.³ Recent studies on the effects of nicotinic receptor stimulation in neural dysfunction show the potential for therapeutic utility of nicotinic drugs.

Neuronal nicotinic receptors

Nicotinic receptors are cationic channels mediating fast synaptic transmission whose opening is controlled by ACh and nicotinic receptor agonists such as nicotine.45 They belong to a large family of homologous receptors including GABA, glycine and the 5-HT₂ receptor.⁶ A number of different subtypes exist with individual pharmacological and physiological profiles and distinct anatomical distribution in the brain.7 To date, eight alpha (alpha2-7, 9, 10) and three beta (beta2 - beta4) nAChR subunits have been identified in mammals.8 By analogy with the muscle nAChRs, neuronal nAChRs are believed to have a pentameric structure consisting of five membrane spanning regions around a central ion channel. Although much is known about the structure and functional properties of neuronal nAChRs, relatively little is understood about their physiological role in man.9 Evidence suggests that nAChRs do not appear to function solely in the classical postsynaptic manner as their muscle counterparts as their location in the brain is not limited to postsynaptic but also to pre-, peri- and extrasynaptic sites

where they can modulate neuronal function by a variety of actions.¹⁰ These include a number of functional processes such as learning and memory, attention, cerebral blood flow and metabolism, as well as a growing list of pathological disorders^{11,12} including Alzheimer's disease (AD) in which there is a significant loss of nAChR sites.¹³

Nicotine withdrawal and reinforcement

Withdrawal from nicotine following smoking cessation results in symptoms such as depression, frustration, agitation, anxiety, difficulty of concentration and craving for tobacco. Although nicotine replacement therapies (NRTs) have been well established as smoking cessation aids following their ability to reverse the effects of nicotine withdrawal^{14,15}, some antidepressants such as fluoxetine and buproprion have also been reported to have beneficial effects on nicotine withdrawal symptoms.¹⁶ Moreover, buproprion appears to work equally well in smokers with and without past history of depression, suggesting that the efficacy of the drug is not due to its antidepressant effect. In behavioural studies using animal models, cessation of continuous nicotine infusions produces withdrawal symptoms similar to opiate withdrawal suggesting a possible common physiological mechanism.¹⁷

Several behavioural studies have demonstrated the reinforcing properties of nicotine in animal models, which are also quite evident in humans. Nicotine can maintain self-administration behaviour in rats, and lesion and discrete microinjection studies have demonstrated a critical role for the mesolimbic DA pathways in nicotine self-administration. Mutant mice lacking the beta2 nAChR subunit do not self-administer nicotine denoting the possible involvement of functional beta2-containing nAChR subtypes in the rewarding effects of nicotine.¹⁸

Nicotine and Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative condition involving the dopaminergic neurons of the substantia nigra. It is characterised by difficulty in initiating and smoothly sustaining movement. In PD there is loss of cholinergic cells in the basal forebrain accompanied by a significant reduction in the number of nicotine binding sites in the brain.⁹ The etiology of the disease is unknown, although it appears to be multifactorial in origin, possibly arising from a complex interaction between genetics and environment.¹⁹ The most commonly used treatment is dopamine replacement therapy. Although initially very effective, L-dopa provides only symptomatic relief with an inevitable disease progression. Moreover it loses efficacy with time and is accompanied by the development of drug-induced side effects.²⁰

The rationale for considering nicotine as a possible therapeutic agent is based on epidemiological findings that PD is less prevalent in smokers. Indeed this is the most robust observation linking environment and PD.²¹Although cigarette smoking is composed of thousands of chemicals, nicotine represents a possible candidate for two reasons: it stimulates dopaminergic neurons that are selectively damaged in the striatum of PD patients and its exposure has been reported to protect against insults in various experimental models. Indeed, the inverse association between smoking and PD has been consistently reported in over 40 independent studies by different investigators over the past 50 years.¹⁹ Furthermore, the effects of smoking are dose dependent and related to the number of cigarette-pack-years.²² Although many questions remain unanswered, a recent study in twins demonstrating a reduced PD risk with smoking led the authors to conclude that there is a protective effect of cigarette smoking.²³

Nicotine and Alzheimer's disease

Cholinergic transmitter replacement therapy forms the mainstay of Alzheimer's disease (AD) symptomatic treatment and it is based on the hypothesis that low levels of ACh are responsible for the cognitive decline associated with the disease. Classically, replacement therapy has involved the use of cholinesterase inhibitors which prevent the breakdown of ACh at the cholinergic terminals, therefore increasing the concentration of the neurotransmitter available to interact with the receptors. It is also likely that the therapeutic benefit of cholinesterase inhibitor treatment occurs at least in part, through the activation of neuronal nAChRs either by direct action of the increased levels of ACh on these receptors or through allosteric modulation of the receptors.9 Neuronal nAChR activation is therefore currently being investigated as a strategy for AD therapy. The potential therapeutic benefit in AD from nAChR stimulation is based on three main observations. Firstly, stimulation of nAChR by nicotine or similar agonists improves memory function in animal models. Secondly, nAChR activation modulates the release of a number of neurotransmitters such as ACh, DA, GABA and glutamate which will enhance the release of ACh. Thirdly, there is evidence to suggest that nicotine provides protection against neurotoxic plaque formation,²⁴ the concentrations of which are elevated in AD. Taking these observations, together with the reported loss of nAChR concentrations in AD, the development of nicotinebased therapies as potential therapeutic agents in AD should be promising. Indeed, clinical studies using nicotine dermal patches have reported a modest enhancement of cognitive performance in AD patients.25,26

Nicotine and psychiatric disorders *Schizophrenia*

Schizophrenia is a chronically deteriorating heterogeneous psychosis beginning in late adolescence or early adulthood and is characterised by hallucinations, delusions, bizarre behaviour, apathy and blunted affect.²⁷ Previous epidemiological studies have shown that there is a high percentage of smokers present in the schizophrenic population (80 - 90%) compared with the general population (25 - 30%) and a low rate of smoking cessation among individuals with schizophrenia.^{28,29}

Schizophrenic patients have also been observed to have high levels of nAChR antibodies, which may be a contributing factor in the reduced number of nAChRs observed in schizophrenia. Smoking also decreases neuroleptic hepatic metabolism³⁰ resulting in smokers needing a higher dose of antipsychotic therapy. While it is possible that smoking causes or exacerbates the condition, most studies suggest that the high incidence of smoking in schizophrenic patients is an attempt on their part to self-medicate nicotine to overcome a deficit in nicotinic neurotransmission.1 On a receptor level, post-mortem studies have shown a reduction in the number of alpha7-containing nAChRs in the hippocampus of schizophrenic patients compared to controls. Although further studies are needed to determine the neurophysiological mechanisms involved, these observations suggest that stimulation of this particular subunit by nicotinic agonists, such as nicotine, may be beneficial in schizophrenia.

Anxiety and depression

nAChRs are apparently involved in the pathophysiology of both anxiety disorders and depression. Nicotine administration has been observed to have anxiolytic effects in humans and in animal models of anxiety.^{31,32} This action may be blocked by antagonists to the nAChRs and by the benzodiazepine (BZ) channel blocker flumazenil suggesting that the anxiolytic action of nicotine may be the result of enhanced release of the inhibitory neurotransmitter GABA, which then acts on the central GABA_A-BZ multi-receptor complex.

Both retrospective and prospective clinical studies have demonstrated a relationship between smoking and major depression. The rate of smoking is much higher in depressed patients than in the general population.² These patients have greater difficulty in stopping smoking and are at an increased risk of suffering mild to severe depression upon smoking cessation. Epidemiological studies have shown that the prevalence of depression in smokers is directly correlated with the prevalence of nicotine dependence,33.34 and smokers with a history of major depression are less likely to quit smoking.34.35 Moreover, smoking cessation frequently precipitates depressive symptoms that can be reversed by the reintroduction of smoking³⁶ and evidence from clinical studies suggests that nicotine patches have antidepressant action.^{37,38} Therefore, it may appear that smoking is a self-medication effort intended to alleviate some symptoms of depression using nicotine. However, it is difficult to evaluate the antidepressant properties of nicotine in smokers because it is difficult to separate the antidepressant effect per se from the alleviation of depression that follows nicotine withdrawal.³⁹ There is also a considerable body of evidence linking the action of classical tricyclic antidepressants (TCAs) and the selective serotonin reuptake inhibitors (SSRIs) to nAChRs. The majority of TCAs, including imipramine, amytriptyline and nortriptyline, all produce a noncompetitive inhibition of nAChRs.⁴⁰ The SSRIs fluoxetine, paroxetine, sertaline and venlafaxine also produce similar

reversible non-competitive inhibition of nAChRs.⁴¹ Furthermore, in rat hippocampal slices, fluoxetine has been found to inhibit nicotine-induced release of noradrenaline in a dose-dependent manner.⁴² Despite the well characterised relationship between smoking, depression, antidepressants, and nicotine, the role of nicotine-sensitive receptors in the brain as targets for antidepressant treatment remains underappreciated.

Conclusion

Smoking has been shown to be associated with the occurrence of many fatal diseases and is currently the single most preventable cause of death. However, the possibility exists that nicotine may be beneficial in the protection against a number of diseases with relatively low frequencies. More studies are needed to clarify the various possible biological effects of tobacco smoking, particularly through its nicotine component in neurodegenerative and psychiatric disorders.

References

- 1. Balfour DJK, Fagerstrom KO. Pharmacology of nicotine and its therapeutic use in smoking cessation and neurodegenerative disorders. Pharmacol Ther. 1996;72:51-81.
- 2. Picciotto MR, Caldarone BJ, King SL, Zachariou V. Nicotinic receptors in the brain. Links between molecular biology and behavior. Neuropsychopharmacology 2000;22:451-465.
- Araki H, Suemaru K, Gomita Y. Neuronal nicotinic receptor and psychiatric disorders: functional and behavioural effects of nicotine. Jpn J Pharmacol. 2002;88:133-138.
- 4. Changeux JP, Bertrand D, Corringer PJ, Dehaene S, Edelstein S, Léna C, Le Novère N, Marubio L, Picciotto M, Zoli M. Brain nicotinic receptors: structure and regulation, role in learning and reinforcement. Brain Res Rev. 1998;26:198-216.
- 5. Hogg RC, Raggenbass M, Bertrand D. Nicotinic acetylcholine receptors: from structure to brain function. Rev Physiol Biochem Pharmacol. 2003;147:1-46.
- Karlin A, Akabas MH. Towards a structural basis for the function of nicotinic acetylcholine receptors and their cousins. Neuron 1995;15:1231-1244.
- 7. Court JA, Martin-Ruiz C, Graham A, Perry E. Nicotinic receptors in human brain: topography and pathology. J Chem Neuroanat. 2000;20:281-298.
- 8. Tribollet E, Bertrand D, Marguerat A, Raggenbass M. Comparative distribution of nicotinic receptor subtypes during development, adulthood and aging: an autoradiographic study in the rat brain. Neuroscience 2004;12:405-420.
- 9. Paterson D, Nordberg A. Neuronal nicotinic receptors in the human brain. Prog Neurobiol. 2000;61:75-111.
- 10. Lindstrøm J. Nicotinic acetylcholine receptors in health and disease. Mol Neurobiol. 1997;15:193-222.
- Levin ED, Simon BB. Nicotinic acetylcholine involvement in cognitive function in animals. Psychopharmacology (Berl). 1998;138:217-230.
- 12. Cordero-Erausquin M, Marubio LM, Klink R, Changeux JP. Nicotinic receptor function: new perspectives from knockout mice. Trends Pharmacol Sci. 2000;21:211-217.
- 13. Whitehouse PJ, Martino AM, Wagster MV, Price DL, Mayeux R, Atack JR, Kellar KJ. Reductions in [³H]nicotinic acetylcholine binding in Alzheimer's disease and Parkinson's disease: an autoradiographic study. Neurology 1988;38:720-723.
- West R, Shiffman S. Effect of oral nicotine dosing forms on cigarette withdrawal symptoms and craving: a systemic review. Psychopharmacology (Berl). 2001;155:115-122.
- 15. Fagerstrom KO, Hughes JR. Nicotine concentrations with concurrent use of cigarettes and nicotine replacement: a review. Nicotine Tob Res. 2002;4:S73-S79.

- 16. Hitsman B, Pingitore R, Spring B, Mahableshwarkar A, Mizes JS, Segraves KA, Kristeller JL, Xu W. Antidepressant pharmacotherapy helps some cigarette smokers more than others. J Consult Clin Psychol. 1999;67:547-554.
- 17. Pontieri FE, Tanda G, Orzi F, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature 1996;382:255-257.
- Picciotto MR, Zoli M, Rimondini R, Lena C, Marubio LM, Pich EN, Fuxe K, Changeux JP. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. Nature 1998;391:173-177.
- 19. Quik M. Smoking, nicotine and Parkinson's disease. Trends Neurosci. 2004; 27:561-568.
- 20.Olanow CW, Tatton WG. Etiology and pathogenesis of Parkinson's disease. Annu Rev Neurosci. 1999;22:123-144.
- 21. Quik M, Kulak JM. Nicotine and nicotinic receptors: relevance to Parkinson's disease. Neurotoxicology 2002;23:581-594.
- 22.Gorell JM, Rybicki BA, Johnson CC, Peterson EL. Smoking and Parkinson's disease: a dose-response relationship. Neurology 1999;52:115-119.
- 23. Tanner CM, Goldman SM, Aston DA, Ottman R, Ellenberg J, Mayeux R, Langston JW. Smoking and Parkinson's disease in twins. Neurology 2002;58:581-588.
- 24. Kihara T, Shimohama S, Urushitani M, Sawada H, Kimura J, Kume T, Maeda T, Akaike A. Stimulation of alpha4 beta2 nicotinic acetylcholine receptors inhibits beta-amyloid toxicity. Brain Res. 1998;792:331-334.
- 25. Wilson AL, Langley LK, Monley J, Bauer T, Rottunda S, McFalls E, Kovera C, McCarten JR. Nicotine patches in Alzheimer's disease: pilot study on learning, memory, and safety. Pharmacol Biochem Behav. 1995;51:509-514.
- 26. White HK, Levin ED. Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. Psychopharmacology (Berl). 1999;143:158-165.
- 27. Arnold SE, Trojanowski JQ. Recent advances in defining the neuropathology of schizophrenia. Acta Neuropathol (Berl). 1996;92:217-231.
- 28.Ripoll N, Bronnec M, Bourin M. Nicotinic receptors and schizophrenia. Curr Med Res Opin. 2004;20:1057-1074.
- 29.Dalack GW, Healy DJ, Meador-Woodruff JH. Nicotine dependence in schizophrenia: clinical phenomenon and laboratory findings. Am J Psychiatry. 1998;155:1490-1501.

- 30.Salokangas RK, Saarijarvi S, Taiminen T, Lehto H, Niemi H, Ahola V, Syvalahti E. Effect of smoking on neuroleptics in schizophrenia. Schizophr Res. 1997;23:55-60.
- 31. Decker MW, Brioni JD, Sullivan JP, Buckley MJ, Radek RJ, Raszkiewicz JL, Kang CH, Kim DJ, Giardina WJ, Wasicak JT. (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. 1994;270:319-328.
- 32. Cheeta S, Kenny PJ, File SE. Hippocampal and septal injections of nicotine and 8-OH-DPAT distinguish among different animal tests of anxiety. Prog Neuropsychopharmacol Biol Psychiatry. 2000;24:1053-1067.
- 33. Breslau N, Klein DF. Smoking and panic attacks: an epidemiological investigation. Arch Gen Psychiatry 1999;56: 1141-1147.
- 34. Wilhelm K, Arnold K, Niven H, Richmond R. Grey lungs and blue moods: smoking cessation in the context of lifetime depression history. Aust N Z J Psychiatry. 2004;38:896-905.
- 35. Covey LS, Glassman AH, Stetner F. Cigarette smoking and major depression. J Addict Dis. 1998;17:35-46.
- 36.Stage KB, Glassman AH, Covey LS. Depression after smoking cessation: case reports. J Clin Psychiatry. 1996;57:467-469.
- 37. Salin-Pascual RJ, Rosas M, Jimenez-Genchi A, Rivera-Meza BL, Delgrado-Parra V. Antidepressant effect of transdermal nicotine patches in non-smoking patients with major depression. J Clin Psychiatry. 1996;57:387-389.
- 38.Haustein KO, Haffner S, Woodcock BG. A review of the pharmacological and psychopharmacological aspects of smoking and smoking cessation in psychiatric patients. Int J Clin Pharmacol Ther. 2002;40:404-418.
- 39.Breslau N, Peterson EL, Schultz LR, Chilcoat HD, Andreski P. Major depression and the stages of smoking. A longitudinal investigation. Arch Gen Psychiatry. 1998;55:161-166.
- 40.Rana B, McMorn SO, Reeve HL, Wyatt CN, Vaughan PF, Peers C. Inhibition of neuronal nicotinic acetylcholine receptors by imipramine and desipramine. Eur J Pharmacol. 1993;250: 247-251.
- Fryer J, Lukas R. Antidepressants noncompetitively inhibit nicotinic acetylcholine receptor function. J Neurochem. 1999;72:1117-1124.
- 42. Hennings EC, Kiss JP, Vizi ES. Nicotinic acetylcholine receptor antagonist effect of fluoxetine in rat hippocampal slices. Brain Res. 1997;759:292-294.

Corinthia Group Prize in Paediatrics, 2005

Dr Amanda Bartolo was this year's winner of the Corinthia Group Prize in Paediatrics, having obtained the top aggregate mark over the combined examinations in Paediatrics in the fourth and final year of the undergraduate course. As always, competition for the Corinthia Group Prize was as stiff as ever, with several candidates vying for the honour. Whilst offering our congratulations to Dr Bartolo, we would also like to congratulate all those undergraduates (now doctors) who performed admirably during the undergraduate course in Paediatrics. In the accompanying photograph, Dr Bartolo is seen receiving a cheque for Lm100 from Dr Simon Attard Montalto, Head of Paediatrics at the Medical School. Finally, we are extremely grateful to the Corinthia Group for their ongoing support toward the Academic Department of Paediatrics.

