



Nicotinic Receptor Intervention in Parkinson's Disease: Future Directions

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Abstract: Sufficient preclinical and epidemiological data are available to justify nicotinic intervention in Parkinson's disease (PD). Although use of nicotine patch has been suggested in some neurodegenerative disorders, including PD, the key for success with nicotinic intervention, particularly in PD, appears to rely not only on the dose but also on the mode of nicotine administration. Our aim in this short review is to provide justification for such contention. Thus, following a short introduction of nicotinic receptor pharmacology, the potential of nicotine in alleviating not only the motor symptoms, but also the mood disorders (e.g. depression) and mild cognitive impairments that are commonly co-morbid with PD will be presented. Moreover, since current PD therapy is associated with dyskinesia, the effectiveness of nicotine in ameliorating levodopa (L-Dopa)-induced dyskinesia will also be discussed. It is suggested that pulsatile nicotine administration (e.g. via inhalation or nasal spray) may be the optimal route in nicotinic intervention in PD.

Keywords: Parkinson's disease, Nicotine, Nicotinic Receptors, Depression, Cognitive Function, Dyskinesia

Introduction

Parkinson's disease

Parkinson's disease (PD), the second most common progressive neurodegenerative disorder, is associated with loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) that leads to basal ganglia dopamine (DA) deficiency [1]. This dopaminergic loss results in motor deficits characterized by: akinesia, rigidity, resting tremor and postural instability as well as non-motor symptoms that might also involve other neurotransmitter systems [2]. The non-motor symptoms may include: cognitive deficits (e.g., mild to severe memory impairment), emotional changes (e.g., depression, apathy and anxiety), sleep perturbations (e.g., insomnia/hypersomnia), autonomic dysfunction (e.g., bladder disturbances, orthostatic hypotension, sweating), sensory symptoms (e.g., pain, visual and olfactory deficits) and gastrointestinal symptoms (e.g., constipation, nausea) [2]. The most common treatment is focused on dopamine replacement (e.g. levodopa=L-Dopa), which unfortunately loses its full efficacy in a few years and can induce severe dyskinesia. The other limitation of current interventions is that none truly addresses the root cause (i.e., progressive neurodegeneration) [3]. Hence, more efficacious interventions without such severe side effects are urgently needed.

The consistent observation of an inverse relationship between smoking regular cigarettes [4-12] or smokeless tobacco [13-15] and PD, combined with convincing evidence of potential neuroprotective effects of nicotine (discussed below) suggest a possible novel intervention in PD.

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Nicotine and Nicotinic Receptors

Nicotine's main targets are nicotinic receptors that are widely distributed in the central nervous system (CNS) [16, 17]. These receptors have been directly implicated not only in reward pathway and addiction to nicotine [18], but also in a variety of central functions such as mood regulation [19], cognitive and attention processes [20], pain [21, 22] neuronal plasticity [23] and neuronal protection [24-27]. Nicotinic receptor involvement in neuronal plasticity is considered as one of nicotine's main mechanisms responsible for its neuroprotective effects [28-31].

Nicotinic acetylcholine receptors (nAChRs) belong to the ionotropic class of receptors, which directly regulate the opening of a cation channel in the neuronal membrane [17, 32-35]. Considerable information on interaction between these receptors and other neurotransmitter systems is now available and as indicated above, therapeutic potentials for selective nicotinic receptor agonists in a myriad of neuropsychiatric and neurodegenerative disorders have been suggested. Various subtypes (currently, 11 neuronal nACh receptors alpha2-alpha7, alpha 9, alpha 10, beta2-beta4), which assemble into pentameric complexes and provide subunit diversity and distinct anatomical, physiological, and pharmacological characteristics have been identified [17, 32, 33, 35-38]. The predominant and most extensively studied subtype in the brain has a high affinity for cytosine, nicotine or acetylcholine and is formed from $\alpha 4$ and $\beta 2$ subunits [39-42]. This subtype is commonly referred to as high-affinity binding site. The other major class with a high affinity for α -bungarotoxin but low affinity for nicotine is formed from $\alpha 7$ subunits and can be labeled by [¹²⁵I] α -bungarotoxin. This subtype is commonly referred to as low-affinity binding site. It should be noted that [¹²⁵I] α -bungarotoxin also binds with high affinity to neuro-muscular nicotinic receptors and in some cases to ganglionic nicotinic receptors [43]. However, the subunit structures of the nicotinic receptors in the muscle are different from those in the ganglia, which are different from those in the CNS [33-35]. Further distinction between nicotinic receptor subtypes

is evident in their central distribution as well as their physiological roles. For example, [¹²⁵I]α-bungarotoxin binding sites in the brain are most abundant in the hippocampus [39] and are believed to have a prominent role in neuronal growth and survival [44]. Furthermore, these receptors appear to be involved in cognitive functions, particularly attentional processes [36, 45, 46]. A role for α7 receptor subtype in central reward pathway has also been suggested [47, 48]. High-affinity nicotinic receptors (e.g., α4-β2), on the other hand, are more prominent in mesolimbic or nigrostriatal pathways and appear to be more involved in rewarding or addictive behavior, locomotor activity and antinociception [32, 42, 49-52]. Both receptors appear to be involved in neuroprotection as well [29, 53-55]. Interestingly, nicotine may also exert antidepressant-like effects that are likely mediated through high-affinity nicotinic receptors [56, 57, 26].

Role of the Nicotinic Cholinergic System in PD

Multiple studies indicate that normal function of the basal ganglia is dependent on the equilibrium between the midbrain dopaminergic and striatal cholinergic systems [58]. Thus, acetylcholine can regulate striatal DA release via an interaction at various nicotinic receptors [59-65]. Moreover, in 6-OHDA-lesioned rodents (an animal model of PD), the behavioral consequence of the impairment in DA release may be ameliorated by nicotine, suggesting nicotinic receptors as a therapeutic target in PD [66, 67]. Indeed, a number of in-vitro and in-vivo studies in rodents including genetically modified mice, and in non-human primates have shown protective effects of nicotine against neuronal damage induced by 6-OHDA, MPTP, rotenone, paraquat, methamphetamine, glutamate and β-amyloid [68]. These effects are mediated via selective nicotinic receptor subtypes containing β2 and α7 subunits [69-75]. We have also observed protective effects of nicotine against endogenous substances such as salsolinol and aminochrome that selectively damage dopaminergic cells [25,76-80]. Nicotine's effects are likely to involve suppression of oxidative stress, pro-inflammatory cytokines, apoptosis as well as stimulation of neurotrophic factors [2, 28, 68, 81-83].

Several clinical trials, using nicotine patch primarily for prevention or treatment of PD have been conducted or are ongoing [Table 1].

Whereas previous trials have not provided a clear beneficial effects of nicotine transdermal patch [84, 85] a more recent study reports modest positive effects [86]. The modest or lack of nicotine patch effect in such studies may be due to variation in dosing or duration of nicotine, but perhaps most importantly, due to the mode of nicotine administration, as discussed below.

Importance of Mode of Nicotine Administration in PD

Of central relevance to this review is that the majority of human studies assessing the effects of nicotine have used the gum or patch to administer nicotine, which may not activate nicotinic receptors as strongly as smoking [87]. Indeed, the very complex dynamic interaction of nicotine with its receptors, where initial stimulation can be followed by rapid and differential desensitization of receptor subtypes, are crucial in experimental paradigms, and have to be seriously considered for an optimal outcome involving nicotinic intervention [17, 73]. It is well established that nicotinic receptor stimulation can lead to desensitization followed by recovery [88]. The time course of these events, i.e., stimulation, desensitization and recovery depend not only on the dose of nicotine, but also on the receptor subtype, its location and the duration of nicotine exposure [17, 30, 89]. In this regard, it is important to note that some of the beneficial effects of nicotine, for example on weight control, may be mostly due to desensitization of selective nicotinic receptor subtype in discrete circuitry [90]. Nonetheless, it is also a known fact that smokers indicate their most pleasure (or reward) from the first cigarette in the morning, which occurs following few hours of abstinence during sleep (TTURC 2007). This enhanced feeling of reward following a relatively short abstinence (withdrawal) may be due to sensitization of selective nicotinic receptor subtype in the reward circuitry, which may entail increased release of dopamine in the nucleus accumbens shell [27, 91-93]. Thus, it could be suggested that pulsatile stimulation of specific nicotinic receptors in selective brain regions, particularly in the nigrostriatal pathway would be critical for its maximal therapeutic effects in PD. This may be achieved by administering nicotine via inhalation (or nasal spray), as this mode would be mimicking the smoking paradigm that has been associated with protection against PD.

Table 1. Select Studies on Nicotine intervention in PD as reported in ClinicalTrials.gov (2017)

Study	Study Design	Intervention/Outcome
Disease-modifying Potential of Transdermal Nicotine in Early Parkinson's Disease	Allocation: Randomized Intervention Model: Parallel Double Blind Primary Purpose: Prevention	Nicotine transdermal patch Status: ongoing (recruiting) Outcome: No study results available
Study of NP002 in Subjects with Idiopathic Parkinson's Disease to Treat Dyskinesias Due to Levodopa Therapy	Allocation: Randomized Intervention Model: Parallel Double Blind Primary Purpose: Treatment	Nicotine Other: placebo comparator Status: Completed Outcome: No study results available
Efficacy of Transdermal Nicotine, on Motor Symptoms in Advanced Parkinson's Disease	Allocation: Randomized Intervention Model: Parallel Open Label Primary Purpose: Treatment	Transdermal nicotine with usual drug treatment of Parkinson's disease Status: Completed Outcome: Positive
Nicotine Treatment of Impulsivity in Parkinson's Disease	Allocation: Randomized Intervention Model: Crossover Double Blind Primary Purpose: Treatment	Nicotine patch; Placebo Status: Unknown Outcome: No study results available
The Effects of Nicotine Chewing Gum in Parkinson's Disease	Intervention Model: Single Open Label Primary Purpose: Treatment	Dietary Supplement: Nicotine gum Status: ongoing (recruiting) Outcome: No study results available

Nicotine-Depression-Cognition

It is also of importance to note that, in addition to its potential usefulness for improving motor dysfunctions and neuroprotection against nigrostriatal damage, nicotine administration may also be helpful in non-motor symptoms (e.g. depression and cognitive decline) that are commonly associated with neurological disorders such as PD [68, 73, 94]. Below, we will briefly discuss the antidepressant and cognitive enhancement properties of nicotine.

Nicotine as an antidepressant

As reviewed recently [68, 82], a number of preclinical [26, 56, 57, 95-97] as well as a limited number of clinical studies [98-102] have verified an antidepressant effect of nicotine. Indeed, the high incidence of smoking among depressed patients has generated the "self-medication" hypothesis, which posits that these individuals derive some relief of their symptoms via inhaled nicotine [97, 103, 104]. This hypothesis is further supported by the findings that nicotine-withdrawal induces depression, which likely contributes to higher failure rate of smoking cessation among depressed individuals [105-109]. Hence, sufficient data for applicability of nicotine or nicotinic compounds in neuropsychiatric disorders including major depressive disorder (MDD) is provided in the literature [19, 28, 110, 111].

Nicotine as a Cognitive Enhancer

Considerable evidence supports the cognitive enhancing effects of nicotine [112]. Thus, a number of animal studies have shown that nicotine can block or reverse the cognitive impairment induced by chronic stress [113, 114]; glutamate N-methyl-D-aspartate (NMDA) receptor antagonist [115, 116]; lipopolysaccharide [117] and methamphetamine [75]. Moreover, allosteric potentiation of nAChRs by galantamine ameliorates the cognitive dysfunction induced by beta amyloid [118]. Importantly, a clinical study has verified the beneficial effects of nicotine patch in mild cognitive impairment [119]. These effects of nicotine are likely due to its anti-inflammatory, anti-apoptotic, neurotrophic and anti-protein aggregation effects [120]. Indeed, a role for nicotinic receptor subtypes in the formation and retrieval of memory has lately been suggested [117, 121].

Nicotine and Dyskinesia

Quik's group has shown that nicotine may also protect against L-Dopa-induced dyskinesia in non-human primate models of PD [59, 73, 122], suggesting that nicotine may be effective in amelioration of the dyskinesia induced by drug treatments in PD. Thus, nicotine administration in PD, in addition to providing neuroprotection, may also reduce the required dose of L-Dopa and hence reduce the chance of dyskinesia.

Related neurodegenerative and/or neuropsychiatric disorders

It is also of significance to note that the aforementioned effects of nicotine on neuroplasticity, inflammatory processes, apoptosis, oxidative stress and protein aggregation may also extend its beneficial effects to other CNS diseases such as autism schizophrenia, epilepsy or Tourette syndrome [24, 30].

In summary, nicotine has a great potential in PD treatment due to its neuroprotective and other positive properties. It may not only address the movement symptoms, but also the mood and cognitive impairment associated with PD. However, its route of administration appears to be a critical determinant of its optimal effects. Pulsatile

nicotine administration (e.g. via inhalation or nasal spray) that mimics smoking, may be the optimal route for its maximal benefit in PD.

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