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Targeting the Nicotinic Acetylcholine Receptors (nAChRs) in Astrocytes as a Potential Therapeutic Target in Parkinson's Disease

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Abstract: Parkinson's disease (PD) is a relatively common disorder of the Central Nervous System (CNS), whose etiology is characterized by a selective and progressive degeneration of dopaminergic neurons, and the presence of Lewy bodies in the pars compacta of the substantia nigra, and gaping dopamine depletion in the striatum. Patients with this disease suffer from tremors, slowness of movements, gait instability, and rigidity. These patients may also present functional disability, reduced quality of life, and rapid cognitive decline. It has been shown that nicotine exerts beneficial effects in patients with PD and in in-vitro and in-vivo models of this disease. Astrocytes are an important component in the immune response associated with PD, and that nicotine might be able to inhibit the inflammation-related apoptosis of these cells, being this a potential strategy for PD treatment. This action of nicotine could be due mainly to activation of α7 nicotinic acetylcholine receptors (α7-nAChRs) expressed in glial cells. However, nicotine administration can protect dopaminergic neurons against degeneration by inhibiting astrocytes activation in the substantia nigra pars compacta (SNpc) and therefore reduce inflammation. Owing to the toxicity and capacity of nicotine to induce addiction, analogues of this substance have been designed and tested in various experimental paradigms, and targeting α7-nAChRs expressed in glial cells may be a novel therapeutic strategy for PD treatment.

Keywords: Parkinson disease, nicotine, astrocytes, nAChRs, neuroinflammation, neuroprotection, apoptosis.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder that affects the Substantia Nigra pars compacta (SNpc), characterized by a progressive loss of dopaminergic neurons [1-4] and presence of intraneuronal inclusions (Lewy bodies) [5]. Etiology of PD involves oxidative stress, accumulation of toxic proteins, apoptosis, and mitochondrial dysfunction [6, 7]. PD patients present rigidity, tremor, bradykinesia, sleep disturbances and postural instability due to dopaminergic neurons death in the SNpc [8, 9]. It is not exactly known what the cause of PD is, but neuroinflammation plays an important role in this disorder. Neuroinflammation is caused by activated microglial and astroglial cells that release neurotoxic products related with PD pathogenesis (pro-inflammatory cytokines, reactive oxygen species and nitric oxide) [9]. Also, glial reaction and inflammation participate in the signaling pathways leading to neuronal degeneration in PD [10].

Interactions between glia and neurons are very important for the normal development of critical functions in the health and diseased brain [1, 11, 12]. Among glial cells in the brain, astrocytes are the most abundant, and are of great importance for neuronal survival [13]. In fact, both astrocytes overactivation and apoptosis contribute to the development of neurodegenerative diseases such as PD; therefore, a strategy seeking to delay, or inhibit, death signaling mechanisms and reduce astrocyte activation could be of great importance in PD treatment. Astrocytes are important for PD neuropathogenesis, contributing to neuroprotection and survival of neurons during this disease through secretion of various neurotrophic factors [1, 9, 12, 14, 15]. Because of this, any impairment of astrocyte function induces neuronal dysfunction, therefore these cells are a potential target of drugs aimed at inhibiting inflammation-induced neuronal dysfunction in PD [15, 16].

Neuron-glia interactions are also important for glia cells functions by regulating their activation [17]. It has been found that decreased levels of astrocyte-derived neurotrophic factors are in part responsible for dopaminergic cells death in PD [18], as astrocytes constitute the main defense system against oxidative stress, and express disease-related proteins such as alpha- synuclein (αSYN), parkin, and p-tau during the development of PD [9].

Nicotine is considered the main alkaloid responsible for tobacco dependence [19], however, it has been recognized that exerts beneficial effects in patients with PD [20-22]. For example, previous epidemiologic studies have shown an inverse correlation between smoking and PD prevalence [23-26]. Nicotine exerts its effect by binding to nicotinic acetylcholine receptors (nAChRs), which are members of the cysteine loop superfamily of ligand-gated ion channels [17]. These receptors have a pentameric structure consisting of homomeric or heteromeric combination of 12 different subunits (α2- α10, β2- β4), each of which have different biophysical and pharmacological properties [19]. The most abundant receptor subtypes are the heteromeric nAChRs with a β2 subunit and the homomeric α7-nAChRs [27-29].

THE EXPRESSION AND ACTIVITY OF nAChRs IN ASTROCYTES

Like neurons, astrocytes express neurotransmitter receptors that enable them to respond to signaling factors acting on neurons and consequently to influence neuronal responses [17]. The presence of

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nAChRs on astrocytes was first demonstrated 20 years ago, and α3, α4, α7, β3 and β4 subunits of nAChRs in these cells have been detected, with the α7 subunit being the most abundant in the brain [29]. Fluorescence-labeled alpha-bungarotoxin binding and immunofluorescence for the α7 subunit showed that immunopositive images for the receptor almost overlapped with those immunopositive for an astrocyte marker. Also, they found evidence that suggests that the α4β2 subtype was the main functional receptor in subfornical neurons, while α2, α3, α6, and β4 subunits may have minor effects. Since the homomeric alpha7 subtype has an important role in both neuroinflammation and neurodegeneration, targeting these receptors with nicotine and its active analogues in astrocytes represents a reasonable therapeutic strategy to reduce proinflammatory cytokines associated with PD [30]. Taking this into account, selective activation α7-nAChRs in astrocytes might prove to be a promising therapeutic avenue that should be assessed throughouly using *in vitro* and *in vivo* models of PD [31] (Fig. **1**). On the other hand, according to Graham *et al*. [32] the other most important nAChRs receptors in astrocytes are α3β4 and α4β2, which are found to be present in astrocyte soma and processes, respectively. The function of these types of receptors in astrocytes is not well understood, but probably they are important for neuronal synaptic connectivity and for their presynaptic modulation by astrocytes [29].

NICOTINE AND ITS ACTION OVER ASTROCYTE ACTIVATION IN NEUROINFLAMMATION

Inflammation plays an important role in the pathogenesis of PD and degeneration of the nigrostriatal dopaminergic pathway through overactivation of microglia and astrocytes, which release soluble neuroinflammatory factors such as free radicals, cytokines and lipid metabolites [33]. Data from post-mortem studies gave the first clues to understand that neuroinflammatory processes are present in PD [6]. Most studies in this regard have been conducted to explore the microglia function, maybe because microglia play a more important role in the release of neurotoxic factors that entail dopaminergic neurodegeneration. Because few studies have investigated the influence of astrocytes activation over inflammation in PD models, the role of astrocytes in PD is not well understood. According to Hirsch and Hunot [6] microgliosis in PD would be more important because it involves an increased amount of microglial cells with morphological changes, while in astrocytosis there is only a phenotypical change of astrocytes that show an enhanced expression of glial fibrillary acidic protein (GFAP). The role of astrocytes in PD has been investigated in *in vitro* and *in vivo* models using 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone and annonacin [6] [34]. In these models, it has been consistently observed reactive astrocytes in brain areas showing significant cell loss in PD [34]. These astrocytes contribute to the inflammatory process by the release of cytokines such as interleukin-6 (IL-6), IL-1β and tumor necrosis factor-α (TNF- α) [35]. Likewise, Mogi *et al*. [36] found an increase of TNF-α, β2-microglobulin, epidermal growth factor (EGF), transforming growth factor (TGFα), TGFβ1 and IL- 1β, IL-6 and IL-2 in PD patients.

Glial reaction and inflammatory processes are important factors in the selective loss of dopaminergic neurons in the SNpc. In this regard, it is thought that TNF-α release from astrocytes may mediate progression of nigral degeneration in PD [8]. TNF-α induces the apoptosis of dopaminergic neurons by inducing mitochondrial dysfunction, free radical generation and NF-κB activation, thus contributing to oxidative stress, and promoting the progression of PD [37]. Although activated astrocytes synthesize pro- and anti-inflammatory cytokines during neuroinflammation and interact with other immune cells, the production of pro-inflammatory substances seems to be more related to the development of PD. Indeed, these pro-inflammatory substances act as double-edged swords, because

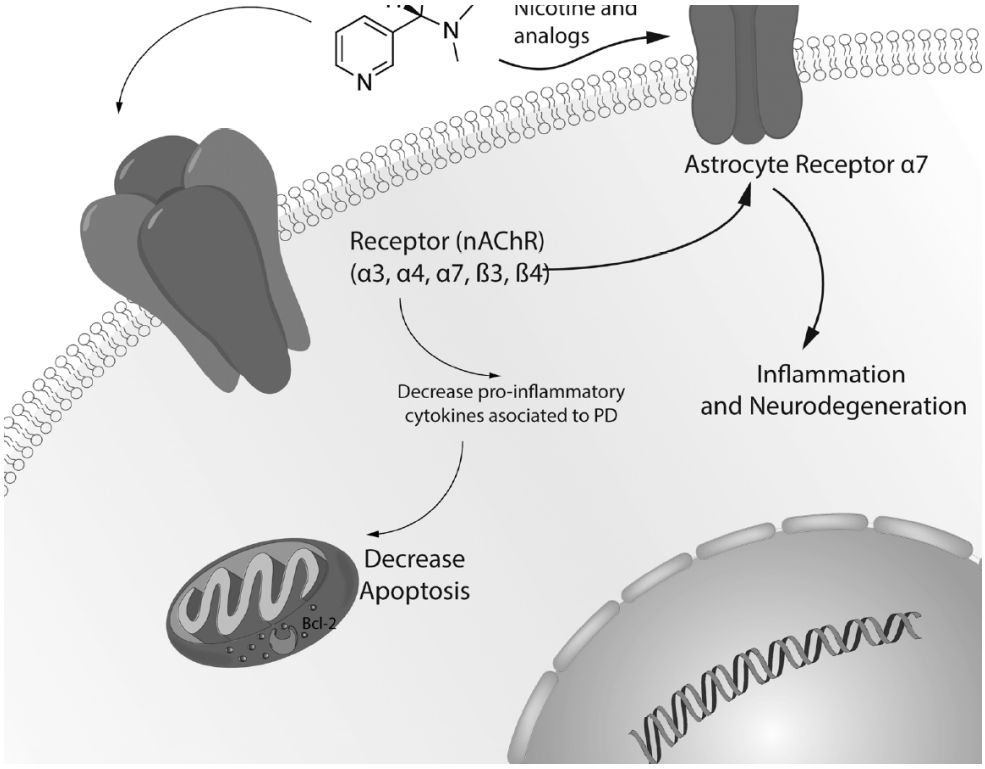

Fig. (1). Nicotine and likely its analogs are able to bind to different nAChRs subtypes in astrocytes. Their action is mainly through activation of α7-nAChR subtype, which reduces astrocyte apoptosis and secretion of pro-inflammatory cytokines, thus protecting dopaminergic neurons.

they have the capacity to exert both detrimental and neuroprotective effects [9], but when there is an overactivation, the detrimental effects are indisputable higher than the beneficial actions over the brain. The positive modulation of the α7-nAChR in astrocytes by cholinergic agonists and positive modulators of this receptor such as cotinine is an anti-inflammatory mechanism that represents a novel therapeutic strategy against neurodegenerative conditions [38]. Furthermore, reactive oxygen species (ROS) generated by activated astrocytes are mediators of the dopaminergic degeneration caused by inflammation-induced lipid peroxidation, DNA damage, protein oxidation and mitochondrial dysfunction [33]. Thus, the reduction of astrocytic ROS production may be also considered as a promising therapeutic approach.

To treat the origin of neuroinflammatory processes in PD, it would be important to assess protective agents that are able to prevent or attenuate these mechanisms in order to stop or delay the onset and progression of this disease. Pre-clinical studies using astrocytes in PD models have demonstrated that nicotine, and likely its analogues, could be potential therapeutic agents in this regard. α7-nAChRs agonists such as quinuclidines and PHA-709829 have been proved to exert beneficial effects in PD by targeting glial cells [6] (Fig. **2**).

Lipopolysaccharide (LPS), a bacterial endotoxin present in the outer membrane of gram-negative bacteria, is the most used glial activator for the production of inflammatory dopaminergic neurodegeneration. This endotoxin activates glial cells causing the release of proinflammatory and neurotoxic factors [33]. Liu *et al* [38] found that pre-treatment with nicotine prevented astrocyte activation caused by 1-methyl-4-phenylpyridinium ion (MPP^+) and LPS in primary astrocytes, and that this suppression was accompanied by a decrease in TNF-α production, a suppression of extracellular regulated kinase1/2 (Erk1/2) and activation of p38. TNF-α is considered an important mediator of dopaminergic neurons loss, because there is an elevation of TNF-α in the striatum and mesencephalon of rats exposed to LPS [39], possibly by mechanisms involving Erk1/2 and p38 [31]. Therefore, activation of nAChRs by nicotine may decrease astrocytes activation, induce inflammation resolution and improve the outcome. It is important to note that MPP^+ induces dopaminergic cell death directly, while LPS induces an indirect mechanism by activating astroglia, which release proinflammatory cytokines and lipid mediators [9]. Also, Li *et al*. [35] found that nicotine pre-treatment suppressed the LPS-induced inflammatory reaction in rat mesencephalic neuron-glia cultures by modulating astrocytes reactivity and IL-6 production, thus protecting dopaminergic neurons from inflammation-induced cell death. These effects were tightly dependent on α7-nAChRs activation. In another study, Park *et al*. [10] used *in vitro* and *in vivo* LPS-induced inflammation models to investigate whether nicotine exerted neuroprotection in dopaminergic cells through anti-inflammatory mechanisms. The authors found that nicotine reduced both the LPS-induced release of TNF-α and the decrease in cell viability of dopaminergic neurons [10]. On the other hand, Son *et al*. [8] studied the effect of nicotine pre-treatment on the expression of TNF-α mRNA in human fetal astrocytes (HFA) that have been stimulated with IL-1. They observed that pre-treatment with 0.1 µg/ml nicotine

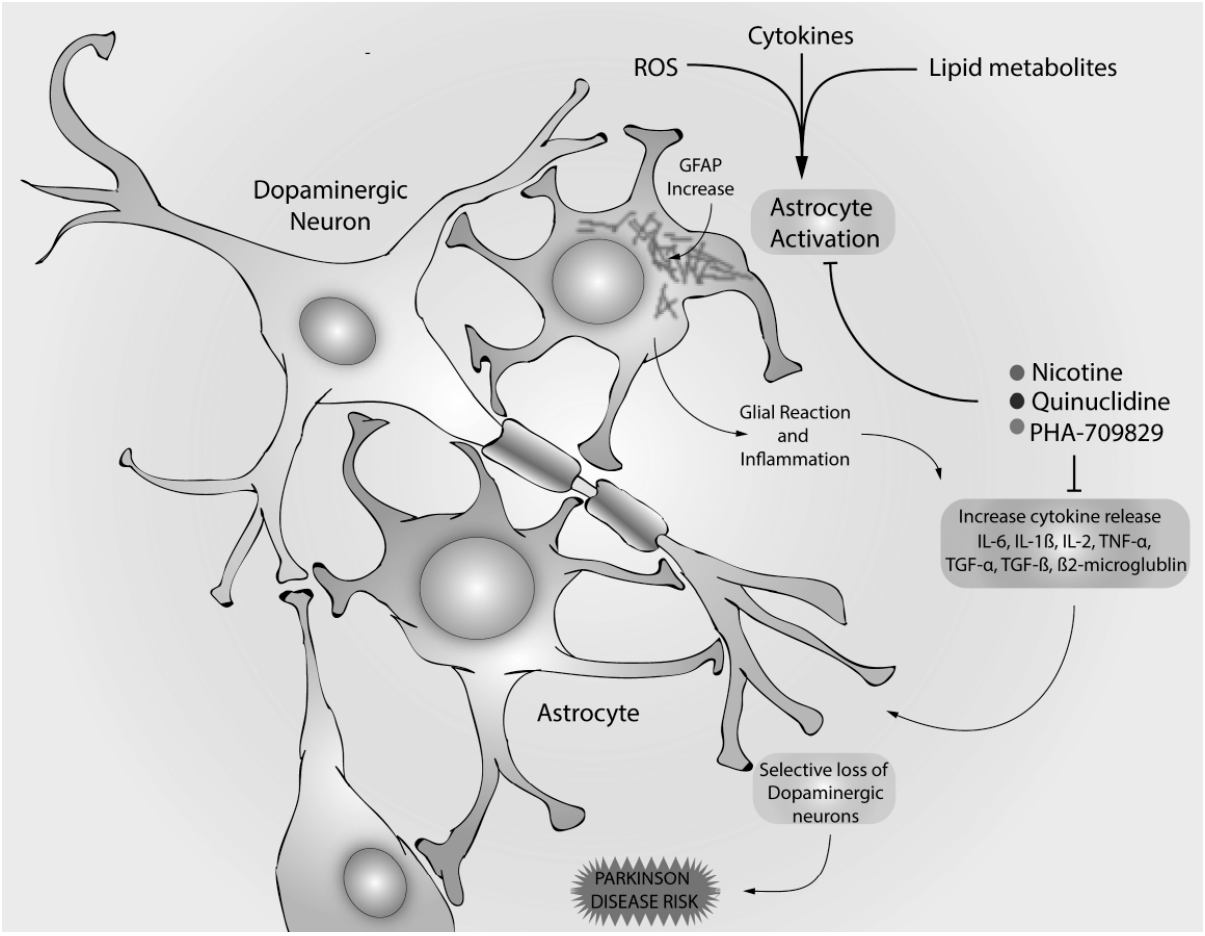

Fig. (2). Nicotine, quinuclidines and PHA-709829 are nAChRs agonists that when activated may decrease glial activation and release of cytokines, in which may impact on the neuroinflammation and the loss of dopaminergic neurons in PD.

inhibited TNF-α transcription with a maximum effect at 12 h. It is well characterized that NF-κB activates the immune cells by upregulating the expression of cytokines [40]. In this context, the authors also found that nicotine inhibited IL-1-induced NF-κB activation, and concluded that the inhibition of TNF-α mRNA was achieved by diminishing NF-κB activation [8]. In studies investigating the effect of transdermal nicotine over astrocytes, it has been found that nicotine reduces α-synuclein aggregation [41], oxidative stress [42, 43], regulates calcium homeostasis and suppresses proinflammatory pathways [44]. Clinical trials investigating the use of transdermal nicotine in PD reported beneficial effects in four trials, with no significant effects in other four trials and negative results (worsen effects) in one of them [42]. Bradford *et al*., found that nicotine increased gene expression of TNF-α, IL-18 and IL-1β, and decreased gene expression of anti-inflammatory factors such as Bcl6, IL-10 and CCL25 [45]. Based on this evidence, he proposed that nicotine can act as a double-edged sword, acting as an anti-inflammatory agent, but also as a pro-inflammatory agent, affecting PD progress. Besides high doses of nicotine could desensitize the nicotinic receptors in astrocytes reducing its potential anti-inflammatory activity [46].

NICOTINE PREVENTS ASTROCYTE APOPTOSIS: IMPORTANCE FOR PD TREATMENT

In patients with PD there is a low density of astrocytes in the SNpc, therefore, neurons in this area are more vulnerable because they do not have enough surrounding astrocytes that detoxify oxygen free radicals by glutathione peroxidase [6]. Liu *et al*. [31] investigated whether nicotine has protective effects on oxidative stress-induced astrocyte apoptosis by acting on α7-nAChRs. They found that pre-treatment with 0.1, 1 and 10μM nicotine inhibited H_2O_2-induced astrocyte apoptosis in a concentration-dependent manner. Because this effect was supressed by administering methyllycaconitine (MLA), an α7-nAChR antagonist, the authors concluded that nicotine exerted its action through this receptor [31]. This decrease in apoptosis was accompanied by a significant reduction in the H_2O_2-induced glial cell-derived neurotrophic factor (GDNF), preservation of mitochondrial membrane potential, stabilization of BAX/Bcl-2 ratio and suppression of caspase-9 activation [31].

Bcl-2 is a survival signal that responds to a wide range of apoptotic stimuli through the inhibition of mitochondrial cytochrome c release, and modulates mitochondrial calcium homeostasis and proton flux, while BAX is a critical component of the apoptosis pathway associated with mitochondrial stress [47]. On the other hand, cleaved caspase-9 activates other caspase members, such as caspase-3 and caspase-7, and triggers the canonical apoptotic pathway [31]. All of the effects exerted by nicotine were sought to happen through α7-nAChR activation, which was reversed by MLA [31]. According to the evidence described above, the anti-apoptotic effect exerted by nicotine in astrocytes is mostly mediated by the inhibition of mitochondria-dependent apoptosis pathways. Furthermore, Oikawa *et al.* found evidence that suggests that nicotine influences astrocyte viability by increasing intracellular Ca^{2+} concentration [48]. Furhermore, Hernández-Morales & García-Colunga, showed that nicotine activated nAChRs in CA1 astrocytes, inhibited K^+ currents and increased membrane conductance [19]. These effects caused an intracellular Ca^{2+} increase and modulated synaptic transmission [19].They also found that this intracellular Ca^{2+} increase was due to direct activation of nAChRs in astrocytes, without depending on K^+ currents [19]. This last observation could be of great importance in PD treatment, indicating that by targeting these receptors is possible to ameliorate dopaminergic synaptic function and dopaminergic cells viability. This is specially important since astrocyte nAChRs are important for bidirectional glia-neuron communication and modulate neuroprotection. Furthermore, nicotine acting on nAChRs in astrocytes upregulates the expression of GDNF, implicated in neuroprotection and increases secretion of S100B, which is an indicator of brain injury [19]. Moreover, nicotine acts on neuron-astrocyte interaction, thus improving astrocytes viability and therefore enhancing hippocampal synaptic transmission and memory [49], suggesting that this effect might be important in PD patients with memory loss.

Neuroinflammation is an important pathophysiological feature of PD. Until now there are few studies investigating the role of astrocytes in inflammation causing dopaminergic cells death [50-53]. Despite most research has been perfomed on the relation between microglia activation and neuronal apoptosis in PD models [54-57], it has been shown that there are various nAChRs subtypes present in astrocytes, such as α7, α3β4 and α4β2 [58, 59]. From these receptors the α7 subtype is considered the more promising target for the development of therapeutic agents for PD.

Nicotine protects astrocytes from apoptosis caused by agents such as H_2O_2, MPTP or 6-OHDA by acting on α7-nAChRs, inhibiting the mitochondrial apoptotic pathway [31], reducing astrogliosis and blocking the downregulation of GDNF [35]. Moreover, it has been shown that nicotine decreases the production of pro-inflammatory factors and inhibits MPTP and LPS-induced astrocyte activation acting on α7-nAChRs, [8]. Furthermore, nicotine suppresses TNF-α mRNA expression, which in turn decreases NF-κB translocation to nucleus, and this compound may be considered as a neuroprotective agent for dopaminergic neurons in SNpc and therefore reducing PD incidence [9]. These actions protect dopaminergic neurons against toxicity and inflammation; therefore, α7-nAChRs activation in astrocytes could play an important role in dopaminergic neuron damage in PD.

ASTROCYTES AND SYNAPTIC PLASTICITY

Synaptic transmission is determined by the environment in which a synapse is embedded, which is very tightly controlled by glial cells. Among them, astrocytes play a key role by providing trophic support and regulating synaptic transmission, as well as synapse formation [60-62]. It is well established that astrocytes exist in close association with glutamatergic synapses and regulate neuronal and synaptic function from development through to adulthood [63, 64]. However, the exact role of astrocytes in regulating the glutamatergic synapse is still a matter of debate and under investigation. Astrocytes by uptaking glutamate from the synaptic cleft can control the amount of glutamate reaching extrasynaptic receptors [65, 66]. Astrocytes also control other aspects of neuronal function such as ion and water homeostasis [67, 68]. Current evidence suggests that the neuron-astrocyte communication is facilitated by neurotransmitters-dependent activation of intracellular calcium cell signaling in astrocytes [69, 70]. Astrocytes rapidly restructure their processes and modify their coverage of the synaptic elements, a phenomenon named structural plasticity [71]. This modulation of neuronal function and structure involves also the release and/or uptake of numerous neuronal modulators, such as ATP [72], adenosine [73], TNF-α [74], TNF-β[75], thrombospondin (an adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions) [63], secreted proteinacidic and rich in cysteine [76], neurotrophic factors, as well as neurotransmitters such as D-serine [77, 78], GABA, and glutamate [79-83]. For example, TNF-α can exacerbate glutamate neurotoxicity by inhibiting glutamate transport on astrocytes, and stimulating the expression of AMPA and NMDA receptors, while reducing $GABA_A$ receptors on neurons. This effect results in a imbalance of the excitatory *versus* inhibitory transmission at the synapse [74]. Heterosynaptic long-term depression (hLTD) is an important form of synaptic plasticity that permits to spatially circumscribe the activity-induced synaptic potentiation during LTP. Previous evidence indicated that hLTD in untetanized synaptic terminals from the CA1 region of the hippocampus, results from the suppression of neurotransmitter release by ATP, released from astrocytes via activation of P2Y receptors. This activity-dependent release of ATP required Ca^{2+} elevation but not

NMDA receptors. Blocking P2Y receptors or buffering astrocyte intracellular Ca^{2+} at a low level prevented hLTD [72]. Furthermore, experimental evidence also supports the view that activated astrocytes can decrease the neurotransmitter release probability by diminishing the vesicular release probability at inactive synapses and by slowing the recovery of the ready pool of vesicles after depletion [84].

In PD, glutamate excitotoxicity has been suggested to play a main role mediating the functional decline of striatal neurons. Using the MPTP mouse model of PD, and probenecid (MPTP/p), it was found that after 1-2 months into treatment, mice showed a significant loss of dopaminergic terminals in the striatum and astrogliosis as indicated by a significant increase in the number of GFAP-immunopositive astrocytes. However, no changes in the levels or uptake of extracellular glutamate were detected. However, they found a reduction in the number of transporters per astrocyte in the MPTP/p-treated mice when compared to controls. Based in these results the authors suggested that a reactive gliosis may compensate dopamine loss in the striatum. But that changes in their ability to regulate glutamate homeostasis may be involved as well in the progression of PD [85]. It is a generally accepted concept that astrocytes are functional elements of tripartite glutamatergic synaptic complexes in the cortex and hippocampus. Studies performed in non-human primates showed that cortical and thalamic glutamatergic synapses undergo significant structural remodeling in the striatum of MPTP-treated parkinsonian monkeys. These changes were accompanied by a significant growth of the astrocytic coverage of striatal synapses in the MPTP-treated brains, providing evidence that astrocytes are involved in compensatory changes that affect both neuronal and glial elements during PD–like pathology [86]. On the other hand, astrocytes express α7-nAChRs and they can be identified in CA1 [19] and CA3 region of the hippocampus [87]. New evidence suggests that α7-nAChRs activation in the astrocytes may be the switch modulating the transition of glutamatergic synapses from silent to active. It has been shown that stimulation of α7-nAChRs on astrocytes releases components that induce hippocampal neurons to express higher numbers of post-synaptic AMPA receptors at the glutamatergic synapses (GluA1s, GluA2s) [4]. This increases in AMPA receptors expression is accompanied by increased spontaneous miniature synaptic currents mediated by AMPA receptors. The authors found that thrombospondin was necessary, but not sufficient for this effect, while tumor necrosis factor-α was sufficient but not necessary. Thus, α7-nAChRs in the astrocyte can promote the synaptic plasticity of glutamatergic neurons [4]. This evidence indicates that the activation of the nAChRs by nicotine or other modulators such as cotinine that also enhance nicotinic receptor activity, not only can decrease neuroinflammation but also stimulate synaptic plasticity in the brain of persons suffering from PD and/or AD.

CONCLUSION

Further studies are required in order to search new agents that influence synaptic activity and modify astrocyte function in neurodegenerative disorders associated with inflammation and gliosis such as PD, targeting especially the α7-nAChRs subtype, since inhibition of astrocyte activation could be a potential therapeutic strategy for PD treatment. Nicotine analogues, positive allosteric modulators and nicotinic partial agonists targeting the α7-nAChRs are interesting odds in the research of PD potential therapeutic agents, and should be preferred because the addictive and harmful effects of nicotine.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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