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Mini Review Open Access

What Animal Models of Parkinsonism Tell us About the Distinct Nicotinic Acetylcholine Receptors Involved in Pathogenesis?

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Abstract

A prominent degeneration of dopaminergic (DA-ergic) neurons in basal ganglia (striatum and substantia nigra) and a profound loss of dopamine resulting in patient motor dysfunctions are the main characteristics of Parkinson's disease (PD). The data available indicate a substantial role of nicotinic acetylcholine receptors (nAChR) in molecular mechanisms underlying PD. nAChRs belong to the superfamily of ligand-gated ion channels, their pharmacological profile being determined by an array of subunits forming a distinct receptor subtype. Acetylcholine modulates dopamine release via an interaction with multiple nAChRs subtypes present on the nigrosriatal neurons. This suggests nAChRs as possible targets in the treatment of PD, however the knowledge of subunit composition is necessary for effective drug design. As studies in humans are quite limited, animal models are broadly used for these purposes. For creating experimental Parkinsonism models, low molecular weight toxic organic compounds are commonly used. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), 1,1'-Dimethyl-4-4'-bypiridinium dichloride (paraquat), pesticide rotenone and ubiquitin proteasome system inhibitors, such as lactacystin and epoxomicin, can be mentioned as applied more often. Both mammalian and non-mammalian animals are used as model organisms, rodent and non-human primates being used mainly as mammalian models. This review summarizes the data obtained on toxic animal models about the involvement of different nAChR subtypes in PD at different stages. The present data suggest that degeneration of nigrostriatal DA-ergic neurons in the animal PD models is accompanied by alterations in the expression level and functional activity of different nAChR subtypes. Both heterooligomeric α6- and/or α4-containing and α7 homooligomeric subtypes are affected and can be regarded as possible targets for intervention.

Keywords: Parkinson's Disease; Animal model; Dopaminergic neuron; Nicotinic acetylcholine receptor; Striatum; Substantia nigra

Introduction

Parkinson's disease (PD), a progressive neurodegenerative disorder, pathogenesis of which is characterized by a prominent degeneration of dopaminergic (DA-ergic) neurons in basal ganglia (striatum and substantia nigra (SN)) and a profound loss of dopamine resulting in patient motor dysfunctions [1]. The data available indicate multilateral pathogenesis of PD. Thus, the degeneration of nigrostriatal DA-ergic neurons is accompanied by alterations in the expression and functional activity of different subtypes of nicotinic acetylcholine receptors (nAChR) [2-4]. nAChRs belong to the superfamily of ligand-gated ion channels [5]. These are transmembrane proteins, composed of five homologous subunits, 18 different subunits being so far identified. Pharmacological profile of nAChR is determined by an array of subunits forming one or another receptor subtype. The cholinergic neurons represent a small percentage of the neuronal cell bodies in basal ganglia; however nAChRs are abundantly expressed in striatum and SN, occupying pre-, and extra-synaptic locations. Most of neuronal nAChRs are localized pre-synaptically on nerve terminals, have a regulatory function and are involved in the brain plasticity by modulating calcium-dependent release of different neurotransmitters including dopamine [6,7]. Acetylcholine modulates dopamine release via an interaction with multiple subtypes of nAChRs present on the nigrosriatal neurons. This suggests nAChRs as possible targets in the treatment of PD. However the knowledge of subunit composition is necessary for effective drug design. As studies in humans are quite limited, animal models are broadly used for these purposes. The animal models with lesions produced by toxins are most commonly used for PD study, and the data obtained on such models are considered in the review.

Toxic animal models of Parkinsonism

For creating toxic experimental Parkinsonism, several toxic compounds are commonly used. Neurotoxins 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) are utilized in PD models on rodent and non-human primates [8,9]. Another toxic agents used for PD modeling are herbicide 1,1'-Dimethyl-4-4'-bypiridinium dichloride (paraquat), pesticide rotenone and ubiquitin proteasome system inhibitors such as lactacystin and epoxomicin [9]. Certain advantages are provided by the non-mammalian rotenone models which include nematode Caenorhabditis *elegans,* fruit fly *Drosophila melanogaster*, zebrafish and pond snail *Lymnaea stagnalis*. These models demonstrate a number of certain pathological features of Parkinson's disease in combination with simpler nervous system and a short life cycle [10]. Mammalian models differ in their particular response to the toxic damage. Thus, the chronic progressive degeneration of nigrostriatal dopaminergic neurons and the motor dysfunction may be created in monkeys, but not in mice [11].

As concerns the molecular mechanisms of toxin effects, MPTP

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penetrates through blood-brain barrier and is converted in astrocytes to neurotoxin 1-methyl-4-phenylpyridinium ion (MPP+) followed by its transfer with the DA membrane transporter into DA-ergic neurons which are then eliminated by oxidative stress. The severity of neuronal lesion and of the clinical manifestations of Parkinsonism is significantly dependent on the schedules of MPTP treatment [12,13]. MPTP models in mice reproduce the pathological processes not only in the nigrostriatal system but also in other brain regions and in the periphery [14]. 6-OHDA cannot cross the blood-brain barrier; this neurotoxin is unilateraly administrated into the SN pars compacta, medial forebrain bundle or striatum [15]. The death of DA-ergic neurons is observed over 12h to 2-3days.

In relation to nAChRs, toxic animal PD models are used for studying the composition and localization of individual subtypes of nAChRs in the nigrostriatal system. To do this in animals with clinical signs of Parkinsonism, the correlation between the level of degeneration of DA-ergic neuron bodies and their terminals in the striatum and the level of mRNA and expression of individual nAChR subunits are investigated [16-20]. The animal models also contribute substantially to the development of the new methods of neuroprotective therapy and of nAChR agonists for preventing, or at least for retarding, the degradation of DA-ergic neurons [21-23]. Another contribution of animal models is in the study of nAChR ligand effects on the reduction of dyskinesias induced by L-3,4-dihydroxyphenylalanine (DOPA) used in the clinical treatment of PD [24,25].

Although nAChRs affect the DA-ergic neuron functioning in different parts of the nervous system they are the most important in nigrostriatal system, which we consider in more details.

Involvement of nigrostriatal nAChRs in PD models

Among the different neuronal nAChR subtypes, homooligomeric α7 as well as heterooligomeric α4β2* and α6β2* (asterisk indicates possible presence of other subunits in the receptor complex) receptors are represented most abundantly in the mammalian brain [26]. However, in the nigrostriatal system, appreciable differences in the level of expression and subunit composition of nAChRs exist. In rodents, DA-ergic neurons express a noticeable levels of mRNA encoding α4, α5, α6, β2 and β3 subunits, with lower levels encoding α7 and α3 ones [27,28]. A variety of nAChR subtypes with different pharmacological properties can be formed by various combinations of these subunits.

An important hallmark of the striatum is the high expression level of the α6-contaning nAChR. These receptors in striatum are localized exclusively on terminals of DA-ergic neurons [29]. It was shown that in PD models with MPTP injury the degradation of neuron bodies in SN proceeds slower and is less pronounced than degeneration of DA-ergic axonal terminals in striatum [13]. In the MPTP-induced mouse models of acute clinical PD, a predominant loss of the α6β2* nAChRs was found [19, 30,31], and this decline closely corresponded to loss of DA-ergic neurons [31,32]. Current evidence suggests that α6β2* receptors play an important role in modulating the release of dopamine in the nigrostriatal system, in animal PD models the extent and severity of the disease correlates with a reduction of α6β2* nAChRs [33].

In contrast to α6* nAChRs, α4* receptors are present both on DA-ergic nerve terminals and other striatal neurons [29,34]. In rodent SN the presence of α4 in DA-ergic neurons was demonstrated by several methods including single-cell RT-PCR and patch-clamp [27,35]. In the rodent PD models, the amounts of α4* in mild to moderately lesioned animals remained unchanged and decreased only with more severe lesions, when statistically significant motor decrease was observed [19,31].

It has been proposed that there are two possible α6-containing nAChR variations in mouse striatum, the α6α4β2β3 and α6β2β3 subtypes [36]. Under moderate MPTP-induced lesions, dopaminergic terminals expressing α6α4β2β3 nAChR population may be more susceptible to toxic injury, while the survived neurons express the α6β2β3 nAChR population [31]. Most of publications on PD models concerning a possible role of nAChRs describes the changes in the striatum only [18,19, 30] whereas the data about SN are limited. The experiments made on MPTP-lesioned monkeys have shown the decrease of α4* nAChR in SN [17,32]. In the mouse model of pre-symptomatic PD it was demonstrated, that α4* nigrostriatal nAChRs are involved in the mechanisms of brain plasticity under MPTP damage [37]. It was shown that the level of expression of heterooligomeric nAChRs in alive neurons increased approximately twofold as compared to the control. Therefore, the increase in the content of nAChRs in SN in response to the damaging effect of MPTP may have a compensatory role, resulting in the absence of clinical symptoms of the disease.

The assumption that α4* nAChRs are the most probable modulators of DA level is confirmed by the character of nicotine action. Nicotine enhances the DA release [38] and the PD incidence is much lower in smoking people as compared to non-smoking [39]. In the models of chronic nicotine dependence, the increase of the α4β2* nAChRs content in the brain was observed [40], while the expression level and functional activity of α6β2* nAChR decreased [41]. nAChRs of α7 type are predominant in mammalian brains [26]. The abundance of these receptors in the striatum is much lower than that of α4*, α6* and β2-containing nAChRs. Alpha7 nAChRs are located on about 50% of DA-ergic neurons as well as on the other type of neurons and astroglial cells [2,16,27]. In SN α7 nAChRs are present on DA-ergic neuron bodies, on GABA-ergic neurons and astrocytes [35]. There are indications of the involvement of α7 nAChRs in PD pathogenesis: for example, 3-[2,4-dimethoxybenzylidene]anabaseine, a selective agonist of α7 nAChR, exerted a neuroprotective effect in rats with parkinsonism model induced by 6-hydroxydopamine [42]. PNU-282987, a potent and selective agonist for the α7 subtype, improved dopaminergic function in MPTP-lesioned mice [43]. A transient 2-fold increase in the α7 mRNA was detected in the striatum and SN in the acute symptomatic model of PD [44]. It was shown recently that nAChR agonist ABT-107, highly selective for α7 subtype, improved striatal dopaminergic function in 6-OHDA-lesioned rat [20]. However earlier it was shown that the amount of this receptor subtype did not change in striatum at nigrostriatal lesions [30]. Not only α7 nAChRs on DA-ergic neurons, but also those present on the other types of neurons in SN, striatum or basal ganglia may be involved in regulating DA-ergic activity. A possible molecular mechanism is explained by the recently proposed hypothesis of α7 nAChR-mediated protection by activation of phosphotidylinositol 3-kinase (PI3K) system [45]. Another possible mechanism for the α7 nAChR participation in brain plasticity is its role in the nicotinic anti-inflammatory pathway. Neuro-inflammation is involved in the PD pathogenesis [46], and activation of α7 nAChRs by nicotine affects an anti-inflammatory response by inhibiting the production of the inflammatory cytokines [47].

Outlook

The data presented in this mini-review indicates that animal models of Parkinsonism can help in identifying distinct subtypes of nAChRs, which may be involved in disease. However, the models have some limitations and do not cover all the major pathological and phenotypic features of PD. Thus, in toxic models considered in the review, substantial nigrostriatal degeneration is generally obtained, although

no consistent Lewy body-like formation is found [48]. On the other hand, there are great species differences between humans and animals used to produce the models. Still the role of nAChRs in human brain is not completely understood and future studies are needed to further uncover the impact of the nicotinic cholinergic system on the human brain functioning. Recent *in vivo* studies of brain nAChR distribution in cognitively intact patients with early stage of PD showed an up-regulated cholinergic activity at the striatal and possibly cortical level [49]. Higher nAChR density may occur as a compensatory mechanism to maintain dopaminergic tone [50], however more detailed studies are necessary to address this hypothesis. It can be assumed that the upregulation of distinct nAChR subtypes may result in improvement of patient conditions, but the possible ways to achieve this task are still to be discovered.

Conclusion

In summary, the present review indicates involvement of different nAChR subtypes in the molecular pathogenesis PD. Thus, degeneration of nigrostriatal DA-ergic neurons in the animal PD models is accompanied by alterations in the expression level and functional activity of particular nAChR subtypes. However, some questions concerning the role of nAChRs in PD remain to be answered. In this relation animal models may shed light on the participation of specific nAChR subtypes in mechanisms of brain plasticity and the trigger mechanism responsible for the transition from pre-symptomatic stage to symptomatic one. Furthermore, the involvement of the central and peripheral nAChRs in the manifestation of such PD symptoms as autonomic dysfunction, pain, sleep deficits and the development of dementia in the latter stages requires further investigation.

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