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ORIGINAL PAPER

Purinergic Antagonism Prevents Mitochondrial Dysfunction and Behavioral Deficits Associated with Dopaminergic Toxicity Induced by 6-OHDA in Rats

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Abstract Purinoceptors are present in neurons, microglia and oligodendrocytes and regulate dopamine (DA) release, striatal-related function and striatal neuronal and DA cells damage. Therefore, purinoceptors may be involved in the pathology of Parkinson's disease (PD) and purinergic antagonism may show neuroprotective effect. The study investigated the role of the non-selective purinergic receptor antagonist pyridoxalphosphate-6-azophenyl-2′, 4′-disulfonic acid (PPADS) and a selective purinergic receptor P2X7 receptor antagonist Brilliant Blue G (BBG) against 6-OHDA induced dopaminergic neurotoxicity in rats; while adenosine triphosphate (ATP) was used as a P2X receptor agonist. Behavioral parameters like spontaneous motor activity, narrow beam walk, footprint, bar catalepsy, grip strength and rotarod tests were performed to evaluate motor deficits in PD. Striatal DA contents were estimated as neurochemical measures of PD. Mitochondrial studies and oxidative status were assessed to investigate the mechanism of purinergic system antagonists. Involvement of purinergic receptors in apoptosis was assessed by expressing cytochrome-C, caspase-9 and caspase-3. Both the antagonists not only attenuated 6-OHDA induced motor deficits but also protected against 6-OHDA induced DA depletion in the striatum. Oxidative stress, mitochondrial integrity and dysfunction were attenuated by purinergic antagonists. Further, they attenuated mitochondrial-linked apoptosis as observed by a decrease in expression of cytochrome-C, caspase-9 and caspase-3. Therefore, purinoceptor antagonism shows neuroprotective effect in 6-OHDA induced dopamine toxicity through preservation of mitochondrial bioenergetics and anti-apoptotic activities.

Keywords Parkinson's disease · Purinergic receptors · Mitochondrial dysfunction · Pyridoxalphosphate-6-azophenyl-2′,4′-disulfonic acid · Brilliant Blue G · Adenosine triphosphate

Introduction

Parkinson's disease (PD) is one of the major progressive neurodegenerative movement disorders that results primarily from 50 to 70% dopaminergic (DA) neuronal loss in the substantia-nigra-pars-compacta (SNPC) of basal ganglia [1]. 6-OHDA also induces PD-like symptoms by reducing tyrosine hydroxylase (TH) immunoreactive cells and causes upto 85% loss of nigral neurons and 50% reduction in striatal DA concentration in ipsilateral side [2, 3]. The current therapy involves the use of drugs which augment striatal DA levels [4]. However, the pathogenesis of PD remains obscure [1]. Previous studies showed that neuroprotective strategy is useful in the management of PD and several agents have been used as neuroprotectants such as monoamine oxidase-B (MAO-B) inhibitors, glutamate antagonists and antioxidants [5–7]. One of the most common mechanisms responsible for neuronal degeneration in PD is oxidative stress. PD patients are found with the high amount of oxidized proteins, lipids, DNA, RNA and low levels of cellular antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) [8, 9]. Mitochondrial dysfunction is one of the primary sources of ROS. Mitochondrial dysfunction plays a crucial role in PD pathogenesis [10]. High ROS levels

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