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Brain mast cells and therapeutic potential of vasoactive intestinal peptide in a Parkinson's disease model in rats: Brain microdialysis, behavior, and microscopy

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Abstract

In the present study, the effect of systemically administered vasoactive intestinal peptide (VIP) (25 ng/kg i.p.) was investigated on drug-induced rotational behavior, extra-cellular dopamine levels and histology of corpus striatum in a 6-hydroxydopamine (6-OHDA)-induced rat model of Parkinson's disease. After 15 days of 6-OHDA lesion, apomorphine-induced (0.05 mg/kg s.c.) rotational behavior of the animals significantly increased and extra-cellular dopamine levels of corpus striatum were significantly reduced. VIP reversed the rotational deficits but did not alter the decrease in striatal dopamine levels. On the other hand, histological data indicate that VIP significantly reduced neuronal death and demyelination. Electron microscopic appearance of mast cells showed ultra-structural variety between VIP-treated and 6-OHDA lesioned groups. VIP activates mast cells without any evidence of typical exocytosis, and possibly mast cells could participate in neuroprotection. Our results suggest that systemically administered VIP can attenuate the motor response changes, neuronal cell death, and myelin sheet loss characteristically associated with 12 μg 6-OHDA administration into the rat striatum. Brain mast cells seem to participate in neuronal protection. Possibly, protective cues could be produced by brain mast cells.

Keywords: 6-OHDA toxicity; Corpus striatum; Dopamine; Rotational behavior

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder with no effective treatment, characterized by massive degeneration of dopaminergic neurons in the substantia nigra and the subsequent loss of their projecting nerve fibers in the striatum. Current available treatments, frequently inducing major side effects, have a limited beneficial effect in halting and slowing down the progression of the underlying neurodegenerative process [31,48,49,59].

Although the etiology and pathogenesis of cell death in most cases of Parkinson's disease remain unknown, it has been postulated that oxidative stress, inflammation, glutamate-mediated neurotoxicity, apoptosis, nitric oxide over production, along with insufficient neurotrophins and astroglial cells, plus activated microglial cells may be responsible for progression of nigrostriatal dopaminergic neuron degeneration [24,31,46,48,50,53,55,91]. It has been suggested that microglial cells and/or subpopulation of astroglial cells,

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releasing cytokines and various cytotoxic compounds, play a deleterious role in the loss of midbrain dopaminergic neurons.

Mast cells, like macrophages/microglias, are also resident in the brain of many species [9,75,78]. The presence of mast cells in the CNS and their potential role in normal brain and pathophysiology has a long, controversial history. Mast cells, producing up to 20 mediators, can potentially mediate neurotransmission, neurit outgrow and neuronal survival in the brain [9,75]. Recently, large numbers of different proteoglycans including chondroitin sulfate and heparin, which are present in granules of mucosal mast cells (MMC) and connective tissue (CTMC) mast cells, respectively have received great attention in terms of neuronal protection [26,35,65]. Association of brain mast cells with various physiological and pathophysiological conditions, such as the estrus cycle, behavior, vascular headaches and multiple sclerosis has been well documented [8,10,27,74,79,93]. However, no relationship between brain mast cells and Parkinson's disease has yet been reported.

Vasoactive intestinal peptide (VIP), a 28-amino acid peptide, was first discovered, isolated, and purified from porcine intestinal extract [67]. It is now recognized as a major neuropeptide in the brain, with function ranging from neurotransmission to neuromodulation with neurotrophic properties [68]. VIPergic neurons and VIP receptors were found in various regions of the CNS including basal ganglia. VIP is found in high concentration in the cerebral cortex, suprachiasmatic nucleus, amygdala, striatum, hippocampus, midbrain, periaqeductal gray matter and sacral spinal cord [69]. Distribution of VIP receptors in the rat brain basal ganglia was reported high in the nucleus caudatus [61]. VIP has the ability to stimulate astrocytic mitosis and neurit outgrow, increase neuronal survival, prevent exitotoxic glutamate toxicity, and promote early embryonic growth [13,15,33,34,36,54,63,94]. Recently, an in vitro study in neuronal culture and in vivo study in mice showed that VIP acts against the toxicity of 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) [24,58]. In the MPTP-induced mouse model, VIP prevents microglia-induced inflammation in the substantia nigra and striatum of mice, and decreases loss of dopaminergic neurons [24]. Concentration of VIP was significantly reduced in the substantia nigra of an MPTP-induced animal model of Parkinson's disease [2]. Stoddard et al. showed that levels of VIP significantly decrease in parkinsonian adrenal medullae [77].

VIP is a neuropeptide with a potent anti-inflammatory, anti-oxidant and anti-apoptotic effect [22,32,71]. It has been found to be protective in several inflammatory and oxidative disorders, such as septic shock, rheumatoid arthritis and ischemia-reperfusion injuries [21,38,82,85,88]. Additionally, VIP has a modulatory effect on various immune cells including mast cells [17,23,86]. The modulator effect of VIP on phenotypes, degranulation and the granular content of mast cells is suggested as one of the important mechanisms of its potent protective activity on various tissue injuries [17,83,84,86].

Recently, it has been found that VIP can cross the blood-brain barrier from blood to the brain by transmembrane diffusion system [29]. Thus, in accordance with the various crucial aspects mentioned above, VIP seems to have an important physiological role in basal ganglia functions and can be a good candidate agent against multifactorial pathogenesis of Parkinson's disease.

Several rodent models have been developed which mimic many of the features of clinical Parkinson's disease in the human. Commonly, the injection of selective neurotoxin, such as MPTP in mice or 6-OHDA in rats is used to create acute neurodegenerative lesions in the nigrostriatal pathway [73]. 6-OHDA lesions of the striatum have been shown to induce retrograde degenerative changes in the dopaminergic neurons of the substantia nigra, which are progressive over the first weeks after the lesion [41]. 6-OHDA-induced nerve terminal lesions of the nigrostriatal system provide a model of progressive dopamine neuron degeneration useful for the assessment of neuroprotective treatments and behavioral recovery after therapeutic intervention [41].

Thus, the present study was planned to elucidate the action of systemic administered (i.p.) VIP on Parkinson's disease model in rats. The effect of VIP on neuronal protection, rotational behavior, brain mast cells and extra-cellular dopamine levels of the corpus striatum was determined in 6-OHDA-lesioned rats.

2. Experimental procedures

Young adult Sprague–Dawley rats (either sex) weighing 200–250 g were used. At the beginning of the experiment, the rats were housed three to four to a cage under a 12 h light–dark cycle with free access to rat chow and water. The study was approved by a local ethical committee on animal use and care (Medical Faculty of Osmangazi University).

For the stereotaxic lesion surgery 6-OHDA hydrochloride (Sigma, USA) was dissolved in 0.3% ascorbic acid/0.9% saline, and one injection 2 μl (6 μg/μl) was made into the site of the right striatum of the anesthetized rat (Ketamine, 75 mg/kg + xylazine, 38 mg/kg) using a 10 μl Hamilton micro syringe [44]. Lesion coordinates: AP:1.60; L:2.6; V:5.1 relative to bregma and ventral from dura by the atlas of Paxinos and Watson [62]. After injection of 6-OHDA at the rate of 1 μl/min, the canula was left in place for 2 min before slow retraction.

The experimental animals were divided into three groups. Group I ($n = 12$): sham operated, intrastriatal vehicle-injected (2 μl), i.p. saline-injected control; Group II ($n = 12$): intrastriatal 6-OHDA-injected, i.p. saline-injected; Group III ($n = 12$): intrastriatal 6-OHDA-injected, i.p. VIP (Sigma, USA)-injected (25 ng/kg) every 2 days throughout 15 days. The first i.p. injection of VIP was made 1 h after the intrastriatal 6-OHDA microinjection.

Two weeks after the operation the rats were subjected to drug-induced rotational behavior. After the rotation metric