Anatomical and Biochemical Study of the Facial Nerve Nucleus and Other Brain Regions in ١-methyl ٤-phenyl ١,٢,٣,٦-Tetrahydropyridine Induced Parkinsonian Rat Model

By

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease that affects ١-٢% of population worldwide over ٦٠ years old (Brown *et al.*, ٢٠٠٥) and it is mainly due to chronic dopamine (DA) deficiency in nigrostriatal pathway (Hassler, ١٩٣٨; Pattarini *et al.*, ٢٠٠٧). Also PD is considered as an idiopathic disorder and the exact aetiology and molecular basis of which are still vague and incomplete with exception of few genetically inherited forms (Pattarini *et al.*, ٢٠٠٧). Despite the tremendous effort of the scientists to identify the factors and underlying mechanisms for the PD'S pathology, there are still missing chains that require further exploration (Pattarini *et al.*, ٢٠٠٧). The pathology of the disease was initially described as the degeneration of the nerve endings of dopamenergic neurons of substantia nigra pars compacta (SNpc) in the striatum followed by degeneration of the cell bodies in the SNpc (Burns *et al.*, ١٩٨٤, Bradbury *et al.*, ١٩٨٦, Eberling *et al.*, ١٩٩٧, Pattarini *et al.*, ٢٠٠٧). Another suggestion was that PD is characterised by neuronal degeneration of the mesencephalic dopaminergic cells of substantia nigra (SN) and subsequent striatal DA depletion (Alavian et al., ٢٠٠٩).

PD is the second most common age- related neurodegenerative disease after Alzheimer's disease (AD) (Dauer and Przedborski, ٢٠٠٣). It is characterised by cardinal signs such as tremor, rigidity, slowness in movements and gait instability (Savitt *et al.*, ٢٠٠٦).

It has been confirmed that about ٨٠ % or more of the striatal DA content was diminished in PD patients as a consequence of nigral cell loss (Poirer & Sourkes, ١٩٦٥; Bernheimer *et al.*, ١٩٧٣; Agid *et al.*, ١٩٨٧; Marsden, ١٩٩٢; Savitt *et al.*, ٢٠٠٦). Most of the scientists' effort has focused on how to improve these symptoms through trials to compensate the DA deficiency. In spite of the efficiency of the therapies to relief the early symptoms of the disease, its progression neither has been stopped nor have the non- motor symptoms been treated (Savitt *et al.*, ٢٠٠٦).

Moreover, PD has been categorised as one of the Parkinsonian disorders along with other types of diseases such as multiple system atrophy (MSA) and dementia with Lewy bodies (DLB) (Constantinescu *et al.*, ٢٠٠٩). They share common features in the early symptoms of the disease but differ greatly with

the disease progression into various specific signs for each of them (Constantinescu *et al.*, ٢٠٠٩).

The main cholinergic nuclei were recognized as pedunculopontine tegmental nucleus (PPTg) and the laterodorsal tegmental nucleus (LDTg) or Ch٥ and Ch٦ respectively (Mesulam *et al.* ١٩٨٣). Collectively, they both are subdivided under the mesopomtine tegmentum (MPT) (Maskos, ٢٠٠٨).

Furthermore, it was proved that these nuclei provide cholinergic innervations which in turn modulate dopaminergic release from different brain areas (Maskos, ٢٠٠٨). PPTg nucleus has been demonstrated to be the major locomotor and muscle tone suppression centre in the brainstem. Also, it was proved that PPTg has been related to gait freezing and poor balance, the two most disabling manifestation of late stage of PD (Nandi *et al.,* ٢٠٠٨).

Moreover, it was reported that in idiopathic PD there is a neuronal loss in the PPTg (Hirsch *et al.,* ١٩٨٧; Jellinger, ١٩٨٨) that is also observed in hydrocarbon-induced PD (Pezzoli *et al.,* ١٩٩٦). Meanwhile, cholinergic innervation to the SN has increased (Anglade *et al.,* ١٩٩٣, ١٩٩٥ a, b).

It has been reported that balanced interaction between dompaminergic and cholinergic system is so crucial for basal ganglia function (Graybiel, ١٩٩٥; Calabresi *et al.,* ٢٠٠٠; *Zhou et al.,* ٢٠٠٣; Morris *et al.,* ٢٠٠٤) and in turn in PD. Basal ganglia are known to be collection of different brain structures including the caudate putamen striatum (Mamah *et al.*, ٢٠٠٧).

Also, it has been demonstrated that striatal acetyl choline (ACh) and DA are very intimately spaced and hence an interaction between DA and ACh strongly takes place in the striatum. In another way, both neurotransmitters are locally and robustly regulating each other. So, the disruption of this balance due to cholinergic deterioration may be an important factor in PD pathology.

Subsequently, it was of great importance to study cholinergic system variation in the striatum specifically as well as in other brain regions generally in comparison to alterations in the dopaminergic system following acute MPTP treatment in our rat model to confirm or disagree with this hypothesis. Also, to discuss if exercise can exert a neuroprotective effect on this neurotransmitter system

Many efforts have been done to study motor deficits that accompany PD patients. Earlier to motor impairments, depression, anxiety and cognitive

dysfunctions have reported to be recognised in the preclinical stage (Lees & Smith, ١٩٨٣; Levin *et al.,* ١٩٨٩). It is also well known that cognitive control functions are related to the hippocampus and the cortex while the executive activities are related to prefrontal and cingulated cortex.

In addition, it is well recognized that Parkisonian people develop dementia two to three times more than normal age matched individuals (Marder *et al.,* ١٩٩٥; Aarsland *et al.,* ٢٠٠٣). Also, it is documented that about ٣٠-٥٠% of parkinsonian patients reveal dementia within ٤-٨ years following the disease symptoms' appearance (Aarsland *et al.,* ٢٠٠٣; Williams-Gray *et al.,* ٢٠٠٧), the risk factor increases by the disease propagation (Braak *et al.,* ٢٠٠٥). Many hypotheses have been set to explain the executive deficits and memory impairments that are correlated to PD. It was suggested that nigrostriatal dopaminergic neuronal loss with consequent dopamine depletion in the striatum and a correlated deficits in the frontostriatal circuitry (Owen *et al.,* ١٩٩٨; Dagher *et al.,* ٢٠٠١; Lewis *et al.,* ٢٠٠٣).

It has been confirmed that rodents reveal an age-dependent decrease in nerve growth factor (NGF) and basal forebrain (BF) cholinergic cells and also in learning and memory ability (Koh & Loy, ١٩٨٨; Koh *et al.,* ١٩٨٩). Additionally it was reported that rats and mice show an age-related decline in ACh and cell loss in the septohippocampal and BF regions (Strong *et al.,* ١٩٨٠; Luine *et al.,* ١٩٨٦; Gilad *et al.,* ١٩٨٧; Springer *et al.,* ١٩٨٧).

It has been reported that hypomamia or mask-like face is one of the prominent symptoms of PD that altered facial expressions which are very important non- verbal part of communication (Stern & Lees, ١٩٩١; Schroeder *et al.,* ٢٠٠٤). In humans, facial nerve is the seventh cranial nerve responsible for the innervations of facial muscle through the cortical regulation of facial nucleus (Costa *et al.,* ٢٠٠٧). Therefore, it contributes in a great way for social interaction between people (Moran *et al.,* ٢٠٠٣). It is believed that these facial impairments in PD are indication of facial neuronal degeneration. Also facial expression changes are considered as one of the early symptoms in the diagnosis of PD (Stern & Lees, ١٩٩١).

Moreover, it has been reported that subthalamic nucleus (STN) deep brain stimulation, a tool that has been used for PD control via implantation of electrode in the sensorimotor part of STN, has a direct impact on the perception

of facial expressions of the emotion (Schroeder *et al.,* ٢٠٠٤). It is also proved that there is a link between selective difficulty in recognizing angry faces and STN stimulation affecting anterior cingulated cortex function (Schroeder et al., ٢٠٠٤).

Interestingly, it has been postulated that there is polysynaptic corticobulbar projections to facial muscles and that fibres from the unilateral tract innervate upper and lower facial muscles of both sides at the internal capsule level (Costa *et al.,* ٢٠٠٧). Furthermore, Costa et al has proposed that facial motoneurons are likely to get inputs from multiple cortical motor areas.