Dampening of Serotonergic System through 5HT_{1A} Receptors is a Promising Target for Treatment of Levodopa Induced Motor Problems

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ABSTRACT

During long-term treatment with Levodopa, majority of patients with Parkinson's disease experience some abnormal motor problems including of Levodopa induced dyskinesia (LID) and wearing off. Incredible evidences suggest that serotonergic neurons compensate some functions of lost dopaminergic neurons in Parkinson's disease especially in advanced disease stages. Therefore, it has been postulated that serotonergic neurons are the major source for development of these unwanted effects. 5HT_{1A} receptors are located on the serotonergic neurons and are involved in regulation of normal motor functions. With respect to the role of serotonergic projection in Parkinson's disease and importance of 5HT_{1A} receptors in motor activity it seems that inactivation of these neurons by stimulation of 5HT_{1A} receptors could provide benefits in treatment of Levodopa induced motor impairments.

Introduction

Parkinson’s disease is an age related disorder. Approximately 1-2 % of population over the 60 years old affected by this disease.¹² Loss of dopaminergic function in the substantia nigra compact pars (SNc) is responsible for appearance of Parkinson’s disease clinical symptoms.¹³,¹⁴ Replacement therapy with dopamine precursor L-3,4-dihydroxyphenylalanine, levodopa, (L-Dopa) is widely used for reduction of Parkinson’s disease symptoms such as resting tremor, bradykinesia and rigidity.¹⁵ However chronic administration of L-Dopa results in development of some motor dysfunctions such as L-Dopa induced dyskinesia (LID) and wearing off in patients with Parkinson’s disease.⁸,⁹ At the time course between 5 to 10 years after L-Dopa administration 50-90 % of Parkinson’s disease patients experience these motor disorders, respectively.⁹ Although the precise mechanisms of these motor disturbances are poorly understood but these unwanted conditions have been contributed to the abnormal neuronal alterations.² In these conditions patients experience some of the motor fluctuations between immobility and involuntary movements.¹⁰ Accordingly, L-Dopa induced dyskinesia includes of dystonia and chorea is appeared at the peak effect of L-Dopa or is initially produced after administration of each L-Dopa dose.¹¹ Moreover, appearance of wearing off or on-off phenomena takes place at the time course between doses of L-Dopa. In these conditions patients suddenly face to abrupt alterations in response to L-Dopa.¹² L-Dopa is converted to dopamine within the spared dopaminergic neurons in the SNc in initial stages of disease.² This converting is mainly mediated by aromatic amino acid decarboxylase (AADC).²¹² In the second step, dopamine is carried into synaptic vesicles by vesicular monoamine transporter2 (VMAT2).²³ The up-regulation of 5-HT receptors and hyperinnervation of serotonergic neurons which manipulates some dopaminergic system-related lost functions are occurred in 6-OHDA lesioned rats.⁹ It has been shown that serotonergic neurons are able to express both AADC and VMAT2.¹⁵ The mentioned ability leads to converting of L-Dopa to dopamine and loading of produced dopamine into synaptic vesicles.¹⁵ This L-Dopa derived dopamine is co-stored with serotonin in the same vesicles and therefore, known as a false neurotransmitter.¹⁶,¹⁷ Indeed, this paradigm of co-transmission is the unique condition and could be considered as a compensatory co-transmission. Since dopaminergic neurons have both inhibitory D₂ autoreceptors and dopamine transporters, therefore they are able to regulate dopamine levels at the physiologic level.¹⁴,¹⁸ The absence of these machineries on the serotonergic neurons disables these neurons to regulate

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dopamine level in the striatum.\textsuperscript{13} Hence dopamine is released from these neurons in an activity dependent manner.\textsuperscript{14} Apparently, this releasing paradigm leads to pulsatile stimulation of dopaminergic receptors and consequently causes motor fluctuations.\textsuperscript{13} It has been shown that the transplantation of serotonin neuron-rich grafts to the striatum of 6-OHDA-lesioned rats markedly increase the magnitude and duration of dyskinesia.\textsuperscript{5} Serotonin depletion by fenfluramine and 5,7-dihydroxytryptamine (5,7-DHT) also exert anti-dyskinetic effect in parkinsonian animals.\textsuperscript{14} Studies show that the serotonergic system has important role in the regulation of normal motor functions.\textsuperscript{5} This effect is mediated through 5-HT\textsubscript{1A} receptors within the basal ganglia. 5-HT\textsubscript{1A} receptors which modify their own activity are also found in dorsal raphe neurons and on cortical neurons. These neurons send serotonergic and glutamatergic projection to the basal ganglia, respectively.\textsuperscript{14} Activation of these receptors leads to dopamine release.\textsuperscript{7} This effect is mediated by inhibition of adenyl cyclase and opening of potassium channels,\textsuperscript{14} resulting in prolong dopamine effect in parkinsonian animals.\textsuperscript{5} It has been shown that the anti-dyskinetic effect of 5-HT\textsubscript{1A} receptors may be mediated through the activation of these receptors in the striatum.\textsuperscript{5} Recent studies have been reported that stimulation of 5HT\textsubscript{1A} receptors could improve motor behaviors in parkinsonian rodents.\textsuperscript{3,8,14,19} Additionally, it has been shown that anti- parkinsonian effect of L-Dopa could be enhanced by 5HT\textsubscript{1A} receptors activators such as buspirone, 8-OHDA\textsuperscript{T} and tandospirone in 6-OHDA lesioned rats.\textsuperscript{5} Consequently, it may be postulated that pharmacological damping of serotonergic systems by 5HT\textsubscript{1A} receptors agonists could provide benefits in treatment of L-Dopa induced motor disorders.

**Conflict of Interest**
The authors report no conflicts of interest.

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