Stereological analysis of projection neurons and interneurons in control and parkinsonian monkeys in the primate striatum

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INTRODUCTION

The striatum is primarily made up of projection neurons. Interneurons, which modulate and control striatal output, are also present. The current study sought to determine the percentages of projection neurons and interneuron populations in the striatum's of control and parkinsonian monkeys.

The volume density of each neuron population in the caudate, putamen, and ventral striatum of control monkeys and monkeys treated with MPTP, which causes striatal dopamine depletion, was estimated using unbiased stereology. Immunohistochemistry was used to identify the various neuron population phenotypes. All analyses were carried out on the same subjects with the same processing and analysis parameters, allowing for reliable data comparisons.

The striatum is the basal ganglia's largest nucleus. It helps with motor control, compulsive behavior, and habit formation. The striatum is primarily made up of projection neurons, which are GABAergic and express the Dopamine and CAMP Regulated Phosphoprotein, 32-KDa (DARPP-32). Furthermore, the striatum has a small population of interneurons that modulate striatal output. Most interneurons are GABAergic; they are classified according to immunostaining for proteins such as Parvalbumin (Pv), Calretinin (Cr), neuropeptide Y/somatostatin/Nicotinamide Adenine Dinucleotide Phosphate diaphorase (NADPH), and Tyrosine Hydroxylase (TH). A non-GABAergic interneuron type exists as well, consisting of cholinergic interneurons that express the enzyme Choline Acetyltransferase (ChAT).

DESCRIPTION

This is the first study to look at all neuron populations in the ventral and dorsal striatum in the same brains from control and MPTP treated macaques at various stages of disease (non-symptomatic and symptomatic). Thus, accurate comparisons between interneuron populations are possible because they are derived from the same subjects and use analogous experimental and analysis methods. The discovery that most striatal neuron populations are DA depleted has implications for understanding the pathophysiology of the DA depleted striatum and designing therapeutic approaches in Parkinson's disease and parkinsonian conditions.

To the best of our knowledge, this is the first quantitative study to show the numerical stability of most striatal neuron populations in the DA depleted striatum, including both projection neurons (DARPP-32+) and interneurons. We found significant axonal and neuron body changes, mostly loss, in the brains of the MPTP treated monkeys used in this study, particularly in the meso-striatal and thalamic dopaminergic systems. However, the serotonin innervation of the striatum did not change in the same brains. Taking all factors into account, some brain systems are vulnerable and undergo significant changes as a result of DA depletion, while others are not. The striatal neuron populations, both projection neurons and interneurons, survive the MPTP insult and maintain their densities.

The loss of DA innervation in the striatum is causally and directly related to the cardinal features of Parkinson's disease. Furthermore, it is now accepted that striatal interneurons are important determinants of network activity and behavior in Parkinson's disease and L-DOPA induced dyskinesia. Indeed, all striatal interneurons express DA receptors, adding a new dimension to the mechanisms of DA modulation of striatal activity and their impairment in Parkinson's disease and L-DOPA induced dyskinesia. The networks involving projection neurons and their cortical and thalamic inputs are also refined by striatal interneurons. Furthermore, the functional effect of cortical and thalamic inputs on the striatum is highly dependent on the connectivity of various types of striatal interneurons.

More specifically, the organization of corticostriatal and thalamostriatal inputs is dependent on distinct striatal functional territories and specific postsynaptic cell types. Acetylcholine and DA, in particular, dynamically modulate striatal activity, both of which are required for motor function. As a result, numerous recent studies have suggested that pharmacological interventions targeting $ChAT^+$ interneurons may improve motor dysfunction and L-DOPA induced dyskinesia in Parkinson's disease. Other interneuron populations that have been proposed as potential targets to alleviate parkinsonian symptoms include Pv^+ interneurons, which produce the majority of striatal glial cell line-Derived Neurotrophic Factor (GDNF) and $NADPH^+$ interneurons, whose inhibition has been suggested to alleviate L-DOPA induced dyskinesia.

Future drug development should enable efficient targeting of specific neuron populations not only in Parkinson's disease, but also in other brain disorders such as Huntington's disease, Tourette's syndrome, and addiction. The information presented here may aid in the study and comprehension of the cellular and functional effects of such interventions in the primate striatum.

CONCLUSION

Based on an unbiased quantitative approach, the current study provides information on the numerical volume densities and relative percentages of the projection and interneuron populations of the macaque striatum. The current findings will be useful for comparative studies on striatal circuitry in rodents, monkeys, and humans. Furthermore, the discovery that DA depletion has no effect on the numbers of striatal neuron populations (except for the meagre TH^+) is important for understanding the functional connectivity of striatal networks in the DA depleted striatum and for developing therapeutic interventions directed at striatal interneurons in Parkinson's disease.

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