Cholinergic interneurons in striatal microcircuit dynamics studied with anatomical and behavioral methods

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by

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Abstract

Basal ganglia (BG) refer to a group of nuclei in the brain's subcortical regions. They are associated with cerebral cortex, thalamus and brainstem structures that perform many functions including motor control, procedural learning and memory. The largest nucleus of the BG is striatum that has two major neuronal cell types: medium spiny neurons and interneurons. This thesis focuses on one class of interneurons containing choline acetyltransferase (ChAT), the cholinergic interneurons (ChIs). This thesis investigated the role of ChIs in striatal microcircuit dynamics by anatomical and behavior approaches. ChIs participate in voluntary motor control, associated in learning, procedural memory, action selection, planning and execution of movement, through strong cholinergic inputs to other striatal neurons. However, the basic anatomical properties of ChIs after targeted lesion is poorly understood, though others have studied the behavioral consequences of toxin injection. The immunotoxin ribosome inactivating protein (saporin, sap) physically linked to choline acetyltransferase (ChAT-sap) selectively damaged striatal ChIs in toxin-treated mice monitored at 2, 4 and 6 weeks after application of the toxin. Systematic random cell counting, reach-to-grasp behavior task and open field test (OFT) was used to explore anatomical and behavioral differences in animals where the ChIs were destroyed in dorsolateral striatum (DLS). The thesis analyses yielded an unexpected outcome of specific ChIs lesion in DLS where vesicular acetylcholine transporter (vAChT) positive terminal numbers increased while the numbers of neurons themselves were reduced. The increase in vAChT positive terminals might derive from compensatory axonal sprouting from surviving ChIs, or from afferent axonal terminal fields of cholinergic mesopontine neurons. But the source was not further investigated in this study. In addition, the

study showed the decreased number of ChIs in injection site with no recovery after 2, 4, and 6 weeks' time in this study. The thesis also reports the effect of a selective depletion of ChIs from the DLS in a reach-to-grasp task. The mean percentage of successful grasps for the last 6 training sessions was almost half of the value for intact control, and sham operated mice. These results indicate that striatal depletion of ChIs impairs success rate, learning, motor skills in the reach-to-grasp task was observed. These results suggest that the participation of ChIs in striatal mediated motor learning impacts the function of the whole striatal microcircuitry. The lack of ChIs also altered rearing behavior (total number and duration), travelled distance and speed of movement in an open field. In addition, the results are consistent with an important participation of acetylcholine in striatal mediated behaviors possibly by their significant innervation from motor cortex.