9. Summary

Investigation of the interaction of aminergic transmission systems: effects of serotonergic lesions on the striatal high affinity dopamine uptake in rats

The fundamental physiological functions of the brain can be described by interactive regulation models of various transmission systems. A better understanding of physiological and pathophysiological connections can be achieved, if, rather than describing transmissions systems singly, the functions of the central nervous system are seen as an interactive network.

Previous research on cross-relations between the dopamine and serotonin transmission systems suggest a complexity, with reciprocal compensation of functional deficits. The objective of this study was to investigate the interaction of both transmission systems by characterising regulative mechanisms of dopaminergic transmission in the striatum. *In vivo* voltammetry was used to examine the function of the striatal dopamine transporter (DAT) after 5,7-dihydroxytryptamine-lesion of the cranial raphe nuclei of Sprague Dawley rats. The aim was to describe the DAT-mediated high affinity dopamine uptake after lesions to the dorsal or median raphe nucleus and also to detect any lesion-related time-dependent or age-dependent effects.

Seven and ten weeks old animals were lesioned with the neurotoxin 5,7-DHT injected in one of the cranial raphe nuclei to ensure direct lesion of the original areas of serotonergic projection. The electrically evoked striatal dopamine clearance was measured one, three or nine weeks after lesion using continuous amperometry. Measurements were conducted before and after the DAT was blocked by the DAT-inhibitor GBR 12909. Following the voltammetric investigations brains were preserved by perfusion, and successful lesions were confirmed by 5-HT immunohistochemistry. A kinetic model was used to calculate the rateconstante k [1/s] of high affinity dopamine uptake from the measured amperometric signals.

The results of this study demonstrate the dependence of the striatal DAT on the serotonin function. A slow down of the striatal high affinity dopamine uptake one week after 5-HT lesion was observed in both, young and old animals, when compared to sham-lesioned rats

and untreated controls. Young animals, but not adults, showed the same effect three weeks post-lesion, while no functional DAT-changes were detected after nine weeks. Measurements taken before and after administration of GBR 12909 also suggest additional regulatory mechanisms, which appear with serotonergic lesions and reduced DAT-function.

The results of this study show, that the serotonergic and dopaminergic systems have a close interaction and interdependence. The importance of the dopamine system for the striatal and general basal ganglia functions emphasises necessity of understanding regulative control mechanisms. The demonstrated age-dependent effect is in agreement with studies on aging processes of the CNS, which describe anatomical, biochemical and electrophysiological changes. It appears therefore that functional disturbances are compensated by various regulatory mechanisms, dependent on age. The data of this study do not allow extensive interpretation. However, based on the knowledge of the interaction of the serotonin and dopamine transmission systems, one could suggest that the recorded changes of dopamine transmission are produced as a compensatory effort of the CNS to balance out the deficit of central serotonin.