

7. SUMMARY

Svenja Kammann

Pharmacological and immunohistological investigations of the involvement of striatal alterations in the glutamatergic system in a genetic animal model of primary paroxysmal dystonia

Dystonia is one of the most common human movement disorders, characterized by involuntary muscle cocontractions, which cause repetitive twisting movements. At present, the dt^{sz} -hamster represents the only established and thoroughly characterized animal model of the human so called primary paroxysmal non-kinesiogenic dystonic choreoathetosis (PDC), in which dystonic attacks can be induced by stress and last up to several hours. In PDC and other types of primary dystonia, pathomorphological alterations of the CNS are not detectable by using standard techniques. Findings in secondary dystonia point to biochemical dysfunctions within the basal ganglia, especially the striatum. In view of the lack of knowledge about the pathophysiology of this disease, rational therapeutic strategies are missing.

The age-dependent character of primary dystonia in the dt^{sz} -hamster allows comparative studies between animals at the age of maximum expression of dystonia (age: 30.- 42. day of life) and at an age after spontaneous remission of dystonic attacks (>90. day of life). Previous immunohistochemical studies demonstrated an ontogenetic deficit of inhibitory striatal GABAergic parvalbumin-immunoreactive (PV^+) interneurons, which probably represents the primary defect in the dt^{sz} mutant (Richter und Hamann, 2002). In order to clarify if other types of striatal interneurons of the dt^{sz} -hamster also show an altered density, nitric oxide synthase-immunoreactive (NOS^+) interneurons, which closely interact with the glutamatergic system, were examined by immunohistochemical investigations in the present study. Recent electrophysiological and neurochemical studies pointed to an involvement of an increased corticostriatal glutamatergic activity in the manifestation of dystonic attacks in the dt^{sz} -mutants. Therefore, in the present study, striatal manipulations of glutamate receptors were carried out. In order to clarify the role of an abnormal striatal NMDA-receptor-stimulated NO-release and of a deficit of NOS^+ -interneurons, as found in the present study, striatal applications of inhibitors of neuronal nitric oxide synthase (nNOS) were performed.

The density of the immunohistochemical marked striatal NOS⁺-interneurons at the age of maximum expression was significantly reduced within the whole striatum (-21%) of mutant hamsters in comparison to age-matched control animals. This deficit disappeared after spontaneous remission of dystonia. The lack of effects of striatal injections of the nNOS-inhibitors 7-nitroindazole and N^o-propyl-L-arginine on the severity of dystonia indicated that striatal changes in nNOS are not critically involved in the pathophysiology of the PDC of the *dt^{sz}*-Hamster. In contrast to the central relevance of the reduced density of striatal PV⁺-interneurons in primary paroxysmal dystonia in the mutant hamster, the decreased density of striatal NOS⁺-interneurons may be an epiphenomenon, probably caused by an overall retarded postnatal cell migration of striatal interneurons in the *dt^{sz}* mutant.

An antidystonic effect, as observed in previous studies after systemic administration of glutamate receptor antagonists, was only achieved by striatal microinjections of the AMPA receptor antagonist NBQX at the dosage of 0,08 µg per hemisphere. Combined treatment of 0,08µg NBQX and the NMDA receptor antagonist AP-5 failed to show a potentiation of the antidystonic efficacy in the mutant hamster. Three other doses of 0,03 µg, 0,16 µg and 0,25 µg per hemisphere did not produce any reduction of the severity of dystonic attacks. The lack of antidystonic effects at higher concentrations was possibly due to inhibition of the already deficient PV⁺-interneurons. None of the NMDA receptor antagonists decreased the severity of dystonia in the *dt^{sz}*-hamster after single injection in the striatum. With regard to the antidystonic effects of glutamate receptor antagonists after systemic administration, demonstrated in previous studies in the *dt^{sz}*-mutant, these results suggest an involvement of the glutamatergic system of other brain regions in the pathophysiology of the primary dystonia in the mutant hamster.

In conclusion, these results do not support the hypothesis of an involvement of an abnormal activity of the striatal glutamatergic system in the manifestation of dystonic attacks in the *dt^{sz}*-hamster. The reduced density of striatal NOS⁺-interneurons should initiate ongoing examinations of other types of striatal (inter-)neurons.