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ABSTRACT ZUR DISSERTATION

" NEUROCHEMICAL CONSEQUENCES OF JUVENILE SEPARATION STRESS: STUDIES IN THE LIMBIC STRUCTURES OF TRUMPET-TAILED RAT (*OCTODON DEGUS*)"

Environmental influences during certain early life periods, particularly those provided by the mother or both parents, are generally considered to have a strong impact on the development of brain and behavior of the offspring. Using the semi-precocial South American species *Octodon degus*, a rodent becoming increasingly popular in different laboratory research fields, in the first part of this dissertation I aimed to examine the developmental pattern of serotonergic, dopaminergic and amino acid neurotransmitting systems. Moreover, the consequences of disturbance of the parent-offspring interaction induced by parental separation on the serotonergic neurotransmission were assessed. Based on a quantitative neurochemical approach using brain homogenates obtained from cortical regions and the hippocampus my results revealed that (*i*) levels of monoamines and amino acids reach adult-like levels relatively early in ontogeny, i.e. mainly between postnatal day (PND) 3 and 21, depending on the brain region and substance examined, indicating a relatively matured neurotransmission in cortical regions and hippocampus at birth. In addition, an age-, region- and sex-specific pattern of changes in the serotonergic system has been found induced by (*ii*) an acute stress challenge early in life (parental separation at PND 3, 8, 14 and 21) with the most pronounced effects at earlier ages (PND 3 – PND 14) in the female cortex, and (*iii*) repeated stress exposure (measured at PND 21) with the most pronounced effects in the cortex of both sexes. Taken together, these data indicate that early life stress (i.e., parental separation) influences the developing serotonergic system in the semi-precocial *Octodon degus*, even if the brain is relatively well matured at the early stages of postnatal development.

The second part of my dissertation presents the pattern of dopaminergic responses to methylphenidate in the prestressed, juvenile, immature and still developing brain of *Octodon degus*, which mimics the clinical situation in human children and the use of MP treatment much more appropriately than studies performed in normal adult rodent brains. Methylphenidate (MP) is a drug of choice in the treatment of attention-deficit hyperactivity disorder (ADHD) in human children. Previous studies performed by other members of our group have shown, that exposing the newborn animal to repeated episodes of emotional stress

(=separation from the family for one hour per day from PND 1-21) can induce hyperactive behavior and inattentiveness towards maternal vocalizations in juvenile *Octodon degus*. Using *in vivo* microdialysis I measured the levels of dopamine in the medial prefrontal cortex and nucleus accumbens of awake, normal control and hyperactive degus. These results revealed that (*i*) methylphenidate induces minute response in the mPFC of control animals at PND 22-24 (juveniles), whereas in age-matched prestressed degus dopamine levels significantly decline after acute MP injection (10 mg/kg); (*ii*) chronic injection of methylphenidate between PND 22 and 45 results in the sensitization to the drug; in unstressed control animals pretreated with MP the dopamine levels were elevated to a higher extent in response to MP injection than in the vehicle pretreated controls, (*iii*) at the age of PND 46-48 (adolescent animals) the prestressed, hyperactive animals, which were chronically MP-treated, show potentiated dopamine increases in response to MP administration, compared to the unstressed controls. My study indicates that methylphenidate acts differently in the non-fully developed and mature brain. Moreover, early emotional experience as well as chronic drug treatment strongly influence the action of MP in the brain.

Taken together, these results indicate that experience-induced modulation of limbic structures during development may influence their neurochemical responsiveness later in life.