



Marie Curie Host Fellowships for Early Stage Research Training:

Interdisciplinary, international PhD-program of the
Center for Systems Neuroscience Hannover
www.zsn-hannover.de

Project No. 9:

Seasonal Changes in Cerebral Structural Plasticity

Supervisors:

Prof. Dr. Stephan Steinlechner, Zoological Institute, School of Veterinary Medicine Hannover

Dr. Paul Pévet, Director of Federal Institute of Neurosciences Strasbourg (IFR 37)

Aims:

Until a decade ago, the adult mammalian brain was viewed as a fixed-wired structure with only minimal capacities to adapt its adult connectivity. In recent years, a wide range of neuronal plasticity phenomena have been discovered. Neurogenesis in the adult mammalian brain has become a hot topic in neuroscience, although we now know that this adult neurogenesis is restricted to a few brain structures.

The aim of this project is to examine seasonal structural plasticity in a photoperiodic rodent, the Djungarian hamster *Phodopus sungorus*. We will focus our study on the vasopressinergic BNST/MeA – lateral septum/lateral habenula projection. This study should clarify the mechanisms by which steroid hormones can feed back on brain functions, possibly through the induction of structural plasticity. In a broader context, this study aims to explore the extent to which an adult brain can be altered in its connectivity.

State-of-the-art:

Several structures in the brain of Djungarian hamsters show striking variations in its morphology throughout the year. These include especially steroid hormone-dependent structures as well as hypothalamic nuclei involved in regulation of body weight and energy metabolism. These changes are controlled by several factors. The seasons are perceived through the photoperiod, i.e. the length of the day, an astronomic parameter independent of climatic conditions, which allows animals to synchronize their physiologic functions to the change of seasons. Photoperiod acts mainly through the secretion of melatonin from the pineal gland. Melatonin is secreted only during the night and thus reflects the photoperiod. Melatonin controls among many other factors the sexual activity and the secretion of sex steroids. Both melatonin and sex steroids feed back on the brain, where they are responsible for the seasonal changes in neurotransmitter function.

The Bed Nucleus of the Stria Terminalis (BNST) and the medial amygdala (MeA) is such a system which displays changes in the expression of neurotransmitters in response to the photoperiod-dependent levels of sex steroids. (Dubois-Dauphin et al. 1994, Kalsbeek et al. 2002). This vasopressin system projects to the lateral septum, the lateral habenula and the hippocampus, as well as several other structures. It has been implicated in the control of seasonal functions such as hibernation (Hermes et al. 1989) but also in that of sex related behaviors such as scent marking, pair bonding and mate choice, sexual behaviour, parental behavior and aggression which all present seasonal expressions (for review see Goodson et al. 2001).

In hamsters in short photoperiod (winter), sexual activity is blocked, resulting in reduced testosterone levels, which causes a dramatic reduction in the expression of vasopressin mRNA and protein in the BNST. This results in reduced vasopressin immunoreactivity in the nerve fibres projecting from the BNST and the MeA to the lateral septum and habenula. Similar changes in this vasopressin system have been described in non-photoperiodic rodents, such as the rat, after castration. These changes represent a neurochemical plasticity. The reduction in vasopressin immunoreactivity in the lateral septum can be explained by the reduction in the synthesis and transport of vasopressin. However, in parallel to the reduction of vasopressin synthesis and transport, the nerve fibres are probably retracting at least partially from the lateral septum. This implies that when sexual activity is restored in spring and testosterone levels rise again, these retracted fibres will have to re-grow into their target areas in the lateral septum. We have recently shown that testosterone supplementation increases vasopressin expression within 2 days to long photoperiod levels. However, vasopressin positive axons appear in the lateral septum only between 21 to 28 days. This delay is probably due to the re-growth of the nerve fibres into their target area. Thus the neurochemical plasticity may be complemented by a structural plasticity. Such a structural plasticity is very well known in song birds, where several brain structures degenerate in winter, and re-establish a new functional system in spring with the generation of new neurons, migration of these neurons to different brain structures, and reconnection of these neurons into the neural network through axonal and dendritic growth and synaptogenesis (Brenowitz 2004). In mammals, structural plasticity with axonal and dendritic growth followed by synaptogenesis, whether controlled by sex steroids or by photoperiod, has not yet been evaluated.

Specific Research Projects:

Different experimental models modifying the sex steroid level (testosterone administration in sexually inactive animals under short photoperiod, castration of sexually active animals, etc.) will be used to induce neurochemical and structural changes in the BNST/MEA vasopressin system. These structural changes will be followed and analysed using immunocytochemistry

for proteins located in growth cones, as well as modification in cell adhesion molecules involved in axonal growth (e.g. polysialylated NCAM).

Furthermore, axonal growth will be assessed by *in situ* hybridisation for genes involved in axonal growth (GAP43, SCG10, NAP22, PRG3 and neuritin). The testosterone-sensitive vasopressin cells will be identified by co-localization of the vasopressin mRNA with the androgen receptor mRNA or protein. We will try to identify other non-vasopressinergic, testosterone-sensitive neurons subject to a similar structural plasticity using these tools.

The models used in this study are ideal to analyse structural plasticity and axonal growth in an adult brain. They represent a physiologically relevant situation and can be induced through simple modulation of sex steroids or the photoperiod. Thus no lesion inducing a rupture in the blood brain barrier and / or massive liberation of cytokines is involved. Furthermore, this plasticity results in physiologically relevant functional circuits. We think that understanding the mechanisms of this adult structural plasticity should help us develop strategies for the successful integration of stem cell grafts into functional neuronal circuits to cure neurodegenerative diseases.

Literature:

Brenowitz EA. (2004) Plasticity of the adult avian song control system. *Ann N Y Acad Sci* 1016: 560-585

Dubois-Dauphin M., Theler J.M., Ouarour A., Pevet P., Barberis C., Dreifuss J.J. (1994) Regional differences in testosterone effects on vasopressin receptors and on vasopressin immunoreactivity in intact and castrated Siberian hamsters. *Brain Research* 638: 267-276

Goodson J.L. & Bass A.H. (2001) Social behavior functions and related anatomical characteristics of vasotocin/vasopressin systems in vertebrates. *Brain Research Reviews* 35: 246-265

Hermes M.L., Buijs R.M., Masson-Pevet M., van der Woude T.P., Pevet P., Brenkle R. & Kirsch R. (1989) Central vasopressin infusion prevents hibernation in the European hamster (*Cricetus cricetus*). *Proc Natl Acad Sci U S A* 86: 6408-6411.

Kalsbeek A., Palm I.F. & Buijs R.M. (2002) Central vasopressin systems and steroid hormones. *Progress in Brain Research* 139: 57-73