# Hippocampal Neuroplasticity and Depression

**Ph.D. Thesis**

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Pécs, 2007.

## *INTRODUCTION*

Major depressive disorder (MDD) is a common, recurrent, and often life-threatening illness. Epidemiological studies have shown that up to 10-25% of the population is getting depressed in their lives. In humans, loss of rank or social status is associated with a greater risk of depression.

Despite extensive studies on MDD, relatively little is known about its etiology. The traditional monoamine hypothesis fails to explain sufficiently the neurobiological mechanisms underlying major depressive disorder (MDD). Although MDD indisputably has a strong genetic basis, severe environmental stressors have been associated with a considerable increase in risk for MDD in vulnerable individuals. Recent findings in molecular biology, histopathology and brain imaging revealed that MDD is related with impairments of structural plasticity and cellular resilience in brain areas regulating mood and emotions. Although MDD has traditionally been connected to neurochemical alterations, recent neuroimaging studies have demonstrated selective structural and functional changes across various limbic and nonlimbic regions in the brains of depressed individuals. In particular, both metabolism and volume of the prefrontal and cingulate cortex are reduced, while—with further progression of the syndrome—hippocampal volume loss can also occur. Postmortem morphometric studies revealed decreased neuronal size and glial density in some cortical and limbic brain areas. Moreover, iIt has been revealed that antidepressants and lithium seem to have neuroprotective properties, mediated by neurotrophic intracellular signaling pathways.

The hippocampal formation is one of the most widely studied brain structures associated to depression. This dissertation focuses on the ***cellular alterations in the hippocampus in an animal model for depression.*** Since histological studies are limited in humans, the ***chronic psychosocial stress paradigm in tree shrews*** (*Tupaia belangeri*), a valid animal model of depression, was used to study the morphological changes as a result of chronic stress and concomitant antidepressant treatment. Following aspects of the cellular plasticity have been investigated:

i. the changes of ***cytogenesis in the dentate gyrus***

ii. the possible involvement of inhibitory ***interneurons***

iii. the role of ***astroglia*** in the structural changes of hippocampus

iv. finally**,** a novel possible antidepressant agent, a ***non-monoaminergic $NK_1$ receptor antagonist*** was tested in the chronic psychosocial stress model.

## *MAIN EXPREIMENTAL METHODS*

### Chronic psychosocial stress paradigm in tree shrews: a valid animal model of depression

Tree shrews (*Tupaia belangeri*) are small, squirrel-like animals, phylogenetically close to primates, naturally living in South-East Asia. Males live solitarily, exhibiting pronounced territoriality, which can be utilized to establish challenging situations under experimental control. To induce social conflict one naïve male is introduced into the cage of a socially experienced male. This results in active competition for control over the territory, and after a clear dominant–subordinate relationship has been established, the two animals are separated by a wire mesh barrier. The barrier is removed every experimental day for about one hour, thereby allowing physical contact between the two males during this time only. Beyond this time period, the subordinate animal is protected from repeated physical attacks, but it is constantly exposed to olfactory, visual and acoustic cues from the dominant animal.

During periods of daily social stress, subordinate male tree shrews develop symptoms that are very similar to what can be observed in many patients with major depression, such as hyperactivities of the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis, disturbances in sleeping patterns, and reduced motor activity. Some of these parameters are renormalized by antidepressant treatment. In addition, suppressed neurogenesis and structural changes in neurons, e.g. retraction of the dendrites of hippocampal pyramidal neurons, can be observed too. These processes are counteracted by antidepressants, whereas the anxiolytic diazepam was ineffective. Taken together, the chronic social conflict in the male tree shrew appears to be a valid model for studying stress-related disorders such as depression. The chronic social stress in tree shrews can be regarded as a '*homologous model*' of depression, because it mimics several aspects of the human disease.

### Quantitative stereology and volumetry

Cell (neuron and astrocyte) numbers were estimated with the modified optical fractionator technique. The optical fractionator is an unbiased counting method, which is independent of the size, shape and orientation of the cells to be counted, and combines the optical disector with the fractionator-sampling scheme. The parameters of the fractionator-sampling scheme were established in pilot experiments, and were uniformly applied to all animals. Before quantitative analysis, slides were coded, and the code was not broken until the analysis was completed. Cell counting was conducted using a Zeiss III RS microscope with the aid of the Stereoinvestigator 3.16 software (Microbrightfield, Colchester, VT, USA). The optical

disector frame area, and the sampling area, were selected such that 1–3 neurons per optical disector were counted on average.

**Bromo-deoxi-uridine positive cells**: Every fifth section (an average of 26) through the dorso-ventral extent of the left hippocampal formation was examined. All BrdU-labeled cells in the granule cell layer including the subgranular zone, defined as a two-cell-body-wide zone along the border of the granule cell layer, were counted regardless of size or shape. To enable counting of cell clusters, cells were examined under 400× and 1,000× magnification, omitting cells in the outermost focal planes. The total number of BrdU-labeled cells was estimated by multiplying the number of cells counted in every fifth section by five.

**Parvalbumin-immunreactive interneurons**: For examination, every tenth section (an average of 14 sections per animal) was systematically sampled through the dorso-ventral extent of the left hippocampus. The border of the region was outlined using a 6.3× objective (N.A. 0.16), and for counting cells a 16× (N.A. 0.16) objective was used. The size of the disector frame area was 200 μm × 300 μm, and the sampling area, was 300 μm × 300 μm.

**Glial fibrilar acidic protein (GFAP) positive astrocytes**: every tenth sections along the dorso-ventral extent of the hippocampus were selected, yielding an average of 14 section per animal for analysis. The area associated with each movement (sampling area) was 500 μm × 500 μm; the area of the counting frame was 50 μm × 50 μm; the thickness of the section (24.3 μm); and *h* is the height of the of the dissector ( 20μm).

**The somal volume of the GFAP positive astrocyte**s: The somal volume of astrocyte cell body was calculated in every fifth counted glial cell using the nucleator probe. For each cell, eight isotropic lines converged on the nucleus and intersected the somal boundary.

**Hippocampal volumes** were assessed in the same sections as those used for counting astrocytes. The volumes were estimated according to the formula based on the Cavalieri principle. First, the cross sectional hippocampal area was measured by tracing the borders of the hippocampus (Ammon's horn together with the dentate gyrus) using the StereoInvestigator 4.04 software. Then, this value was multiplied by the the nominal section thickness of 50 μm; and by the sampling section fraction (1/10).

## *EXPERIMETS*

### *1. Age-dependent susceptibility of adult hippocampal cell proliferation to chronic psychosocial stress*

Adult hippocampal neurogenesis is a form of neuroplasticity that has been shown to persist throughout the entire lifespan of mammals, including humans. A number of environmental and endogenous factors have been demonstrated to modulate this process. Two examples are age and stress, both of which are powerful inhibitors.

- ***Objective***: Stress is one of the most potent environmental factors known to suppress both the proliferation and survival rate of newly generated hippocampal granule cells. This has been demonstrated using various stress paradigms in several species. It is not known whether dentate cell proliferation in individuals of various ages might be differentially susceptible to stress. Here, we focused on this.
- ***Method***: We subjected adult male tree shrews ($n$ = 27) to five weeks of psychosocial stress, after which dentate cytogenesis was determined using BrdU immunohistochemistry. Stressed animals were compared with non-stressed controls ($n$ = 18). The number of BrdU positive celles was plotted as a function of age. Regression curves were fitted to the data. The regression parameters of the stressed and nonstressed group were compared.
- ***Results:*** Chronic psychosocial stress resulted in a significant decrease (-46%) of the total number of BrdU-positive cells (Student's $t$-test: $t = 3.47$, df = 43, $p = 0.001$). For BrdU data plotted as a function of age, we found the best fit with the following regression:

  $$\text{Log}_e (Y) = \log_e (a) - bx$$

  Where Y is the number of BrdU positive cells, and x is the age. While comparing slope (b value in the equation) the stressed and non-stressed groups, the slope of the stressed group showed a significantly more decline in the cytogenesis along the age.
- ***Conclusion:*** We found that older animals were significantly more vulnerable to the adverse effect of stress on dentate cell proliferation.

### *2. Chronic Social Defeat Stress Decreases the Number of Parvalbumin-Immunoreactive Interneurons in the Hippocampus: Prevention by Treatment with a Substance P Receptor ($NK_1$) Antagonist*

Several lines of evidence originating from both animal and human studies suggest the involvement of the GABAergic system in the pathophysiology of depressive disorders Changes in the number of local inhibitory neurons have been reported, especially in the anterior cingulate and prefrontal cortices, and in the hippocampi of schizophrenic and bipolar patients. These observations are often interpreted as a consequence of altered neurodevelopment, therefore the contribution of stressful experiences, especially in the perinatal period should be also taken into account. Because parvalbumin-containing interneurons receive robust excitatory input from the mossy fibers, one may assume that they might eventually die from excitotoxic injury due to the excessive glutamate levels that has been reported in the hippocampus during stress.

- ***Objective***: Here, we examined whether long-term social defeat stress influenced the number of parvalbumin-containing GABAergic cells, known to provide the most powerful inhibitory input to the perisomatic region of principal cells.
- ***Method***: Adult male tree shrews were submitted to five weeks of stress, after which immunocytochemical and quantitative stereological techniques were used to estimate the total number of hippocampal parvalbumin-immunoreactive (PV-IR) neurons. Additionally, we examined whether antidepressant treatment offered protection from this stress-induced effect. We administered fluoxetine (15 mg/kg per day) and SLV-323 (20 mg/kg per day), a novel neurokinin 1 receptor ($NK_1R$) antagonist, because the $NK_1R$ has been proposed as a possible target for novel antidepressant therapies. Animals were subjected to a seven-day period of psychosocial stress before the onset of daily oral administration of the drugs, with stress continued throughout the 28-day treatment period.
- ***Results***: Stress significantly decreased the number of PV-IR cells in the dentate gyrus (–33%), CA2 (–28%) and CA3 (–29%), whereas the CA1 was not affected. $NK_1R$ antagonist administration completely prevented the stress-induced reduction of the number of PV-IR interneurons, whereas fluoxetine attenuated this decrement in the dentate gyrus, without affecting the CA2 and CA3.
- ***Conclusions***: The effect of stress on interneuron numbers may reflect real cell loss; alternatively, parvalbumin concentration is diminished in the neurons, which might

indicate a compensatory attempt. In either case, antidepressant treatment offered protection from the effect of stress and appears to modulate the hippocampal GABAergic system. Furthermore, the NK1R antagonist SLV-323 showed neurobiological efficacy similar to that of fluoxetine.

***3. Astroglial plasticity in the hippocampus after chronic psychosocial stress and concomitant fluoxetine treatment***

Recently, numerous in vivo imaging studies revealed that both the hippocampus and prefrontal cortex undergoes selective volume reduction in several stress-related neuropsychiatric illnesses particularly in PTSD and major depressive disorder however, the exact cellular basis for this volume decrease has not yet been elucidated.

- ***Objective***: Analysis of postmortem tissue from patients with affective disorders has revealed decreased number of glial cells in several brain areas. Here, we examined whether long-term psychosocial stress influences the number and morphology of hippocampal astrocytes in an animal model with high validity for research on the pathophysiology of major depression.
- ***Method***: Adult male tree shrews were submitted to five weeks of psychosocial stress, after which immunocytochemical and quantitative stereological techniques were used to estimate the total number and somal volume of glial fibrillary acidic protein (GFAP)-positive astrocytes in the hippocampal formation. Additionally, we examined whether antidepressant treatment with fluoxetine, a serotonin selective reuptake inhibitor, offered protection from these stress-induced effects. Animals were subjected to a seven-day period of psychosocial stress before the onset of daily oral administration of fluoxetine (15 mg/kg per day), with stress continued throughout the 28-day treatment period.
- ***Results:*** Stress significantly decreased both the number (-25%) and somal volume (-25%) of astroglia. Fluoxetine treatment prevented the stress-induced numerical decrease of astrocytes, but had no counteracting effect on somal volume shrinkage. In non-stressed animals, fluoxetine treatment had no effect on the number of astrocytes, but similarly to stress exposure significantly reduced their somal volumes (-20%).
- ***Conclusions:*** These notable changes of astroglial structural plasticity in response to stress and antidepressant treatment support the notion that glial changes may

contribute to the pathophysiology of affective disorders as well as to the cellular actions of antidepressants.

***4. Examining SLV-323, a Novel NK1 Receptor Antagonist, in a Chronic Social Defeat Stress Model for Depression***

Several lines of evidence suggest that the Substance P – $NK_1R$ system plays an important role in the regulation of emotional behavior. Substance P antagonists have been proposed as candidates for a new class of antidepressant compounds.

- ***Objective***: We examined the effects of SLV-323, a novel neurokinin 1 receptor (NK1R) antagonist, in the chronic psychosocial stress paradigm of adult male tree shrews.
- ***Methods:*** Animals were subjected to a 7-day period of psychosocial stress before being treated daily with SLV-323 (20 mg/kg per day). The psychosocial stress continued throughout the treatment period of 28 days. Brain metabolite concentrations were determined in vivo by proton magnetic resonance spectroscopy. Norepinephrine excretion was monitored from daily urine samples, and serum testosterone concentrations were measured at the end of the experiment. All animals were videotaped daily to analyze scent marking behavior and locomotor activity. Cell proliferation in the dentate gyrus and hippocampal volume were measured post mortem.
- ***Results:*** Stress significantly decreased cerebral concentrations of *N*-acetyl-aspartate, total creatine, and choline-containing compounds *in vivo* and resulted in an increase of urinary norepinephrine and decrease of serum testosterone concentrations. Moreover, stressed animals displayed decreased scent marking behavior and locomotor activity. The proliferation rate of the granule precursor cells in the dentate gyrus was reduced, and hippocampal volume was mildly decreased. The stress-induced alterations in the central nervous system were partially prevented by concomitant administration of SLV-323, while drug treatment had only a minor effect on the stress-induced behavioral changes.
- ***Conclusions:*** The novel NK1R antagonist SLV-323 has certain antidepressant-like effects in a valid animal model of depression.

## SUMMARY OF THE MAIN FINDINGS AND POTENTIAL CLINICAL RELEVANCES

1. Age is a significant modulator of the stress-vulnerability in the adult hippocampus; i.e. we found that older animals were significantly more vulnerable to the adverse effect of stress on dentate cell proliferation
2. Both chronic social defeat stress and antidepressant treatment (with fluoxetine or an NK1 receptor antagonist) appear to influence directly or indirectly the hippocampal GABAergic system.
3. Chronic stress significantly decreased the number of astrocytes in the hippocampus and this numerical decrease correlated with the hippocampal volume shrinkage. Fluoxetine treatment prevented the stress-induced numerical reduction of astrocytes.
4. The novel NK1R antagonist SLV-323 has certain antidepressant-like effects in a valid animal model of depression.

The stress hypothesis of depression is one of the oldest theories of the biological psychiatry. Our results support the neuroplasticity theory of depression, in contrast to the "hypercortisolism – neurotoxicity" theory formulated during the mid ´80s. Although, until now there is no experimental evidence demonstrating any alterations in the incidence of adult neurogenesis in the dentate of depressed patients, our results still support the neuroplasticity theory of depression, in contrast to the "hypercortisolism – neurotoxicity" theory formulated during the mid ´80s. This recently formulated neuroplasticy theory of depression may explain such empirical observations in the clinical practice as the delayed effectiveness of antidepressant drug therapy, the frequent relapses during the early phase and the kindling sensitisation phenomenon. Furthermore, the reversibility of the structural changes detected by the *in vivo* imaging techniques in depressed patients argue that the underlying cellular changes are plastic in nature and not irreversible cell loss. Finally, the cognitive deficits of depressed patients, i.e. the pseudodementia – and its reversibility – imply impaired hippocampal neuroplasticity in this disorder.

The exact mechanism of the therapeutic effect of antidepressant treatment is not yet fully understood. Findings of this thesis – in line with results of other groups – prove that these agents have a clear effect on the cellular plasticity. The role of neurogenesis and its functional role are the most questionable. Antidepressant treatment has a beneficial effect on many aspects of cellular and structural plasticity, but its immediate therapeutic role has not yet been established. The rate of neurogenesis can be rather regarded as a general aspect of cellular plasticity.

*LIST OF PUBLICATIONS*

**I. Publications related to the thesis**

**Scientific papers:**

8. Czéh B., **Simon M**. (2005): Neuroplaszticitás és depresszió. *Psychiatr Hung*. 20:4-17.
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**impact factor: 5,369**

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***Cumulative impact factor: 44.80***