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Effect of chronic psychosocial stress and long-term cortisol treatment on hippocampus-mediated memory and hippocampal volume: a pilot-study in tree shrews

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Abstract

We investigated the impact of chronic psychosocial stress and long-term cortisol treatment on hippocampus-mediated memory processes and hippocampal volume in male tree shrews. By combining cognitive tests on a hole board, magnetic resonance imaging (MRI), and saliva cortisol analysis, we were able to follow in individual animals the stress- and cortisol-induced temporal effects on HPA axis activity and the hippocampus and its executive functions during 15 weeks. Four weeks of either cortisol treatment or psychosocial stress affected hippocampus-mediated memory. Cortisol-induced impairments were observed only at the end of the treatment phase while in stressed animals a negative effect on hippocampus-mediated memory was monitored after 7 weeks of recovery. A trend towards a reduction of the hippocampal volume was found in both experimental groups. The present preclinical study demonstrated that major life events, such as psychosocial stress, or chronic cortisol treatment leave traces in hippocampus-dependent memory. This finding requires systematic analysis to understand how brain areas critical for information processing such as the hippocampal

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formation are affected by stress and stress hormones.

Keywords: Tree shrew; Stress; Memory; Glucocorticoids; MRI; Hippocampal volume

1. Introduction

The hippocampal formation is of crucial importance for cognitive processes (see McEwen, 1997) and alterations in this brain area are associated with a selective impairment of hippocampus-mediated memory performance (Squire, 1992). Increasing evidence suggests a connection between structural alterations and volumetric reduction of the hippocampal formation, cognitive impairments and disturbances of the activity of the hypothalamo–pituitary–adrenal (HPA) axis. Several cross sectional studies in humans demonstrated that both a hyperactivity of the HPA axis with elevated levels of circulating adrenal glucocorticoid (GC) hormones such as cortisol, as well as a hypoactivity of the axis with low GC plasma levels are accompanied by hippocampal atrophy and cognitive impairments (Gurvits et al., 1996; Lupien et al., 1998). Since the underlying mechanisms leading to these impairments are not well understood, there is great interest to establish animal models which mimic these neuropathological processes. One of the models is the psychosocial stress paradigm in male tree shrews. In subordinate animals, chronic stress experience is characterized by constantly elevated cortisol levels, pronounced structural changes in the hippocampal formation (see Fuchs and Flügge, 1998), and impaired hippocampus-dependent memory functions (Ohl and Fuchs, 1999).

Using this well-characterized paradigm, the purpose of the present study was to investigate the temporal dynamic effects of chronic stress exposure on the volume of the hippocampal formation and hippocampus-mediated memory performance. To assess the specific effects of chronically elevated GC levels, a second group of animals received cortisol via the drinking water. Hippocampal volume was measured with a recently established magnetic resonance imaging (MRI) protocol enabling repetitive volumetric measurements of the tree shrew's hippocampus (Ohl et al., 1999b). Saliva samples were collected for cortisol analysis (Ohl et al., 1999a). To investigate the cognitive performances in tree shrews, we used a modified hole board paradigm which allows memory testing under various experimental conditions (Ohl et al., 1998). By combining these methods, animals' hippocampus-mediated memory and hippocampal volume were determined before, during and after the stress exposure and cortisol treatment.

2. Animals and methods

Adult male tree shrews (*Tupaia belangeri*) were from the breeding colony at the German Primate Center (Göttingen, Germany); for housing conditions see Fuchs