

Sub-type specific hippocampal glutamate levels in the chronic mild stress rat model for depression

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Introduction:

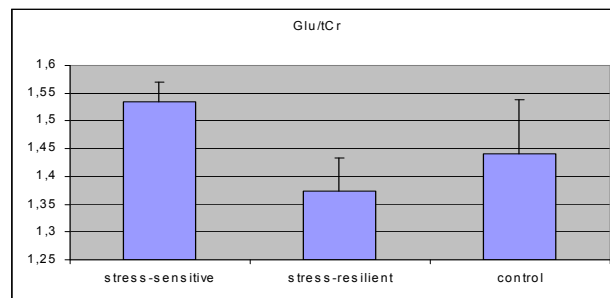
Major depressive disorder is a devastating disease with high prevalence and mortality. It imposes severe suffering and puts a significant socioeconomic burden on our society. Despite of its importance, the pathophysiology of affective disorders and the mode of action of antidepressants have been poorly understood. Currently, there is an increasing interest in cognitive disturbances related to major depression, as impaired cognition is one of the core elements of this disorder. Studies have shown that cognitive impairment in depression correlates with changes in hippocampal volume and morphology, a brain region known to be involved in cognitive function. In addition, the hippocampus has an important function in regulation of the stress-response axis. Corticoid receptors are highly expressed in the hippocampus, and regulate the HPA-system via a feedback mechanism, an indispensable regulatory system to deal with stress (1). The role of the hippocampus is mainly inhibitory: vast excitatory glutamatergic projections from the hippocampus, modulate inhibitory gabaergic projections to the hypothalamus, attenuating activity of the hypothalamic-pituitary-adrenal (HPA) axis when cortisol levels become dangerously high. This mechanism is important in order to modulate the global stress reaction, and to limit the damage done by stress-related physiological processes (2). Taken altogether, it is clear that the hippocampal formation is closely involved in the pathophysiology of depression. In this study we use the chronic mild stress (CMS) rat model for depression, to assess neurochemical changes in the hippocampus. Animals subjected to the CMS protocol display a reduction in the consumption of a palatable sucrose solution. Decreased sucrose consumption is believed to reflect anhedonic behaviour, and in the CMS paradigm it is used to confirm the overall state of depression. In addition, CMS exposure results in other behavioural and physiological changes related to major depression, including dysregulation of the HPA-axis. Recent findings from Ove Wiborg *et al.*(3) however, indicate that rats subjected to CMS segregate into two sub-groups: a group that develops anhedonia-like symptoms (stress-sensitive) and a subgroup of 30% that appears to be resilient to the influence of chronic stress on hedonic status (stress-resilient) as assessed by higher to normal sucrose intake profiles. This segregation was further confirmed by place preference conditioning test and on molecular levels by global gene and protein expression analysis. Consequently, together with the unstressed control rats and the stress-sensitive rats, we also included stress-resilient rats in this study.

Materials and methods:

The chronic mild stress (CMS) rat model was used which mimicks the clinical condition of depression in humans. Animals were chronically exposed to a variety of mild stressors during a period of 6 weeks, and were divided into stress-resilient and stress-sensitive subgroups depending on the weekly uptake of a palatable sucrose solution. Consequently, three groups of animals were obtained: unstressed control rats (n=7), stress-sensitive anhedonic rats (n=7) which drink less sucrose and stress-resilient rats which drink more sucrose (n=7). Animals were anesthetized with isoflurane. 1H magnetic resonance spectroscopy (1H-MRS) was used to assess neurochemical changes in a ROI of 8µl in the hippocampus, using a 9.4T MRI system (Bruker), and a PRESS acquisition scheme (TR=3s, TE=12ms, NA=512). Up to 17 metabolites were successfully quantified using LCModel software (4). In order for metabolites to be incorporated in this study, Cramer-Rao bounds were not allowed to exceed 50%. Metabolite concentrations are expressed as ratio of the amplitude of the respective signal to the amplitude of the summed creatine and phosphocreatine signals (tCr). Differences in metabolite concentrations were analysed with one-way ANOVA and corrected for multiple comparisons (p=0.05).

Results:

In this study, we observed a significant increase of glutamate (Glu/tCr) in the hippocampus of stress-sensitive rats as compared to stress-resilient rats (p<0.005) and the control group (p<0.05) respectively. No additional differences in metabolite concentration were found between groups.



Discussion and Conclusion:

Previous studies in animal models and patients show aberrations in the hippocampal glutamatergic/gabaergic system. Changes in glutamate levels are often implicated in excitotoxic events. In the CMS model, cognitive impairment and neural cell fate in the hippocampus seem to be related with subjection to stress, rather than with the hedonic status, excluding the excitotoxicity hypothesis (3). Consequently, we suggest that the lack of a rise in glutamate concentration in stress-resilient rats reflects different modulation of the HPA-axis, thereby causing different behavioural responses to stress. This is in line with previous studies in the CMS model, which point to an increased HPA activity in the stress-resilient subtype, as assessed with mRNA profiling (5). Prolonged exposure to high cortisol levels due to failing HPA attenuating mechanisms can lead to profound physiological changes, influencing the insulin-regulatory system and the dopaminergic system. Moreover, differences in the HPA attenuating mechanisms can cause different subtypes of depression. Additionally, different subtypes of depression can be characterized by different concentrations of occipital glutamate and GABA. For instance, patients suffering from atypical depression express lower levels of glutamate as compared to patients with melancholic depression (6). Strikingly, patients with atypical depression typically display a hunger for carbohydrates, while patients with melancholic depression display a loss of appetite and anhedonia. Atypical depression covers probably about 40% of the depressed patients. In summary, using hippocampal glutamate levels as a readout, our results suggest that a difference in the attenuating mechanism of the HPA is responsible for a different response towards chronic stressors, similar to what happens in different subtypes of depression in humans. Possibly, stress-resilient animals are a model for depression with an impairment in the HPA attenuating mechanism. Our present study underlines the importance of the hippocampus in the modulation of stress-coping mechanisms and sheds a new light on animal modelling of affective disorders.

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