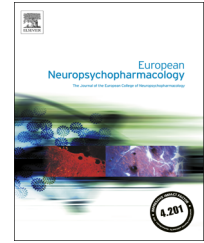




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Electroconvulsive stimulation reverses anhedonia and cognitive impairments in rats exposed to chronic mild stress



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Abstract

Electroconvulsive therapy remains the most effective treatment for depression including a fast onset of action. However, this therapeutic approach suffers from some potential drawbacks. In the acute phase this includes amnesia. Electroconvulsive stimulation (ECS) has previously been shown to reverse a depression-like state in the chronic mild stress model of depression (CMS), but the effect of ECS on cognition has not previously been investigated. In this study the CMS model was used to induce a depressive-like condition in rats. The study was designed to investigate the acute effect of ECS treatment on working memory and the chronic effect of repeated ECS treatments on depression-like behavior and working memory. The results indicated that, in the acute phase, ECS treatment induced a working memory deficit in healthy controls unexposed to stress, while repeated treatments reversed stress-induced decline in working memory, as well as recovering rats submitted to the CMS paradigm from the anhedonic-like state. Like in the clinical setting, a single ECS exposure was ineffective in inducing remission from a depression-like state.

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1. Introduction

Depression is a common and severely disabling disease with a lifetime prevalence of 15–20% (Kessler et al., 1994; Kruijshaar et al., 2005). The main treatment options are pharmacotherapy and psychological interventions (2009);

however, in severe and refractory depression, electroconvulsive therapy (ECT) is a widely used and very effective treatment of depression, with remission rates above 70% (Daly et al., 2001; Medda et al., 2009). Reports of associated negative side effects on cognition are a downside to ECT treatment (Fink, 2001; Porter et al., 2008; Semkowska et al., 2011). Cognition refers to mental processes, including memory and attention. Memory can be further divided into long-term and short-term memory. Long-term memory includes both explicit and implicit memory function while short-term memory refers to a short-term storage of information. Attention includes the theoretical concept of

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working memory, which is the process of temporarily storing a limited capacity of information (Baddeley, 2003).

The exact nature of the relationship between ECT and cognitive impairments is still unresolved, but a recent meta-analysis on the subject concluded that cognitive abnormalities are mainly limited to the first 3 days post-treatment (Semkowska and McLoughlin, 2010). Memory systems affected are primarily explicit and working memory functions. Moreover, at 15 days post-treatment, some memory functions, here amongst working memory, were found to be improved beyond baseline levels (Semkowska and McLoughlin, 2010). A confounding factor to a deduction of potential ECT-induced negative effects on cognition is the cognitive deficits associated with depression (Christensen et al., 1997; Henry and Crawford, 2005). Studies have shown that both explicit and working memory functions are impaired during depression (Austin et al., 1992; Christopher and MacDonald, 2005), while implicit memory appears to be spared (Bazin et al., 1994). This relation between cognitive function and depression has led to a debate as to whether amnesia associated with ECT is, in fact, an intrinsic component of the disease pathology (Berg, 2011).

In animals, the analog to ECT is electroconvulsive stimulation (ECS). Studies on the effect of ECS in animal models of depression are sparse; however, ECS has been shown to reverse stress-induced anhedonia in the chronic mild stress model (CMS) (Moreau et al., 1995).

To our knowledge, the effect of ECS on cognition has only been investigated in healthy animals and with the aim of modeling a potential epileptic pathological condition (Majak and Pitkanen, 2004; Hidaka et al., 2008).

The aim of the present study was two-fold. First, to investigate the acute effect of ECS on working memory function in healthy rats, measured by performance in the spontaneous alternation behavior (SAB) task. Second, to investigate the effect of repeated ECS treatments on rats exposed to CMS, focusing on two behavioral readouts, namely sucrose intake and performance in the SAB task. Sucrose intake is a valid measure of hedonic status (Willner, 2005; Henningsen et al., 2009, 2012; Christensen et al., 2011) and provides the animal analog of depression-like behavior, i.e. reward sensitivity. Performance in the SAB task is used to measure working memory function, and we

have previously shown that exposure to CMS causes a decline in SAB performance (Henningsen et al., 2009). We therefore aimed at investigating the effect of ECS on stress-induced cognitive impairments in the CMS model using the SAB task as a readout on working memory function. Our results showed, that the acute effect of exposure to ECS, was a reduced performance in the SAB task in control rats unexposed to stress. Repeated ECS treatments on rats exposed to the CMS paradigm, however, showed a positive effect on performance in the SAB task and a significant increase in sucrose intake. A single ECS exposure, on CMS rats, did not alter sucrose intake.

2. Experimental procedures

Subjects: Forty-four male Wistar rats (Taconic M&B, Ry, Denmark) were used in the study. The animals were singly housed, food and water was available ad libitum, and animals were kept on a standard 12-h light/dark cycle (lights on at 6.00) except when one of these parameters was changed due to the stress regime. All animal procedures were approved by the Danish National Committee for Ethics in Animal Experimentation (2008/561-447).

The study design is shown in Fig. 1.

Chronic mild stress (CMS): The CMS procedure was done according to our previously described protocol, which has been used to investigate behavioral and molecular aspects of depression (Henningsen et al., 2009, 2012; Christensen et al., 2011). On the basis of sucrose intake in the three final baseline tests, animals were divided into two matched groups and placed in separate rooms. One group was exposed to nine weeks of chronic mild stressors and the other was left unchallenged. All animals were food and water deprived 14 h before sucrose consumption test.

The stress protocol consisted of seven different stress conditions each lasting 10-14 h: one period of intermittent illumination, stroboscopic light, grouping, food or water deprivation, and two periods of soiled cage and no stress, and three periods of 45° cage-tilting.

Sucrose consumption test: Sucrose consumption analysis was done as described previously (Henningsen et al., 2012). Initially, the animals were trained to consume a palatable sucrose solution (1.5%). The training lasted for five weeks, with sucrose test conducted twice a week during the first two weeks and once a week during the last three weeks. Animals were food and water deprived 14 h before the test, which was performed by free access to a bottle with sucrose solution for 1 h. During the entire stress

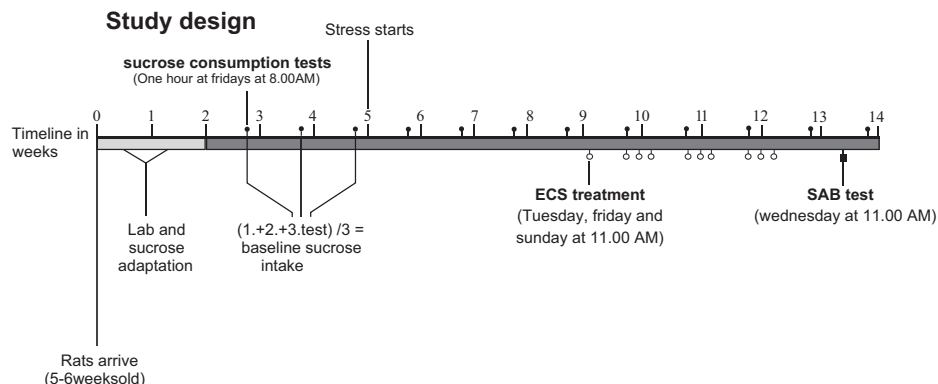


Fig. 1 Study design showing the 14 week long schedule. Closed circles indicate weekly sucrose consumption tests, open circles indicate ECS treatments, closed square indicates conduction of SAB test 8 days after final ECS treatment. SAB test was also performed on control rats 24 h after final ECS treatment. The CMS paradigm was initiated at the beginning of week 6 and ECS treatments were initiated in week 10.

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