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Research report

Lasting downregulation of the lipid peroxidation enzymes in the prefrontal cortex of mice susceptible to stress-induced anhedonia

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HIGHLIGHTS

- Chronic stress affects brain peroxidation in anhedonic but not resilient mice.
- Acute stress elicits opposing effects to chronic stress on peroxidation.
- Imipramine precludes changes in peroxidation after chronic and acute stress.
- Stress-induced changes in peroxidation and behaviour last after anhedonia recovery.
- Altered peroxidation may reflect individual susceptibility to depression.

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ABSTRACT

Antioxidant enzymes and lipid peroxidation in the brain are involved in neuropsychiatric pathologies, including depression. 14- or 28-day chronic stress model induced a depressive syndrome defined by lowered reward sensitivity in C57BL/6J mice and changed gene expression of peroxidation enzymes as shown in microarray assays. We studied how susceptibility or resilience to anhedonia is related to lipid peroxidation in the prefrontal cortex (PFC). With 14-day stress, a comparison of the activities of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPX) and accumulation of malondialdehyde (MDA) revealed a decrease of the first two measures in susceptible, but not in resilient animals or in stressed mice chronically dosed with imipramine (7 mg/kg/day). Acute stress elevated activity of CAT and SOD and dynamics of MDA accumulation in the PFC that was prevented by imipramine (30 mg/kg). 28-day stress evoked anhedonia lasting two but not five weeks while behavioural invigoration was detected at the latter time point in anhedonic but not non-anhedonic mice; enhanced aggressive traits were observed in both groups. After two weeks of a stress-free period, CAT and SOD activity levels in the PFC were reduced in anhedonic animals; after five weeks, only CAT was diminished. Thus, in the present chronic

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stress depression paradigm, lasting alterations in brain peroxidation occur not only during anhedonia but also in the recovery period and are accompanied by behavioural abnormalities in mice. This mimics behavioural and neurochemical deficits observed in depressed patients during remission which could be used to develop remedies preventing their relapse.

1. Introduction

It has been widely demonstrated that the generation of reactive oxygen species plays a critical role in the pathophysiology of several neuropsychiatric disorders [1,2]. The brain is particularly vulnerable to reactive oxygen species production because it metabolizes 20% of total body oxygen and has a limited amount of antioxidant capacity [1]. In situations where the generation of free radicals exceeds the capacity of antioxidant defence, oxidative stress may lead to membrane degradation, cellular dysfunction and apoptosis [3,4]. This might be relevant for the pathogenesis of affective disorders, because in vivo magnetic resonance spectroscopy studies have demonstrated changes in brain compounds related to oxidative phosphorylation, energy production and phospholipid metabolism [5]. In addition, it has been hypothesized that affective disorders are associated with mitochondrial dysfunction, and abnormalities in respiratory complex activity and energy production may lead to cellular degeneration [6,7]. Recent studies have consistently reported increased products of lipid peroxidation and alterations of the major antioxidant enzymes in patients with affective disorders, in particular, with depression [1,8–10]. The associations between oxidative and antioxidative systems during depressive disorder and efficacy of antidepressant therapies have been demonstrated in pharmacological studies as well [11].

Yet, the outcome so far from clinical and pre-clinical studies, particularly undertaken with various translational approaches to model depression, did not result in a clear picture of which and how lipid peroxidation enzymes are changed in the CNS during depression. Moreover, some studies reported an increase while others evidenced a decrease or no change in the main enzymes of peroxidation [9,12]. Scarce data are available concerning lipid peroxidation during a recovery phase from depression and residual behavioural abnormalities in animals and patients with preceding depressive syndrome [13,14]. Meanwhile, early relapse of depressive episodes remain a substantial medical and social problem, since about 20% of patients experience persistent subsyndromal depression during the recovery phase [15] and display aberrant behaviour including high impulsivity and aggression, as well as an increased stress response. Importantly, these mechanisms seem to differ from those of depression development and treatment resistance [16].

The identification of how lipid peroxidation enzymes in the brain is altered during depression/remission states is challenged by the limitations of the use of non-invasive research tools that are applicable in clinical studies. As for the translational approach, the investigation of these questions is greatly constrained by the use of experimental procedures of modelling depression, which per se affect brain peroxidation. As for instance, frequently used stress techniques that evoke learned helplessness, behavioural despair and/or deficient sensitivity to reward in experimental animals, can change brain peroxidation irrespectively to the induction of a depressive-like state [17–20].

On this basis, to investigate whether the activities of lipid peroxidation enzymes are changed during depressive/recovery states, we have used variants of a recently validated 14- and 28-days chronic stress depression models with internal control for stress in mice [19–21]. Since anhedonia, a decreased ability to experience pleasure from activities normally thought to be enjoyable, is a key feature of major depressive syndrome [21], an animal paradigm that would mimic this feature to address such question [22,23], was selected. We have chosen to employ experimental protocols in which inbred C57BL/6J mice can be differentiated upon their individual vulnerability to the stress-induced anhedonic state as defined by a decrease in the preference to sucrose solution over water. Stressed mice either have shown a decrease of sucrose preference below the lowest control values (sucrose preference <65%) and were defined as susceptible to stress-induced anhedonia, or did not show such changes (sucrose preference >65%) and were considered as resilient to the induction of this deficit [24]. As such, resilient, non-anhedonic mice were used as an internal control that enables the analysis of potential peroxidation changes in stressed mice specifically in relation to anhedonia versus the consequences of stress alone. The use of a subgroup of individuals who are negative for the induction of a desired phenotype during experimental paradigms as an internal control for more refined modelling of neurobiological phenomena and medical conditions is not novel [25]. It was recently implemented in modelling depression with chronic stress, allowing the separation of resilient from susceptible to depressive-like state animals [24,26] and, this way, to increase the validity of such paradigms (for a review, see Strekalova et al. [27]).

Given the fact that profound changes such as increased SERT, COX-1, TNF-α, 5-HT2A receptor expression and increased microglia activation, seen in a mouse model with stress-induced anhedonia, were found in the prefrontal cortex [28], we have chosen this brain structure to assess the activity of peroxidation enzymes. Notably, while similar changes were observed also in the hippocampus, they were less pronounced than in the prefrontal cortex. Microarray analysis of hippocampal expression of genes of peroxidation enzymes after 14-day stress was supplementary included in the study. Additionally, we have included stressed imipramine-treated animals, as preliminary data have shown that most of the molecular changes observed in the prefrontal cortex of stressed anhedonic mice are precluded by chronic imipramine treatment in a 10-day stress paradigm [29]. In order to segregate potential overlap between the effects of chronic stress and the last stressor applied in a course of the procedure, we have separately analyzed the effects of a single rat exposure in naive mice, also under conditions of a pre-treatment with bolus injection of imipramine.

To relay potential changes in the brain peroxidation to behavioural signs of anhedonia and residual symptoms that are characteristic for remission periods from depression, a sensitivity to reward in sucrose test, triggered by bright illumination behavioural invigoration in locomotor tests and parameters of aggression were evaluated in mice at various time points with respect to stress. We anticipated defining whether or not behavioural and brain peroxidation measures can be specifically attributed to individual susceptibility to stress-induced anhedonia and if any of the behavioural and neurochemical deficits can be observed during remission from the anhedonia phase.

2. Materials and methods

2.1. Animals

Studies were performed using 3.5-month-old male C57BL/6J mice. 3.5-month-old male CD1 mice were used as resident