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Imipramine protects against the deleterious effects of chronic corticosterone on depression-like behavior, hippocampal reelin expression, and neuronal maturation

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ABSTRACT

We have hypothesized that a downregulation of reelin and deficient maturation of adult-born hippocampal neurons are important factors in the pathogenesis of depression. This hypothesis is based on previous work showing that depression-like behavior in rats treated with protracted corticosterone develops in concert with decreased dendritic complexity in newborn hippocampal granule neurons and decreased reelin expression in the proliferative subgranular zone of the dentate gyrus. In addition, heterozygous reeler mice with approximately 50% of normal brain levels of reelin are more vulnerable to the depressogenic effects of corticosterone than wild-type mice. The purpose of this experiment was to provide pharmacological validation for the link between reelin, neuronal maturation, and depression by examining whether the deleterious effects of corticosterone on these measures could be prevented by co-administration of the antidepressant imipramine. Rats received corticosterone injections, corticosterone injections plus either 10 or 15mg/kg imipramine injections, or vehicle injections for 21 consecutive days. They were then subjected to the forced swim test to assess depression-like behavior and sacrificed for immunohistochemical examination of immature neuron number and dendritic complexity and the presence of reelin + cells. We found that corticosterone increases depression-like behavior, decreases the number of reelin + cells in the subgranular zone, and decreases the number and complexity of immature neurons in the granule cell layer. All of these behavioral and cellular phenotypes were prevented by imipramine, providing further support for the idea that reelin is involved in the pathogenesis of depression.

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1. Introduction

Chronic stress is an important risk factor for the development of major depression (e.g., Kendler and Gardner, 2010). However, the underlying mechanisms by which stress hormones such as corticosterone (CORT) can promote depressive symptoms are not well understood. Accumulating evidence suggests that the hippocampus is critically involved in the etiology of depression (e.g., Sterner and Kalynchuk, 2010; Willner et al., 2013). Indeed, both neuroimaging and post-mortem studies have revealed decreased hippocampal volume and altered cell morphology in tissue samples from depressed patients (e.g., MacQueen et al., 2003). This has stimulated the idea that depression is related in some way to altered hippocampal neurogenesis. This idea is supported by evidence that chronic stress or CORT exposure in rodents can decrease the proliferation and survival of newborns neurons (Bambico and Belzung, 2013; Lussier et al., 2013) and that most antidepressant drugs have the opposite effect (Castren and Hen, 2013). Indeed, some studies have demonstrated a direct role for hippocampal neurogenesis in the behavioral actions of antidepressant treatments (Mateus-Pinheiro et al., 2013; Santarelli et al., 2003). These data have fuelled intense research efforts aimed at characterizing the molecular mechanisms governing adult neurogenesis and their relationship to depression and antidepressant treatment.

In a series of experiments, we have been testing the hypothesis that a deficit in the extracellular matrix protein reelin could delay neuronal maturation in newborn granule neurons and that this process could be involved in the pathogenesis of depression. Reelin is best known for its role in guiding cell migration in the developing brain (Caruncho et al., 2004; Franco and Muller, 2011). In the adult brain, reelin is

Abbreviations: CORT, corticosterone; HRM, heterozygous reeler mice; CI-10, corticosterone + 10 mg/kg imipramine; CI-15, corticosterone + 15 mg/kg imipramine; PBS, phosphate-buffered saline; DCX, doublecortin SSRI - serotonin specific reuptake inhibitor.

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secreted by a subset of GABAergic interneurons in the cortex and hippocampus. Hippocampal reelin acts to promote dendritic spine development, regulate cell migration and integration, enhance synaptic plasticity and neurogenesis, and facilitate learning and memory (Fournier et al., 2010; Frotscher et al., 2003; Niu et al., 2008; Pujadas et al., 2010; Qiu et al., 2006; Weeber et al., 2002). Previous work has suggested that hippocampal reelin could be decreased in both depressed patients (Fatemi et al., 2000) and in chronically stressed rodents with behavioral symptoms of depression (Lussier et al., 2009, 2013). We recently reported that the timeline for the emergence of deficient granule neuron maturation and decreased subgranular zone reelin expression coincides with the onset of depression-like behavior in rats treated with protracted CORT (Lussier et al., 2013). In addition, heterozygous reeler mice (HRM), which typically have about 50% of normal levels of reelin, are more susceptible to the depressogenic effects of corticosterone than wild-type mice (Lussier et al., 2011), suggesting that individual differences in baseline levels of reelin may regulate vulnerability to depression symptoms.

To our knowledge, there have been no studies that have examined the effect of antidepressant treatment on hippocampal reelin in a preclinical model of depression. If reelin plays a role in the pathogenesis of depression, then chronic antidepressant treatment that reverses behavioral symptoms of depression and deficient neuronal maturation in chronically stressed rats should also resolve deficits in hippocampal reelin expression. In this experiment, we examined this hypothesis using a preclinical rat model in which 21 daily injections of the stress hormone CORT produce robust increases in depression-like behavior (Brummelte and Galea, 2010; Gregus et al., 2005; Hill et al., 2003; Kalynchuk et al., 2004; Mao et al., 2012; Marks et al., 2009; Ulloa et al., 2010; Wong et al., 2011; Workman et al., 2013). Our findings revealed that CORT increases depression-like behavior in the forced swim test, decreases the number of reelin + cells in the subgranular zone and hilus, and alters the number and complexity of immature neurons in the granule cell layer. These behavioral and cellular phenotypes were dose-dependently prevented by co-administration of the tricyclic antidepressant imipramine. These results show for the first time that hippocampal reelin is protected by antidepressant treatment and that reelin may be important for the functional consequences of antidepressant treatment.

2. Materials and methods

2.1. Animals

Adult male Long–Evans rats ($N = 73$) were purchased from Charles River (Montreal). They weighed approximately 200–250g at the time of arrival. The rats were housed individually in standard rectangular polypropylene cages with rat chow and water available *ad libitum*. The colony room was maintained at 21 ± 1 °C with a 12-h light/dark cycle. All experimental procedures were conducted under a protocol approved by the University of Saskatchewan Committee on Animal Care and Supply.

2.2. CORT and imipramine treatment

We handled the rats briefly once per day for 7 days prior to the start of CORT injections. We then weight-matched the rats and randomly assigned them to one of the following four treatment groups: CORT only (CORT rats; $n = 19$), CORT plus 10 mg/kg imipramine (CI-10 rats; $n = 18$), CORT plus 15mg/kg imipramine (CI-15 rats; $n = 17$), or vehicle (control rats; $n = 19$). All drugs were delivered by subcutaneous injection at a volume of 1 ml/kg once per day for 21 consecutive days; CORT and imipramine injections were delivered 6 h apart. CORT (MP Biomedicals) was suspended in physiological saline with 2% Tween-80 and imipramine hydrochloride (Sigma) was dissolved in 0.9% saline. CORT was given at 40 mg/kg in a volume of 1 ml/kg as this dose reliably increases depression-like behavior in rats without altering nonspecific motor activity (Marks et al., 2009). Imipramine doses were chosen based on previous findings, indicating their ability to reverse depression-like behavior in rats (Bessa et al., 2009). All rats were weighed daily during the period of CORT treatment. Separate groups of rats were used for the behavioral and postmortem analyses.

2.3. Forced swim test

We used a modified 1-day forced swim test to assess depression-like behavior. The forced swim test, as developed by Porsolt et al. (1978), was originally designed to serve as a behavioral assay for antidepressant drug efficacy. In this case, a 2-day version of the test is needed, where the first day is an induction phase to teach the rat that escape is not possible, and the second day is a test day, in which the amount of "despair" acquired by the rats on day one is reflected in increased immobility and fewer active attempts to escape. However, the forced swim test is now reliably used to detect a depressive phenotype in rodents previously subjected to chronic stress (Cryan et al., 2005). Here, a 1-day version of the test is appropriate under the premise that prior exposure to stress should induce despair on its own, making the induction day unnecessary. Indeed, we have shown that a 1-day version of the forced swim test is just as effective as a 2-day version of the test in assessing the depression-like behavior produced by repeated CORT treatment (Marks et al., 2009).

All behavioral testing was done in a different room from the rooms used for the CORT injections and housing. We videotaped all behaviors and scored them at a later date. Rats (control $n = 10$; CORT $n = 10$; CI-10 $n = 10$; CI-15 $n = 9$) were placed individually into a rectangular Plexiglas swim tank (25 cm long × 25 cm wide × 60 cm high) that was filled with 27 °C (±2 °C) water to a depth of 30 cm. Rats remained in the tank for 10 min. During this time, we scored active and inactive components of behavior, including the time spent climbing, time spent swimming, and time spent immobile (Cryan et al., 2005).

2.4. Tissue Preparation and Immunohistochemistry

A subset of rats from each group (control $n = 9$; CORT $n = 9$; CI-10 $n = 8$; CI-15 $n = 8$) was deeply anesthetized with sodium pentobarbital and transcardially perfused with saline, followed by 4% paraformaldehyde. Brains were post-fixed in 4% paraformaldehyde for 72 h at 4 °C, and then sectioned on a vibrating microtome at 50 μm.

To visualize reelin + cells, we used an immunohistochemical protocol as previously described (Fournier et al., 2010; Lussier et al., 2013). Briefly, free-floating sections were washed in 0.3% (v/v) H_2O_2 in PBS for 30 min to block endogenous peroxidase activity. They were then pre-incubated for 30 min in a blocking solution containing 0.3% (v/v) Triton X-100, 5% (v/v) normal horse serum (NHS), and 1% (v/v) bovine serum albumin (BSA) dissolved in PBS in order to block any nonspecific antibody binding. The sections were then incubated with a mouse anti-reelin primary monoclonal antibody (1:2000 Chemicon International, 48 h, 4 °C), followed with a secondary biotinylated antibody (horse anti-mouse, 1:200, 2 h, Vector Labs) diluted in 0.3% (v/v) Triton X-100 PBS. This was followed by incubation in an avidin–biotin peroxidase complex (1:200, 1 h, Vecta Stain Elite ABC reagent, Vector Labs). Immunolabeled cells were visualized with a 0.033% 3,3′-diaminobenzidine (DAB) solution dissolved in 0.00786% (v/v) H_2O_2 and PBS. The reaction was stopped using PBS as a rinse. The sections were then mounted onto slides and left to dry overnight and then coverslipped using Entallen resin solution.

To visualize immature neurons, we used the microtubule binding protein doublecortin (DCX) (Brown et al., 2003). DCX immunohistochemistry was conducted as previously described (Fournier et al., 2010; Lussier et al., 2013). Briefly, free-floating tissue sections were

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