



Research report

Chronic corticosterone-induced impaired cognitive flexibility is not due to suppressed adult hippocampal neurogenesis



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ABSTRACT

Hippocampal neurogenesis has been implicated in the etiology of depression. Recent studies suggest new neurons add flexibility to hippocampal-dependent learning and memory. We hypothesized that suppressed hippocampal neurogenesis may contribute to impaired cognitive flexibility associated with depression. The chronic corticosterone (CORT)-induced animal model of depression was used. In Experiment 1, rats received either CORT (40 mg/kg) or vehicle injections for 21 days and were subjected to Water maze during the last six days of drug treatment. No group differences were found during the spatial learning phase; however, cognitive flexibility, measured by reversal training, was significantly impaired in the CORT-treated rats. The probe test revealed enhanced memory of the new platform location for the CORT-treated rats. Given the time newborn neurons require to mature, we presumed if impaired cognitive flexibility seen in Experiment 1 were due to suppressed neurogenesis, terminating CORT treatment 3 days prior to behavioural testing should still induce the impairment. Therefore, Experiment 2 was similar to Experiment 1, except that CORT injections were terminated 3 days prior to behavioural assessment. However, not only was spatial learning significantly enhanced in the CORT-treated rats, but there were also no group differences during reversal or probe tests. Bromodeoxyuridine, administered a day after the first drug treatments in both experiments, was quantified and revealed the number of new neurons were the same in both groups in both experiments. Results suggest cognitive flexibility is impaired in the CORT-induced animal model of depression; an effect that is reversible and independent of suppressed hippocampal neurogenesis.

1. Introduction

Depression is associated with prolonged emotional disturbances and it is one of the leading causes of disability and global burden of disease [1]. Various cognitive domains, such as attention, psychomotor speed, executive function, cognitive flexibility and some aspects of episodic memory are impaired in individuals suffering from major depression [2–7]. Magnetic resonance imaging (MRI) in individuals with major depression has revealed a significant reduction in the whole hippocampal volume [8–12] and high resolution MRI imaging has shown smaller volumes of all the sub-regions of the hippocampus including the dentate gyrus and the CA1-3 [13]. However, the hippocampal volume reduction in depressed individuals is not the results of cell loss [14] and appears to be the results of abnormal hippocampal microstructure [15], including neuropil loss and decreased in neuronal soma size [16]. Nonetheless, a recent cross-sectional post-mortem analysis study reported fewer mature granule cells in the anterior dentate gyrus of untreated depressed individuals, suggesting impaired hippocampal

neurogenesis [17]. Experimental studies on animal models have also highlighted the importance of the hippocampus and, in particular, adult hippocampal neurogenesis in depression [18–21]. Understanding how depression may be related to hippocampal function and neurogenesis may thus enhance our knowledge about the pathogenesis of this major mental health disorder [22].

Recent findings suggest hippocampal neurogenesis may be important in promoting cognitive flexibility to hippocampal-dependent learning and memory [23–25]. For example, experimental suppression of adult hippocampal neurogenesis by temozolomide [24], X-irradiation, or through genetic ablation of progenitor cells [23] induces specific impairment in tasks requiring spatial cognitive flexibility, without impairing initial training of the spatial tasks. Likewise, individuals with clinical depression have reported difficulties on tasks assessing executive function, cognitive flexibility, inhibition, and control [26–28]. It is generally accepted that cognitive processes involved in executive function including cognitive flexibility are mediated by prefrontal cortical region [29,30]. However, it is not clear whether impaired

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spatial cognitive flexibility associated with depression may, in part, be the results of suppressed adult hippocampal neurogenesis. The aim of the present study, using chronic exogenous corticosterone (CORT)-induced depression model, was to investigate this possibility.

Chronic exogenous CORT treatment in adult rodents has been found to reliably produce depressive-like symptoms, such as behavioral despair measured by increased immobility and decreased swimming behaviors in the forced swim test [31–41] and increased immobility in the tail suspension test [37]. Anhedonic-like state measured by decreased sucrose preference has also been reported following chronic exogenous CORT treatment [36,38]. In fact, chronic exogenous CORT treatment has been suggested to be a useful model to study the effects of stress hormones on the etiology and treatment of stress-induced depression [42,43].

Stress hormone CORT is known to modulate adult hippocampal neurogenesis [44]. For example, proliferation of progenitor cells in the dentate gyrus is suppressed by both acute and chronic stress in various species [45–48]. Exogenous high levels of acute and chronic CORT treatment have also been reported to reduce cell proliferation in both male [31,39,49–52] and female rats [49]. Additionally, suppressive effects of chronic exogenous CORT treatment on survival of BrdU-labelled cells [53,54] and their differentiation into new neurons [55] have been documented.

Therefore, we hypothesized that rats chronically treated with CORT, with presumably reduced level of hippocampal neurogenesis, should exhibit impaired spatial cognitive flexibility. Nonetheless, animal studies have provided convincing evidence that many effects of chronic stress [56–60] and chronic exogenous CORT treatment [56,59] on brain and cognitive functions are reversible. However, in regards to hippocampal neurogenesis, a very short recovery or washout period after chronic CORT injection should not reverse the expected impaired spatial cognitive flexibility, if such behavioral deficit is due to suppressed hippocampal neurogenesis. This is because, in rats, once generated, it takes about 2 weeks for newborn neurons to mature and functionally integrate into the hippocampal circuitry [61]. Thus, the rationale behind the present study was twofold: 1) to investigate whether spatial cognitive flexibility is affected in this chronic CORT animal model of depression, and 2) to assess whether a deficit in spatial cognitive flexibility is due to suppressed adult hippocampal neurogenesis. To address these objectives, two experiments were designed. In Experiment 1, rats were chronically injected with CORT and in the final days of injection, rats underwent a spatial learning and memory task that requires spatial cognitive flexibility. Given that spatial cognitive flexibility has been shown to be related to functional adult hippocampal neurogenesis [23–25,62] and chronic CORT injection has suppressive effects on adult hippocampal neurogenesis [49,53–55], we expected to observe deficit in spatial cognitive flexibility in the CORT-treated rats in this first Experiment. To ensure impaired spatial cognitive flexibility induced by chronic CORT injection in Experiment 1 is due to suppressed hippocampal neurogenesis, we designed a second experiment that was similar to Experiment 1 in all respects, except that CORT and vehicle administrations were terminated only 3 days prior to behavioural testing. We hypothesized that any deficit in spatial cognitive flexibility observed in Experiment 1 should persist in Experiment 2, if suppressed adult hippocampal neurogenesis was the underlying factor to induce such deficit. In order to quantify the number of surviving newborn neurons, rats were injected with bromodeoxyuridine (BrdU) in both experiments and we expected to find fewer surviving newborn neurons in the CORT-treated rats in both Experiments.

2. Methods

2.1. Animals

Twenty-three male Sprague-Dawley rats (Harlan, USA), three months of age, were single-housed in standard shoebox cages

(47 × 25 × 20 cm) on a 12:12 h light/dark cycle (lights on at 7:00 AM). Food and water were provided *ad libitum*. Body weights were measured daily. All procedures followed the Canadian Council on Animal Care guidelines, and was approved by the University of Waterloo's Animal Care Committee.

2.2. Drugs

2.2.1. Corticosterone (CORT) and vehicle

In each experiment, animals were randomly assigned to either receive subcutaneous injections of 40 mg/kg CORT (Sigma-Aldrich) or vehicle. CORT was dissolved in 37 °C, 35% w/v 2-hydroxypropyl-beta-cyclodextrin (2-H β C; OnBio) and delivered in a volume of 1.25 ml/kg body weight. A similar volume of 35% w/v 2-H β C was used as the vehicle for control groups.

2.2.2. Bromodeoxyuridine (BrdU)

All rats received 50 mg/kg BrdU (Sigma-Aldrich) dissolved in 37 °C 0.9% physiological saline. BrdU injections were delivered intraperitoneally in a volume of 2 ml/kg body weight. All rats received four injections of BrdU separated by 150 min. In both experiments, BrdU injections occurred on the second day of CORT or vehicle administrations to ensure high blood levels of CORT, thus allowing for optimal distinction between the two treatments [54].

2.3. Behavioural tasks

2.3.1. Water maze

A circular pool (150 cm in diameter) filled with 23 ± 1 °C water, made opaque with dark non-toxic tempera paint was used in both experiments. Tracking software (EthoVision XT Video Tracking System, Noldus) monitored each rats' movement in the water maze. A hidden platform (20 cm in diameter) was located in the centre of the northeast quadrant of the pool, 2 cm under the surface of the water for the first three days of training.

2.3.2. Spatial training

Spatial training consisted of one block of 4 trials per day over three consecutive days. Each trial began by placing the rats in the pool facing the wall in a pseudo-random starting location (North, East, South, West). Once rats found the platform, they were allowed to remain on the platform for 20 s. If a rat was unable to find the hidden platform within 60 s, the rat was guided through the water to the platform, where the rat remained for 20 s. Next trial started after a 30 s inter-trial interval, during which time, rats were kept in a small opaque holding cage with a cover.

2.3.3. Cognitive flexibility

To assess cognitive flexibility, reversal training was utilized by placing the hidden platform in the opposite (Southwest) quadrant of the pool. Rats were given a pseudo-random location to start each trial. The procedure was identical to spatial training and the rats were given two consecutive days of training of the reversal protocol.

2.3.4. Probe test

On the sixth day, a 60 s probe test was given to each rat. Probe test involved the removal of the platform from the pool, to assess memory retention.

2.4. Procedure

2.4.1. Experiment 1

Following a week of handling, eleven rats were randomized to receive injection of either CORT (n = 6) or vehicle (n = 5) once per day for 22 days with the dosages described. All rats received four injections of BrdU, one day following the first administration of CORT or vehicle.

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