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ADOLESCENT SOCIAL ISOLATION STRESS UNMASKS THE COMBINED EFFECTS OF ADOLESCENT EXERCISE AND ADULT INFLAMMATION ON HIPPOCAMPAL NEUROGENESIS AND BEHAVIOR

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Abstract—Hippocampal neurogenesis and associated cognitive behaviors are regulated by a number of factors including stress, inflammation, and exercise. However, the interplay between these factors remains relatively unexplored, especially across the lifespan. In the current study, the effect of social isolation stress during the adolescent period on neurogenesis and hippocampal-dependent cognitive behaviors was examined. This period of the lifespan has been demonstrated to be an important time for hippocampal growth and plasticity, during which changes to hippocampal neurogenesis may have long lasting effects. Additionally, we aimed to determine whether a 'dual-hit' of adolescent stress and adult chronic neuroinflammation would potentiate any negative effects of either insult alone. Lastly, the potential positive effects of exercise during adolescence was examined to determine whether exercise could attenuate any negative impacts of these insults on hippocampal neurogenesis and behavior. The results from the current study demonstrate that social isolation stress during adolescence followed by intra-hippocampal exposure to the pro-inflammatory cytokine IL-1β in early adulthood produces deficits in both spontaneous alternations and novel object recognition. Exercise attenuated deficits in neurogenesis and novel object recognition in mice that had been exposed to the 'dual-hit' of stress and neuroinflammation. These findings indicate that adolescence represents a key period of the lifespan during which external factors such as stress and exercise can impact on hippocampal development, and may alter the response to challenges such as neuroinflammation in later life. © **2017 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: exercise, neuroinflammation, neurogenesis, cognition, adolescence, interleukin-1β.

INTRODUCTION

Hippocampal neurogenesis, the production, differentiation and integration of new neurons in the subgranular zone of the dentate gyrus (DG; Ming and Song, 2005) is integral for certain behavioral tasks that are reliant on spatial memory, contextual memory, and recognition memory during adulthood (Snyder et al., 2005; Saxe et al., 2006; Clelland et al., 2009; Jessberger et al., 2009). Hippocampal neurogenesis is also implicated in emotional regulation, including anxiety and the stress response (Levone et al., 2015). Indeed, repeated stressor exposure has a detrimental impact on adult hippocampal neurogenesis (Cameron et al., 1997; Heine et al., 2004; Mirescu and Gould, 2006; Lagace et al., 2010) and associated cognitive behaviors (Conrad et al., 1996; Song et al., 2006; Elizalde et al., 2008; Howland and Cazakoff, 2010). Moreover, increased expression of the pro-inflammatory and stress-related cytokine interleukin-1β (IL-1β; Hueston et al., 2011; Nguyen et al., 1998; Hueston and Deak, 2014) has a negative impact on hippocampal neurogenesis both *in vitro* (Green et al., 2012; Zunszain et al., 2012; Ryan et al., 2013) and *in vivo* (Vallières et al., 2002; McPherson et al., 2011; Wu et al., 2013). Additionally, IL-1β has been shown to mediate the stress-induced impairments in adult hippocampal neurogenesis and spatial and contextual memory (Ben Menachem-Zidon et al., 2008; Goshen et al., 2008; Koo and Duman, 2008).

In contrast to stress and IL-1β aerobic exercise promotes both adult hippocampal neurogenesis and cognitive function (Radák et al., 2001; Ferris et al., 2007; Kamijo et al., 2009; Hötting and Röder, 2013; van Praag et al., 1999; Voss et al., 2013). Indeed, it is hypothesized that the beneficial effects of exercise on hippocampal-dependent memory is due to its pro-neurogenic effect (Clark et al., 2008; Ji et al., 2014). Although it has been demonstrated that exercise can reverse the negative impact of stress on adult hippocampal neurogenesis and memory (Castilla-Ortega et al., 2014; Kannangara et al., 2009), it is unclear if such effects generalize to the counteraction of the negative effects of IL-1β (Ryan and Nolan, 2016).

Adolescence is a critical period for maturation of the hippocampal circuitry (Bayer, 1982) and heightened neurogenesis (He and Crews, 2007; Knoth et al., 2010) as well as a key period for susceptibility to stress and the emergence of psychiatric disorders (Paus et al., 2008; McGorry et al., 2011). Thus, adolescence may be a

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Abbreviations: BrdU, 5-bromo-2′-deoxyuridine; DCX, doublecortin; DG, dentate gyrus; GFP, green fluorescent protein; IL-1β, interleukin-1 beta; NeuN,, neuronal nuclei; PBS, phosphate-buffered saline; PND, post-natal day.

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critical period during which alterations to hippocampal function may result in organizational effects which last throughout adulthood. However, it is only in relatively recent years that the impact of adolescent stress on hippocampal neurogenesis has been reported (Hueston et al., 2017). As adolescence represents a time of increased social activity (Forbes and Dahl, 2010; Vanderschuren et al., 2016), stressors which involve social disruption such as social isolation stress may have an increased detrimental impact on hippocampal function at this time compared to adulthood (Cinini et al., 2015; Ibi et al., 2008; Sterlemann et al., 2010; Hueston et al., 2017). In addition, this period of the lifespan represents a transitional phase where the programing of adult behaviors occurs (Sawyer et al., 2012), and as such, lifestyle modifications such as exercise during this time may also have a long-lasting impact on cognitive function (Hueston et al., 2017).

Based on these studies, we hypothesized that isolation housing stress during adolescence would impair hippocampal neurogenesis and associated cognitive behaviors, that inflammation caused by increased hippocampal IL-1β would have a detrimental impact on both hippocampal neurogenesis and cognitive performance under both housing conditions, and that exercise would have a beneficial effect on these negative regulators of neurogenesis and behavior. Thus, the aim of this study was to examine the impact of both social isolation stress and exercise during adolescence on hippocampal neurogenesis and associated behaviors in the adult mouse. Given previous evidence for an anti-neurogenic effect of IL-1β in the adult hippocampus, we further investigated the effect of chronic IL-1β overexpression in adult mice following stress and exercise exposure during the adolescent period.

EXPERIMENTAL PROCEDURES

Animals

Male C57Bl/6 mice (n = 10 for behavioral cohort, n = 4–6 for tissue cohort) were obtained from Harlan UK at post-natal day (PND)21, and were housed in a colony maintained at 22 ± 1 °C, with a 12:12-h light–dark cycle (lights on 0630-1830). Mice had *ad libitum* access to food and water throughout the experiment, and were weighed weekly. All animal procedures were performed under licenses issued by the Department of Health and Children (Ireland) and the Health Products Regulatory Authority (HPRA, Ireland), in accordance with the European Communities Council Directive (2010/63/EU), and approved by the Animal Experimentation Ethics Committee of University College Cork. Mice were group housed in standard Plexiglas cages for 10 days, after which time they were either single or pair housed. Mice were allowed free access to low-profile running wheels (MedAssociates) starting at PND31 (exercise condition), or were placed in the same size cage with no wheel (sedentary condition; see Fig. 1A for experimental timeline) for the duration of the experiment. Pair housed animals were allowed access to two wheels. Wheels were wirelessly connected via a USB hub to a computer running the Wheel Manager software (MedAssociates), which allowed rotations of the wheels to be monitored continuously.

Stereotaxic surgery

Following 4 weeks of access to running wheels (PND66), mice were anesthetized with ketamine/xylazine and placed into a Kopf stereotaxic frame. A pLL4.0-backbone lentivirus for the overexpression of IL-1β or green fluorescent protein (GFP) as a control under the U6 promoter (gift from Dr. Karen Keeshan, University of Glasgow) was injected bilaterally into the dorsal hippocampus using a 10-μL Hamilton syringe fitted with a bevelled needle. The lentivirus was administered at a dose of 1–1.5 × 10^5 TU in a volume of 2–3 μL to the following coordinates, AP: −2.0 mm; ML: ±1.6 mm; DV: −2.0 mm, relative to Bregma. Mice were allowed to recover for 1 week following surgery in individually ventilated caging (with or without continuous running wheel access as appropriate).

Spontaneous alternation test

Spontaneous alternation was measured in a Y-maze two weeks post-surgery (PND 80) to assess hippocampal-dependent working memory. The Y-maze consisted of three 16 cm long arms 6.5 cm high and 120° apart. Mice were placed into the end of one arm, facing the wall, and behavior was recorded for 5 min. The total number of arm entries (all four paws entering one arm) and number of alternations (defined as entry into 3 consecutive arms) was recorded. The percentage of alternations was calculated as % = alternations/(entries-2). The Y-maze was cleaned with 50% ethanol between animals to remove odor cues.

Object recognition tests

A novel object recognition task was conducted 3 weeks post-surgery (starting PND87). Mice were first habituated to an empty chamber (32 × 40 cm) under dim light for 10 min. Twenty-four hours later, mice were exposed to 2 identical objects for 10 min, followed by a 3-h inter-trial interval. After the delay, mice were placed back into the arena for 5 min where the object in the one of the objects had been switched for a novel object. All behaviors were recorded, and videos were scored to determine the amount of time the mice spent attending to the novel vs. familiar objects. Novel objects were counterbalanced between groups. The arena and objects were cleaned with 50% ethanol between tests to remove odor cues. Data are expressed as a discrimination ratio using the formula $\frac{Time\ with\ Novel}{Time\ with\ Novel+Familiar}$.

BrdU injections and immunohistochemistry for neurogenesis

A separate group of mice that did not undergo behavioral tests were administered daily injections of bromo-deoxyuridine (BrdU; 50 mg/kg i.p.; Sigma) for 7 days starting one week following surgery to label dividing cells. Mice were euthanized 3 weeks post-surgery with

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