Behavioural Brain Research 296 (2016) 30–34

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Short communication

Corticotropin releasing factor impairs sustained attention in male and female rats

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HIGHLIGHTS

- Corticotropin releasing factor (CRF) impairs sustained attention in rats.
- Females with lower levels of ovarian hormones were more vulnerable to this effect.
- CRF may contribute to cognitive deficits in stress-related psychiatric disorders.

ARTICLE INFO

Article history:
Received 22 June 2015
Received in revised form 31 July 2015
Accepted 18 August 2015
Available online 22 August 2015

Keywords:
Stress
Corticotropin releasing hormone
Cognition
Sex difference
Estrous cycle

ABSTRACT

Stressful life events and stress-related psychiatric disorders impair sustained attention, the ability to monitor rare and unpredictable stimulus events over prolonged periods of time. Despite the link between stress and attentional disruptions, the neurobiological basis for stress regulation of attention systems remains underexplored. Here we examined whether corticotropin releasing factor (CRF), which orchestrates stress responses and is hypersecreted in patients with stress-related psychiatric disorders, impairs sustained attention. To this end, male and female rats received central infusions of CRF prior to testing on an operant sustained attention task (SAT), where rats were trained to discriminate signaled from non-signaled events. CRF caused a dose-dependent decrease in SAT performance in both male and female rats. Females were more impaired than males following a moderate dose of CRF, particularly during the middle part of the session. This sex difference was moderated by ovarian hormones. Females in the estrous cycle stage characterized by lower ovarian hormones had a greater CRF-induced attentional impairment than males and females in other cycle stages. Collectively, these studies highlight CRF as a critical stress-related factor that can regulate attentional performance. As sustained attention subserves other cognitive processes, these studies suggest that mitigating high levels of CRF in patients with stress-related psychiatric disorders may ameliorate their cognitive deficits.

Stressful life events can alter attention and disrupt vigilance [1]. Moreover, patients with stress-related psychiatric disorders, such as major depression and post-traumatic stress disorder (PTSD), have trouble sustaining attention [2,3], or continuously monitoring situations for rare and unpredictably occurring events over prolonged periods of time. Sustained attention represents a fundamental component of attention that determines the effectiveness of other attentional processes, such as divided attention and selective attention, and cognitive performance in general [4]. Thus, stress-induced disruptions in sustained attention could impact many cognitive functions simultaneously, thereby contributing to a variety of cognitive changes observed during stress and in patients with stress-related psychiatric disorders. Despite the potentially devastating impacts of stress on sustained attention, how stress mediates this cognitive process is unknown.

One neuropeptide that orchestrates stress responses is corticotropin releasing factor (CRF). During a stressful event, CRF acts as a hormone to initiate the hypothalamic-pituitary-adrenal axis response to stress, as well as a neurotransmitter to centrally modulate brain circuits required for behavioral and cognitive responses to stress [5,6]. Evidence for central CRF hypersecretion has been found in patients with depression and PTSD [7,8], and this central elevation in CRF is thought to contribute to both the mood and cognitive disruptions that characterize these disorders [9,10]. In rodent models, where the CRF system is easily manipulated, many mnemonic processes have been demonstrated to be regulated by

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http://dx.doi.org/10.1016/j.bbr.2015.08.023
0166-4328/

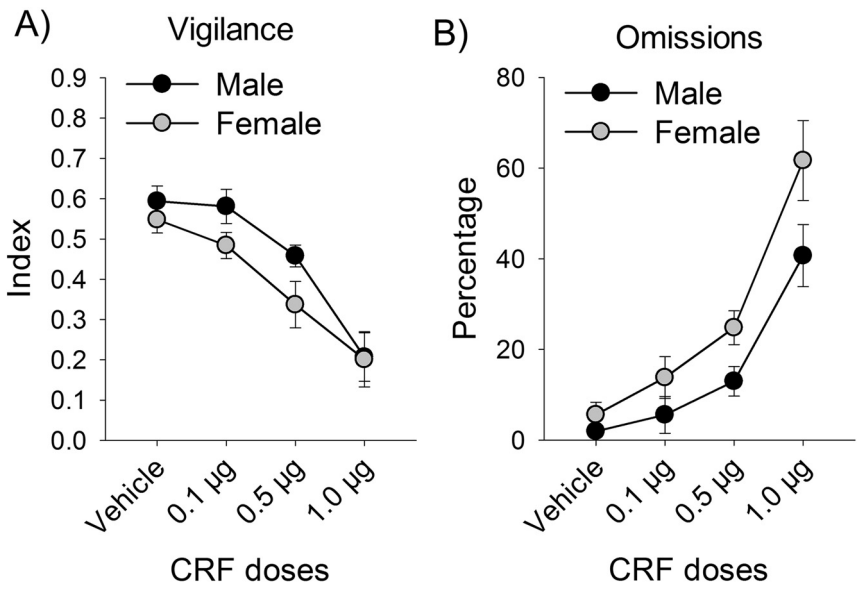

Fig. 1. CRF impaired SAT performance. In male and female rats, CRF administration caused a dose-dependent decrease in the vigilance index (A), while it increased omissions (B).

CRF (for review see, [10]). However, how CRF specifically effects sustained attention has not been the focus of this previous work. The present study addressed this gap by determining whether central CRF disrupted sustained attention using a well-established sustained attention task (SAT) in which rats were trained to detect signaled from non-signaled trials [11,12]. Both male and female rats were tested here because of previously reported increased neuronal sensitivity to CRF in females relative to males [13,14].

Male and female adult (~60 days old) Sprague-Dawley rats (Charles River, Wilmington, MA) were housed individually with a 12 h light/dark cycle (lights on at 9:00am) and *ad libitum* access to food. After acclimation to the facility, rats were progressively water-restricted to 10-min/day for 7 days before beginning behavioral training (5–6 days/week). During nonperforming days, rats received 15 min access to water. The estrous cycle was tracked in female rats with vaginal cytology. All experimental procedures were approved by the Institutional Animal Care and Use Committee of Temple University and were conducted in accordance with the National Institute of Health guidelines.

Rats were trained on the operant SAT as described previously [11,15,16]. Briefly, after learning to lever press, rats were trained to discriminate between two levers: one paired to signaled events (light presentations) and one paired to non-signal events (no light). Following training sessions where rats had correction trials and the signal duration was 1 s, rats were exposed to the basic SAT procedure where the duration of the signal was reduced and varied (25 ms, 50 ms, and 500 ms), the houselight was illuminated, the intertrial interval was 9 ± 3 s, and no correction trials were allowed. Each session, which typical lasted 40 min, consisted of 162 trials divided into three blocks of 54 trials that contained pseudorandomized, equal presentations of signaled (27) and nonsignaled trials (27). Following each event (2 s), both levers were presented for 4 s, and if a rat failed to respond during this time, an omission was recorded. Other responses on signaled trials included, a correct response or "hit", which was rewarded (0.02 mL of water) or an incorrect response or "miss", which was not rewarded. On non-signaled trials, a correct response or "correct rejection" was rewarded (0.02 mL of water), while an incorrect response or "false alarm" was not rewarded. An additional important measure was the vigilance index, which takes into account hits and false alarms and is thought to reflect overall attentional performance, and was calculated using the following formula: vigilance index = (hits – false alarms)/[2(hits + false alarms) – (hits + false alarms)^2]. [11]. Rats were defined as reaching baseline criteria after three consecutive days of at least 70% correct responding to the 500 ms signal presentation events, at least 70% correct rejections, and <30% omissions.

After attaining criterion performance, aseptic stereotaxic surgery was performed to implant each rat with a cannula (22 gauge guide cannula, Plastics One, Roanoke, VA) aimed at the right lateral ventricle (A/P = −1.1 mm and M/L = +1.5 mm from Bregma, D/V = −4.4 mm from the surface of the skull) as previously described [17]. Following recovery and reacquisition of baseline SAT criteria, rats received intracerebroventricular (i.c.v.) infusions of vehicle (artificial cerebral spinal fluid, aCSF) or one of three doses (0.1 μg, 0.5 μg, and 1.0 μg in vehicle) of ovine CRF (America Peptides, Vista, CA, USA) as previously described [17]. All infusions were made at a rate of (1 μL/min) and a total volume of 3 μL solution was infused. Ten minutes following the infusion, rats were tested for performance using the SAT procedure. As this study utilized a within subjects design, subsequent doses of CRF or vehicle were administered in a counterbalanced fashion with at least a one week wash out period, during which no infusions were given but SAT training continued. Criteria performance was met before each infusion.

Following administration of all doses and vehicle, rats were transcardially perfused, tissue was sectioned (30 μm coronal) and stained with cresyl violet, and cannula placements were verified as detailed previously [17]. One female rat was dropped from analysis due to a poor cannula placement.

First we confirmed that the dosing schedule did not affect behavioral outcomes by comparing dose, sex, and schedule for all performance variables with mixed factor ANOVAs. No significant interactions [$F(9,24) < .45$, $p > .75$] or main effect of schedules [$F(3,8) < 0.40$, $p > .76$] were identified for the vigilance index or omissions (data not depicted). Thus, as expected, the counterbalancing was effective.

To determine whether CRF altered sustained attention, CRF dose response curves for the vigilance index and omissions were generated for male and female rats and analyzed with mixed factors ANOVAs. CRF dose-dependently decreased the vigilance index [$F(3,39) = 19.49$, $p < .001$] (Fig. 1A), while it increased omissions [$F(3,42) = 24.42$, $p < .001$] (Fig. 1B). Additionally, there was a main effect of sex with omissions, such that females omitted more trials