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ADOLESCENT CHRONIC MILD STRESS ALTERS HIPPOCAMPAL CB1 RECEPTOR-MEDIATED EXCITATORY NEUROTRANSMISSION AND PLASTICITY

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Abstract—Endocannabinoids (eCBs) are involved in the stress response and alterations in eCB signaling may contribute to the etiology of mood disorders. Exposure to chronic mild stress (CMS), a model of depression, produces downregulation of the cannabinoid 1 (CB1) receptor in the hippocampus of male rats. However, it is unknown how this stress-induced change in CB1 levels affects eCB-mediated neurotransmission. *In vitro*, field potential recordings from CMS-exposed (21-days) rats were performed to assess the effects of stress on eCB-regulated glutamatergic neurotransmission in/on hippocampal area CA1. We observed that application of the CB1 agonist, WIN 55,212-5 (1 μM), in stress animals resulted in a ~135% increase in excitatory neurotransmission, whereas CB1 activation in non-stress animals leads to a ~30% decrease. However, during blockade of GABA(A) neurotransmission with picrotoxin, CB1 activation yielded a ~35% decrease in stress animals. These findings indicate that CMS does not directly affect glutamatergic neurotransmission. Rather, CMS sensitizes CB1 function on GABAergic terminals, leading to less inhibition and an increase in excitatory neurotransmission. This finding is reinforced in that induction of weak long-term-potentiation (LTP) is enhanced in CMS-exposed animals compared to controls and this enhancement is CB1-dependent. Lastly, we observed that the LTP-blocking property of WIN 55,212-5 shifts from being glutamate-dependent in non-stress animals to being GABA-dependent in stress animals. These results effectively demonstrate that CMS significantly alters hippocampal eCB-mediated neurotransmission and synaptic plasticity. **© 2013 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: CB1 receptor, LTP, depression, hippocampus.

INTRODUCTION

Mood disorders such as major depressive disorder are serious mental illnesses that affect approximately 20% of Americans (Kessler et al., 2010). The cannabinoid receptor, CB1 and its ligands, the endocannabinoids (eCBs), are intricately involved in the stress response (Hill et al., 2010; Gorzalka and Hill, 2011) and are therefore putative contributors to the etiology of depressive disorders. Martin et al. (2002) first demonstrated that mutant mice deficient in CB1 receptors show an enhanced vulnerability to the depressive effects of a chronic mild stress (CMS) protocol, a valid preclinical model of depression (Willner, 2005). Buttressing this finding, 3-week exposure to a similar CMS protocol produced a ~50% reduction in CB1 levels in several limbic structures including the hippocampus (Hill et al., 2005, 2008b; Reich et al., 2009). Exposure to both CMS and chronic restraint stress (CRS) consistently reduces the endocannabinoid/endovanniloid anandamide (AEA), in the hippocampus, amygdala, striatum, medial prefrontal cortex and hypothalamus (Gorzalka and Hill, 2011). Conversely, the other major eCB, 2-arachidonoyl-glycerol (2-AG), is transiently enhanced by chronic or acute restraint stress but is either reduced or not affected by CMS (Gorzalka and Hill, 2011; Wang et al., 2012). This differential modulation of eCBs is intriguing considering that 2-AG mediates depolarization-induced-suppression of inhibition (DSI), a short-term suppression of GABA release caused by eCB signaling (Kano et al., 2009), whereas AEA is involved in the tonic activation of CB1 (Kim and Alger, 2010). Indeed, chronic stress is capable of impairing both short and long-term eCB synaptic plasticities in the striatum, hypothalamus, nucleus accumbens and hippocampus (Rossi et al., 2008; Wamsteeker et al., 2010; Wang et al., 2010; Hu et al., 2011), although 10 days of CRS enhances eCB signaling in the amygdala (Patel et al., 2009; Sumislawski et al., 2011). Notably, these stress effects on eCB function are mimicked by the administration of chronic corticosterone to animals (Hill et al., 2008a; Bowles et al., 2011) and blocked by antagonizing glucocorticoid (GC) receptors (Gorzalka and Hill, 2011). Thus, stress appears to modulate eCB signaling via the hypothalamic–pituitary–adrenal-axis (HPA), which is responsible for regulating GC levels (stress hormones) in response to environmental stressors.

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Abbreviations: 2-AG, 2-arachidonoyl-glycerol; ACSF, artificial cerebrospinal fluid; AEA, endocannabinoid/endovanniloid anandamide; ANOVA, analysis of variance; CB, cannabinoid; CCK, cholecystokinin; CMS, chronic mild stress; CRS, chronic restraint stress; DMSO, dimethyl sulfoxide; DSI, depolarization-induced-suppression of inhibition; eCBs, endocannabinoids; GC, glucocorticoid; HPA, hypothalamic–pituitary–adrenal; LTP, long-term-potentiation; MANOVAs, multivariate ANOVA; NS, non-stress; PND, post natal day; PTSD, post-traumatic-stress-disorder; PTX, picrotoxin; S, stress; TBS, theta-burst stimulation.

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Twenty-one days of CRS impairs DSI in the hippocampus of adult male animals (Hu et al., 2011); providing evidence that chronic stress is capable of affecting GABAergic-CB1 function. CRS is a validated method to increase HPA activity to achieve hypersecretion of GCs; however this homotypic stress usually produces habituation of the HPA response (Vyas et al., 2002; Hill et al., 2010). In contrast, CMS paradigms that use heterotypic stressors tend to produce non-habituating HPA responses. CMS is considered a valid animal model of depression partly due to the fact that incorporating multiple stressors minimizes HPA habituation (Willner, 2005). Furthermore, Vyas et al. (2002) observed that CRS produces more severe dendritic atrophy than CMS in the hippocampus. They also reported that CRS, but not CMS, causes dendritic hypertrophy in the amygdala. These differences in the two most common chronic stress protocols suggest that CMS may result in different effects on the eCB system. This highlights the necessity to investigate stress-modulation of eCBs with both methods.

Given that the aforementioned CMS-induced regulation of CB1 was studied using either western immunoblotting (Hill et al., 2005; Reich et al., 2009) or competitive binding assays (Hill et al., 2005, 2008a), it is unknown whether these differences are represented in the general CB1 population or in a particular sub-population. Moreover, it remains unclear how these stress-induced changes affect synaptic physiology in the hippocampus. For example, in the CA1 region of the rodent hippocampus, CB1 resides primarily on the nerve terminals of cholecystokinin (CCK)-containing interneurons (Freund, 2003) and at the glutamatergic synapse between the CA3 Schaffer collateral/commissural terminals and CA1 pyramidal cells (Domenici et al., 2006; Kawamura et al., 2006). Although, compared to the CCK-GABA cells, the glutamatergic-CA3 cells contain a much lower density of CB1 (Domenici et al., 2006; Kawamura et al., 2006). Thus, the primary purpose of this study is to assess if CMS differentially affects CB1-mediated glutamatergic and GABAergic neurotransmission.

In a recent study from our lab, CMS exposure during adolescence selectively enhanced hippocampal-dependent fear conditioning in male rats. This enhancement in aversive learning was prevented by exogenous CB1 activation (Reich et al., 2013). These findings are consistent with previous observations that peri-adolescent/adolescent exposure to chronic stress alters CB1 signaling in the hypothalamus, amygdala and prefrontal cortex (Wamsteeker et al., 2010; Lee and Hill, 2013). To date, these are the only three studies that directly address the effects of adolescent stress on the eCB system. This is surprising, given that adolescence is a period of neuronal maturation that is highly vulnerable to stress (Spear, 2000; Lee and Gorzalka, 2012). Exploring the relationship between stress and eCB signaling during this developmental period may assist in elucidating the etiology of stress-related pathologies such as Major Depressive Disorder and post-traumatic-stress-disorder (PTSD). Using hippocampal field potential recordings from adolescent male animals exposed to CMS, we hypothesized that CMS-downregulation of CB1 would impair function on both glutamatergic and GABAergic synapses. However, we observed that CMS does not affect glutamate-CB1 function directly but does increase glutamatergic neurotransmission through a sensitized GABA-CB1 function. This enhanced CB1 function on GABAergic neurotransmission also facilitates long-term-potentiation (LTP) induction to weak theta-burst stimulation (TBS) and shifts the dependency of LTP inhibition by CB1 agonists from glutamatergic to GABAergic neurotransmission.

EXPERIMENTAL PROCEDURES

Subjects

Male Sprague–Dawley rats (Charles River, Boston, MA, USA) were group-caged (three per cage) and allowed to acclimate for 5–7 days prior to experimental testing. All animals were 40–45 days-old at the beginning of experimental procedures and maintained on a 12-h/12-h light–dark cycle with lights on at 8:00 a.m. Food and water were available *ad libitum* in the home cages, unless otherwise noted. All experimental procedures were carried out in accordance with protocols established by the Institutional Animal Care and Use Committee of the Ramapo College of New Jersey.

CMS protocol

Animals were subjected to either the CMS protocol or the non-stress protocol (handled daily). Each day, 1–3 stressors were administered according to a set schedule. The complete regimen lasted 7 days/week for 3 weeks. This protocol is modeled after Willner (2005) in that no individual stressor is considered severe but that the unpredictability of the protocol constitutes much of the stress. The stressors were: (1) 5-min swim in 20 °C water, (2) cage rotation (social stress), (3) 18-h social isolation with damp bedding, (4) 14-h food deprivation, 14-h water deprivation or 14-h food and water deprivation, (5) 30-min physical restraint, (6) 30-min strobe light exposure and (7) 3-h cage tilt. In previous studies, we observed that this particular CMS protocol resulted in decreased body weight gain in both male and female animals and reduced sucrose preference in male animals (Reich et al., 2009). These effects are in accordance with the published behavioral effects of CMS protocols (Hill et al., 2005; Willner, 2005).

Electrophysiology

Animals were deeply anesthetized with halothane and decapitated from approximately 10:00 am–11:00 am. Stress animals were sacrificed 24–72 h following the last stressor. The brain was rapidly removed and hippocampi dissected. Transverse hippocampal slices, 400-μM thick, were cut on a Vibrotome (Leica-Microsystems, Buffalo Grove, IL). Slices were kept in a holding chamber at room temperature at the interface of artificial cerebrospinal fluid (ACSF) and a humidified 95%/5% O_2/CO_2 atmosphere for > 1 h. The slices were

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