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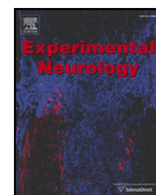

Stress-induced sensitization of cortical adrenergic receptors following a history of cannabinoid exposure

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ABSTRACT

The cannabinoid receptor agonist, WIN 55,212-2, increases extracellular norepinephrine levels in the rat frontal cortex under basal conditions, likely via desensitization of inhibitory α2-adrenergic receptors located on norepinephrine terminals. Here, the effect of WIN 55,212-2 on stress-induced norepinephrine release was assessed in the medial prefrontal cortex (mPFC), in adult male Sprague–Dawley rats using in vivo microdialysis. Systemic administration of WIN 55,212-2 30 min prior to stressor exposure prevented stress-induced cortical norepinephrine release induced by a single exposure to swim when compared to vehicle. To further probe cortical cannabinoid–adrenergic interactions, postsynaptic α2-adrenergic receptor (AR)-mediated responses were assessed in mPFC pyramidal neurons using electrophysiological analysis in an in vitro cortical slice preparation. We confirm prior studies showing that clonidine increases cortical pyramidal cell excitability and that this was unaffected by exposure to acute stress. WIN 55,212-2, via bath application, blocked postsynaptic α2-AR mediated responses in cortical neurons irrespective of exposure to stress. Interestingly, stress exposure prevented the desensitization of α2-AR mediated responses produced by a history of cannabinoid exposure. Together, these data indicate the stress-dependent nature of cannabinoid interactions via both pre- and postsynaptic ARs. In summary, microdialysis data indicate that cannabinoids restrain stress-induced cortical NE efflux. Electrophysiology data indicate that cannabinoids also restrain cortical cell excitability under basal conditions; however, stress interferes with these CB1–α2 AR interactions, potentially contributing to over-activation of pyramidal neurons in mPFC. Overall, cannabinoids are protective of the NE system and cortical excitability but stress can derail this protective effect, potentially contributing to stress-related psychopathology. These data add to the growing evidence of complex, stress-dependent modulation of monoaminergic systems by cannabinoids and support the potential use of cannabinoids in the treatment of stress-induced noradrenergic dysfunction.

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Introduction

Endogenous and exogenous cannabinoids acting through cannabinoid type 1 (CB1) receptors have been implicated in the regulation of a variety of behavioral and cognitive functions (D'Souza et al., 2008; Egashira et al., 2008; Senn et al., 2008) as well as emotional (Moreira and Lutz, 2008) and learning and memory processes (Freund et al., 2003; Gerdeman and Lovinger, 2003; Makela et al., 2006). A widespread function of CB1 receptor modulation involves inhibition of neurotransmitter release (Doherty and Dingledine, 2003; Schlicker and Kathmann, 2001; Szabo and Schlicker, 2005). However, increases in neurotransmitter release have also been reported following exposure to cannabinoid receptor agonists (Acquas et al., 2000; Fortin and Levine, 2007).

Our previous studies have shown that administration of the cannabinoid receptor agonist, WIN 55,212-2, significantly increases norepinephrine efflux in the frontal cortex (Oropeza et al., 2005; Page et al., 2007). Similarly, direct local infusion of WIN 55,212-2 into the PFC increases cortical norepinephrine efflux (Page et al., 2008), an effect that is inhibited by local (Page et al., 2008) or systemic (Oropeza et al., 2005) pre-treatment with the selective CB1 receptor antagonist, SR 141716A, demonstrating a specific role for CB1 receptors in these effects. In addition, we have shown that systemic administration of WIN 55,212-2 stimulates c-Fos expression in noradrenergic neurons in the locus coeruleus (LC) (Oropeza et al., 2005) and significantly increases the expression of tyrosine hydroxylase (TH), the rate-limiting enzyme in the synthesis of catecholamines, in the LC (Foote et al., 1983). WIN 55,212-2-induced neurochemical alterations were accompanied by changes in anxiety-like

Abbreviations: CB1r, cortical norepinephrine and stress.

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behaviors (Page et al., 2007). Our previous neuroanatomical studies characterized the cellular substrates for interactions between noradrenergic axon terminals and CB1r (Oropeza et al., 2007).

The endocannabinoid and noradrenergic systems are significantly and dynamically impacted by stress (Cassens et al., 1980; Flugge et al., 2004; Gorzalka et al., 2008; Hill and McEwen, 2010; Shinba et al., 2010) and noradrenergic transmission is responsible for cannabinoid-induced activation of the hypothalamic-pituitary-adrenal axis (McLaughlin et al., 2009). Under conditions of acute stress, norepinephrine is increased centrally and peripherally (Abercrombie and Jacobs, 1987; Ferry et al., 1999; Nestler et al., 1999; Page and Valentino, 1994; Sands et al., 2000; Valentino et al., 1998) while the endocannabinoid system (EC) tonically constrains activation of neural circuits, including the hypothalamic-pituitary-adrenal axis (Gorzalka et al., 2008; Steiner and Wotjak, 2008). However, disrupted noradrenergic and EC signaling are associated with an inability to adapt to chronic stress (Flugge et al., 2004; Gorzalka et al., 2008; Hill and Gorzalka, 2004; Hill et al., 2008; Nestler et al., 1999; Wong et al., 2000).

Dysfunction in the noradrenergic system has been implicated in a number of affective disorders (e.g. depression, anxiety), many of which are precipitated by chronic stress (Leonard and Myint, 2009; Morilak and Frazer, 2004). Upregulation in the activity of TH has been suggested to lead to changes in noradrenergic transmission that contributes to behavioral, cognitive, emotional and physiological manifestations of depression and anxiety (Duncko et al., 2001; Miller et al., 1996; Sands et al., 2000). Therefore, although norepinephrine transmission is critical for proper functioning of PFC neurons (Franowicz et al., 2002), high levels of catecholamine receptor stimulation during stress can impair cortical function and may contribute to exacerbating or precipitating a number of psychiatric disorders (Arnsten, 1997).

In the present study, we sought to determine whether CB1 receptors modulate stress-induced increases in norepinephrine efflux by assessing extracellular levels of norepinephrine in the PFC in rats that received a systemic injection of WIN 55,212-2 or vehicle prior to stress exposure. Indices of coping behaviors during a 15-minute swim were also measured. In addition, we examined a history of cannabinoid exposure and the impact of stress on cannabinoid–adrenergic interactions in the mPFC using in vitro electrophysiology.

Materials and methods

Experimental animals

For microdialysis and behavioral studies, adult male Sprague–Dawley rats (Harlan Laboratories, Indianapolis, IN) weighing 250–300 g were used. For electrophysiology experiments, male Sprague–Dawley rats (Taconic Farms Germantown, NY) initially weighing 50–75 g were used because brain slice viability is much improved in the juvenile compared to adult rodent brain (Alger et al., 1984; Gibb and Edwards, 1994). However, cortical CB1 and α2-adrenergic receptors (α2-AR) are fully functional by this age in rats (Berrendero et al., 1998; Winzer-Serhan and Leslie, 1999). Animals were housed 2–3 per cage on a 12 hour light:dark schedule in a temperature-controlled (25 °C) colony room. Rats were given ad libitum access to standard rat chow and water. The Thomas Jefferson and Temple University Institutional Animal Care and Use Committees (IACUC) approved the protocol and all studies were conducted in accordance with the *NIH Guide for the Care and Use of Laboratory Animals*. All efforts were made to minimize animal suffering and reduce the number of animals used.

Microdialysis

Following an acclimation period of approximately one week, rats were anesthetized with isoflurane (Abbott Laboratories, North Chicago, IL; 0.5–1.0%, in air) and via a specialized nose cone affixed to the sterotaxic frame (Stoelting Corp., Wood Dale, IL). A small burr hole was made in the skull centered at 3.2 mm anterior and ±0.7 mm lateral to bregma. The dura was removed, and the microdialysis probe was slowly lowered 5 mm from the brain surface into the infralimbic and prelimbic areas of the PFC (plates 8–10) (Paxinos and Watson, 1986) and secured with skull screws and dental acrylic. The inlet of the probe was connected to a fluid swivel (Instech Laboratories, Plymouth Meeting, PA) and the rat was placed into a cylindrical plexiglass container covered with bedding. Food and water were given ad libitum. Artificial cerebrospinal fluid (aCSF; Oropeza et al., 2005) was continuously perfused through the probe at a rate of 1.5 ul/min by a microliter infusion pump (Harvard Pump '11' VPF Dual syringe, Harvard Apparatus, Holliston, MA). Rats were allowed to recover overnight. Approximately 24 h following surgery, dialysate samples were collected every 20 min. After collecting dialysate samples for at least 2 h to establish stable baseline levels, the cannabinoid agonist WIN 55,212-2 (Sigma-Aldrich Inc., St. Louis, MO) was administered to the rats via intraperitoneal injection at 3.0 mg/kg. Dilutions of the drug were prepared immediately prior to the start of each experiment by dissolving in 0.4% Tween 80 (Sigma-Aldrich Inc., St. Louis, MO). A control group was treated with vehicle only (water containing 0.4% Tween 80) and deionized water. Dialysate samples were collected and 60 min after cannabinoid injection, rats were gently moved from the animal apparatus to an adjacent Pyrex Cylinder (21×46 cm; Fisher Scientific, Liberty Lane Hampton, NH), which was filled with room temperature water to a 30-cm depth. The 15-minute swim session was videotaped from above for subsequent analysis of the behavioral response. Following swim, rats were returned to the animal apparatus and sample collection continued for an additional 3 h. Dialysate samples were stored at −80 °C for subsequent analysis by high performance liquid chromatography with electrochemical detection (HPLC-ED). At the conclusion of the experiment, rats were deeply anesthetized with pentobarbital (60 mg/kg; Ovation Pharmaceuticals, Inc., Deerfield, IL) intraperitoneally and 2% pontamine sky blue dye (Alfa Aesar, Ward Hill, MA) was infused through the probe to mark its location. The rats were transcardially perfused with 10% formalin (Fisher Scientific, Pittsburgh, PA), decapitated and the brains removed for subsequent histological verification of probe placement. Fig. 1 shows a representative example of the placement of the dialysis probe in the PFC. The data were not included if the placement was outside the infralimbic and prelimbic areas of the PFC.

Custom build vertical concentric microdialysis probes were used. A piece of fused silica (Polymicro Technologies, Phoeniz, AZ) was inserted through PE 10 tubing and semipermeable membrane made from hollow rayon fibers with a 223 μm o.d. and 35,000 MW cutoff was fixed over the fused silica and into the PE 10 tubing with epoxy. The open end of the dialysis fiber was sealed with a 0.5 mm epoxy plug, and 2 mm of the top of the membrane was coated with epoxy leaving an active area of 3 mm for exchange across the membrane. The in vitro recovery rate was determined by placing the probe in a beaker of aCSF containing a known concentration of NE standard. The concentration of norepinephrine in the dialysate was compared to the amount in the bath. Probes that did not correspond to an acceptable range of recovery (12–24%) were eliminated. Because the diffusion properties of neurochemicals in brain tissue are likely different from in vivo conditions, reported dialysate values were not corrected for recovery of the probe.

High performance liquid chromatography

Catecholamine levels were determined using HPLC-ED. Twenty-five microliters of dialysate sample is diluted in 75 μl of diluent containing the following antioxidants: ascorbic acid, L-cysteine, and oxalic acid. Samples and standards are kept at 4 °C and injections of 50 μl are made overnight using an ESA autosampler. Mobile phase is 0.113 M phosphate buffer, 0.13 mM EDTA, 0.17 mM octyl sulfate, 4% acetonitrile, and pH of 3.1. Detection was performed using an ESA

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