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Prefrontal endocannabinoids, stress controllability and resilience: A hypothesis

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ABSTRACT

Stressor exposure is a predisposing risk factor for many psychiatric conditions such as PTSD and depression. However, stressors do not influence all individuals equally and in response to an identical stressor some individuals may be vulnerable while others are resilient. While various biological and behavioral factors contribute to vulnerability versus resilience, an individual's degree of control over the stressor is among the most potent. Even with only one experience with control over stress, behavioral control has been shown to have acute and long-lasting stress-mitigating effects. This suggests that control both blunts the response to acute stress and prepares the subject to be resilient to future stressors. In this review, we first summarize the evidence which suggests the ventromedial prefrontal cortex (vmPFC) is a critical component of stressor controllability circuits and a locus of neuroplasticity supporting the acute and long-lasting consequences of control. We next review the central endocannabinoid (eCB) system as a possible mediator of short and long-term synaptic transmission in the vmPFC, and offer a hypothesis whereby eCBs regulate vmPFC circuits engaged when a subject has control over stress and may contribute to the encoding of acute stress coping into long lasting stressor resilience.

1. Introduction

Stressor exposure is a risk factor for PTSD and depression (Gillikin et al., 2016). However, stressors do not influence all individuals equally. In response to an identical stressor, some individuals may develop chronic PTSD (i.e. vulnerable population), while others may experience transient symptoms of trauma but recover quickly (i.e. resilient population). Genetic and behavioral factors contribute to vulnerability versus resilience within an individual (Southwick and Charney, 2012) and these have been the focus of considerable clinical and preclinical research (Russo et al., 2012). Identifying the biological basis to account for individual responses to stressors could lead to significant advances in the treatment and diagnosis of psychiatric disease (Ménard et al., 2016). In terms of behavioral factors that can dramatically alter the consequences of a stressor, an individual's degree of control over the stressor is among the most significant (Maier and Watkins, 2005; Maier et al., 2006). The stress-protective effects of control over stressors have been investigated in a stressor controllability paradigm for several decades (Maier and Seligman, 2016). Accordingly, much is known regarding the neuroanatomical circuits engaged when a stressor is controllable, and it is well understood that control over stress can mitigate the development of stressor induced anxiety and depressive-like behaviors (Christianson and Greenwood, 2014). In this review, we first summarize the evidence which suggests the ventromedial prefrontal cortex (vmPFC), composed of the prelimbic (PL) and infralibic regions (Uylings and van Eden, 1990), is a critical component of stressor controllability circuits and a locus of neuroplasticity. We next review the central endocannabinoid system which we hypothesize maintains activity of critical vmPFC circuits when control over stress occurs and may contribute to the encoding of acute stress coping into long lasting stressor resilience.

Stressor controllability research has roots in the early investigations of “learned helplessness”. Learned helplessness is a term that intended to capture the psychological process that mediated the phenomenon that dogs exposed to inescapable shocks failed to learn instrumental escape-avoidance responses at a later time in a new situation (Overmier and Seligman, 1967; Seligman and Maier, 1967). Indeed, the phenomenon of uncontrollable stressors negatively influencing later behaviors is a widely replicated and useful experimental tool; accordingly, the mechanisms underlying the various effects of stress on behavior are quite well known (See reviews by Maier and Watkins (2005) and Hammack et al. (2012)). Shortly after the initial report of learned helplessness, a number of studies began to experimentally determine whether the consequences of inescapable stress exposure were, in fact,

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due to their inescapable, uncontrollable nature (Maier and Seligman, 1976). In these experiments, a pair of subjects, typically rats, received a series of shocks which were unpredictable. One of the subjects could terminate the shock for itself (escapable shock condition; ES) and the yoked partner (inescapable shock condition: IS) by performing a behavioral response, typically turning a wheel. This preparation allows the investigator to isolate the contribution of stressor controllability from the contribution of stress itself in causing stress-related behaviors. For example, rats exposed to IS exhibited reduced social interaction behavior, an indication of stressor-induced anxiety, but rats given control over stress had normal social behavior even after identical shock exposure (Short and Maier, 1993; Christianson et al., 2008). As we will summarize below, many of the effects of IS do not occur when the subject is able to perform a behavioral response to terminate the stressor which makes the stressor controllability paradigm a powerful tool for investigating the biological basis of resilience to trauma.

Perhaps the first step in understanding the mechanisms of resilience is to understand how trauma affects behavior and brain systems. This informs the next step which is to examine how control over trauma alters these consequences and to identify behavioral or neural correlates that are unique to subjects with control. Many studies have investigated the various behavioral sequelae that result from exposure to IS, of which many endure for up to a week. For example, IS exposure leads to failure to learn to escape in a shuttlebox (Maier et al., 1973), reduced activity in the forced swim test (Weiss et al., 1981), reduced activity in the presence of an aversive stimuli (Jackson et al., 1980), exaggerated fear conditioning (Maier, 1990; Baratta et al., 2007; Rau and Fanselow, 2009), reduced social interaction (Short and Maier, 1993; Haller and Bakos, 2002; Christianson et al., 2008), opioid analgesia (Grau et al., 1981), potentiation of morphine conditioned place preference (Will et al., 1998), decreased aggression and dominance (Maier et al., 1972), reduced eating and drinking, and neophobia (Maier and Watkins, 2005). In each of these cases, rats given control over the stressor did not display the stressor induced behaviors.

Control over the stressor not only mitigates the effects of the stressor observed during initial stress exposure, but also has an “immunizing” effect against future uncontrollable stressors. This effect was discovered when rats were first given either controllable or uncontrollable stress and at a later time given a second uncontrollable stressor. Rats that first had control did not develop learned helplessness to the second, uncontrollable stressor (Williams and Maier, 1977). These effects have been repeated recently (Amat et al., 2006; Christianson et al., 2008) and have been shown to transfer to protection against stressors that are quite different than shock including social defeat (Amat et al., 2010) and forced swim (Christianson et al., 2013). Furthermore, the immunizing effects of stressor controllability are long-lasting, in that exposure to ES during adolescents can block the sequelae of later IS exposure in adulthood (Kubala et al., 2012). The combination of acute and long-lasting consequences of one experience with control over stress suggests that control both blunts the response to acute stress but also prepares the subject to be resilient to future stressors.

2. Brain mechanisms of stressor controllability

2.1. The neural circuitry of inescapable stress

Investigations into the neural mechanisms of IS date back to the 1970s when the laboratories of Weiss and Anisman sought to understand the role of catecholamines in the generation of stressor induced depression e.g. (Anisman et al., 1981; Weiss et al., 1981). These and later investigations of the hypothalamic-pituitary-adrenal axis (Maier et al., 1986) did not account for the broad array of behavioral changes produced by uncontrollable stress. In the 1990s, Maier and colleagues began to explore the role of the serotonin (5-HT) system and the dorsal raphe nucleus (DRN). DRN 5-HT neurons are the primary source of central 5-HT and innervate a wide range of forebrain structures such as the vmPFC, basal ganglia, and amygdala, (Jacobs and Azmitia, 1992; Hale et al., 2012) which were thought to be important to the expression of learned helplessness. It was hypothesized that as a consequence of its forebrain projections sensitivity to stressors, activation of 5-HT in the DRN could mediate the broad effects of IS (Maier and Watkins, 2005; Christianson and Greenwood, 2014).

The DRN was first shown to be necessary to produce the behavioral effects of IS by Maier et al. (1993). They demonstrated that electrolytic lesions in the DRN prior to exposure to IS prevented the enhanced fear conditioning and shuttle box escape deficit that was observed after IS in sham lesion controls. Importantly, the DRN lesions had no effect on these measures in non-stressed rats. Furthermore, through reversible pharmacological inhibition either before IS or before shuttlebox escape and fear conditioning it was shown that the DRN is critical to both the acquisition and later expression of learned helplessness (Maier et al., 1995b). Next, activation of the DRN with the benzodiazepine receptor inverse agonist, Methyl 6,7-Dimethoxy-4-ethyl-β3-carboline-3-carboxylate (DMCM) without exposure to stress enhanced fear conditioning and interfered with shuttle box escape 24 h later (Maier et al., 1995a). Thus pharmacological stimulation of the DRN in the absence of IS was sufficient to produce the behavioral effects of IS. Taken together, these results demonstrate that activation of the DRN itself was shown to be necessary and sufficient to produce the behavioral effects of IS.

It was also suggested that 5-HT neurons, which are regulated by the inhibitory 5-HT1A autoreceptor, are the critical population of DRN cells because administration of a 5-HT1A agonist, which inhibits 5-HT firing (Kirby et al., 2003), prevented both the acquisition and later expression of learned helplessness (Maier et al., 1995b). Importantly, in order to appreciate the effects of IS on DRN 5-HT activity and distinguish these from the effects of stress per se, it is necessary to make comparisons between IS and ES. Thus, in subsequent descriptive studies, Maier and colleagues quantified the activity of 5-HT neurons during and after either ES or IS, to determine if these cells are sensitive to the dimension of behavioral control; differences between ES and IS emerged on several levels of analysis which have been reviewed (Maier and Watkins, 2005; Maier and Seligman, 2016). The key differences between ES and IS include: greater Fos expression in DRN 5-HT neurons after IS compared to ES (Grahn et al., 1999), greater extracellular 5-HT, indicative of 5-HT release, during IS compared to ES in the DRN (Maswood et al., 1998) basolateral amygdala (Amat et al., 1998b), ventral hippocampus (Amat et al., 1998a), vmPFC (Bland et al., 2003a), and nucleus accumbens shell (Bland et al., 2003b).

Intense activation of DRN 5-HT neurons and increased extracellular 5-HT are only transient effects of IS, but the behavioral changes that result can be observed up to a week later. It was discovered that not only does IS result in increased activation of the DRN at the time of IS exposure, but also alters DRN activity to subsequent stressors including footshock (Amat et al., 1998b), drugs of abuse (Bland et al., 2003a) and social defeat (Amat et al., 2010). Using our recent study as an example, we conducted in vivo microdialysis to quantify extracellular 5-HT in the basolateral amygdala during an innocuous social interaction test given 24 h after exposure to ES, IS or no stress. Only in rats that were exposed to IS did the social interaction evoke a significant increase in amygdala 5-HT (Christianson et al., 2010). We hypothesized that exaggerated release of 5-HT in the basolateral amygdala was the proximal cause of social anxiety in rats exposed to IS, and indeed the IS effect was prevented if a 5-HT2C receptor antagonist was infused to the basolateral amygdala prior to social interaction tests, but not when given before IS. In sum, control over stress is a powerful determinant of DRN 5-HT activity during shock and prevents long-lasting changes in the stress sensitivity of the DRN system.

The foregoing was consistent with a hypothesis set forward by Greenwood et al. (2003) who suggested that inescapable stress caused sensitization of the raphe, in part, via downregulation of 5-HT1A autoreceptors. 5HT1A are somatodendritically expressed GPCRs which activate inward rectifying K channels and when activated by 5-HT from