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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

recurrent collaterals they inhibit 5-HT cell firing and release of 5-HT. Recently, Rozeske et al. (2011) directly tested the 5-HT1A down-regulation hypothesis by quantifying 5-HT1A receptor tone in the DRN with in vitro electrophysiology. They found that putative 5-HT neurons required significantly larger concentrations of 5-HT or 5-HT1A agonists to produce inhibition of spontaneous firing after IS directly pointing to downregulation of 5-HT1A receptors (Rozeske et al., 2011). To summarize, exposure to uncontrollable stress provides sustained excitatory drive to the DRN which in turn leads to downregulation of DRN somatodendritic 5-HT1A autoreceptors. This downregulation sensitizes the DRN for a period of time (1–7 days) in which subsequent milder stressors will evoke greater 5-HT activation and release in projection regions, such as the amygdala, where high levels of 5-HT modulate neural circuits which are the proximate mediators of stressor induced behaviors; and this is the mechanism by which inescapable stress alters many behaviors from shuttle learning, to social interaction, to drug seeking (Christianson and Greenwood, 2014).

2.2. The neural circuits and neurochemistry of escapable stress

What are the neuroanatomical loci that detect control over stress and so prevent the sequelae of stress? It is unlikely to be the DRN, and it has been suggested that this is because the DRN does not receive the necessary inputs to detect whether the onset or offset of a stressor is temporally related to a behavior (Maier, 2015). Interestingly, both IS and ES activate brain regions that send excitatory input to the DRN (Amat et al., 2001; Takase et al., 2005; McDevitt et al., 2009), but only IS results in the sustained activation of 5-HT neurons. Thus, the differential net impact of IS and ES would seem to require ES-induced inhibitory inputs to the DRN. The DRN primarily receives its cortical input from vmPFC, a region proposed as critical to stress resilience (Jordan et al., 1994; Maier and Watkins, 2010; McEwen and Morrison, 2013; Sinha et al., 2016). Furthermore, unlike the DRN, the vmPFC has been shown to be involved in action-outcome learning (Ostlund and Balleine, 2005; Alexander and Brown, 2011) and receives inputs that would allow for the detection of control. Consistent with this, it has been shown that the PL receives thalamocortical inputs relating to actions and projects to the dorsomedial striatum which is critical for associating actions with their outcomes (Balleine and O'Doherty, 2010). In the case of stressor controllability, the behavior is performing a wheel-turn which has the desirable outcome of shock termination. The vmPFC projection to the DRN provides monosynaptic glutamatergic input to both the local inhibitory GABAergic neurons and to 5-HT principle neurons (Jankowski and Sesack, 2004; Geddes et al., 2016). Thus, activation of descending vmPFC pyramidal neurons can both inhibit or excite the DRN 5-HT neurons by driving inhibitory interneurons which synapse onto 5-HT neurons (Hajós et al., 1998; Celada et al., 2001) or by directly exciting 5-HT cells (Warden et al., 2012; Geddes et al., 2016).

Given the vmPFC's anatomical position to integrate information about control over stress (i.e. the action/outcome contingency between the turning a wheel and shock termination) with regulation of the DRN stress response, Amat and colleagues proposed that inhibition of the vmPFC during controllable stress would cause these rats to later behave as if their stressor exposure had been uncontrollable. Indeed, in rats with pharmacological inactivation of the vmPFC during an exposure to controllable stress displayed sustained DRN activation, exaggerated fear expression, shuttle box learning deficits (Amat et al., 2005), social anxiety (Christianson et al., 2008), increased drug seeking (Rozeske et al., 2012), and downregulated DRN 5-HT1A receptors (Rozeske et al., 2011) all of which typically only occur when the stressor is uncontrollable. Going further, vmPFC inactivation also prevented the long-lasting immunizing effects of controllable stress (Amat et al., 2006) which suggests that the vmPFC is involved in both the acute regulation of the stress response and also to the long-term processes that afford resilience.

In a corresponding set of descriptive experiments, a number of findings suggest that it is the PL that is selectively engaged during controllable stress to regulate the DRN. First, ES led to greater Fos immunoreactivity in the PL neurons that project from the vmPFC to the DRN; and this pathway was also activated upon subsequent exposure to IS in the immunization paradigm (Baratta et al., 2009). Next, controllable stress exposure increased the intrinsic excitability of deep layer pyramidal neurons in the PL, but uncontrollable stress exposure did not (Varela et al., 2012). Third, controllable stress selectively upregulated levels of phosphorylated extracellular signal-regulated kinase (ERK), a marker of synaptic plasticity (Thomas and Huganir, 2004), within the PL (Christianson et al., 2014). Together these findings suggest that during controllable stress there is a high level of neuronal activity and plasticity in the PL that mediate the acute and long-lasting resilience conferred by stressor controllability. Accordingly, pharmacological blockade of either PL protein synthesis (Amat et al., 2006), NMDA receptors or ERK signaling (Christianson et al., 2014) all prevented the acute and immunizing effects of ES.

The foregoing reviewed the compelling evidence that the PL is a locus of neuroplasticity critical to stress resilience. However, we must reconcile these studies with a seemingly contradictory finding about learned helplessness and the vmPFC. In the studies of Li and colleagues in which mice were exposed to uncontrollable stress, they report that synaptic potentiation within the PL is critical to the development of learned helplessness-like behaviors—the exact opposite of what occurs in stressor controllability (Perova et al., 2015). One way of resolving this discrepancy would be considering the underlying circuitry that may be potentiated during exposure to IS versus exposure to ES. Stress per se in the form of IS and ES both lead to robust activation within the PL, but only ES leads to selective activation of DRN projecting output neurons (Baratta et al., 2009). It is not yet known whether activation of the PL during IS serves a necessary function in the development of the behaviors in the stressor controllability paradigm. Presumably, the Fos observed in the PL during IS reflects activity of PL neurons that project to regions that drive the stress response such as the lateral habenula (Li et al., 2011), among others. How can controllable stressors drive one PFC circuit, the one projecting to the DRN, while uncontrollable stressors drive another to maintain the stress the response? One possibility is a synaptic mechanism engaged during stress that could alter the balance of excitation and inhibition within select vmPFC circuits depending on the presence of behavioral control.

3. The endocannabinoid system

3.1. Endocannabinoids regulate excitatory/inhibitory balance

Excitatory/inhibitory balance is driven by myriad mechanisms within the cortex; however, one interesting regulatory mechanism within the vmPFC is through retrograde endocannabinoid (eCB) signaling (Yoshino et al., 2011). There are two known cannabinoid receptors, CB1 receptor (CB1R) and CB2 receptor, with CB1R being the primary cannabinoid receptor within the brain. CB1R is an inhibitory, G-protein coupled receptor (GPCR) coupled to intracellular Gi/o proteins. Activation of CB1Rs inhibits adenylyl cyclase activity leading to a subsequent reduction in the cyclic adenosine monophosphate (cAMP) cascade, augmentation of inward rectifying potassium channels, and inhibition of subsequent calcium influx via voltage-gated calcium channels (Howlett, 2002). Neuroanatomical studies have confirmed prominent widespread expression of the CB1R throughout the forebrain, basal ganglia, and limbic system (Glass, 1997; Mato et al., 2004) with greatest expression in the neocortex, hippocampus, striatum, substantia nigra, and cerebellum, while moderate CB1R immunoreactivity has been detected in the cingulate, entorhinal and piriform cortical areas, olfactory bulbs, amygdala, and nucleus accumbens (Herkenham et al., 1990). Important to this review, CB1Rs are abundantly expressed in the vmPFC (Marsicano and Lutz, 1999;

Moldrich and Wenger, 2000). At the cellular level, CB1Rs are located on presynaptic axon terminals of glutamatergic principal neurons as well as on a subpopulation of cholecystokinin-positive GABAergic basket cells (Katona and Freund, 2012). Thus, eCBs are positioned to modulate the balance of excitation and inhibition within a given neural circuit by action at the CB1R.

There are two well characterized naturally occurring endogenous ligands with potent agonist activity at the CB1R. These are the arachidonate-derived lipophilic molecules *N*-arachidonylethanolamide (anandamide; AEA) and 2-arachidonylglycerol (2-AG; (Devane et al., 1992; Sugiura et al., 1995). Both AEA and 2-AG are synthesized in postsynaptic neurons by activity-dependent cleavage of phospholipid head groups via activation of specific enzymes. As such, eCBs are synthesized on demand in postsynaptic cells following postsynaptic membrane depolarization. While 2-AG is synthesized primarily though diacylglycerol lipase (DGL), several synthesis pathways have been proposed for the production of AEA; however, it remains unclear which AEA synthesis pathway is primarily employed in the brain (Bisogno, 2008). Once synthesized, they then travel in a retrograde manner to bind CB1Rs located on the presynaptic membrane of either the original afferent (homosynaptic) or nearby afferents (heterosynaptic) where cellular effects include suppression of axonal calcium influx, and activation of GIRKs to hyperpolarize the presynaptic terminal and inhibit neurotransmitter release (Di Marzo, 1999; Katona and Freund, 2012). Termination of AEA and 2-AG signaling begins with transport across the plasma membrane followed by enzymatic hydrolysis (Ahn et al., 2008). This is accomplished via their respective hydrolytic enzymes; fatty acid amide hydrolase (FAAH) – the primary catabolic enzyme for AEA – and monoacylglycerol lipase (MGL) – the primary catabolic enzyme of 2-AG (Bisogno, 2008).

Although 2-AG and AEA bind to the same receptor, the evidence suggests they play dissociable roles in synaptic transmission. For instance, AEA exhibits a high affinity for CB1Rs, but its efficacy at inducing intracellular signal transduction is somewhat poor, with only partial agonist properties. AEA appears to contribute to the tonic level of circuit output by reducing presynaptic GABAergic release probability (Kim and Alger, 2010; Xia et al., 2016). In contrast, 2-AG has a lower affinity for CB1R but induces a robust intracellular response (Hillard, 2000). The short-term plasticity phenomena depolarization induced suppression of inhibition (DSI) and depolarization induced suppression of excitation (DSE) as well as in long term plasticity such as eCB mediated long-term depression (eCB-LTD) are mediated by 2-AG (Heifets and Castillo, 2009; Katona and Freund, 2012; Shonesy et al., 2014; Guggenhuber et al., 2015). DSI occurs after a postsynaptic neuron is depolarized for a protracted period and is evinced by fewer somatic inhibitory post synaptic currents. This phenomenon would permit the postsynaptic cell to remain in a relatively more excitable state (due to reduced presynaptic inhibition) after firing a train of action potentials. DSE, on the other hand, occurs at dendritic excitatory synapses; after a brief train of high frequency synaptic stimulation fewer excitatory post synaptic potentials are evident. Both DSI and DSE are relatively brief phenomena, recovering on the order of 10s of seconds, but can shape the flow of information through a circuit and shape the development of longer lasting synaptic plasticity at specific synapses. Prolonged exposure to eCBs can result in a form of chemical LTD and has been observed at both excitatory and inhibitory synapses (Heifets and Castillo, 2009). Importantly, this eCB mediated LTD is dependent on both NMDA receptors (Sjöström et al., 2003) and protein synthesis (Yin et al., 2006). In the vmPFC, DSI appears to be mediated by 2-AG. Yoshino et al. demonstrated that DSI within the vmPFC neurons can be abolished by either application of a DGL inhibitor or knockout of the DGLα gene. Furthermore, they demonstrated that DSI in the vmPFC neurons was enhanced after raising 2-AG levels, but not affected by changes in AEA (Yoshino et al., 2011). Similarly, MGL, but not FAAH, administration has been shown to block DSE, thus demonstrating that 2AG rather than AEA is necessary to induce DSE (Su et al., 2013). AEA, on the other hand, regulates tonic circuit inhibition by regulation of presynaptic GABAergic neurons and so may play a significant role in tuning excitatory/inhibitory balance in the vmPFC (Ahn et al., 2011; Katona and Freund, 2012; Morena et al., 2016). Thus, 2-AG is thought to induce a rapid and robust CB1R response that is required for modulation of activity-induced synaptic plasticity, while AEA operates in parallel to regulate overall circuit excitability.

Spatial segregation within distinct microcircuits and within subcellular compartments may also allow for AEA and 2-AG to act as independent regulators of neuronal excitability (Katona and Freund, 2012) and it is likely that the release of eCBs are determined by very specific synaptic antecedents (Kim and Alger, 2010). To summarize, dissociable roles for 2-AG and AEA acting on the same receptor may be achieved by action on separate timescales, phasic versus tonic respectively, or by spatial segregation at the level of the subcellular or microcircuit level. Although more research is needed to clarify the exact roles of 2-AG and AEA in the vmPFC, the extant data indicate that 2-AG is critical for modulating both excitatory and inhibitory presynaptic inputs in response to various physiological stimuli or patterns of neural activity, while AEA plays a homeostatic role gating overall circuit excitatory tone. Going further, it is conceivable that 2-AG can both boost circuit excitability via modulation of presynaptic interneurons (that is, by DSI or LTD of inhibitory synapses) and constrain certain presynaptic glutamatergic inputs (that is, by DSE or LTD of excitatory inputs) within the same microcircuit.

3.2. Endocannabinoids and stress

Recently there has been a significant investment in research into the eCB system in the context of stress (Lutz et al., 2015; Morena et al., 2016). Disruption of eCB synthesis or blockade of the CB1R promotes activation of the HPA axis suggesting a role for the cannabinoid system in regulating the stress response (Patel et al., 2004; Hill and McEwen, 2010). Regarding eCBs in the vmPFC there are several studies involving uncontrollable stressors. In response to acute, uncontrollable stressors, AEA levels have been found to decrease within the mPFC in a relatively rapid manner being seen as early as 5 min following swim stress (McLaughlin et al., 2012), but by 1 h post onset of restraint stress, these changes have returned to baseline levels (Hill et al., 2011). 2-AG, on the other hand, has a delayed response to stress with no changes found immediately after a 5 or 15 min swim stress exposure (McLaughlin et al., 2012) but a delayed increase at 1 h post-stress onset that is mediated by glucocorticoids (Hill et al., 2011). This divergent regulation of AEA and 2-AG within the vmPFC following exposure to acute stress becomes amplified and prolonged following exposure to repeated stress or sustained glucocorticoid exposure (Hill et al., 2008; Rademacher et al., 2008; Hill et al., 2010; Dubreucq et al., 2012; Gray et al., 2016).

Second, eCB signaling in the vmPFC can also modulate neurobehavioral and endocrine responses to stress. For example, antagonism of CB1R locally within the vmPFC prolonged corticosterone secretion following cessation of stress in rats (Hill et al., 2011) and facilitated passive coping responses to a behavioral challenge in animals who had a history of stress exposure (McLaughlin et al., 2013). Additionally, lentivirus-mediated local over expression of FAAH in the vmPFC, which elicits a marked decrease in AEA signaling in this region similar to what is seen following exposure to stress, has been shown to be sufficient to elicit an anxiogenic response (Rubino et al., 2008a). Consistent with these data suggesting that *interfering with eCB* signaling in the vmPFC can worsen or mimick the effects of stress, *augmenting eCB* signaling has been found to reduce stress. Local elevation of AEA by inhibition of FAAH within the vmPFC can dampen stress-induced activation of the HPA axis (McLaughlin et al., 2014), temper behavioral responses to shifts in environmental threat (Aliczki et al., 2016), reduce anxiety (Rubino et al., 2008b; Lisboa et al., 2015), attenuate fear expression (Lisboa et al., 2010) and promote active coping responses to stress

(McLaughlin et al., 2012; Sartim et al., 2016). Comparable effects are seen following direct activation of CB1Rs exclusively in the vmPFC whereby CB1R agonists reduce anxiety (Rubino et al., 2008a,b; McLaughlin et al., 2014; Fogaça et al., 2016), fear expression (Lin et al., 2009) and increase active coping responses to stress (Bambico et al., 2007; Sartim et al., 2016).

Together, these data indicate that eCB signaling within the vmPFC gates emotional behavior, stress coping strategies and neuroendocrine function. As such, disruptions in eCB signaling result in prolonged and exaggerated responses to stress, while elevations in prefrontal eCB signaling may confer a state of stress resilience by tempering neurobehavioral responses to stress. Given that eCB signaling in the vmPFC can particularly regulate GABAergic transmission (Chiu et al., 2010; Hill et al., 2011), it's possible that deficits in eCB signaling here could result in feedforward inhibition of pyramidal neurons in the vmPFC, while elevated eCB signaling may increase the excitability of prefrontal projection neurons and enhance their top down control of subcortical circuits. This model is consistent with electrophysiological work demonstrating that elevating eCB signaling can restore deficient prefrontal output in a model of chronic pain and improve decision making processes (Kiritoshi et al., 2013; Kiritoshi et al., 2016). Similarly, human fMRI work has demonstrated that the CB1R agonist tetrahydrocannabinol can increase vmPFC activity during extinction memory recall (Rabinak et al., 2014). Collectively, these data suggest that eCB signaling can enhance prefrontal cortical excitability and top down control over stress responsivity.

Although there are no studies of eCBs in controllable stress, there is evidence that eCBs may alter PFC-DRN signaling which we have shown is important for stress coping. For example, systemic administration of a CB1R agonist increased active coping during a forced swim – an effect that was prevented by transection of DRN projecting vmPFC fibers (Bambico et al., 2007). Furthermore, CB1R agonist locally administered within the vmPFC increased 5-HT single unit firing in the DRN, an effect that could be blocked by co-administration with CB1R antagonist or by transection of the vmPFC-DRN connection (Bambico et al., 2007). As previously mentioned, intra-vmPFC administration of CB1R agonist increased active coping, but simultaneous administration of a 5HT1A antagonist, which would increase DRN 5-HT unit activity, blocked this effect (Sartim et al., 2016). Finally, blocking AEA hydrolysis in the vmPFC increased firing of 5-HT neurons (McLaughlin et al., 2012). That CB1R agonist administration or AEA upregulation within the vmPFC results in excitation of the DRN contradicts the hypothesis that vmPFC eCBs are important to blunting DRN activity during controllable stress. Consideration of a few methodological disparities may help reconcile the view presented here and the results of reviewed above. First, the experiments with DRN unit recordings after vmPFC eCB manipulations were conducted in anesthetized rats while the observations of 5-HT activity in the stressor controllability experiments were made using in vivo microdialysis in freely behaving rats. It is an empirical question as to whether the actions of eCB on vmPFC-DRN projection neurons would be the same in the awake versus anesthetized brain. Second, the pyramidal neurons projecting from the vmPFC synapse onto both GABAergic interneurons and 5-HT neurons within the DRN (Jankowski and Sesack, 2004; Geddes et al., 2016) providing a synaptic basis for bidirectional modulation of the DRN by the vmPFC. Finally, prior work with both eCBs and stressor controllability has treated the vmPFC as a whole rather than isolating manipulations to either the PL or IL region. This is admittedly difficult with conventional microinjection approaches, but it is important to note that it is PL-DRN projections, and not IL-DRN projections, which have been shown to be selectively activated during controllable stress (Baratta et al., 2009). Thus, nonselective engagement of vmPFC CB1Rs in an anesthetized rat may result in a net excitation within the DRN through direct excitation of vmPFC-DRN projections that synapse onto 5-HT neurons while the activity-dependent action of eCBs that occurs in a rat experiencing control over stress may lead to DRN inhibition by selectively activating the PL neurons that synapse with DRN GABAergic interneurons. In light of these issues, the role of 2-AG signaling, either alone or in concert with AEA, may lead to different effects on vmPFC output to the DRN. Importantly, these disparities and new questions can be tested directly in future experiments with improved anatomical resolution. In sum, ample empirical data suggest that eCBs play a role in regulating the excitability of vmPFC to DRN projection.

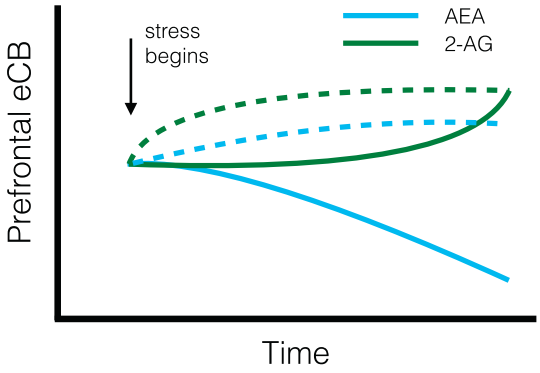

Fig. 1. Predicted timecourse of prefrontal endocannabinoid (eCB) level relative to the beginning of stress. 2-AG (green) rises well after the start of uncontrollable stress while AEA (blue) gradually decreases as stress continues. Hypothetical values following from (Hill et al., 2011; McLaughlin et al., 2012). When the stressor is controllable (dashed lines) 2-AG increases rapidly as a consequence of high frequency firing in the prefrontal action/outcome system causing sustained depolarization and retrograde release of 2-AG. Accordingly, sustained neuronal activity would raise AEA levels leading to a gradual reduction in tonic inhibition in the prefrontal cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Endocannabinoids, prefrontal cortex and stressor controllability

The preceding established that uncontrollable stressful experiences alter eCB signaling in the vmPFC as evidenced by stressor induced reductions in AEA and delayed increases in 2-AG. Here we will argue that the controllability of the stressor will reshape the pattern of eCB release in the vmPFC; control will prevent of the reduction of and even elevate AEA and accelerate the increase in 2-AG (Fig. 1). The evidence that intra-PFC administration of eCBergic compounds can dramatically alter the expression of stress-related behaviors and even modulate the vmPFC-DRN tract have much in common with what has been observed during or as a consequence of controllable stress exposure. Given the important functions of eCBs in circuit excitability and synaptic plasticity, which occur in the vmPFC of rats given control over stress, we hypothesize that eCBs are critical to the resilience from stress afforded by controllability because they permit input selection in the action/outcome system and maintain sustained activation of the vmPFC-DRN projections throughout ES. (See Fig. 2.)

Consider that while ES and IS “activate” the vmPFC, they do so as a consequence of differential inputs. Exposure to stressful noxious stimuli activates numerous brain regions that project to the vmPFC including the raphe, hypothalamus, amygdala, and hippocampus to name a few. However, only when control is present, the vmPFC receives input that encodes the action/outcome contingency between performing the escape response and the termination of shock. The PL and dorsomedial striatum are key components of the action/outcome learning circuit (Balleine and O'Doherty, 2010) and we have demonstrated that controllable stress induces Fos in both regions to a greater extent than uncontrollable stress (Baratta et al., 2009; Amat et al., 2014). Preventing synaptic plasticity in either of these structures eliminates the protective effects of stressor controllability (Amat et al., 2014; Christianson et al., 2014). Further evidence that neural activity related to the action/outcome contingency was reported using optogenetics. Silencing activity in the vmPFC, specifically during the wheel-turn

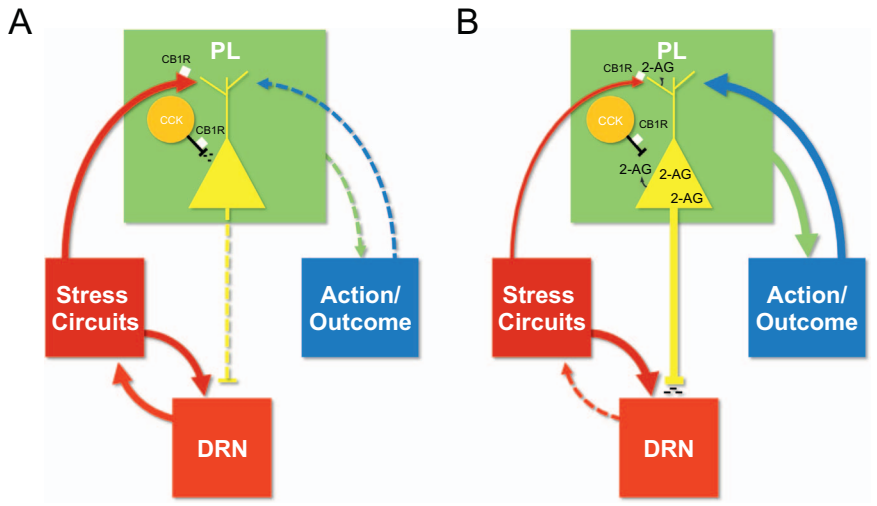

Fig. 2. Neural circuits engaged during uncontrollable stress (A) or controllable stress (B) and the hypothetical role of endocannabinoid (eCB) signaling. A. Exposure to traumatic stressors activates numerous brain systems that enable fight or flight responses. These systems excite both the prelimbic prefrontal cortex (PL) and the serotonergic dorsal raphe nucleus (DRN). Excitation of the DRN initiates a feed-forward loop which perpetuates the stress response and ultimately renders the DRN sensitized to subsequent stressors which is the critical mechanism of fear and anxiety behaviors following uncontrollable stress. B. When the traumatic stressor is controllable, an action/outcome learning circuit is engaged in parallel to the stress response circuits. Thalamocortical inputs to the PL then activate the PL and potentiate its outputs to the dorsomedial striatum which together coordinate coping behaviors. The high degree of activity within the PL that results from having control causes the release of 2-arachidonylglycerol (2-AG) which serve to shunt inputs from the stress circuits through retrograde inhibition of excitatory synapses while increasing output of the PL more generally through disinhibition of presynaptic cholecystokinin (CCK) GABAergic neurons. One consequence of this disinhibition activation is sustained activity in PL neurons that silences 5-HT activity via direct projections to inhibitory interneurons within the DRN. Thus, when control is present the action/outcome and top-down inhibitory systems of the PL gain priority over stress responsive systems and eCBs are positioned to be critical to this circuit selection and stress resilience.

response, was shown to eliminate the long-lasting resilience after controllable stress; whereas silencing the vmPFC during inter-trial intervals, that is when the action/outcome circuit is presumed to be less important, had no effect (Baratta et al., 2015). Although a direct test is required, we assume that the activity that occurs during controllable stress in the action/outcome circuit is a critical antecedent to the activation of PL-DRN neurons that lead to DRN inhibition.

How are the action/outcome inputs to the PL selected for plasticity during controllable stress while other "non-control" inputs (such as from amygdala or hypothalamus) are not? We believe the eCB mediated phenomena of DSE and LTD of excitatory inputs are possible mechanisms that could account for this selectivity. At the outset of stress, a PL output neuron would receive a torrent of dendritic EPSPs from myriad stress responsive circuits. If the subject has control over stress it will learn that its actions determine the offset of stress and the thalamocortical action/outcome inputs to the PL neuron would continue to excite the post synaptic cells projecting to the DMS leading to a) Hebbian long-term potentiation at only the PL synapses involved in action/outcome learning b) sustained depolarization leading to increased intracellular calcium and c) the retrograde release of 2-AG. 2-AG would then suppress the excitatory inputs that are not related to stressor controllability through heterosynaptic DSE which could eventually lead to a relatively permanent suppression of these inputs via eCB-LTD. Strengthening the action/outcome inputs through LTP while blunting other inputs would result in a specialized pattern of control-related information in the PL microcircuit that could maintain coping behavior during ES.

Importantly, several of the electrophysiological and molecular antecedents of eCB signaling have been demonstrated within the PL following an experience with control over stress. Control over stress alters the intrinsic excitability of PL pyramidal neurons, in part by increasing voltage gated Ca^{2+} channel (VGCC) currents underlying the after depolarization (Varela et al., 2012). Given that many forms of eCB signaling are Ca^{2+} dependent, augmenting the conductance of VGCCs would increase intracellular Ca^{2+} concentrations within these pyramidal neurons would cause them to be more likely to release eCB which could in turn promote DSI, DSE, or eCB-LTD locally within the PL. Second, both eCB-LTD in the cortex (Sjöström et al., 2003) and the protective effects of controllable stress (Christianson et al., 2014) are NMDA receptor dependent. Accordingly, both eCB induced plasticity (Yin et al., 2006; Yuan and Burrell, 2013) and the effects of controllable stress (Amat et al., 2006) depend on protein synthesis. While it is yet to be shown that controllable stress results in eCB release and subsequent eCB-mediated changes in plasticity, the extant data suggest that eCB-mediated plasticity is likely to occur in the PL during controllable stress.

The weight of evidence from stressor controllability research indicates that the experience of control over stress results in sustained activation of PL output neurons which regulate the DRN. This would be difficult to achieve under low AEA levels that have been reported during uncontrollable stress. Building on the above hypothesis regarding circuit selection, here we propose that in addition to raising 2-AG levels, the sustained activity of the PL-DMS action/outcome circuit over the course of ES would lead to greater AEA in this circuit. The increase in AEA could augment the tonic level of circuit activity by modulating presynaptic inhibitory neurons. We expect that an acute effect of this release is to disinhibit the PL as a consequence of DSI in cholecystokinin expressing GABAergic interneurons which selectively express CB1R. Over time, rising levels of AEA will lead to further disinhibition, possibly through eCB mediated LTD of inhibition (Azad et al., 2004). This would sensitize PL-DRN output neurons and support a high level of firing in these cells over the duration of a stress exposure.

To summarize the model, we posit that eCBs play an acute function in dampening non-control related inputs to the PFC while simultaneously elevating the level of circuit output. Continued inputs relating to action/outcome contingencies will result in sustained drive of a select population of PL neurons which could play a key role in maintaining high activity in the stress-suppressing PL-DRN output neurons. The long-lasting effects of eCBs could be to allow plasticity or consolidation in the action/outcome circuit leaving the subject prepared to respond with coping strategies to subsequent stressors. On the flip side, if the subject does not have control, the high levels of eCBs will depotentiate many inputs to the PFC and enhance circuit inhibition, rendering it less excitable and less responsive during subsequent stressors as suggested previously (McLaughlin et al., 2014).

5. Conclusion

It is clear that behavioral control over stress is a key factor in determining the consequences of a traumatic experience but at this point in time, there are many open questions pertaining to the specific neural mechanisms that provide for resilience in subjects that can control the stressor. We reviewed the compelling evidence that activity and plasticity within the PL leads to learning an action/outcome contingency and top-down inhibition of stress responsive brain regions like the DRN. We hypothesized that the eCB system could be a key contributor to shaping the PL circuits during stress and suggested a model to guide future research. With regard to eCBs, our model makes several predictions. First, it predicts that the pattern and timecourse of eCB release in the vmPFC will be influenced by the controllability of stress, with controllable stressors leading to more rapid and greater concentrations of both 2-AG and AEA than uncontrollable stress. Second, perturbations of the eCB system, such as a CB1R blockade, will prevent resilience in rats that have control over stress. Third, neuronal activity observed in PL-DRN neurons depends upon eCB mediated potentiation of specific excitatory inputs to these PL neurons and disinhibition of presynaptic GABAergic cell populations. While this framework does not address how the action/outcome circuit is linked to the PL-DRN inhibitory circuit, clearly, the link is in the PL. A translational extension of this work, which echoes the suggestions of numerous others (Hill and Gorzalka, 2009; Korem et al., 2015; Papini et al., 2015; Wyrofsky et al., 2015), is that pharmacological interventions that augment either AEA or 2-AG activity within the PL could be potent pharmacotherapies for stress-related psychopathologies.

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