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Endocannabinoids and Stress Resilience: Is Deficiency Sufficient to Promote Vulnerability?

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Over the past 2 decades, there has been rapidly growing interest in the role of the endocannabinoid (eCB) system in the regulation of stress and emotional processes. Several lines of converging evidence provide strong evidence that eCB signaling is a key player in these processes. First, genetic ablation or pharmacologic antagonism of the cannabinoid type 1 receptor (CB_1R) results in exaggerated neuroendocrine and behavioral responses to acute stress (1). More so, sustained disruption of CB_1R signaling produces an array of neurobiological changes consistent with alterations seen after chronic stress or in mood disorders, such as reductions in neurotrophin levels, neuro-genesis and dendritic complexity, and increased levels of central neuroinflammation (2,3). Second, facilitation of eCB signaling can dampen the impact of both acute and chronic stress on almost every variable examined, including alterations in anxiety, reward sensitivity, hyperalgesia, morphologic changes in the amygdala, and hippocampal synaptic plasticity (1). Third, the eCB system is highly sensitive to stress exposure. Specifically, under conditions of acute stress, the eCB system plays an important buffering role by limiting the magnitude of the stress response and facilitating recovery to basal function after cessation of stress exposure (1). However, under conditions of chronic stress, the eCB system appears to “collapse” in the sense that CB_1Rs downregulate and lose their ability to modulate the synaptic release of neurotransmitters, such as glutamate and gamma-aminobutyric acid (1).

Finally, at a translational level, many studies have indicated that the eCB system likely contributes to the regulation of stress and emotional behavior in humans. Individuals with posttraumatic stress disorder or major depressive disorder have been found to exhibit reductions in the circulating levels of the two primary eCB molecules: anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (1). In addition, genetic polymorphisms in the eCB system that are associated with elevated tonic AEA signaling are associated with reduced anxiety, blunted activation and accelerated habituation of the amygdala in response to threat cues, and greater coupling of prefrontal cortical and amygdala circuits, suggesting enhanced top-down control of emotionality (4,5). Consistent with this, clinical trials of the CB_1R

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antagonist, rimonabant, in the early 2000s revealed that a significant proportion of individuals developed indices of anxiety and depression after pharmacologic blockade of CB_1R signaling (1). Taken together, these data create a compelling argument that eCB signaling is a critical component of stress resilience and that impairments in this system may result in an increased vulnerability to the adverse effects of stress and, potentially, may be a biological substrate related to the development of stress-related psychiatric illnesses.

As comprehensive as this line of research has been, in the context of the classic approach to determine the biological role of endocannabinoids (examining both necessity and sufficiency), there has been a gap in studies examining the sufficiency side of the coin, particularly with respect to whether AEA or 2-AG is the primary eCB molecule mediating the “stress resilient” effect of the eCB system. Through genetic and pharmacologic targeting of the CB_1R, it has been established that CB_1R signaling is both necessary and sufficient to provide this stress resilient response, but the distinct roles of each ligand has been much more difficult to tackle because of the limited tools available to probe these questions. For instance, to date, it has been possible to demonstrate that inhibition of AEA or 2-AG hydrolysis, through either genetic or pharmacologic approaches, can reduce the impact of chronic stress (1), indicating the potential of these molecules from a therapeutic perspective. However, until recently, there were no specific studies demonstrating that reductions in either AEA or 2-AG alone were sufficient to produce the same phenotype as seen after chronic stress or the symptom profiles associated with mood and anxiety disorders. With respect to AEA, this complication remains unresolved because the biosynthetic mechanisms of AEA appear to be highly redundant, and genetic approaches to ablate enzymes associated with AEA synthesis have been inconsistent, making it difficult to determine if a deficit in AEA signaling, in and of itself, is sufficient to produce changes in stress sensitivity and emotional behavior.

However, for 2-AG, two recent studies have developed new genetic tools that have produced compelling evidence that a deficiency in 2-AG signaling is sufficient to replicate the phenotype seen after chronic stress or ablation of CB_1R signaling. Specifically, studies by Shonesy *et al.* (6) and Jenniches *et al.* (7) (in the current issue of *Biological Psychiatry*) developed novel, independent mouse lines in which the enzyme primarily associated with 2-AG synthesis, diacylglycerol lipase α (DAGL-α), was globally deleted. In both studies, the general outcome indicated that DAGL-α deletion resulted in a robust depletion of 2-AG content throughout the forebrain, which was associated with impaired eCB signaling at the synapse as well as behavioral alterations akin to mood disorders, such as increased anxiety, impaired reward sensitivity, compromised fear extinction, and alterations in structural plasticity. These two studies represent the first evidence that finally begins to close the loop on the lines of scientific evidence to determine the exact nature of how eCB function modulates stress resilience and vulnerability. However, one important caveat to note for these studies is that both of these genetic manipulations were germline deletions, suggesting that the impact of reduced 2-AG signaling could have been through altered neurodevelopmental formation and maturation of circuits regulating stress and emotional behavior—and not so much related to real-time deficiencies in 2-AG signaling in adulthood. This hypothesis would receive support from the fact that 2-AG is known to be an important guidance cue for circuit formation during early development (8), and so deficiencies in 2-AG

signaling could alter the way in which circuits subserving stress resilience are formed. In support of this, work we have done with respect to AEA and genetic variance in the enzyme fatty acid amide hydrolase, which metabolizes AEA, demonstrates that the ability of elevated AEA to promote a stress resilient phenotype may in part be due to neurodevelopmental effects, as both humans and mice bearing this polymorphism exhibit greater connectivity between the pre-frontal cortex and amygdala (5,9). This would suggest that alterations in eCB function during discrete developmental windows could have an influence on adult vulnerability to stress through impacting circuit formation.

Consistent with this idea, the study by Jenniches *et al.* (7) demonstrated that inhibition of 2-AG hydrolysis, in attempts to raise 2-AG levels back up, was not sufficient to normalize changes in emotional behavior in *Dagla*$^{-/-}$ mice (as seen in the forced swim test), suggesting that real-time alterations in 2-AG signaling may not be directly related to alterations in emotional behavior. However, the study by Shonesy *et al.* (6), which administered its inhibitor of 2-AG metabolism in a more bioavailable manner, obtained larger increases in 2-AG content throughout the brain and did exhibit normalizations of alterations in emotional behavior in the *Dagla*$^{-/-}$ mice. Adding more complexity to the story, the *Dagla*$^{-/-}$ mice generated by Jenniches *et al.* (7) exhibited additional reductions in AEA, whereas the mice generated by Shonesy *et al.* (6) did not. Disentangling specific and distinct roles of AEA and 2-AG in these processes is not easy when changes in both ligands are seen. That being said, given that the mice in the study by Shonesy *et al.* (6) demonstrated very similar behavioral changes to the changes demonstrated by the mice in the study by Jenniches *et al.* (7), with no changes in AEA, there is some degree of confidence that these behavioral changes are due to a deficit in 2-AG levels. With the recent development of a specific DAGL-α inhibitor (10), studies examining the role of on-demand 2-AG production with regard to the regulation of stress resilience in adulthood will be much easier to perform, as this will remove the neurodevelopmental complications associated in the *Dagla*$^{-/-}$ mice.

In conclusion, the addition of these two genetic DAGL-α loss-of-function mouse models will benefit the endocannabinoid research community greatly and provide new tools to delineate more specifically how eCB function modulates stress sensitivity. The final piece to this puzzle will be performing similar studies on the role of AEA; however, this research will have to await more refined tools and a greater understanding of the biochemical processes subserving AEA synthesis in the brain. Nevertheless, the studies by Shonesy *et al.* (6) and Jenniches *et al.* (7) have added a significant piece of information to this puzzle and have provided the first scientific evidence that a deficiency in basal eCB signaling is sufficient to produce a phenotype reminiscent of what is seen in mood and anxiety disorders. The work of these two groups will inform novel hypotheses on the role of eCB function in psychiatric illness.

References

1. Morena M, Patel S, Bains JS, Hill MN. Neurobiological interactions between stress and the endocannabinoid system. Neuropsychopharmacology. 2016; 41:80–102. [PubMed: 26068727]
2. Beyer CE, Dwyer JM, Piesla MJ, Platt BJ, Shen R, Rahman Z, et al. Depression-like phenotype following chronic CB1 antagonism. Neurobiol Dis. 2010; 39:148–155. [PubMed: 20381618]

3. Hill MN, Hillard CJ, McEwen BS. Alterations in corticolimbic dendritic morphology and emotional behavior in cannabinoid CB1 receptor-deficient mice parallel the effects of chronic stress. Cereb Cortex. 2011; 21:2056–2064. [PubMed: 21263035]

4. Gunduz-Cinar O, MacPherson KP, Cinar R, Gamble-George J, Sugden K, Williams B, et al. Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity. Mol Psychiatry. 2013; 18:813–823. [PubMed: 22688188]

5. Dincheva I, Drysdale AT, Hartley CA, Johnson DC, Jing D, King EC, et al. FAAH genetic variation enhances fronto-amygdala function in mouse and human. Nat Commun. 2015; 6:6395. [PubMed: 25731744]

6. Shonesy BC, Bluett RJ, Ramikie TS, Baldi R, Hermanson DJ, Kingsley PJ, et al. Genetic disruption of 2-arachidonoylglycerol synthesis reveals a key role for endocannabinoid signaling in anxiety modulation. Cell Rep. 2014; 9:1644–1653. [PubMed: 25466252]

7. Jenniches I, Ternes S, Albayram O, Otte DM, Bach K, Bindila L, et al. Anxiety, stress and fear response in mice with reduced endocannabinoid levels. Biol Psychiatry. 2016; 79:858–868. [PubMed: 25981172]

8. Berghuis P, Rajnicek AM, Morozov YM, Ross RA, Mulder J, Urban GM, et al. Hardwiring the brain: endocannabinoid shape neuronal connectivity. Science. 2007; 316:1212–1216. [PubMed: 17525344]

9. Gee DG, Fetcho RN, Jing D, Li A, Glatt CE, Drysdale AT, et al. Individual differences in frontolimbic circuitry and anxiety emerge with adolescent changes in endocannabinoid signaling across species. Proc Natl Acad Sci. 2016 [published online ahead of print Mar 21].

10. Baggelaar MP, Chameau PJ, Kantae V, Hummel J, Hsu KL, Janssen F, et al. Highly selective, reversible inhibitor identified by comparative chemoproteomics modulates diacylglycerol lipase activity in neurons. J Am Chem Soc. 2015; 137:8851–8857. [PubMed: 26083464]