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# Commentary on "Sex differences in the effect of cannabinoid type 1 receptor deletion on locus coeruleus-norepinephrine neurons and corticotropin releasing factor-mediated responses"

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The recent study by Wyrofsky, Reyes, Yu, Kirby, and Van Bockstaele (2018) has provided important new evidence for sex-driven modulation of endogenous cannabinoid (endocannabinoid) signalling during the stress response. It was reported in this study that cannabinoid receptor type 1 (Cnr1) deletion resulted in increased locus-coeruleus norepinephrine excitability in male but not female mice. The study also reported increased norepinephrine, tyrosine hydroxylase and corticotrophin hormone levels in male but not female Cnr1 knockout mice (Wyrofsky et al., 2018). Both of these findings support the hypothesis that the endocannabinoid system is recruited to a greater extent in males than females during acutely stressful experiences, and may therefore provide buffering against short and long-term negative health effects of traumatic or severe stress for males more so than females (Ney, Matthews, Bruno, & Felmingam, 2018). In our view, this study contributes to growing evidence suggesting that endocannabinoids play a role in determining sex differences in the prevalence of stress and trauma-related disorders. Combined with previous evidence, this study has important implications for the development of cannabinoid pharmaceuticals for stress, trauma and anxiety disorders.

The endocannabinoid system is increasingly recognised to play a pivotal role in the activation and regulation of the stress response (Hill & Tasker, 2012; Morena, Patel, Bains, & Hill, 2016). Consequently, regulation of endocannabinoid levels and function is important for maintaining mental health following severe or traumatic stress (Hill, Campolongo, Yehuda, & Patel, 2018). In fact, several recent studies have found dysregulated endocannabinoid levels in various biological matrices in humans with post-traumatic stress disorder compared to healthy, trauma-exposed control participants (Hill et al., 2013; Wilker et al., 2016).

Importantly, stress and anxiety disorders are reported to be at least twice as prevalent in women than in men (Kessler et al., 2012; Koenen et al., 2017). The search for neurobiological causes underpinning this notable discrepancy extends to hormonal regulation of neurotransmitters such as endocannabinoids, where various sex differences are observed in production and function. In our recent review (Ney et al., 2018), we noted that several recent studies appear to be suggesting that stress responses display sex-specific responses when endocannabinoids are subjected to varying conditions. For instance, Cnr antagonism was reported to result in a significantly more pronounced corticosterone level increase in male

compared to female mice (Atkinson et al., 2010). Similarly, Cnr1 knockout resulted in heightened anxiety responses in male but not female mice (Bowers & Ressler, 2016), and inhibition of the primary catabolic enzyme fatty acid amide hydrolase (FAAH) restored endocannabinoid levels in male but not female rats following stress (Zer-Aviv & Akirav, 2016). Relatedly, human males exhibit stronger physiological responses to cannabis use and are more likely to be dependent on cannabis than females (Haney, 2007; Leatherdale et al., 2007).

We therefore hypothesised as part of this review that a potential mechanism for sex differences in the prevalence of stress and anxiety disorders may be differential recruitment of endocannabinoid signalling as part of the stress response (Ney et al., 2018). The study by Wyrofsky and colleagues (2018) further suggests that phasic regulation of stress hormones is more strongly influenced by endocannabinoid signalling in males compared to females, and also further suggests that the endocannabinoid 'buffer' towards stress may be reduced in females compared to males. This study therefore adds further evidence that differences in endocannabinoid signalling between the sexes may explain the discrepancy observed in clinical prevalence of stress and anxiety disorders following severe stress or trauma.

The hypothesis also has several implications for the impending development of cannabinoid pharmaceuticals for stress and trauma. Firstly, the endocannabinoid system may be a significant target for aiding recovery from trauma in females. Secondly, pharmacological analyses will need to be sensitive to sex differences in cannabinoid signalling and metabolism when developing drugs and running clinical trials for trauma and stress disorders. Thus, it is possible that enhancing endocannabinoid signalling in females may be of additional benefit by increasing cannabinoid responsiveness to a level similar to that of males. Conversely, females may naturally rely on different systems to support recovery from stressful experiences and may not benefit from cannabinoid therapies to the same extent as males. Clinical trials that control for sex will thus be critical in determining the extent to which cannabinoids will be effective for both male and female patients, and future preclinical studies should seek to understand the mechanisms underlying sex differences in endocannabinoid responses to stress.



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