Journal Club

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Serotonin, the Prefrontal Cortex, and the Antidepressant-Like Effect of Cannabinoids

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Review of Bambico et al. (http://www.jneurosci.org/cgi/content/full/27/43/11700)

The herb *Cannabis sativa* (marijuana) and its active component, Δ^9-tetrahydrocannabinol (Δ^9-THC), induce feelings of "high" and euphoria by activating cannabinoid type 1 receptors (CB_1Rs) in the brain. The membrane-lipid derivates arachydonoil ethanolamide (nicknamed anandamide, after "ananda," a Sanskrit word meaning "bliss") and 2-arachydonoil glycerol, referred to as endocannabinoids, are endogenous agonists at this receptor. Their action is terminated by uptake followed by catabolism by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase, respectively (Marsicano and Lutz, 2006).

Considering the influence of marijuana on emotional states, it has been hypothesized that enhancing CB_1R activation, either with agonists or by blockade of FAAH, could be a strategy to develop new anxiolytic and antidepressant drugs (Gobbi et al., 2005; Moreira et al., 2008). The majority of clinically used antidepressants inhibit the reuptake of serotonin that seems to play a major role in the physiopathology of mood disorders. Recently, some results have suggested that serotonin may mediate the antidepressant-like effect of cannabinoids. For instance, FAAH inhibition promotes an increase in firing activity of serotonergic neurons in the dorsal raphe nucleus (Gobbi et al., 2005) and CB_1R mRNA is expressed in these cells as well as in the surroundings (Haring et al., 2007). A recent paper, published in the *Journal of Neuroscience* by Bambico et al. (2007) provides more direct evidence to support this possibility.

The authors tested the synthetic CB_1R agonist *R*(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl) methanone mesylate (WIN55,212-2) in the rat forced swim test, a model used to screen antidepressants. Subchronic treatment with WIN55,212-2 modified behavior in a U-shaped manner: low doses elicited robust antidepressant-like effects, which could prevented by the CB_1R antagonist rimonabant, but high doses were ineffective [Bambico et al. (2007), their Fig. 1*A* (http://www.jneurosci.org/cgi/content/full/27/43/11700/F1)]. Remarkably, the cannabinoid action was prevented by the irreversible serotonin-synthesis inhibitor parachlorophenylalanine [Bambico et al. (2007), their Fig. 1B (http://www.jneurosci.org/cgi/content/full/27/43/11700/F1)]. *In vivo* extracellular single-unit recording complemented these behavioral analyses. Subchronic treatment with low doses of WIN55,212-2 increased the firing rate of dorsal raphe serotonergic neurons, whereas firing rate decreased at higher doses [Bambico et al. (2007), their Fig. 2 (http://www.jneurosci.org/cgi/content/full/27/43/11700/F2)]. A similar result was observed after acute treatment. Rimonabant prevented the effects of low doses, and the transient receptor potential vanilloid type 1 (TRPV1) antagonist capsazepine prevented the effect of high doses [Bambico et al. (2007), their Fig. 3*A–F* (http://www.jneurosci.org/cgi/content/full/27/43/11700/F3)]. The biphasic response is consistent with the behavioral results. Furthermore, a non-CB_1R-mediated mechanism may account for the effects at higher doses.

The dorsal raphe receives excitatory projections from the medial prefrontal cortex (mPFC), a structure that computes the controllability over stressful stimuli. Transection of mPFC abrogated the excitatory responses in the dorsal raphe after systemic cannabinoid injection [Bambico et al. (2007), their Fig. 4 (http://www.jneurosci.org/cgi/content/full/27/43/11700/F4)]. Furthermore, infusion of WIN55,212-2 in the dorsal raphe promoted only modest changes in neuronal activity [Bambico et al. (2007), their Fig. 5*A*, *B* (http://www.jneurosci.org/cgi/content/full/27/43/11700/F5)], whereas infusion in the ventral aspects of the mPFC (mPFCv) yielded similar results as systemic injection, significantly exciting dorsal raphe cells [Bambico et al. (2007), their Fig. 6*A–D* (http://www.jneurosci.org/cgi/content/full/27/43/11700/F6)]. Collectively, these data indicate that the mPFCv may be necessary for the activation of dorsal

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raphe serotonergic neurons by cannabinoids. Finally, local cortical microinjection of WIN55,212-2 mimicked the effect of systemic administration, eliciting antidepressant-like behavior via CB_1R activation [Bambico et al. (2007), their Fig. 7 (http://www.jneurosci.org/cgi/content/full/27/43/11700/F7)].

These results suggest a possible mechanism for the antidepressant-like activity of cannabinoids: a disinhibition of excitatory projections from the mPFCv to serotonergic neurons in the dorsal raphe. This is a major step toward a better understanding of the psychopharmacology of cannabinoids, although some issues are still to be solved. First, the reasons for the U-shaped dose response remain to be further explored. Why high doses induce opposite actions as compared with low ones? An interaction with TRPV1 channels could be an explanation, as Bambico et al. (2007) investigated. The biphasic dose–response curve could also be attributable to the inhibition of different neural populations. Because CB_1Rs are located in presynaptic terminals of both inhibitory and excitatory neurons (Marsicano and Lutz, 2006), multiple types of responses are possible. Another issue to be explored is the consequence of chronic administration. Antidepressants tend to be effective after prolonged treatment, possibly because of the requirement of hippocampal neurogenesis (Santarelli et al., 2003). Cannabinoids may also depend on neurogenesis for their effects in animal models of emotionality (Jiang et al., 2005), suggesting that they might not be an alternative as an acute approach to ameliorate mood disorders. However, few studies have addressed the consequences of prolonged CB_1R activation. Finally, although the experiments were conducted with a CB_1R agonist, FAAH inhibitors may be more promising as a therapeutic strategy. Endocannabinoids are synthesized and released after increase in neuronal activity, although their actions are promptly terminated by uptake followed by hydrolysis. Then, FAAH inhibition could provide "on-demand" defense against stressful stimuli, with less risk of motor impairment, addiction and biphasic effects than CB1 agonists (Gobbi et al., 2005).

In conclusion, the work by Bambico et al. (2007) further clarifies the mechanisms underlying the antidepressant-like effect of cannabinoids. Enhancing the endogenous cannabinoid system could be a new mechanism for medicines that may alleviate depression and related psychiatric disorders.

References

Bambico FR, Katz N, Debonnel G, Gobbi G (2007) Cannabinoids elicit antidepressant-like behavior and activate serotonergic neurons through the medial prefrontal cortex. J Neurosci 27:11700–11711.

Gobbi G, Bambico FR, Mangieri R, Bortolato M, Campolongo P, Solinas M, Cassano T, Morgese MG, Debonnel G, Duranti A, Tontini A, Tarzia G, Mor M, Trezza V, Goldberg SR, Cuomo V, Piomelli D (2005) Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. Proc Natl Acad Sci USA 102:18620–18625.

Haring M, Marsicano G, Lutz B, Monory K (2007) Identification of the cannabinoid receptor type 1 in serotonergic cells of raphe nuclei in mice. Neuroscience 146:1212–1219.

Jiang W, Zhang Y, Xiao L, Van Cleemput J, Ji SP, Bai G, Zhang X (2005) Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. J Clin Invest 115:3104–3116.

Marsicano G, Lutz B (2006) Neuromodulatory functions of the endocannabinoid system. J Endocrinol Invest 29 [Suppl 3]:27–46.

Moreira FA, Kaiser N, Monory K, Lutz B (2008) Reduced anxiety-like behaviour induced by genetic and pharmacological inhibition of the endocannabinoid-degrading enzyme fatty acid amide hydrolase (FAAH) is mediated by CB1 receptors. Neuropharmacology 54:141–150.

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301:805–809.