ANXIETY BEHAVIOR AND ENDOCANNABINOIDS: ROLE OF THE PREFRONTAL CORTEX

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Anxiety can be regarded as a normal emotion representing an adaptative component of the acute stress response under circumstances that threaten the integrity of the individual. However, if anxiety is disproportional in intensity or chronicity it constitutes a maladaptive response or even a psychiatric disorder.
There is an increasing interest in the role of endocannabinoids in anxiety. A recent study (Kathuria et al., 2003) provided support to the hypothesis that endocannabinoids, and anandamide (AEA) in particular, exert an anxiolytic tone in rodents.
Different brain areas seem to be involved in the modulation of anxious states. Among them the prefrontal cortex seems to play an important role since both stress and anxiety have been shown to activate the medial prefrontal cortex in rats.
In order to clarify in this brain region the role of the endocannabinoid tone in the modulation of anxiety behavior, we adopted a multidisciplinary approach including local AEA microinjection, pharmacological blockade of fatty acid amide hydrolase (FAAH), the enzyme responsible for the hydrolysis of AEA, and local overexpression of FAAH by lentivirus-mediated in vivo gene-transfer techniques.
Low doses of the metabolically stable AEA analog, methaAEA, microinjected into the prefrontal cortex, produced an anxiolytic-like response in rats, whereas higher doses induced anxiety-like behavior. Pretreatment with the selective antagonist of CB1 and TRPV1 receptors (AM251 and capsazepine, respectively) suggested that AEA anxiolytic effect might be due to the interaction with the CB1 cannabinoid receptor, whereas vanilloid receptors seem to be involved in AEA anxiogenic action. When we pharmacologically manipulated AEA contents in the prefrontal cortex by microinjecting the selective inhibitor of FAAH, URB597, we observed an anxiolytic response only at low doses, and no effect or even an anxiogenic profile at higher doses. In line with this, pronounced decreases of anandamide contents in the prefrontal cortex, obtained by local overexpression of FAAH through lentiviral vector microinjection, produced an anxiogenic response. The findings support an anxiolytic role for physiological increases in AEA in the prefrontal cortex, whereas when endogenous levels of AEA are too low or increased beyond a certain threshold, they might lead to an anxiogenic response due to the lack of CB1 activation or TRPV1 stimulation, respectively.
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