TARGETING THE ENDOCANNABINOID SYSTEM DURING ADOLESCENCE: PROSOCIAL AND ANTISOCIAL EFFECTS IN WISTAR RATS

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Although preclinical and clinical studies implicate the endocannabinoid system in a wide variety of behavioral and physiological processes, its role in the modulation of social interaction and social motivation has hardly been studied yet. It is well known that cannabis use in humans has a high social value: cannabis is typically smoked in a group setting, with intimate people rather than strangers. Furthermore, the brain opioid system, which closely interacts with the endocannabinoid systems in the regulation of reward processes, plays an important role in social interactions. Therefore, it is reasonable to assume that interacting endocannabinoid and opioid systems positively modulate social behavior. However, several epidemiological data reported that cannabis exposure during adolescence can precipitate psychotic states associated with social withdrawal. Thus, there is a paradoxical relationship between cannabinoid neurotransmission and social interaction. To resolve this paradox, we investigated the role of endocannabinoid neurotransmission in social behavior, and particularly social play, which is highly rewarding and of great importance for behavioral development. We used four-week old male Wistar rats, that were briefly socially isolated before testing. We found that directly stimulating cannabinoid receptors using the CB_1 cannabinoid receptor agonist WIN55,212-2 reduced social play. However, URB597, which inhibits hydrolysis of the endogenous cannabinoid anandamide, enhanced social play, through interaction with opioid neurotransmission. Thus, direct stimulation of cannabinoid receptors throughout the brain, which occurs during cannabis use, inhibits sociability. In contrast, on-demand release of endocannabinoids facilitates social interaction. This suggests that indirect cannabinoid agonists hold promise for the treatment of psychopathological disorders accompanied by social dysfunction. Although the potential side effects of these compounds deserve further investigation, the present studies suggest that the detrimental effects induced by cannabinoid exposure during adolescence are restricted to direct cannabinoid agonists, whereas indirect agonists activate endocannabinoid signaling in a much more selective way, leading to behaviorally meaningful effects.