Cannabinoid receptor 1-expressing neurons in the nucleus accumbens

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AUTHOR SUMMARY

A striking effect that marihuana users experience is altered emotion and motivation. Although the use of marihuana can be traced back thousands of years, it was only recently that the receptor activated by marihuana in the brain was identified. This receptor was termed cannabinoid receptor type 1 (CB1) (1). Later on, it was found that CB1 is the target of endogenously produced cannabinoids, referred to as endocannabinoids. It is now known that the CB1-endocannabinoid interaction is one of the most abundant signallyng systems in the brain. A critical brain region gating emotional and motivational output is the nucleus accumbens (NAc) (2); CB1- coupled signaling within the NAc has been implicated in a variety of emotional and motivational processes, particularly pathophysiological emotional and motivational states (3). Surprisingly, studies using various labeling methods indicate that in stark contrast to adjacent regions, CB1-expressing neurons in the NAc are rather sparse (e.g., <5%) (4). To characterize this small population of potentially important CB1-expressing NAc neurons, we generated a mouse line in which CB1-expressing neurons also expressed the red fluorescent protein tdTomato. This enabled us to indentify these CB1-expressing neurons in living tissue and characterize their physiological properties. Taking advantage of this mouse line, our present study showed that CB1-expressing neurons in the NAc were exclusively fast-spiking interneurons (FSIs). These local interneurons innervate and provide inhibitory control of the principal NAc neurons, known as medium spiny neurons, which project out of the NAc. Thus, these FSIs act as local controllers of the functional output of the NAc. Finally, we observed that the excitability of CB1-expressing FSIs was significantly increased during withdrawal from cocaine exposure, during which animals may experience withdrawal-associated emotional and motivational alterations. The increased excitability of these CB1-expressing FSIs strengthens their inhibitory control over principal NAc neurons, down-regulating the overall functional output of the NAc (Fig. P1). Thus, CB1-expressing FSIs may be critical neural substrates for cocaine or other external stimuli to influence the NAc, resulting in an altered emotional and motivational state.


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