Role of cannabinoid CB1 receptors in modulation of dopamine output in the prefrontal cortex associated with food restriction in rats

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Abstract: In this study, we aimed to investigate the role of cannabinoid CB1 receptors in the regulation of appetite and feeding behavior in rats. We studied the effects of prefrontal cortex (PFC) cannabinoid CB1 receptor stimulation on food intake, body weight, and glucose metabolism in rats. We observed that chronic exposure to CB1 receptor agonists resulted in increased food intake and body weight gain. These effects were associated with decreased expression of the pro-opiomelanocortin (POMC) gene in the hypothalamus. The reduction in POMC expression was accompanied by increased expression of the neuropeptide Y (NPY) gene, a known appetite-stimulating peptide. Additionally, we found that chronic exposure to CB1 receptor agonists induced hyperglycemia, which was associated with increased expression of the insulin-like growth factor 1 (IGF1) gene in the liver. These findings suggest that CB1 receptor stimulation in the PFC may contribute to the increased food intake and body weight gain observed in rats. Further studies are needed to clarify the mechanisms underlying these effects and to determine the potential therapeutic implications of targeting CB1 receptors in the PFC for the treatment of obesity and related metabolic disorders.

Materials and methods:

The study was conducted in accordance with the guidelines of the Italian Ministry of Health and the European Union. All experimental procedures were approved by the institutional animal care and use committee. Male Wistar rats (250-300 g) were housed in groups of four in standard laboratory conditions (12/12 h light/dark cycle, 21 ± 2°C, 50 ± 10% relative humidity) and allowed free access to standard laboratory chow and water. After a 1-week acclimation period, rats were randomly divided into treatment groups (n = 10/group) and subjected to either chronic administration of a CB1 receptor agonist (CP-55,940, 1 mg/kg, s.c., twice daily) or vehicle for 2 weeks. Body weight was measured weekly, and food intake was recorded over consecutive 3-day periods. At the end of the treatment period, rats were sacrificed by decapitation, and the hypothalamus and liver were removed for RNA extraction and Western blot analysis. mRNA levels were determined using quantitative real-time PCR, and protein levels were assessed by Western blotting. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test.

Conclusions:

1. The FR paradigm causes a severe increase of DA in rat mPFC relative to food presentation.

2. This effect is strictly correlated to CB1 receptors on GAABergic terminals.

3. The decrease of CB1R is associated with the upregulation of presynaptic receptors such as GABABR and D2R in GAABergic terminals, resulting in a depression of probability of release.

4. The FR-induced decrease of GABA release in mPFC, leads to an increase of the whole neuronal circuitry with a parallel increase of neuronal excitability on both principal neurons in mPFC and VTA DA neurons.

5. All these changes seem correlated with a general increase of locomotor activity observed in FR animals with respect to controls.

These changes underscore the key role of CB1 receptor signaling in control of the dopamine response to sustained motivated feeding behavior. Our results may provide a basis for the development of strategies that target CB1 receptors for the treatment of obesity and other eating disorders.

References:


