NEUROFUNCTIONAL AND METABOLIC ALTERATIONS INDUCED BY MALADAPTIVE EATING AND STRESS: SERCHING FOR NOVEL PHARMACOLOGICAL TARGETS

High palatable food exposure and pain behavior: beyond cannabinoid receptors

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Epidemiological evidence suggest that obesity might be linked to increased incidence of depressive and anxiety disorders and to increased pain levels (1–3), although the link to these comorbidities was much less investigated with respect to other pathologies. The observation of addiction-like deficits in the brain reward system in obese patients (4–6), suggests that the increased risk for such disturbances might derive from neuroadaptive changes. The wearing off of the hedonical rewarding properties of food may gradually lead to a shift away from positive reinforcement and towards negative reinforcement so that consumption becomes necessary to prevent or relieve negative states (anxiety, depression, irritability and possibly somatic symptoms) that would result from abstinence (7). In support to this hypothesis, reward hypofunctionality, compulsive-like eating, anxiety and reduced pain threshold were observed in rats and mice that volitionally overate a palatable cafeteria diet consisting of palatable energy-dense food available for human consumption (8). Endocannabinoids play an important role in modulating all the neurobehavioral components of this scenario. Most of the evidence focused on anandamide (AEA), through the activation of type 1 cannabinoid receptor (CB1). Based on these considerations, in this study we investigated whether the long-term exposure to a “cafeteria-style” diet could modify pain sensitivity, whether the pharmacological manipulation of endogenous acylethanolamides, by PF-3845, a FAAH inhibitor, can ameliorate this alteration and the mechanisms responsible for these possible pharmacological effects. Animals were divided into 2 groups, the first group was labeled as “chow only” (CO) and was no access the cafeteria diet, the second group was labeled “extended access” (EA) and was ad libitum access (24 h/day) to the cafeteria diet. At the end of the 40 days EA rats were undergo an “abstinence” period of 28 days. Pain threshold was evaluated by hot plate and tail flick tests, at the end of the cafeteria exposure (day 40), and at the end of the abstinence period (day 68). On day 40, EA rats showed a significant increase of threshold pain respect CO rats both in hot plate test (23.2s vs 13.9s) and in tail flick (16.2s vs 5s). These animals were scarified and brain was removed for western blot analysis. Ex vivo experiments showed that CB1 and MU receptors were up regulated, whereas PPAR-α did not modify. Interesting, at end of abstinence period, at day 68, EA rats did not show a significant difference in pain behavioral respect to CO animals. Finally, we used a FAAH inhibitor, PF-3845, during abstinence period to verify if endocannabinoid system are involved. Repeated treatment

with PF-3845 (10mg/kg) induced a significant analgesic effect on both tests (hot plate and tail flick) and surprisingly, western blot analysis showed that MU and PPAR-α receptors were up regulated, but no CB1. Our data clearly indicated that high-palatable food for 40 consecutive days produce an increase of threshold of pain, probably, due to up regulation of CB1 an MU receptor, and that pharmacological manipulation of AEA during abstinence period, play a key role in pain threshold through opioidergic system and nuclear receptor of peroxisome.

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