The endocannabinoid system: possible new pharmacological target in the treatment of anorexia nervosa

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Anorexia nervosa (AN) is the most severe eating disorder with the high rate of mortality in adolescent women. Patients affected by AN develop aberrant eating patterns and weight-control behaviors, such as excessive dieting and physical hyperactivity, aimed to control their altered body image perception. The etiology of AN is poorly understood and there is currently no effective pharmacological treatment of the disease. Brain imaging studies have shown both neuroanatomical abnormalities and dysfunctional activation of brain areas modulating reward in AN patients [1, 2, 3]. The endocannabinoid system (ECs) has been shown a key role in the regulation of both homeostatic and hedonic aspects of eating behavior [4] and in the recent years, several reports have led to hypothesise a strong link between a defect in the ECs and AN. In fact, significantly enhanced plasma levels of the endogenous cannabinoid anandamide (arachidonoylethanolamide, AEA) were found in patients affected by AN [5]. Moreover, brain imaging studies showed an increased number of the cannabinoid type-1 receptor (CB1r) in cortical and subcortical brain areas of AN patients [6].

Using the activity-based anorexia (ABA) model of AN, which reproduces some key aspects of the human condition, such as a massive decline in body weight coupled with physical hyperactivity [7] and endocrine dysregulation, we performed studies to deeply investigate the involvement of the ECs in the physiopathology of AN.

Firstly, we analyzed arachidonic acid (AA), endocannabinoids levels and CB1R density in both feeding and reward-related brain areas of animals subjected to the ABA paradigm, and then, we evaluated whether pharmacological modulation with both cannabinoid receptors agonists and antagonist was able to modify typical symptomatology in anorexic-like animals. Our results showed that female rats exposed to the ABA paradigm developed an anorexic-like state characterized by marked body weight loss and increased running wheel activity (RWA). According to literature, our data showed that plasma levels of the anorexic mediator leptin were decreased in ABA animals, while, levels of the orexigenic mediator ghrelin and of the stress hormone corticosterone were increased. Moreover, we have seen that this anorexic-like phenotype was associated with an altered ECs signaling. In particular, we found a significant alteration of AA and endocannabinoids levels, as well as of the CB1R density in different brain areas involved in circuits regulating eating behavior, reward, but also mood and cognition (i.e. hypothalamus, nucleus accumbens, amygdala and prefrontal cortex). Then, we have seen that the administration of the natural CB1/CB2 receptor agonist Δ9-tetrahydrocannabinol and the synthetic CB1R agonist CP-55,940 significantly reduced both body weight loss and physical activity, and increased food

intake. Conversely, administration of the CB1R inverse agonist/antagonist rimonabant did not modify body weight loss, physical activity and food intake. Changes in levels of these hormones were found after pharmacological treatments with both agonists.

Finally we have analyzed dopamine (DA) and serotonin (5-HT)levels in post-mortem tissue of ABA rats in selected central brain areas: DA and 5-HT were differently modulated in brain areas involved in circuits regulating reward and hedonic aspects of eating behaviour.

Taken together our results demonstrate that animals subjected to the ABA model show an alteration of the ECs that could have a key involvement in the pathophysiology of AN, and that pharmacological therapies based on the modulation of endocannabinoid signaling might be effective in the treatment of this dramatic eating disorder.

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