# Possible role of endocannabinoid system in the physiopathology of eating disorders

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According to DSM-V eating disorders include three distinct illnesses: anorexia nervosa (AN), bulimia nervosa and binge eating disorders plus other specificied feeding and eating disorders and unspecificied feeding and eating disorders. Among the eating disorders AN is the most severe illness with a high rate of mortality in adolescent woman. AN is characterized by excessive body weight loss accompanied by physical hyperactivity difficult to control. The etiology of AN is poorly understood and there is currently no effective pharmacological treatment of this disease. Brain imaging studies have shown both neuroanatomical abnormalities and dysfunctional activation of brain areas modulating reward in AN patients (Kaye et al., 2009; Keating et al., 2012; Holsen et al., 2012).The endocannabinoid system (ECs) has been shown to contribute significantly in the modulation of the hedonic aspects of eating behaviour (Di Marzo et al., 2009), and a link between its dysregulation and AN symptoms could be possible (Di Marzo and Matias, 2005). In fact, plasma concentrations of the endogenous cannabinoid anandamide (arachidonoylethanolamide, AEA) were found significantly enhanced in patients with AN (Monteleone et al., 2005). To further elucidate the role of the ECs in the pathophysiology of AN, the aim of our study was to investigate whether the pharmacological modulation of the ECs was able to modify the aberrant eating behaviour present in a widely validated rodent model of AN. In the 'activity-based anorexia' (ABA) paradigm, animals subjected to a restricted feeding schedule and with free access to a running wheel show paradoxical increased running wheel activity (RWA) and a dramatic weight loss. Our data show that subchronic treatment with both the CB1/CB2 receptor agonist Δ9-tetrahydrocannabinol (0.5 and 0.75 mg/kg) and the synthetic CB1 receptor agonist CP 55,940 (0.03 and 0.06 mg/kg) at the higher doses tested significantly reduced body weight loss. Moreover, each dose attenuated the RWA and produced a transient increase in food intake. On the contrary, subchronic treatment with the CB1 receptor inverse agonist/antagonist rimonabant at the doses tested (0.15 and 0.3 mg/kg) did not modify either body weight loss or RWA and produced a decrease in food intake. We have also found that plasma levels of leptin were significantly decreased in ABA animals in comparison with control group; on the contrary, circulating levels of ghrelin and corticosterone were increased. Changes in levels of these hormones were found after pharmacological treatments with both agonists and the antagonist tested. Taken together our results demonstrate the possible involvement of the ECs in the pathophysiology of AN and suggest that pharmacological therapies based on the modulation of the endocannabinoid signaling might be effective in the treatment of AN.

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