PRECLINICAL AND CLINICAL EVIDENCE FOR A DISTINCT REGULATION OF MU OPIOID AND TYPE 1CANNABINOID RECEPTOR GENES EXPRESSION IN OBESITY

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Introduction: Among endogenous signaling networks involved in both rewarding and homeostatic mechanisms of obesity, a relevant role is played by the endocannabinoid (ECS) and the opioid (EOS) systems.

Material and methods: We here studied the transcriptional regulation of ECS and EOS genes in the hypothalamus of Diet induced obesity (DIO) rats, a preclinical model of obesity, as well as in humans with obesity and healthy controls.

Results: A significant and selective increase in type 1cannabinoid receptor gene (Cnr1) expression was observed at the beginning of obesity development (5weeks on high fat diet) as well as after 21weeks of high diet exposure. After 5weeks on high fat diet, selective up-regulation of mu opioid receptor gene (Oprm1) expression was also observed. Consistently, epigenetic studies showed a selective and significant decrease in DNA methylation at specific CpG sites at both gene promoters in overweight rats, but only after 5weeks on high fat diet. Moreover, significantly lower levels of DNA methylation were observed at selected CpG sites of both receptor gene promoters, analyzed in peripheral blood mononuclear cells from younger (< 30 years old) humans with obesity, as well as in those with shorter time length from disease onset.

Discussion and conclusions: Taken together, we here provide evidence of selective, synergistic and time-dependent transcriptional regulation of CNR1and OPRM1genes in overweight rats, as well as in human subjects. These alterations in genes regulation could contribute to the development of the obese phenotype, and we thus suggest CNR1and OPRM1epigenetic modulation as possible biomarkers of obesity development. Due to the reversible nature of the epigenetic hallmark, our data might also open new avenue to early environmental strategies of intervention.