

## ACTIVITY-BASED ANOREXIA ALTERS NEUROMETABOLIC MEASURES IN ADOLESCENT FEMALE RATS

1)Fumagalli F. 2)Bonacina F. 3)Messa G. 4)Uboldi P. 5)Norata GD. 6)Caffino L.

*University of Milan*

Anorexia nervosa (AN) is a complex mental illness characterized by restricted eating, an intense fear of gaining weight, body weight below 85% of expected body mass index, long-term amenorrhea and high mortality rate. AN begins with a restrictive diet and weight loss and progresses to an out-of-control spiral, in which the control on food intake is highly rewarding for the patient, reinforcing the dieting behavior. Further, AN patients frequently undergo also strenuous exercise regimens. AN onset occurs at puberty, with 90–95% of the cases among females. Despite an incidence rate of 1-2% in adolescent females and its high mortality rate, little is known about its aetiology or predictive factors. Interestingly, a growing body of evidence supports the hypothesis that dysregulated activation of appetite modulators might be involved in the modulation of reward-related processes, suggesting a crosstalk between peripheral signals and brain functions.

Thus, the major aim of this work was to evaluate the dysregulation of PGC-1 $\alpha$ /FND5/Irisin/BDNF pathway as critical for the crosstalk between muscle and brain in anorexia nervosa pointing to such axis, and in particular to the neurotrophin BDNF, as critical to drive weight loss seeking through food restriction and compulsive exercise.

To this end, activity-based anorexia (ABA) rat model, that mimicks the two hallmarks of AN pathology, such as self-starvation and high level of exercise, was set up. Female adolescent Sprague-Dawley rats at postnatal day (P) 35 were individually housed and divided in two groups: controls (CTRL, food ad libitum–sedentary) and ABA (food restricted and free access to an activity wheel). On P38, food access for the ABA group was limited to 2 h per day but unlimited in amount, at the beginning of the dark cycle, till P42, when all ABA rats reached the anorexic phenotype. On P42, all the animals were sacrificed and trunk blood, soleus muscle, hippocampus and medial prefrontal cortex were collected.

When food restriction began (P38), ABA rats started to reduce food intake and starting from 24h later ABA rats significantly reduced body weight. All the animals exhibited a voluntary and stable wheel running before food restriction (from P35 to P38), showing their acclimation to the apparatus and the natural reward of wheel running. When food restriction began, wheel activity constantly increased over days, as expected in this model. Moreover, the combination of food restriction and free access to the activity wheel markedly altered plasma lipid profile of ABA rats reducing triglycerides and cholesterol plasma levels. In the soleus muscles of ABA rats, we found a dramatic increase of PGC1- $\alpha$  levels, indicating an increased oxidative versus glycolytic metabolism of muscle cells. The increased expression of the metabolic regulator PGC1- $\alpha$  may suggest an enhanced expression of its target FND5 that, cleaved and secreted as irisin, has been shown to increase the brain expression of the neurotrophin BDNF, for instance in a condition of

intense exercise. Accordingly, the expression of total BDNF and BDNF exon IV, its most abundant isoform sensitive to neuronal activity, are significantly increased in two brain areas, hippocampus and medial prefrontal cortex, involved in associative reward learning and motivation, respectively.

These data suggest that, in ABA rats, peripheral increase of PGC1- $\alpha$  levels may determine a series of events ultimately leading to increase brain levels of BDNF. Since it has been previously demonstrated that increased brain levels of BDNF are rewarding, we suggest that, perhaps, up-regulation of BDNF levels in cortico-limbic structures could represent a signal of altered processing of food reward, a mechanism that could participate in inducing the anorexic phenotype.

Sponsored by: Nando Peretti Foundation