THE GLUTAMATE SYNAPSE IN AN ANIMAL MODEL OF ANOREXIA NERVOSA

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Introduction: Anorexia nervosa (AN) is a multifactorial psychiatric disorder characterized by restricted eating, an extremely low body weight, an intense fear of gaining weight, strenuous exercise regimens and body image disturbance. Despite the high incidence rate in adolescent females and its high mortality rate the etiopathogenesis remains unclear. Recently, glutamate, the main excitatory neurotransmitter in the brain, has been proposed as a target of food restriction and wheel access within mesocorticolimbic structures, pointing to its modulation as a signal of altered processing of food reward. Interestingly, in a recent pilot sudy at 7Tesla AN participants showed reduced glutamate levels in different regions of the cortex.
Based on these lines of evidence, we hypothesized that a dysregulation of the excitatory signaling may play a pivotal role in AN-induced impairment of cognitive abilities. Thus, the major aim of our work was to identify molecular determinants of maladaptive plasticity involved in AN focusing our attention on the alterations in the excitatory (glutamatergic) signaling and in structural plasticity in the medial prefrontal cortex (mPFC), a brain area of the reward network that is still developing during adolescence, in an animal model of anorexia nervosa.

Materials and methods: Female adolescent Sprague-Dawley rats were exposed to the combination of self-starvation and high level of exercise, the so-called activity-based anorexia (ABA) rat model. At postnatal day (P) 35rats were individually housed and divided in four groups: controls (CTRL, food ad libitum–sedentary), FR (food restricted–sedentary), EXE (food ad libitum-exercise) and ABA (food restricted-exercise). On P38, the ABA group was food-restricted (2h/d) till P42, when ABA rats reached the anorexic phenotype. At the scheduled time, i.e. on P42and on P49, after seven days of weight recovery, one group of animals was sacrificed and the medial prefrontal cortex (mPFC) was dissected. Western blot analyses on critical determinants of the glutamate synapse were run on protein extracts of the post-synaptic density. Another group of animals was deeply anesthetized and perfused with 1.5% paraformaldehyde in phosphate buffer to evaluate dendritic spine density and morphology via dyolistic labeling technique.

Results: After three days of AN induction, ABA rats reduced body weight significantly more than FR rats. When food restriction began, wheel activity constantly increased over days, as expected in this model, while EXE animals maintained a stable activity. At P42, there were no major changes in the main critical determinants of glutamate homeostasis, such as NMDA and AMPA receptor subunit as well as their related scaffolding protein levels, in the mPFC of ABA rats. Interestingly, seven days of recovery restored body weight of ABA rats but it caused an overall reduction of the glutamatergic signalling in the post-synaptic density of the mPFC, an effect that is, at least partially, coupled with altered dendritic spine density and morphology.

Discussion and conclusions: These data suggest that the combination between reduced food intake and hyperactivity may determine a series of events ultimately leading to an altered composition and structure of the glutamatergic synapse even when the body weight is restored. These molecular determinants of maladaptive plasticity could represent a signal of altered processing of food reward, and a vulnerability trait for relapse. Moreover, the herein shown AN-induced dysregulation of the excitatory signaling coupled with an altered structural plasticity might be the trigger for the motivational mechanisms underlying AN that could lead, in turn, to cognitive dysfunction, consistently observed in AN patients.

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