Mice exposed to chronic psychosocial stress overeat palatable energy dense food and show altered expression of selected neuropeptides in key brain areas.

B. Tempesta[1], A. Romano[1], R. Coccurello[2], S. Cianci[1], S. Bellantuono[2], A. Moles[2,3], S. Gaetani[1], V. Cuomo[1]

[1]Dept. of Physiology and Pharmacology 'V. Erspamer', Sapienza Univ. of Rome
[2]Institute of Cell Biology and Neurobiology (IBCN), National Research Council (CNR)/S. Lucia Foundation, Rome
[3]Genomnia srl, Lainate, Milan

Stress is considered a pathogenetic factor for the vulnerability to compulsive eating and obesity, although little is known about the neurobiological mechanisms underlying this association. Hypothalamic neuropetides are key players in the complex system that homeostatically controls food intake and energy balance. Moreover, several of the same neuropeptides are expressed also in other brain areas involved in the emotional response to stress. Therefore, in this study we evaluated whether alteration of neuropeptide expression might be involved in the effects of stress exposure on food intake and energy balance.

According to the role of 'comfort food' in attenuating the HPA axis response to stress, we used a murine model of chronic psychosocial stress coupled to diet manipulations. In particular, we used a chronic psychosocial stress (CPS) model, in which two mice were housed in the same cage, separated by a grid partition that permitted only sensory, not physical, contact. The partition was removed twice a day to allow agonistic interactions to occur. Each couple was composed by a C57/BL6 (i.e. obesity prone strain) mouse and an outbred NMRI. C57/BL6 mice were always defeated by NMRI mice. Two control groups were included in the study: one individually housed C57/BL6 mice (ISO) and paired C57/BL6 housed mice (CO). Animals were exposed to different diets: i) high-fat diet (HF), ii) high-fat-high-palatable diet (HFP), and iii) standard diet as control (CD), to observe whether social stress may alter feeding behavior and metabolic rate and influecence the expression of orexigenic and anorexigenic neuropeptides in selected brain areas.

The different experimental conditions were set as soon as the CPS mice showed persistent defeated behavior and were maintained for a period of four weeks, including a brief initial habituation period of four days to the diet.

In this model we analyzed daily caloric intake, body weight gain, locomotor activity, metabolic rate (measured by indirect calorimetry) and, by in situ hybridization, the mRNA levels of different neuropeptides in selected brain areas. In particular we focused on pro-opiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript (CART) and neuropeptide Y (NPY) in the arcuate nucleus (ARC); on oxytocin (OXY) in the paraventricular (PVN) and sopraoptic (SON) nuclei; and on CART in the basolateral amygdala (BLA).

Our results showed that all defeated animals ingested more calories compared to controls. This difference was particularly evident when animals received the HFP diet. However their body weight did not increase as the CO and ISO mice. This effects was probably due to the increase of energy expenditure and locomotor activity displayed by CPS mice. Moreover, differently from CO group, POMC mRNA levels in the ARC did not increase in CPS and ISO mice on HF diet. By contrast, in CPS mice on CD there was an increase of OXY expression in the PVN that was abolished by the exposure to HF and HFP diet. CPS mice on HFP did not show the increase in CART expression at ARC level as observed in CO and ISO groups on the same diet. Exposure to HFP increased CART expression in the BLA of all groups, while exposure to HF diet increased CART expression only in CPS and ISO mice. Finally, an increase of NPY mRNA levels was observed only in CPS mice on CD and such amplification was suppressed by the exposure to HF and HFP.

Overall, our study confirms that the chronic activation of the stress response can be associated with altered feeding behaviour and energy homeostasis and might suggest that the overlap of the homeostatic adaptation of brain neuropeptidergic system induced by the high caloric intake with the effects of the stress exposure can cause a deregulation of neuropeptide expression in key brain areas. Such effects might be able to hijack the homeostatic controlling system that regulates feeding and cause the food overconsumption observed in CPS mice.