Regulation of the expression of the IL-18 \ IL-18R system in the hypothalamus of a rat model of binge eating: effect of the phase of the estrous cycle

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Episodes of binge eating (BE) in humans are characterized by compulsive, non-homeostatic consumption of an unusually large quantity of highly palatable food (HPF) in a short period of time. Considerable evidence suggests that BE may be caused by a unique interaction between dieting and stress. In the model adopted by our group [1] BE for HPF is evoked in rats by the combination of cyclic food restrictions and stress. The model uses female rats in relation to the higher prevalence of BE disorders in women. According to the inverse association between plasma estradiol levels and BE we demonstrated that during the estrous phase, BE was not induced in our experimental conditions in female rats [2].
We aimed to evaluate the role of the interleukin (IL)-18 \ IL-18receptor(R) system in the development of the BE behaviour in this animal model. IL-18 is a pro-inflammatory cytokine belonging to the IL-1 family. Beside its well established role both in innate and adaptative immune responses IL-18 mediates a variety of effects also in the brain [3] by interacting with its heterodimer receptor (IL-18R). The IL-18R consists of a subunit α (IL-18Rα type I, required for binding), and a subunit β (full-length IL-18Rβ, responsible for signal transduction). A complex regulation of IL-18 activity has been suggested. Indeed, aside the first characterized negative regulator of IL-18- mediated actions, IL-18 binding protein (BP), a short transcript of IL-18Rα (IL-18Rα type II) and a soluble form of IL-18Rβ (small IL-18Rβ) exist [4-5]. Works on IL-18\ and on IL-18BP overexpressing mice indicated that IL-18 can negatively regulate food-intake [6-7] through mechanisms that are still largely unknown. However, a central action was proposed following the observation that i.c.v. injections of exogenous IL-18 induce anorexia.
Two groups of rats were used: 1) NR+NS was normally fed and not stressed on day 25 and 2) R+S was exposed to 3 cycles of yo-yo dieting and stressed on day 25. All groups were fed HPF for 2 h on day 5-6 and 13-14. On the test day the rats were sacrificed and the preoptic and anterior plus tuberal hypothalamus dissected for gene expression analyses. Estrous phase was determined by examination of vaginal smears.
By means of quantitative RT-PCR we observed in the anterior and tuberal hypothalamus (that includes the main nucleus involved in feeding control) specific differences in the regulation of the expression of the mRNAs of the IL-18 \ IL-+18R system in the R+S group compared to the NR+NS group depending on the phase of the rat estrous cycle. In particular in R+S animals not in estrous phase $_{(NE)}$ we found increased levels of IL-18BP and decreased levels of IL-18R type I mRNAs expression when compared to NR+$NS_{(NE)}$ group whereas in R+S (estrous-$_{E}$) rats we demonstrated increased levels of IL-18 mRNA expression with respect to NR+$NS_{(E)}$ rats. These effects were typical of this brain region. In fact, in the preoptic hypothalamus we found reduced levels of IL-18 mRNA expression specifically in R+$S_{(NE)}$ animals when compared to their controls(NR+$NS_{(NE)}$). No significant effects were observed in the expression of the other components of the IL-18 \ IL-18R system immediately after stress exposure.
Our data support a role for the IL-18 \ IL-18R system in the developing of the BE behaviour. Given that R+$S_{(NE)}$ rats develop BE while R+$S_{(E)}$ do not, it is possible to speculate that a reduction of the anorexigenic activity of IL-18 in R+$S_{(NE)}$ animals may contribute to the development of the impaired feeding behaviour whereas the increased expression of IL-18 may prevent the development of BE in R+$S_{(E)}$ animals.

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