Allopregnanolone effects on food intake and weight gain

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt förvar i hörsal Betula, byggnad 6M på Norrlands universitetssjukhus, Umeå onsdagen den 13 maj, kl 9.00.
Avhandlingen kommer att förvaras på svenska.

Fakultetsopponent: Professor Bo Söderpalm,
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Abstract

Background Obesity is currently one of the major causes of ill health and it is clear that overeating is the cause of obesity. However, the actions of many endogenous factors that contribute to overeating are still not well understood. Gamma-aminobutyric acid (GABA)-ergic transmission has been shown to be of great importance for food intake regulation. The progesterone metabolite allopregnanolone is a potent positive GABA$_{A}$ receptor modulating steroid (GAMS) and in humans, elevated allopregnanolone levels have been suggested to be involved in increased food intake, and also with overweight and obesity. GABA$_{A}$ receptors that express the α2 and α3 subunits are proposed to be the main subtypes involved in food intake regulation. Therefore, the aims of the work in this thesis were to further investigate the effect of allopregnanolone on food intake, feeding behaviour, possible effects on weight gain and also to characterize a possible antagonist at α2β3γ2 and α3β3γ2 GABA$_{A}$ receptors.

Methods Allopregnanolone effects on food intake of different food items were recorded in male Wistar rats. Feeding patterns were analyzed. Food preference tests were also conducted and rats were repeatedly exposed to allopregnanolone under different feeding conditions to elucidate possible effects on body weight gain. To deeper investigate GABA$_{A}$ receptor subtypes suggested to be involved in food intake regulation, electrophysiological whole-cell patch-clamp recordings were performed to identify the specificity of the GAMS antagonist UC1020, at human α2β3γ2 and α3β3γ2 GABA$_{A}$ receptors expressed in HEK293-cells.

Results Allopregnanolone increased the intake of standard chow, cookies and a high fat diet in male Wistar rats. Preferentially, allopregnanolone increased the rats´intake of the more calorie dense food type. Allopregnanolone reduced feeding latency and prolonged feeding duration. The increased chow intake induced by allopregnanolone was more pronounced at the beginning of the rats´ active period compared to the inactive. Repeated allopregnanolone administration during 5 consecutive days led to an increased body weight gain, more evident in schedule fed rats on a high fat diet. Both obesity prone and obesity resistant rats gained significantly more weight with repeated allopregnanolone exposure and the increased body weight gain correlated with increased food intake. The compound UC1020 was a potent antagonist of GAMS-enhanced GABA evoked currents at human α3β3γ2 GABA$_{A}$ receptors, whereas it had no effect at α2β3γ2 GABA$_{A}$ receptors.

Conclusions Our findings indicate that allopregnanolone induced hyperphagia may be one of the endogenous factors involved in weight gain, especially when the diet is energy-rich. The compound UC1020 may prove useful for investigating the involvement of the α2 and α3 GABA$_{A}$ receptor subtype in GAMS-induced hyperphagia.