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Thema

**Zentrale Bedeutung des adrenocorticotropen Hormons
(ACTH) bei der Regulation des Körpergewichtes
- experimentelle Untersuchungen zum Wirkmechanismus -**

Abstract

The melanocortin system within the hypothalamus is substantially involved in the regulation of body weight. As was shown in this study, the adrenocorticotrophic hormone (ACTH), which is processed by proteolytic cleavage from the proopiomelanocortin (POMC) precursor peptide is an important component of this system.

We caused demonstrate that intracerebroventricular (i.c.v.) administration of ACTH significantly reduced food and water intake in male Wistar rats. Removal of adrenal steroids by adrenalectomy in a subgroup of animals, in order to prevent a potential stimulation of the glucocorticoid release and thus increase of food intake, did not affect the anorexigenic effect of ACTH. The i.c.v. application of ACTH caused a significant increase of brain derived neurotrophic factor (BDNF) mRNA expression in the ventromedial nucleus of the hypothalamus (VMN), as detected by in-situ hybridization. In contrast to BDNF mRNA expression, the expression of melanocortin receptor 4 (MC4-R) was decreased, suggesting a compensatory effect to high central nervous ACTH levels.

Thus far no studies on the physiological relevance of the endogenous ACTH for the homeostasis of the body weight have been published. The investigation of this topic is made more difficult by the fact that another potent anorexigenic hormone, the alpha-melanocyte-stimulating hormone (α -MSH), is derived from ACTH by enzymatic processing. By the use of before specific antibodies (Ab), that were before tested on their effectiveness, the involvement of the two peptides, i.e. ACTH and α -MSH, in the regulation of body weight could be examined separately. By a special food regime, animals satiated in the evening hours, at the time of the Ab application, were generated. They thus possessed high endogenous level of the POMC-derived anorexigenic peptides. In these animals the central application of ACTH-Ab and α -MSH-Ab caused an increase of food intake and a decrease of BDNF mRNA expression in the VMN by blocking endogenous peptides. Other animals were fed ad-libitum and thus in the evening, at the time of Ab application, were hungry, since this is the beginning of their feeding period. In contrast to satiated rats, endogenous POMC-derived peptide level were low under this feeding condition. As a consequence, the injection of ACTH-Ab and α -MSH-Ab were not effective on food intake and mRNA expression.

The twice-daily application (morning and evening) of ACTH-Ab over one week confirmed the results from the experiments mentioned above. The injection affected only food intake during the day, when animals were satiated and endogenous levels of POMC-derived peptides were high.

Furthermore we showed that the application of α -MSH-Ab into the hypothalamus did not block the effect ACTH i.c.v., thus proving that the observed anorexigenic effect of the ACTH is caused by the peptide itself and not by α -MSH.

With the help of the experiments summarized here the physiological role of endogenous ACTH in the regulation of body weight was demonstrated for the first time.