Central effects of cholecystokinin (CCK) on metabolic/thermoregulatory parameters of the energy homeostasis during the course of aging.

Erika Petervari, Alexandra Miko, Margit Szekeres-Solymar, Szilvia Soos, Miklos Szekely, Marta Balasko. *Depatment of Pathophysiology and Gerontology Medical School University of Pecs, Pecs, Hungary*

Background: Cholecystokinin (CCK) a catabolic peptide of the brain-gut axis has long been known to induce satiety by activating the peripheral (vagal) CCK type 1 receptors: the effect is very strong in young adult and old rats but minimal in middle aged ones. Central administration of CCK, via brain CCK type 2 receptors, can also evoke satiety in experimental animals, although the efficacy changes with age: it is low in middle-aged animals. Intracerebroventricular (ICV) administration of CCK has also been shown to elicit a regulated rise in core temperature involving increased heat production (metabolic rate, MR) and diminished heat loss, i.e. showing features of a fever-like hyperthermia (with anorexia fitting the pattern of sickness behavior). Moreover, the administration of a CCK type 2 receptor antagonist suppressed the first phase of experimental endotoxin fever in rats. These observations suggest a complex role for the central CCK type 2 receptors in the regulation of energy homeostasis.

Aims: During aging both the intrinsic plasma level of CCK and the responsiveness to peripherally applied CCK have been shown to increase. Thus, age-related changes in the CCK system may contribute to such regulatory alterations that may be assumed in the background of aging anorexia frequently resulting in cachexia and sarcopenia in old humans and mammals. In the present study age-related variations in the metabolic/thermoregulatory responsiveness of rats to centrally administered CCK were analyzed.

Methods: Male Wistar rats aged 3-, 6- or 12- and 18-24 months (young adult, early or late middle-aged and old, respectively) were injected ICV with 200, 500 or 1000 ng CCK to test thermoregulatory actions. Thermoregulatory analysis was performed using thermocouples [recording core (Tc) and tail skin temperature (Ts, to assess heat loss) with thermocouples attached to a Cole-Parmer Benchtop Thermometer] in metabolic chambers of an indirect calorimeter system (Oxymax, Columbus) registering oxygen consumption.

Results: An acute ICV CCK injection induced a regulated rise in core temperature (an increase in oxygen consumption was associated with low tail skin temperature indicating suppressed heat loss) in all age-groups. No dose dependence was observed. The strong hyperthermic effects seen in young rats gradually diminished with aging.

Conclusions: On the one hand, the anorexic effects of peripherally administered CCK showed well-defined age-related shifts with strongly diminished responsiveness in middle-aged and a very pronounced one in old age-groups (compared to the standard significant response seen in young adult rats), which pattern partially also apply for the anorexic effects of central CCK. On the other hand, the central metabolic and thermoregulatory effects of CCK show a monotonous age-related decline, presumably due to a progressive decrease in capacity to elevate metabolic rate. Thus, age-related alterations in thermoregulatory vs. anorexic CCK effects are disparate. (OTKA PD84241, PTE AOK-KA-34039-02/2010, 34039/KA-OTKA/11-01)