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Effects of central or peripheral cholecystokinin (CCK) on food intake during the course of aging.

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Background: Cholecystokinin (CCK), a catabolic peptide of the brain-gut axis, has been known to activate the intestinal feedback control of gastrointestinal function in response to gastric stretch and to induce satiety mainly through CCK type 1 receptors and capsaicin-sensitive afferent fibers of the abdominal vagus. However, not only peripheral, but also central administration of CCK can evoke satiety in experimental animals. The latter effect is exerted mainly by CCK type 2 receptors of the brain.

Aims: During the course of aging both the intrinsic plasma level of CCK and the responsiveness to peripherally applied CCK have been shown to increase. Age-related changes in the peripheral and central CCK system may, therefore contribute to those 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 anorexigenic responsiveness of rats to extrinsic CCK administered centrally and peripherally were analyzed.

Methods: Male Wistar rats aged 2-, 3-, 6- or 12- and 18-24 months (juvenile, young adult, early or late middle-aged and aging-old, respectively) were injected by CCK intraperitoneally (at an 1, 2 or 5 μg dose) or intracerebroventricularly (at an 500 dose) to test anorexic effects of this catabolic peptide on short-term (3-h) re-feeding following 48-h fasting. Twelve months old calorie-restricted (40% reduction of caloric intake, CR) and 6 months old high-fat diet-induced obese (60% fat calories via special high-fat IPS TestDiet, HF) groups were also established. Food intake was recorded in an automated FeedScale system (Columbus).

Results: Peripherally administered CCK suppressed re-feeding in young adult, early middle-aged and old, but not in juvenile and late middle-aged animals. CCK-resistance of late middle-aged rats was prevented by life-long CR. Conversely, in HF rats the CCK-induced suppression of re-feeding was diminished already in the early middle-aged group. Upon central administration the applied dose elicited a stronger anorexic response that showed a similar age-related pattern from the juvenile to the late middle aged groups. The weakest effect was seen in the juvenile, the strongest responsiveness appeared in the young adult and early middle-aged, followed by a strongly diminished response in the late middle-aged group. The anorexic reaction of old rats to central CCK administration remains to be seen.

In conclusion, age-related changes in the responsiveness to CCK may contribute not only to the explanation of the anorexia seen in old animals, but also to that of the obesity of middle-aged rats. CCK-responsiveness is also influenced by body composition: restricted diet prevents the resistance to CCK, pre-existing obesity enhances it. (OTKA PD84241, PTE AOK-KA-34039-02/2010, 34039/KA-OTKA/11-01)