Peptides 85 (2016) 63–72

Contents lists available at ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides

Acute central effects of corticotropin-releasing factor (CRF) on energy balance: Effects of age and gender

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ARTICLE INFO

Article history:
Received 6 June 2016
Received in revised form
12 September 2016
Accepted 12 September 2016
Available online 13 September 2016

Keywords:
Corticotropin-releasing factor (CRF)
Energy balance
Food intake
Metabolic rate
Aging
Gender

ABSTRACT

Previously demonstrated age-related changes in the catabolic melanocortin system that may contribute to middle-aged obesity and aging anorexia, raise the question of the potential involvement of corticotropin-releasing factor (CRF) in these phenomena, as this catabolic hypothalamic mediator acts downstream to melanocortins. Catabolic effects of CRF were shown to be mediated by both CRF1 (hypermetabolism) and CRF2 (anorexia) receptors. To test the potential role of CRF in age-related obesity and aging anorexia, we investigated acute central effects of the peptide on energy balance in male and female rats during the course of aging.

Effects of an intracerebroventricular CRF injection on food intake (FI), oxygen-consumption (VO_2), core- and tail skin temperatures (Tc and Ts) were studied in male and female Wistar rats of five different age-groups (from 3- to 24-month). Anorexigenic responsiveness was tested during 180-min re-feeding (FeedScale) following 24-h fasting. Thermoregulatory analysis was performed by indirect calorimetry (Oxymax) complemented by thermocouples recording Tc and Ts (indicating heat loss).

CRF suppressed FI in 3-month male and female animals. In males, CRF-induced anorexia declined with aging, whereas in females it was maintained in all groups. The peptide increased VO_2 and Tc in all male age-groups, while the weaker hypermetabolic response characterizing 3-month females declined rapidly with aging.

Thus, age-related alterations in acute central anorexigenic and hypermetabolic effects of CRF show different non-parallel patterns in males and females. Our findings underline the importance of gender differences. They also call the attention to the differential age-related changes in the CRF1 and CRF2 receptor systems.

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1. Introduction

Long-term regulation of body weight (BW) and body composition shows two different trends in mammals: obesity develops typically in the middle-aged, whereas old age is characterized by anorexia, weight loss and sarcopenia [15,38,55]. Both trends imply world-wide public health burdens [69,70]. As most mammals also show similar trends in their long-term BW development [63], a dysregulation of energy homeostasis may also contribute to these phenomena. Therefore, the investigation of regulatory alterations in energy balance during the course of aging, are of outstanding importance. And indeed, earlier studies demonstrated the potential role of age-related shifts in the responsiveness to such centrally administered catabolic mediators as leptin [44] or endogenous melanocortin agonist alpha-melanocyte-stimulating

Abbreviations: BW, body weight; CRF, corticotropin- releasing factor; CRF1 receptor, corticotropin- releasing factor type 1 receptor; CRF2 receptor, corticotropin- releasing factor type 2 receptor; F, female; FI, food intake; HPA, hypothalamic-pituitary-adrenal; ICV, intracerebroventricular; IP, intraperitoneal; M, male; MSH, melanocyte- stimulating hormone; PFS, pyrogen-free saline; Tc, core body temperature; Ts, tail skin temperature; Ucn2, urocortin 2; Ucn3, urocortin 3; VO_2, oxygen-consumption.

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http://dx.doi.org/10.1016/j.peptides.2016.09.005
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hormone (alpha-MSH) in the development of the above mentioned BW trends [43,52]. Based on these previous findings, the question arises, whether corticotropins (downstream to melanocortins and leptin) may also contribute to the metabolic dysregulation characterizing aging.

The first member of the corticotropin peptide family, corticotropin-releasing factor (CRF), a 41-aa neuropeptide was described by Vale and coworkers in 1981 [66]. This peptide is produced predominantly in the parvocellular neurons of the paraventricular nucleus of the hypothalamus [66], but expression of CRF mRNA has been detected, among other sites, in the cerebral cortex, amygdala and in the hippocampus [37,68].

Although the main functions of CRF are thought to be the activation of the hypothalamic-pituitary-adrenal (HPA) axis [39,49], the activation of the sympathetic tone [8] and coordination of the body's responses to stress [32], this peptide also participates in a great variety of regulatory processes. It has been shown to induce fear, to participate in anxiety and in depressive disorders of animals [9] and humans [2]. In addition, CRF elicits coordinated catabolic effects via inducing anorexia [48] and hypermetabolism accompanied by increased brown-fat thermogenesis [8,10,33]. Moreover, in genetically obese rats (fa/fa) the peptide prevented weight gain [50].

Two subtypes of G-protein coupled receptors (CRF1 and CRF2) mediate the effects of corticotropins, CRF activates mainly CRF1 and to a lesser extent CRF2 receptor [35,42,67], while urocortin 1, another member of the corticotropin family shows similar affinity to both receptor types [35,42,67]. Widespread expression of CRF1 receptor was described in hypothalamic nuclei [45,47,65] and also in the anterior pituitary [65]. Additionally, they are found in the forebrain, in the septal region and amygdala [29], in the cerebral cortex and in the cerebellum [47,65]. Anxiogenic actions, depressive behavior and hyperthermic/hypermetabolic effects have been attributed to the activation of this receptor type [18,47,65]. Its anorexigenic effects are thought to be based on emotional stress [28]. In contrast, CRF2 receptor expression appears to be more restricted in the brain, these receptors were mainly detected in the lateral septum, amygdala, hippocampus, also in hypothalamic nuclei (e.g. in the ventromedial hypothalamus) [65] or in the nucleus of the solitary tract [6]. Type 2 receptors mediate anorexia, anxiolytic and antidepressive effects [13,47,65]. This latter receptor type has been shown to mediate anorexigenic actions of centrally applied CRF or those of other members of the corticotropin peptide family, such as urocortin 2 (Ucn2) or urocortin 3 (Ucn3) [13,40,58]. The latter members of the corticotropin family show enhanced affinity to CRF2 receptors [13,34,40,60].

During the course of aging, characteristic changes of the corticotropin system have been reported in humans and mammals [25]. Most studies found increased hypothalamic CRF expression in old age compensated by some CRF1 receptor downregulation [1,11,56,64]. Nevertheless, a few studies described reduced or unchanged CRF expression in old age-groups [12,31]. *Post mortem* investigations in men demonstrated increased activity of CRF, especially in depressed subjects or in deceased patients with Alzheimer's disease [4,46]. Other investigators suggested a role for the hyperactive HPA axis in neuronal deterioration of aged humans and in old experimental animals [16,54,61].

An intriguing additional feature of the corticotropin system is that its functions show gender differences [22,26,36]. Therefore, age-related alterations of the hypothalamic corticotropin system may also show different patterns in males and females. Such differences may also provide some explanation for the gender differences in the long-term BW development of male and female rats: in contrast with males showing middle-aged obesity and a decline in BW in old age-groups, females maintain a stable low BW throughout life [17,63].

Therefore, we aimed to investigate the potential involvement of acute central catabolic CRF effects (anorexia and hypermetabolism) in the development of age-related obesity and aging anorexia leading to weight loss in old male Wistar rats. These acute central catabolic effects of CRF were also analyzed in females during the course of aging to test their potential contribution to gender differences in long-term BW development in this strain.

2. Methods

2.1. Animals

Various age-groups of male (n = 79) and female (n = 75) Wistar rats (M and F, respectively) from the Colony of the Institute for Translational Medicine of the Medical School, University of Pécs, Hungary were used in the experiments of the present study: young adult (M = 14, F = 12), younger (M = 14, F = 16) and older middle-aged (M = 15, F = 13), aging (M = 16, F = 16) and old (M = 10, F = 18) (3-, 6- and 12-, 18- and 24-months old, respectively). (Maximal lifespan of our Colony reaches 30 months, about 50% of rats survive 26 months, but after the age of 24 months surgical interventions involve high mortality). In this study altogether 7 rats failed to survive surgery. For thermoregulatory analysis and for tests of food intake separate groups of animals had to be used. Each animal in each age-group received CRF and its solvent in random order. Such tests were divided by 7 days. Following tests, animals were sacrificed; no repeated testing across age-groups was possible.

After they have reached the appropriate age, rats were kept in individual plastic home-cages containing wood-chip bedding at an ambient temperature of 22–25 °C. Cages were equipped with a steel grid top with feeder and bottle container. This environment provided a thermoneutral temperature in the nest. Lights were on between 06.00 and 18.00 h. Standard rat chow (11 kJ/g; CRLT/N rodent chow, Szindbád Kft., Gödöllő, Hungary) and tap water were available *ad libitum*, except for the 24-h fasting period when only water was provided for the appropriate groups. All animals were accustomed to regular handling. Spontaneous daily food intake (FI) and BW were measured every day at 09.00 h. Table 1 shows BW values of the different male and female age-groups. Initial BW-s of treated and those of control animals did not differ within age-groups, as shown by one-way ANOVA ($p > 0.05$ in all cases, Table 1).

2.2. Surgeries, drug administration

A 22-gauge stainless-steel guide cannula was implanted into the right lateral cerebral ventricle of rats using a stereotaxic apparatus for the purpose of intracerebroventricular (ICV) injections. The tip of the guide cannula (fixed to the skull by dental cement) was positioned at A: −1.0 mm (to bregma), L: 1.5 mm (right lateral to bregma), V: 3.5 mm (ventral to dura) (coordinates according to the Rat Brain Atlas, [41]). A stylet closed the lumen of the guide cannula which was replaced during the experiments by a 28-gauge injection cannula outreaching the guide cannula by about 0.5 mm. Surgical interventions were performed under intraperitoneal (IP) ketamine-xylazine [78 mg/kg (Calypsol, Richter) + 13 mg/kg (Sedaxylan, Eurovet)] anesthesia. Gentamycin (2 mg IP) was used for the prevention of infections. In order to check the appropriate location of the guide cannula angiotensin II (Sigma, A9525, 20 ng/5 μl) was injected through a pp10 polyethylene tube attachment around 3 days after the implantation. Appropriate location was assumed if at least 5 ml water was consumed within 30 min [43]. Experiments started 7 days after the cannula implantation.

After the experiments rats were sacrificed by an IP overdose of urethane (3–5 g/kg, Reanal). *Post mortem* check of the injection sites

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