AGE- AND NUTRITIONAL STATE-RELATED CHANGES IN CENTRAL LEPTIN EFFECTS ON ENERGY BALANCE

Doctoral (PhD) Thesis

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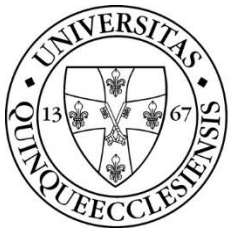

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INTRODUCTION

Abnormalities of energy balance present major public health problems with rapidly increasing prevalence (WHO 2015, 2016). They include changes of body weight (BW) and/or body composition. Obesity is defined as excessive accumulation of body fat, while wasting disorders are characterized by progressive loss of BW, especially that of muscle mass. During aging two common tendencies are observed: middle-aged people tend to gain weight and develop obesity (Scarpace et al., 2000b), while at old age, anorexia (loss of appetite) with a consequent cachexia and progressive muscle atrophy (sarcopenia) develops. As population aging became a global phenomenon, the impact of middle-age obesity and aging anorexia is enormous. Moreover, obesity appears to accelerate aging and age-related degenerative processes (e.g. muscle atrophy, neurodegeneration) (Carter et al., 2013; Balaskó et al., 2014).

Age-related changes can be observed not only in humans, but also in other mammals suggesting the contribution of altered basic regulatory mechanisms, in addition to environmental factors (e.g. increasingly sedentary lifestyle and imbalanced dietary choices). One of the common features of aging and obesity is a dysregulation of energy homeostasis. Such dysregulation involves resistance to different regulatory peptide hormones, e.g. leptin or insulin, leading to abnormalities of BW and/or body composition (Ahima, 2009; Carter et al., 2013).

As both types of body composition changes increase the risk of morbidity and mortality, investigation of regulatory alterations that develop in obesity or during the course of aging is of outstanding importance.

1. Regulation of energy balance

Energy balance involves two interconnected regulatory circles. One is responsible for the maintenance of BW. This long-term regulation is based on the balance between food intake (FI) and metabolic rate (MR). The other short-term balance refers to thermoregulation, it defends the stability of core body temperature (Tc) via adjusting MR (heat production) and heat loss. Acute changes in FI and MR determine the feeding status (hunger, satiety), chronic dysregulation leads to abnormal nutritional states (obesity, cachexia). These changes also have an influence on the thermoregulatory status. Fasting or starvation induces hypometabolism and a tendency for hypothermia, while a postprandial state is characterized by hypermetabolism and hyperthermia. On the other hand, temperature changes also modify feeding behaviour (Székely and Szelényi, 2005).

Neuroendocrine regulation of energy balance involves a cross-talk between the periphery and the central nervous system, consisting of sensory inputs, central integrative circuits, and autonomic outputs (Carrascosa et al., 2009; Münzberg et al., 2016). Sensory input to the brain is accomplished by neural or humoral route; signals may act on chemo- and mechanosensitive endings of the abdominal vagus (Székely, 2000), humoral substances in the circulation (e.g. secreted from peripheral organs) may act directly at the brain (Janig, 1996). These factors interact with specific brain areas such as hypothalamic or brainstem nuclei. These brain areas play a key role in integrating peripheral signals which modify the activity of

central regulatory peptides, and generate homeostatic responses, transmitted by the autonomic nervous system to regulate FI and energy expenditure (Badman and Flier, 2005).

2. Leptin

Leptin is one of the most important adipokines that is produced predominantly in the white adipose tissue (Friedman and Halaas, 1998). The protein has emerged as probably the most important peripheral feedback signal to hypothalamic nuclei involved in the long-term central regulation of energy balance (Benoit et al., 2004). Leptin has coordinated catabolic activity: it does not only decrease food intake (anorexigenic), but it also increases MR (hypermetabolic) and Tc (hyperthermic) (Hwa et al., 1996; Sahu, 2004; Steiner and Romanovsky, 2007). Increasing leptin levels are assumed to suppress overeating and to enhance energy expenditure in order to prevent further energy (fat) accumulation, while the effects are the opposite in case of decreased leptin levels (e.g. suppression of energy loss during starvation).

The hormone exerts its effects through the long isoform of the leptin receptor (Ob-Rb). Central catabolic leptin actions are mainly mediated by alterations in the expression of neuropeptides in the arcuate nucleus of the hypothalamus (ARC). On the one hand it activates anorexigenic–catabolic mechanisms conveyed by proopiomelanocortin (POMC)-derived melanocortins [primarily by alpha-melanocyte stimulating hormone (alpha-MSH)] and by cocaine-amphetamine-regulated transcript (CART), while on the other hand it inhibits orexigenic–anabolic pathways connected with neuropeptide Y (NPY) and also with agouti-related peptide (AgRP). Peptides released from second order neurons [orexins, corticotropin-releasing hormone (CRH), etc.] downstream to the cells of the ARC contribute to these mechanisms (Baskin et al., 1999; Valassi et al., 2008). The metabolic and thermogenic effects of leptin are partly mediated via the sympathetic nervous system through different hypothalamic nuclei (Pandit et al., 2017). In the periphery, leptin also acts on different sites of the afferent vagus (Wang et al., 1997; Gaigé et al., 2002), transmitting information to the brainstem (e.g. to the nucleus of the solitary tract) (Buyse et al., 2001; Székely and Szelényi, 2005).

3. Leptin resistance with aging and obesity

The vast majority of obese people are insensitive to leptin treatment, indicating the existence of "leptin resistance" in common forms of obesity (Hukshorn et al., 2002; Moon et al., 2011). It has long been recognized that the responsiveness to leptin changes both with adiposity (Lin et al., 2000) and with age (Scarpace et al., 2000b). The combination of aging and obesity, *i.e.* age-related obesity is characterized by a tendency towards progressive weight gain starting at a younger age in humans and mammals reaching a peak in late middle-aged or aging groups. Such a weight gain has been associated with the development of progressive peripheral and, later on, also with central leptin resistance (van Heek et al., 1997; Sahu, 2004).

However, several questions remain unresolved in this field. For example, evidence is not conclusive whether age *per se* or rather the accompanying obesity leads to the

development of leptin resistance. Moreover, very old age-groups of humans and mammals tend to lose weight [aging anorexia (Morley, 2001)] that cannot be explained on the basis of aging-induced leptin resistance.

Previously, different, even inverse leptin effects have been shown upon central chronic and acute applications of the protein (García-Cáceres et al., 2011). It would be therefore important to also investigate the age-related pattern of acute and chronic central leptin effects with regard to energy metabolism.

Central leptin responsiveness appears to be maintained longer than the peripheral one during the development of obesity (van Heek et al., 1997). Investigation of the development of age- and obesity-related changes in central leptin resistance may therefore implicate later therapeutic possibilities (e.g. regarding intranasal application of leptin in obesity, Schulz et al., 2012; Spetter and Hallschmid, 2015).

AIMS

1. We aimed to investigate age-related changes in acute central leptin effects on parameters of energy balance.

We tested the anorexigenic and hypermetabolic responsiveness to intracerebroventricular (ICV) injections of the hormone in different age-groups of male Wistar rats (3, 6, 12, 18 or 24 months old). In addition, we carried out a detailed thermoregulatory analysis of hypermetabolic leptin effects. Regarding the mechanism of age-related changes in leptin-induced anorexia and hypermetabolism, expression of the long isoform of the leptin receptor (Ob-Rb) and that of the signal transduction inhibitor suppressor of cytokine signaling 3 (SOCS3) gene in the ARC was studied by quantitative real-time polymerase chain reaction (qRT-PCR). The influence of high-fat diet-induced obesity on the anorexigenic effects of leptin was also analyzed in the 6- and 12-month age-groups.

2. We also aimed to investigate the influence of aging and that of nutritional states on chronic central leptin effects on parameters of energy balance.

The effects of a 7-day large dose ICV leptin infusion on FI, BW, heart rate [HR, representing MR (Butler, 1993)], Tc and spontaneous locomotor activity (ACT) were investigated in normally fed (NF) rats aged 3, 6, 12, 18 or 24 months. Regarding nutritional states, 6-, 12- and 24-month calorie-restricted (CR) age-groups were established (rats were maintained on a reduced energy diet from age 2 months). For further comparison, 6- and 18-month old obese rats (maintained on high-fat diet from age 2 months) were also infused ICV with leptin.

MATERIALS AND METHODS

1. Animals

Different age-groups of male Wistar rats from the Colony of the Institute for Translational Medicine were used in the present study. Rats were maintained at an ambient temperature (Ta) of 22–25 °C. Lights were on between 06.00 and 18.00 h. The following age-groups were established: 3 (young adult), 6 (younger middle-aged), 12 (older middle-aged), 18 (aging) and 24 (old) months old.

At certain age-groups, animals were divided into subgroups: NF, high-fat diet-induced obese (HF), or CR. NF rats were fed standard laboratory rat chow (11 kJ/g) ad libitum, HF rats received IPS TestDiet (containing 60 % energy from fat, 21.6 kJ/kg) from 2 months of age. CR animals received 2/3rd of the normal daily amount of standard powdered chow (16 g/day) from age 2 months, with vitamin and mineral supplementation. Tap water was continuously available in all groups. All animals were accustomed to regular handling. Spontaneous daily FI and BW were measured every day at 09.00 h.

The following groups were tested in the experiments: (1) NF animals at ages 3, 6, 12, 18 and 24 months (NF3, NF6, NF12, NF18 and NF24, respectively); (2) HF 6-, 12- and 18-month old rats (HF6, HF12 and HF18 – the HF rats usually died before the age of 24 months); (3) CR animals of three age-groups (CR6, CR12 and CR24, respectively).

All experiments were in accord with regulations of the University of Pécs Ethical Committee for the Protection of Animals in Research (BA 02/200-11/2011) and National Ethical Council for Animal Research and those of the European Communities Council (86/609/EEC, Directive 2010/63/EU of the European Parliament and of the Council).

2. Acute experiments

2.1. Surgical interventions

Rats were operated on for the purpose of implanting a 22 gauge stainless-steel leading cannula into the right lateral cerebral ventricle in a stereotaxic apparatus, for ICV injections. Surgeries were performed under intraperitoneal (IP) ketamine-xylazine [78 mg/kg (Calypsol, Richter) + 13 mg/kg (Sedaxylan, Eurovet)] general anesthesia and 2 mg IP Gentamicin was used to prevent infections. The tip of the leading cannula was at A: -1.0 mm (posterior to bregma), L: 1.5 mm (right lateral to bregma), V: 3.5 mm (ventral to dura).

2.2. Administration of substances

When measuring acute anorexigenic effects, the animals received leptin (1 μg, recombinant leptin, Bachem) dissolved in 5 μl pyrogen-free saline (PFS, solvent 0.9 % NaCl) or 5 μl PFS alone after 48-h fasting. In acute thermoregulatory experiments 4 μg of the protein was dissolved in PFS (5 μl), control rats received only 5 μl PFS. Injections were given remotely, without causing discomfort to the animals and administered at around 09.00 h.

2.3. Assessment of food consumption

For 10-14 days before the experiments rats were transferred to the automated Feed-Scale system (Columbus, OH) to get habituated to the environment and to the powdered form of rat chow (in order to avoid hoarding behavior). Standard or high-fat rat chow and tap water were provided ad libitum, except for the 48-h fasting period when only water was available for the appropriate groups.

On day 1 at 09.00 h food was removed for 48-h. Five minutes before the re-feeding started (on day 3 at 09.00) assigned rat groups received 1 μg ICV leptin injection to measure the inhibitory effect of the hormone on 4-h cumulative FI. NF animals at ages 3, 6, 12, 18 and 24 months and two groups of HF rats (HF6 and HF12) were tested in these experiments.

2.4. Assessment of metabolic and thermoregulatory functions

Oxygen consumption (VO_2, representing MR), Tc and tail skin temperature (Ts, indicating heat loss) were measured on semi-restrained rats, singly enclosed in cylindrical wire-mesh confiners. As the animals were previously accustomed to the semi-restraining cages, we could minimize the stress during the experiments. During the measurements, the rats could not eat or drink. The animals in their confiners were placed singly into a plexiglass metabolic chamber ventilated with room air. The chambers were immersed into a thermostatically controlled water-bath. A slightly subthermoneutral environment (25 ºC) was applied that elicits a constant skin vasoconstriction without fluctuations in the Ts, but also leads to a slight decrease in initial Tc that facilitates the observation of hyperthermic responses (Romanovsky et al., 2002).

Following the ICV injection data was registered in 10-min intervals for 3 hours. The colon thermocouple (for measuring Tc) was inserted 10 cm beyond the anal sphincter, the tail skin thermocouple (for measuring Ts) was fixed on the dorsal skin of the distal part of the tail. Oxygen consumption (ml O_2/kg/min) and carbon-dioxide production (ml CO_2/kg/min) from the air perfusing the chamber were determined by indirect calorimetry (Oxymax, Equal Flow, Columbus, OH). Temperature data were collected by a Digi-Sense Benchtop Thermomether (Cole-Parmer) for electronic processing and evaluation. Thermoregulatory functions were tested in NF animals at ages 3, 6, 12, 18 and 24.

3. Chronic experiments

3.1. Surgical interventions

In chronic experiments, an IP transmitter was implanted under IP ketamine + xylazine general anesthesia (as described in 2.1.) after an at least 7-day adaptation of the rats in the biotelemetric system (MiniMitter VMFH series 4000, Sunriver, OR). After one week of recovery they had a second operation under similar anesthesia. This time an ICV cannula was implanted into the right lateral cerebral ventricle as it was described earlier (2.1.). At the same time an Alzet osmotic minipump filled with leptin or PFS was inserted underneath the skin of the nape which was connected to the outer end of the ICV cannula. After the experiments rats

were euthanized by an overdose of IP injection of urethane (3-5 g/kg, Reanal), the site of the brain's injection cannula was checked macroscopically.

3.2. Administration of substances

The osmotic minipump was filled with leptin or PFS. The infusion reached the brain after 8-10 h and secured a standard slow ICV infusion (1 μg/μl/h leptin or 1 μl/h PFS) for a period of 7 days.

3.3. Assessment of food consumption and energy expenditure

The IP transmitters conveyed signals of Tc, HR (for indirect assessment of MR) and spontaneous (horizontal) ACT of freely moving animals in the MiniMitter cage of the biotelemetric system. The automatically recorded 5-min data were collected and integrated into two mean 12-h values per day, one characterizing values of the daytime (resting) period, another one the nighttime (active) period. For data analysis the VitalView software provided by the manufacturer was used. By the help of an attached food container the daily FI was measured manually every day, together with BW. Normally fed animals at ages 3, 6, 12, 18 and 24 months, two groups of HF rats (HF6 and HF18), and three CR groups (CR6, CR12 and CR24) were tested in these experiments.

4. Post mortem examinations

4.1. Body composition measurements

At the autopsy following the ICV infusion (day 8) indicators of body composition of NF, HF and CR rats were determined: the wet weights of the anterior tibial muscle, the retroperitoneal fat tissue and the epididymal fat pad were measured and expressed as percentage of the actual BW (Soós et al., 2010; Balaskó et al., 2013).

4.2. Studies on gene expression

These experiments were performed in collaboration with the Department of Anatomy, Medical School and the Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, University of Pécs. Intact NF rats of each age-group (n = 6-7/group) were decapitated. The brains were quickly dissected, frozen in liquid nitrogen. ARC samples were punched from 1 mm thick slices [-2 to -3 mm from the bregma (Paxinos and Watson, 2006)] of the brains cut on a brain matrix (Ted Pella, CA, USA) by two razor blades. Sections were placed on a chilled mat and the mediobasal hypothalamic area containing the ARC was microdissected by a 1 mm diameter Harris punching needle (Sigma-Aldrich Budapest, Hungary). Samples were stored at -70°C until further processing.

The total ribonucleic acid (RNA) was isolated with the Pure Link^{TM} RNA Mini Kit (Life Sciences, Carlsbad CA, USA) according to the protocol suggested by the manufacturer. Samples were homogenized, RNA was purified by ethanol treatment, and eluted from the membrane. The total amount of RNA was determined by NanoDrop (Thermo Scientific).

High-capacity complementary deoxyribonucleic acid (cDNA) kit was applied (Applied Biosystems, Foster City, CA, USA) to perform cDNA synthesis, using 1 μg of total RNA sample according to the official protocol.

For gene expression analysis, qRT-PCR was performed using SensiFast SYBR Green reagent (BioLine). Amplifications were run on ABI StepOnePlus system. StepOne software was used to analyze gene expressions, which was normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) housekeeping gene. PCR conditions were set according to previous studies (Füredi et al., 2016): one cycle 95°C for 2 minutes, 40 cycles at 95°C for 5 seconds and 60°C for 30 seconds. The amplification of PCR products were calculated according to the $2^{-\Delta\Delta Ct}$ method.

5. Statistical analysis

Data were statistically analyzed by one-way, two-way and repeated-measures ANOVA tests, complemented by Tukey's or Scheffe's *post hoc* tests, when more than two groups were compared (SPSS 11.0 for Windows). All experimental groups contained at least 6-8 rats. The level of significance was set at $p < 0.05$.

RESULTS

1. Acute leptin administration

1.1. Characteristics of the experimental groups

Mean BW of NF animlas showed a rising tendency up to 18 months of age, then it started to decline slightly in the oldest group. Mean BW values of HF rats exceeded those of age-matched NF groups. In HF12 BW values were significantly higher than those of all NF rats.

Upon 48-h fasting weight loss of NF age-groups ranged from 20-45 g (7 % to 11 % of initial BW). Weight loss of HF animals reached 25-35 g (4-6 % of initial BW). In NF rats, the cumulative 4-h energy intake (during re-feeding) ranged from 80 to 110 kJ. Re-feeding (in kJ) was largest in the HF animals, values of HF12 exceeded those of HF6.

1.2. Effects of central leptin injection on FI

In young adult rats (NF3) the ICV administered acute leptin injection caused a strong suppression of 4-h cumulative FI during re-feeding following 48-h fasting. Leptin failed to induce a significant anorexigenic response in younger and older middle-aged and also in aging rats. Interestingly, the leptin-induced anorexigenic response became significant again in old rats. These results suggest that the anorexigenic effects of an acute central administration of leptin show non-linear changes with aging.

Regarding the obese animal groups (HF6, HF12), alterations in the nutritional state influenced the responsiveness to the hormone. The younger obese group failed to show a

significant reduction in re-feeding FI. Surprisingly, older middle-aged obese rats, demonstrated a significant anorexigenic responsiveness to leptin.

1.3. Effects of central leptin injection on MR and thermoregulation

The maximal increase in Tc and VO_2 varied with aging. The young adult age-group showed a leptin-induced significant increase in MR (represented by VO_2), with a consequent significant rise in Tc. These NF3 animals showed the biggest leptin-induced hyperthermic and hypermetabolic response. Younger- and older middle-aged animals showed more moderate leptin-induced increases in Tc and VO_2. In contrast, in aging and old rats leptin failed to increase Tc or VO_2 to a significant extent. Heat loss mechanisms did not seem to be activated as no vasodilation developed in any of the groups. Leptin appears to induce a coordinated hyperthermic response, similar to febrile reactions, such as prostaglandin E-induced hyperthermia or experimental endotoxin fever. The hypermetabolic/hyperthermic effects of leptin seem to show a monotonous decline with aging. The age-dependence of the hypermetabolic/hyperthermic responses appears to be different from that of the anorexigenic ones.

2. Chronic leptin administration

2.1. Effects of central leptin infusion on BW and body composition indicators

The 7-day leptin infusion suppressed BW in the two youngest and the oldest NF age-groups, while the smaller weight loss of the NF12 and NF18 rats did not reach statistical significance. Regarding body composition indicators following leptin infusion, muscle mass failed to change significantly in any group. Both fat pads were found to be significantly reduced in the two youngest NF age-groups, corresponding to changes in BW. While leptin failed to reduce fat pads in the late middle-aged NF12 and in aging NF18 animals, in the old NF24 rats leptin decreased the retroperitoneal fat by more than 50 %.

Groups of altered nutritional states failed to lose BW during the leptin infusion as compared with their PFS-treated controls with the exception of CR24. Leptin-induced loss of fat mass was significant in HF6 but not in HF18. Although in CR groups, fat pads practically disappeared upon leptin administration, statistical tests failed to show significance due to the very low fat content of PFS-treated CR rats. No infusion-induced change in muscle mass was observed.

2.2. Effects of central leptin infusion on FI

The ICV leptin infusion suppressed the daily FI values of NF rats throughout the infusion. The reduction of the 7-day cumulative energy intake (in kJ, from day 1 to day 7) was found to be significant in all age-groups. This suppression (the difference between the values of corresponding control and leptin-treated groups expressed as percentage of the control energy intake) was similar (though kept decreasing gradually) in the three youngest age-groups (NF3: 54.4 %, NF6: 43.6 %, NF12: 39.5 %), became weak in NF18 (19.0 %), but returned again to a higher value in old NF24 rats (38.8 %). Two-way repeated-measures

ANOVA revealed an effect of age on leptin-induced anorexia with a significantly weaker responsiveness in NF18 rats. Their values differed from all other NF age-groups.

High-fat diet-induced obesity diminished the leptin-induced anorexia in HF6 (36.8 % vs. 43.6 % in NF6) and abolished it completely in HF18 (8.7 % vs. 19.0 % in NF18).

In contrast, in CR animals the age-dependence was different: no leptin-induced anorexia was found in the 6- and 12-month-old rats (these hungry animals consumed practically all the provided food), but the suppression of cumulative FI became significant in CR24 (42.2 %) exceeding even the corresponding NF24 value (38.8 %).

2.3. Effects of central leptin infusion on HR

Basic HR (indirectly indicating changes of MR) gradually declined with aging in NF rats. During the leptin infusion the mean daytime HR values (inactive period, nadir of the circadian rhythm) rose significantly in the three youngest NF age-groups (with significant differences from day 1 to day 6). Regarding the mean nighttime HR data (active period, maxima of the circadian rhythm), in NF3 a moderate transient rise (from the day 3 to day 6), in NF12 a more sustained elevation (from day 1 to day 6) was observed. Mean HR values did not change in the two oldest NF18 or NF24 animals.

High-fat diet-induced obesity tended to increase the basal HR values. Obesity decreased leptin-induced daytime tachycardia in HF6 to a more moderate level, and abolished it completely in HF18.

In contrast, calorie-restriction tended to decrease the basal HR values. A pronounced HR-rise seen in CR6 rats (day and night, exceeding those seen in NF6) was attenuated in middle-aged CR12 (moderate rise in day- and nighttime values) and became pronounced again for daytime values in old CR24 animals.

2.4. Effects of central leptin infusion on Tc

In NF3 rats, ICV leptin infusion was accompanied by an elevation of both mean daytime and nighttime body temperatures. In NF6 animals only the daytime (resting) body temperature rose significantly from day 1 to day 6. This hyperthermia was less pronounced and of shorter duration in NF12 and NF18 rats, and was completely missing in the oldest group.

High-fat diet-induced obesity abolished leptin-induced hyperthermia in both HF groups.

Calorie-restriction enhanced leptin-induced day- and nighttime hyperthermia in comparison with those of their NF counterparts.

2.5. Effects of central leptin infusion on spontaneous ACT

Leptin-induced hyperthermia can not be explained by enhanced ACT, considering that daytime or nighttime ACT failed to show a significant rise during the infusion in any group.

3. Age-related alterations in gene expressions of Ob-Rb and SOCS3 in the ARC

Our study qRT-PCR measurements revealed that in the ARC of different NF age-groups, Ob-Rb expression was maximal in young adult rats and declined severely by the age of 12 months, to rise again somewhat in the aging and old animals. Thus, NF12 rats have the lowest value that is significantly different from all other NF groups. Our findings suggest that Ob-Rb expression in the ARC show non-linear changes with aging, similar to those seen in case of acute central anorexigenic leptin effects.

Regarding inhibitory SOCS3 gene expression in the ARC, it was highest in NF18 and NF6 followed by NF24, while it remained low in NF3 and NF12. Significant differences were found between NF18 versus NF3, NF12 and NF24 and also between NF6 and NF12. These findings may contribute to the explanation of a weak anorexigenic responsiveness to leptin in NF6 and NF18, despite their relatively high Ob-Rb expression. In addition, the relatively lower SOCS3 expression of NF24 might help explain the significant anorexigenic responsiveness to leptin in old NF rats.

DISCUSSION

1. Variations of resistance to the anorexigenic effect of acute central leptin injection

Regarding anorexigenic responsiveness to leptin, we found that aging does not cause a continuous progressive decline in the efficacy of the protein. Instead, characteristic age-related shifts were demonstrated: significant leptin-induced reduction in re-feeding was recorded in the normally fed young adult (NF3) group, while the anorexigenic response failed to reach a significant level in younger or older middle-aged (NF6 or NF12) and also in aging (NF18) rats. This response became significant again in old (NF24) animals. Age-related changes in the gene expression of Ob-Rb (high in NF3, NF6, very low in NF12 and moderately increased in NF18 and NF24) and that of inhibitory SOCS3 (high in NF6 and NF18 followed by NF24 and low in NF3 and NF12) in the ARC may provide some indications for this phenomenon. Results concerning gene expression contribute to the explanation of the low responsiveness of NF18 (diminished Ob-Rb and high SOCS3) and to some extent to that of NF12 (very low Ob-Rb and low SOCS3). Our findings cannot fully explain the relatively higher anorexigenic responsiveness of NF24, since diminished Ob-Rb expression appears to be coupled with an intermediate level of SOCS3 expression.

The above demonstrated age-related shifts in acute central anorexigenic leptin responsiveness may contribute to the explanation of middle-aged obesity and provide some indications of the background of aging anorexia observed in humans and other mammals (Scarpace et al., 2000b; Morley, 2001).

In our study, high-fat diet-induced obesity appeared to accelerate the development of the above described age-related regulatory alterations resulting in a significant leptin-induced anorexia in older middle-aged fat rats. Our present findings appear to be contradictory to those observations that describe a strong correlation between obesity and leptin resistance

(Lin et al., 2000; Myers et al., 2012). However, similar age-related pattern of anorexigenic effects and similar obesity-induced acceleration of these age-related regulatory alterations were described in case of peripherally administered CCK (Balaskó et al., 2013), as well. In addition, adaptive reduction in hypothalamic NPY expression in prolonged (5-month) high-fat diet-induced obesity described by previous reports (Stricker-Krongrad et al. 1998; Beck, 2006) may also contribute to the explanation of the enhanced anorexigenic responsiveness to centrally administered leptin in our HF12 rats.

This enhanced responsiveness to centrally applied leptin in chronically obese middle-aged animals may be, at least in part, explained by a possible hypothalamic leptin receptor upregulation. This, as yet hypothesized, may be a result of the long-term suppression of leptin transport from the periphery to the brain via the blood-brain barrier (Banks et al., 1996).

2. Variations of resistance to the hypermetabolic/hyperthermic effect of acute central leptin injection

With regard to the hypermetabolic effects, leptin injection induced significant increase in MR accompanied by a simultaneous tail vasoconstriction leading to strong hyperthermia in young adult animals (NF3). This response appears to be coordinated from a thermoregulatory point of view, leptin-induced hyperthermia resembles experimental endotoxin fever or CCK-induced hyperthermia (Székely and Szelényi, 1979; Balaskó et al., 2013). The coordinated feature of leptin-induced hyperthermia supports the potential role of leptin in thermoregulation (Steiner and Romanovsky, 2007).

Hypermetabolic/hyperthermic actions declined with aging, whereas anorexigenic actions are diminished by middle age and become relatively stronger by old age. Thus, acute central hypermetabolic/hyperthermic and anorexigenic actions of leptin show disparate age-related patterns. The possibility of different hypothalamic regions regulating different components of the leptin response has also been raised (Correia et al., 2002). Moreover, recently different signal transduction pathways of the anorexigenic versus hypermetabolic leptin actions in the neurons (Zhou and Rui, 2013) were identified that may also contribute to the explanation of these disparate age-related patterns.

Due to the multifaceted endocrine effects of leptin, the mechanisms behind this phenomenon may also involve other central and peripheral hormonal changes. During fasting or long-term food deprivation (such as hypothalamic amenorrhoea), low leptin level has been associated with suppressed peripheral thyroid and sex hormone levels, which recover upon leptin supplementation (Welt et al., 2004; Park and Ahima, 2015). As the levels of these hormones, with well-documented hypermetabolic effects, decline during aging, their diminished release upon central leptin administration may also help explain the lower hypermetabolic responsiveness in older age-groups.

3. Variations of resistance to the anorexigenic effect of chronic central leptin infusion

All NF groups maintained significant responsiveness to the anorexigenic effects of leptin throughout the 7-day infusion. Regarding age-related alterations, this effect of leptin was strong in NF3, NF6 and NF12 rats, it was attenuated by the age of 18 months, to become

more pronounced again in the oldest group. It appears, that the anorexigenic action of leptin varies with age in a non-linear fashion. A similar age-related pattern has been demonstrated for central melanocortins, and also for the anorexigenic effect of peripheral catabolic mediator CCK (Balaskó et al., 2013).

Leptin effects on BW gradually declined in older animals (falling just below statistical significance in NF12) indicating age-related leptin resistance. No reduction in BW of the aging NF18 animals was seen, while the oldest NF24 age-group regained the responsiveness to leptin suggested by their weight loss.

Regarding the effects of diet-induced obesity, HF6 rats failed to lose weight in response to the leptin infusion in contrast to the NF6 rats. This functional leptin resistance was further aggravated in older (HF18) obese rats that failed to show any leptin-induced anorexia, weight or fat loss. These results also underline the important contribution of aging to leptin resistance.

Life-long calorie-restriction in 6- or 12-month old age-groups appeared to completely prevent the anorexigenic effect. Additionally, leptin did not induce any fall in BW in CR6 or CR12 rats, possibly suggesting leptin resistance affecting anorexigenic actions already in middle-aged animals. However, chronic calorie-restriction may induce such an extreme orexigenic tone due to upregulation of orexigenic NPY and AgRP, and simultaneous downregulation of POMC, CART and CRH gene expressions of the hypothalamus (McShane et al., 1999; Chiba et al., 2009) that even a high-dose leptin infusion cannot overcome it (Soós et al., 2010).

Moreover, in the oldest CR24 group (following life-long calorie-restriction), leptin suppressed energy intake significantly that led to significant weight loss slightly exceeding that of NF24 animals. These results appear to support earlier observations (Fernández-Galaz et al., 2002) of maintained anorexic leptin effects in old CR animals.

4. Variations of resistance to the hypermetabolic/hyperthermic effect of chronic central leptin infusion

Unlike basal Tc data, basal HR values of NF rats gradually declined with aging. During the course of the leptin infusion the HR and Tc values rose in the younger NF age-groups, whereas in the oldest rats the leptin-induced tachycardia or hyperthermia failed to develop. These findings may suggest the development of leptin resistance in the course of aging and/or it may be explained by the diminished sympathetic activity and molecular pathways of thermogenesis (Scarpace et al., 2000a; Eikelis et al., 2003).

In diet-induced obese rats the hypermetabolic/hyperthermic leptin effects were strongly attenuated. Only daytime HR values showed a moderate increase in the young obese animals that disappeared altogether in the older obese rats.

In CR animals the hypermetabolic/hyperthermic effects were very pronounced as compared with their age-matched NF counterparts. This extreme hypermetabolic response was maintained even in the CR24 group in which the thermogenic capacity would otherwise be expected to be limited due to their old age (Horan et al., 1988), in accordance with their low basal HR values (and sympathetic activity).

5. Age- and nutritional state-associated changes in the catabolic effects of a chronic central leptin infusion

In the present studies different components of the catabolic leptin effects showed non-parallel changes with aging: the non-linear age-related alterations in the anorexigenic leptin actions were coupled by age-dependent decline in the hypermetabolic/hyperthermic leptin effects across the NF age-groups. Another example of disparate age-related alterations on catabolic peptidergic regulation has been provided by the central melanocortin system (Pétervári et al., 2011). Moreover, dissociation of the anorexigenic and thermogenic effects of leptin has already been described in a different experimental model. In our study the overall catabolic effect of leptin caused weight loss in the two younger NF groups and moderately in the oldest one, but not in NF12 and NF18 animals.

Obesity diminishes catabolic leptin responsiveness via suppression of hypermetabolic responses, while allowing maintenance of some anorexigenic effects in HF6 rats. In older HF18 animals even the anorexigenic effects were completely abolished. In addition, the present study indicates that the diet-induced obesity affects hypermetabolic actions prior to the anorexigenic ones.

The partial leptin resistance of younger CR rats and the reinforced full-scale responsiveness of the old ones suggest that aging *per se* does not have an exclusive and aggravating role in the development of leptin resistance. These findings also underline the potential importance of CR in the prevention or reversal of leptin resistance in animals (Wilsey and Scarpace, 2004).

It may be concluded that different nutritional states – whether obesity or calorie-restriction – influence predominantly the hypermetabolic mechanisms.

Experimental data presented here seem to shed some light on the progressive feature of obesity and leptin resistance: the early appearance of obesity leads to the gradual loss of hypermetabolic effects that in turn decreases protective mechanisms against further weight gain and leads to progressive fat accumulation. Furthermore, aging aggravates this obesity-induced leptin resistance by abolishing even the anorexigenic effects, producing a self-perpetuating process. Life-long calorie-restriction prevents deterioration of hypermetabolic leptin-effects in animals. However, these experimental findings have restricted significance with regard to nutritional treatments in humans, as therapeutic dietary restrictions are usually temporary.

Surprisingly, the oldest CR rats exhibit full-scale leptin-responsiveness including very pronounced anorexigenic and hypermetabolic effects. In addition, in NF rats following a gradual decrease in leptin responsiveness up to age 18 months, the leptin-induced anorexia and weight loss become pronounced again in the oldest age group. Incidentally, such old rats start losing muscle. Thus, apart from the decreased catabolic leptin effects promoting middle-age obesity, our data has some implication for the contribution of leptin responsiveness also in the later development of aging anorexia and sarcopenia.

SUMMARY

1. Central acute hypermetabolic/hyperthermic leptin effects are coordinated from a thermoregulatory point of view (increased heat production is accompanied by suppressed heat loss), i.e. they resemble fever-like hyperthermia.

2. Central anorexigenic and hypermetabolic leptin effects (acute and chronic) show disparate age-dependent changes: anorexigenic actions become diminished in middle age and increase again in old age, while hypermetabolic/hyperthermic actions decline with aging.

3. Aging *per se* does not have an exclusive and aggravating role in the development of leptin resistance regarding anorexia. Age-related changes in the central catabolic effects of leptin may contribute to the explanation of middle-aged obesity and aging anorexia.

4. Obesity suppresses hypermetabolic/hyperthermic leptin effects in all age-groups. However, central anorexigenic leptin responsiveness remains maintained in middle-aged groups**.**

5. Life-long calorie-restriction enhances hypermetabolic/hyperthermic central leptin-effects in all age-groups and enhances central anorexigenic effects in old rats.

6. Different nutritional states – whether obesity or calorie-restriction – influence predominantly the hypermetabolic/hyperthermic central leptin effects.

PERSPECTIVES

Our findings concerning central anorexigenic leptin effects in middle-aged obese rats may support the possibility of efficient central (intranasal) leptin treatment of obesity of long standing. In addition, some leptin release of the human brain has also been demonstrated (Wiesner et al., 1999; Li et al., 2001), although the extent of it appears to be rather small, and specific sites have not been identified (Wiesner et al., 1999). Moreover, obesity appeared to enhance this leptin release (Eikelis et al., 2007) instead of suppressing it. As central leptin receptor expression was also shown to remain unimpaired in obese subjects (Eikelis et al., 2007), potential activation of leptin production of the central nervous system may also offer future therapeutic choices in age-related obesity.

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LIST OF PUBLICATIONS

1. Peer-reviewed articles related to this thesis

1. Pétervári E, **Rostás I**, Soós S, Tenk J, Mikó A, Füredi N, Székely M, Balaskó M. (2014) Age versus nutritional state in the development of central leptin resistance. Peptides, 56C: 59–67.
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2. **Rostás I**, Tenk J, Mikó A, Füredi N, Soós S, Solymár M, Lengyel A, Székely M, Gaszner B, Feller D, Pétervári E, Balaskó M. (2016) Age-related changes in acute central leptin effects on energy balance are promoted by obesity. Exp Gerontol, 85: 118–127.
   IF: 3.340

2. Peer-reviewed articles unrelated to this thesis

1. Balaskó M, **Rostás I**, Füredi N, Mikó A, Tenk J, Cséplő P, Koncsecskó-Gáspár M, Soós S, Székely M, Pétervári E. (2013) Age and nutritional state influence the effects of cholecystokinin on energy balance. Exp Gerontol, 48(11): 1180–1188.
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3. Conference presentations related to this thesis

1. **Ildikó Rostás**, Péter Novinszky, Judit Tenk, Szilvia Soós, Miklós Székely, Erika Pétervári, Márta Balaskó. Central catabolic effects of leptin during the course of aging. IBRO Workshop, Debrecen, January 16-17, 2014.
2. **Rostás Ildikó**, Rimai Tamás. Centrális energetikai leptin hatások életkor-függő eltérései. XIX. Korányi Frigyes Tudományos Fórum, Budapest, March 6-7, 2014.
3. **Ildikó Rostás**, Tamás Rimai, Eszter Varga, Judit Tenk, Szilvia Soós, Miklós Székely, Erika Pétervári, Márta Balaskó. Age- and nutritional state-related catabolic effects of a central leptin infusion. Joint Meeting of the Federation of European Physiological Societies (FEPS) and the Hungarian Physiological Society, Budapest, August 27-30, 2014.
   Acta Physiologica Hungarica (2014) 211(S697): 130.
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4. **Ildikó Rostás**, Eszter Varga, Tamás Rimai, Judit Tenk, Szilvia Soós, Erika Pétervári, Márta Balaskó. Catabolic effects of central leptin infusion during aging. 9th Young European Scientist Meeting, Porto, Portugal, September 18-21, 2014.
5. **Ildikó Rostás**, Rebeka Pagáts, Péter Klespitz, Judit Tenk, Márta Balaskó. Leptin in age-related metabolyc dysregulation. Third International Symposium on Hypertension, Osijek, Croatia, November 28-30, 2014.
6. **Ildikó Rostás**, Zsófia Csernela, Judit Tenk, Szilvia Soós, Erika Pétervári, Miklós Székely, Márta Balaskó. Leptin in metabolic dysregulation: the influence of age and nutritional state. 5th Central European Congress on Obesity, Budapest, October 1-3, 2015.
7. **Rostás Ildikó**, Szakács Zsolt, Serényi Dóra, Soós Szilvia, Pétervári Erika, Balaskó Márta. Az akut centrális leptin injekció életkor- és elhízás-függő energetikai hatásai. FAMÉ Tudományos Konferencia, Pécs, June 1-4, 2016.
8. Márta Balaskó, Péter Nagy, **Ildikó Rostás**, Judit Tenk, Szilvia Soós, Miklós Székely, Erika Pétervári. Age-related central leptin-reistance in different nutritional states. IBRO Workshop, Debrecen, January 16-17, 2014.
9. Rimai Tamás, **Rostás Ildikó**. A leptin centrális katabolikus hatásainak korfüggő eltérései. VI. Nemzetközi és XII. Országos Interdiszciplináris Grastyán Konferencia, Pécs, March 18-20, 2014.
10. Márta Balaskó, Zsófia Csernela, Melanie Ehlers, **Ildikó Rostás**, Judit Tenk. Leptin in age-related metabolic dysregulation: the influence of nutritional states. Third International Symposium on Hypertension, Osijek, Croatia, November 28-30, 2014.
11. Márta Balaskó, **Ildikó Rostás**, Alexandra Mikó, Nóra Füredi, Judit Tenk, Szilvia Soós, Miklós Székely, Erika Pétervári. Age-related shifts in the acute anorexic effects of leptin: the influence of body composition. 15th Biannual Conference of the Hungarian Neuroscience Society (MITT), Budapest, January 22-23, 2015.
12. Pétervári Erika, Mikó Alexandra, **Rostás Ildikó**. Centrális anorexigén leptin hatások korfüggő változásai: a testösszetétel szerepe. Magyar Gerontológiai és Geriátriai Társaság XXXVIII. Kongresszusa, Gyula, May 28-29, 2015.
13. Erika Pétervári, **Ildikó Rostás**, Nóra Füredi, Margit Gáspár-Koncsecskó, Szilvia Soós, Miklós Székely, Márta Balaskó. Age-related shifts in the responsiveness to centrally applied leptin.

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Experimental Gerontology (2015) 68: 101.
IF: 3.485

4. Conference presentations unrelated to this thesis

1. **Ildikó Rostás**, Veronika Sipos, Szilvia Soós, Miklós Székely, Márta Balaskó. The thermoregulatory effects of alpha-melanocyte stimulating hormone and its antagonist HS024. IBRO International Workshop, Pécs, January 21-23, 2010.
2. **Rostás Ildikó**, Sipos Veronika, Barcza Zsófia. Az alpha-melanocyta stimuláló hormon és az antagonista HS024 hatása a hőszabályozásra. XVI. Nemzetközi Marosvásárelyi TDK konferencia, Marosvásárhely, Romania, March 18-21, 2010.
3. **Rostás Ildikó**. A melanocortin rendszer hőszabályozási hatásai. PTE ÁOK Házi TDK Konferencia, Pécs, April 15-17, 2010.
4. **Rostás Ildikó**, Szabad Árpád Olivér. Az alpha-melanocyta stimuláló hormon hőszabályozási hatásai. XV. Korányi Frigyes Tudományos Fórum, Budapest, April 29-30, 2010.
5. **Rostás Ildikó**, Szabad Árpád Olivér, Sipos Veronika, Andreas Thomas Schmidt, Barcza Zsófia, Tore Schjottelvik. Az alpha-melanocyta stimuláló hormon hatása a hőszabályozásra. HMAA balatonfüredi diákkonferencia, Balatonfüred, August 20-21, 2010.
6. **Rostás Ildikó**, Szabad Árpád Olivér, Sipos Veronika. Az alpha-melanocyta stimuláló hormon hőszabályozási hatásainak vizsgálata patkányokon. IV. Intézményi Tudományos Grastyán konferencia, Pécs, December 2-3, 2010.
7. **Rostás Ildikó**, Sipos Veronika, Szabad Árpád Olivér. Életkorfüggő eltérések az alpha-melanocyta-stimuláló-hormon hőszabályozási hatásaiban. Nemzetközi Marosvásárelyi TDK konferencia, Marosvásárhely, Romania, March 17-20, 2011.
8. **Rostás Ildikó**, Szabad Árpád Olivér. Akut centális α-MSH injekció hőszabályozási hatásai az életkor függvényében. XVI. Korányi Frigyes Tudományos Fórum, Budapest, April 14-15, 2011.
9. **Rostás Ildikó**, Sipos Veronika, Soós Szilvia, Balaskó Márta, Pétervári Erika, Székely Miklós. Age-related alterations in the thermoregulatory effects of alpha-melanocyte-stimulating hormone. FAMÉ Tudományos Konferencia, Pécs, June 8-11, 2011.
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10. **Ildikó Rostás**, Árpád Olivér Szabad, Veronika Sipos. Aging modifies the thermoregulatory effects of alpha-melanocyte-stimulating hormone. HMAA balatonfüredi diákkonferencia, Balatonfüred, August 19-20, 2011.
11. **Ildikó Rostás**, Nóra Füredi, Judit Tenk, Alexandra Mikó. Thermoregulatory effects of alpha-melanocyte-stimulating hormone depend on age. János Szentágothai Memorial Conference & Student Competition, Pécs, October 29-30, 2012.
12. **Ildikó Rostás**, Alexandra Mikó, Nóra Füredi, Judit Tenk. Complex effects of neuropeptide alpha-melanocyte stimulating hormone on energy homeostasis during the course of aging. Leiden International Medical Student Conference, Leiden, The Netherlands, March 13-17, 2013.
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