INTRODUCTION, AIMS

Energy balance of the body means a balanced regulation of energy quantities present in different forms (stored and mobilizable calorie-containing nutrients, heat-calories) in the body. This necessitates adequate intake and utilization (physical exercise, heat, etc.) of nutrients. Besides, removal of the heat originating from this energy is also indispensable. Accordingly, energy balance is a dynamic state. This balance is realized partly by the regulation of food intake, metabolism and body weight, partly by the regulation of body temperature. The normal function of this system requires resilient adaptation to continuously changing exogenous/endogenous environment. Disorders of energy balance may be manifested in abnormalities of body weight/composition (e.g. obesity, cachexia) or in abnormalities of body temperature.

The *short-term* regulation of energy balance refers to the relationship between metabolic rate (heat production) and heat loss, the main factors of thermoregulation. Active changes of this type of regulation may result in regulated shifts in body temperature (fever, anapyrexia). Regulatory imbalance due to insufficient compensatory mechanisms can cause passive hyper- or hypothermia.

The *long-term* regulation refers to the nutritional status of the body, various stores of metabolizable substrates, making up for a decisive part of body weight, and their regulation is based on a balance between food intake and metabolic rate. They may change according to two co-ordinated regulatory patterns. A positive long-term imbalance (large food intake /"orexis"/ with low metabolic rate) is regarded *anabolic*, in contrast to the *catabolic* type negative imbalance (decreased food intake /"anorexia"/ with high metabolic rate). The long-term (tonic) regulation is manifested via repeated episodic (acute) changes in feeding, which can initiate or stop food intake through hunger and satiety. The short-term (episodic) regulation of food intake does not depend exclusively on the *nutritional status*, but it is influenced by *feeding state* as well (both hunger and satiety can develop irrespective of an eventual obesity or cachexia).

Metabolic rate/heat production is regarded fundamental in the determination of both regulated factors, i.e. the body weight and the body temperature. On the one hand, metabolic rate should be adjusted to the general nutritional and actual feeding status in order to maintain the normal body weight regulation, on the other hand, it should counterbalance the heat loss in order to defend normothermia. These regulatory forms are interrelated: on the one hand, changes of either the feeding or the nutritional state may influence the thermoregulatory

status, on the other hand, thermal signals, primary alterations of temperature regulation also modify consumption behavior. It may be assumed that afferent signals of both body weight/feeding state and body temperature (e.g. gastric distension, circulating levels of nutrients, or peripheral/central thermosensors) reaching the central regulatory systems via neural or humoral pathways, may involve similar or identical central mediator factors, while they initiate their effector actions (e.g. an increase in heat production/body temperature, orexia, anorexia, etc.) irrespective of the origin of the afferent signals. Different afferentations may act to enhance or inhibit each other initiaing competitions between homeostatic regulatory processes.

The aim of our present studies was to analyze the role of various peripheral afferent and central factors involved in changes of energy homeostasis while focusing on special situations that require adaptive mechanisms. These states investigated in our experiments were the following: complex adaptive regulatory mechanisms in acute feeding status (**fasting or postprandial state**), in altered ambient temperatures (chronic cold-exposure, **cold-adaptation**), in case of excessive endogenous heat-production (primary hypermetabolism due to **hyperthyroidism**). In our animal models the complex role of vagal afferents (especially the capsaicin-sensitive fibers) was examined, and the function of chemo- mechano- and thermosensitive peripheral elements and neuropeptide mediators – as with special regard to neuropeptide Y (NPY), orexin-A and cholecystokinin (CCK) – was studied.

MATERIALS AND METHODS

Animals, thermal adaptation

Wistar rats of 220-260 g body weight were used. The rats had standard laboratory chow and water supply *ad libitum.* They were kept at a temperature of 20-26°C (non-adapted group, NA), or in a cold room of 3-5°C (cold-adapted group, CA), with a 12/12-h light-dark cycle. Cold-adapted stage developed after 3 weeks in the cold, before that time the earlier phases of the adaptation process were investigated.

Surgeries

Operations were performed under intraperitoneal (i.p.) ketamine + xylazine [Calypsol (Richter) + Rometar (Spofa)] anesthesia (78 + 13 mg/kg, respectively). For the purpose of intracerebroventricular (i.c.v.) injections or infusions, stainless-steel guide cannula was implanted into the right lateral cerebral ventricle. Before experiments an injection cannula

connected with pp10 polythene tube (Portex) was attached to the guide cannula. The rats, placed into a metabolic chamber, were injected the required substances in a volume of 5 μl through the extension of the cannula (in order to avoid acute disturbance of the animals). For chronic (7-day-long) infusions an injection cannula was connected by a polythene tube to an Alzet osmotic minipump implanted underneath the dorsal skin.

Prior to the postprandial tests a pp10 jugular (i.v.) or pp30 polythene chronic gastric cannula was preimplanted. On test-days, substances were injected/infused through the extension of the tube pulled from the metabolic chamber, without disturbance of the unanesthesized rat.

For subcutaneous (s.c.) or i.p. injections cannulae were acutely inserted and fixed (carried out under aether anaesthesia).

Measurement of metabolic rate and body temperature

In acute tests, the unanesthesized rats having been previously habituated to a semi-restrained state were placed into an open-circuit metabolic chamber. The standard temperature inside the chamber was secured by a thermostatically controlled waterbath. A Kipp-Noyons diaferometer was used for CO_2 analysis of samples from the metabolic chamber, indicating metabolic rate (MR). Along with MR, copper-constantan thermocouples (introduced into the colon or placed on the skin surface of the tail) served for continuous temperature measurement of the core (T_c) and the tail skin (T_s), the latter indicating the heat loss.

In chronic tests, i.p. preimplanted radiotelemetric transmitters (Minimitter-VMFH, series 4000, Sunriver, OR) allowed continuous measurements of core temperature and general activity in freely moving animals, both were recorded by a computer system (VitalView software).

Capsaicin pretreatments

In order to investigate the abdominal capsaicin-sensitive afferent fibers of the vagus nerve, capsaicin pretreatments were performed. Application of small capsaicin doses was followed by local desensitization of abdominal afferent fibers, without systemic desensitization (Székely and Romanovsky, 1997). *Intraperitoneal capsaicin* (5 mg/kg, in two fractions) caused damage mainly to the chemo- and mechano-sensitive abdominal afferents. *Perineural capsaicin* pretreatment induced selective desensitization of vagal afferents, without affecting efferent fibers, non-vagal afferents, or some other target points (before the vagal afferent receptors) of i.p. capsaicin treatment in the liver. In anesthesized rats a 3-4-mm

wide strip of cotton wool was introduced closely below the diaphragm to surround the anterior and posterior trunks of the abdominal vagus, proximal to the early-dividing hepatic branches. The cotton wool was isolated from the surrounding tissues by a small sheet of polythene, then wetted with a freshly prepared 1% solution of capsaicin. This wrapping had been kept in place for 20 min, before it was removed carefully.

Cold exposure

In order to analyze thermoregulatory responsiveness, acute cold exposure was performed for 60 min. The temperature of the waterbath of the metabolic chamber was suddenly cooled to 5^{o}C by adding ice to it, then water temperature was re-warmed by added hot water.

Fasting and re-feeding, measurement of food intake and body weight

To induce fasting state, food (but not water) was removed. Food deprivation lasted for 48-h or 24-h in CA and for 120-h or 48-h in NA rats to reach comparable weight loss (thyroxine treated animals and their controls were fasted only for a period of 24 h). Fasted animals were placed into a metabolic chamber to measure their metabolic state (resting MR and Tc) and thermoregulatory responsiveness to acute cold exposure or to administration of different substances. After offering the chow, body weight changes were followed every 30 min (for an indirect assessment of the dynamics of food intake) and cumulative chow consumption was measured during the 3-h re-feeding period in freely moving animals. In some cases, food intake and body weight changes were also measured in the following 21-h (to calculate the cumulative changes for 24 h). Similar methods were used for investigation of feeding behavior in other experiments (e.g. following i.c.v. administration of NPY or orexines).

In some cases of re-feeding, the rats were offered calorie-free, saccharine-sweetened $CaCO_3$ pellets, consumption of which caused gastric distension. In other series of experiments either 2.5 ml of 20 % fat emulsion (Intralipid, Pharmacia) or 4 ml of 40 % glucose (Pannonpharm) was infused i.v. within 150 min for parenteral calorie replacement without affecting gastric volume, but providing nutrients. In still other cases— in order to avoid afferent oro-pharyngeal stimuli —either a calorie-rich thick suspension of nutrients („fast weight gain" formula of body builders) or a calorie-free one (high-density X-ray contrast material $BaSO_4$) was injected through a preimplanted gastric tube in a volume of 3 ml/100 g body weight.

Thyroxine treatment

For a model of hyperthyroidism, the spontaneous daily food intake and weight gain rate were studied during a chronic thyroxine treatment (s.c. injections of D-L thyroxine to NA rats for 28 days in a dose of 50, 100 or 200 μg/day), together with the analysis of changes in resting metabolic rate and body temperature, as well as thermoregulatory and feeding responses to different stimuli.

Substances applied

Capsaicin (Sigma; 2+3 mg/kg i.p. or perineural treatment with 1% solution of capsaicin); Prostaglandin E_1 (PGE_1; Sigma; 100 ng i.c.v. injection); CCK-A antagonist devazepide (ML Laboratories, London; 100 μg/kg i.p. injection 30-min before gastric injection); CCK-B antagonist L-365,260 (MSD Research Laboratories, USA; 100 ng i.c.v. injection 10-min before gastric injection); NPY (Bachem; 2-10 μg i.c.v. injection or 1 μg/μl/h infusion); orexin-A and orexin-B (Bachem; 2-20 μg i.c.v. injection); NPY receptor-antagonist D-$Tyr^{27,36}$,D-Thr^{32}-NPY(27,36) (H-3328; Bachem; 10 μg i.c.v., 10 min before other treatment); functional (second messenger) NPY-antagonist D-myo-inositol-1,2,6-trisphosphate (α-trinositol; Perstorp, Sweden; 20 μg i.c.v., 10 min before other treatment); D-L-thyroxine (Reanal; s.c. 50, 100 or 200 μg/day).

Statistical analysis

ANOVA with repeated measures, one-way ANOVA with Scheffe's, Bonferroni's or Tukey's *post-hoc* tests, or the one- or two-tailed Student's t-test were used for statistical analysis, as appropriate.

RESULTS AND DISCUSSION

Chapter 1.: Fasting and postprandial states: metabolic and thermoregulatory adaptation to the feeding status

Starvation, food intake (postprandial state) and the resulting changes in body weight initiate alterations in the energy homeostasis including metabolic and thermoregulatory adaptations. Adaptation to deficient calorie intake means a restricion of metabolic rate (MR) to its lowest possible level that might be accompanied by a moderate fall in core temperature (Tc) („vita parva"). Fasting hypometabolism and hypothermia do not necessarily imply

simply a lack of available substrates, they may also be a result of regulatory changes, in this sense the phenomenon can be regarded as an adaptive process.

In postprandial states adaptation to gastrointestinal distension and calorie excess is belived to help avoiding energy accumulation. For this purpose, as a first step, it is necessary to stop further food intake that is ensured by satiety and to burn some of the surplus calories carried out by postprandial hypermetabolism and hyperthermia. The simultaneous appearance of these two factors also involve central regulation. This phenomenon is not due to the specific dynamic action of nutrients, nor is it identical to the diet-induced thermogenesis (IUPS Thermal Physiology Commission: Glossary of terms for thermal physiology, 2003). The appearance of postprandial hypermetabolism can be partly explained by the process of food intake (chewing, motility, digestive processes), partly by stimuli originating from the gastrointestinal tract that increase energy metabolism. In its development stretch signals caused by the volume of the food, ingested (but hardly absorbed) nutrients and by the action of gastrointestinal hormones produced as a result of these two processes may play a role as afferent „satiety" signals.

Topic 1./A: Afferent factors in the changes of energy homeostasis following food deprivation and postprandial states

Question 1.: Is it directly the depletion or refilling of energy stores (loss or gain of body weight) or rather changes in central regulation due to gastrointestinal stimuli that is responsible for the development of fasting hypometabolism and hypothermia or postprandial hypermetabolism and hyperthermia?

Study design:

1., To demonstrate the hypothesized regulated feature of fasting hypometabolism and hypothermia we studied the responsiveness of starving animals to specific thermoregulatory stimuli (acute cold exposure) or to centrally administered PGE. Both stimuli induce specific co-ordinated thermoregulatory reaction with enhanced heat production and suppressed heat loss (Székely and Mercer, 1999).

Despite their tendency for hypothermia starving animals were capable of reversing the suppression of their resting MR, i.e. they could increase the MR and Tc in response to acute cold exposure or to i.c.v. PGE_1 injection. This can be especially well demonstrated in CA rats, whose normal daily metabolic rate is high, but whose MR and Tc are significantly suppressed by even a relatively short fasting (24 or 48 h). Upon cold exposure (transferring the rats from

their thermoneutrality, 25 ^{o}C to a cold environment, 5 ^{o}C) their characteristic „overshoot" metabolic increase and consequent paradox elevation of body temperature were observed. Despite even extreme fasting (72-h food deprivation with 25% weight loss) MR-values comparable to those of *ad libitum* fed controls were reached. These changes indicate that fasting-induced MR suppression is not caused by the lack of metabolic substrates.

2., We have analyzed the effect of the caloric content of food during re-feeding: following the re-feeding of starving laboratory animals by foods of various caloric contents (oral administration of standard laboratory chow or calorie-free $CaCO_3$, i.v. infusion of glucose solution or lipid emulsion) we observed changes in MR, Tc and body weight.

During a 3-h re-feeding MR and Tc of rats were practically fully normalized (without the complete normalization of body weight), even following the ingestion of calorie-free $CaCO_3$. Parenteral calorie intake of similarly deprived animals failed to normalize either MR or Tc in acute experiments. Therefore, the previously observed suppression may not have been caused by the low body weight or the deficient energy stores; for the reversal of the suppression not the calorie intake but rather the gastrointestinal (fast, neural) afferent stimuli could be responsible.

***Question 2.*:** The short-term regulation of food intake is mainly based on afferent information of gastrointestinal origin, especially on afferent function of the abdominal vagus (Smith, 1998); it is capable of influencing various complex adaptive processes of energy metabolism via its capsaicin-sensitive fibers. Neural signals are responsible for fast but short-term anabolic or catabolic effects: they may influence the regulation of Tc and food intake as well (Zafra et al., 2003). The glucose-sensitive fibers of the vagus may present satiety signals, but they can also activate sympathetic fibers reaching brown fat (Sakaguchi and Yamazaki, 1988). We intended to study, whether vagal afferents (especially capsaicin-sensitive fibers) have a role in metabolic and thermal responses accompanying changes in the feeding status.

Study design:

We analyzed changes of the characteristics of fasting and oral re-feeding adaptive processes (food intake, body weight, MR, Tc) in rats after local (i.p.) capsaicin-desensitisation.

During the course of 120-h fasting the rate of weight loss was significantly higher in desensitized animals than in intact ones indicating an insufficient MR suppression during starvation. (There may be a difference in daily metabolism and activity too.) The MR suppression compensating food deprivation may be explained by vagal capsaicin sensitive

suppression-inducing stimuli. When animal groups with similar initial fasting body weights were studied, desensitized animals ate more during the first 3 hours of re-feeding, their weight gain was faster than that of intact rats. Capsaicin desensitization therefore also diminish (vagal) satiety signals.

***Question 3.*:** Among the gastrointestinal hormones, CCK may play a role in the development of postprandial regulatory changes. Both peripherally and centrally administered CCK decreases food intake. Capsaicin-sensitive vagal afferents may play a role in the development of CCK-induced satiety (South and Ritter, 1988). Besides, CCK also has thermoregulatory effects: upon central application it elicits a regulatory rise of Tc via CCK-B (CCK2) receptor mediation, upon peripheral administration a CCK-A (CCK1) receptor associated hypothermia (presumably through direct vasomotor effect) develops (Szelényi, 2001), but via stimulation of the abdominal vagus central CCK effects may also contribute to the phenomenon.

Studying separately the effects of the preabsorptive (stretch) and postabsorptive (nutrient-derived) signals, we wanted to clarify the role of the capsaicin-sensitive vagal afferents or central CCK in the postprandial changes of MR and Tc.

Study design:

1., Since the participation of oropharyngeal afferents in the development of postprandial changes of energy metabolism can not be excluded, to avoid their effects, we injected calorie-free (stimulating only stretch receptors) and calorie rich (besides stretch the effects of nutrients also appear) suspension via a pre-implanted gastric cannula into the stomach of starving animals and then recorded their thermoregulatory effects. To study the correlation of these changes with ambient temperature, the tests were carried out in thermoneutral and cool environments and thermoregulatory analysis was made.

2., To clarify the role of neural afferent factors we administered similar suspensions to rats with prior capsaicin desensitization or perineural capsaicin pretreatment.

3., For the study of the possible role of CCK we repeated administration of intragastric suspensions following i.p. injection of CCK-A receptor antagonist devazepide or i.c.v. injection of CCK-B receptor antagonist, L-365,260.

Although the effect of the calorie free substance appeared after a 1-h delay in a thermoneutral environment, the application of both suspensions lead to a similar increases of the resting MR and Tc. In thermoneutral ambient temperature, hyperthermia was accompanied by a compensatory increase in heat loss. In cool environment this increase in

MR was masked by cold-induced MR rise. In NA rats the effects of the suspensions were smaller indicating that brown fat may have a role in the development of feeding state-dependent MR changes.

Intraperitoneal or vagal perineural capsaicin pretreatment prevented the development of postprandial hyperthermia induced by the intragastric injection of calorie free suspension, so stretch stimuli may have initiated afferent impulses via vagal capsaicin-sensitive fibers. The pretreatments failed to influence the effects of the calorie rich suspension indicating that the neural pathway for satiety signals is not exclusive.

Following the administration of either CCK receptor antagonist the calorie free suspension failed to induce hyperthermia, while the calorie rich substance remained effective in both cases. These data might indicate that besides stretching, peripheral CCK has an additive role in this phenomenon and central CCK acts as a mediator of the process.

Topic 1./B: The role of central mediators in changes of energy homeostasis following food deprivation and postprandial states

In the *central regulation* of food intake nowadays the role of neuropeptides appears to have primary importance (Leibowitz et al., 2004). The aim of our studies was to analyze the role and general effects of *NPY and orexins* on energy homeostasis.

The effects of central NPY on energy homeostasis

Neuropeptide Y is the strongest known orexigenic (food intake increasing) central mediator (Williams et al., 2001). It is produced mainly in the arcuate nucleus, the most important effects concerning energy homeostasis are seen after its release in the paraventricular, the perifornical, the ventromedial nuclei, or in the lateral hypothalamus. The level of NPY in the hypothalamus is elevated during starvation, while it is decreased following acute food intake (Sahu et al., 1988). Central infusion of NPY leads to hyperphagia and weight gain (Beck et al., 1992). Upon central administration of NPY metabolic rate is suppressed via mechanisms involving the ventromedial nuclei, brown fat function is also decreased and there is also a fall in body temperature. The latter effects can only be demonstrated in cool environments (at the presence of a higher than basal metabolic rate) but not at thermoneutrality (Bouali et al., 1995a). Therefore metabolic suppression seen during fasting may be related to the central (endogenic) effects of NPY. Some hours after a paraventricular NPY injection an elevation of MR and Tc was observed that with regard to the

enhanced food intake would not fit into a co-ordinated response pattern in energy homeostasis (Bouali et al., 1995b).

***Question 4.*:** Does NPY elicit a co-ordinated thermoregulatory response or would the NPY-induced changes in Tc appear to be rather passive compensatory in nature? The emergence of a special pattern in the changes of the heat production and heat losss mechanisms would indicate a co-ordinated response originating from the central nervous system, whereas the absence of central co-ordination suggests a passive compensatory feature or secondary role of thermoregulation as compared to that of other regulatory systems. How can we evaluate the role of NPY in energy homeostasis?

Study design:

1., We analyzed the feeding and metabolic/thermoregulatory responses to acute, subacute (i.c.v. injection) and chronic (infusion) of NPY in rats exposed to different ambient temperatures.

2., With the help of central injections of NPY antagonists (non-specific receptor antagonist H-3328, α-trinositol affecting post-receptorial mechanisms) we studied the endogenous activity of NPY in food-deprivation.

The i.c.v. administered (exogenic) NPY has similar anabolic effects to that of endogenic peptide produced during starvation: it induced food intake and an elevation in MR (in semi-restrained animals), indicating a co-ordinated response from the point of view of body weight regulation. Concerning thermoregulation, NPY did not cause a co-ordinated response: the decrease in MR was not accompanied by enhanced heat loss. The fall in Tc was only seen in cold environments, where it was possible to reduce the already high cold-stimulated MR (NA animals at 20 ^{o}C, CA rats at 15 ^{o}C showed a Tc drop exceeding 1 ^{o}C during the first hour following injection). At thermoneutrality, where MR is minimal, NPY failed to elicit such a response. As an indirect effect at both types of ambient temperatures, NPY injections were followed by a late (starting at 2-3 hours and still seen after 24 hours) elevation of Tc and simultaneous suppression in food intake.

The infusion of the peptide caused a temporary increase in food intake (and consequently in body weight) and a suppression of the circadian body temperature peaks (dark cycle values): it inhibited further rise of MR above the level of basal metabolic rate (that was the presumed level during the light cycle).

Antagonists of NPY significantly reduced not only the feeding and thermoregulatory effects of exogenic NPY, but also the hyperphagia following food deprivation.

Question 5.: Do capsaicin-sensitive vagal afferent signals influence NPY-induced food intake?

Study design:

Centrally applied NPY-induced food intake was also measured in capsaicin desensitised rats.

In capsaicin desensitized rats NPY elicited a food intake response of similar magnitude as in controls. The lack of significant differences between these groups in fasting-induced re-feeding may be explained by the fact that the high endogenous NPY level-induced feeding activity could not be influenced by peripheral capsaicin-sensitive vagal feedback signals (that may primarily suppress NPY release).

The effects of central orexin-A and B on energy homeostasis

Orexin-A and B belong to the orexigenic peptides of the lateral hypothalamic area. It has been observed that centrally injected orexin-A increases spontaneous food intake to a greater degree than orexin-B, and that during fasting the amount of prepro-orexin mRNA is elevated (Yamamoto et al., 2000). In contrast to NPY, a chronic i.c.v. infusion of orexin-A increases food intake only temporarily and does not lead to obesity (Yamanaka et al., 1999). Specific receptor antagonist of orexin can inhibit spontaneous nocturnal food intake, anti-orexin antibodies prevent fasting-induced re-feeding (Haynes et al., 2000). Orexin-A and NPY may have different biological roles: while orexin-A is considered to be important in food-seeking behavior (Sakurai, 2003), NPY enhances food intake in states with negative energy balance. There are a number of ovelaps between the effects of the two peptides: orexin-A-induced food intake can be attenuated by NPY antagonists (Yamanaka et al., 2000). The whole range of complex effects of orexins on energy homeostasis have not been fully clarifyed yet. Orexin-induced hypothermia has been described (Jászberényi et al., 2002) but i.c.v. administred orexin-A induced MR elevations in mice (Lubkin and Stricker-Krongrad, 1998). The latter together with the simultaneous hyperphagia would not fit a co-ordinated response pattern in the regulation of energy homeostasis.

Question 6.: How can we evaluate the effects of orexin-A and orexin-B on thermoregulation and energy homeostasis?

Study design:

1., The thermoregulatory effects of central injections of orexin-A or orexin-B were analyzed at different ambient temperatures and in different feeding states by careful

comparison of the time courses of effects on food intake, metabolic rate and thermoregulation induced by the two peptides. We tried to determine whether the orexins might have co-ordinated effects on energy homeostasis.

2., We tested whether the thermoregulatory effects of orexin-A may be influenced by an NPY-antagonist (non-specific NPY receptor-antagonist H-3328).

Following an orexin-A injection a co-ordinated anabolic reaction was observed, similar to that of NPY: dose-dependent hyperphagia with a simultaneous drop in MR with hypothermia in a cool environment. This hypothermia also proved to be passive, since no accompanying enhancement of heat loss was seen (the NPY receptor-antagonist also inhibited this phenomenon). As after NPY administration, some hours following the injection the orexin effect was reversed; hyperthermia developed. Starvation enhanced the effects of orexin, as if it made the animal more sensitive to the mediator. Following a central orexin-B injection a dose-dependent late hyperthermia was observed. In fact NPY seems to play a role in the effects of orexin-A on energy metabolism, orexin-B, on the other hand, does not appear to be important in the regulation of energy balance.

Chapter 2.: Adaptation to temperature and energy metabolism

Topic 2./A: Thermal adaptation and the regulation of energy metabolism: the role of peripheral thermal afferents and central mediators, mediators in cold-adaptation

The regulation of heat (energy) balance is based on the activity of thermal receptors. We studied therefore how the thermal afferent information from the peripheral (cold-sensitive) thermoreceptors or the thermal-adaptation can influence thermoregulatory reactions or feeding behavior.

Question 7.: In a cold environment despite the maximal activation of heat conserving mechanisms heat loss is significantly increased that may only be compensated by an increased heat production, the maintenance of which requires a higher caloric intake. The development of a new stable energy balance needs time. How and with what speed/dynamics do the parameters of energy balance change during the course of cold-adaptation?

Study design:

The dynamics of the changes in energy metabolism (actual and resting MR and Tc), food intake/body weight were followed during the course of cold-adaptation, while initial pre-adaptation values, those measured during the first, after the third week of adaptation (cold-adapted) and also after return to the thermoneutral environment were compared.

Food intake was already doubled on the first day of cold-exposure, although it reached steady-state (at approximately 2.5 times higher level) only after 4-7 days. The normal rate of body weight gain (characterizing rats kept at thermoneutrality) stopped temporarily but after approximately a week it continued at a rate comparable to that of NA controls. After return to thermoneutrality food intake dropped immediately to a value that exceeded control levels by 20-25%. Activation of the cold thermal receptors and partly a somewhat enhanced NPY activity may explain the very fast development of cold-induced elevation in food intake (McCarthy et al., 1993). Upon return to thermoneutral ambient temperature the activation of cold receptors stops, the persistent moderate spontaneous hyperphagia also indicates the cold-adaptation induced activation of some orexigenic system (e.g. NPY).

Telemetric measurements confirmed that cold-exposure was accompanied by an initial drop in Tc that lasted for some hours, but then it returned soon to normal pre-exposure values presumably based on MR elevation. In the cold, MR rises quickly to values 2.5-2.8 times of than those seen at thermoneutrality, and is maintained at this high level even after more than 3 weeks of cold-exposure. At the late adapted phase (but not sooner) the thermoneutral ambient temperature decreases from 30 ˚C to 25 ˚C, but MR measured in this environment is significantly higher than before cold-adaptation, resting Tc (and the whole circadian temperature rhythm in the cold) on the other hand is 0.4-0.6 ˚C lower than that recorded in NA controls, or values measured during the first week of the adaptation process. This is merely a moderate, although statistically significant temperature difference.

Question 8.: Among the changes involved during the course of the adaption process a special significance of the constant activation of the peripheral cold receptors is indicated by the fact that upon acute transfer from their thermoneutral zone to a cold environment CA rats respond with an “overshoot” reaction with excessive elevation of the MR leading to an immediate paradoxical rise in their Tc. Re-warming is followed by an also paradoxical drop in Tc. Internal cooling does not elicit such a response (Székely and Mercer, 1999). Besides an elevated metabolic tone (enhanced capacity of heat production in the tissues) and a higher sensitivity of the surface cold receptors (or even due to an increased tone based on these signals) the *central responsiveness* may also be enhanced in CA animals.

This presumed change in the sensitivity of the central regulation was analysed by the central administration of mediators to CA and NA rats.

Study design:

1., In CA and NA rats we compared the rises of Tc and MR induced by the same dose of PGE given i.c.v.

2., Since besides the importance of cold receptor-activation the possible role of enhanced NPY-activity in the development of cold-induced increase in food intake was also suggested, we observed the changes in central NPY-sensitivity to i.c.v. injections of NPY or its antagonists during the process of cold-adaptation by measuring feeding and thermoregulatory responses.

When measured at thermoneutrality, the same dose of PGE_1 injected i.c.v. elicited a significantly higher rise in MR and Tc in CA than in NA rats.

Following a central injection of 2 or 10 μg NPY, CA animals ate more than NA ones, at the same time NPY-antagonists inhibited NPY-hyperphagia more efficiently in CA than in NA rats. A slightly enhanced NPY-hyperphagia was already observed after 1 week of cold-exposure indicating that a cold environment may promote the efficacy of hunger signals. Full sensitization to NPY developed only after 4 weeks, the results no longer depended on the actual ambient temperature, at which the test was carried out (no difference was detected whether the feeding was conducted at 3-5 ^{o}C or at room temperature) but only on the phase of adaptation. This excludes any possible direct role of acute temperature signals in the development of NPY-induced hyperphagia.

The difference between CA and NA animals in the size of NPY-hypothermia is difficult to judge, because the MR and Tc-suppression can be detected only at lower than thermoneutral ambient temperatures (the colder the environment, the stronger the hypothermic effect): similar cold temperatures may mean different severities of cold stress in NA and CA rats. However, besides its orexigenic effects, NPY-induced hypothermia was also effectively inhibited by i.c.v. administration of the receptor-antagonist.

Question 9.: How do re-feeding and thermoregulatory responses after fasting change during the course of cold-adaptation?

Study design:

1., Feeding and thermal responses of fasting CA rats were analyzed. Thermoregulatory responsiveness was tested using acute cold-exposure and central PGE_1 injections.

2., To study the role of endogenic NPY activity we tested the inhibitory effects of i.c.v. injected NPY antagonists on re-feeding in CA rats.

The thermoregulatory responsiveness to acute cold-exposure or PGE was enhanced in fasting CA rats compared to NA ones. Following fasting – either of equal duration (24 hours),

or of equal severity (a 24-h food deprivation causes similar weight loss in the CA group as a 48-h fasting in NA animals) – the food intake of CA rats was larger and faster than that of NA animals, CA rats regained more of their lost body weight during the 3 hours of re-feeding. These observations indicate that in feeding behavior the feedback via satiety signals is diminished or that central orexigenic mechanisms become more effective. Such enhancement of re-feeding hyperphagia was observed only in fully adapted (at least 3 weeks) animals. Although spontaneous daily food intake was already elevated after a 1-week cold-exposure, the fasting-induced acute hyperphagic response did not increase indicating that endogenic orexigenic mechanisms were not (yet) activated, although the sensitization to NPY has already begun. These imply different mechanisms for cold vs. fasting-induced hyperphagia. Orexigenic factors involved in food deprivation start to be activated only in late phases of cold-adaptation, in earlier stages hyperphagia develops even without the increased activity of these starvation-associated signals. During the early stages of adaptation cold-signals are likely to be directly responsible for the spontaneously occurring hyperphagia, in later phases these effects may be somewhat further enhanced by the activation of the NPY system.

A merely additive/secondary role for the endogenic NPY-activity is also indicated by the fact that while NPY-antagonists prevented the exogenic NPY administration-induced hyperphagia in the CA group they failed to influence re-feeding hyperphagia, whereas they proved to be effective in both cases in NA animals.

Question 10.: How does the enhanced NPY activity, the role of which was suggested in the hyperphagia of CA animals, (that could also lead to severe/dangerous hypothermia in a cold environment) appear in the relationship of different homeostatic systems (such as the regulation of body weigh and body temperature) during chronic cold exposure?

Study design:

The relationship of orexigenic and thermoregulatory effects of a chronic central NPY-infusion was observed via recording the body weight and core temperature of CA animals.

NPY-infusion increased food intake in CA rats but caused only a temporary moderate decrease in temperature with regard to nighttime peaks and daytime minimum values. (Hypothermia failed to develop in NA rats only the nocturnal temperature peaks were diminished.) In contrast, upon food deprivation in the cold, daytime temperature minimums became more pronounced while nighttime peaks remained in place (Yoda et al., 2000). These observations indicate that only a moderate role of NPY may be presumed and that the orexigenic and thermal effects of NPY might be dissociated. Even moderate changes in

temperature cuold initiate such thermal feedback signals via surface thermal receptors to the hypothalamus. Despite the constant presence of NPY this does not permit a further decrease in MR and the development of a dramatic hypothermia, but may allow orexigenic effects (cold thermal signals may even promote them further), so hyperphagia will be significant.

Question 11.: Do the effects of orexin-A on energy balance depend on thermal adaptation?

Study design:

Thermoregulatory effects of centrally injected orexin-A were analysed in CA rats exposed to different ambient temperatures and feeding states. We also compared feeding metabolic/thermoregulatory effects of these peptides to those of NA animals.

The thermoregulatory effects and the hyperphagia to centrally applied orexin-A were more pronounced in CA rats than in NA ones. In particular, non-fasted CA animals in a cool environment (15 ^{o}C) exhibitet a drop in MR accompanied by passive hypothermia when challenged with i.c.v. orexin-A. Since these were effectively inhibited by NPY-antagonist, in the mediation of the effects of orexin-A on energy balance the role of NPY may be decisive.

Topic 2./B: Changes in energy metabolism in hyperthyroidism

Because of the high metabolic rate and consequent heat accumulation in hyperthyroidism an increase in heat loss becomes a necessary changing thermoregulation, but the threat of weight loss requires an increase in food intake, in which the activation of orexigenic/anabolic factors may be supposed (Ishii et al., 2003).

12. question: What happens when – as seen in hyperthyroidism – without any exogenic thermal influence a primary increase in metabolism/heat production occurs? How would the regulation of food intake change in such a case? Does it increase proportionately with increasing demands of hypermetabolism or, to avoid hyperthermia, would it remain relatively suppressed? What are the afferent factors involved and how central mediation is modified during the development of hyperthyroidism?

Study design:

Changes in energy metabolism, food intake/body weight were observed in chronic thyroxine (s.c. 50, 100 vagy 200 μg/day) treatment. We also studied the dynamics of development of hypermetabolism/hyperthermia and body weight-loss.

Hyperthyroidism developed gradually: during the first week of a 100 μg/day treatment the thermoneutral zone shifted to a lower level of 26-27 ^{o}C with parallel elevation of the resting MR and Tc. After week 3 of treatment the changes became more pronounced, and the thermoneutral zone was found at 23-25 ^{o}C. Changes in food intake could not keep up with these metabolic alterations, body weight development slowed down almost immediately, with aggravation of hyperthyroidism it showed increasingly severe impairment or it was significantly reduced compared to normal. Substantial increase of the spontaneous daily food intake followed the quick rise of MR with a long delay (it doubled after around 10 days). Heat loss also failed to increase sufficiently with rising MR, more and more severe hyperthermia developed even at the lower thermoneutral temperature of 23-25 ^{o}C.

Question 13.: Does the increase in resting MR also imply an enhanced thermoregulatory responsiveness as in cold-adaptation?

Study design:

Thermoregulatory responses to acute cold-exposure and to central PGE administration were examined in thyroxine-treated rats to gain information about the activity of (warm) thermal receptors. The results were compared to those of hypermetabolic CA rats.

In contrast to CA rats, in thyroxine-treated NA animals the metabolic/thermoregulatory responses to either acute cold-exposure or to central PGE_1-injection were not enhanced but rather blunted as seen in untreated NA ones.

Question 14.: May NPY play a role in the development of hyperthyroidism-induced hyperphagia?

Study design:

The possible role of NPY in feeding reactions of thyroxine-treated rats was studied by central NPY administration or by the application of NPY-antagonist following a 24-h food deprivation.

Similar to the gradual and slow increase of spontaneous food intake during the development of hyperthyroidism, the enhancement of re-feeding hyperphagia became pronounced quite late (after 3-4 weeks treatment). By this time (as seen from the fall in body weight) an undernourished state developed slowly and gradually, similar to that seen in starvation. In contrast to long-term thyroxine-treatment, after just 1 week of treatment re-feeding hyperphagia was not more pronounced but rather significantly weaker than that of controls, an increase appeared only after the 3 week and then it was restricted to the first 30

minutes of the re-feeding period. Contrary to the fact that i.c.v. NPY-induced hyperphagia was hardly increased compared to controls, it showed a non-significant elevation even after 4 weeks. NPY-effects were not enhanced but rather suppressed in animals with thyrotoxicosis (200 μg/day dose).

It appears that during the early phase of hyperthyroidism (first 10 days) a rather pronounced suppression of endogenic orexigenic activity (e.g. impaired NPY activity) occurs that may correlate with simultanous hyperthermia. Anorexigenic effect of the high peripheral temperature is well-known (Spector et al., 1968). In a warm environment food intake may be suppressed to such extent even without significant hyperthermia that body weight development may become impaired (Harikai, 2003). In a warm environment or in case of pre-existing hyperthermia, additional postprandial hyperthermia may cause an early cessation of food intake leading to an overall deficiency in food intake.

Among other mediators NPY-activity may play a role in the slowly developing hyperphagia appearing in late phases: such re-feeding hyperphagia was effectively inhibited by NPY-antagonist H-3328. Since the effects of exogenic NPY remained still unchanged, the alterations are possibly due to the increase in the endogenic NPY-release. The activation of NPY may not be a direct consequence of hyperthyroidism (since hyperthyroidism was already present in earlier phases) but more of a consequence of the relative undernutrition. Hyperthermia probably acts towards suppression of feeding responses even in this phase.

CONCLUSIONS

1., Energy stores temporarily blocked because of food deprivation can be mobilized upon acute cold-exposure or central PGE administration, therefore fasting hypometabolism/hypothermia cannot be explained simply by the lack of substrates but it is rather a result of regulatory changes – for this reason it may be regarded as an adaptive process. Simultaneous appearance of hypometabolism and enhanced sensation of hunger implies a *complex co-ordinated anabolic regulatory state*.

In *postprandial states* the combined appearance of satiety, hypermetabolism and hyperthermia represents a *complex catabolic state,* each component of which involves *central regulation*, since the body does not burn more substrates "because more substrates are available" but because the effectors responsible for the development of hypermetabolism receive appropriate efferent signals. Although humoral signals of the feeding status (e.g. inhibition of leptin and insulin) may also change during fasting-associated weight loss, and

these changes could also play a role in regulatory alterations, both metabolic rate and body temperature may be normalized quickly by acute re-feeding without the restoration of active body weight and feeding status.

2., In *starvation* the substantial suppression of metabolic rate can be explained mainly by *suppressive vagal signals* that may be impaired by local capsaicin desensitization.

3., The extent of postprandial increase in metabolic rate and body temperature was similar, but the dynamics of these changes were different following the intragastric injection of a calorie-rich or calorie-free suspension. Since a compensatory increase of heat loss accompanies this hyperthermia, it is not thermoregulation that is primarily affected, but the elevation of metabolic rate appears to be decisive. Postprandial hyperthermia is observed only at thermoneutral or warmer ambient temperatures, in a cold environment the heat released in this way will be incorporated in the MR-rise needed in the cold.

Gastrointestinal distension initiates afferentation via the mechano-sensitive fibers of the vagal nerve, while nutrients and humoral substances may affect vagal chemo-sensitive afferents, but nutrients rich in calories may also contribute to the development of postprandial hyperthermia via vagus-independent mechanisms.

Cholecystokinin-release induced by stretch signals following the administration of calorie-free suspension, may act on CCK-A receptors located on vagal afferent fibers finally exciting special sites in the central nervous system (involving CCK-B receptors), and inducing an increase in body temperature.

4., Central effects of NPY are not co-ordinated from a thermoregulatory point of view (NPY-induced temperature suppression cannot be called anapyrexia, but rather a passive hypothermia): the direct effects of NPY do not affect the thermoregulatory system as a whole, but only metabolic rate. On the other hand, the orexigenic and hypometabolic effects appear to be co-ordinated, therefore NPY can be regarded as an anabolic peptide: i. e. its effects are aimed at increasing energy intake and conservation.

In the development of fasting hypometabolism the role of NPY-activation cannot be exclusive. During starvation and NPY-effects, a certain dissociation of orexigenic and thermoregulatory effects can be detected: the orexigenic effects are enhanced, while the thermoregulatory ones appear to be diminished.

5., Capsaicin-desensitization may also induce suppression of such (vagal) stimuli that would have inhibited, among other things, NPY activity/release. Since desensitization did not influence the feeding effects of centrally applied NPY, it is likely that vagal stimuli act at the level of release.

6., The effects of a central injection of exogenic orexin-A were mostly similar to NPY-actions. There is also considerable overlap between the effects of the two peptides: NPY-antagonists prevented not only the orexin-A induced food intake but also the hypothermia elicited by orexin-A. Accordingly, in eliciting the main effects on energy metabolism, NPY appears to be more important. Data in the literature indicate that endogenous orexins would mostly contribute to vigilance and food-seeking behavior and not so much to the ingestion of food. Although orexin-B is also capable of influencing the body temperature, it does not play an important role in the regulation of energy balance.

7., In late phases of cold-adaptation (at least 3 weeks of cold-exposure) an adaptive downward shift of thermoneutrality is observed (homeothermia is maintained), metabolic rate measured here is much higher but resting body temperature is lower, than before adaptation. Upon cold-exposure, to sustain the constantly high metabolic rate, the spontaneous daily food intake increases almost immediately, which event – after a temporary stagnation – allows a normal rate of body weight development.

8., Peripheral cold sensors appear to play a dominant role in metabolic adaptation to cold – their chronic stimulation also leads to alterations in central responsiveness (e.g. to i.c.v. PGE, NPY or orexin-A). In cold-adapted animals the sensory mechanisms, central regulation and peripheral effectors are all modified providing efficient defense of homeothermia.

The hyperphagia induced by cold-adaptation does not depend only on the actual ambient thermal conditions during food intake; presumably it cannot be explained directly and exclusively by the higher activity of cold sensors. It seems more likely that, as results of a high metabolic rate, with consequent relative changes in nutrition, and a negative energy balance, those humoral feeding signals (leptin, insulin), which indicate the feeding status do not suppress central orexigenic mechanisms to the baseline. The enhanced activity of orexigenic mediators may also contribute to the development of hyperphagia.

9., Upon fasting of comparable severity, CA rats ate more than NA animals and in the CA group NPY-antagonists failed to inhibit re-feeding. Therefore, enhanced central NPY-sensitivity may have at most an additive role in the hyperphagia of cold-adapted animals, i.e. it may add to the hyperphagia induced by cold receptor activation.

10., During cold-adaptation orexigenic effects of anabolic substances are magnified, whereas the hypothermic effects are not (or hardly) apparent, which indicates that some other – probably thermoregulatory – effects counteract the hypothermia. Thus, a certain dissociation of the orexigenic and thermoregulatory effects of NPY and orexin-A may be observed, which may indicate competition among different homeostatic systems.

11., Autonomic effects of orexin-A on energy homeostasis resembling those of NPY are also more pronounced in CA than in NA animals. This could be a consequence of enhanced central sensitivity observed in cold-adaptation.

12., Resting metabolic rate and body temperature of rats with chronic thyroxine treatment start to increase substantially within some days of treatment. The increase in spontaneous daily food intake follows the rise in metabolic rate only with a delay and then it provides merely a partial compensation, so the body weight development starts to be stunted immediately and significantly.

13., In contrast with cold-adapted rats with similarly high metabolic rate, rats chronically treated with thyroxine do not show enhanced responsiveness to acute cold-exposure or i.c.v. PGE. This means that, the increased thermoregulatory responsiveness or the paradoxical "overshoot" reaction of CA rats is not primarily due to the increased heat-production capacity of their tissues.

14., During the early phase of hyperthyroidism the delay of the onset of spontaneous hyperphagia and the blunted hyperphagic response to a fixed period of fasting suggest a diminished production or release of orexigenic substances, since the effects of exogenous NPY are still maintained during this phase of hyperthyroidism. In the development of such a situation hyperthermic thermal signals may play a role: heat loss mechanisms cannot keep pace with this hypermetabolism, so an increasingly severe hyperthermia may cause anorexia via activation of warm receptors.

During the late phase of hyperthyroidism when spontaneous food intake increases due to a substantial, relative weight loss, the re-feeding hyperphagia also becomes enhanced. These changes may develop as a result of an increased release of endogenous NPY that may be caused by relative undernutrition. In hyperthyroidism the signals derived from the nutritional/feeding status and from thermoregulation appear to antagonize one another instead of the synergism seen in cold-adaptation.

SUMMARY

We studied the mechanisms of changes in energy metabolism in various states requiring such adaptation. Energy homeostasis was analyzed along with correlations among food intake – metabolic rate – body weight and heat production (metabolic rate) – heat loss – body temperature. Different adaptive changes in energy homeostasis may affect these factors in a complex way: i.e. in different combinations and with different causative mechanisms. We presumed that some peripheral neural factors participate in the regulation of such processes in

an identical or similar way, as there are also similarities/overlaps in the roles of putative central mediators.

Since food intake-associated information passes through the abdominal vagus, we have also presumed that this nerve may have a dominant role in adaptive processes of energy homeostasis. Similar universal importance in the regulation of energy homeostasis might be attributed to thermal receptors. The two neural pathways may mutually affect food intake and thermoregulation: the vagal afferents may influence energy metabolism and thermoregulation, while thermal receptors may have an effect on thermoregulation and food intake. Concerning central mediators, our aim was to study the role of certain neuropeptides that may have importance in these adaptive regulatory processes.

Important findings

1) In the adaptive processes of energy homeostasis, besides afferent fibers of the abdominal vagus, peripheral thermal receptors may also have an outstanding role, though neither of them appears to be exclusive. Capsaicin-sensitive vagal fibers may participate in the metabolic adaptation to feeding status (both starvation-hypometabolism and postprandial hypermetabolism also affect thermoregulation in a secondary way). During cold-adaptation, the activity of the peripheral (surface) cold sensors is the primary factor that alters both food intake and the sensitivity of thermoregulatory processes. Peripheral cold sensors stimulate only the orexigenic effects of anabolic mediators, the suppressive effects on metabolic rate and body temperature are rather inhibited by them. Warm sensors may be important in the limitation of orexigenic effects or in the development of full-fledged anorexia (hyperthyroidism).
2) Cholecystokinin plays a role in postprandial hypermetabolism and in the appearance of satiety. In starvation-induced hypometabolism and hypothermia, on the other hand, the participation of central NPY may be detected: besides hunger, hypometabolism also develops that may be accompanied by hypothermia in cool environments. These actions cannot be considered to be co-ordinated from a thermoregulatory point of view, because no augmentation of heat loss can be detected to help the development of hypothermia. Neuropeptide Y may have a role in the late phases of cold-adaptation and hyperthyroidism.
3) In some regulatory processes a competition of various homeostatic systems can be observed. During food deprivation or cold-exposure an orexigenic reaction is required,

but the accompanying hypometabolism and hypothermia of anabolic processes would present undesirable side effects, and the thermoregulatory mechanisms can prevent the development of hypothermia. Postprandial hyperthermia is observed only at thermoneutral or warmer ambient temperatures, while in a cool environment the energy released in this way merges with the cold-induced heat production. In hyperthyroidism high metabolic rate and elevated body temperature effectively prevent the development of hyperphagia until such a substantial body weight loss occurs that it would correspond to a starvation state.

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