Ghreliu is a peptide hormone with a strong stimulatory effect on growth hormone (GH) secretion. Ghrelin was origiu;i!íy isolated from the rat stomach as an endogenous secretagogue for the
growth hormone secretagogue receptor (GHS-R). Although the first coinpoimds of the group of
growth hormone seeretagogues were synthesized already in 1997, the isolation of the GHS-R and
ghrelin is a matter of tlie last decade.
Our study was aimed at the determination of the physiological role of endogenous ghrelin in GH secretion in certain pathological conditions and its associations with tlie GH/IGF-1 axis compounds. Our study was the first one detecíing also active ghrelin coucentrations. We assumed, that
ghrelin secretion is aflected by the GH secretory statě.
In patíents with acroinegaly we expected low ghrelin coucentrations (hypothesis 1) aud in patients with GHD we presuined, that ghrelin concentrations will be elevated (hypothesis 2) in
comparison with healthy subjects as an effect of the negative feedback regulation by GH. Our findings
however did not support tliese hypotheses, active and total ghrelin concentrations did not differ
between patients and healthy controls. These data do not support an important role tor ghrelin in GH
secretion in these conditions as well as the existence of a negative feedback regulation between tliese
hormones.
Ghrelin production was also found in the kidney. Therefore we assumed, that in case of renal failure ghrelin concentrations will be deereased due to its diminished production and due to llie
supposed negative feedback regulation by elevated GH concentrations (hypothesis 3). Agaiu we
coníirmed neither our hypothesis, nor the existence of a negative feedback regulation between ghrelin
and GH. It is probably the impaíred clearance and/or metabolism of gltrelin in the kiduey in renal
faihire, whicli is responsible for liigh ghrelin concentrations.
Acylated ghrelin is the most potent stiinulator of GH secretion in vitro sis well as in vivo, but the data available so far do not support its unique role in GH secretion as well as the existence of a
negative feedback regulation between ghrelin and GH. Even the total absence of ghrelin in experiments on laboratory animals does not cause any changes in body composition and concentrations of GH/IGF-1 axis compounds. This is a result of compensatoiy processes, which
substitute for ghreliu fuuctions in tlie organism. Ghrelin is together with GHRH, soinatostatiue and a
negative teedback regulation by IGF-1 only one of regulators of GH secretion.
This situation is probably preserved also in case of acromegaly aud GHD, which is supported by our results and observations of anoíher authors. Ghrelin concentrations are in these conditions not
affected by tlie secretion of GH and their regulation is more complex. It includes chronic nutritional

statě and tlie degree of adiposity in case of total ghrelin, and some so far unknown mechanisms in case
of active ghrelin. On the other hand we can not exelude a possible role of ghrelin in GH secretion incase of renal failnre, although the main mechanism, which is causiug llic elevation of GH and ghrelin
concentrations in Ihis condition is tite ímpairmeut of clearance of both compounds.
Problematic inaíter in the study of physiological Íuncíions of ghrelin in connection with the GH/IGF-I axis is the detemiínation of ghrelin concentrations locally in hypothalamus/pituitary glaud.
Plasma concentrations of ghrelin may not reflect its concentrations ín the hypothalamus/pituitary
gland, where the role qf ghrelin in GH secretion and tbe existence of a negative feedback regulation
between glirelin and GH may exist and fiirther research is needed to confirm oř exclude this hypothesis.
Based 011 many observations it is possible to conclude, that the total ghrelin concentrations are
affected by acute and chronic changes of nutritional statě and by insulin concentrations. Otir results
howevcr do not support the vicw, that similar regulátory ntechanisms are involved in case of active
ghrelin concentrations. Total ghrelin concentrations correlate positively with BMI and body fát mass,
are decreased in obese and elevated in lean or cachectic subjects. The noraialization of body weight
leads to llie normalization of total ghrelin concentrations and a resloration of the diurnal rhythm of
glirelin.
Exogenously administcrcd ghrelin leads in rodents lo Ihe stimulation of food ingestion and to weight gain, due to the increase in fat tissue. It decreases fal utilization and favors the utilization of
sacliarides as the inain metabohc substráte in energetíc metabolism. This effect of ghrelin scems to be
independent of GH activities, silice GH stimulates energy expenditure and decreases the amount of fat
tissue due to the stimulation of Iipolysis. Tbe orexigenic and anabolic effects of ghrelin migíit represent an adaptation mechanism, which completes the effects of GH and ensures metabolic substráte for growth.
Insulin is one of the most imporfant regulators of ghrelin secretion. Many experiments showed
negative coireiations between ghrelin and insulin concentrations, liyperinsulinaemia had been shown
to lower ghrelin conceutralions. Although the relationship between both hormones is not understood in
detail so far, it is plausible, that insulin directly or indirectly mediates the effect of nutrition or actual
energy statě on plasma ghrelin concentrations and vice versa. The deerease of insulin concentrations in
starving leads to the elevation of ghrelin concentrations, while postprandial hyperinsulinaemia causes

an opposite effect. Clironic hyperinsulinism in obese subjects and low insulin concentrations in lean
and cachectic individuals might affect glirelin concentrations in clironic nutritional changes by the
same mechanism. Reciprocally hyperghrelinaemia in starving might deerease insulin synthesis and by
this mechanism maintain glucose concentrations in normál range, and postprandial hyperinsulinaemia
might be the effect of a deerease in ghrelin secretion.
After the discovery of ghrelin it was pnniarily thought, that ghrelin could be a key factor causing simple obesity in man. But studies in obese individuals ha ve shown, that its concentrations are
suppressed in obesity and elevated in lean and cachectic subjects. We suppose, tíiat this is nn effect of
a negative feedback regulation between ghrelin and insulin, when ghrelin secretion is suppressed byelevated insulin concentrations. Our own results let us presurae, that a different situation occurs in
case of pathologic overproduction of ghrelin, insusceptible to a negative feedback regulation.
Exogenously administered ghrelin exerts orexigenic effects and leads to fat accumulation in iaboratory
animals. Also in patients with a GIT tumor secreting ghrelin (ghrelinoma) and in patients with Prader-
Willy syndrome, where high glirelin concentrations are piobably caused by autonomous secretion of
ghrelin in centrál nervous systém, there are elevated ghrelin concentrations associated with a high
BMI and body fat content. Our patients with renal failure had tnereased concentrations of active
glirelin, probably due to an impaired clearance ín the kidney. These patients had a high body fat
content at the same tinie and ghrelin concentrations correlated positively with body fat content.
Elevated concentrations of active ghrelin might therefore play a role in the etiopathogenesis of fat
tissue fonnation. Ghrelin tlius could have diabetogenic effects due to an increase in gluconeogenesis
and due to a suppression of insulin production, which was proved in patients with ghrelinomas and in
Iaboratory animals.
At preseut ghrelin is considered by many authors to be an orexigenic signál front stomach, whose secretion is regulated by meal intakc aud insulin coucentrations, which completes the proteosynthetic effects of GH. On the other haud in mice, where the glirelin gene was knocked out, no
significant ábnonnalities were observed in food intake, body composition, size, growth rate or reproduction. Even in these animals exogenously administered ghrelin stimulates food intake, but its
endogenous total absence does not lead to anorexia. Therefore the orexigenic function of ghrelin is not
irreplaceable and other coinpensatory mechanisms substituting for this fiutction are involved in the

regulation of food intake in ghrelin knocked out animals. In physiologic conditions ghrelin is not the
maitt orexigenic factor. However in conditions associated with high ghrelin concentrations, which can
not be down regulated by insulin (e.g. exogenous administration of glirelin in animals, Prader-Willy
syndrome, hulimia nervosa, ghrelinoma and according to our findings patients with renal insufficiency) ghrelin might exert adipogenic and diabetogenic effects.