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Growth hormone and growth hormone gene of the American mink (*Neovison vison*) – the current state of knowledge of one of the key hormones in one of the most intensively economically exploited species

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Abstract Despite the fact, that the American mink (*Neovison vison*) is one of the most intensively economically exploited and problematic, from the ecological point of view, fur-bearing animal, it remains one of the least studied livestock species. It can be proven by the fact, that the research on one of the key hormones, which has systemic effects, that is the growth hormone, are rather poorly advanced. The purpose of this review is to present the summary and the critical analysis of the current state of knowledge on the topic of the growth hormone in the American mink, its biological function, production in physiological conditions, regulation of secretion and transduction of the hormone's signal. The article contains also an up to date information on the Amrican mink growth growth hormone gene and its protein product.

Hormon wzrostu i gen hormonu wzrostu norki amerykańskiej (*Neovison vison*) – stan wiedzy na temat kluczowego hormonu u jednego z najintensywniej eksploatowanych gospodarczo gatunków zwierząt

Słowa kluczowe Norka amerykańska, hormon wzrostu, gen hormonu wzrostu, funkcje fizjologiczne, wydzielanie, transdukcja sygnału

Streszczenie Mimo że norka amerykańska (*Neovison vison*) jest jednym z najintensywniej eksploatowanych gospodarczo, a także problematycznych, z ekologicznego punktu widzenia, gatunków zwierząt futerkowych, pozostaje jednym z najsłabiej zbadanych gatunków zwierząt gospodarskich. Dowodzi tego, między innymi fakt, że badania nad jednym z kluczowych hormonów o działaniu systemowym, jakim jest hormon wzrostu, są słabo zaawansowane. Celem niniejszego artykułu jest przegląd i krytyczna analiza aktualnego stanu wiedzy na temat hormonu wzrostu u norki amerykańskiej, jego funkcji biologicznej, produkcji w warunkach fizjologicznych, regulacji wydzielania oraz transdukcji sygnału. Artykuł zawiera również aktualne informacje o genie hormonu wzrostu oraz jego produkcie białkowym.

Introduction

The history of the systematic farm breeding of the American mink (*Neovison vison* Schreb., 1777) has only began in the sixties of the XIX c. when, due to the fear of the excessive depletion of the wild population and difficulties in obtaining fur in quantities to meet the growing market demand, the first permanent farms were established (Shackelford, 1949; Bowman et al., 2007). The dynamic development of the farm breeding of *N. vison* can be evidenced by the fact that only 90 years from the initiation of the domestication process, the number of animals kept on farms around the world was approx. 10–11 million (Thompson, 1968). Today, this dynamics is much greater – in 2001 the world production of mink fur was approx. 29.5 million furs, while in 2012 already approx. 59.1 million were produced (Kopenhagen Fur, 2013). At the same time, the value of the global market for the American mink furs increased from over 9.8 to over 14.0 billion US dollars (Ward, 2011).

The cited data indicate that the American mink is today one of the most intensively economically exploited livestock species. All the more surprising is the fact that the research on one of the key hormones, which has systemic effects, that is the growth hormone (GH, somatotropin), are rather poorly advanced (Sereikaite et al., 2006). The summary and the critical analysis of the current state of knowledge on the topic of somatotropin in the American mink, which is the aim of the present paper, seems particularly important from this point of view.

The first international standard of the growth hormone was developed in 1955 for the bovine somatotropin, while in 1982 for the human growth hormone (Bristow, 1999). Such a standard is lacking for somatotropin of *N. vison* (Sereikaite et al., 2007).

The amino acid sequence of the growth hormone of the American mink (*mGH*) was for the first time reported in 1990 (Shoji et al.). Two efficient methods of a recombinant mink somatotropin production were developed in the cells of *Escherichia coli* – the first one in 1992 (Harada et al., 1994), while the second one in 2006 (Sereikaite et al., 2006; Sereikaite et al., 2007). Previously, this hormone has only been obtained in small amounts, by extraction from the mink pituitary glands (Harada et al., 1994).

It should be noted that a few studies on the mink somatotropin polypeptide are limited substantially to the development and improvement of methods for the obtaining the recombinant *mGH* in bacterial cells (Harada et al., 1994; Sereikaite et al., 2006; Sereikaite et al., 2007), as well as by optimizing the conditions of its storage and processing (Bajorunaite et al., 2007; Borromeo et al., 2008; Cirkovas, Sereikaite, 2010; Cirkovas, Sereikaite, 2011a,b; Zilinskas, Sereikaite 2011). This fact explains the scarcity of the available literature data on the specificity of the growth hormone molecule of *N. vison* (Sereikaite et al., 2006).

Hormone of growth only?

A characteristic feature of the growth hormone is the functional and systemic multidirectional impact (Waters et al., 1999; Sirotkin, 2005). Somatotropin is the major non-genetic factor stimulating the postnatal body growth, by induction of growth and differentiation of cells of the mesenchyme-derivative tissues. However, its action is not limited to the stimulation of growth, regeneration, differentiation and development of cells, tissues and organs, but it also includes the metabolic interaction on proteins, carbohydrates and fats, participation in the mineral economy and in processes connected with reproduction and immune functions of the body (Chawla et al.,

1983; Hull, Harvey, 2000a; Okada, Kopchick, 2001; Li et al., 2005; Huising et al., 2006; Giustina et al., 2008; Breederveld, Tuinebreijer, 2012; Skottner 2012).

The primary function of the growth hormone is the postnatal stimulation of the bone, cartilage, muscle and fat tissue development, taking place both directly – by the presence of specific receptors on the cells of these tissues, as well as indirectly – by the insulin-like growth factor-1 (IGF-1) (Okada, Kopchick, 2001; Li et al., 2005; Huising et al., 2006). It is particularly important to stimulate the growth of bones at length, by the direct interaction with receptors present on the surface of cells of the proliferative layer of the growth plate of long bones (Giustina et al., 2008; Skrzypczak et al., 2011). It has also been shown that the GH has an effect on the activation of growth and differentiation of chondrocytes, osteoblasts and osteoclasts, leading to the increase of the bone mass (Sims et al., 2000; Giustina et al., 2008). This process is promoted by the stimulation of the collagen synthesis, as well as the effect of the hormone on the mineralisation of the bone tissue, by the regulation of the activity of the renal 1α-hydroxylase 25(OH)D (EC 1.14.13.13), and thus the calcium-phosphate metabolism (Roy et al., 1997; Vestergaard et al., 2012).

The GH impact on the muscles refers to the hypertrophy of muscle fibres, creation of new fibres and their regeneration (Iida et al., 2004; West et al., 2010). The growth hormone also conditions the proper composition of the body, mostly within the volume and topography of the fat tissue, as well as it regulates the proper development and functioning of many organs and organ systems, like heart and circulatory system, brain and nervous system, stomach and digestive system, kidneys and excretory system, as well as lungs and respiratory tract (Nass et al., 1995; Merola et al., 1996; Parks et al., 1998; Waters et al., 1999; Frago et al., 2002; Napoli et al., 2003; Dattani, Preece, 2004; Biller, 2007; Krysiak, Okopień, 2007; Harvey, 2010).

The crucial role of somatotropin was proven in the stimulation of proliferation and regeneration of trophoblast, blastocyst, cells of the immune system, pancreas and endothelial cells (Ikeo et al., 2001; Nielsen et al., 2001; Jeay et al., 2002; Markham, Kaye, 2003; Lacroix et al., 2005; Breederveld, Tuinebreijer, 2012). It was stated that GH, next to the promotion of the proliferative activity, shows the ability to inhibit apoptosis (Kölle et al., 2003; Bogazzi et al., 2004). The growth hormone also has a great meaning in the regeneration of nervous fibres and in wound healing (Breederveld, Tuinebreijer, 2012; Devesa et al., 2012). GH stimulates migration and proliferation of neural stem cell (NSC), as well as induction of differentiation of progenitor nervous cells (Pathipati et al., 2011). On the other hand, it has been proven that this hormone stimulates, in an autocrine path, the cancer transformation, being able to participate in the process of carcinogenesis in some tissues (Perry et al., 2006; Harvey, 2010).

It is very important that promoting growth through GH takes place indirectly, by inducing the synthesis of IGF-1 in the liver, muscles, lungs, bones, or cartilage (Okada, Kopchick, 2001). In fact, distinction of functions and involvement of GH and IGF-1 in particular physiological processes is often very difficult (Mauras, Haymond, 2005). Although IGF-1 is a major systemic factor mediating in the growth hormone action, it has been proven that this hormone stimulates synthesis of many other growth factors and receptors specific for them, e.g. Fibroblast Growth Factor (FGF), Hepatocyte Growth Factor Receptor (HGFR), Epidermal Growth Factor Receptor (EGFR), Nerve Growth Factor Receptor (NGFR) (Ekberg et al., 1989; Ekberg et al., 1992; Scharfmann et al., 1994; Izumi et al., 1995). It should be noted that the synthesis of certain growth factors, induced by somatotropin, shows clear tissue-organ specificity (Waters et al., 1999).

In the American mink the most intense growth of the body takes place during the first eight months of life. This is evident in the body weight growth in the time function, while the top and

stabilization of the body weight of the pups born in April takes place in November (Ahlstrøm et al., 2006; Liu et al., 2011).

The growth hormone participates in the metabolism of basic organic compounds for the body functioning – proteins, carbohydrates, lipids and vitamins (Feld, Hirschberg, 1996; Chen et al., 1997; Møller, Jørgensen, 2009; Vijayakumar et al., 2010). Metabolic effects exerted by somatotropin are frequently matched with those caused by insulin and, therefore, divided into the insulin-like effects (anabolic – metabolism of proteins) and against-insulin effects (catabolic, diabetogenic – metabolism of fats and carbohydrates) (Renaville et al., 2002; Dominici et al., 2005; Mauras, Haymond, 2005; Vijayakumar et al., 2010). Generally speaking, metabolic effects of the growth hormone manifests in synthesis and increase of the protein amounts, lowering the use and consumption of carbohydrates and mobilization of fat reserves (Renaville et al., 2002; Vijayakumar et al., 2010).

In the scope of the systemic protein metabolism GH increases the uptake and trans-membrane transport of amino acids into the cell (synergistic effect with respect to insulin) and stimulation of translation (Breier, 1999; Hossner, 2005). Protein synthesis relates primarily to the muscle tissue (Fryburg, Barrett, 1993; Hossner, 2005). Participation of the growth hormone in the protein metabolism is connected with the retention of nitrogen compounds in the blood and the limitation of their urinary excretion, as well as the decrease of catabolic transformations of proteins, their increased assimilation and utilisation (Breier, 1999; Hossner, 2005).

With regard to the carbohydrate metabolism, the growth hormone shows the insulin-like and antagonistic effects towards insulin at the same time (Renaville et al., 2002; Mauras, Haymond, 2005). This hormone also affects the increased uptake of glucose in the muscles and the decrease of its uptake in the adipose tissue, as well as stimulates gluconeogenesis and glycogenolysis in the liver and its increased release from this gland, causing the increase of the glucose level in the blood (diabetogenic effect) (Dominici et al., 2005; Hossner, 2005; Møller, Jørgensen, 2009; Kim et al., 2012). GH affects the reduction of sensitivity of the cells to insulin (especially adipocytes), and also stimulates its release (Manson, Wilmore, 1986; Nam et al., 2001; Renaville et al., 2002; Dominici et al., 2005; Hossner, 2005; Freda et al., 2008). This is mainly done by increasing the level of sugar in the blood and stimulation of the hypertrophy of pancreatic β-cells (Nielsen, Serup, 1998; Nielsen et al., 2001; Dominici et al., 2005). The sustained hyperglycemia associated with the persistence of the elevated levels of somatotropin, again stimulates the pancreatic islets to secrete insulin and can lead to the depletion of β-cells of Langerhans islets (Hellerström et al., 1984; Dimitriadis et al., 1985). In the glucose metabolism GH can be considered the "hunger hormone", promoting lipolysis, hyperglycemia and insulin resistance (Desborough, 2000; Clemmons, 2004; Freda et al., 2008).

Also in the case of the lipid economy the growth hormone shows the effect opposite to the insulin interaction, demonstrating lipolytic effects and affecting the reduction of lipogenesis (Etherton, 2000; Hossner, 2005; Freda et al., 2008; Bergman et al., 2012). Somatotropin causes the hydrolysis of triacylglycerol of the fat tissue, releasing free fatty acids (FFA) and glycerol to the blood (Manson, Wilmore, 1986; Møller et al., 1990; Richelsen, 1997). Mobilization of FFA from the adipose tissue contributes to the reduction of body weight and decrease of the adipose tissue volume (Etherton, 2000; Nam et al., 2001; Pasarica et al., 2007). GH also causes the reduction of cholesterol concentration in the plasma, stimulates the conversion of fatty acids to acetyl coenzyme A, exhibits ketogenic effects, leading to the increase of the ketone bodies concentration in the blood (ketosis) and their increased excretion in the urine (Manson, Wilmore, 1986; Møller et al., 1990; Nam et al., 2001; Møller et al., 2007; Vijayakumar et al., 2010; Palakawong, Arakaki,

2012). Somatotropin also conditions the proper differentiation and maturation of adipocytes (Nam, Lobie, 2000; Farnier et al., 2003).

The growth hormone participates in the systemic mineral metabolism, affecting the positive balance of nitrogen, phosphorus, potassium, calcium, sodium and magnesium (Manson, Wilmore, 1986; Pointillart et al., 1994; Baum et al., 1996; Dimke et al., 2007; Kamenicky et al., 2008; Auriemma et al., 2010). This is done, among others, by the increase of the alkaline phosphatase content (EC 3.1.3.1) and inorganic phosphorus in the plasma, reduction of the content of nitrogen in urea, increase of absorption of calcium in the gastrointestinal tract (more efficient than the secretion of this element in the urine, under the influence of GH), increase of resorption of electrolytes in renal tubules and their retention (Gertner et al., 1979; Dahms et al., 1989; Marcus et al., 1990; Yeh, Aloia, 1990; Baum et al., 1996; Dimke et al., 2007; Kamenicky et al., 2008; Auriemma et al., 2010). By participating in the systemic electrolyte economy GH plays an important role in maintaining water homeostasis of the body (Dimke et al., 2007; Auriemma et al., 2010).

The growth hormone plays an important role in many physiological functions related to reproduction, both in females and males (Woliński, 1964; Sirotkin, 2005). In both sexes this hormone participates in sexual maturation and conditions the sexual dimorphism (Hull, Harvey, 2001; Low et al., 2001). It has been shown that somatotropin stimulates fertility and animal fecundity (Sirotkin, 2005).

In females, the growth hormone, together with gonadotropins, stimulates folliculogenesis and the luteinisation process, as well as participates in the regulation of ovulation (Eckery et al., 1997; Hull, Harvey, 2001). GH also participates in the regulation of the secretory function of follicle, stimulating the synthesis of steroid hormones (steroidogenesis) in granulosa cells and ovarian theca (Gregoraszczuk et al., 2000; Hull, Harvey, 2001). Somatotropin here acts both directly and through the IGF-1 produced locally in ovary (Hull, Harvey, 2001). It is also suggested that the synergistic effect of the growth hormone and gonadotropins, consisting of the mutual increase of the number of specific receptors in the follicle cells by these hormones (Adashi et al., 1994). It should be noted that in the case of the reproductive system of females, GH can show the effects on the endocrine path, through pituitary somatotropin, as well as auto-, para- or intracrine, through the hormone produced locally in the ovary (Schwärzler et al., 1997). The presence of receptors for GH was shown in the luteal tissue in many mammal species, where it stimulates secretion of progesterone (P_4) and maintains the function of the corpus luteum (Carlsson et al., 1993; Liebermann, Schams, 1994; Juengel et al., 1997). The stimulation of the increase of proliferation and uterine cells has also been shown (Gunin, 1997).

Although, the growth hormone is of secondary importance to the foetus, it is essential for the proper development in the prenatal period – it conditions the implantation of blastocyst, regulates trophoblast growth and development of placenta, as well as participates in the pre-birth regulation of metabolism of liver in mammal foetuses (Labastie et al., 1998; Markham, Kaye, 2003). In the body of the pregnant female, GH conditions the repartition of nutrients between the mother's body and the foetus (Hull, Harvey, 2001).

GH plays a very important role in the metabolic adaptation of the female's body to pregnancy (Handwerger, 2009). Somatotropin also shows outstanding lactogen effects, thanks to the trophic and mitogene impact to the cells of the mammary gland (Mulhall et al., 2005). GH also induces the expression of key genes of milk proteins – casein and lactabumin (Sakamoto et al., 2005; Zhou et al., 2008; Johnson et al., 2010).

In males, GH conditions the proper growth and development of testes (Ohyama et al., 1999; Hull, Harvey, 2000b). Somatotropin takes part in the differentiation of Leydig cells (Kulin et al.,

1981; Kanzaki, Morris, 1999). This hormone is involved in the regulation of steroidogenesis on the endocrine path, by sensitizing the Leydig cells to the effects of the luteinizing hormone (LH), in turn leading to the increase of testosterone secretion and induction of expression of genes for the crucial enzymes and regulatory proteins in the steroidogenesis process (Chatelaine et al., 1991; Ohyama et al., 1995; Kanzaki, Morris, 1999; Mani et al., 2000). By acting on the Sertoli cells, GH stimulates the differentiation of germ cells at all stages of spermatogenesis (Swanlund et al., 1995). The growth hormone is therefore an important factor regulating both spermatocytogenesis and spermiogenesis (Hull, Harvey, 2000b). It has also been shown that GH conditions the proper development of Wolff ducts in males, and in the post-natal period the proper functioning of their derivative structures – prostate and vas deferens (Reiter et al., 1992; Ghosh, Bartke, 1993; Nguyen et al., 1996).

The growth hormone participates in the proper functioning of the immune system, among others, by regulation of the functioning of thymus and spleen (de Mello-Coelho et al., 1998; Dialynas et al., 1999). This takes place by stimulation of proliferation of thymus cells, inducing the thymulin production, conditioning the blast transformation of T lymphocytes and participation in the regulation of their apoptosis (Timsit et al., 1992; de Mello-Coelho et al., 1998; Dobashi et al., 2001). It was also shown that GH conditions the survival of thymus-dependent lymphocytes in the stress conditions (Murphy et al., 1999). Receptors of the growth hormone are present on the surface of the immune system cells and the production of GH was stated by the lymphoid tissue (Jeay et al., 2002). Somatotropin also stimulates the production of interleukin 6 (Saggese et al., 1993).

In addition to these physiological functions, the growth hormone is characterised, through the signal path of the insulin-like growth factor-I, with the notably systemic effects on the process of the body aging and conditioning of the length of life of the individual (Okada, Kopchick, 2001; Holzenberger, 2004). It has been shown that the reduced level of somatotropin greatly increases the life span of animals (Holzenberger et al., 2004; Masternak, Bartke, 2012). A clear positive correlation between the systemic level of GH and the progress of the body aging processes is connected, most probably, with the great energy and substrate absorption of processes conditioned by this hormone (mainly the stimulation of growth and development and regulation of the body composition) (Masternak, Bartke, 2012). It was also shown that the increase of the hormone level in mature individuals results in the reduction of resistance to oxidative stress, and consequently may lead to metabolic complications and the increase of the risk of occurrence of cancerous changes (Hoffman, Ceda, 2004; Janssen, Lamberts, 2004).

The growth hormone, prolactin and placental lactogen show considerable structural and functional similarities, among others, in the stimulation of proliferation and differentiation of cells of many tissues (Wallis, 1992). Functionally, the growth hormone belongs to the so-called somatotropic axis, which also includes somatoliberin (GHRH), prolactin (PRL), receptors of the growth hormone (GHR) and prolactin (PRLR), insulin-like growth factor-I, transcription factor Pit-I and transcription factor STAT5 (Parmentier et al., 1999; Katoh et al., 2007; Bideci, Çamurdan, 2009).

Production in physiological conditions

The growth hormone in American mink, like in other mammals, is produced and secreted by the somatotropic cells and somatomammotropic cells of the frontal lobe of pituitary (*adeno-hypophysis*) (Machnik, Lechniak, 2000; Borromeo et al., 2008; Harvey, 2010). In addition to the

pituitary, the growth hormone is produced in, among others, gonads, uterus, placenta, mammary gland and by leukocytes, while the growth hormone receptor (GHR) is present on the surface of cells of most tissues (Kelly et al., 1991; Hull, Harvey, 2000a, 2000b; Hull, Harvey, 2001; Harvey, 2010).

Somatotropic cells of *N. vison* have the spherical or polygonal shape, and GH is stored and released from their electron-thick granules, with a diameter of approx. 210 nm (Vidal et al., 1995). It has been shown that the number of somatotropic cells considerably varies, depending on the age and physiological state of minks – the number of cells producing GH decreases during lactation, for the prolactin-secreting cells (PRL) (Vidal et al., 1995). An intermediate form between the somatotropic cells and the ones producting PRL mammotropic cells are the mammosomatotropic cells, which produce both the growth hormone and prolactin (Vidal et al., 1995, 1997).

The GH concentration in the mink blood is approx. 0.38 ng/ml in males and approx. 0.53 ng/ml in females (Ryökkynen et al., 2003). These are values lower than those stated in rats (2.4–2.8 ng/ml) and people (1.1–1.9 ng/ml) and higher from the concentration of GH marked in the raccoon dog plasma (0.1–0.3 ng/ml) (Mustonen et al., 2001; Nieminen et al., 2002; Barkan et al., 2003). It has also been proven that there exists a positive correlation between the concentration of the growth hormone in the blood and the body weight, as well as between the concentration of leptin and ghrelin in the blood plasma of American mink (Ryökkynen et al., 2003).

Mink growth hormone's protein

The growth hormone is included to the group of peptide hormones. The mGH particle (accession code *UNIPROT: P19795 SOMA_MUSVI*) has the structure of a simple polypeptide chain, composed of 190 amino acids (in the largest amount there is leucine, consisting 13.2% of all amino acids, while in the smallest one – tryptophan, consisting 0,5%), with the molecular weight of 21,717.84 Da (Harada et al., 1990; Rice et al., 2000). The mature hormone is formed from the precursor molecule, consisting of 216 amino acids, of which 26 form a signal peptide proteolytically cleaved during the post-translational processing (Shoji et al., 1990). The molecular formula of mGH is $C_{973}H_{1519}N_{263}O_{285}S_8$, and the theoretical value of the isoelectric point (pI) is 7.38 (Rice et al., 2000; Artimo et al., 2012). It was also found that the growth hormone is rapidly metabolised – the period of its half-life in the blood is approx. 20–50 min. (Goya et al., 1987; Faryna 2009; de Graaf-Roelfsema et al., 2011).

According to the system of structural classification of proteins SCOP, GH polypeptide has the *all-α* over-secondary structure type and belongs to super-family of 4-helical cytokines and the family of long-chain cytokines (Murzin et al., 2009). In the spatial structure of the growth hormone we can distinguish four left α-helix in the system of a bundle and spatial orientation of the "*up-up-down-down"* type, covering up to 70% of the polypeptide. The remaining part are the turns and random structures (Kopchick et al., 2002; Borromeo et al., 2008; Murzin et al., 2009). The GH particle also contains the hydrophobic core, consisting of approx. 20 amino acids (Kopchick et al., 2002).

The growth hormone of American mink, like in case of other mammals, contains in its structure of the polypeptide chain two internal disulfide bonds (disulfide bridges) between cysteines in the position of Cys78-Cys189 and Cys206-Cys214 (Watahiki et al., 1989; Shoji et al., 1990). Also the presence of two zinc binding sites in the amino acid sequence of the GH polypeptide of *N. vison* was shown – in the position of His45 and Glu198 (The UniProt Consortium, 2012).

The analysis of the primary structure of the growth hormone protein of American mink, for the presence of characteristic functional amino acids motifs, proves the existence of 14 such motifs (program PPSearch PROSITE, www.ebi.ac.uk/Tools/ppsearch). These include protein kinase C phosphorylation site (EC 2.7.11.13), casein kinase II phosphorylation site (EC 2.7.11.1), N-myristoylation site, leucine zipper pattern, somatotropin, prolactin and related hormones signature 1 and the motif of somatotropin, prolactin and related hormones signature 2.

The growth hormone has a high heterogeneity, i.e., multitude of structural forms (structural polymorphism); so far we approx. 30 isoforms of the human GH were identified (Baumann, 2009). Heterogeneity of the macro-molecule of somatotropin is the result of the alternative splicing, post-translation modifications, oligomerisation and polymerisation, existence of different variants of the quaternary structure and binding to the growth hormone binding protein (GHBP) (Junnila et al., 2008).

The alternative splicing of the translation product of the primary GH gene transcript in human leads to the synthesis of five isoforms of somatotropin, differing in size (from 7.4 to 22.0 kDa), binding to other binding places on the growth hormone receptor and showing the different biological activity (Takahashi, 2002; Longhi, 2003; Piekiełko-Witkowska, Nauman, 2011). So far also a series of post-translation modifications of the GH particle were described, like glycosylation, acetylation, deamidation, phosphorylation, proteolysis and oxidation (Lewis, 1984; Baumann, 1991; Diaz, 1993; Haro, Lewis, 1996; Baumann, 1999; Garcia-Barros, 2000; Baumann, 2009). Also the occurrence of different mer forms was observed (monomers, dimmers, oligomers and heteropolymers) of the variants of the growth hormone particle, however, their biological significance is not fully explained (Baumann, 1991; Junnila et al., 2008).

The growth hormone circulating in the blood is present partially in the form connected with GH proteins (Baumann, 2001; Baumann, 2009). Two types of these proteins were identified – GHBP with high-affinity, being the extracellular domain of the growth hormone receptor or the product of the alternative splicing of the GHR gene product, and GHBP with low affinity, being α2-macroglobulin or its modified form (Baumann, 2001). It is estimated that even 55% of the GH present in the human blood occurs in the form connected with GHBP with high-affinity, while with GHBP with low affinity – to 8% (Baumann et al., 1990; Veldhuis et al., 1993). It is also known that the amount of GH connected with GHBP subjects to the very dynamic fluctuations, constituting a significant reserve of the free hormone in the system (Veldhuis et al., 1993). This binding is reversible, and the growth hormone in the form of the GH-GHBP complex loses the ability to bind with the specific trans-membrane receptor, what results in the functional inactivation of the hormone (Baumann, 2009). On the other hand, the said complex protects the growth hormone from degradation and secretion from the system (Baumann, 1994).

The growth hormone of American mink exhibits a high level of homology of the primary structure with GH of other mammalian species (Morozov, Malchenko, 1993). For example, there was demonstrated the 97% relative similarity of the amino acid mGH sequence with somatotropin of the fox (Li et al., 1989) and dog (Queiroga et al., 2008), 96% with GH of the cat (Wallis, 2008) and pig (Seeburg et al., 1983), 94% with the growth hormone of the rat (Bailey-Downs, 2012), 88% with the domestic cattle (Heidari et al., 2012) and 66% – human (Martial et al., 1979). Despite the relatively small differences in the structure of polypeptide of somatotropin of different species of vertebrate, this hormone exhibits an excellent specificity of the species in relation to the biological activity (Lindholm, 2006). Such high species functional specificity is mainly connected to the different amino acid sequence of receptors for GH in different animals (Allan et al., 1999).

Studies, conducted in the recent years, on the biological activity of the purified mGH showed that it is equivalent only in 8% of activity proper for the growth hormone of cattle and in 63% for somatotropin of pigs. The concentration value of mGH causing the 50% of the maximal response (EC_{50}) in mink is approx. 103 ng/ml (Sereikaite et al., 2007).

Regulation of secretion

The concentration of the growth hormone in the blood is subject to fluctuations in the circadian rhythm (Veldhuis et al., 1991). Secretion of GH is pulsating, while its episodic nature depends on the gender and age (Veldhuis et al., 1991; Jaffe et al., 1998; Skottner, 2012). In humans approx. 10 secretions, lasting for about 30 minutes, of somatotropin in men and approx. 20 in women a day are observed, while the total amount of the released hormone in a day is greater in men (Cauter et al., 1992; Jaffe et al., 1998). With regard to the degree of GH secretion per year, no changes in the level of GH were stated in the pituitary of minks in different seasons, and only its reduction in feeding mothers was reported (Vitale et al., 2001).

The hormone content decreases with age – the decrease begins after the end of puberty, it is strictly correlated with the aging process and is determined in mature individuals as somatopause (Anawalt, Merriam, 2001; Krysiak et al., 2009).

The increased GH concentration in the blood is observed in gigantism (young individuals) and acromegaly (mature individuals), as well as liver cirrhosis, renal failure, anorexia nervosa, type 1 diabetes, hyperthyroidism, some cancerous changes of pituitary and in normal physiological conditions in pregnant females (Scheithauer et al., 1995; Barkan et al., 1997; Kuol et al., 2002; Grottoli et al., 2003; Pedersen et al., 2010). While the reduction of the growth hormone level usually proves the diseases damaging the pituitary gland or hypothalamus, caused for example by inflammation or degeneration, cancers and mechanical injuries of the head (Diaz-Espiñeira et al., 2008; Gardner et al., 2013; Hirohata et al., 2013). The low level of GH in the blood also occurs in dwarfism, obesity, hypothyrodism, hyperthyroidism and adrenal hypogonadism (Giustina et al., 1997; Kohn, Kopchick, 2002; Arnaldi et al., 2003; Diaz-Espiñeira et al., 2008; Alvarez-Castro et al., 2013).

The regulation of secretion of growth hormone is a highly complex and comprehensive process, including the hormonal factors, as well as environmental and behavioural ones, and the proliferation of somatotroph cells (Müller et al., 1999; Bideci, Çamurdan, 2009). The important meaning in the regulation of GH secretion is played by hypothalamic neurohormones and neurotransmitters, interacting with adrenergic receptors, dopaminergic, serotonergic, gabaergic or cholinergic (Ginalska-Malinowska, Malinowska, 2009). Release of the growth hormone in the pituitary gland primarily subjects to the double regulation by the hypothalamus – the hypothalamic growth hormone releasing hormone (GHRH, somatoliberine) stimulates, while growth hormone release inhibiting hormone (GHRIH, somatostatine) inhibits the secretion of the growth hormone, what is connected with the increased or reduced sensitivity of somatotroph cells to these neurohormones (Gianotti et al., 1999; Tannenbaum et al., 2007). Both of these neurohormones remain in the mutual feedback (Skoczylas, Więcek, 2006).

Among the peripheral hormones of endocrine glands the synthesis and GH secretion are stimulated by estrogens and androgens (especially testosterone, which acts here in a systemic way), gherlin, leptin, motilin, luteinizing hormone (LH), corticosterone (CORT), progesterone and vasopressin (Dean, Porter, 1999; Watanobe, Habu, 2002; Peeters, 2003; Katoh et al., 2005; Veldhuis et al., 2005; Tannenbaum et al., 2007). There were conducted studies on the associations

of leptin with fluctuations of the body weight in *N. vison*, which were indirectly affected by the growth hormone (Tauson et al., 2004).

A separate group of factors regulating the growth hormone secretion are the biologically active peptides and synthetic compounds. The first ones include somatotropin stimulating secretion, polypeptide activating pituitary adenylate cyclase activating polypeptide (PACAP) and the group, so-called growth hormone secretagogue (GHS) (McDowell et al., 1995; Montero et al., 2000; Smith et al., 2004; Skoczylas, Więcek, 2006). The most important synthetic chemical compounds stimulating the GH secretion are apomorphine (APO), propranolol, clonidine and synthetic growth hormone releasing peptide (GHRP), e.g. GHRP-6 and hexarelin (Low, 1991; Scacchi et al., 1999; Lengyel, 2006). The GH level also increases under the influence of glucogenic amino acids (arginine, glycine, glutamine), L-Doop, niacin, opioid peptides, galanin, vitamin A, or glucagon (Morita et al., 1989; Johnson et al., 1993; Zdrojewicz et al., 2000; Gómez et al., 2002; Arwert et al., 2003; Ginalska-Malinowska, Malinowska, 2009; Skottner, 2012; Vught et al., 2012).

Environmental factors, stimulating the growth hormone secretion, include the stressful stimuli (Desborough, 2000). Studies conducting on the impact of photoperiod on the secretion of somatotropin in American mink showed the lack of connection between the length of the light day and changes of GH content in the blood (Meunier et al., 1988).

The most important behavioural factor connected with the regulation of growth hormone secretion is the dream (Kim et al., 2010). The peak of GH secretion takes place within two hours from the occurrence of deep sleep (Born, Wagner, 2009). The behavioural factors stimulating the GH secretion are the states of deficiency of energy substrates (starvation, hypoglycaemia, presence of 2-deoxyglucose, physical effort) and high-protein diet (Daughaday, 1989; Sato et al., 1995; Kanaley et al., 1997; Nørrelund, 2005; Matthiesen et al., 2008; Goldstein et al., 2011). The stimulating effect of starvation on the secretion of the growth hormone in American mink is confirmed by the results of experiments by Rouvinen-Watt et al. (2010). However, at the same time, studies on the impact of the winter deficiency of food on the GH content in the blood of *N. vison* indicates the significant drop of the concentration of this hormone already after five days of starvation (Mustonen et al., 2005).

An important element of regulation of the production and secretion of GH is the stimulation of proliferation and differentiation of somatotrophic and somatomammotropic cells (Dean, Porter, 1999). The most important role here is played by glucocorticoids, thyroid hormones, corticosterone, cAMP, as well as CXC chemokines (Nogami et al., 1999; Dean, Porter, 1999; Lee et al., 2008; Lania et al., 2012). The direct cause of the growth hormone secretion, from granulates produced by eosinophils, is the increase of cytoplasmic level of cAMP and Ca^{2+} ions (Strobl, Thomas, 1994).

The factors inhibiting the growth hormone secretion include hyperglycaemia, cortisol, chronic lack of sleep, free fatty acids, neuropeptide Y (NPY), vitamin D, thyroid hormones and melatonin (Rettori et al., 1990; Barb et al., 1995; Giustina, Wehrenberg, 1995; Thompson et al., 1995; Seoane et al., 2002; Karasek et al., 2007; Kim et al., 2010; Skrzypczak et al., 2011). An important, inhibitory effect on the secretion activity of acid-absorbant cells of the pituitary gland is shown, in the mechanism of the negative feedback, by GH and IGF-1 present in the peripheral circulation (Yamasaki et al., 1991; Grilli et al., 1997; Skottner, 2012).

Transduction of the signal

The growth hormone affects the target tissues (cells) both directly, like hormone or cytokine, or indirectly, by stimulating the production and secretion of *insulin-like growth factor-I* (IGF-1),

mostly by the liver (Waters et al., 1999; Borst, 2004; Krysiak et al., 2009; Frystyk, 2010; Skottner, 2012). As a hormone, GH acts on the target cells on the classic endocrine way, like cytokine, on the about-crine path, paracrine and autocrine (Waters et al., 1999; Jeay et al., 2002; Soares, 2004; Harvey, 2010). The para- and autocrine impact most of all is shown by the locally produced somatotropin outside pituitary, while the pituitary nature of GH is rather systemic and endocrine (Harvey, 2010).

The mechanism of the direct effect of somatotropin is based, most of all, on its interaction with growth hormone receptor (GHR) and induced by this interaction intracellular transduction of the signal (Lanning, Carter-Su, 2006; Zych et al., 2006).

GHR belongs to the super-family of cytokine receptors of IA class and shows great structural-functional resemblance to the prolactin receptor (Goffin, Kelly, 1996; Zych et al., 2006). The somatotropin receptor is a transmembrane protein consisting of three domains: 1 – extracellular, binding ligands (GH molecule), 2 – transmembrane, anchoring receptor in the plasma, 3 – cytoplasmic, responsible for the transduction of the signal (Goffin, Kelly, 1997; Zych et al., 2006). Extracellular domain (ECD, identical to GHBP) contains two conservative evolutionary sub-domains – D1, containing six cysteines connected with disulfide bridges, and D2, with a characteristic motif YXXFS (tyrosine-glycine, serine, lysine or glutamic acid-phenylalanine-serine) (Moutoussamy et al., 1998; Zych et al., 2006; Conway-Campbell et al., 2008). Transmembrane domain (TMD) consists of a short polypeptide chain with the α-helical structure (Michalik, Bartoszewicz, 2002). While the characteristic elements of the cytoplasmic fragments of GHR (ICD, intracellular domain) is the box1 region, containing numerous prolines, and box2 region, consisting of the hydrophobic and acidic amino acids alternating in arrangement (Argetsinger, Carter-Su, 1996; Bole-Feysot, 1998; Moutoussamy et al., 1998). There were described several isoforms of the growth hormone differentiating in size and resulting from the alternative splicing (Moutoussamy et al., 1998).

GHR is activated by the dimerization induced by the binding of a receptor with the GH particle (Wells, 1996). The growth hormone in its particle has two receptor binding sites – high-affinity binding site 1 and low-affinity binding site 2 (Waters et al., 1999). Binding the growth hormone to the receptor particle with high-affinity binding site 1, results in the formation of the hormone-receptor complex (GH-GHR), activating low-affinity binding site 2 (Waters et al., 1999). Only binding of the second receptor particle (GHR homodimerization) by one GH particle gives an active complex GHR-GH-GHR (GH-GHR_2), which activates tyrosine kinases JAK2 (Janus kinase 2, EC 2.7.10.2), constitutively connected to the region box1 of both monomers GHR (Dinerstein et al., 1995; Wells, 1996; Zych et al., 2006). The activated kinases JAK2 phosphorylate themselves mutually and the tyrosine residues of the intracellular parts of the receptor itself (Ceseña et al., 2007). In such state receptor initiates the transduction of a signal into the cell, which results in the induction of the specific biological effect (Moutoussamy et al., 1998; Ceseña et al., 2007).

The transduction of the signal, inuced by the activation of the complex GH-GHR-JAK2, can take place through the engagement of the STAT1, STAT3, STAT5a and STAT5b proteins (Signal Transducer and Activator of Transcription) (Argetsinger, Carter-Su, 1996; Lanning, Carter-Su, 2006). Phosphorylated tyrosine residues of GHR enable the phospohorylation of the STAT protein particle, which then undergoes homodimerisation (Lanning, Carter-Su, 2006). The resultant STAT-STAT dimmers get into the nucleus, where they connect with specific nucleotide sequences of promoters of the target genes and activate them (Herrington et al., 2000; Waxman, O'Connor, 2006). STAT5a and STAT5b proteins exhibit strong affinity to specific sequences of the IGF-1 gene promoter, what proves the somatotropin dependent activation of transcription of this gene

and the crucial role of these proteins in the realization of the basic physiological functions of the growth hormone (Herrington et al., 2000; Waxman, O'Connor, 2006). On the other hand, it has been proven that the growth hormone and IGF-1 interact synergistically with respect to transduction of the induced intracellular signal and that this last one can efficiently strengthen the signal transmitted through GHR (Huang et al., 2004).

Signal paths of the growth hormone receptor can also be connected to phosphorylated cytoplasmic domain of proteins with the SH2 domain (Src Homology 2) (VanderKuur et al., 1995a). This happens in the case of activation of the signal path by the mitogen activated protein kinase (MAPK). In this case, the phosphorylated tyrosine residues of GHR enable the connection to the GHR-GH-GHR complex of the adaptor proteins Shc/Grb2/SOS, which in turn activate the cascade Ras/Raf/MAPK, responsible for the activation of many transcription factors and enzymes (VanderKuur et al., 1995b, 1997). The growth hormone can also use the signal path of the protein A kinase (EC 2.7.11.1), dependent on cAMP (Vijayakumar et al., 2011).

It is believed that the growth hormone can stimulate the phosphorylation of tyrosine residues of particles proper for the signal paths of insulin – insulin receptor substrates IRS-1, IRS-2 and IRS-3 (Insulin Receptor Substrate) and kinase 3'-phosphatidylinositol PI-3K (Tsuruzoe et al., 2001; Lanning, Carter-Su, 2006; Xu, Messina, 2009). The last one participates in the transmembrane transport of glucose, DNA synthesis and activation of ribosomal kinase $p70^{rsk}$, involved in the protein biosynthesis (Argetsinger, Carter-Su, 1996). Also important is the mediation of kinase 3'-phosphatidylinositol in GH-dependent re-arrangements of the actin and micro-tubular cytoskeleton (Goh et al., 1997; Goh et al., 1998). Through its receptor, the growth hormone can also activate the intracellular signal paths independent of kinase JAK2 (Lanning, Carter-Su, 2006). An example is the participation of the growth hormone in the cellular calcium economy, taking place through the tyrosine kinase Src (Zhang et al., 2006). Transduction of the signal induced by GH is sometimes connected with the intracellular changes of the concentration of calcium ions and takes place through the calcium channels dependent on kinase PI3-K and activation of protein kinase C (PKC, Protein Kinase C) (Moutoussamy et al., 1998).

In addition to the most important, above mentioned paths regulating the transcription of target genes, the growth hormone acts on many other levels of modulation of expression of the selected genes (Ceseña et al., 2007). The best known contain:

- epigenetic control of expression, by affecting the methylation and demethylation of DNA and the reversible conversion of euchromatin to heterochromatin (Waxman, O'Connor, 2006),
- GH participation in post-translational modifications (phosphorylation, acetylation, methylation, ubiquitination, sumoylation) of nuclear proteins included in the transcription complexes (Ceseña et al., 2007),
- the effect of somatotropin on the composition of nucleo-protein complexes (Ceseña et al., 2007),
- regulation of intracellular translocation of elements of the GH signal paths (Ceseña et al., 2007).

There was described the signal path independent of the membrane growth hormone receptor, through which GH directly regulates the metabolic activity of mitochondria, demonstrating the direct inhibiting effect on the succinate dehydrogenesis (EC 1.3.99.1) and cytochrome c oxidase (EC 1.9.3.1) (Ardail et al., 2010). The growth hormone also shows the ability to bind with the prolactin receptor, thus being the competitive antagonist of this hormone (Rose et al., 1986; Kelly et al., 1991).

Also the silencing factors of this signal are involved in the regulation of the transduction signal induced by GH, such as the suppressor of cytokine signalling (SOCS) protein and tyrosine phosphatase (EC 3.1.3.48) (Greenhalgh et al., 2002; Lanning, Carter-Su, 2006; Martinez et al., 2012). These molecules are involved in the molecular mechanism of ubiquitination, internalisation and degradation of GHR and dephosphorylation of the phosphorylated elements of the signal paths of the growth hormone (van Kerkhof et al., 2000; Rico-Bautista et al., 2004; Lanning, Carter-Su, 2006). Of fundamental importance is also the reduction of the number of free receptors and reduction of their affinity to GH, with the increase of its concentration (Deng et al., 2007).

In desensitization of intracellular signal mechanisms of GH there is also involved the phospholipase C (EC 3.1.4.3) and the reversible process of GHBP formation, through the GHR proteolysis, leading to the split of its extracellular domain (Fernández et al., 1998; Rui et al., 2000; Guan et al., 2001). This process takes place through the protein kinase path C (EC 2.7.11.13), involving the platelet-derived growth factor (PDGF) and lysophosphatidic acid (LPA) (Rui et al., 2000).

Recently, it has been proven that an important role in the regulation of the GH transduction signal is played by the environmental factors, such as body temperature – its decrease under the optimal value for the given species results in the prominent limitation of the response to the signal induced by the growth hormone (Nespital, Strous, 2012).

Growth hormone gene

The growth hormone gene, the prolactin gene (*PRL*), the placental lactogen (*PL*, chorionic sommatomammotropine, *CS*), the somatolactine (*SL*) occurring in fish and genes of a series of the GH-like proteins and prolactine-like proteins show great structural-functional similarity and belong to one, monophyletic family of the somatomammotrophic genes (Wallis, 1992; Goffin et al., 1995; Lin et al., 1997; Soares, 2004; Huising et al., 2006; Fukamachi, Meyer, 2007). Numerous data indicate that these genes evolved from the ancestral gene through duplication, deletion and insertion, resulting in its divergent evolution (Owerbach et al., 1981; Nicoll et al., 1986; Vidal et al., 1995). It is assumed that the closest to this original gene is currently the growth hormone gene, and the formation of a separate gene for prolactin probably took place not earlier than 400 million years ago (Miller, Eberhardt, 1983; Cooke et al., 1988; Kawauchi et al., 2002).

In most mammals (except for primate and some members of the Caprinae family) the growth hormone gene occurs in one copy (Chen et al., 1989; Cooke, Liebhaber 1995; Wallis et al., 1998; Krawczak et al., 1999). In American mink it is located in chromosome 5 (pp. 25–23) (Malchenko et al., 1994; Serov, Rubtsov, 1998). This location was specified thanks to the comparative genomics (Serov, 1998). Characteristic, also for *N. vison*, is the synteny of *GH*, *ALDC* (aldolase C gene), *HOXB* (homeotic B gene), *GALK* (galactokinase gene), *TK1* (thymidine kinase gene 1) and *UMPH2* (phosphohydrolasis 2 gene uridine-5'monophosphate) genes (Koroleva et al., 1996; Serov, 1998).

cDNA for the GH gene of American mink (*mGH*) was sequenced and described for the first time by Shoji et al. (1990) (GenBank: X56120.1). The sequence deposited in GenBank was then verified and supplemented by Harada et al. (1990) (GenBank: E04303.1) and Perelygina et al. (1991) (GenBank: E04303.1). The total length coding sequence (CDS) was specified on 648 bp (Shoji et al., 1990). There is also known the sequence of untranslated regios (UTR) in position 5' (fragment) and 3', enabling the localisation of the poliadenylation signal (5'-AATAAA-3') in position c.*84 –*89, as well as the flanking region 3' (Harada et al., 1990; Shoji et al., 1990). The complete sequence of the growth hormone gene in American mink was described by Skorupski (2017).

The *mGH* gene consists of 5 exons (10 bp, 161 bp, 117 bp, 162 bp, 201 bp) and 4 introns (245 bp, 171 bp, 176 bp, 290 bp), and its total length is 1745 bp (Skorupski, 2017).

Skorupski (2017) identified fourteen polymorphic variable sites – 12 SNP substitutions (g.616G>C, g.703G>A, g.742G>A, g.748T>C, g.775G>A, g.778G>A, g.837G>C, g.846A>G, g.931C>T, g.1156A>G, g.1219C>G, g.1329T>C), one single nucleotide deletion (g.885delC) and one ins/del polymorphism (18-nucleotide motif – g.1219_1236delCTCTTGCAGGGGCAGGGG) . It was shown that the biological effect of the American mink growth hormone gene is related to changes in a splicing regulatory sequences and sequence motifs, different reading of codons and on an influence on the mRNA secondary structure (Skorupski, 2015).

Haplotype analysis of polymorphisms in the American mink growth hormone gene revealed exsistence of four haplotype blocks, with a correlation coefficient ranging from 50 to 94% (Skorupski, 2016). The described LD proves a relatively low frequency of recombination events between variable sites of the *mGH* (Skorupski, 2016).

The expression on the level of growth hormone gene transcription regulates, most of all, a specific transactivator of the POU domain specific for the pituitary gland – transcription factor Pit-1 (Li et al., 1990; Gil-Puig et al., 2005). The key role in promoting the expression of the *GH* gene in somatotropic and somatomammotropic cells, as well as silencing of this expression in lactotropic cells, plays a supersensitive place for deoxyribonuclease I (HSI, deoxyribonuclease I hypersensitive site I), located from several to several dozens of kb under the gene promoter (Aizawa et al., 1995; Su et al., 2000; Ho et al., 2011). In some species HSI is located in the *locus* control region (LCR) of the somatotropin gene, also grouping other transcription regulatory genes (Su et al., 2000; Ho et al., 2011). In addition, the epigenetic regulation of the GH gene transcription was reported, connected to the acetylation of chromatin domains in the LCR region (Ho et al., 2002).

The coding sequence of the *mGH* shows a strong resemblance to the cDNA of the growth hormone gene of other mammalian species. The number of synonymous substitutions per nucleotide, compared to the gene of somatotropin of domestic goat, pig, rat, mouse, human and cattle is, respectively, 0.44, 0.33, 0.52, 0.48, 0.53 and 0.44. While the number of non-synonymous substitutions on average per nucleotide, compared to those species, is, respectively, 0.05, 0.01, 0.03, 0.03, 0.18 and 0.05 (Ohta 1993). At the same time, it is estimated that the *mGH* gene is divided, from ancestral growth hormone gene for mammals, by three non-synonymous substitutions and nine synonymous substitutions (Adkins et al., 2001).

It is worth mentioning that the growth hormone gene is characterised in mammals with low basic evolutionary rate, estimated at 0.25 substitutions/codon/year x 10^9 (Wallis, 2001). However, characteristic for the evolution of this gene are the periods of discrete, rapid changes, during which the evolution rate increases even 50 times in relation to the basic rate (Wallis, 1994; Wallis, 2001). Two similar cases of evolutionary acceleration in Mammalia group were described – in the evolutionary line of even-toed ungulates and primate (Wallis, 2001). Currently, it is estimated that approx. 58% of substitutions in the nucleotide sequence of the growth hormone gene of different mammalian groups is the result of the above described evolutionary changes of a step (punctualistic) nature and constitutes the confirmation of the hypothesis of the so-called episodic nature of the somatotropin gene evolution (Ohta, 1993; Wallis, 2001).

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