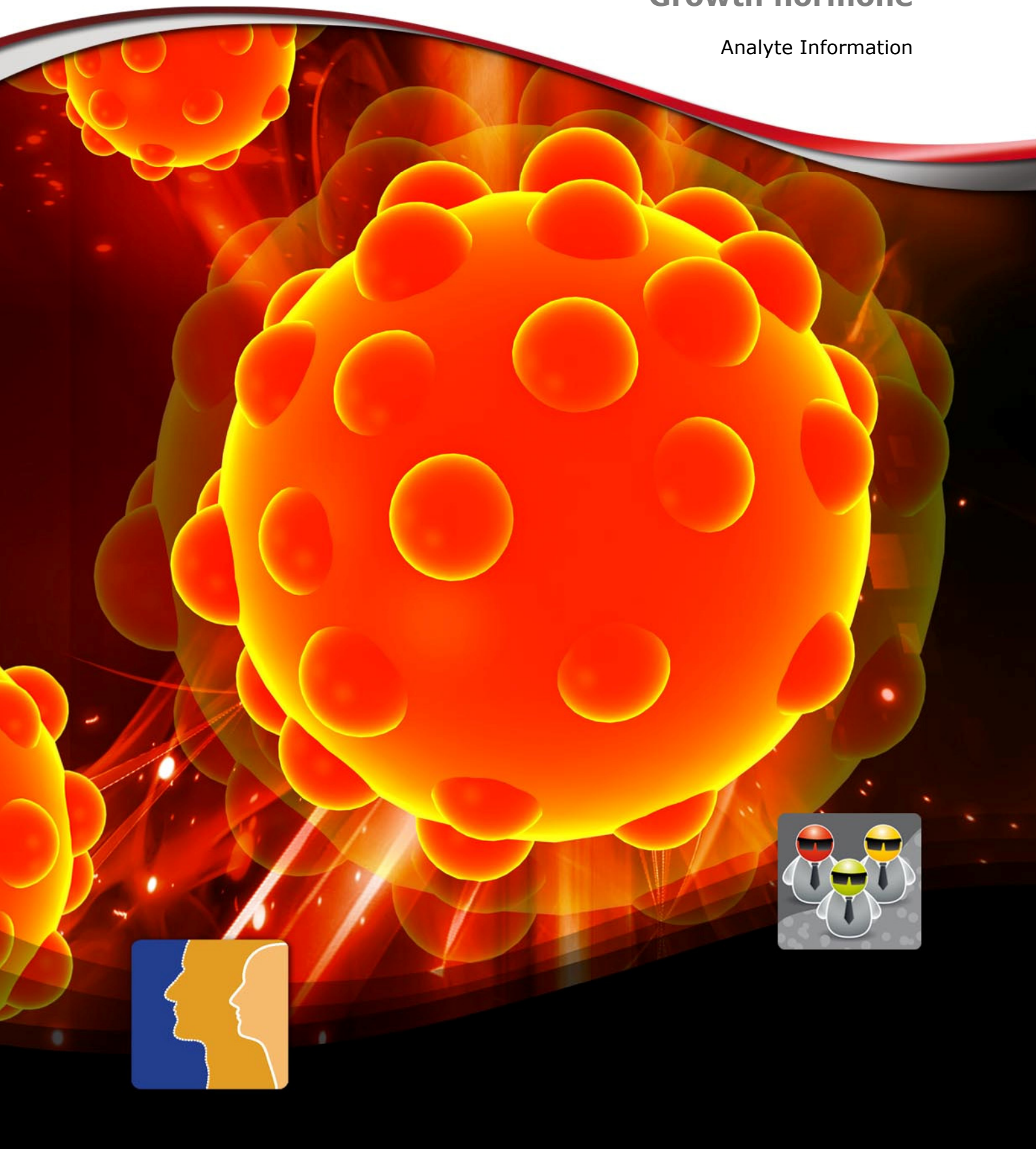
Growth

Growth hormone

Analyte Information



Growth hormone

Introduction

Growth hormone (GH) is a single chain polypeptide, the principal isoform consists of 191 amino acids and has molecular mass 22 kDa, containing two intramolecular disulfide bridges. It is structurally similar to prolactin and to the placental hormone called either chorionic somatomammotropin (hCS) or placental lactogen. Several other molecular isoforms of GH exist in the pituitary gland and are released to blood.

GH is the most abundant protein produced by the anterior pituitary gland (adenohypophysis). It is released into the bloodstream in a pulsatile manner under the regulatory control of hypothalamic GH-releasing hormone (GHRH) and somatostatin (SST).

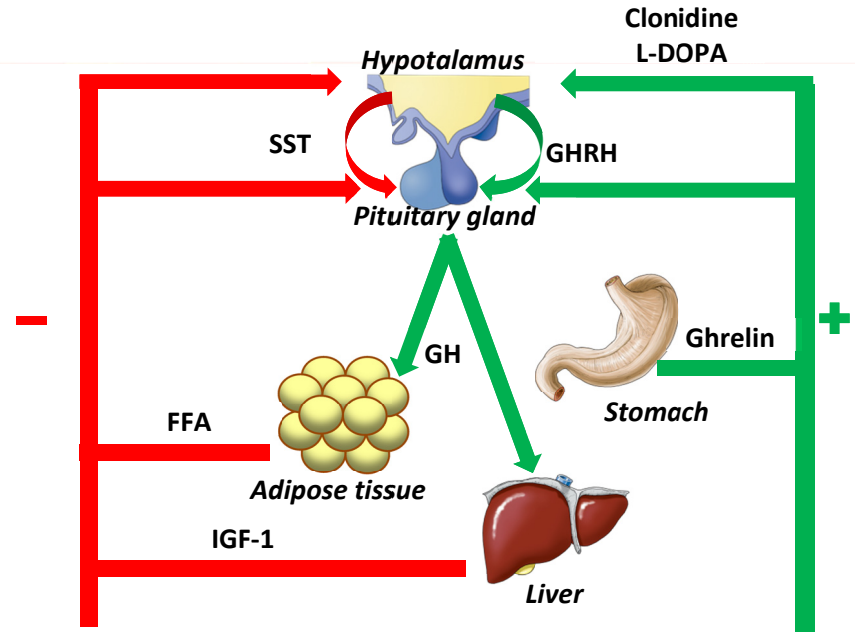
Its main biological function is to promote growth in soft tissue, cartilage and bone, either directly or via the effects of insulin like growth factors (IGFs).

GH produced naturally in humans and animals is also called somatotropin (STH), whereas the term somatropin refers to GH produced by recombinant DNA technology.

Biosynthesis

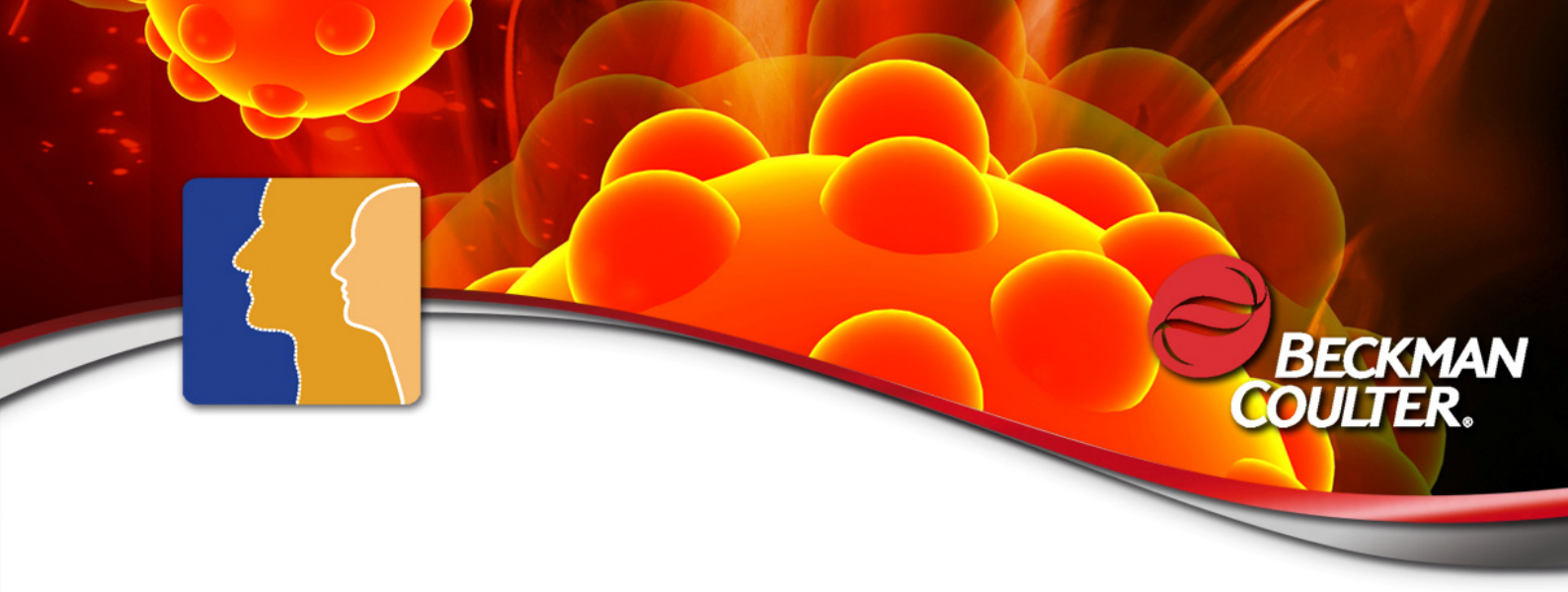
GH is synthesized by special cells in the anterior pituitary called somatotropes, where it is stored in secretory granules. It is the most abundant hormone in the pituitary accounting for 25% of the gland's hormones. Its secretion is regulated by two hypothalamic hormones: GH-releasing hormone (GHRH), which increases GH release, and somatostatin, which inhibits GH release. Somatostatin and GHRH are created in response to various neural, metabolic, and hormonal stimuli, including exercise, stress, hypoglycemia, amino acid concentration, or in response to hormones such as ghrelin, testosterone, estrogens or thyroxine. GH stimulating and inhibiting factors are listed in Tab.1., simplified scheme in Fig.1.

Fig.1.: Factors stimulating and inhibiting GH secretion



Abbrev.: FFA – free fatty acids; SST – somatostatin; GH – growth hormone; GHRH - Growth hormone-releasing hormone; L-DOPA - L-3,4-dihydroxyphenylalanine; IGF-1 – insulin-like growth factor-1

GH is synthesized and secreted in a pulsatile manner throughout the day. For most of the time, the levels are relatively low and stable, but there are several secretory peaks occurring approximately 3 hours after meal or physical activity. Marked rise of GH levels appears approximately 90 minutes after the onset of sleep, reaching maximal value during the period of the deepest sleep.

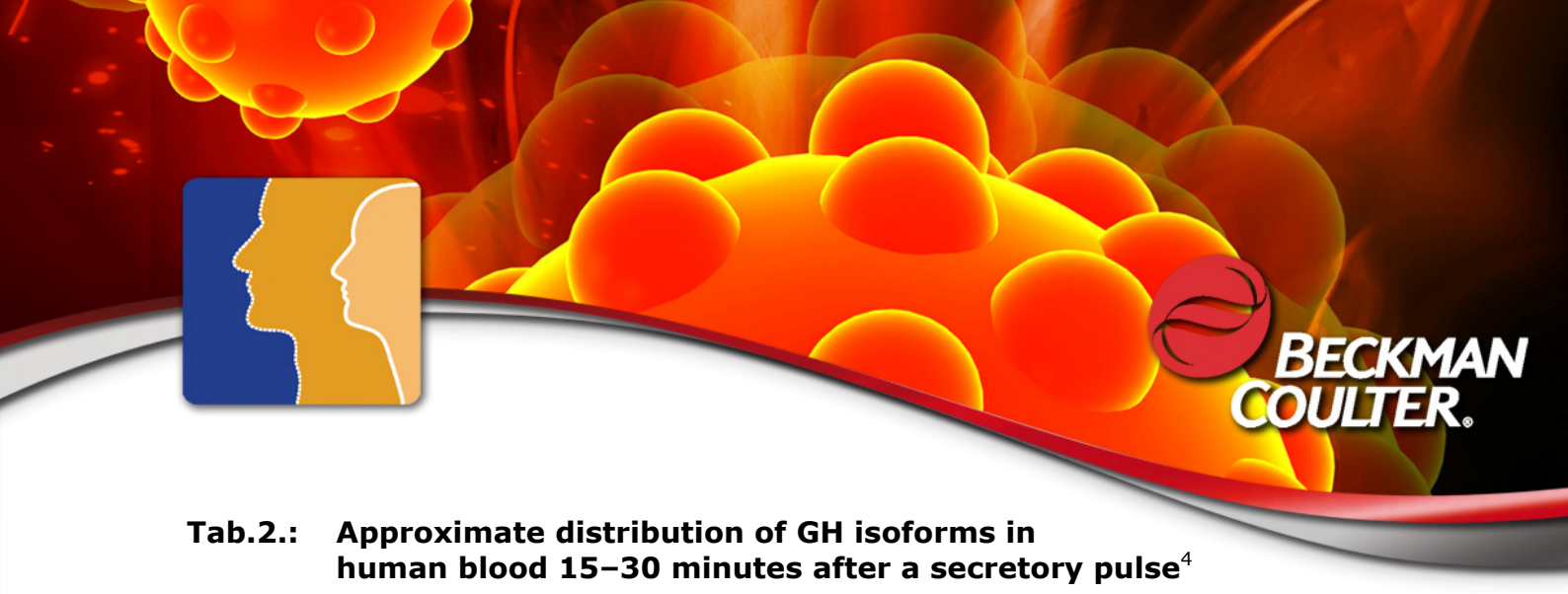


Tab.1.: Factors stimulating and inhibiting GH secretion

Stimulators of GH secretion	Inhibitors of GH secretion

○ Peptide hormones
  ○ Growth hormone-releasing hormone (GHRH) through binding to the growth hormone-releasing hormone receptor (GHRHR)
  ○ Ghrelin through binding to growth hormone secretagogue receptors (GHSR)
○ Sex hormones
  ○ Increased androgen secretion during puberty (in males from testis and in females from adrenal cortex)
  ○ Estrogen
○ Clonidine and L-DOPA by stimulating GHRH release
○ Hypoglycemia, arginine and propranolol by inhibiting somatostatin release
○ Deep sleep
○ Niacin as nicotinic acid
○ Fasting
○ Vigorous exercise
	○ Somatostatin (SST) from the periventricular nucleus
	○ Circulating concentrations of GH and IGF-1 (negative feedback on the pituitary and hypothalamus)
	○ Hyperglycemia
	○ Glucocorticoids

Growth hormone is a heterogeneous protein hormone consisting of several isoforms. All isoforms are released together from pituitary gland, and their distribution in blood differs with time after the secretion, because of different biological half-lives of various isoforms. The exact distribution and biological activity of all the isoforms are not completely known yet. Complexity of their distribution in blood is shown in Tab.2.



Tab.2.: Approximate distribution of GH isoforms in human blood 15–30 minutes after a secretory pulse[4]

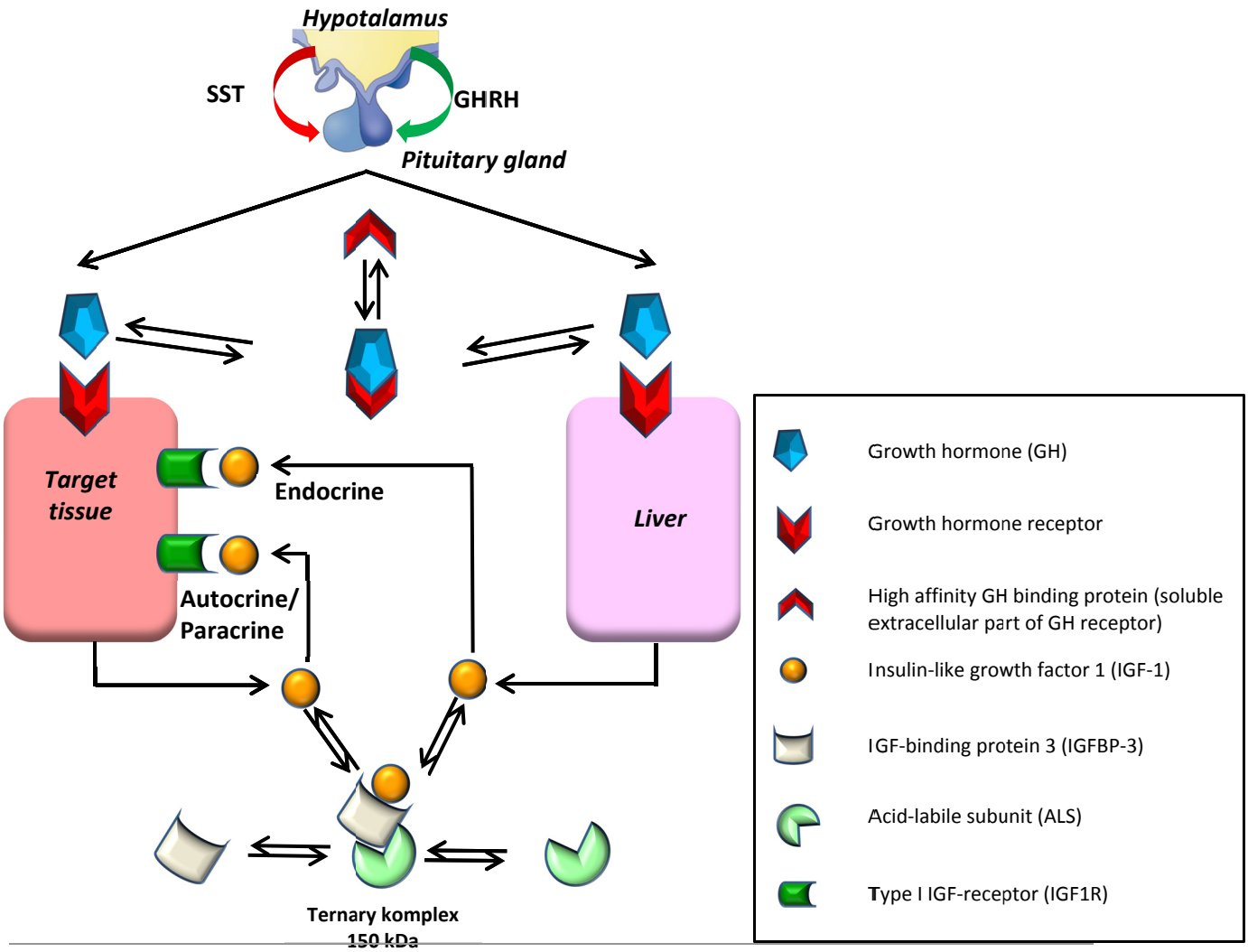
Monomeric GH	
22 kDa GH	
Free	22%
Bound to high affinity GHBP	21%
Bound to low affinity GHBP (α2-macroglobulin)	2%
Total 22 kDa GH	45%
20 kDa GH	
Free	2%
Bound to high affinity GHBP	0.5%
Bound to low affinity GHBP (α2-macroglobulin)	2%
Total 20 kDa GH	5%
Acidic GH (desamido-, acylated and glycosylated GH)	5%
Dimeric GH	
22 kDa GH Dimers	
Non-covalent dimers	14%
Disulfide dimers	6%
Total 22 kDa GH dimers (bound fractions unknown)	20%
20 kDa GH Dimers	
Non-covalent dimers	3%
Disulfide dimers	2%
Total 20 kDa GH (bound fractions unknown)	5%
Acidic GH Dimers (desamido-, acylated and glycosylated GH)	
Non-covalent dimers	1.5%
Disulfide dimers	0.5%
Total acidic GH dimers (bound fractions unknown)	2%
Oligomeric GH (trimer-pentamer)	
22 kDa GH Oligomers	
Non-covalent oligomers	7%
Disulfide oligomers	3%
Total 22 kDa GH oligomers (bound fractions unknown)	10%
20 kDa GH Oligomers	
Non-covalent oligomers	1%
Disulfide oligomers	0.5%
Total 20 kDa GH oligomers (bound fractions unknown)	2%
Acidic GH Oligomers (desamido-, acylated and glycosylated GH)	
Non-covalent oligomers	1%
Disulfide oligomers	0.5%
Total acidic GH oligomers (bound fractions unknown)	2%
Fragments (12, 16 and 30 KDa immunoreactive species)	variable

Placental variant of GH (placental GH) is produced exclusively by placenta during pregnancy. It differs in 13 amino acids from 22 kDa pituitary form, and its production is independent on hypothalamus. Production starts at gestation weeks 5-8 and its concentration in maternal blood increases until reaching plateau at week 36.

Metabolism

GH is cleared mainly by renal mechanism. Biological half-life differs for various isoforms, and it is approximately 20 minutes for 22 kDa isoform.

Fig.2.: GH-IGF axis



Physiological function

GH is important in promoting somatic growth and in regulating body composition, intermediary muscle and bone metabolism. GH acts by interacting with a specific receptor on the surface of cells. The overall effect of GH on the body is anabolic, it promotes growth in soft tissue, cartilage and bone. Some of GH effects are direct actions whereas others are mediated via insulin-like growth factors (IGFs), particularly IGF-1. The cascade is called GH-IGF axis (or somatotropic axis) – see Fig. 2.

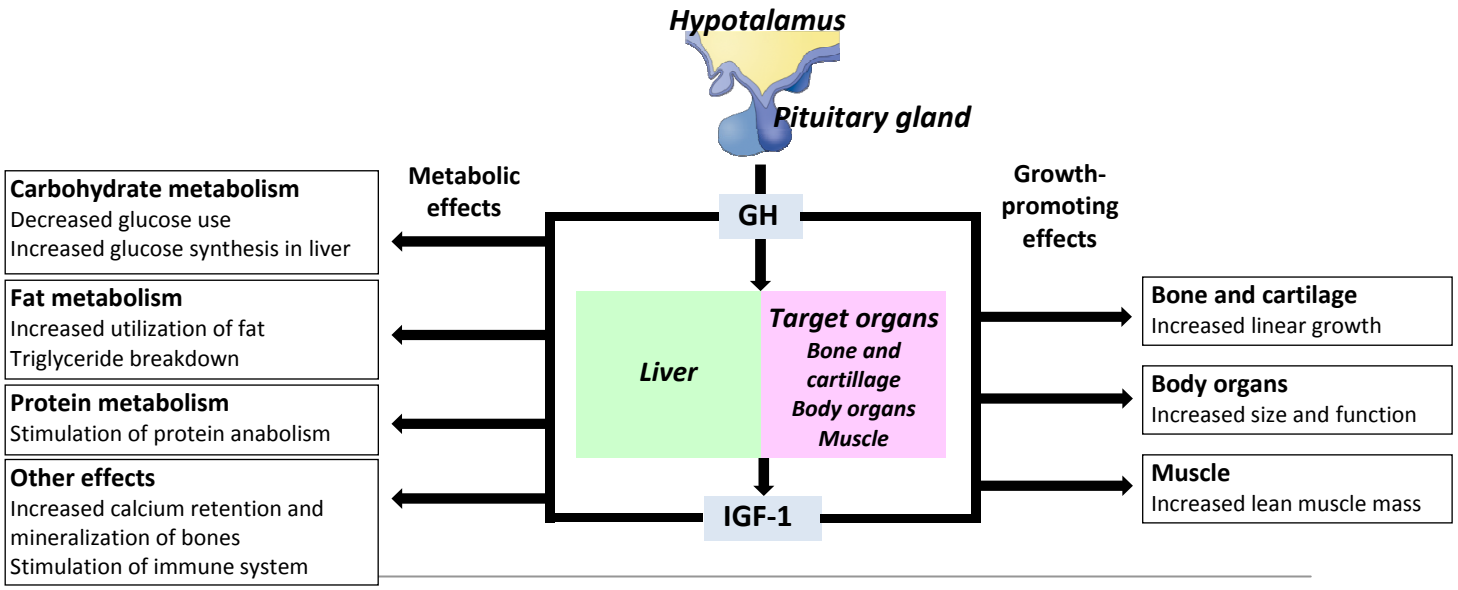
Effects on growth

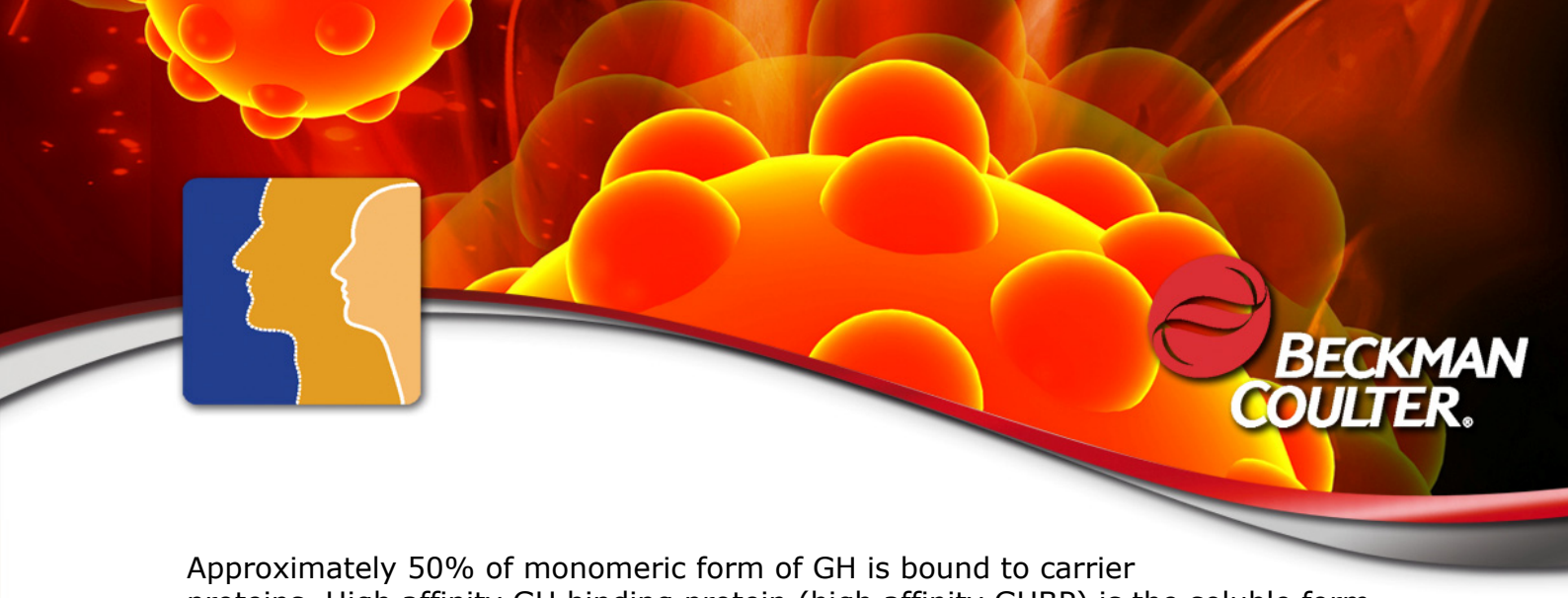
Growth hormone seem to have a direct effect on bone growth in stimulating differentiation of chondrocytes. Nevertheless, the major role of GH in induction of body growth is to stimulate the liver and other tissues to secrete IGF-1. IGF-1 has growth-stimulating effects on a wide variety of tissues. Although the principal source of IGF-1 in the circulation is the liver, it seems that the major determinant of body growth is IGF-1 produced in response to GH stimulation in target tissues and acting by autocrine or paracrine mechanism.

Metabolic effects

Growth hormone has also significant effects on protein, lipid and carbohydrate metabolism. Again, direct GH action is combined with indirect effects mediated by IGF-1. Its action on protein, fat, and carbohydrate metabolism is shown in Fig.3.

Fig.3.: Effects of GH and IGF-1 in the body





Approximately 50% of monomeric form of GH is bound to carrier proteins. High affinity GH binding protein (high affinity GHBP) is the soluble form of the extracellular part of the GH receptor. Its concentration is relatively low (around 1 nM), whereas the concentration of low affinity GHBP is much higher (around 0.7 µM).

Levels

GH is synthesized and secreted in a pulsatile manner throughout the day. The blood concentration of GH during these peaks may range from 5 to even 45 ng/mL. The largest and most predictable of these GH peaks occurs about an hour after onset of sleep. There is wide variation between days and individuals. Nearly 50% of GH secretion occurs during the third and fourth NREM (non rapid eye movement) sleep stages. Between the peaks, basal GH levels are low, usually less than 5 ng/mL for most of the day and the night.

The pulsatile release of GH can make a single blood level measurement of GH difficult to interpret clinically, GH determination after stimulation test provides more reliable information.

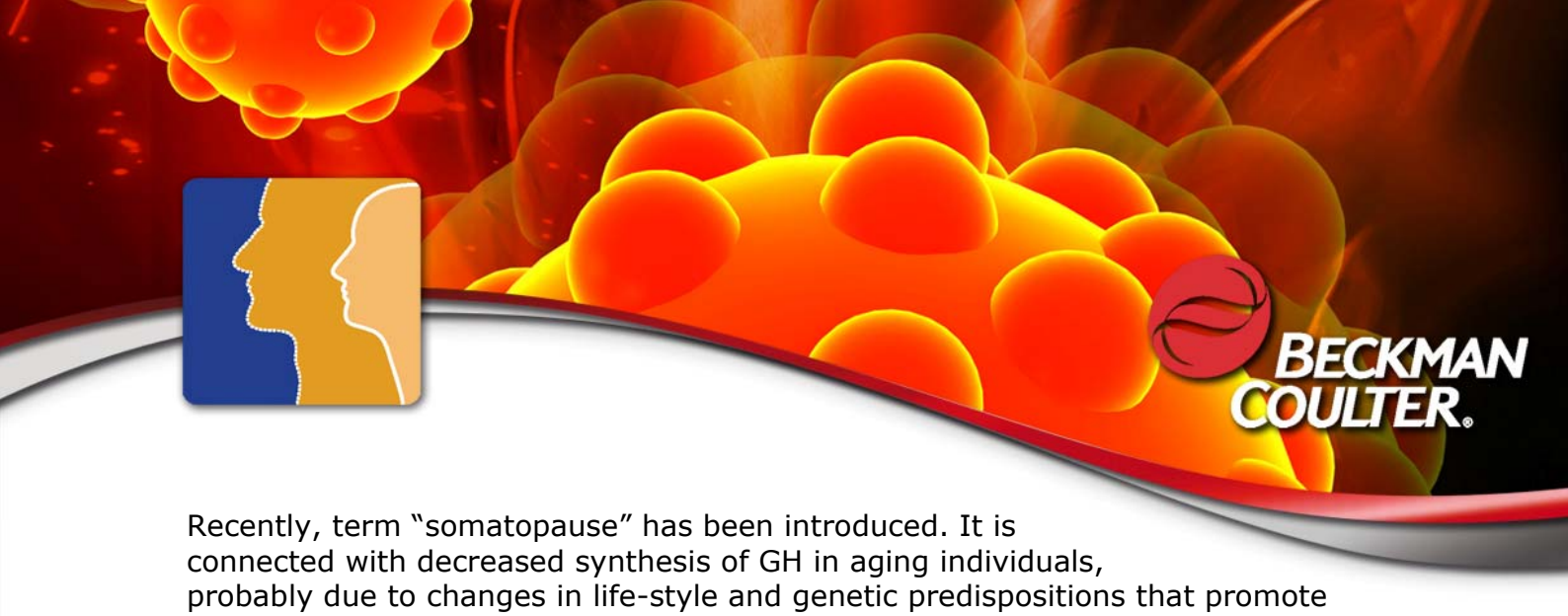
GH is produced by the pituitary gland of the fetus starting from the end of the 1st trimester of gestation.

The level of GH increase signigicantly during first hours of postnatal life in response to decrease in IGF-1 level. GH then decreases during several months and stays at low levels (<3-5 ng/mL) until puberty.

The onset of puberty is associated with a marked increase in GH, IGF-1 and IGFBP-3 levels, in response to increased levels of sex steroid hormones.

In pregnancy, placental form of GH is produced by placenta. It differs in 13 amino acids from 22 kDa pituitary form, and its production is independent on hypothalamus. Production starts at gestation weeks 5-8 and its concentration in maternal blood increases until reaching plateau at week 36.

GH secresion decreases progressively during adulthood.



Recently, term "somatopause" has been introduced. It is connected with decreased synthesis of GH in aging individuals, probably due to changes in life-style and genetic predispositions that promote accumulation of body fat and, in consequence, suppress pituitary GH release. In spite of all recent findings, it seems very premature to recommend GH treatment to reverse the age-associated deterioration in body composition and physical performance.

Typical GH levels[2] of children and adult males and females are given in Tab. 3.

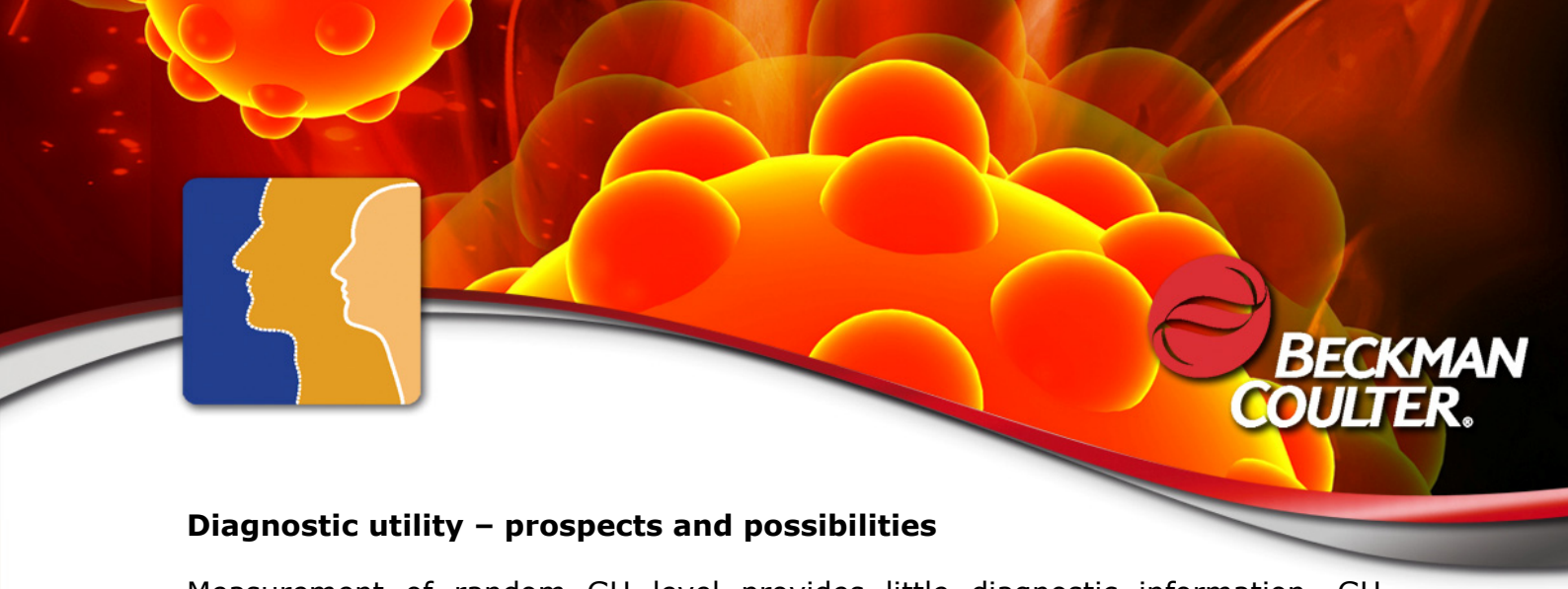
For each assay, the relevant reference values are shown in the appropriate Instructions for Use (IFU).

Table 3: Typical GH levels

Serum	**Reference interval** (ng/mL)*
Cord blood:	8–41
Child	
1–7 years	1–13.6
Puberty	
7–11 years	1–16.4
11–15 years	1–14.4
15–19 years	1–13.4
7–11 years	1–16
Adult	
Male:	0–4
Female	0–18
Male >60 years	1–9
Female >60 years	1–16

* WHO 2nd IS 98/574

Equation for the conversion of the units: 1 ng / mL = 3 mIU / L



Diagnostic utility – prospects and possibilities

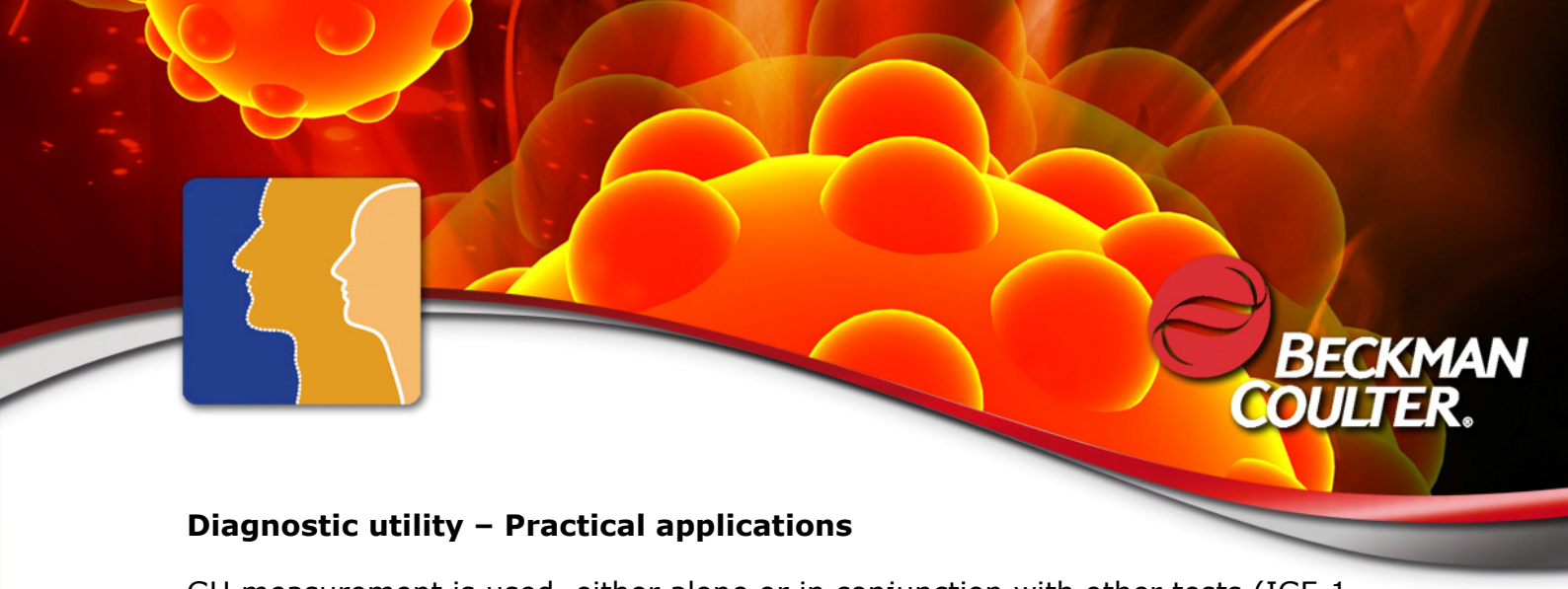
Measurement of random GH level provides little diagnostic information. GH secretion is best assessed during tests that stimulate or supress GH release. Altered GH levels can be found in a broad spectrum of conditions, e.g.:

Elevated GH levels

- pituitary gigantism
- acromegaly
- Laron dwarfism
- ectopic GH secretion (neoplasms of stomac, lung)
- malnutrition, prolonged fasting, anorexia nervosa
- renal failure
- cirrhosis
- stress; excercise
- uncontrolled diabetes mellitus

Decreased GH levels

- pituitary dwarfism
- hypopituitarism
- adrenocortical hyperfunction



Diagnostic utility – Practical applications

GH measurement is used, either alone or in conjunction with other tests (IGF-1, IGFBP-3) to diagnose diseases of GH-IGF axis and to monitor their treatment.

GH deficiency (GHD) in childhood and in adults [5,8]

The evaluation for GHD in a short child should be initiated when other possible causes like hypothyroidism, chronic systemic disease etc. are excluded. The diagnosis should be confirmed by two GH provocation tests, in which the concentration of GH fails to rise above 20 mIU/L. Arginine, clonidine, glucagon or L-dopa are recommended stimulation agents.

It is beneficial to determine also IGF-1 and/or IGFBP-3 concentrations. Low levels correspond with diagnosis of GHD.

In case of discordant results of stimulated GH level and IGF-1 and/or IGFBP-3 levels, evaluation of spontaneous GH secretion over time (12 or 24 hours) may help to set up diagnosis.

Both GH deficiency and mild-to-moderate GH-resistance is treated with recombinant human GH (rhGH) injections.

The aim of GH replacement therapy is to improve height velocity and restore IGF-1 and IGFBP-3 levels to within the reference range, ideally into the middle third. Higher levels are rarely associated with any further therapeutic gain, but can potentially lead to certain long-term problems associated with an excess of GH.

GH replacement therapy is also profitable in GH deficient adults. Nevertheless, there is an ongoing debate about the correct dose adjustment.

Acromegaly, gigantism[6]

Glucose normally suppresses GH production (hGH) (<1-2 ng/mL). Individuals with acromegaly or gigantism show no decrease or a paradoxical increase in GH level after OGTT (oral glucose tolerance test). In well treated acromegaly, IGF-1 level should be within normal range and GH nadir values should be below 0.4 ng/mL during OGTT. IGFBP-3 determination may be useful when GH and IGF-1 levels are discordant.

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