ASSESSMENT OF GROWTH HORMONE LEVEL IN NEWBORNS WITH INTRA-UTERINE GROWTH RESTRICTION

Thesis

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Master Degree in
Pediatrics

By

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INTRODUCTION

The fetus with intrauterine growth restriction (IUGR) is a fetus that does not reach his potential of growth and becomes growth restricted (birth weight <10th percentile) because of maternal, fetal, or placental disorders occurring alone or in combination ***(Giancarlo Mari, 2006).***

In developing countries, approximately 70% of low birth weight infants have intrauterine growth restriction ***(Stoll et al., 2008)***.

Children with IUGR are at higher risk for intellectual deficit and permanent debilitating short stature ***(Holeman et al., 2003)***.

Growth hormone (GH) has been detected in the fetal circulation by 10 weeks gestation and appears to originate exclusively from the fetal pituitary, independently of growth hormone releasing hormone (GHRH), pituitary GH or placental GH in the maternal circulation ***(Frankenne et al., 1988)***.

The mitogenic actions of growth hormone are mediated through increases in the synthesis of insulin like growth factor-I (IGF-I) which are mostly secreted

by the liver and their secretion is regulated mainly by GH and nutritional status ***(Parks et al., 2008)***. In mice knockout or disruption of the IGF-I genes or IGF-type I receptor leads to severe growth retardation ***(Lassere et al., 1991)***.

IUGR newborns were found previously to have low insulin levels ***(Setia et al., 2007)***, which were found to correlate more strongly with ponderal index ***(Setia et al., 2006)***. A significant positive correlation between pulses of insulin and coincident pulses of GH in relation to neonatal feeds has been found ***(Ogilvy-Stuart et al., 1998)***.

Association of intrauterine growth restriction with fetal hypersomatotropinaemia and GH hyper-sensitivity to GHRH was established in ovine species ***(Bauer et al., 1995)***.

AIM OF THE WORK

The aim of this work was to study the relationship of GH level at birth with birth weight.

GROWTH HORMONE

Structure of growth hormone:

Growth hormone (GH), also called somatotropin or somatotrophic hormone, is the most abundant hormone in the human pituitary gland ***(Muller et al., 1999)***.

Human GH is a simple peptide of molecular weight 22,005 that contains 191 amino acids in a single chain with two disulfide bridges and four helical structures ***(Ezeilo, 2002)***.

Normally 70-75% of pituitary secreted GH is in a 22 kilodalton form, while 20 kilodalton GH represents the second largest contributor to the circulating GH pool ***(Wit et al., 2005)***.

The GH molecule has a single tryptophan residue at position 85, it is devoid of carbohydrate substituent and 2 homologous disulphide bonds stabilize its structure ***(Leschek et al., 2004)***.

The gene encoding for the human GH is present on the long arm of chromosome 17(q22-24) ***(Parks et al., 2008)***.

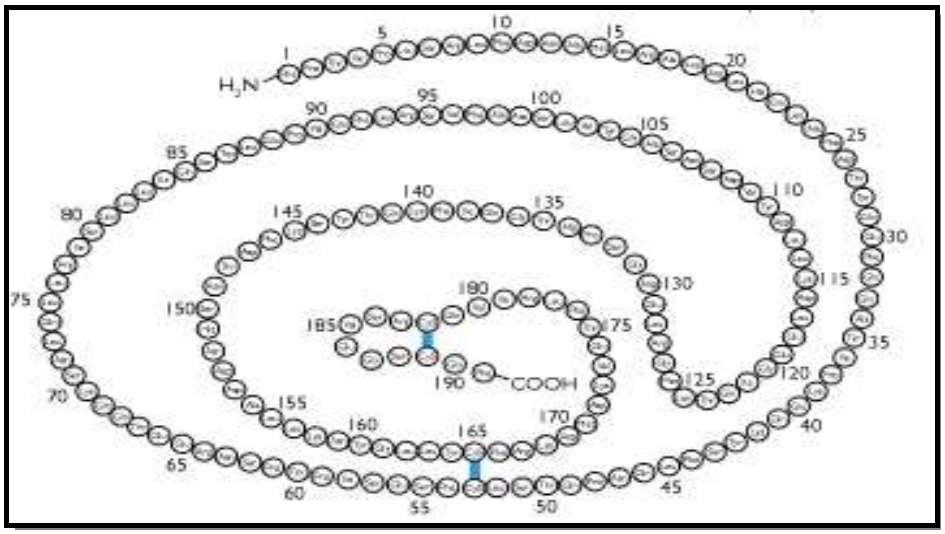

Fig. (1): Structure of growth hormone ***(Barrett et al., 2010).***

Physiological secretion of GH:

GH is synthesized and released from somatotropes, one of two of acidophilic cells present in the anterior pituitary gland ***(Blake et al., 2005)***.

GH is bound to a protein in plasma that is a large fragment of extracellular domain of the GH receptor. About half the GH activity is bound, providing a reservoir of the hormone to compensate for the wide fluctuations that occur in secretion .The half-life of circulating GH in human is 6-20 minutes ***(Amar et al., 2003)***.

Growth hormone is formed in the fetal pituitary gland after about 5 weeks gestation. There is a brief postnatal rise in term infant followed by fall to childhood levels. In premature infants, a prolonged postnatal rise may occur ***(Gluckman et al., 1997)***.

The level of circulating GH is high in children and higher during puberty. After adolescence, secretion decreases slowly with aging, finally falling to about 25% of the adolescent level in very old age ***(Rogol, 2010).***

The normal concentration of GH in the plasma of a child or adolescent is about 6ng/mL and between 1.6 and 3ng/mL in adults ***(Hall, 2006)***.

Growth hormone receptors:

The GH receptor is a single chain molecule of 620 amino acids. It has an extracellular domain, single membrane spanning domain and a cytoplasmic domain. Proteolytically cleaved fragments of the extra- cellular domain circulated in plasma and act as a GH-binding protein ***(Amar et al., 2003)***.

GH has two binding sites for receptors. When it binds to one of the receptor subunits, the other binding site attracts another subunit producing a

homodimer. Dimerization is essential for receptor activation ***(Barrett et al., 2010)***.

Regulation of GH secretion:

The secretion of GH is mediated by two hypothalamic hormones: growth hormone-releasing hormone (GHRH) and somatostatin (growth hormone inhibitory hormone). These hypothalamic influences are tightly regulated by an integrated system of neural, metabolic and hormonal factors ***(Amar et al., 2003)***.

Table (1): Summarizes the factors that affect GH secretion

Increase	Decrease
❖ Physiologic Sleep Exercise Stress (physical or psychological) ❖ Postprandial Hyperaminoacidemia Hypoglycemia(relative)	❖ Postprandial hyperglycemia ❖ Elevated free fatty acids
❖ Pharmacologic: Hypoglycemia: Absolute: insulin or 2-dexoyglucose Relative:postglucagon Hormone: GHRH ACTH, vasopressin Estrogen Thyroid stimulating hormone Gonadotropin releasing hormone Neurotransmitters: α-adrenergic agonists(clonidine) B-adrenergic antagonist (propranolol) Serotonin precursors Dopamine agonists GABA agonists	❖ Hormones: Somatostatin Growth hormone Progesterone Glucocorticoids Neurotransmitters: Alpha-adrenergic antagonists (phentolamine) Beta-adrenergic agonists (isoproterenol) Serotonin antagonists (phenothiazines)

Increase	Decrease
Potassium infusion Pyrogens (pseudomonas endotoxin)	
❖ Pathologic states: Protein depletion and starvation Anorexia nervosa Ectopic production of GHRH Chronic renal failure Acromegaly	❖ Obesity Hypo-and hyperthyroidism

(Aron et al., 2007)

A. Growth Hormone Releasing Hormone (GHRH)

Control of GH is probably mediated through GHRH rather than through the inhibitory hormone somatostatin ***(Mayo et al., 2000).***

GHRH stimulates cyclic adenosine mono-phosphate (cAMP) production by somatotropes which has both short and long term effects. The short term effect is to increase calcium ion transport into the cell, which causes fusion of GH secretory vesicles with the cell membrane and release of GH into the blood within minutes. The long term effect is to increase nucleus transcription by the genes to cause new GH synthesis ***(Hall, 2006)***.

Ghrelin is produced by the stomach and in the arcuate nucleus of the hypothalamus .GH secretion may be influenced by ghrelin levels in the hypothalamic-pituitary circulation and the systemic circulation ***(Kejioma et al., 1999).***

B- Somatostatin:

Somatostatin, a tetradecapeptide, is a potent inhibitor of GH secretion. It decreases cAMP production in GH-secreting cells and inhibits both basal and stimulated GH secretion. Somatostatin secretion is increased by elevated levels of GH and insulin-like growth factor-1 (IGF-1*)* ***(Guillermet-Guibert et al., 2005)***.

Alternating secretion of GHRH and somatostatin accounts for the rhythmic secretion of GH. Peaks of GH occur when peak of GHRH coincide with troughs of somatostatin. So secretion of GH is pulsatile, with the highest peaks occurring during sleep ***(Howlett et al., 2000)***.

C- The role of somatomedins in GH secretion and action:

Somatomedins are also called insulin like growth factors (IGF) because some of their actions are

like those of insulin. They promote lipogensis, protein synthesis, epiphyseal growth, inhibit lipolysis and increase transport of glucose and amino acids into muscle. Their insulin-like activity on glucose metabolism and anti-lipolytic activity are opposite those of GH ***(Hartman et al., 1993)***.

There are four different somatomedins, but the most important of these is somatomedin C (IGF-I) ***(Hall, 2006)***.

Circulating IGF-I is synthesized primarily in the liver and formed locally in mesoderm and ectodermic cells. Circulating level of IGF-I is related to blood levels of GH and to nutritional status ***(Woelfle et al., 2003)***.

Hypocaloric states are associated with GH resistance; therefore IGF-I levels are low with cachexia, malnutrition, and sepsis ***(Kasper et al., 2005)***.

The mitogenic actions of GH are mediated through increases in the synthesis of (IGF-I) ***(Moller et al., 2009).***

IGF-I production is highly GH dependent whereas IGF-II production is less dependent on GH.

IGF act both locally in a paracrine/autocrine fashion and distantly in a hormone like mode. They act through the type I IGF receptor which is structurally similar to the insulin receptor ***(Becker and Kenneth, 2001)***.

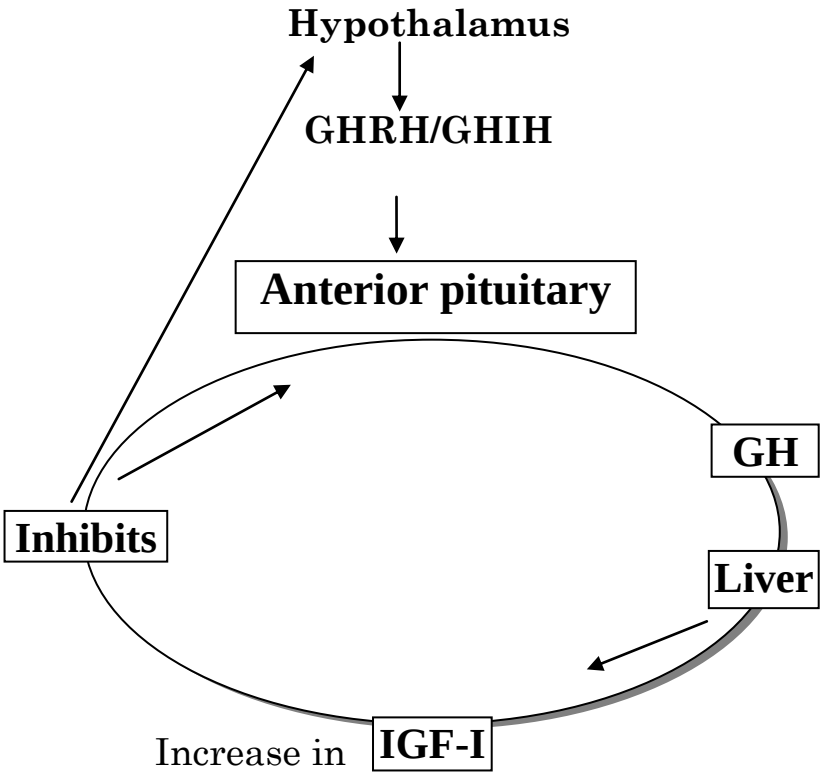

Fig. (2): Shows negative feedback regulation of GH ***(Ezeilo, 2002).***

D- Neural Control:

Neural control of GH Secretion results in irregular intermittent release associated with sleep