Fundamentals of Testosterone Production in Men

Dr. HHJ Leliefeld  Bruges, Belgium  25-26 September, 2014

PRISM IV
Why should we know?

Essential for understanding the ratio of diagnosis and treatment of:

- Late Onset Hypogonadism
- Early Onset Hypogonadism: Klinefelter, Kallmann
- Infertility
- Carcinoma of the prostate
- Gender problems
- Erectile dysfunction
- Male contraception
- BPH-therapy with 5α-Reductase Inhibitors (5ARI’s)
- Auto-immune diseases
- ED after radical prostatectomy
Topics of the lecture

• Endocrine Control System
• Feedback system
• The “Axis”
• Male hormone regulation
• Pulsatility
• Hormone receptors
• Down Regulation
• Testosteron-biosynthesis
• Pathophysiologival concept of LOH
The Endocrine Control System

- Releasing Hormones: Hypothalamus
- Tropic Hormones: Pituitary
- Neuroendocrine Control Centre: Hypothalamus, Pituitary, Connecting Stalk
• **Releasing Hormones**

  LHRH : LH- Releasing Hormone

• **Tropic Hormones:**

  TSH : Thyroid Stimulating Hormone  
  ACTH : AdrenoCortico Tropic Hormone  
  LH : Luteinising Hormone  
  FSH : Follicle Stimulating Hormone
Control of Endocrine System

• Feedback Mechanism

• Hormone Receptors

• Genes
Male Hormone Regulation

Feedback mechanism
The Hypothalamo-
PITUITARY-
Gonadal Axis
→ “The Axis”
Male Hormone Regulation

• Pulsatile secretion of LHRH from hypothalamus
• Schally and Guillemin, 1971, Nobel prize
• Unravelled the structure of this peptide hormone
• Analogues of this peptide were synthesized
• 10 to 100 fold more active: LHRH-agonists
• Paradoxic action when given in high dosage
• Down Regulation of the LHRH-receptors
Hormone Receptors: most significant discovery

The extent of binding of a hormone depends on three factors:

1. The concentration of the hormone
2. The number of receptors at a target cell
3. The receptor’s affinity for the particular hormone: genes role!

Testosterone receptors are present in nearly all organs/systems of men
Binding of Peptide Hormones: LHRH

- Specific receptors in the cell membrane
- Natural hormones
- Analogues of the natural hormones
  - agonists
  - superagonists
- Antagonists
Down Regulation = receptor response to hormone concentration

Initially: increased cell activation: LH and FSH ↑

Finally: loss of receptors: LH and FSH ↓

*Synthetic LH-RH leads to chemical castration*
Binding of Steroid Hormones: Testosterone

Prostate as target organ:
Prostate as an active endocrine organ

• Arguments:

  - after radical prostatectomy: 5α-DHT ↓
    T, LH and FSH ↑

  - after bilateral nerve sparing radical prostatectomy: 56% ED

  n: 1291 men; after 18 months
  despite 30 years of experience with nerve sparing operations

Prostate as an active endocrine organ

- Prostate: high expression of Type II-isoform of 5α-reductase
  leading to high concentrations of 5α-DHT; local and systemic

  5α-DHT: potent stimulator of axonal regeneration in animal model
  - maintaining structural and functional integrity of penile tissue

- Prostate as a source of the hormone 5α-DHT

Kacker, Morgentaler, J Sex Med, 2014; 11: 1898-1902
Two sources for Testosterone-production:

• Testes: 90% by the Leydig cells

• Adrenals: 10% in the adrenal cortex
Dual function of the testis:

• Endocrine gland: hormone-producing

• Exocrine gland: sperm-producing
Testosterone biosynthesis

• 5-7 mg Testosterone are produced each day by the Leydig cells of an adult man

• The parental substance of Testosterone biosynthesis is cholesterol which is mainly synthesized by the Leydig cells

• Through a total of 5 enzymatic stages, cholesterol is hydrolyzed to Testosterone

• Half-life time: 10-20 minutes
Biosynthesis of Testosterone in the Leydig cells

Crucial enzyme: Cytochrome P450ssc leading to Pregnenolone
Transport of Testosterone in the blood

• 60% tightly bound to SHBG
• 38% loosely bound to albumin
• 2% free Testosterone
Effects of T / E₂ during week 8-14 of pregnancy

• Ratio ringfinger / forefinger

• Volume right / left hemisfere

• Testicle

• Breast
Effects of T / E₂ during week 8-14 of pregnancy

• Testosterone : ringfinger longer than forefinger : better sperm
• Oestrogens : forefinger longer than ringfinger : more fertile

• Testosterone : right hemisfere larger : better spatial understanding
• Oestrogens : left hemisfere larger : better linguistic expression

• Testosterone : larger right testicle
• Oestrogens : larger left breast

The pathophysiological concept of LOH

4 factors: functioning of the Hypothalamo-Pituitary-Gonadal Axis

• Diminishing of the Leydig cell function : T decreases

• The negative feedback is diminishing : LH doesn’t increase

• SHBG increases with age : bioactive T decreases

• Diminishing of number and sensitiveness of the Androgen Receptors
Prism IV Bruges, Belgium

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