CALCIUM AND THYROID METABOLISM

Westmead Primary Exam Group

THYROID HORMONES

- Chemistry - principle hormones are:
  - T3 (Triiodothyronine)
    - Can be formed in peripheral tissues by de-iodination of T4
      - T3 is more active than T4
  - T4 (Thyroxine)

IODINE METABOLISM

- Raw material - essential for thyroid hormone synthesis
- Ingested iodine to iodide absorbed
  - Need 150mcg/day
- Mainly used by thyroid and kidney
- The Na/I symporter
  - Iodine pump transports Na and I into the cell (a process of secondary active transport in conjunction with Na/K ATPase)
  - Iodine is essential for normal thyroid function but both iodide deficiency and excess suppress thyroid function

THYROID HORMONE SYNTHESIS

- Iodide is oxidised to iodine
- Iodine is bound to tyrosine residues that are part of the THYROGLOBULIN molecule in the colloid
- Thyroglobulin is a glycoprotien
  - Synthesised by thyroid cells and secreted into the colloid by exocytosis of granules which also contain thyroid peroxidase
    - thyroid peroxidase enables iodine binding to thyroglobulin
- Thyroid hormone is part of thyroglobulin, and remains so until it is secreted
  - when required the thyrocytes endocytose the colloid trapping the Thyroid hormone and allow free T3 and T4 to be released into the circulation

THYROID CELLS

- Thyroid cells have three functions:
  - Collect and transport iodine
  - Synthesise thyroglobulin and secrete it into colloid
  - Remove thyroid hormone from thyroglobulin and secrete them into the circulation

SECRETION

- Thyroid hormone secretes mostly T4
  - 80mcg of T4
  - 4 mcg of T 3
  - 2mcg of rT3
- Thyroid cells ingest the colloid by endocytosis, they merge with lysosomes
- Peptide bonds between the iodinated residues and thyroglobulin are broken down by proteases in the lysosomes
- T4, T3, RT3, MIT, DIT are liberated into the cytoplasm
- The iodinated tyrosine are deiodinated by a microsomal iodotyrosine deiodinase
  - DIT + DIT = T4 + alanine
  - MIT + DIT = T3 + alanine

TRANSPORT AND METABOLISM OF THYROID HORMONES

- Protein binding - large amounts of T3 and T4 are protein bound
  - free thyroid hormones in plasma are in EQUILIBRIUM with protein bound thyroid hormones in plasma and in tissues
  - only free thyroid hormones in plasma are active
  - the protein binding maintains a large pool of readily availible thyroid hormone
- Proteins which bind are: albumin, thyoixine binding globulin,
  - Albumin is the most populous of the proteins but because the affinity of TBG is so high it actually binds most of the T4
  - 99.98% of T4 is plasma bound
  - Vd is less than that of ECF
  - 99.8% of T3 is bound

METABOLISM OF THYROID HORMONE

- Deiodinated in the liver, kidney
- One third of circulating T4 is converted to T3
- About 13% of circulating T3 is secreted by the thyroid the rest comes from T4
- There are three different deiodinases
  - D1 - present in high concentrations in liver, kidney, thyroid and pituitary - contributes to formation of T3
  - D2 - brain and brown fat - contributes to formation of T3
  - D3 - reproductive tissues

EFFECTS OF THYROID HORMONES

- T3 binds to recepotrs in nucleus (T4 binds avidly) —> receptor complex binds DNA and facilitates transcription of effector factors
- Stimualtes O2 consumption
- Regulates levels of metabolism
- Regulates lipid and carbohydrate metabolism
- Influences body mass

PHYSIOLOGICAL EFFECTS OF THYROID HORMONES

TABLE 1 ■ Physiologic Effects of Thyroid Hormones[1,4,7]

System	Effects
Cardiovascular	Increases heart rate Increases the force of cardiac contractions Increases cardiac output as a result of the previous two effects Promotes peripheral vasodilation
Central nervous	Essential for normal brain development, such as cerebellar growth and nerve myelination Necessary for normal intellectual development in infants Necessary for emotional stability in adults
Gastrointestinal	Increases appetite Increases secretion of "digestive juices" Increases gastric motility
Hematopoietic	Influences erythropoiesis
Metabolic	Profoundly affects oxidative metabolism Increases oxygen consumption in all tissues except the brain, gonads, and spleen Promotes heat production Influences synthesis and degradation of carbohydrate, fat, and protein
Respiratory	Influences lung development Necessary for surfactant production Increases rate and depth of respirations
Skeletal	Indirectly promotes growth formation by actions on the pituitary gland Acts synergistically with growth hormone and other growth factors that promote bone formation Directly affects skeletal maturation **Necessary** for progression of tooth development and eruption
Skin	Necessary for growth and maturation of the epidermis and hair follicles

REGULATION OF SECRETION

- Regulated primary by TSH
- TSH secretion is increased by hypohysiotrophic hormone Thyrotropin releasing hormone
  - It is inhibited by -ve feed back by T3 and T4
- TSH secretion is also inhibited by stress

REGULATION OF CALCIUM

- Adult has approximately 1100g of calcium in the body
- 99% of this is present in the skeleton
- Plasma calcium is partially bound to proteins
  - Plasma protiens are more ionised when pH is high, therefore providing more anion to bind with Ca and reducing free Ca
- Free ionized calcium is a key second messenger in cellular proceses
- Key in nerve function, muscle contraction and coagulation
- Nearly all calcium is excreted by the kidneys but 98 - 99% of the filtered Ca is reabsorbed - 60% of this occurs in the proximal tubule and the remainder occurs in the ascending loop of Henle
  - Distal tubular reabsorbtion is regulated by PTH

BONE PHYSIOLOGY

- Two types -
  - Compact - makes up the outer layer (80%)
    - Receives nutrients by way of canaliculi HAVERSIAN CANALS
  - Trabecullar bone - remaining 20%
    - made up of spicules or plates
- There is a readily accessible pool of 100mmol of Ca in bone
- And a stable pool of 27200mmol of Ca which is slower accessed
- Osteoclasts - break down bone
- Osteoblasts - lay down new osteomatric which gets reabsorbed

VITAMIN D

- Increases active transport of Ca and PO4 from the gut
- Vit D3 = Cholecalciferol
  - 7-Dehydrochoelstrol + light = Vit D3
  - Vit D3 in liver = 25 - Hydroxycholecalciferol by CYP 450 system
  - 25 - Hydroxycholecalciferol in kidney becomes 1, 15 - Hydroxycholecalciferol (CALCITRIOL)
- Calcitriol is a steroid —> increase Ca transport intracellularly
  - Calcium reabsorbtion in kidney
  - Increases synthetic activity of osteoblasts
  - Nessecary for normal calcification of bony matrix
- Feedback:
  - 1 alph hydroxylase which forms the calcitriol is regulated by -ve feedback by Ca and PO4 levels
    - The formation of this enzyme is facilitated by PTH, and when Ca is low PTH secretion is increased
    - Converse happens when Ca is high

PARATHYROID GLANDS

- 4 glands (lots of variation)
- 2 types of cells
  - Chief cells - synthesis and secretion of PTH
  - Oxyphil cells - ? purpose
- Half life of PTH is 10 minutes
- Actions of PTH
  - Increase bone reabsorption and mobilise free Ca
  - Depresses plasma phosphate by increasing phosphate secretion in kidney
  - Increases calcium reabsorbtion in distal tubules
  - Increases calcitriol formation
    - Over a long period of time PTH stimulates both osteoclasts and osteoblasts - the net effect is usually anabolic
- Feedback: Calcium -ve feedback
  - Increased plasma phosphate stimulate PTH function
  - Need magnesium to maintain normal secretion

CALCITONIN

- Made by parafollicular cells/clear cells of the thyroid
- Half life of about 10 minutes
- Actions
  - Inhibits osteoclasts and therefore decreases bone reabsorption and lowers plasma calcium
  - Increases calcium excretion in the urine
- Regulation
  - secreted when Ca is high
- Stimulated by
  - Beta agonsits, gastrin (gastrin secreting tumors and in cases of pernicious anaemia - calcitonin levels are high)