Thyroid physiology and congenital hypothyroidism – cram sheet

Key genes expressed in thyroid development: FOXE1 (Bamforth-Lazarus syndrome), NKX-2.1 (Brain-Lung-Thyroid syndrome), PAX8 (kidney/hemiagenesis), and NKX2-5 (heart defects).

Steps in thyroid hormone synthesis: 1) TSH binds to receptor and activates cAMP; 2) Activation of NIS (on basolateral membrane) and iodide trapping; 3) Iodide diffuses to apex and enters colloid via Cl/I symporter (Pendrin); 4) Oxidation of iodide to iodine via H2O2; 5) Organification (iodine binds to tyrosine residues in TG); 6) Coupling; 7) Endocytosis; 8) Hydrolysis; 9) Deiodination.

Majority of thyroid hormone is bound to proteins (TBG >> transthyretin >>> albumin).

MCT8 is the most important plasma membrane transporter. MCT8 deficiency (Allen-Herndon-Dudley syndrome): ↓ T4, ↑↑ T3, ↓↓ rT3, normal or slightly ↑TSH

Iodine deficiency can cause congenital hypothyroidism (rare in USA due to iodination of salt).

Thyroid dysgenesis is the most common cause of congenital hypothyroidism: agenesis, ectopic, sublingual, hemiagenesis, or hypoplastic. Less than 2% of the time is it inherited or familial – most often a sporadic event.

Thyroid dyshormonogenesis is the 2nd most common cause of congenital hypothyroidism – most commonly due to an organification defect; autosomal recessive.

Signs/symptoms of congenital hypothyroidism are not evident until 3 m.o.

TSH is the most commonly used test for the newborn screen – picks up most cases but can miss central hypothyroidism and potentially mild primary hypothyroidism.

Imaging in congenital hypothyroidism helps to determine if it is a permanent or transient condition: thyroid ultrasound or scintigraphy (Tc99m or I-123).

Absent radionuclide uptake in scintigraphy can occur in conditions with a normally positioned thyroid gland (e.g. TSH beta gene mutation, TSH receptor inactivating mutation, iodine trapping defect, and maternal TSH receptor blocking antibodies).

Central hypothyroidism is often associated with other pituitary (or hypothalamic) hormone deficiencies (e.g. GH, ACTH, LH/FSH, or ADH deficiency).

Goal in congenital hypothyroidism is to start levothyroxine within the first 2 weeks of life – starting dose is 10-15 mcg/kg/day.

Goal is to normalize the free T4 within 2 weeks (and then keep it in the mid to upper part of the reference range for age) and normalize TSH within a month.

Thyroid hormone is critically important for normal brain growth and development within the first 3 years of life.