POSTNATAL MORPHOGENESIS OF SHEEP THYROID GLANDS RAISED IN DIFFERENT NATURAL AREAS.

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Annotation: The present results, considered with results of other investigations of the effects of thyroid hormone deficiency in fetal and newborn mammals, indicate that hypothyroidism impairs somatic growth, delays bone growth and maturation, delays cell growth and replication in the CNS, and inhibits CNS myelination. The critical period for these effects varies in different species. In the rat this period is postnatal, whereas in the sheep it extends into the third trimester of pregnancy.

Keywords: sheep thyroid, postnatal morphogenesis, heart growth and development.

Both during fetal life and the postnatal period, thyroid hormone plays a crucial role in controlling heart growth and development. In light of recent findings that thyroid hormone arouses a burst of cardiomyocyte proliferation in the murine heart during preadolescence, we review thyroid hormone's role in postnatal cardiac development here. This response is necessary to meet the massive increase in circulatory demand caused by an almost quadrupling of body weight during the roughly 21-day period between birth and adolescence. Crucially, the metabolism of thyroid hormones is affected by long-term conditions like ischemic heart disease and heart failure, as well as by extremely ill children who need surgery for hereditary heart diseases. This leads to low T3 syndrome, which worsens cardiovascular function and is linked to a poor prognosis. Therapy with T3 or thyroid hormone analogs has been demonstrated to improve cardiac contractility; however, the mechanism is as yet unknown. More thought should be given to T3's capacity to improve heart function by encouraging the proliferation of cardiomyocytes, especially in light of its postnatal cardiomyocyte mitogenic potential.

Thyroid hormone is a critical regulator of many physiological and developmental processes, following its activation from the stable prohormone (l-thyroxine, T4) to the short-lived active hormone, triiodothyronine 3,5,3′-triiodo-l-thyronine, T3 induces amphibian metamorphosis by stimulating the remodeling of specific tissues and organs.In mammals, T3 is essential for development, with congenital hypothyroidism resulting in growth retardation, deafness, impaired neurogenesis, and congenital heart malformations

THs also have important effects on oxygen consumption and metabolism. The actions of THs are mediated by the products of two TH receptor (TR) genes, the nuclear proteins, TRα and TRβ, which show differential patterns of expression in development and in adult tissues. Stimulation of these receptors results in the direct transcriptional activation of a wide range of genes (genomic effects). More recently, non-genomic effects of TH initiated at the cell surface, in the cytoplasm or in mitochondria have also been identified. Adding further complexity, TH signaling is highly regulated by the expression of cell and tissue-specific TH transporters that concentrate THs in target cells, by the relative expression and distribution of TR isoforms, by interaction of TRs with corepressors and coactivators, by cross-talk with several other signaling pathways, and by the sequence and location of the TH response element. Furthermore, TH signaling is tightly regulated by the activation and catabolism of THs by three selenoenzyme iodothyronine deiodinases: D1, D2 and D3—considerations that have been comprehensively reviewed elsewhere.

Mounting evidence led us to hypothesize that i) function of the thyroid hormone (TH) axis can be programed by late gestation undernutrition (LG-UN) and ii) early-postnatal-life overnutrition (EL-ON) exacerbates the fetal impacts on TH axis function. In a 2 × 2 factorial experiment, 21 twin-bearing sheep were fed one of two diets during late gestation: NORM (fulfilling energy and protein requirements) or LOW (50% of NORM). From day 3 to 6 months after birth (around puberty), the twin lambs were assigned to each their diet: conventional (CONV) or high-carbohydrate, high-fat, where after half the lambs were killed. Remaining sheep (exclusively females) were fed the same moderate diet until 2 years of age (young adults). At 6 months and 2 years of age, fasting challenges were conducted and target tissues were collected at autopsy. LG-UN caused adult hyperthyroidism associated with increased thyroid expression of genes regulating TH synthesis and deiodination. In one or more of the target tissues, liver, cardiac muscle, and longissimus dorsi muscle, gene expressions were increased by LG-UN for TH receptors (THRA and THRB) and deiodinases but were decreased in visceral and subcutaneous adipose tissues. EL-ON increased TH levels in adolescent lambs, but this was reversed

after diet correction and not evident in adulthood. We conclude that LG-UN programed TH axis function at the secretory level and differentially in target tissues, which was increasingly manifested with age. Differential TH signaling in adipose vs other tissues may be part of a mechanism whereby fetal malnutrition can predispose for obesity and other metabolic disorders.

In addition to profound changes in cardiac contractility, postnatal development is associated with an increase in blood volume that is driven by the rapid body growth that occurs during this period, as well as by increases in blood pressure, stroke volume and cardiac output .TH is an important regulator of these hemodynamic alterations. Supporting this are the findings that hyperthyroidism is associated with an increase in blood volume, venous volume return, cardiac output, contractility, heart rate and pulse pressure, and a decrease in systemic vascular resistance .And conversely, hypothyroidism is associated with a decrease in cardiac output, a narrow pulse pressure, and an increase in systemic vascular resistance .The T3-induced decline in systemic vascular resistance stimulates renin release and sodium reabsorption, resulting in blood volume expansion and an increase in venous return .Erythropoietin stimulation also contributes to the rise in blood volume. Heart rate and cardiac output increase significantly (by up to 300%) in the hyperthyroid state versus euthyroid controls. The net effect of these hemodynamic changes is a rise in systolic blood pressure and a widening of pulse pressure.The increase in cardiovascular hemodynamics allows for increased blood flow leading to enhanced perfusion to provide for the substrate and oxygen demands of peripheral tissues .

Cardiac morphology

Preload is the hemodynamic force exerted on the ventricular wall during filling and, thus, is directly responsible for ventricular end-diastolic wall stress or tension *sensu strictu*. It contributes greatly to the determination of ventricular end-diastolic volume and modulates myocardial performance significantly. That is, it governs the extent and velocity of wall shortening. Thus, preload plays a major role in regulating stroke volume via the Frank–Starling mechanism. Recently, we found in the mouse that a growth

spurt that almost quadruples body weight (and hence circulatory volume) between P10 and P35 is associated with a commensurate 3.5-fold increase in stroke volume .This profound maturational adaptation leads to left ventricular (LV) chamber remodeling, which is characterized by an 86% increase in LV end diastolic dimension (LVEDD) that results in a 4.6-fold increase in LV volume at diastole without a significant change in LV free wall thickness at diastole .These changes in ventricular morphology produced a 52% decrease in the LV *h/Ri* ratio (where *Ri* is the internal LV chamber radius), consistent with eccentric hypertrophy, and maintained LV weight-to-stroke volume ratio (1.76:1 at P10 versus 1.78:1 at P35). Also, between P10 and P35, LVEDD length-to-diameter ratio decreased by 40% indicating an increase in LV sphericity. At the cellular level, CM length increased 1.7-fold between P10 and P35, with little change in CM width. Detailed analysis of the morphological changes in heart size during this postnatal period from P10 to P35, revealed three distinct growth phases: the first and third between P10 and P14, and P18 and P35, respectively, involve a physiological-type of hypertrophic growth with no change in the number of CMs, whereas an intervening period between P11 and P18 involves heart growth due to CM hyperplasia that results from proliferation of existing CMs, rather than to the maturation of cardiac stem cells .Importantly, the adaptive LV remodeling of postnatal maturational growth represents a distinct form of physiological hypertrophy that differs from the pathological hypertrophy associated with the LV volume-overload of mitral regurgitation, where cardiac performance continuously degrades over time , and from the physiological hypertrophy associated with endurance exercise, where the increases in LV chamber volume are accommodated by elliptical remodeling of the heart that limits the increase in LVEDD and, thus, in LV end-diastolic wall stress.

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