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Review

The role and potential sites of action of thyroid hormone in timing the onset of puberty in male primates

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ABSTRACT

Puberty in primates is first delayed by a neurobiological switch that arrests pulsatile GnRH release during infancy and then triggered, after a protracted period of juvenile development, by resurgence in intermittent release of this hypothalamic peptide. The purpose of this chapter is to review recent studies conducted in our laboratories to begin to examine the role of thyroid hormone (TH) in governing this postnatal development of pulsatile GnRH release in primates and therefore the timing of puberty in these species. The male rhesus monkey was used as the experimental model and TH activity was manipulated by surgical and chemical thyroidectomy on the one hand, and by thyroxine (T_4) and triiodothyronine (T_3) replacement on the other. Our results indicate that the resurgence in pulsatile GnRH release at the termination of the juvenile phase of development is dependent on a permissive action of TH. Whether this action of TH is mediated directly on hypothalamic centers regulating the pulsatile release of GnRH, or indirectly by circulating signals reflecting TH action on somatic development remains to be determined.

Contents

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Abbreviations: GnRH, gonadotropin releasing hormone; PSA-NCAM, embryonic neuronal cell adhesion molecule; MBH, medial basal hypothalamus; TSH, thyroid stimulating hormone; TH, thyroid hormone; T_4, thyroxine; T_3, triiodothyronine; D1, type 1 deiodinase; D2, type 2 deiodinase; CNS, central nervous system; Tx, thyroidectomized; MMI, methimazole; FSH, follicle stimulating hormone; LH, luteinizing hormone; OATP, organic anion-transporting polypeptide; MCT, monocarboxylate anion transporter; MBH, mediobasal hypothalamus

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1. Introduction

Puberty in primates is initiated by a resurgence of robust pulsatile GnRH release after a prolonged phase of juvenile (and childhood in man) development when the hypothalamic network responsible for the release of this hypophysiotropic hormone (the GnRH pulse generator, Plant, 1986) is held in check[1] by mechanisms that are poorly understood (Plant and Witchel, 2006). During early infancy, however, before the check on GnRH release is applied, circulating gonadotropin levels are elevated and, in infantile male primates, associated with blood testosterone levels in the adult range (Mann et al., 1984; Plant and Witchel, 2006). Thus, the timing of puberty in primates may be viewed to be governed by two major postnatal switches; the first is activated during infancy and suppresses pulsatile GnRH release that results in a hypogonadotropic state that in turn guarantees the quiescence of the prepubertal gonad; the second is activated at the termination of juvenile development and leads to the pubertal resurgence in pulsatile GnRH release that results in stimulation of the pituitary–gonadal axis culminating in gonadarche, the major physiological process underlying primate puberty (Plant and Witchel, 2006).

The foregoing "on-off-on" pattern of hypothalamic GnRH pulse generator activity that is characteristic of postnatal development in primates is largely independent of the gonad. This was first demonstrated by Conte et al. (1975) who found that circulating gonadotropin levels in children with gonadal dysgenesis were elevated during infancy and at ages when puberty would have been anticipated in gonadally intact subjects but were low during the intervening childhood years. This pattern in gonadotropin secretion throughout postnatal development in primates was called diphasic (Conte et al, 1975) and is exemplified by the agonadal male rhesus monkey (Plant, 1985; Fig. 1).

While the switch that results in the pubertal resurgence of pulsatile GnRH release has been studied more extensively than that which suppresses the GnRH pulse generator in late infancy, in neither situation is the underlying neurobiology well understood. In both cases, however, it is reasonable to propose that the marked developmental changes in GnRH pulsatility are associated with structural remodeling of the GnRH pulse generator and/or with molecular changes in the hypothalamus. In the case of structural plasticity, PSA-NCAM, a marker of neuronal plasticity (Sunshine et al., 1987; Theodosis et al., 1991), is expressed in the MBH of prepubertal monkeys (Perera et al., 1993), and a decrease in synaptic input to GnRH perikarya in the MBH has been reported between the juvenile and adult stages of development in the male monkey (Perera and Plant, 1997).

[1] The check or brake on pulsatile GnRH release during juvenile development is a conceptual check or brake. It may be occasioned by the loss of a stimulatory input or the addition of an inhibitory input or a combination of the two.

2. Thyroid hormone (TH) and brain development

The thyroid gland under the stimulation of thyroid stimulating hormone (TSH) produces two hormones, thyroxine (T_4) and triiodothyronine (T_3) (Kopp, 2005). The vast majority of the TH secreted by the thyroid gland is T_4; T_3 is produced primarily from deiodination of T_4 in target tissue. T_3 is the most biologically active form of the hormone and tissue and circulating levels of T_3 are regulated, in part, by two deiodinases (D1 and D2) (Bianco and Larsen, 2005). TH (both T_4 and T_3) secretion in humans begins at ~4 months of gestation and progressively rises until parturition (Fisher and Polk, 1989; Thorpe-Beeston et al., 1992; Porterfield and Hendrich, 1993). At birth there is a surge of TSH secretion initiating a rise in T_4 production

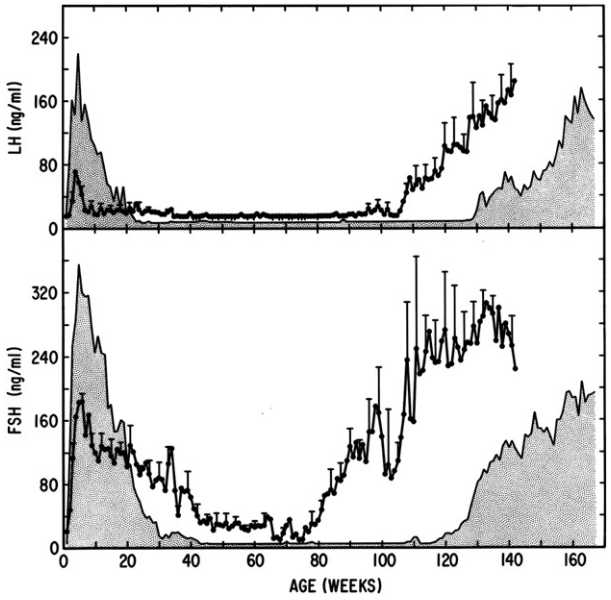

Fig. 1 – The on-off-on pattern of gonadotropin-releasing hormone release during postnatal development in agonadal male (stippled area) and female (closed data points ± error bars) rhesus monkeys, as reflected by circulating mean luteinizing hormone (LH) (top panel) and follicle-stimulating hormone (FSH) (bottom panel) concentrations from birth to 142–166 weeks of age. Note, in males, the intensity and duration of the prepubertal hiatus in the secretion of FSH, and LH to a lesser extent, is exaggerated in comparison to females. Adapted from TM Plant. Puberty in primates. In E. Knobil, JD Neill, eds. The Physiology of Reproduction, 2nd edn. New York: Raven Press Ltd, 1994: vol. 2, chapter 42, 453–485, Copyright Elsevier, 1994.