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Review

Defining adrenarche in the rhesus macaque (*Macaca mulatta*), a non-human primate model for adrenal androgen secretion

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ABSTRACT

Adrenarche, defined as a prepubertal increase in adrenal androgen secretion resulting from zona reticularis (ZR) maturation, is thought to occur only in humans and some Great Apes. In the rhesus macaque, studies of circulating dehydroepiandrosterone (DHEA) or its sulpho-conjugate (DHEAS) have failed to demonstrate a prepubertal rise typical of human adrenarche, but available data are cross-sectional and include few neonatal or early infant samples. However, ZR maturation is complete in rhesus infants by 3 months of age based on morphological and biochemical analyses. Furthermore, preliminary longitudinal studies from birth through infancy of castrated males, and intact males and females, suggests for the first time that there is a transient, prepubertal elevation of adrenal androgen in rhesus macaques. Serum DHEAS concentration increased, peaking between 6 and 8 weeks of age in castrate males, and intact males and females, then declined. These longitudinal profiles add endocrinological support to the morphological and biochemical evidence that adrenarche occurs in a narrow developmental window in infant rhesus macaques. Adrenarche in any species should be defined only after careful longitudinal hormone analysis have been conducted in stages of development that are suggested by morphological and biochemical evidence of ZR maturation.

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Abbreviations: ZR, zona reticularis; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; P450c17, 17α-hydroxylase/17,20-lyase cytochrome P450; DZ, definitive zone; FTZ, foetal zone; ACTH, adrenocorticotropic hormone.

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1. Introduction – the definition of adrenarche

The appearance of axillary and pubic hair in boys and girls represents a response to the increased secretion of C19 steroids by the zona reticularis (ZR) of the developing adrenal cortex years before the pubertal increase in gonadal steroid secretion (Albright, 1947). The increase in the so-called "adrenal androgens", dehydroepiandrosterone (DHEA) or its sulphate (DHEAS), is known as adrenarche (Havelock et al., 2004; Rainey and Nakamura, 2008; Miller, 2009), and it is an event thought to be unique to humans (evident by 6–9 years of age) and certain Great Apes (Arlt et al., 2002). However, there is scant definitive evidence with which to establish the occurrence of adrenarche in either Great Apes or other non-human primates (Nguyen and Conley, 2008). The general view of which species do, is for obvious reasons not based on the appearance of axillary hair, but it is seldom based on definitive evidence of adrenal development either. Instead, conclusions about the occurrence of adrenarche in non-human primates rest on a few studies that have measured circulating concentrations of DHEA and DHEAS. Circulating steroid concentrations reflect the balance between synthesis and metabolism, and are subject to considerable individual (Orentreich et al., 1984), diurnal and even seasonal variation (Garde et al., 2000). In the case of the rhesus macaque, where adrenal morphological development has been best studied (Mesiano and Jaffe, 1997), these endocrine data are entirely cross-sectional and especially limited in observations from neonatal and infant subjects (Koritnik et al., 1983; Seron-Ferre et al., 1983, 1986). Since puberty is initiated in the rhesus macaque between two and three years of age (Plant and Witchel, 2006), an "adrenarche" preceding puberty by years may occur at a very young age, perhaps in the first months of life. Concentrations of adrenal androgens in rhesus newborns are reportedly twice those in neonatal and infant rhesus (Seron-Ferre et al., 1983), but longitudinal studies of adrenal androgen secretion have yet to be reported for this species. Relevant hormonal data covering this early developmental window are lacking among non-human primates in all but the baboon (Ducsay et al., 1991). Progress in understanding the processes that regulate adrenarche specifically, and adrenal androgen secretion in general, may be slowed as a result of the current reliance on endocrine data alone as the sole defining criterion, and of the narrow perspective it engenders. Still, a broad assessment of adrenarche that encompasses endocrinological, morphological and biochemical facets of the phenomenon is yet to be completed for any primate. Data will be reviewed herein, emphasizing recent evidence from all three aspects that together support and define the occurrence of adrenarche in the rhesus monkey, discussing how it differs from the event as we know it in humans.

2. Adrenarche defined morphologically

Notwithstanding the logistical constraints in gathering such data, the definition of adrenarche should rest as much on the morphological and biochemical aspects of adrenal development, as it now does on the hormones that reflect those biological processes. The increase in adrenal androgen output associated with adrenarche in human children coincides with morphological development and differentiation of the innermost adreno-cortical zone, the ZR (Suzuki et al., 2000). The human foetal zone disappears over the course of the first year of life (Benner, 1940; Lanman, 1953; Sucheston and Cannon, 1968; Dhom, 1973), and the ZR, first recognizable as early as three years of age (Dhom, 1973), reaches morphological maturity in the second decade (Sucheston and Cannon, 1968; Dhom, 1973). The human adrenal develops increased functional capacity for androgen secretion with the expression of requisite enzymes (Hui et al., 2009; Narasaka et al., 2001; Suzuki et al., 2000), especially of cytochrome b5 (Yanase et al., 1998), a well known positive regulator of androgen synthesis (Katagiri et al., 1982; Onoda and Hall, 1982; Auchus et al., 1998; Miller et al., 1997; Miller and Auchus, 2000). Human adrenarche has a functional, morphological signature consistent with the production of androgens by a maturing ZR.

The adrenal cortex of the adult rhesus has a distinct ZR, essentially identical in its enzymatic differentiation (Mapes et al., 1999) to that of the human ZR (Nguyen and Conley, 2008), and its development follows collapse of an adrenal foetal zone (Mesiano and Jaffe, 1997; Seron-Ferre et al., 1986; Seron-Ferre and Jaffe, 1981), much as in humans (Hill, 1930; Mesiano and Jaffe, 1997; Lanman, 1957). However, development and differentiation of the ZR proceeds considerably faster in rhesus monkeys than humans, over a period of months rather than years (McNulty, 1981). Recent studies have characterized the ontogeny of steroidogenic enzyme expression during morphological adrenarche in this primate (Nguyen et al., 2008). The establishment of the ZR through expansion of the "dense band" that separates the foetal and definitive zones of the developing rhesus adrenal gland was highlighted by the prominent expression of cytochrome b5 (Fig. 1). Based on the establishment of a continuous band of cytochrome b5-expressing cells at the corticomedullary junction, maturation of the rhesus ZR was essentially complete by three months of age, during which there was also regression of the foetal zone (Nguyen et al., 2008). Thus, the interval encompassing morphological adrenarche in the rhesus is very rapid by comparison with the human, but follows a similar differentiation process with respect to the expression of steroidgenic and associated enzymes.

3. Adrenarche defined biochemically

The synthesis of DHEA, and thereby DHEAS, results directly from the 17,20-lyase activity of the enzyme 17α-hydroxylase/17,20-lyase cytochrome P450 (P450c17) (Hall, 1991; Zuber et al., 1986) and human adrenarche is thought to result from a selective increase in 17,20-lyase activity (Rich et al., 1981; Kelnar and Brook, 1983). Cytochrome b5 selectively augments 17,20-lyase over 17α-hydroxylase activity (Katagiri et al., 1982; Onoda and Hall, 1982; Lee-Robichaud et al., 1995; Auchus et al., 1998; Brock and Waterman, 1999; Sakai et al., 1993). Based on the functional morphology of human ZR development described above (Suzuki et al., 2000; Narasaka et al., 2001; Hui et al., 2009; Nakamura et al., 2009), cytochrome b5 is thought to be a key factor augmenting adrenal androgen secretion during adrenarche (Miller, 2009). Couch et al. investigated 17,20-lyase activity in human adrenal tissues, but found no significant increase during adrenarche (Couch et al., 1986). However, biochemical evidence of adrenarche was investigated in rhesus adrenal gland tissues focusing on the window of ZR development between birth and three months of age established by the functional morphological studies described above (Nguyen et al., 2009). Three important observations were made for the first time in any primate. First, 17,20-lyase activity in rhesus adrenal microsomal protein was shown to increase with age (and ZR development), from a level of 2.9 nmol/mg/h in a specimen from a 5 day old perinatal subject to a peak average of 22.9 nmol/mg/h in two specimens from 8 week old infants. Thereafter, 17,20-lyase activity declined on average in specimens collected from juveniles at 26 weeks of age (Fig. 2, dashed line). Second, there was a concomitant and positively correlated increase in cytochrome b5 expression during this developmental window. The levels of expression of cytochrome b5 peaked in specimens from 8 and 12 week old infants, steadily decreasing in specimens taken from juveniles over a year of age (Fig. 2, solid line). Third, adrenal microsomal 17,20-lyase activity was increased sig-