THEMATIC REVIEW

Adrenarche in nonhuman primates: the evidence for it and the need to redefine it

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Abstract

Adrenarche is most commonly defined as a prepubertal increase in circulating adrenal androgens, dehydroepiandrosterone (DHEA) and its sulfo-conjugate (DHEAS). This event is thought to have evolved in humans and some great apes but not in Old World monkeys, perhaps to promote brain development. Whether adrenarche represents a shared, derived developmental event in humans and our closest relatives, adrenal androgen secretion (and its regulation) is of considerable clinical interest. Specifically, adrenal androgens play a significant role in the pathophysiology of polycystic ovarian disease and breast and prostate cancers. Understanding the development of androgen secretion by the human adrenal cortex and identifying a suitable model for its study are therefore of central importance for clinical and evolutionary concerns. This review will examine the evidence for adrenarche in nonhuman primates (NHP) and suggest that a broader definition of this developmental event is needed, including morphological, biochemical, and endocrine criteria. Using such a definition, evidence from recent studies suggests that adrenarche evolved in Old World primates but spans a relatively brief period early in development compared with humans and some great apes. This emphasizes the need for frequent longitudinal sampling in evaluating developmental changes in adrenal androgen secretion as well as the tenuous nature of existing evidence of adrenarche in some species among the great apes. Central to an understanding of the regulation of adrenal androgen production in humans is the recognition of the complex nature of adrenarche and the need for more carefully conducted comparative studies and a broader definition in order to promote investigation among NHP in particular.

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Introduction

The current review attempts to provide a balanced but thorough examination of the evidence for adrenarche in nonhuman primates (NHP) species, which the authors believe is lacking in the current literature and suffers from both misunderstanding and under-statement, in part due to how it is defined. In the view of the authors, the definition of adrenarche has been a barrier to progress because it has narrowed opinions of what might reasonably represent the same phenomenon in other species, most notably NHP. Most NHP species have been dismissed as relevant models of adrenarche based on a very limited number of studies that have been constrained logistically in their design. The need for animal models is clear if only given the general lack of understanding of the biology of human adrenarche that persists more than six decades after the phenomenon was first described. Human studies, especially on children, are very restricted, ethically and otherwise, in what they can accomplish, but would be crucial once essential questions become clear from advances made in animal models. The potential value of animal models in elucidating physiological mechanisms and the pathophysiology of disease is self-evident in history (Bynum 1990). But the value of an animal model is often judged by how much its physiology resembles that of the species of primary interest. The perception of similarity between species is, in turn, heavily influenced by how a process or a phenomenon is defined, however useful the definition for humans or poor the experimental evidence in a

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proposed model species. As a result, potentially valuable information is dismissed with little scientific rationale, and very real opportunities for advances using animal models are simply lost. While adrenarche itself is seldom associated with serious illness or disease, normal adrenal androgen production and over-production complicate some of the most common endocrinopathies among women and in cancers in both sexes, and secretion by the adrenal cortex contributes significantly, even after gonadal steroid secretion ceases or is ablated. Studies on adrenal androgen secretion in accessible NHPs are hampered by the misconception that they do not experience adrenarche. Based on a comprehensive review of the NHP literature, a biologically informed definition of the phenomenon, and recent studies in their own laboratories, the authors will argue that the rhesus macaque experiences adrenarche and is an under-utilized model for adrenal androgen secretion.

The first definition of adrenarche recognized the growth of axillary and pubic hair in response to androgens produced presumptively by the adrenal cortex of boys and girls long before the testes or ovaries begin to secrete sex steroids (Albright 1947). The prepubertal increase in circulating adrenal androgens (the term used here, as it often is, to denote dehydroepiandrosterone (DHEA) and its sulfo-conjugate (DHEAS) despite their lack of androgenic biopotency) is now the most commonly used definition of adrenarche, an event thought to have evolved in humans and some great apes but not in Old World monkeys (Arlt *et al.* 2002). The innermost zone of the adrenal cortex, the zona reticularis (ZR), is the site of adrenal androgen biosynthesis and secretion in humans (Wilkins *et al.* 1940, Blackman 1946, Wieland *et al.* 1965, Endoh *et al.* 1996, Gell *et al.* 1998) and in rhesus macaque (*Macaca mulatta*; Mapes *et al.* 1999), and adrenarche coincides with the differentiation and maturation of the ZR (Suzuki *et al.* 2000, Rainey *et al.* 2001, Nguyen *et al.* 2008, Hui *et al.* 2009, Nakamura *et al.* 2009). In general, however, evidence on adrenarche in NHP is scant, almost completely lacking with respect to the development of the functional morphology of the adrenal ZR in any species except the rhesus macaque (Nguyen & Conley 2008). For obvious reasons, the appearance of axillary hair provides no insight into adrenal androgen secretion in NHP, and it is likely that current understanding, even misunderstanding, of adrenarche among primate taxa suffers considerably as a consequence.

Evolution of adrenarche

Given the neurobiological effects of DHEA and DHEAS in primates and other species (Maninger *et al.* 2009), it has been proposed that the evolution of adrenarche extended the maturation of the human brain (Campbell 2011). If this is true, then correlations between the onset (adrenarche) of adrenal androgen secretion and brain development would be expected across NHP. Indeed, looking at comparative patterns of brain maturation may provide a window into the linkage of adrenal output with important periods of cognitive and social development in different primate species. The process of synapse proliferation followed by synapse elimination and acquisition of efficiency, especially in the prefrontal cortex, can be considered to provide flexibility for learning in different environments (Skoyles 2008). Rhesus monkeys undergo an early, rapid phase of synaptogenesis that characterizes the entirety of the cerebral cortex between 2 and 4 months of age (Rakic *et al.* 1986, Jabes *et al.* 2010), and human prefrontal cortex synaptogenesis peaks between 4 and 6 years (Glantz *et al.* 2007). Peaks in both rhesus and human brain glucose utilization overlap with these peak times of synapse proliferation (Jacobs *et al.* 1995, Muzik *et al.* 1999). While no studies have focused on synaptogenesis in the marmoset prefrontal cortex, studies on the primary visual cortex suggest that a doubling of the volume of this area takes place between birth and 3 months of age, characterized by the same 'overshoot' in growth that is followed by reduction (Missler *et al.* 1993). A recent study using longitudinal magnetic resonance imaging scans of three chimpanzees between 6 months and 6 years of age, in comparison with humans and rhesus macaques, showed that the proportion of white matter in the chimpanzee prefrontal cortex increases at a slower rate than in humans (Sakai *et al.* 2011). These results provide further support for the suggestion that the maximum increase in prefrontal white matter takes place slightly earlier in chimpanzees than in humans. Though correlations between the brain maturation and ZR function have been interpreted as an effect of adrenal androgens on the brain, it is equally plausible that adrenarche may reflect the influence of brain development and differentiation on adrenal maturation. This is in essence how adrenal development is inhibited in anencephalic fetuses (Benirschke *et al.* 1956), even if hypoplasia involves the entire adrenal cortex due to the lack of corticotropic-releasing hormone. In any case, relationships between adrenal androgen secretion and brain development of selective significance among primates are likely subtle, even though affecting fitness. Any direct effects of adrenal androgens on brain development would be expected to be evident only when considered over evolutionary time frames. Increased understanding of such events is no less valuable for that.

Clinical significance of adrenarche

Physiology and evolution aside, adrenal androgen secretion is of considerable interest also because it is a significant component of the hyperandrogenism that accompanies polycystic ovarian disease (Yildiz & Azziz 2007), afflicting millions of women who suffer hirsutism and infertility. There is equally compelling evidence that adrenal androgen secretion can drive the synthesis of biopotent androgen and estrogen synthesis in prostate (Chodak 2004, Evaul *et al.* 2010) and breast cancers (Dorgan *et al.* 1997*a*,*b*). Therefore, it is important to understand how androgen secretion by the human adrenal cortex and ovary develops a goal that requires a suitable animal model (Abbott & Bird 2008,

Pattison *et al.* 2009). Adrenal androgen secretion and maturation of the ZR in the rhesus monkey were recently demonstrated to be complete within the first few months of life (Nguyen *et al.* 2008, 2009, Conley *et al.* 2011*a*). Based on the results of the recent studies, it is clear that DHEA and DHEAS secretions increase (adrenarche), but only for a few weeks of neonatal life in the rhesus (Conley *et al.* 2011*b*). Thus, it appears that adrenarche may well have evolved in at least some Old World primates but occupies a narrow developmental window of weeks in duration. If true, what has evolved is not the occurrence of adrenarche, but its timing and duration, from a few months in infancy to many years of childhood in humans and chimpanzees (Smail *et al.* 1982), promoting a much longer period of neural development perhaps. It should also be recognized that adrenal androgen secretion of physiological significance is not unique to primates (Boonstra *et al.* 2011) and may be very transient in other species (Pignatelli *et al.* 2006). Adrenarche has been the subject of numerous reviews (Parker *et al.* 1978, Auchus & Rainey 2004, Havelock *et al.* 2004, Campbell 2006, 2011, Nader 2007, Belgorosky *et al.* 2008, Miller 2009, Conley *et al.* 2011*a*) but seldom has the evidence for or against its occurrence in the NHP been reviewed objectively.

Adrenarche among primates

The lack of an identifiable, prepubertal rise in adrenal androgens is the sole evidence cited to support the fact that most NHP like the rhesus macaque and baboon do not experience adrenarche (Cutler *et al.* 1978). DHEAS increases as a result of anatomical and functional maturation of the ZR, which when available provides a useful, morphological definition of adrenarche (Gell *et al.* 1998, Suzuki *et al.* 2000, Rainey *et al.* 2001, Nguyen *et al.* 2008, Hui *et al.* 2009, Nakamura *et al.* 2009). The rhesus also has a functional fetal zone (Mapes *et al.* 2002), but perinatal regression overlaps the establishment of a ZR that is morphologically (McNulty *et al.* 1981) and perhaps functionally (Mapes *et al.* 1999) equivalent to its human counterpart. The lack of clear temporal separation between fetal zone regression and ZR maturation (Nguyen *et al.* 2008) likely makes it more difficult to distinguish a peak in DHEAS in neonatal or infant rhesus monkeys and thus adrenarche defined by hormone levels alone. However, DHEAS has not been carefully assessed during this developmental window in NHPs, certainly not longitudinally, as is needed. Nonetheless, the 17,20-lyase activity directly responsible for DHEA synthesis increases from birth to 3 months of age in the neonatal rhesus adrenal with ZR maturation, a biochemical adrenarche in effect (Nguyen *et al.* 2009). Without an appreciation of all aspects of the adrenocortical transition from an immature to a fully differentiated state, it is unlikely that the processes regulating adrenarche, and androgen synthesis in general, will be understood. For that reason, a broader definition of adrenarche is needed, one that includes morphological, biochemical, and endocrine correlates, not all signs of which may be obvious concurrently in some species. It must also be acknowledged that adrenarche is a complex process, one requiring appropriate NHP models to unravel because of the difficulties of conducting studies on human subjects, particularly children. Studies on those NHP species experiencing adrenarche, and those not, offer the greatest promise for progress to be made, therapeutic and otherwise, into the regulation of adrenal androgen production in humans.

How best to define adrenarche

The acceptance of NHP as models for human adrenal development and function has been influenced overly on expectations of finding a secretory pattern of circulating DHEA or DHEAS in a species that overlays that of the accepted human profile throughout the lifespan. That any primate would recapitulate a 'human' profile of adrenal androgen secretion seems to be a flawed expectation if only given the marked differences in life histories, life spans, and the timing of pubarche across the Order. The panoply of adrenal androgen production across Primates is even evident from an examination of fetal zone development and androgen secretion that fuels estrogen secretion during gestation (Conley *et al.* 2004). Czekala *et al.* (1983) concluded that 'the orangutan would be a better model for the human pregnancy than either the gorilla or the chimpanzee' based on their morphological observations of fetal zone development and urinary estrogen excretion in hominoids. Yet DHEAS concentrations in adult orangutans are far below human levels (Bernstein *et al.* 2012). The notion that there might be a singularly superior model species of human adrenal androgen secretion among NHPs is simply flawed based on the paucity of detailed knowledge of adrenal development in almost any single species. It is especially true given that detailed longitudinal data on hormone profiles may be crucial in minimizing the substantial individual variation that exists among primates in general (Bernstein *et al.* 2012). Individual variability is certainly well recognized among human populations (Rotter *et al.* 1985, Pratt *et al.* 1994). It is likely that much less will be learned about how adrenal androgen secretion is regulated without focused studies on the processes of adrenal morphological development and the biochemical correlates that accompany it. Therefore, we propose that adrenarche in the NHP must be defined morphologically, biochemically, and endocrinologically, and that until such data are acquired, conclusions about the occurrence of the phenomenon in any species are premature, confusing, and potentially misleading.

Morphological adrenarche

The morphological basis of adrenarche is the development of the mature, functional ZR, but there is a dearth of such

information available for NHP. The comprehensive histological studies needed to define the development of a ZR in the postnatal period have been conducted only in the rhesus and baboon. Even then, true functional morphology is available only for the rhesus. For instance, Lanman (1957) identified a ZR in the adult rhesus but not in the adult chimpanzee in an examination of a very limited number of specimens of these species. Solid morphological data on the development of the mature adrenal gland among NHP exist only for the rhesus macaque (McNulty *et al.* 1981) and baboon (Ducsay *et al.* 1991). McNulty *et al.* reported that in the developing rhesus adrenal gland, the so-called 'dense band', some cells of which they proposed might give rise to the ZR became progressively displaced toward the medulla from birth through 6 months of age, effectively replacing the fetal zone (McNulty 1981, McNulty *et al.* 1981). Ducsay *et al.* (1991) reported that the development of the baboon neonatal adrenal gland paralleled that of the rhesus. The authors, however, noted that adrenal weight did not change in the baboon in early neonatal period but declined concurrent with degeneration or shrinking of the fetal zone in rhesus neonates. From this, they speculated that the decrease in weight associated with fetal zone regression might be compensated for by development of the ZR in the baboon but not in the rhesus adrenal cortex (Ducsay *et al.* 1991). However, adrenal weight decreased at 2 weeks of age in rhesus neonates (Kerr *et al.* 1974, McNulty *et al.* 1981), suggesting that fetal zone regression and ZR development might not be concurrent in this species, despite histological similarities between the rhesus and baboon. Thus, limited investigation by routine histological examination in the rhesus and baboon suggests similarities in cellular development of the ZR, but differences based on adrenal weights suggest that there is a greater synchronicity of fetal zone regression and ZR development in the baboon than in the rhesus.

Interestingly, of all NHP studied to date, the squirrel monkey exhibits the clearest temporal separation between regression of the fetal zone and establishment of the mature ZR. The fetal zone disappears by the third week of life and the ZR appears around week 6, with adrenocortical morphology resembling the human adrenal by the fifth month (Miller *et al.* 1990). Given the potential links between brain and cognitive development and adrenal androgens already discussed, it is particularly notable that squirrel monkeys exhibit extremely rapid brain growth compared with other New World primates and reach adult brain size before 6 months of age (Leigh 2004). As well as achieving adult brain size at an early age, behavioral competencies mature early in these primates. Adult-like locomotor and foraging behaviors develop between 4 and 6 months in the wild and with greater frequency in females than in males (Boinski 1988). Unfortunately, there are no data on the developmental pattern of adrenal androgen secretion from birth through the first few months of age for this species. Potential sex differences in adrenal androgen secretion among infant squirrel monkeys would be of special interest in light of the earlier onset of adrenarche among girls (Sulcova *et al.* 1997, Rehman & Carr 2004).

Recent studies by the authors have attempted to extend these earlier studies by examining the functional morphology of adrenal development in the rhesus monkey, focusing on the interval from birth through the first months of life. Functional morphology is defined here as the expression of key enzymes and proteins involved in androgen synthesis (Conley & Bird 1997, Conley *et al.* 2004, Nguyen & Conley 2008) including 17α-hydroxylase/17,20-lyase cytochrome P450 (P450c17 (CYP17A1)), the redox partner protein NADPH-cytochrome P450 oxidoreductase (CPR), and the partner protein cytochrome b5 and 3β-hydroxysteroid dehydrogenase (3βHSD) among others. Results of previous studies provided convincing evidence that the expression of cytochrome b5 in particular was an excellent marker of ZR differentiation, establishing a clear picture of functional maturation (Mapes *et al.* 1999). Based on the development of a perimedullary zone of cells with typical ZR morphology and strong expression of cytochrome b5 (Fig. 1), it was concluded that ZR development was essentially complete by 2–3 months of age (Nguyen *et al.* 2008). Several studies on human adrenal functional morphology show the same developmental course, but one that is far more protracted over time, occurring over a 6- to 8-year period, which corresponds temporally with adrenarche (Suzuki *et al.* 2000, Hui *et al.* 2009, Nakamura *et al.* 2009). Thus, morphologically, adrenarche would appear to be completed in infancy in rhesus macaques as early as 2–3 months of age. There is no comparable morphological evidence for or against adrenarche in any other NHP.

Biochemical adrenarche

The central importance of cytochrome b5 in supporting androgen synthesis by P450c17, and its significance as a functional marker of ZR maturation and androgen production (Sakai *et al.* 1993, Yanase *et al.* 1998), is supported by many elegant biochemical studies from a number of laboratories that have demonstrated its effects on recombinant P450c17 protein activity (Katagiri *et al.* 1995, Lee-Robichaud *et al.* 1995, Auchus *et al.* 1998, Brock & Waterman 1999, Soucy & Luu-The 2000, Shet *et al.* 2007). Specifically, cytochrome b5 selectively augments the 17,20-lyase activity of P450c17 that cleaves the pregnane to an androgen in the last committed step. Importantly, there is no appreciable, inherent difference in the 17,20-lyase activity of P450c17 among the NHP in which P450c17 has been cloned and expressed (Arlt *et al.* 2002, Swart *et al.* 2002, Pattison *et al.* 2004). Therefore, an increase in cytochrome b5 would be expected to accompany an increase in 17,20-lyase activity and androgen synthesis, such as that which occurs at adrenarche, if cytochrome b5 levels *in vivo* are not already saturated. Very little data exist to support this hypothesis, even in human studies, and few have assessed 17,20-lyase activity directly in adrenal microsomes. Although the 17,20-lyase activity in

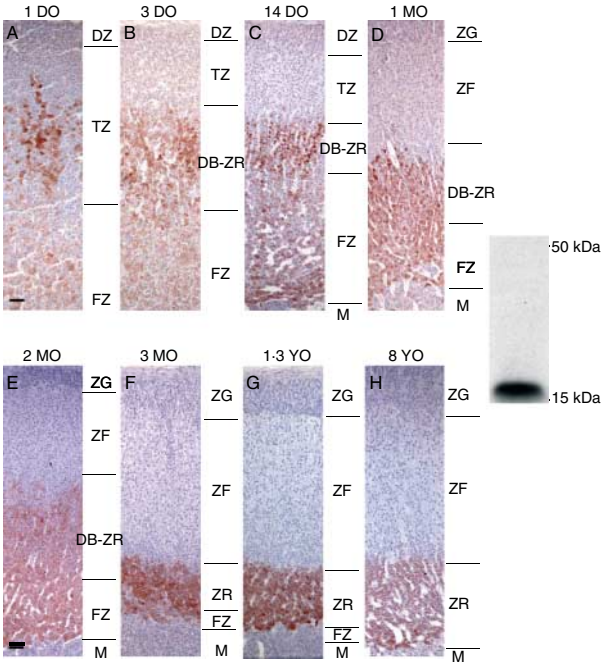

Figure 1 Cytochrome b5 expression in the developing rhesus adrenal cortex (1-day old (DO) – 1-month old (MO; A, B, C and D) and 2 MO – 8 years of age (YO; E, F, G and H)). (A and B) Perinatal period (1 and 3 DO respectively); there is patchy expression throughout the fetal zone (FZ) and the transitional zone (TZ) adjacent to it, but expression is more intense in the positive cells of the TZ. The dense band zona reticularis (DB-ZR) is evident between the TZ and FZ in the 3 DO tissue, consisting of compact cells with intense b5 expression, much greater than cells of either the FZ or the TZ. The outermost definitive (DZ) has no detectable b5 expression by comparison. (C) Perinatal period (14 DO); there is increased intensity of b5 expression in the FZ, although expression in the DB-ZR is still greater. The DZ and medulla (M) are negative for b5 expression. A small number of TZ cells near the DB-ZR show b5 expression. (D) Neonatal period (1 MO); nearly all DB-ZR and FZ cells are positive for b5 expression in the region between a distinct b5-negative zona fasciculata (ZF) and M. The FZ, while still b5 positive, is decreasing in size, and there is no detectable b5 expression in the zona glomerulosa (ZG). (E) Neonatal period (2 MO); all DB-ZR and FZ cells are positive for b5 expression in the region between a distinct b5-negative ZF and M. Compact cells of the DB-ZR exhibit increased intensity of expression, similar to perinatal adrenals. The FZ, while still b5 positive, continues to shrink in size. There is no detectable b5 expression in the ZG or M. (F) Neonatal period (3 MO); there is uniform b5 expression throughout the ZR, as seen in adrenal cortex of mature rhesus. Between the b5-positive compact cells of the ZR and the b5-negative cells of the M is a thin layer of large, vacuolated b5-positive cells of the diminished FZ. (G) Juvenile (1·3 YO); expression of b5 is similar to that observed in the ZR of neonates 3 MO and older. (H) Adult (8 YO); note expression is uniform in intensity in all cells, similar to that seen in the 3 MO ZR. In adults, no cells exhibiting FZ morphology were detected within the b5-positive region between the b5-deficient ZF and M. An immunoblot of cytochrome b5 expression in rhesus adrenal microsomes is shown at the right, demonstrating that the antisera clearly recognize a single immunoreactive band consistent in size with that expected for the protein. Bars = 50 μm, all panels have same magnification. Reproduced from Nguyen *et al.* (2008).

adrenal microsomes of a single infant was lower than similar samples from 11 other older individuals, there was no obvious increase in 17,20-lyase activity with age (Couch *et al.* 1986). Schiebinger *et al.* (1981) observed an increase in 17α-hydroxylase, 17,20-lyase, and 21-hydroxylase activities in human adrenal microsomes from tissues that represented preadrenarche and postadrenarche periods of development but saw no selective increase in 17,20-lyase activity and no decrease in 3βHSD activity. Therefore, while increases in 17,20-lyase activity are assumed to take place based on ratios of circulating steroid concentrations (Rich *et al.* 1981, Kelnar & Brook 1983, Lashansky *et al.* 1991, Palmert *et al.* 2001), no direct evidence from human studies exists to support such a conclusion. However, recent results from investigations on adrenal development in the neonatal and infant rhesus have demonstrated an increase in 17,20-lyase activity with age without an increase in P450c17 expression (Nguyen *et al.* 2009). This corresponds with the functional differentiation of the ZR defined morphologically and especially with an increase in expression of cytochrome b5. Moreover, cytochrome b5 stimulated 17,20-lyase activity when added to adrenal microsomes, and the lower were the endogenous levels of cytochrome b5 levels in microsomes, the greater was the stimulated 17,20-lyase response (Nguyen *et al.* 2009). These data thereby affirm, for the first time in any primate, that ZR maturation is associated with an increase in 17,20-lyase activity and that increased expression of cytochrome b5 is a key element in the molecular regulation of adrenarche.

Endocrinological adrenarche

As noted above, characterization of adrenarche in NHP is largely based on examination of circulating DHEA and DHEAS levels, conducted around the time of puberty. Specifically, an endocrinological profile similar to humans, with an increase in adrenal androgen levels immediately preceding puberty, is often used as the basis for the presence of this phenomenon in NHP species (Cutler *et al.* 1978, Castracane *et al.* 1981, Smail *et al.* 1982, Winter 1992). Among the few NHP that have been studied in detail, the chimpanzee and gorilla have been reported to meet these endocrinological criteria (Cutler *et al.* 1978, Smail *et al.* 1982). In the chimpanzee, several studies found significant increases in DHEA or DHEAS in prepubertal/pubertal groups (Cutler *et al.* 1978, Smail *et al.* 1982) or prepubertal chimpanzees alone (Copeland *et al.* 1985), when compared with younger age groups. These much cited results suggest that a rise in adrenal androgen levels may occur as early as 3–4 years, several years before the onset of puberty (Copeland *et al.* 1985, Marson *et al.* 1991). However, studies reporting individual hormone levels (rather than age-specific groups) found no discernible increase in DHEA or DHEAS during the peripubertal period (Nadler *et al.* 1987, Bernstein *et al.* 2012). Furthermore, fecal concentrations of DHEAS were actually higher in juveniles (5–9 years of age) than in either

subadults (10–15 years) or adults (16+ years) (Seraphin *et al.* 2008). The earliest studies on circulating adrenal androgen concentrations in gorillas had a limited number of subjects, none of which were prepubertal age (Cutler *et al.* 1978). As such, there was insufficient data to determine whether the gorilla experiences adrenarche. However, a recent detailed survey of NHP found that the gorilla exhibits a prepubertal rise in circulating DHEAS and DHEA levels, starting at 4 years (Bernstein *et al.* 2012). Relative to humans (Parker 1999), the duration of the rise is brief, lasting either 2 (DHEA) or 8 (DHEAS) years (Bernstein *et al.* 2012). Further examination of these dynamic periods, especially utilizing analysis of longitudinally collected samples, is necessary to construct more detailed profiles of adrenarche in these species.

Very limited hormonal data of adrenal androgen secretion exist for other NHPs, most failing to identify a prepubertal rise in concentrations, thereby suggesting that these species do not experience adrenarche. The limited data available on the orangutan show no significant difference between pre- and postpubertal adrenal androgen levels (Cutler *et al.* 1978, Collins *et al.* 1981). In the sooty mangabey (*Cercocebus atys*; Mann *et al.* 1983), baboon (Castracane *et al.* 1981, Ducsay *et al.* 1991), pig-tailed macaque (*Macaca nemestrina*; Smail *et al.* 1982, Muehlenbein *et al.* 2002), marmoset (Levine *et al.* 1982), crab-eating monkey (*Macaca fascicularis*; Meusy-Dessolle & Dang 1985), and rhesus macaque (Koritnik *et al.* 1983, Kemnitz *et al.* 2000), circulating levels of DHEA and/or DHEAS rapidly decline after infancy. No rise immediately preceding puberty was observed. With only one notable exception, however, these data were from cross-sectional studies on relatively few subjects without knowledge as to whether the samples collected even span the period during which the adrenal ZR becomes established. Thus, these reports provide little or no verifiable evidence relevant to adrenarche.

By contrast, and as stated previously, the authors have recently identified the neonatal and infant period as a time of extensive adrenocortical remodeling and ZR development in the rhesus macaque (Nguyen *et al.* 2008). Though circulating levels of adrenal androgens have been extensively studied in the rhesus macaque (Snipes *et al.* 1969, Cutler *et al.* 1978, Seron-Ferre *et al.* 1978, 1983, 1986, Smail *et al.* 1982, Koritnik *et al.* 1983, Lane *et al.* 1997, Kemnitz *et al.* 2000, Muehlenbein *et al.* 2002), few studies included neonates and infants (Cutler *et al.* 1978, Smail *et al.* 1982, Koritnik *et al.* 1983, Seron-Ferre *et al.* 1983, 1986), and fewer still separated these into age groups (Koritnik *et al.* 1983, Seron-Ferre *et al.* 1983, 1986). More importantly, with the exception of the studies of Lane *et al.* (1997), which did not include animals <1 year, all previously reported data are derived from cross-sectional studies. Several studies reported that DHEA and DHEAS decline after the first year of life (Cutler *et al.* 1978, Koritnik *et al.* 1983, Lane *et al.* 1997). The only study that has measured DHEAS in subjects from birth through the first few months of life found no evidence of a transient, postnatal increase, only a decline after the first 2 months of age (Koritnik *et al.* 1983). But as noted, sampling was cross-sectional.

To better define the developmental period most likely to encompass adrenarche in rhesus monkeys, a longitudinal study with frequent sampling from birth through infancy was conducted on intact males and on castrates to exclude any potential testicular contribution to the androgen profile. Both groups experienced a prepubertal rise in circulating androgen levels, with DHEA and DHEAS peaking by 8 and 7 weeks of age respectively (Conley *et al.* 2011*b*). DHEAS levels increased nearly threefold in castrates and nearly twofold in intact animals, while DHEA increased over eightfold in castrates and over tenfold in intact males (Conley *et al.* 2011*b*; Fig. 2). Moreover, the time course of the rise in circulating adrenal androgens coincided (Conley *et al.* 2011*a*) with the morphological differentiation of the rhesus ZR (Nguyen *et al.* 2008) and the increase in 17,20-lyase activity in adrenal microsomes from neonatal and infant rhesus monkeys (Nguyen *et al.* 2009), as noted above. Together, these data strongly support the occurrence of adrenarche in the prepubertal rhesus macaque, by morphological, biochemical, and endocrinological definitions, but between 2 and 3 months of age, much earlier than might ever have been expected. No data set documenting adrenarche in any primate is as complete, not even in humans.

Gonadectomy apparently influences adrenal androgen secretion as adrenal androgen secretion was greater in castrates than intact male rhesus (Conley *et al.* 2011*b*). This is reminiscent of an induction of a recognizable, cytochrome b5-expressing ZR in gonadectomized female marmosets when none was detected in intact controls (Pattison *et al.* 2007). Gonadotropin concentrations would be elevated after gonadectomy in both these cases (Plant 1980, 1985) and have been suggested to influence human adrenocortical function (Carlson 2007). However, data comparable to the effects of gonadectomy on adrenal androgen concentrations are hard to find in the human literature. The data most cited are represented by children who are hypogonadal due to a hypogonadotropism. These studies necessarily involve small numbers of affected subjects, and data are often cross-sectional with innumerable confounding factors, potential concurrent genetic defects not least among them. Comparisons of hypogonadotropic hypogonadal (<10) with normal subjects can also be made based on chronological age or bone age (Copeland *et al.* 1977, Sklar *et al.* 1980) and even tanner stage (Counts *et al.* 1987), further complicating analysis. Though finding no difference in concentrations between affected and normal control subjects in these studies, the rise in DHEAS was reported to be delayed in gonadotropin-deficient boys (Van Dop *et al.* 1987). In contrast to hypogonadotropic hypogonadism, gonadotropins are elevated in boys with hypogonadism due to Prader–Willi syndrome (Siemensma *et al.* 2011), and hypogonadism is associated with elevated DHEAS in these subjects (Unanue *et al.* 2007). Similarly, gonadotropins are elevated in patients with Turner syndrome (Martin *et al.* 2004) and so are DHEAS concentrations (Teller *et al.* 1986, Balducci *et al.* 1998, Martin *et al.* 2004). To the

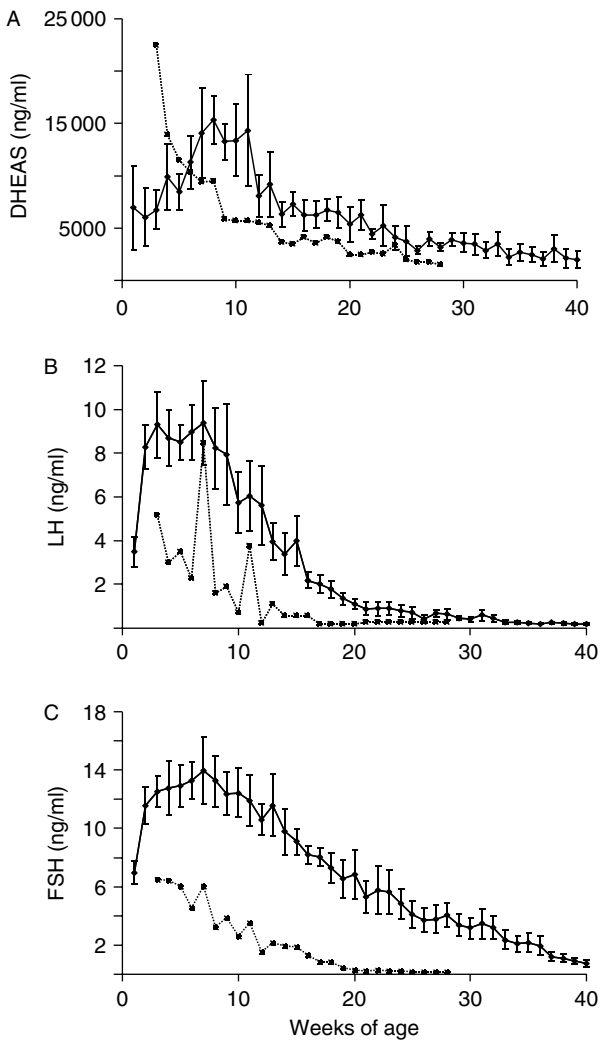

Figure 2 Adrenal androgen (A, DHEAS) and gonadotropin (B, luteinizing hormone (LH); C, follicle-stimulating hormone (FSH)) concentrations in peripheral blood of male rhesus macaques castrated and sampled longitudinally every week from 1 through 40 weeks of age. Shown are the means and S.E.M. of determinations from five subjects (solid line, diamonds) and an additional outlier (dotted line, squares). Note the lack of any increase in DHEAS in the outlier (as is seen in the cohort around 8 weeks of age) is also associated with abnormally low and constantly decreasing concentrations of LH and FSH (hypogonadotropism). Data redrawn from Conley *et al.* (2011*b*).

best of the authors' knowledge, human studies on adrenal androgen secretion following prepubertal castration have not been reported, and the role of gonadotropins in adrenal androgen secretion remains controversial (Bernichtein *et al.* 2008). Nonetheless, in the longitudinal analysis of adrenal androgen and gonadotropin concentrations in castrated male rhesus monkeys, one subject stood out as an outlier in which no increase in DHEAS was evident. Interestingly, this one castrated male was also hypogonadotropic by comparison with the others of his cohort (Fig. 2), although no other abnormality of growth or endocrinology was apparent. Clearly, no conclusions can be drawn from this one individual, but the data are consistent with a potential role for a long-term effect of gonadotropins on growth and development of the primate ZR.

In conclusion, while the peaks in DHEA and DHEAS levels in the rhesus occur prepubertally rather than in adulthood (as in humans), adrenal androgen levels rise years before puberty (Wilen & Naftolin 1976) nonetheless, much like humans and chimpanzees. Earlier studies investigating adrenarche in the rhesus macaque often placed neonates, infants, and juveniles in the same group and compared them to postpubertal groups. As noted in numerous earlier reports, and as emphasized by recent longitudinal analysis (Conley *et al.* 2011*b*), adrenal androgen levels during these developmental periods are highly variable, especially within the first 2 months of life. To identify a rise in circulating androgens that might help to define adrenarche requires frequent longitudinal sampling from a very early age at least in some primates and even in human development (Remer *et al.* 2005). Such data still do not elucidate the biology provided by morphology and biochemical analysis of adrenal tissue, nor do they edify the physiological control of adrenal androgen secretion, which studies in NHP species have a better chance of providing.

Summary

The lack of an identifiable, prepubertal rise in adrenal androgens is the sole evidence cited that most NHP, like the rhesus macaque and baboon, do not experience adrenarche. DHEAS increases as a result of anatomical and functional maturation of the adrenal ZR and is sometimes a useful definition of adrenarche. However, perinatal regression of the androgen-secreting fetal zone overlaps the establishment of a ZR in rhesus monkeys, and frequent longitudinal sampling is required to detect the rise in adrenal androgens associated with adrenarche. The absence of temporal separation between fetal zone regression and ZR maturation in baboons probably precludes detecting adrenarche as defined by adrenal androgen concentrations alone. In any case, without an appreciation of associated morphological and biochemical transitions, it is unlikely that the processes regulating ZR maturation, adrenarche, and androgen synthesis in general will be understood. For that reason, a broader definition of adrenarche is needed, one that includes morphological, biochemical, and endocrine correlates, not all signs of which may be obvious concurrently in some primate species. It must also be acknowledged that adrenarche is a complex process, one requiring appropriate NHP models to unravel because properly controlled experiments cannot be conducted in human subjects. Studies on those species experiencing it, and those not, offers the greatest promise for progress to be made, therapeutic and otherwise, into the regulation of adrenal androgen production in humans.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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