

Review Article

Adrenarche in Comparative Perspective

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Objectives: To address the hypothesis that human adrenarche is associated with extended juvenile brain development by comparing the timing of adrenal androgen production, brain development and lactation in a larger comparative mammalian context.

Methods: Findings from published literature are used to compare the developmental timing of adrenal androgens, brain glucose utilization and lactation in rats, rhesus macaques and humans.

Results: Comparison of the timing of androstenedione and progesterone production with developmental patterns of cortical glucose utilization and the timing of lactation in laboratory rats suggest that the rise and fall of adrenal hormone production centered on weaning plays a role in synaptogenesis during lactation as well as post weaning synaptic pruning. Comparison of the timing of cortical glucose utilization, DHEAS production and weaning in rhesus macaques also suggests that postnatally elevated levels of DHEAS may be related to patterns of synaptic formation and pruning centered on weaning. In contrast among humans, peak cortical glucose utilization occurs well after weaning and the rise in adrenal androgen production coincides with declining cortical glucose utilization with the onset of the juvenile stage.

Conclusions: Compared to rats and macaque, in humans the energetic demands of brain development and increased production of adrenal androgens are divorced from the timing of lactation, while the timing of adrenarche and brain development are still associated. Thus the neuroprotective effects of DHEAS may protect synaptic plasticity in metabolically active parts of the brain starting approximately at the age of 7, promoting prolonged development of the human prefrontal cortex. *Am. J. Hum. Biol.* 23:44–52, 2011. © 2010 Wiley-Liss, Inc.

Adrenarche, the prepubertal increase in the adrenal production of the androgens dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), is a distinctive element of hominoid life history, known to be shared only by humans, chimpanzees, and gorillas (Collins et al., 1981; Cutler et al., 1978). DHEAS have been associated with timing of reproductive maturation in species of rodents (Cherry et al., 2002), and primates (Pattison et al., 2007) and it has been hypothesized that adrenarche in humans may desensitize the hypothalamus to gonadal steroids (Genazzini et al., 2000; Grumbach et al., 1974). However, among humans, adrenarche is not necessary for pubertal onset (Counts et al., 1987; Cutler and Loriaux, 1982) suggest it has no direct implication for reproduction, and leaving its significance a mystery.

Recent findings demonstrating the production of DHEA within the brain (Balieu, 1988; Baulieu and Robel, 1990), implicate DHEA in brain function. DHEAS has been shown to promote growth of fetal cortical cells (Compagnone and Mellon, 1998; Suzuki et al., 2004) as well as dendritic spines in the postnatal hippocampus (Hajszan et al., 2004; Krishna and Herbert, 2002). DHEA also has been demonstrated to increase levels of synapsin I, a marker of synaptic terminals, in the rat (Shirayama et al., 2005). Given the space filling nature of dendritic growth and synaptogenesis, the co-occurrence of high levels of circulating DHEAS and large brain size in the humans and great apes suggests a role for adrenarche in human brain maturation.

I have previously argued that adrenarche represents an adaptation to support brain maturation and social learning in humans and the great apes starting prior to puberty and continuing into young adulthood (Campbell, 2006). In particular, I suggested that as an anti-glucocorticoid, DHEAS (Muller et al., 2006) may provide protection against the neurotoxic effects of stress during middle childhood when the cortex begins to mature.

Here, I sharpen that argument by comparing the role of the adrenal gland in brain maturation among rodents, and nonhuman primates, to that of humans. In some species of rodent, DHEA has been related to suppression of reproductive maturation (Cherry et al., 2002). However, in the rat adrenal androgen production (Pignatelli et al., 2006) which peaks around the time of weaning (Levine, 2002) increases in parallel with brain glucose utilization (Nehlig, 1999) and cortical maturation (Bock et al., 2005, 2008), suggesting the involvement of adrenal steroids in early brain development.

Similarly in primates, DHEAS has been associated with reproductive maturation and suppression in nonanthropoid species (Pattison et al., 2007; Perret and Aujard, 2005). But available data from the rhesus macaque suggests that the development of the adrenal zona reticularis which produces DHEAS (Nguyen et al., 2008) coincides with the onset of weaning (Fooden, 2000), while proceeding peak glucose metabolism (Jacobs et al., 1995), and cortical maturation (Malkova et al., 2006). The timing of these events also suggests a role for adrenal androgens in early postnatal brain development, thought it may differ from that of the rat.

In humans circulating levels of DHEAS begin to rise around the age of 7 (Sulcova et al., 1997) just around the end of peak cortical glucose utilization (Muzik et al., 1999) at age 8 and the attainment of 95% adult brain size (Caviness et al., 1996). All three events are well past the age of

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weaning (Sellen, 2001), linking adrenarche more directly to brain maturation. Furthermore, the post-adrenal rise in DHEAS parallels a decline in cortical glucose utilization, suggesting that DHEAS does not simply promote synaptogenesis. Instead, I suggest DHEA plays a role in protecting synaptogenesis and myelination against stress in brain regions that are still actively developing during middle childhood. In particular, DHEA may promote the development of corticolimbic dopaminergic circuits critical to emotion which are particularly vulnerable to oxidative damage.

ADRENARCHE IN RODENTS

Finding from the prairie deer mouse, *Peromyscus maniculatus*, demonstrate that adrenal androgens can play a role in reproductive development among rodents. The prairie deer mouse exhibits the development of the adrenal zona reticularis and the production of DHEA prior to reproductive maturation (Cherry et al., 2002). When kept in a group laboratory population of *Peromyscus maniculatus* show reproductive inhibition which is reversed when individuals are removed and put in mating pairs. During development, reproductively suppressed males and females demonstrate small zona reticulari and lower DHEA levels, along with reduced thyroid hormone and lower resting and active metabolic rates, relative to reproductively capable individuals (Cherry et al., 2002).

These findings are in line with early experimental work suggesting a role for the adrenal gland in normal pubertal maturation in the rat (Corey and Britton, 1931; Gorsky and Lawton, 1973; Moon, 1937). Adrenalectomy resulted in delayed onset of puberty, which could be reversed with the administration of ATCH (Moon, 1937), while the administration of adrenal extracts induced the onset of puberty (Corey and Britton, 1931). However, the effects of adrenalectomy appeared confined to the time of weaning (Days 18–25) and puberty was not delayed by adrenalectomy at the beginning of puberty, i.e., on Day 35 (Gorsky and Lawton, 1973), indicating the impact of the adrenal gland took place earlier in development, not during puberty itself.

Subsequent work in rats demonstrated that adrenalectomy on postnatal Day 11 leads to increased brain growth and heavier brains in adults (Meyer, 1983). Growth of the cortex and the midbrain were most immediately apparent with increases within a week, while changes in the cerebellum and hippocampus took 1–2 weeks longer (Yehuda and Meyers, 1991). Growth of the brain was based on increased myelination (Meyer, 1983; Meyer and Fairman, 1985). Furthermore, the impact of adrenalectomy was blocked by the administration of corticosterone (Meyer, 1987), providing evidence that cortisol inhibits the myelination of early developing neural tracts with potential consequences for puberty and the rest of the lifespan.

More naturalistic work on behavioral development in the rat has demonstrated a stress hyporesponsive period (SHRP) prior to weaning during which the adrenal gland is less responsive to stress (Oliver et al., 1994). Maternal interaction with the pup appear to suppress the activation of the hypothalamic adrenal axis (Levine, 2001, 2002), making weaning a key developmental change in the pup's environment. In addition, maternal deprivation leads to increased neuronal death prior to, but not after, weaning (Zhang et al., 2002), clearly suggesting that weaning

demarcates a changes in the effect of the adrenal axis on brain development.

Recently, Pignatelli et al. (2006) have reported detailed histological observations showing the development of the adrenal zona reticularis in the rat by Day 10, with growth in size until adulthood. Furthermore, production of adrenal steroids, including androstenedione, cortisol (corticosterone is the glucocorticoid normally produced by the rat), and 17-OH-progesterone, but not DHEA or DHEAS, starts about Day 10, reaches a peaks around Day 20, and declines to very low levels by Day 30 (Pignatelli et al., 2006). Importantly, there are no apparent sex differences in the size of the zona reticularis or the production of androstenedione, cortisol, and 17-OH-progesterone.

These changes in the production of adrenal steroids mark the period of peri-weaning development, with the peak at Day 20 coinciding with weaning, around Day 21–24, and the return to baseline at Day 30 coinciding with the onset of puberty at Day 30–35. Furthermore, increasing adrenal steroid production coincides with cortical glucose utilization and cortical growth prior to weaning. Until Day 10 glucose utilization is low and homogenous throughout the brain. Starting around Day 14, increases in glucose utilization rates are noticeable with a dramatic increase between Days 17 and 21 [as much as 100% in some brain regions (Nehlig, 1999; Nehlig et al., 1988)]. Brain glucose utilization continues to rise after weaning until Day 35, increasing roughly 25% across a range of brain structures (Nehlig et al., 1988; see Fig. 1 for a graphic depiction of developmental patterns of adrenal androgens and cortical glucose utilization).

Importantly, growth in different regions of the cortex appear to diverge at this point. The orbital PFC reaches maximal size at Day 30 and the declines in size, while the medial prefrontal cortex increases in size until Day 24 and then decreases until Day 30, when it reaches adult volume (Van Eden and Uylings, 1985). Interestingly as a whole brain weight continues to increase past puberty at Day 60 (Culley and Lineberger, 1969).

Increases in cortical volume are associated with the growth of dendritic trees and the development of synapses (Bock et al., 2008) while cortical shrinkage is thought to represent a period of dendritic loss and synaptic refinement (Bock et al., 2008). Synapses are energetically costly (Rocher et al., 2003). Thus it is not surprising that the growth of the cortex is paralleled by an increase in glucose utilization from Days 14 to 21.

After weaning, declining levels of adrenal hormones may help to explain the differential impact of stress on regions of the rat cortex until Day 35 (Bock et al., 2005; Gos et al., 2008). Androstenedione is not only a weak androgen, like DHEA and DHEAS in humans, but a direct precursor for estrogen, which also has neurodevelopmental effects, while 17-OH progesterone is a precursor of allopregesterone, a neurosteroid that also promotes dendritic growth and synaptogenesis (Tsutsui, 2006, 2008).

Overall, increasing levels of both androstenedione and 17-OH progesterone prior to weaning may promote dendritic growth and protect synaptic formation throughout the brain leading to many potential neuronal connections. In contrast, declining levels of these hormones after weaning would expose neurons to the effects of metabolic stress associated with increasing corticosterone production that begin with weaning (Pignatelli et al., 2006). Large dendritic spines, associated with the creation of stable and long

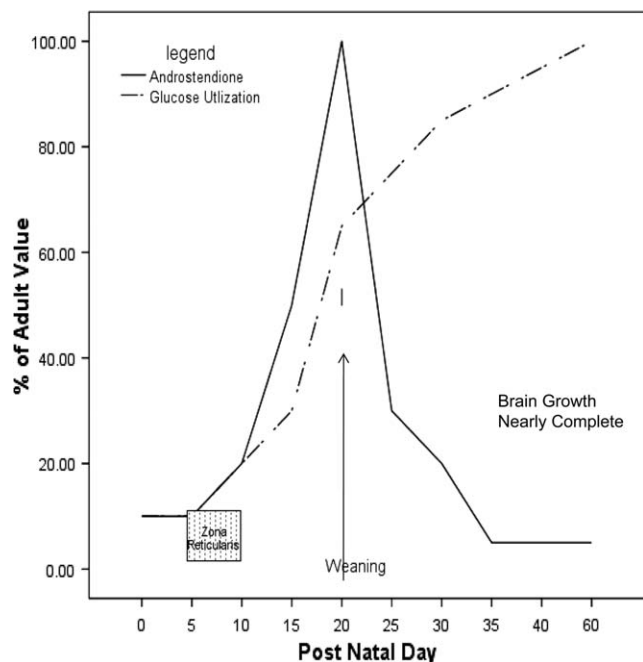


Fig. 1. Timing of glucose utilization and adrenal androgen production in the rat. This schematic representation shows the timing of cortical glucose utilization and adrenal hormone production in the laboratory rat relative to weaning. Profiles of cortical glucose utilization and adrenal androgen production are synchronous prior to weaning. After weaning glucose utilization rates continue to rise slightly while adrenal androgen levels decline to baseline. Initial development of the zona reticularis from Day 5–10 come well before weaning and precedes the rise in androstenedione, as would be expected. Brain volume continues to increase into adulthood. Based on data from Pignatelli et al. (2006), Nehlig et al. (1988), and Cully and Lineberger (1969).

lasting neural connections, are particularly affected by stress (Radley et al., 2008). Thus the period after weaning and before puberty appears to be involved in the refinement of longer range neural circuits (Bock et al., 2005, 2008).

As Pignatelli et al. (2006) have pointed out adrenarche in the rat cannot, strictly speaking, be considered a model for human adrenarche. Not only does the rat adrenal gland produce androstenedione rather than DHEAS, but the zona reticularis itself continues to increase in size even after the production of androstenedione has returned to baseline (Pignatelli et al., 2006). In contrast, among humans adrenarche is a direct function of the growth of the zona reticularis. Once initiated DHEAS production continues to increase with the thickness of the zona reticularis (Havelock et al., 2004; Rainey et al., 2002). Furthermore, the much shorter developmental period of the rat means that the timing of weaning, brain glucose utilization, and synaptogenesis may appear linked temporally, regardless of any mechanisms linking them directly.

Nonetheless, recent experiments indicate that exogenous DHEA given to neonatal rats can lead to lasting changes in the brain (Iwata et al., 2005; Shirayama et al., 2005). Shirayama et al. (2005) report increased levels at puberty of synapsin I, a presynaptic protein marker, and GFAP (glial fibrillary acidic protein) reactive astrocytes in the hippocampus, in rats administered DHEA on post-

natal Days 4–7. Iwata et al. (2005) found that administration of DHEA to rat pups lead to increased expression of MAP-2 (microtubule associated protein 2), a dendritic marker in the hippocampus and nucleus accumbens at 7 weeks of age. No effect of DHEA administration on the prefrontal cortex was evident. However, as indicated earlier, postnatal Days 4–7 precede the period of active cortical synaptogenesis in the rat, presumably precluding the chance for DHEA-related effects.

These results clearly suggest that DHEA can have demonstrable effects on post-natal neuronal development in the rat brain. Given the absence of exogenous DHEAS production by the rat adrenal gland, however, any such impact says little about the role of DHEAS in normal brain development, including that of humans. For potential understanding of that case, we have to turn to primates who naturally produce DHEA and DHEAS in the adrenal gland. Unfortunately, while there is data on DHEA profiles from a variety of primate species, information pertinent to its relationship to brain development is lacking.

ADRENARCHE IN PRIMATES

Primates are one of the few mammalian groups that show substantial adrenal production of DHEAS during both fetal development and as adults (Conley et al., 2004). The production of DHEAS by the so-called fetal zone of the adrenal gland during prenatal development has been taken as a universal primate trait (see Mesiano and Yaffe, 1997) while the existence of detectable levels of postnatal DHEA varies across taxa. Substantial postnatal levels of DHEAS has been demonstrated in several anthropoid primates, including macaques (Muehlenbein et al., 2002), baboons (Crawford et al., 1997; Muehlenbein et al., 2003), and sooty manglebys (Mann et al., 1983). In addition, recent work has documented postnatal DHEAS production in the gray mouse lemur (Perret and Aujard, 2005), as well as the common marmoset (Pattison et al., 2007).

Based on histological similarity between macaques and humans, DHEAS production by the adrenal zona reticularis has been suggested as homologous across primates (Conley et al., 2004), though a conclusion based on two species is tentative at best. Support for the homology of the zona reticularis comes from the similarity of genetic sequence for P450c17, an enzyme crucial to the production of DHEA from pregnenolone, across humans, chimps, baboons and rhesus macaques (Arlt et al., 2002). If the zona reticularis is homologous across primates, then contrary to earlier conclusions (Cutler et al., 1978; Levine et al., 1982; Smail et al., 1982) it is the timing of adrenarche among the hominids that is derived from primates in general, not the postnatal production of DHEA and DHEAS per se.

Nonanthropoid primates

The gray or lesser mouse lemur (*Microcebus murinus*) demonstrates that among primates, as with rodents, DHEAS can play a role in reproductive suppression. Gray mouse lemurs are small animals that inhabit a dramatically fluctuating environment and show pronounced seasonality associated with photo period (Génin and Perret, 2003). During the winter both sexes are sexually inactive with reduced levels of reproductive hormones, along with decreased physical activity, hypothermia and an increase

in fat (Perret and Aujard, 2001). During the breeding season, the reproductive function and behavior of subordinate males is suppressed by the presence of a dominant male (Perret, 1992).

Based on 175 males aged 8 months to 11 years from a captive colony located in France, Perret and Aujard (2005) report fluctuations in DHEAS levels across the year, with low and constant levels during the winter off-season and higher levels during the summer breeding season. Summer levels reach a small peak at 3 years of age, the age of reproductive maturation, and then decline to 20% of maximal values by the age of 6. Reductions in DHEAS during the off season are associated with decreased metabolic activity and weight gain in the absence of reproduction. Nonetheless, the specific function(s) of DHEAS in gray mouse lemurs remains unclear. It could serve as a precursor to testosterone production, or protect against the neurotoxic effects of cortisol during the breeding season.

The demonstration of seasonal variation in DHEA levels among red squirrels (Boonstra et al., 2008) underscore the similarity of lemurs and rodents as small mammals subject to seasonal environmental variation and emphasize the importance of seasonal changes in DHEA. Recent work indicating increased production of DHEA during the nonbreeding season in both song sparrows (*Melospiza melodia morpha*), (Soma and Wingfield, 2001) and spotted ant birds antbirds (*Hylophylax n. naevioides*), (Hau et al., 2004) further underscores a role of DHEA as a non-gonadal source of steroid hormones in seasonally breeding animals.

Anthropoid primates

Despite an early report that marmosets lacked adrenarche (Levine et al., 1982), more recently Pattison et al. (2007) have reported postnatal development of a zona reticularis among common marmosets. However, in an interesting twist, Pattison et al. (2005, 2007) find the development of a zona reticularis limited to females, thus explaining why Levine et al. (1982) failed to find evidence of adrenarche—they looked only at males! In particular, the zona reticularis is prominent in reproductively suppressed adolescent females and female adults who had been ovariectomized (Pattison et al., 2007).

The association of DHEA and reproductive suppression among common marmoset females is reminiscent of prairie mice (Cherry et al., 2002). However, in contrast to the prairie mouse, the zona reticularis is thicker, not thinner, among reproductively suppressed individuals (Pattison et al., 2007). Pattison et al. suggest that increased DHEA production in reproductively suppressed females serves as a precursor for estrogen and compensates for reduced ovarian estrogen production. If so, DHEA may protect existing and developing dendritic connections potentially jeopardized by reduced estrogen exposure. This would mitigate the impact of reproductive suppression on brain development and allow for the resumption of normal adult brain function once reproductive suppression ends.

Among the relatively well-studied old world monkey species, including the rhesus macaque and baboons, none show an increase in DHEA or DHEAS postnatally. Smail et al. (1982) reported decreasing levels of DHEA and DHEAS among rhesus macaques from 3 months to 5 years of age, along with an increase in DHEAS among pig tail macaques over the age of 9 relative to those 6–9 years of

age. In both species, females exhibited significantly higher values than males. Recent work using more specific assays confirmed a decline in DHEAS from 4 to 14 years of age among males of both macaque species (Muehlenbein et al., 2002). No results were reported for females, leaving the finding of higher levels in females unconfirmed.

Early results from yellow baboons reported declining levels of DHEAS from birth on, while DHEA levels remain elevated (but did not increase), with females showing higher levels than males (Castracane et al., 1981). More recent work in both yellow (Muehlenbein et al., 2003) and hamadryas baboons (Crawford et al., 1997) support an age related decline in DHEAS. However, neither study reports on DHEA, leaving open the question of whether DHEA/DHEAS ratios with age are fundamentally different than those seen in humans.

Sooty mangabeys, the only other member of the cercopithecines for which published reports are available, show a strong decline in DHEAS from birth to 6 years of age, with no evidence of sex differences (Mann et al., 1983). The lack of a sex difference has been replicated (Bernstein et al., 2007). Like both rhesus and baboons, DHEAS level drop rapidly after birth reaching a low by 19–36 months, well before pubertal increases in testosterone at 55–72 months. Thus the conclusion that cercopithecines do not exhibit adrenarche has strong support. Unfortunately, more detailed DHEA or DHEAS profiles during infancy needed to explore its relationship with early brain development are not available.

It is worth noting that all of the studies of DHEA and DHEAS in primates are based on captive populations, leaving open the possibility of fluctuations among seasonally breeding species. In fact, circulating levels of DHEAS in humans, like other steroid hormones, are subject to various sources of variation, including genetic (Meikle et al., 1997; Pratt et al., 1994) and social stressors (Shirtcliff et al., 2007). Such individual and contextual effects could obscure age related patterns, especially given the relatively small sample sizes of the available studies. On the other hand, the development of the zona reticularis, the primary source of circulating DHEAS, is a cumulative process and may provide a more robust characterization of species-specific age patterns of adrenal function.

In fact, a recent analysis of adrenal development in rhesus macaques demonstrates post-natal maturation of the zona reticularis (Nguyen et al., 2008). Macaques have long been known to produce DHEAS throughout their life span. However, levels of DHEAS drop rapidly from birth with involution of the fetal adrenal zone [responsible for the production of DHEAS in utero (Mesiano and Jaffe, 1997)]. This may obscure postnatal zona reticularis production. Only recently have Nyugen et al., (2008) reported postnatal development of the zona reticularis in rhesus macaques starting late in gestation and finishing by the age of 3 months.

As in the rat, development of zona reticularis in the rhesus macaque precedes both weaning and peak glucose utilization as in the rat. Onset of weaning is initiated by mothers around the age of 4 months (Fooden, 2000), while peak cortical glucose utilization appears to be around 6 months, though the data are very scanty (Jacobs et al., 1995). However, unlike the rat, peak glucose utilization rates exceed those of adults, by as much as 50% (see Fig. 2 for a visual representation of developmental patterns of adrenal androgens and glucose utilization).

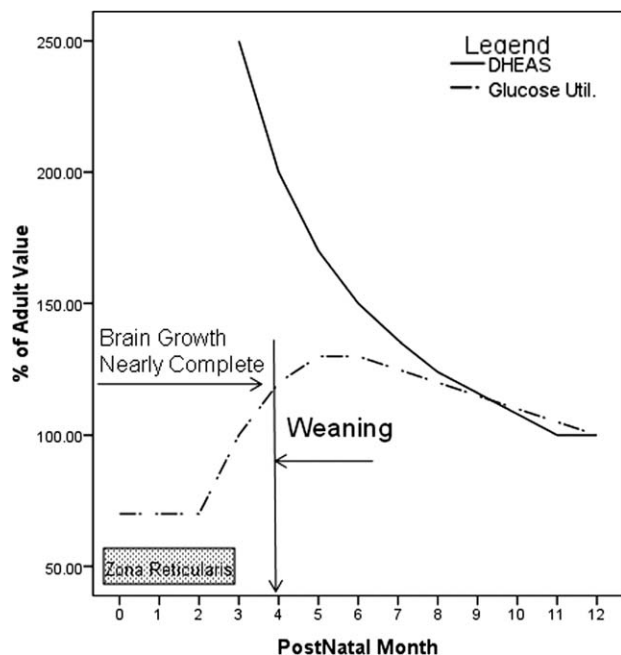


Fig. 2. Timing of glucose utilization and DHEAS production in the rhesus macaque. This schematic representation shows the timing of cortical glucose utilization and adrenal hormone production in the laboratory rat relative to weaning. Profiles of cortical glucose utilization and circulating levels of DHEAS do not parallel each other either after or before weaning. Maximal glucose utilization is after nearly adult brain size is attained. Note that maximal glucose utilization comes after weaning, while the initial development of the zona reticularis which starts from the end of gestation is complete by the onset of weaning. Based on data from Jacobs et al. (1995), Smail et al. (1982), Malkova et al. (2006), and Nyugen et al. (2009).

Furthermore, peak cortical glucose utilization rates come after rapid brain growth is completed. A recent fMRI study of rhesus macaques reported rapid increase in brain growth until 4 months after which only a small increase was evident (Malkova et al., 2006). Along with total volume, increases in white matter volume also peaked from 3 to 4 months. Thus elevated glucose utilization from 4 to 6 months appears related to the production of synapses over and above those present in the adult brain.

This is at odds with changes in cortical synaptic density reported for the rhesus macaque (Bourgeois et al., 1994; Rakic et al., 1986). Across the entire cortex, the number of synapses increases prenatally and during infancy, peaking around 2–3 months (Rakic et al., 1986). The number of cortical synapses then declines slowly until puberty (Bourgeois et al., 1994). This age pattern characterizes the primary visual area (Bourgeois and Rakic, 1993), as well as the prefrontal cortex (Bourgeois et al., 1994), suggesting that all areas of the cortex develop synchronously.

Recent MR imaging of rhesus macaque brains, however, clearly indicates regional differences in the timing of white matter development (Malkova et al., 2006) during the first 4 years, much like those seen in humans starting around the age of 6 years (Gogtay et al., 2004; Shaw et al., 2008). Furthermore, differences in the regional expression of neurotrophin-3, a neuronal growth factor, suggests that sensory and motor neocortical areas develop before association areas in the macaque (Mori et al., 2006), as in humans.

Thus as in the rat, among rhesus macaques the early growth and development of the brain appears to be related to the timing of lactation. Prior to weaning, the energetically expensive process of synaptogenesis appears to be supported energetically by mother's milk, and socially by her presence. On the other hand, the process of synaptic refinement takes place after weaning when the juvenile is dependent on itself for food, and contact with mother no longer dominates its social environment.

However, the longer developmental period of primates means that weaning and brain development are more temporally distinct in the rhesus macaque. Elevated rates of brain glucose metabolism from 4 to 6 months in the rhesus macaques suggest that synaptogenesis is at its highest rate at the onset of weaning. While dendritic retraction in the rat cortex proceeds quickly after weaning (Bock et al., 2008; Van Eden and Uylings, 1985), in the rhesus macaque the period between weaning and puberty is marked by a slow decline in cortical synaptic density (Bourgeois et al., 1994). Thus the lack of a clear association of DHEA and DHEAS profiles with brain development in the rhesus macaque may reflect differences in the length of synaptic pruning—about 2 weeks (Day 21–35) in the rat compared to two and a half years (4 months to 3 years) in the macaque.

ADRENARCHE IN HUMANS

The relative timing of lactation, brain maturation and adrenarche in humans is difficult to compare easily because of variability in the timing of the events themselves. For instance, the age of weaning among humans varies tremendously across cultures based on differences in breast feeding practices. Furthermore, the introduction of supplemental foods starting at 6 months makes the relationship between the energy mom supplies through lactation and the energetic needs of the infant much more complicated.

Nonetheless, empirical estimates of the age of weaning in nonindustrial populations are between 2 and 3 years of age (Sellen, 2001), while other estimates suggest ages from 2 to 5 years (Dettwyler, 1995). In contrast, peak cortical glucose utilization rates (based on a single sample of 29 children in an industrial society) can be described as a plateau from 4 to 8 years of age (Chugani, 1998), or a single peak at 7.8 years of age (Muzik et al., 1999). In addition, synaptophysin, a marker of synaptic density correlated with glucose utilization (Rocher et al., 2003) peaks from 6 to 10 years of age, based on a sample of 24 specimens from the US (Glantz et al., 2007). It is important to note here that these results supercede earlier canonical findings of maximal synaptic density in the prefrontal cortex at 3 [1/2] years of age (Huttenlocher and Dabholka, 1997). The study lacked subjects between the age of 3/12 and 12 years leaving it unable to describe the intervening pattern.

Regardless of the estimates for weaning age and/or peak glucose utilization chosen, it is clear that maximal cortical glucose at 4 to 8 years is substantially divorced from weaning at 2 to 3 years of age. Similarly, at 7 years of age, increases in circulating DHEAS with adrenarche (Remer et al., 2005) bear little if any association with weaning. In contrast, the onset of adrenarche is roughly consistent with peak cortical glucose utilization as well as the attainment of adult brain volume (Caviness et al., 1996). However, unlike rats and macaques, the continuing increase in circulating levels of adrenal androgens follow-

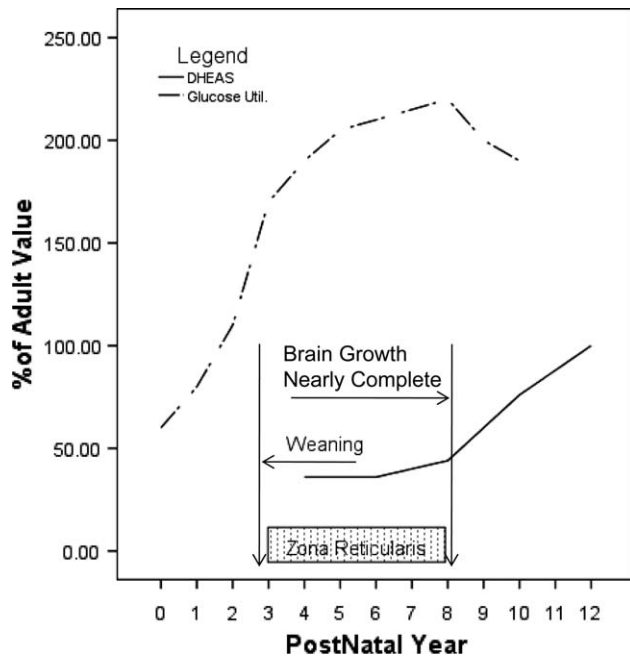


Fig. 3. Timing of glucose utilization and DHEAS production in the human. This schematic representation shows the timing of cortical glucose utilization and adrenal hormone production in the human relative to weaning. Maximal cortical glucose utilization is associated with near completion of brain growth. It comes well as weaning while circulating adrenal androgens begin to rise just as cortical glucose utilization begins to decline. Note that unlike the macaque, development of the zona reticularis is initiated after rather than before weaning. Based on data from Dhom (1973), Remer et al. (2005), Muzik (1999), and Caviness et al. (1996).

ing adrenarche comes at a time of declining cortical glucose utilization (see Fig. 3).

These simple differences in the timing of weaning, adrenarche, and cortical glucose utilization have several important implications for our understanding of human brain development. First, they suggest that among humans, mother is not directly paying the energetic costs of a large brain. In fact with the introduction of supplementary foods well before weaning, lactation itself provides only part of the caloric costs of brain development starting around the age of 6 months (Humphrey, 2010). With other sources for calories to support the bulk of the infants energy needs, the marginal benefits of calories that come directly from the mother's stores are greatly reduced. In terms of her own reproductive output, she will benefit from reducing the transfer of bodily stored energy to the nursing offspring and redirecting such energy to her next offspring, whether in utero or in preparation. Evolutionarily speaking, this circumstance can be expected to result in earlier weaning (Humphrey, 2010).

Second, the similarity of age related patterns of cortical glucose utilization and adrenal androgen profiles in rats suggests that increases in circulating DHEAS at adrenarche are likely to be associated with active synaptogenesis. This conclusion seems inconsistent with the evidence for an overall decline in cortical glucose utilization (Chugani, 1998), and declines in makers of synaptic density (Glantz et al., 2007), somewhere between 6 and 10 while circulating levels of DHEAS are climbing (Remer et al., 2005; Sulcova et al., 1997).

The answer to this apparent paradox appears to may lie in regional differentiation in synpatogenesis (Huttenlocher and Dabholka, 1997). Synaptic production and elimination are co-occurring dynamic processes (Missler et al., 1993; Wolff et al., 1995). Thus even with a net loss of dendritic spines and synapses in the prefrontal cortex between the age of 6 and 10, synaptic plasticity may be maintained in specific areas. For instance, in humans, the anterior cingulate cortex, the insula and thalamus, maintain a higher level of glucose utilization, indicative of plasticity, relative to other areas of the cortex from the age of 6 years into the early 20s (Van Bogaert et al., 1998).

Here I suggest that DHEA/S may play a role in protecting the growth and maintenance of dendritic spines within these brain regions against the effects of metabolic stress, even as the overall rates of cortical energy consumption declines. Exogenous DHEA has been shown to increase neuronal mitochondrial energy production in rats (Patel and Katyare, 2007; Patel et al., 2007) which would provide additional energy for all neuronal activities. Mitochondria are dynamically distributed through the neuron (see MacAskill and Kittler, 2010 for a recent review), including within dendrites where they are essential for dendritic growth related to synpatogenesis (Li et al., 2004).

More specifically stress results in loss of apical dendritic spines in the prefrontal cortex of rats, as well as a reduction in spine density (Shansky and Morrison, 2009). In particular, there is a loss of large spines, thought to be involved in the creation of stable neural connections on apical dendrites (Radley et al., 2008). The loss of apical dendrites relative to basal dendrites close to the soma, shifts the balance toward inter-cortical connections and way from longer range connections to the cortex and is thought to be mediated by corticosterone (Brown et al., 2005; Wellman, 2001).

By promoting energy production, DHEA may help to protect the development and maintenance of large apical dendritic spines from the effects of on-going metabolic stress associated with glucocorticoids and promote the development of longer range neural connection. In addition, DHEAS may promote mylenization, increasing the efficacy of axonal transmission and increasing longer range neuronal signaling. Other neurosteroids, such as progesterone, have been shown to increase mylenization (De Nicola et al., 2009; Roglio et al., 2008). Similar evidence for DHEA or DHEAS is currently lacking, but to the extent that DHEA promotes mitochondrial energy production, it may have a protective effect on myelination as well as synaptogenesis.

In addition to promoting neuronal energy availability, the antioxidant effects of DHEA (Pelissier et al., 2004, 2006) may be particularly noticeable in dopaminergic neurons. Dopamine inhibits complex I respiration in neuronal cell mitochondria (Brenner-Lavie et al., 2009), while cytosolic dopamine can be converted to quinone that produces dopaminergic-specific oxidation (Miyazaki and Asanuma, 2008). Together these processes make dopaminergic neurons particularly sensitive to oxidative stress.

In the rat mPFC circuits particularly vulnerable to stress are found in the anterior cingulate, infralimbic and prelimbic cortex (Shansky and Morrison, 2009), all part of the mesocortical system. In humans, dopaminergic neurons are particularly prominent in the corticolimbic and mesolimbic pathways, including the thalamus, insula and

anterior cingulate cortex (Black et al., 2002). These structures are part of paralimbic dopaminergic reward system underlying social emotions (Craig, 2009; Lamm and Singer, 2010) whose extended development into the early 20s (Steinberg, 2008) may benefit from the neuroprotective effects of DHEA and DHEAS.

There is little direct evidence for neuroprotective effects of DHEA on human brain development. However, at a behavioral level DHEA has been linked to better task performance in individuals with PTSD (Rasmusson et al., 2004) and a higher DHEA/cortisol level to better performance in military training (Morgan et al., 2004). Most recently Wemm et al. (2010) found that DHEA/cortisol ratio was related to academic performance among a sample of college students, independent of standardized test scores and emotional frustration. While, these findings are hard to interpret at a neurological level, the authors suggest that they reflect the impact of behavioral flexibility, a characteristic associated with neural plasticity.

SUMMARY

The function of human adrenarche remains unclear. Adrenarche has long been assumed to play a role in reproductive maturation, and though DHEA production may serve as a reservoir for conversion to other steroids during reproductive maturation in some species of rodents and primates, there is no compelling evidence of a similar function in humans. On the other hand, substantial evidence documents neural effects of DHEA and DHEAS, and the parallels between the timing of adrenal steroid secretion, synaptogenesis and glucose utilization in the laboratory rat suggest a potential for DHEA and DHEAS in brain development.

What I have offered here is a conjecture. Extended brain development in humans involves numerous genetic changes (see Somel et al., 2009 for an example relative to chimps); numerous processes are involved in synaptogenesis along. None the less, from an organismal perspective the parallel timing in humans of asynchronous cortex development starting around the age of 6 years and ending in the mid twenties (Gogtay et al., 2004; Shaw et al., 2008), the parallel rise in DHEA/S production by the adrenal gland (Orentreich et al., 1984; Sulcovka et al., 1997), and evidence that DHEA can promote mitochondrial energy production in rats (Patel and Katyare, 2007; Patel et al., 2007), suggest that adrenarche in human may be related to brain development.

In this article, I have endeavored to elucidate cellular mechanism by which DHEA and DHEAS may play a role in human brain development. Given the lack of concrete evidence for direct effects of DHEA on human brain development, any number of findings can show that my conjecture is not true. Increases in circulating DHEAS during childhood and adolescence may not translate into increasing concentrations in the brain. The demonstrated effects of DHEA on mitochondrial energy production in rats may be more pharmacologic than physiologic, or may not be similar in humans. DHEAS may not have specific antioxidant effects on dopaminergic neurons in the living human brain.

All of these questions are amenable to empirical investigation. Thus time will tell if my conjecture that human adrenarche is fundamentally related to the extended

development of our large brains is pointed in the right direction, or if the evolutionary basis of adrenarche in our species is something all together different.

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