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Age-related changes in neuroendocrine rhythmic function in the rhesus macaque

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Abstract Many environmental conditions show rhythmic changes across the 24-h day; these include changes in light intensity, ambient temperature, food availability, and presence or absence of predators. Consequently, many organisms have developed corresponding adaptations, which ensure that specific physiological and behavioral events occur at an appropriate time of the day. In mammals, the underlying mechanism responsible for synchronizing internal biochemical processes with circadian environmental cues has been well studied and is thought to comprise three major components: (1) photoreception by the retina and transmission of neural signals along the retinohypothalamic tract, (2) integration of photoperiodic information with an internal reference circadian pacemaker located in the suprachiasmatic nucleus, and (3) dissemination of circadian information to target organs, via the autonomic nervous system and through humoral pathways. Given the importance that neuroendocrine rhythms play in coordinating normal circadian physiology and behavior, it is plausible that their perturbation during aging contributes to the etiology of age-related pathologies. This mini-review highlights some of the most dramatic rhythmic neuroendocrine changes that occur in primates during aging, focusing primarily on data from the male rhesus macaques (*Macaca mulatta*). In addition to the age-associated attenuation of hormone levels and reduction of humoral circadian signaling, there are also significant age-related changes in intracrine processing enzymes and hormone receptors which may further affect the functional efficacy of these hormones. Rhesus macaques, like humans, are large diurnal primates and show many of the same physiological and behavioral circadian changes during aging. Consequently, they represent an ideal translational animal model in which to study the causes and consequences of age-associated internal circadian disruption and in which to evaluate novel therapies.

Keywords Adrenal gland · Circadian rhythms · Intracrinology · Neurosteroidogenesis

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Introduction

Humans show a variety of biological rhythms that normally are synchronized with the daily light–dark

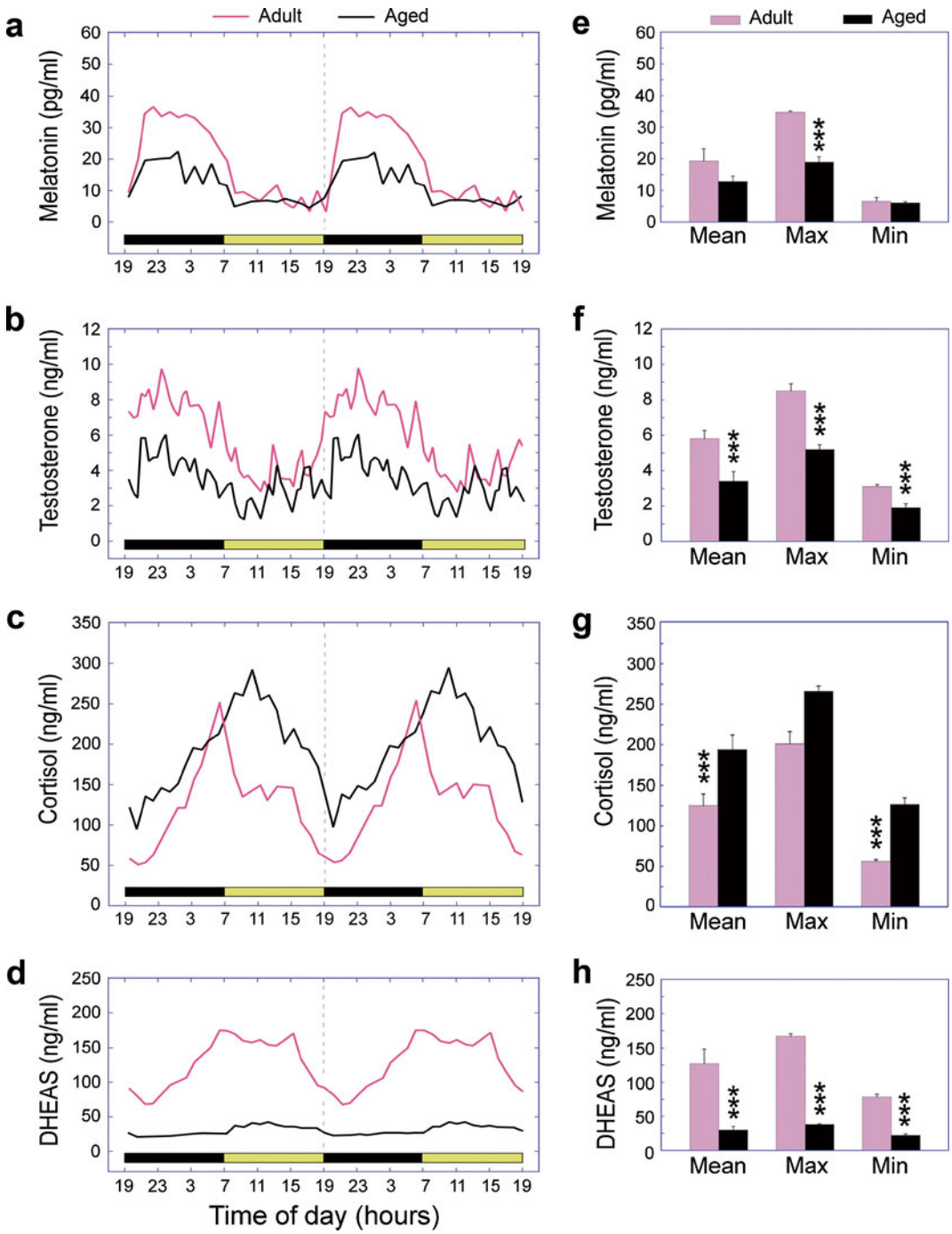
cycle, including sleep, body temperature, and blood pressure (Hastings et al. 2003, 2007). These rhythms have a period of approximately 24 h and are regulated by a highly coordinated circadian neuroendocrine mechanism that comprises three major components: (1) photoreception by the retina and transmission of neural signals along the retinohypothalamic tract, (2) integration of photoperiodic information with an internal reference circadian pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus, and (3) dissemination of synchronized circadian information to target organs, via the autonomic nervous system and through humoral pathways, and integration with local oscillator circuits (Okamura 2004; Karatsoreos and Silver 2007; Maywood et al. 2007; Mendoza and Challet 2009; Bonnefont 2010; Urbanski 2011b). When functioning correctly, this mechanism ensures that various internal biochemical processes are compartmentalized not just spatially but also temporally and that physiological functions and behaviors occur at an appropriate time of day (Lemos et al. 2006; Kalsbeek et al. 2006). There are conditions, however, when this temporal synchronization of internal rhythms becomes disrupted, as when shift workers abruptly change their work schedule or when airline travelers fly across several meridians, resulting in a malaise commonly known as "jet lag." Furthermore, perturbation of the circadian system is thought to contribute to the etiology of a winter depression known as "Seasonal Affective Disorder" or SAD (Urbanski 1999; Lewy et al. 1998, 2006, 2007; Skene and Arendt 2006; Lewy 2007, 2009; Arendt et al. 2008). Because much of the body's circadian organization is mediated through the rhythmic release of various hormones, especially cortisol and melatonin, it is plausible that as the secretion patterns of these hormones change during aging so does the temporal organization of physiological and behavioral functions.

This mini-review highlights recent data from rhesus macaques showing how the 24-h release pattern of various hormones changes during aging and how this may contribute to circadian desynchronization. It also emphasizes that age-associated changes in intracrine processing enzymes and hormone receptors may further affect the functional efficacy of these hormones. Our hope is that a deeper understanding and appreciation of rhythmic neuroendocrine mechanisms could shed new light on the etiology of age-related pathologies and help with the development of more effective circadian-based therapies for the elderly (Yamakazi et al. 2002; Phillips 2009; Monteleone et al. 2011).

Age-related endocrine changes

Like humans, rhesus macaques (*Macaca mulatta*) are large, long-lived diurnal primates with similar organization of their brains and similar consolidated sleep–wake patterns. Importantly, from a research perspective, these nonhuman primates can be maintained under carefully controlled environmental conditions and can be subjected to serial blood sampling with no sedation and minimal restraint (Urbanski 2011a). We have made extensive use of a blood sampling setup that involves remote serial collection of blood via a surgically implanted subclavian vein catheter and a swivel/tether assembly. The advantage of this system is that it enables blood samples to be collected from an adjacent room at any time of the day without disturbing the subjects. Figure 1 depicts various plasma hormone profiles obtained from the same group of male rhesus macaques using this remote blood sampling system: melatonin (an indolamine produced by the pineal gland), cortisol and dehydroepiandrosterone sulfate (DHEAS) (two steroids produced by the adrenal cortex), and testosterone (an androgenic steroid produced by the testicular Leydig cells). All four hormones show clear 24-h rhythms, but their phase relationships are not identical. For example, in both humans and rhesus macaques plasma melatonin levels are high at night and very low in the daytime (Fig. 1a).

Fig. 1 Age-related changes in the 24-h plasma concentrations of **a** melatonin, **b** testosterone, **c** cortisol, and **d** DHEAS in male rhesus macaques. The *left panels* depict mean hormone profiles from ten adult (~10 years) and ten aged (~26 years) animals, and the *horizontal light and dark bars* correspond to the 12L:12D lighting schedule; note that the profiles have been double plotted to facilitate observation of day–night differences. Each hormone showed a distinct 24-h rhythm, with a peak occurring either during the night (melatonin and testosterone) or early in the morning (cortisol and DHEAS). Statistical analysis of the hormone profiles is shown in the *right panels*. The mean, maximum (*Max*; average of five adjacent peak values), and minimum (*Min*; average of five adjacent nadir values) were calculated from each profile, and between-age comparisons were analyzed using Student's *t* test. The *bars* represent the group means and the *vertical lines* represent SEMs. Note that in female rhesus macaques, plasma melatonin, cortisol, and DHEAS levels also show 24-h rhythms, but age-related changes are less clear. ***$P < 0.001$. Data adapted from Downs et al. (2004, 2008) and Garyfallou et al. (2005)



This makes biological sense because in diurnal species melatonin is associated with sleep maintenance and restive physiological processes (Urbanski 1999; Lewy 2007; Arendt et al. 2008). Another hormone that shows a 24-h rhythm with a nocturnal peak, in both humans and rhesus monkeys, is the adipocytic hormone leptin (data not shown) (Sinha et al. 1996; Langendonk et al. 1998; Simon et al. 1998; Downs and Urbanski 2006a). Because leptin is generally associated with suppression of appetite, it also makes biological sense for its peak to occur at night, when diurnal species usually sleep. Similarly, plasma

testosterone shows a nocturnal peak in both men and male rhesus macaques (Bremner et al. 1983; Tenover et al. 1988; Cooke et al. 1993; Downs et al. 2004; Garyfallou et al. 2005; Schlatt et al. 2008; Sitzmann et al. 2010). Note that because of the underlying pulsatile pattern of its release (Tenover et al. 1988; Plant and Witchel 2006), circulating testosterone levels display ultradian fluctuations as well as a 24-h pattern (Fig. 1b). The physiological significance of a nocturnal testosterone peak is unclear, but given its role in anabolic processes there may be physiological consequences if this nocturnal rhythm is perturbed. On the other hand, it is unlikely that the normal age-associated decrease in male sexual performance is triggered by these testosterone changes because in monkeys a decline in sexual behavior occurs well before the age-associated decrease in circulating testosterone levels (Chambers and Phoenix 1981). Even less is known about the physiological significance of the underlying ultradian testosterone pulses, but since there is much variability in the frequency of these pulses between individuals (unpublished observations), they may simply be an inconsequential side effect of the underlying episodic release of gonadotropin-releasing hormone and luteinizing hormone.

In marked contrast to melatonin, leptin, and testosterone, both cortisol and DHEAS show plasma peaks early in the morning when the animals wake up and a nadir late in the evening when they go to sleep (Fig. 1c, d). Cortisol and DHEAS are two of the most abundant steroids in the circulation of adult humans and rhesus macaques, and they are thought to play an important role in regulating responses to stress (Nguyen and Conley 2008; Schwartz and Pashko 2008). Additionally, elevated cortisol levels suppress the immune system, break down tissues, and have a general catabolic effect, whereas DHEA and DHEAS counterbalance the effects of cortisol by activating the immune system and building up tissues (Messaoudi et al. 2011).

Importantly, all of the abovementioned hormones show marked age-related changes in their 24-h plasma profiles. Aged male rhesus macaques, like aged men, show a significant decline in the amplitude of their 24-h melatonin (Figs. 1a, e; Iguchi et al. 1982; Waldhauser et al. 1988; Sharma et al. 1989; Thomas and Miles 1989; Haimov et al. 1994; Zeitzer et al. 1999; Roth et al. 2001; Downs et al. 2004) and testosterone rhythms (Figs. 1b, f; Plymate et al., 1989; Feldman et al. 2002; Luboshitzky et al. 2003; Garyfallou et al. 2005; Kaufman and Vermeulen 2005; Page et al. 2007; Schlatt et al. 2008; Bremner 2010), and an even more pronounced attenuation of their 24-h DHEAS rhythm (Figs. 1d, h; Orentreich et al. 1992; Labrie et al. 1997; Wise 1999; Urbanski et al. 2004; Downs et al. 2008). An age-related decline has also been observed for leptin in old male rhesus macaques (data not shown; Downs and Urbanski 2006a). In marked contrast, circulating cortisol levels do not typically decline with age, but generally stay the same or show an age-associated increase, both in humans and rhesus macaques. Moreover, a well-defined 24-h plasma cortisol rhythm is clearly evident well into old age (Figs. 1c, g; Wise 1999; Purnell et al. 2004; Urbanski et al. 2004; Downs et al. 2008). Although the functional significance of all these age-related hormonal changes is unclear, a significant elevation of the cortisol baseline means that the brain and peripheral organs, such as the liver, will receive little or no daily respite from the influence of cortisol, which may predispose the elderly to insomnia as well as to metabolic disorders (Scheer et al. 2009). Similarly, there is evidence that the age-associated disruption of the circadian leptin rhythm may contribute to the development of metabolic disorders and obesity (Laughlin and Yen 1997; Matkovic et al. 1997; Balligand et al. 1998; Støving et al. 1998), and may have a negative impact on the maintenance of bone mass (Ducy et al. 2000; Elefteriou et al. 2005). Activity rhythms of primates appear to be closely linked to the circadian cortisol rhythm, and they show parallel phase shifts when the photoperiod is changed (Lemos et al. 2009). Consequently, an age-associated alteration in the cortisol and melatonin rhythms is likely to have a profound effect on activity and sleep cycles, which in turn could negatively impact other physiological functions such as immune response and cognition (Haley et al. 2009, 2011; Messaoudi et al. 2011). DHEAS and the non-sulfated form of the steroid (DHEA) are capable of attenuating the deleterious effects of high circulating cortisol levels. Additionally, lower levels of DHEA and DHEAS have been associated with cognitive disorders with a higher prevalence in the elderly, such as Alzheimer's disease (Weill-Engerer et al. 2002) and depression (Michael et al. 2000), while in healthy old men, elevated endogenous DHEAS levels have been linked to better cognitive performance (van Niekerk et al. 2001). Consequently, an age-associated decline in circulating DHEA and DHEAS levels, as well as a decrease in the DHEA/cortisol ratio, may contribute to age-associated cognitive

decline (van Niekerk et al. 2001; Karishma and Herbert 2002).

The age-associated decline in circulating testosterone levels observed in males during normal aging is much less abrupt and extreme than the decline in circulating estradiol and progesterone levels that occurs in females after menopause (Handelsman and Liu 2005; Downs and Urbanski 2006b). For example, during normal aging, circulating testosterone levels generally continue to be maintained above the prepubertal level, and so the physiological consequences of the normal age-related decline could be minimal. On the other hand, the circadian pattern of testosterone becomes less well defined during aging, and so this dampening of the rhythm may further contribute to the general impairment of circadian physiology in the elderly, including perturbed sleep–wake cycles.

Hormonal supplementation

Because circulating melatonin, DHEA/DHEAS, and testosterone levels decline significantly during aging, it is tempting to speculate that hormonal supplements could alleviate or counteract some of the negative symptoms of aging (Wolf and Kirschbaum 1999). Interestingly, in the USA melatonin and DHEA are both classified as food additives and so are not regulated by the Food and Drug Administration. This means that these hormones are readily available to the public without prescription and are widely used for self-medication by the elderly. Various testosterone preparations are also available to elderly men, under prescription, to help promote healthy aging. However, as emphasized by the plasma profiles depicted in Fig. 1, these hormones normally have clear 24-h circulating patterns in the circulation, with specific phase relationships. From a clinical perspective, this means that accurate assessment of endocrine function is dependent upon collecting blood samples at an appropriate time of day relative to phase of the underlying hormonal rhythm. For some hormones, such as melatonin, it might be more appropriate to collect the blood samples during the night in order to detect peak levels, while for other hormones, such as cortisol, it might be more appropriate to collect the samples at the time of the rhythm's nadir in the evening (i.e., if the purpose is to test for elevated baseline levels). The situation is further complicated when dealing with testosterone; not only does the circadian peak of testosterone occur at night but its underlying ultradian rhythm means that single blood samples can yield misleading results (Kaler et al. 1986). To more accurately assess testicular endocrine function, multiple blood samples should be collected and ideally as close to the nocturnal peak as practical. With some hormones, it may also be necessary to collect serial blood samples during a specific phase of the menstrual cycle or at a specific time of the year.

Moreover, clinical treatment of low testosterone levels through androgen supplementation should ideally follow the underlying physiological 24-h profile. For practical reasons, however, this is rarely the case. Common androgen supplementation paradigms typically involve long-term continuous release capsules, which have the advantage of low maintenance but which completely obliterate the 24-h rhythm. Other paradigms involve cyclic transdermal delivery of testosterone, via the daily application of gels. However, the instructions typically specify application of the gel in the morning rather than at night (to avoid accidental transfer of the steroid to a sleeping partner); unfortunately, this means that the daily plasma testosterone peak generated by the gel can be several hours out of phase with the endogenous testosterone rhythm. The long-term impact of these nonphysiological androgen supplementation paradigms is unclear, and alternative approaches may prove to be more beneficial to overall physiology. An interesting novel approach has recently been demonstrated in men (Amory and Bremner 2005; Amory et al. 2006), which involves oral administration of micronized testosterone in sesame oil. Normally, orally administered testosterone has little physiological potency because after being taken up by the gut it is immediately transported to the liver via the hepatic portal vein and then passed back into the gut rather than into the general circulation. It appears that much of this enterohepatic circulation of testosterone can be bypassed if the steroid is mixed with sesame oil. Although the exact mechanism is unclear, it may involve preferential absorption by the lymphatic system, bypassing the liver and reaching the circulation via the thoracic duct. Studies have shown that this administration paradigm can more closely mimic the natural 24-h plasma testosterone rhythm (Amory and Bremner 2005; Amory et al. 2006).

Age-related intracrine changes

Clinically, it is convenient and relatively noninvasive to measure hormone levels in the blood or body secretions, such as urine or saliva. However, these measurements do not necessarily reflect the activity of the hormones at their target site. This is because some hormones can be further processed within target tissues through intracrine enzymatic conversion, and also because the receptors for the hormones may also show dynamic changes during aging. While the vast majority of research on steroid actions in the brain has focused on hormones of peripheral or exogenous origin (e.g., adrenal glands and gonads), another oft-overlooked source of neuroactive steroids is the brain itself. These steroids may be derived de novo from cholesterol (auto- or paracrine) or may be the result of conversion of precursor steroids, such as DHEA, to a target hormone such as testosterone and estradiol (intracrine). The likely involvement of these neurosteroids in cognitive function is supported by findings from rodent studies, showing that locally produced estradiol derived from DHEA can increase hippocampal spine density and synapse frequency, and in turn can improve learning and memory (Hajszan et al. 2004; Hirshman et al. 2004; Rune and Frotscher 2005; Mukai et al. 2010). Depending on negative and positive feedback mechanisms, these auto-, para-, and intracrine hormones ultimately determine how much steroid reaches the brain from the periphery. This additional source of neuroactive hormones provides another point of age modulation of cognition as changes in not only peripheral but central steroid production may contribute to age-related cognitive decline (Sorwell and Urbanski 2010).

As illustrated in Fig. 2a, adrenal DHEAS can be converted into testosterone within target tissues if the appropriate enzymes are present. This enzymatic conversion thus creates a surge of central sex steroids concurrent with the morning peak of circulating DHEAS. This first key enzymatic step involves removal of the sulfate group by the enzyme steroid sulfatase (STS). 3BHSD and AKR1C3 (also referred to as 17BHSD5) then convert DHEA to testosterone, with androstenedione or androstenediol as intermediaries. If aromatase is also expressed, this testosterone may be further converted to estradiol. Importantly, there is evidence that hippocampal expression of *STS*

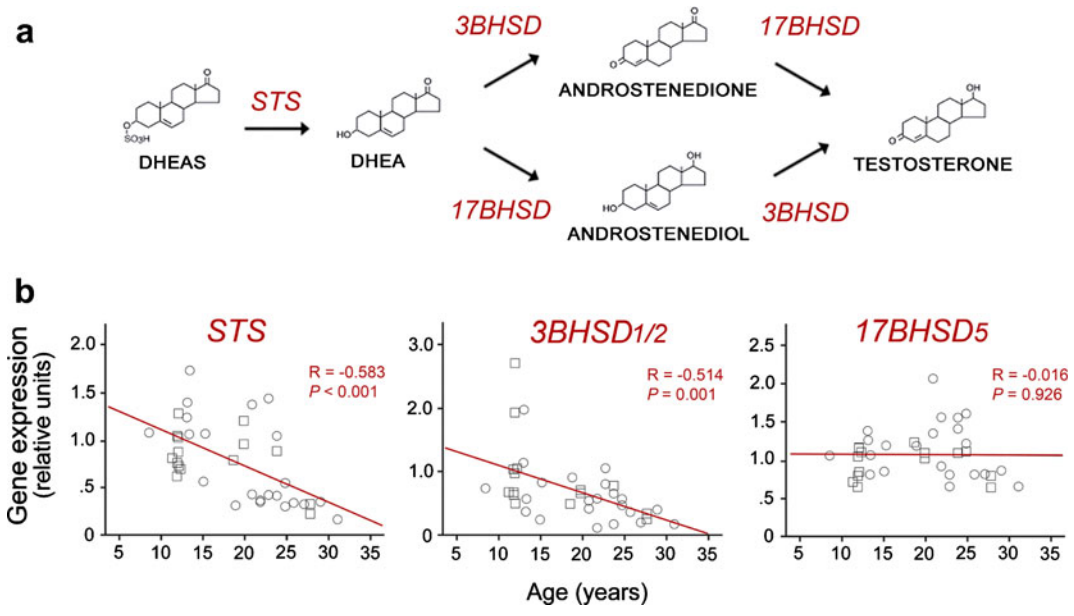


Fig. 2 Biosynthesis of neurosteroids. **a** A schematic diagram showing key enzymes involved in the conversion of DHEAS to testosterone. **b** Age-related changes in the expression of *STS*, *3BHSD2*, but not *17BHSD5*, in the rhesus macaque hippocampus, as determined by quantitative real-time PCR. Note that testosterone can be further converted to estradiol by aromatization. Together, these findings suggest neurosteroidogenesis is likely to be impacted by aging. Data adapted from Sorwell et al. (2011)

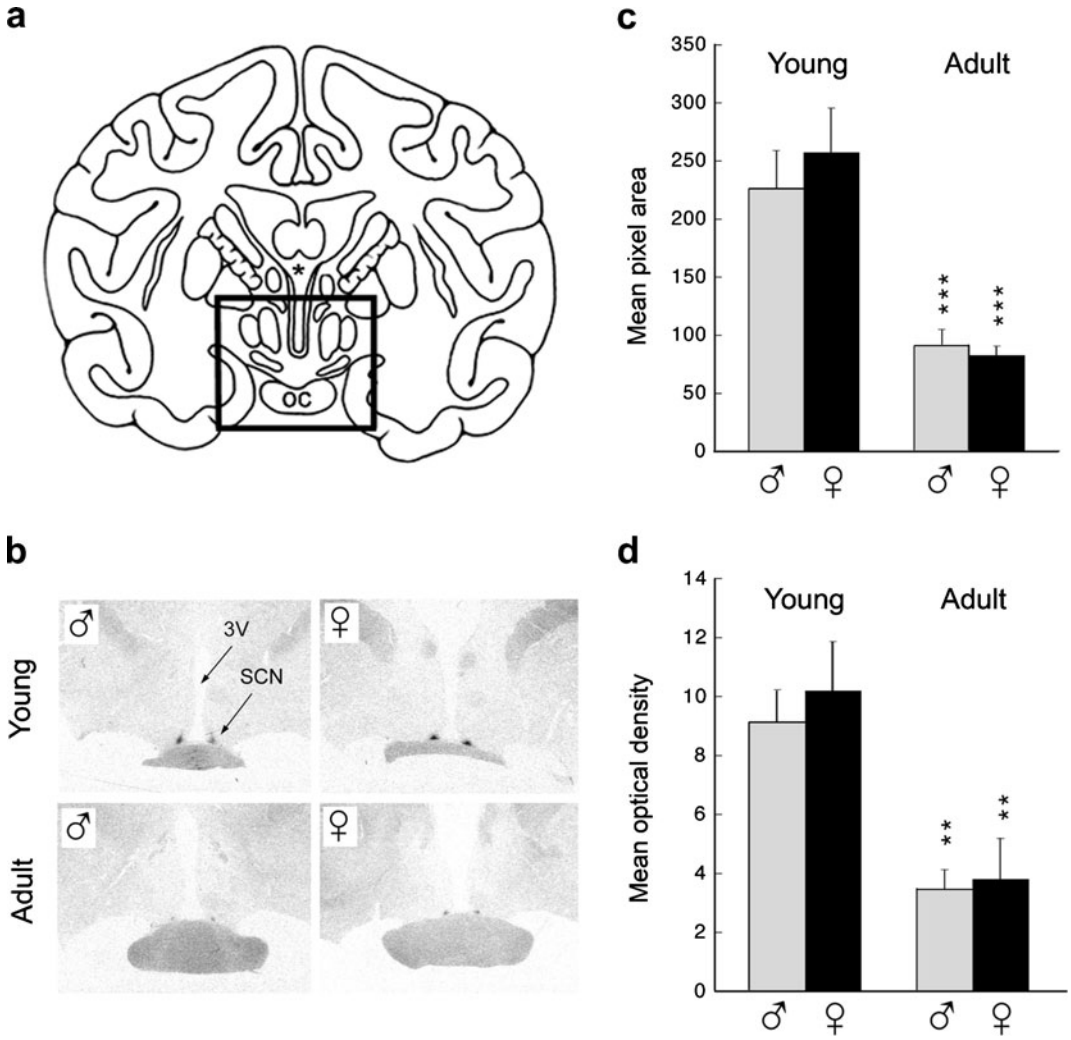


Fig. 3 Age-related changes in melatonin receptor gene expression within the SCN of rhesus macaques. **a** A schematic coronal section through the rhesus macaque brain showing location of the SCN. *OC* optic chiasm, * third ventricle. **b** Representative autoradiographs showing in situ hybridization of a ^{35}S-labeled antisense MT1 (Mel1a) riboprobe in the hypothalamus of young (<1 year) and adult (10–15 years) males and females. *SCN* suprachiasmatic nucleus, *3V* third ventricle. Image analysis of the autoradiographs involved measuring mean pixel area (**c**) and mean optical density (**d**). The *bars* represent mean values from three males or three females, and the *vertical lines* represent SEMs. $^{**}P<0.01$, $^{***}P<0.001$ (between-age comparison). Data adapted from Urbanski et al. (2000)

and *3BHSD2* declines significantly with age in rhesus macaques (Fig. 2b; Sorwell et al. 2011), suggesting a reduction in the ability to convert circulating DHEAS to testosterone. These decreases in enzyme expression amplify the age-related decline in DHEA/S input from the adrenal glands. Thus, not only is the brain exposed to lower levels of peripherally derived testosterone and estradiol in old age but it may also be less able to synthesize its own sex steroids in situ.

Elucidation of the pathways involved in auto-, para-, and intracrine sex steroid synthesis is crucial for understanding the impact of steroids on cognition during aging because they offer three additional mechanisms by which testosterone and estradiol concentrations may be modulated within the brain: (a) a decline in adrenal DHEAS reaching the brain, (b) reduced expression of the enzymes necessary to metabolize DHEAS to testosterone and estradiol, and (c) possible reduction of de novo synthesis of DHEA within the brain itself.

Hormone receptors

Modulation of hormone receptors can have a major effect on the efficacy of endogenous hormones or hormonal supplements, and so a better understanding of how these receptors change during aging would help with the development of more effective therapies. For example, in the context of hormonal supplementation, there is evidence that melatonin can act as a *Zeitgeber* or synchronizer of the neuronal activity in the SCN and can entrain activity rhythms (Arendt et al. 1997; Lewy et al. 1998; Masuda and Zhdanova 2010), and not surprisingly the mammalian SCN has been shown to contain high-affinity melatonin receptors, of which MT1 (Mel1a) and MT2 (Mel1b) are the principal subtypes (Reppert et al. 1988, 1994; von Gall et al. 2002). Furthermore, the functional relevance of these receptors has been demonstrated in mice, through targeted deletion of the MT1 receptor which completely blocked the acute inhibitory effects of melatonin on SCN multiunit activity. On the other hand, the phase-shifting responses to melatonin appeared normal in these animals, suggesting that a functional MT2 receptor is partially able to compensate for the absence of the MT1 receptor. From the perspective of human aging, it is pertinent that MT1 gene expression in the SCN is markedly lower in adults than in children (Weaver and Reppert 1996), and similar age-related differences have been observed in the rhesus macaque SCN (Fig. 3). Together, these findings emphasize that hormone receptor gene expression is dynamic and that marked age-associated changes may occur well before the onset of extreme old age. Such changes in receptor expression could undermine the efficacy of hormonal supplementation in the elderly and so may need to be taken into consideration when developing hormone-based therapies.

Conclusions

Neuroendocrine rhythms play an important role in coordinating a wide range of physiological and behavioral functions. It is highly likely, therefore, that perturbation of their release patterns during aging contributes to the etiology of various pathologies in the elderly. What is often overlooked or underappreciated, however, is that many hormones have well-defined 24-h profiles, with particular phase relationships, which help to temporally synchronize internal biochemical functions with that of the changing external environment. Consequently, disruption of these 24-h hormone patterns, due to normal aging or as a side effect of some pharmaceutical interventions, could lead to internal physiological disharmony. The situation is further complicated because many enzymes involved in the biosynthesis of hormones may also show age-related changes, and the corresponding hormone receptors may themselves be downregulated. Taken together, the data suggest that in cognitive brain areas such as the hippocampus, a decrease in exposure, production, response, and synchrony of neuroactive steroids may collectively contribute to impaired cognitive function during old age. Furthermore, the data suggest that the efficacy of hormone replacement therapies or pharmaceutical interventions in the elderly could be enhanced, and have fewer side effects, if appropriate circadian phase is taken into consideration.

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