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Curr Opin Endocr Metab Res. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

Curr Opin Endocr Metab Res. 2021 April ; 17: 1–7. doi:10.1016/j.coemr.2020.09.009.

Sleep and Puberty

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Abstract

In the 1970's, Boyar and colleagues made the seminal observation that during the early stages of puberty, there is a sleep-specific augmentation of pulsatile luteinizing hormone (LH) secretion. Building on this tantalizing association between sleep and the re-awakening of the neuro-reproductive axis, a number of investigators have since mapped the dynamic relationship between sleep and reproductive hormones across the pubertal transition. In this review, we focus on the complex, reciprocal relationship between sleep and reproductive hormones during adolescence as well as the potential effects of melatonin and orexin on gonadotropin-releasing hormone (GnRH) activity in children with chronic insomnia and narcolepsy, respectively. Given the important interaction between the reproductive and somatotropic axes during puberty, we end with a discussion of sleep and growth hormone (GH) secretion in children.

Reciprocal interactions between sleep and the reproductive axis during puberty

Sleep/wake state and pulsatile LH secretion in pubertal children

The sleep and reproductive axis are intimately related during pubertal development and in adulthood. Indeed, the dramatic increase in LH levels, a biomarker of the re-activation of the hypothalamic gonadotropin-releasing hormone (GnRH) neuronal network, that signals the onset of puberty in boys and girls is initially restricted to sleep. This observation was made nearly 50 years ago in pioneering studies by Boyar et al. that included nocturnal polysomnography and frequent blood sampling in healthy pubertal boys [1]. His group convincingly demonstrated that the increase in nocturnal luteinizing hormone (LH) was specifically related to sleep and not to time of day or to light exposure using sleep-wake reversal studies and/or blindfolding subjects during wakefulness [2]. More recent studies by our group in pubertal children demonstrated that LH pulses during sleep occur during or immediately following deep (slowwave) sleep [3], suggesting that entrance into deep sleep may stimulate pulsatile GnRH/LH secretion during puberty. Interestingly, a similar temporal association between deep sleep and LH pulse onset was also observed in women

Declarations of interest: none

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with polycystic ovarian syndrome (PCOS) [4]. A single night of deep sleep disruption via auditory stimuli did not diminish LH secretion in pubertal children [5], yet it is unknown whether chronic sleep disruption or sleep restriction may interfere with LH secretion and delay pubertal development. We found that girls with obstructive sleep apnea (OSA) who have abnormal sleep architecture have relatively delayed thelarche compared to girls without OSA [6], however, additional studies are necessary to investigate the impact of poor sleep hygiene on the developing reproductive axis in boys and girls.

Cross-sectional studies in girls suggest that as puberty progresses, LH pulse frequency remains relatively constant during sleep (~ q120min), whereas LH pulse frequency begins to rise during wakefulness until it exceeds that of sleep in late puberty [7, 8]. A recent study by Kim et al. suggests that the dynamic patterning of LH secretion during wakefulness across puberty may relate to greater hypothalamic sensitivity to progesterone (P4) negative feedback during wakefulness compared with sleep [9]. In a randomized, placebo-controlled, crossover study of low-dose oral P4 in 11 early post-menarchal girls, P4 acutely reduced waking LH pulse frequency by 26% but had no effect on LH secretion during sleep. The investigators propose that as androgens increase during the course of puberty, they antagonize P4 negative feedback activity, and this allows LH pulse frequency to gradually increase during wakefulness. A study of exogenous P4 ± androgen receptor blockade with spironolactone is now underway in pubertal girls to test this very hypothesis [10].

A final LH secretory pattern emerges after menarche that continues through the reproductive years: sleep-specific slowing of LH pulse frequency during the early/mid-follicular phase (FP) of the cycle (~q120min during sleep vs. q90min during wake) [11–14]. In contrast to early/mid-puberty, when LH pulses appear to be tied to deep sleep, in adult women, LH pulses are more likely to occur during brief awakenings from sleep whereas deep sleep appears to be inhibitory [15]. It has been proposed that this sleep-related slowing of LH pulse frequency in the FP reflects the waning influence of P4 from the preceding luteal phase [16]. Note that during the luteal phase, under the influence of high P4 levels, LH pulse frequency is slow (~ q4hr in mid-luteal phase) during both wake and sleep. In our study of 23 early post-menarchal girls who had a gradation of endogenous P4 exposure (from high levels in normal ovulatory cycles, to intermediate levels in cycles with evidence of luteal insufficiency, to low levels in anovulatory cycles), we observed a strong inverse correlation between P4 exposure and LH pulse frequency during sleep in the FP [17]. Importantly, however, the observation that sleep-related slowing of LH pulses persists in post-menopausal women [18], suggests that P4 exposure alone may not entirely explain LH pulse patterning during sleep and wake during late puberty and adulthood. Other potential mediators include androgens, insulin sensitivity, and/or energy availability [4, 19, 20].

Changes in sleep patterns during adolescence: do sex steroids play a role?

There are significant changes in sleep/wake patterns during puberty including a delayed sleep phase (tendency for later bedtimes), shorter sleep duration, irregular sleep schedules (sleeping longer during weekends compared to weekdays), and a greater ability to maintain wakefulness, indicating a tolerance to the homeostatic drive for sleep (or “sleep pressure”). Pubertal changes in sleep behavior coincide with a steep decline in deep sleep, and its EEG

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correlate, delta spectral power, that begins at age 11–12 years and continues until 16.5 years [21]. The decline in delta power not only coincides with the average age of normal puberty, but, akin to sex differences in pubertal timing, occurs approximately 1 year earlier in girls than in boys. These observations have raised the possibility that changes in the sleep EEG and associated sleep behaviors during puberty may be driven by sex steroids.

Indeed, nearly 30 years ago, Carskadon et al. reported an association between advanced pubertal stage and delayed sleep phase in a cross-sectional study of 6th grade girls [22]. Following up on this early finding, a number of longitudinal cohort studies have investigated the temporal association between pubertal milestones and sleep/wake using a variety of data collection methods. Pubertal status, for example, has been determined by a trained physician (Tanner staging) or by self-report; no studies have included reproductive hormone levels. Sleep measures have been either objective (in-home actigraphy or EEG) or subjective (sleep diary, questionnaire). A study of approximately 100 Israeli school-children, aged 9.9–11.2 years, demonstrated that maturational changes in sleep/wake patterns, including delayed sleep onset and decreased sleep efficiency, occurred before any physical signs of puberty [23], a time when estradiol and testosterone levels are typically undetectable. Of note, this study did not consider pubic hair and genital/breast development separately; rather, the two scores were averaged for analysis. In a longitudinal study of 67 children that included biannual Tanner staging by a physician and EEG studies over the course of 6–7 years, Campbell et al. found that the timing of the decline in delta power was strongly related to the timing of pubic hair development in boys and girls; the relationship to breast and genital development was less robust [24]. Two recent studies of the relationship between pubertal timing and sleep behavior also found an association between earlier pubic hair development and either later bedtimes [25] or shorter sleep duration [26] in girls. Taken together, these studies suggest that adrenal androgens may in fact play a role in sleep maturational changes.

These observational study designs, however, cannot distinguish the effects of pubertal maturation from age *per se* on sleep. Thus, an alternative approach has been to study sleep architecture and behavior in children with precocious or delayed puberty compared to controls. We conducted in-hospital sleep and hormone tests in girls with central precocious puberty (CPP) and age-matched pre-pubertal controls. We found that premature estrogen exposure was not associated with a premature decline in delta power, and hormonal suppression did not affect the natural decline in delta power over time [27]. Further, there was no association between pubertal status and morningness/eveningness preference (a surrogate for chronotype) or between dehydroepiandrosterone sulfate (DHEAS) or estradiol levels and delta power. Jessen et al. [28] investigated the association between pubertal status, reproductive hormones, and chronotype in girls with early puberty (CPP or premature adrenarche), boys with delayed puberty, and historic age- and sex-matched controls. Girls with earlier puberty tended to have delayed sleep timing whereas boys with delayed puberty had earlier sleep timing compared with controls; there were no group differences in sleep duration. In a combined analysis of boys and girls with pubertal disorders, there was a positive (r=0.5) correlation between 17-hydroxy-progesterone (17OHP) levels and later sleep times but no relationship between estradiol, testosterone, LH, follicle-stimulating hormone (FSH), or DHEAS and sleep preferences. While these studies separated the effects of pubertal hormones and age on sleep, they both suffered from small sample sizes, and

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in the latter study, control girls were younger than girls with CPP and pubertal status was unknown in controls (assumed to have normal pubertal development for age). Thus, these pilot studies require replication in a larger group of carefully phenotyped children with disorders of pubertal timing to investigate further the relationship between sex steroids, particularly those associated with adrenarche, and sleep during puberty.

The change in delta power during adolescence is posited to be a biomarker of the decline in cortical synaptic density (so-called 'synaptic pruning') and cerebral metabolic rate that are part of a profound structural reorganization of the adolescent brain [29]. Recent studies suggest further that this natural rewiring of the cerebral cortex is tightly regulated by an interaction between microglia (the resident macrophages of the brain) and complement proteins [30]. Of note, microglia express estrogen, androgen, and progesterone receptors, although expression varies by developmental stage (reviewed in [31]). While it is possible that changes in sex steroids modulate synaptic pruning by microglia during adolescence, and thereby influence cortical electrophysiology and even sleep behavior, studies in the mouse would suggest that sex differences in neural patterning are programmed much earlier in development (fetal and early postnatal periods) [32–34]. Thus, the potential association between prenatal exposures, such as hormones and the microbiome [35], and adolescent sleep/wake patterns deserves further study.

Sleep and puberty - hot topics

Melatonin as a sleep aid and potential effects on pubertal timing

The sleep-promoting effect of melatonin, a hormone secreted by the pineal gland during darkness, has made it an important treatment option for insomnia among children with neurological disorders (autism spectrum disorder [ASD], ADHD), blindness, or delayed sleep-wake phase disorder [36]. Melatonin's role in suppressing the reproductive axis during the non-breeding season in mammals [37, 38], however, has raised concerns that long-term treatment may disrupt pubertal maturation in treated children. Cross-sectional studies in children have shown that melatonin levels decrease across puberty [39, 40], are inversely correlated with serum LH levels [40], and are lower in children with CPP than age-matched controls [41]; these associations are consistent with an inhibitory function of melatonin. Studies in the ewe suggest that melatonin acts in the medial basal hypothalamus [38], upstream of kisspeptin neurons (which lack the melatonin receptor 1A), possibly by influencing local triiodothyronine (T3) output by the pituitary pars tuberalis [42].

Very few studies have investigated pubertal timing in children prescribed melatonin for chronic insomnia. In a follow-up study of 41 children (68% male, mean age 9.9 years) with neurodevelopmental disorders who had been treated with melatonin for an average of 4.3 years, the majority of caregivers reported normally-timed puberty with the exception of 5 children with a history of PP that preceded treatment [43]. Malow et al also reported no delays in pubertal development, as determined by a physician using Tanner pubertal staging and by age at menarche, relative to Dutch standards in a group of 31 children with ASD after 2 years of continuous melatonin use [44]. The same group reported no effect of melatonin on serum gonadotropins and sex steroids in a 14-week dose-finding study in 24 children with ASD, however, all participants in this study were pre-pubertal by study

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design [45]. A follow-up study by Zwart et al. [46] of 33 otherwise healthy children with insomnia (mean age 19 years) who had received melatonin for an average of 10.8 years found that 56% reported normal pubertal timing. However, nearly one-third perceived their pubertal timing to be later than their peers, which was significantly higher than the 17% of participants in a population-based study of nearly 9000 Norwegian students who reported delayed development relative to peers. In addition to self-ratings of puberty, this study was limited by a <50% response rate and subjects were older than controls at the time of the pubertal self-assessment. Taken together, these data provide some reassurance that melatonin is unlikely to harm the developing reproductive system in humans but confirmatory studies in larger cohorts are necessary.

Narcolepsy and central precocious puberty

Narcolepsy is a chronic sleep disorder with an estimated US prevalence of 0.05–0.1% [47]. It is defined by excessive daily sleepiness with or without cataplexy (abrupt muscle weakness) and typically manifests in childhood or adolescence. Narcolepsy is caused by the selective destruction of orexin-producing neurons in the hypothalamus via an interplay of environmental triggers (e.g., H1N1 virus), autoimmunity, and a genetic predisposition [48]. Orexin, or hypocretin, is a neurotransmitter that plays an important role in the regulation of sleep/wakefulness and of multiple neuroendocrine pathways (e.g., stress, arousal, feeding).

Several case reports have also noted an association between pediatric narcolepsy and CPP, suggesting a role for orexin in modulating the neuro-reproductive axis. A 2010 retrospective case series of 51 US children with narcolepsy in fact observed that patients had earlier pubertal onset than their same-sex sibling(s) and parent [49]. A second cohort study of 43 Italian children with narcolepsy observed a high rate of CPP (17%) compared with age-matched obese controls (1.9%) [50]. Boys and girls were affected in equal proportions, in contrast to the female predominance that typifies CPP. Although the onset of narcolepsy symptoms is frequently associated with weight gain, the investigators found that a younger age at narcolepsy symptom onset - not weight gain - was a significant predictor of CPP. In a follow-up study of this cohort (expanded to 72 cases), the investigators again found a high prevalence of CPP (16%; 6 boys, 6 girls) [51] and overweight/obesity. In addition, menarche occurred about 1 year earlier, on average, in the girls who did not meet formal criteria for CPP than in girls in the general Italian population [51]. Lastly, a recent study of 63 consecutive children referred to a French academic hospital for treatment of CPP similarly reported that 14% of children had comorbid narcolepsy [52].

Studies on the effect of orexin on the reproductive axis have produced conflicting results, most likely due to differences among species and sex steroid milieus. However, two recent studies demonstrated that orexin directly inhibits GnRH electrophysiological activity in brain slices from ovariectomized mice [53] and adult zebrafish [54]. A third study in adult male rats demonstrated that interventricular injection of orexin caused a decrease in serum LH and testosterone, sexual behavior, and expression of *GnRH*, *kiss1*, and *NKb* [55], raising the possibility that orexin suppresses both kisspeptin, neurokinin B, and dynorphin (KNDy) and GnRH neuronal activity.

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Sleep and growth hormone secretion during puberty

Pulsatile GH secretion by the anterior pituitary gland primarily reflects the balance of stimulation by growth hormone releasing-hormone (GHRH) and inhibition by somatostatin. GH secretion is also regulated by a number of neuro-transmitters/peptides and is sensitive to stress, hypoglycemia, exercise, sleep stage, sex steroids, ghrelin, and to insulin-like growth factor 1 (IGF-1) negative feedback [56]. During puberty, the rise in estradiol (from the ovary in girls, or via aromatization of testosterone in boys) directly stimulates GH release [57], causing an acceleration of linear growth velocity (i.e., the pubertal growth spurt).

Observational as well as sleep interruption studies in the 1960's by Takahashi et al. were the first to demonstrate that in young adults, the largest GH peak typically occurs just after sleep onset and that there is a close correlation between GH pulse onset and episodes of deep sleep [58]. These findings were confirmed and extended upon in intensive clinical research studies in adults conducted largely by the Van Cauter [59] and Veldhuis [60] labs. Eastman et al. reported a similar association between pulsatile GH secretion, sleep onset, and deep sleep in a group of children referred for short stature [61].

While these studies have clearly demonstrated a temporal concordance between GH pulses and deep sleep, it remains to be determined whether there is a specific quality and quantity of deep sleep that is required to maintain normal GH levels. Obstructive sleep apnea (OSA) has frequently been used as a model to address this question as it is one of the most common sleep disorders and is associated with abnormal sleep architecture (but also with inflammation and hypoxemia). Indeed, before the pediatric obesity epidemic, OSA was often associated with growth failure [62], and it was posited that the increase in serum IGF-1 and improvement in linear growth that occurred after surgical correction of OSA was due to restoration of normal nocturnal GH secretion. As IGF-1 is also a faithful marker of nutritional status, however, an alternative explanation is that correction of OSA led to improved caloric intake and hence improved linear growth. There have been no studies to investigate changes in nocturnal pulsatile GH secretion after treatment of OSA in children. Of interest, a randomized, double-blind, sham-controlled 3-month study of obese men with moderate to severe OSA demonstrated a significant increase in mean GH levels, GH pulse amplitude, and GH pulse frequency (as well as IGF-1) in the group treated with continuous positive airway pressure (CPAP) [63]. However, the change in GH secretion was inversely correlated with the severity of hypoxemia and was not related to changes in deep sleep, suggesting that OSA may not be the ideal model with which to interrogate the dependency of GH secretion on consolidated deep sleep.

Conclusion

There are major changes in sleep patterns and architecture during adolescence that parallel changes in reproductive hormone and growth hormone secretory profiles. Further studies are needed to investigate the causal interactions that may exist among these systems and to determine the potential role of orexin in normal pubertal development.

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REFERENCES

Papers of particular interest, published within the period of review have been highlighted as: * of special interest

[1]. Boyar R, Finkelstein J, Roffwarg H, Kapen S, Weitzman E, Hellman L, Synchronization of augmented luteinizing hormone secretion with sleep during puberty, N.Engl.J Med 287(12) (1972) 582–586. [PubMed: 4341276]

[2]. Kapen S, Boyar RM, Finkelstein JW, Hellman L, Weitzman ED, Effect of sleep-wake cycle reversal on luteinizing hormone secretory pattern in puberty, J.Clin.Endocrinol.Metab 39(2) (1974) 293–299. [PubMed: 4370779]

[3]. Shaw ND, Butler JP, McKinney SM, Nelson SA, Ellenbogen JM, Hall JE, Insights into puberty: The relationship between sleep stages and pulsatile LH secretion, Journal of Clinical Endocrinology and Metabolism 97(11) (2012). * The first study to report a close temporal association between LH pulse onset and deep (slow wave sleep in pubertal children.

[4]. Lu C, Hutchens EG, Farhy LS, Bonner HG, Suratt PM, McCartney CR, Influence of Sleep Stage on LH Pulse Initiation in the Normal Late Follicular Phase and in Polycystic Ovary Syndrome, Neuroendocrinology 107(1) (2018) 60–72. [PubMed: 29506013]

[5]. Shaw ND, Butler JP, Nemati S, Kangarloo T, Ghassemi M, Malhotra A, Hall JE, Accumulated deep sleep is a powerful predictor of LH pulse onset in pubertal children, Journal of Clinical Endocrinology and Metabolism 100(3) (2015) 1062–1070. [PubMed: 25490277]

[6]. Shaw ND, Goodwin JL, Silva GE, Hall JE, Quan SF, Malhotra A, Obstructive Sleep Apnea (OSA) in preadolescent girls is associated with delayed breast development compared to girls without OSA, Journal of Clinical Sleep Medicine 9(8) (2013) 813–818. [PubMed: 23946712]

[7]. Apter D, Butzow TL, Laughlin GA, Yen SS, Gonadotropin-releasing hormone pulse generator activity during pubertal transition in girls: pulsatile and diurnal patterns of circulating gonadotropins, J.Clin.Endocrinol.Metab 76(4) (1993) 940–949. [PubMed: 8473410]

[8]. McCartney CR, Prendergast KA, Blank SK, Helm KD, Chhabra S, Marshall JC, Maturation of luteinizing hormone (gonadotropin-releasing hormone) secretion across puberty: evidence for altered regulation in obese peripubertal girls, J.Clin.Endocrinol.Metab 94(1) (2009) 56–66. [PubMed: 18957503]

[9]. Kim SH, Lundgren JA, Bhabhra R, Collins JS, Patrie JT, Burt Solorzano CM, Marshall JC, McCartney CR, Progesterone-Mediated Inhibition of the GnRH Pulse Generator: Differential Sensitivity as a Function of Sleep Status, J Clin Endocrinol Metab 103(3) (2018) 1112–1121. [PubMed: 29300925] * A rigorous, randomized, placebo-controlled, double-blinded crossover study demonstrating that in pubertal girls, the ability of low-dose progesterone to acutely inhibit LH pulse frequency varies according to sleep/wake state.

[10]. Clinical Trials.gov [Internet] Identifier NCT01421810, Ovarian contribution to androgen production in adolescent girls (CBS001), 2020. (Accessed July 31 2020).

[11]. Filicori M, Santoro N, Merriam GR, Crowley WF Jr., Characterization of the physiological pattern of episodic gonadotropin secretion throughout the human menstrual cycle, J Clin Endocrinol Metab 62(6) (1986) 1136–1144. [PubMed: 3084534]

[12]. Kapen S, Boyar R, Hellman L, Weitzman ED, The relationship of luteinizing hormone secretion to sleep in women during the early follicular phase: effects of sleep reversal and a prolonged three-hour sleep-wake schedule, J Clin Endocrinol Metab 42(6) (1976) 1031–1040. [PubMed: 945300]

[13]. Rossmanith WG, Yen SS, Sleep-associated decrease in luteinizing hormone pulse frequency during the early follicular phase of the menstrual cycle: evidence for an opioidergic mechanism, J. Clin. Endocrinol. Metab. 65(4) (1987) 715–718. [PubMed: 2821052]

[14]. Soules MR, Steiner RA, Cohen NL, Bremner WJ, Clifton DK, Nocturnal slowing of pulsatile luteinizing hormone secretion in women during the follicular phase of the menstrual cycle, J Clin Endocrinol Metab 61(1) (1985) 43–49. [PubMed: 3923031]

[15]. Hall JE, Sullivan JP, Richardson GS, Brief wake episodes modulate sleep-inhibited luteinizing hormone secretion in the early follicular phase, J Clin Endocrinol Metab 90(4) (2005) 2050–2055. [PubMed: 15671093]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[16]. McCartney CR, Gingrich MB, Hu Y, Evans WS, Marshall JC, Hypothalamic regulation of cyclic ovulation: evidence that the increase in gonadotropin-releasing hormone pulse frequency during the follicular phase reflects the gradual loss of the restraining effects of progesterone, J Clin Endocrinol Metab 87(5) (2002) 2194–2200. [PubMed: 11994363]

[17]. Sun BZ, Kangarloo T, Adams JM, Sluss P, Chandler DW, Zava DT, McGrath JA, Umbach DM, Shaw ND, The Relationship Between Progesterone, Sleep, and LH and FSH Secretory Dynamics in Early Postmenarchal Girls, J Clin Endocrinol Metab 104(6) (2019) 2184–2194. [PubMed: 30649404] * This observational study of early post-menarchal girls demonstrated that LH pulse frequency during sleep in the follicular phase is inversely correlated with progesterone exposure in the preceding menstrual cycle, supporting the hypothesis that sleep-related slowing of LH pulses in the follicular phase reflects the waning influence of progesterone.

[18]. Shaw ND, Gill S, Lavoie HB, Marsh EE, Hall JE, Persistence of sleep-associated decrease in GnRH pulse frequency in the absence of gonadal steroids, J.Clin.Endocrinol.Metab 96(8) (2011) 2590–2595. [PubMed: 21646369]

[19]. Loucks AB, Heath EM, Dietary restriction reduces luteinizing hormone (LH) pulse frequency during waking hours and increases LH pulse amplitude during sleep in young menstruating women, J. Clin. Endocrinol. Metab. 78(4) (1994) 910–915. [PubMed: 8157720]

[20]. Pastor CL, Griffin-Korf ML, Aloi JA, Evans WS, Marshall JC, Polycystic ovary syndrome: evidence for reduced sensitivity of the gonadotropin-releasing hormone pulse generator to inhibition by estradiol and progesterone, J. Clin. Endocrinol. Metab. 83(2) (1998) 582–590. [PubMed: 9467578]

[21]. Campbell IG, Feinberg I, Longitudinal trajectories of non-rapid eye movement delta and theta EEG as indicators of adolescent brain maturation, Proc.Natl.Acad.Sci.U.S.A 106(13) (2009) 5177–5180. [PubMed: 19307577]

[22]. Carskadon MA, Vieira C, Acebo C, Association between puberty and delayed phase preference, Sleep 16(3) (1993) 258–262. [PubMed: 8506460]

[23]. Sadeh A, Dahl RE, Shahar G, Rosenblat-Stein S, Sleep and the transition to adolescence: a longitudinal study, Sleep 32(12) (2009) 1602–9. [PubMed: 20041596]

[24]. Campbell IG, Grimm KJ, de Bie E, Feinberg I, Sex, puberty, and the timing of sleep EEG measured adolescent brain maturation, Proc Natl Acad Sci U S A 109(15) (2012) 5740–3. [PubMed: 22451933]

[25]. Foley JE, Ram N, Susman EJ, Weinraub M, Changes to sleep-wake behaviors are associated with trajectories of pubertal timing and tempo of secondary sex characteristics, J Adolesc 68 (2018) 171–186. [PubMed: 30099236] * See below under Reference [26].

[26]. Hoyt LT, Deardorff J, Marceau K, Laurent CA, Windham GC, Greenspan LC, Pinney SM, Teitelbaum S, Grimm KJ, Hagan MJ, Biro FM, Wolff MS, Kushi LH, Hiatt RA, Girls' Sleep Trajectories Across the Pubertal Transition: Emerging Racial/Ethnic Differences, J Adolesc Health 62(4) (2018) 496–503. [PubMed: 29396081] * These two longitudinal studies by Foley et al. and Hoyt et al. in large US pediatric cohorts examined the association between pubertal onset and tempo with typical wake time, bed time, sleep duration, and/or morningness/eveningness scores.

[27]. McHill AW, Klerman EB, Slater B, Kangarloo T, Mankowski PW, Shaw ND, The Relationship Between Estrogen and the Decline in Delta Power During Adolescence, Sleep 40(3) (2017).

[28]. Jessen E, Vetter C, Roenneberg T, Liesenkötter K-P, Werner H, Jenni OG, Lankes E, Blankenstein O, Neumann U, Köhler B, Wiegand S, Krude H, Kühnen P, Sleep Timing in Patients with Precocious and Delayed Pubertal Development, Clocks&Sleep 1(1) (2019) 140–150. [PubMed: 33089160]

[29]. Feinberg I, Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence?, Journal of psychiatric research 17(4) (1982) 319–34. [PubMed: 7187776]

[30]. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, Tooley K, Presumey J, Baum M, Van Doren V, Genovese G, Rose SA, Handsaker RE, Daly MJ, Carroll MC, Stevens B, McCarroll SA, Schizophrenia risk from complex variation of complement component 4, Nature 530(7589) (2016) 177–83. [PubMed: 26814963]

[31]. Villa A, Della Torre S, Maggi A, Sexual differentiation of microglia, Front Neuroendocrinol 52 (2019) 156–164. [PubMed: 30481522]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[32]. Hammond TR, Dufort C, Dissing-Olesen L, Giera S, Young A, Wysoker A, Walker AJ, Gergits F, Segel M, Nemesh J, Marsh SE, Saunders A, Macosko E, Ginhoux F, Chen J, Franklin RJM, Piao X, McCarroll SA, Stevens B, Single-Cell RNA Sequencing of Microglia throughout the Mouse Lifespan and in the Injured Brain Reveals Complex Cell-State Changes, Immunity 50(1) (2019) 253–271 e6. [PubMed: 30471926]

[33]. Hanamsagar R, Alter MD, Block CS, Sullivan H, Bolton JL, Bilbo SD, Generation of a microglial developmental index in mice and in humans reveals a sex difference in maturation and immune reactivity, Glia 65(9) (2017) 1504–1520. [PubMed: 28618077]

[34]. Matcovitch-Natan O, Winter DR, Giladi A, Vargas Aguilar S, Spinrad A, Sarrazin S, Ben-Yehuda H, David E, Zelada Gonzalez F, Perrin P, Keren-Shaul H, Gury M, Lara-Astaiso D, Thaiss CA, Cohen M, Bahar Halpern K, Baruch K, Deczkowska A, Lorenzo-Vivas E, Itzkovitz S, Elinav E, Sieweke MH, Schwartz M, Amit I, Microglia development follows a stepwise program to regulate brain homeostasis, Science 353(6301) (2016) aad8670.

[35]. Thion MS, Low D, Silvin A, Chen J, Grisel P, Schulte-Schrepping J, Blecher R, Ulas T, Squarzoni P, Hoeffel G, Coulpier F, Siopi E, David FS, Scholz C, Shihui F, Lum J, Amoyo AA, Larbi A, Poidinger M, Buttgereit A, Lledo PM, Greter M, Chan JKY, Amit I, Beyer M, Schultze JL, Schlitzer A, Pettersson S, Ginhoux F, Garel S, Microbiome Influences Prenatal and Adult Microglia in a Sex-Specific Manner, Cell 172(3) (2018) 500–516 e16. [PubMed: 29275859]

[36]. Williams Buckley A, Hirtz D, Oskoui M, Armstrong MJ, Batra A, Bridgemohan C, Coury D, Dawson G, Donley D, Findling RL, Gaughan T, Gloss D, Gronseth G, Kessler R, Merillat S, Michelson D, Owens J, Pringsheim T, Sikich L, Stahmer A, Thurm A, Tuchman R, Warren Z, Wetherby A, Wiznitzer M, Ashwal S, Practice guideline: Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology, Neurology 94(9) (2020) 392–404. [PubMed: 32051244]

[37]. Cipolla-Neto J, Amaral FGD, Melatonin as a Hormone: New Physiological and Clinical Insights, Endocr Rev 39(6) (2018) 990–1028. [PubMed: 30215696] * A comprehensive review of melatonin and its endocrine actions.

[38]. Clarke IJ, Caraty A, Kisspeptin and seasonality of reproduction, Advances in experimental medicine and biology 784 (2013) 411–30. [PubMed: 23550017]

[39]. Crowley SJ, Acebo C, Carskadon MA, Human puberty: salivary melatonin profiles in constant conditions, Dev Psychobiol 54(4) (2012) 468–73. [PubMed: 21953482]

[40]. Waldhauser F, Weiszenbacher G, Frisch H, Zeitlhuber U, Waldhauser M, Wurtman RJ, Fall in nocturnal serum melatonin during prepuberty and pubescence, Lancet 1(8373) (1984) 362–5. [PubMed: 6141425]

[41]. Waldhauser F, Boepple PA, Schemper M, Mansfield MJ, Crowley WF Jr., Serum melatonin in central precocious puberty is lower than in age-matched prepubertal children, J Clin Endocrinol Metab 73(4) (1991) 793–6. [PubMed: 1909703]

[42]. Wood S, Loudon A, The pars tuberalis: The site of the circannual clock in mammals?, Gen Comp Endocrinol 258 (2018) 222–235. [PubMed: 28669798]

[43]. Carr R, Wasdell MB, Hamilton D, Weiss MD, Freeman RD, Tai J, Rietveld WJ, Jan JE, Long-term effectiveness outcome of melatonin therapy in children with treatment-resistant circadian rhythm sleep disorders, J Pineal Res 43(4) (2007) 351–9. [PubMed: 17910603]

[44]. Malow BA, Findling RL, Schroder CM, Maras A, Breddy J, Nir T, Zisapel N, Gringras P, Sleep, Growth, and Puberty After 2 Years of Prolonged-Release Melatonin in Children With Autism Spectrum Disorder, J Am Acad Child Adolesc Psychiatry (2020). * Long-term treatment of insomnia with melatonin in children with autism had no adverse effects on childhood growth or pubertal development, based on physician-determined Tanner staging.

[45]. Malow B, Adkins KW, McGrew SG, Wang L, Goldman SE, Fawkes D, Burnette C, Melatonin for sleep in children with autism: a controlled trial examining dose, tolerability, and outcomes, J Autism Dev Disord 42(8) (2012) 1729–37; author reply 1738. [PubMed: 22160300]

[46]. Zwart TC, Smits MG, Egberts TCG, Rademaker CMA, van Geijlswijk IM, Long-Term Melatonin Therapy for Adolescents and Young Adults with Chronic Sleep Onset Insomnia and Late Melatonin Onset: Evaluation of Sleep Quality, Chronotype, and Lifestyle Factors Compared to Age-Related Randomly Selected Population Cohorts, Healthcare (Basel) 6(1) (2018).

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[47]. Scheer D, Schwartz SW, Parr M, Zgibor J, Sanchez-Anguiano A, Rajaram L, Prevalence and incidence of narcolepsy in a US health care claims database, 2008–2010, Sleep Research Society (2019) 1–13.

[48]. Scammell TE, Narcolepsy, The New England Journal of Medicine 373(27) (2015) 2654–2662. [PubMed: 26716917]

[49]. Aran A, Einen M, Lin L, Plazzi G, Nishino S, Mignot E, Clinical and Therapeutic Aspects of Childhood Narcolepsy-Cataplexy: A Retrospective Study of 51 Children, SLEEP 33(11) (2010) 1457–1464. [PubMed: 21102987]

[50]. Poli F, Pizza F, Mignot E, Ferri R, Pagotto U, Taheri S, Finotti E, Bernardi F, Pirazzoli P, Cicognani A, Balsamo A, Nobili L, Bruni O, Plazzi G, High Prevalence of Precocious Puberty and Obesity in Childhood Narcolepsy with Cataplexy, SLEEP 36(2) (2013) 175–181. [PubMed: 23372264] * First comprehensive investigation of pubertal development and overweight/obesity in children with narcolepsy.

[51]. Ponziani V, Gennari M, Pizza F, Balsamo A, Bernardi F, Plazzi G, Growing Up with Type 1 Narcolepsy: Its Anthropometric and Endocrine Features, Journal of Clinical Sleep Medicine 12(12) (2016) 1649–1657. [PubMed: 27707443]

[52]. Wannes S, Elmaleh-Bergès M, Simon D, Zénaty D, Martinerie L, Storey C, Gelwane G, Paulsen A, Ecosse E, De Roux N, Carel JC, Léger J, High prevalence of syndromic disorders in patients with non-isolated central precocious puberty, European Journal of Endocrinology 179(6) (2018) 373–380. [PubMed: 30324796]

[53]. Gaskins GG, Moenter SM, Orexin A Suppresses Gonadotropin-Releasing Hormone (GnRH) Neuron Activity in the Mouse, Endocrinology 153(3) (2012) 3850–3860. [PubMed: 22673226]

[54]. Zhao Y, Singh C, Prober DA, Wayne NL, Morphological and Physiological Interactions Between GnRH3 and Hypocretin/Orexin Neuronal Systems in Zebrafish (Danio rerio), Endocrinology 157(10) (2016) 4012–4020. [PubMed: 27533887]

[55]. Hosseini A, Khazali H, Central Orexin A Affects Reproductive Axis by Modulation of Hypothalamic Kisspeptin/Neurokinin B/Dynorphin Secreting Neurons in the Male Wistar Rats, NeuroMolecular Medicine 20 (2018) 525–536. [PubMed: 30218420]

[56]. Backeljauw PF, Dattani MT, Cohen P, Rosenfeld RG, Disorders of Growth Hormone/Insulin-Like Growth Factor Secretion and Action, in: Sperling M. (Ed.), Pediatric Endocrinology, Elsevier2014, pp. 292–404.

[57]. Ho KY, Evans WS, Blizzard RM, Veldhuis JD, Merriam GR, Samojlik E, Furlanetto R, Rogol AD, Kaiser DL, Thorner MO, Effects of sex and age on the 24-hour profile of growth hormone secretion in man: importance of endogenous estradiol concentrations, J Clin Endocrinol Metab 64(1) (1987) 51–8. [PubMed: 3782436]

[58]. Takahashi Y, Kipnis DM, Daughaday WH, Growth hormone secretion during sleep, J Clin Invest 47(9) (1968) 2079–90. [PubMed: 5675428]

[59]. Van Cauter E, Kerkhofs M, Caufriez A, Van Onderbergen A, Thorner MO, Copinschi G, A quantitative estimation of growth hormone secretion in normal man: reproducibility and relation to sleep and time of day, J Clin Endocrinol Metab 74(6) (1992) 1441–50. [PubMed: 1592892]

[60]. Holl RW, Hartman ML, Veldhuis JD, Taylor WM, Thorner MO, Thirty-second sampling of plasma growth hormone in man: correlation with sleep stages, J Clin Endocrinol Metab 72(4) (1991) 854–61. [PubMed: 2005213]

[61]. Eastman CJ, Lazarus L, Growth hormone release during sleep in growth retarded children, Archives of disease in childhood 48(7) (1973) 502–7. [PubMed: 4719103]

[62]. Bar A, Tarasiuk A, Segev Y, Phillip M, Tal A, The effect of adenotonsillectomy on serum insulin-like growth factor-I and growth in children with obstructive sleep apnea syndrome, J Pediatr 135(1) (1999) 76–80. [PubMed: 10393608]

[63]. Hoyos CM, Killick R, Keenan DM, Baxter RC, Veldhuis JD, Liu PY, Continuous positive airway pressure increases pulsatile growth hormone secretion and circulating insulin-like growth factor-1 in a time-dependent manner in men with obstructive sleep apnea: a randomized sham-controlled study, Sleep 37(4) (2014) 733–41. [PubMed: 24899762] * First randomized, controlled study of adult subjects with obstructive sleep apnea to investigate whether CPAP treatment increases

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nocturnal pulsatile GH secretion via improved sleep architecture (including deep sleep) and/or restoration of normal blood oxygen levels.