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Pubertal development and regulation

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Abstract

Puberty marks the end of childhood and is a period when individuals undergo physiological and psychological changes to achieve sexual maturation and fertility. The hypothalamic-pituitary-gonadal axis controls puberty and reproduction and is tightly regulated by a complex network of excitatory and inhibitory factors. This axis is active in the embryonic and early postnatal stages of life and is subsequently restrained during childhood, and its reactivation culminates in puberty initiation. The mechanisms underlying this reactivation are not completely known. The age of puberty onset varies between individuals and the timing of puberty initiation is associated with several health outcomes in adult life. In this Series paper, we discuss pubertal markers, epidemiological trends of puberty initiation over time, and the mechanisms whereby genetic, metabolic, and other factors control secretion of gonadotropin-releasing hormone to determine initiation of puberty.

Introduction

Puberty is the period of transition between childhood and adulthood, characterised by the development of secondary sexual characteristics, gonadal maturation, and attainment of reproductive capacity. Puberty and reproduction are controlled by the hypothalamic-pituitary-gonadal axis.[1] Gonadotropin-releasing hormone (GnRH) is produced in the preoptic area of the hypothalamus and released from axon terminals in the median eminence in a pulsatile manner to stimulate the secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary, which in turn act on the gonads to promote gametogenesis and the production of sex steroids. In human beings, the hypothalamic-pituitary-gonadal axis is active in the mid-gestational fetus, but silenced towards the end of gestation. This restraint is removed at birth, leading to reactivation of the axis and an increase in gonadotropin concentrations.[2] These concentrations then gradually decrease towards age 6 months, with the exception of FSH concentration in girls, which remains raised until age 3–4 years. In boys, testosterone concentration rises to a peak at age 1–3 months, but then falls in conjunction with the falling LH concentration.[2]

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Prenatal and postnatal activation of the hypothalamic-pituitary-gonadal axis is associated with penile and testicular growth and testicular descent, and is therefore regarded as important for the development of male genitalia. In girls, raised concentrations of gonadotropins result in the maturation of ovarian follicles and an increase in oestradiol concentrations. This period of activity of the hypothalamic-pituitary-gonadal axis in the early stages of life is called minipuberty and has been proposed to lay the groundwork for pituitary LH and FSH responses to GnRH during the later reproductive phase of life.[2]

At about age 6 months in boys and 3–4 years in girls, there is an active inhibition of GnRH secretion, which persists throughout childhood. Puberty is initiated with a sustained increase in pulsatile release of GnRH from the hypothalamus after this quiescent period. The precise mechanisms that trigger the initiation of puberty remain elusive. Evidence suggests that the augmentation of activators of GnRH secretion together with the suppression of inhibitors of GnRH secretion culminates in puberty initiation. Whether the stimulatory tonus acting during minipuberty also contributes to puberty initiation is not yet clear. In this Series paper, we will discuss pubertal markers, epidemiological trends of puberty initiation, the currently known modulators of GnRH secretion, the hypothalamic-pituitary-gonadal axis, and the initiation of puberty.

Normal puberty and pubertal markers

The most visible changes during puberty are growth in stature and development of secondary sexual characteristics (figure 1). Equally profound are changes in body composition and the achievement of fertility. The first sign of puberty initiation is typically thelarche (breast development) in girls and testicular enlargement in boys. The landmark studies of Marshall and Tanner (1969), which classified puberty into five stages in girls and boys on the basis of somatic changes in breast, pubic hair, and genital development, have been widely used to assess puberty development.[3,4] The ideal assessment of puberty initiation in girls is breast bud palpation. Commonly, self-description, visual assessment of breast development, or age of menarche (ie, the time of first menstrual bleeding) are used as markers of puberty in population studies, although these strategies are less accurate for assessment of the time of puberty initiation. Similarly, although testicular examination is a useful and key sign used in clinical practice when assessing boys for pubertal development, it is impractical to use in population studies of puberty. For these reasons and because of differences in study designs and methods used to assess puberty initiation, it can be difficult to determine the exact age of puberty onset in population studies. Although there is some physiological variation, puberty development usually lasts 3–4 years and consists of a series of events that typically proceed in a predictable sequence. Menarche is regarded as the final marker of puberty in girls.[5] In girls with late initiation of puberty, there can be a decrease in the interval between thelarche and menarche.[6] In boys, testicular enlargement is followed by an increase in growth velocity and subsequent spermarche.[7]

The development of axillary and pubic hair, a process termed pubarche, is also incorporated in the Tanner stages, but should not be used as a marker of the onset of puberty. In both sexes, pubarche is dependent on an increase in adrenal androgen production, a physiological event termed adrenarche.[8] The serum concentration of dehydroepiandrosterone sulphate

(DHEAS) is the best marker for the presence of adrenarche. This maturational process generally begins at about age 6 years, several years before activation of the hypothalamic-pituitary-gonadal axis (gonadarche).[9] Although development of axillary and pubic hair requires adrenarchal concentrations of androgen, clinically evident pubarche does not usually appear until shortly after physical evidence of gonadarche (ie, breast development in girls and testicular enlargement in boys). Notably, adrenarche seems to be specific to human and some non-human primates, and the absence of adrenarche in human beings does not seem to prevent fertility nor to substantially affect the timing of gonadarche.[10] Adrenocorticotropic hormone has been suggested as a regulator of adrenarche because of its absence in children with hypopituitarism.[11] However, the precise mechanisms underlying adrenarche are still unknown. Children with precocious puberty do not have a corresponding advance in the timing of adrenarche. Similarly, patients with hypogonadotropic hypogonadism and delayed puberty have no corresponding delay of adrenarche. In both cases, their adrenal androgen concentrations are appropriate for chronological age.

The age at puberty onset varies greatly between individuals, different ethnic populations, and between the sexes; girls on average experience the onset of puberty at younger ages than boys and are more likely to have idiopathic central precocious puberty, whereas boys are more predisposed to idiopathic delayed puberty.[12,13] Puberty is deemed physiological when it begins between the ages of 8 and 12 years in girls and between 9 and 14 years in boys.[14] These limits are selected to be 2·5–3 SDs below and above the mean age of onset of puberty, as defined by population studies. However, population studies have limitations and thus so do the age limits used to define normal pubertal timing. The initiation of puberty at ages younger than these limits is regarded as precocious puberty and at ages beyond these limits, delayed puberty. The age of puberty onset is associated with subsequent health outcomes. Early age at menarche is a risk factor for breast cancer,[15] cardiovascular disease, depression, behavioural disorders, diabetes, and increased all-cause mortality.[16,17] Early puberty in boys is a risk factor for testicular cancer and delayed puberty can be a cause of being bullied, poor self-esteem, and psychosocial distress.[18] A recent study[19] showed that earlier or later timing of puberty in girls or boys was associated with increased risks for 48 adverse outcomes, across a range of cancer, cardiometabolic, gynaecological or obstetric, gastrointestinal, musculoskeletal, and neurocognitive categories. Most of these associations have been based on epidemiological studies and need to be validated and studied further.

Epidemiology and trends

Studies have shown a decrease in the average age of menarche between the mid-19th and the mid-20th centuries in the USA and in some countries in Europe.[20] This change has been attributed to improvements in general health, nutrition, and other living conditions during this period. Although still controversial because of the limited comparability of the data from studies in different populations and the use of different methods, it has also been proposed that there was a trend towards an earlier onset of breast development and menarche in girls from 1940 to 1994.[21] The amount of body fat and exposure to endocrine disruptors, particularly oestrogenic compounds and antiandrogens, have been suggested as important factors associated with this trend in pubertal timing.[21] The effects of endocrine disruptors on GnRH secretion and therefore on the initiation of puberty and reproduction are still

controversial and difficult to assess in human beings.[22] Environmental factors might have effects on the neuroendocrine system, particularly during fetal and early postnatal life;[22] however, we will not discuss the effects of specific compounds in this Series paper because of the controversies around this topic and the paucity of definitive data.

The characterisation of thelarche has varied from study to study. In some studies, breast development was characterised by visualisation only, making appropriate assessment difficult, especially in overweight or obese girls. A large cross-sectional study of about 17 000 girls done in an office setting in the USA (the Pediatric Research in Office Settings [PROS] study) used information obtained from mothers and photography, and the results suggested an advancement of pubertal development in the second half of the 20th century.[23] By contrast, two European studies in which careful physical examination was used to ascertain breast development showed no substantial advance in age of puberty onset.[24,25] However, in a more recent Danish study, 954 girls assessed in 2006–08 were compared with those studied in 1991–93, and substantially earlier breast development was noted in the girls born more recently.[26]

The assessment of secular trends in male pubertal development is even more challenging because there are so few studies analysing puberty development in boys, and pubertal markers are even less reliable in boys than in girls. Similar to what has been reported in girls, results from some studies have suggested that age of puberty onset in boys might be occurring earlier than in the past, but additional studies are required to confirm this tendency.[27]

There are substantial racial differences in sexual maturation; it is thought that non-Hispanic black and Mexican-American ethnic origins are independently associated with earlier pubertal development in girls.[13] The age at menarche of non-Hispanic black girls is substantially earlier than that of non-Hispanic white and Mexican-American girls, and the mean age for onset of breast development in African-American girls is also earlier than that in white girls.[28]

Disorders of puberty

Classification of pubertal disorders

Puberty onset varies between normal individuals and there is a 4–5-year window judged to be the normal age of pubertal development. Changes in the limits of what is regarded as normal puberty initiation have occurred over the past few decades. The onset of puberty before or after these limits is deemed pathological. Precocious puberty generally has been defined as pubertal onset before age 8 years in girls and before age 9 years in boys. Because of the apparent advances in the age of onset of puberty in population studies, researchers have suggested that age 7 years in white girls, and age 6 years in African-American girls, should be used as the thresholds for classification of precocious puberty.[29] However, other investigators have subsequently concluded that signs of puberty in girls aged 6–8 years should not be regarded as normal or benign as this might lead to underdiagnosis of endocrine disorders, so the appropriate thresholds for assessment have returned to the previously recommended parameters.[30]

Precocious puberty

Precocious puberty can be a variant of normal development—eg, premature adrenarche or isolated premature thelarche—or can be attributable to pathological conditions (panel). GnRH-dependent or central precocious puberty is caused by early maturation of the hypothalamic-pituitary-gonadal axis, resulting in pulsatile secretion of GnRH and subsequent activation of the gonads. In these cases, the sexual characteristics are appropriate for the patient's sex (isosexual). Several neurological disorders can cause central precocious puberty, such as tumours, trauma, or malformations (panel). Chronic exposure to sex steroids from external sources or as a result of some disorders with peripheral production of sex steroids have been proposed to result in early activation of the hypothalamic-pituitary-gonadal axis.[31] Most cases of central precocious puberty in girls and up to 60% of cases in boys do not have a detectable CNS lesion and are described as idiopathic central precocious puberty. Some or most of these cases might have a genetic, metabolic, or environmental component, or a combination of these factors.

Panel

Variants of normal pubertal development and classification of pubertal disorders

Variants of normal pubertal development

Isolated precocious thelarche

- Isolated breast development with no other signs of oestrogen action

Isolated precocious pubarche

- Axillary hair, increased growth velocity, and slight advancement of bone age
- Increase in adrenal hormones

Isolated precocious menarche

- Isolated vaginal bleeding without other pubertal signs or advancement of bone age

Constitutional delay of growth and puberty

- Puberty initiation between ages 14 and 18 years
- More frequent in boys with family history

Precocious puberty

Gonadotropin-dependent precocious puberty or central precocious puberty

- Without CNS abnormalities
  - Genetic causes
  - Secondary to previous chronic exposure to sex steroids (rare)

- After exposure to endocrine disruptors (proposed mechanism)
- Idiopathic

- CNS abnormalities
  - Tumours
  - Congenital malformations: hypothalamic hamartoma, arachnoid cyst, and others
  - Acquired diseases: infections and inflammatory processes of the CNS

Gonadotropin-independent precocious puberty or peripheral precocious puberty

- Tumour
  - Adrenal, ovarian, or testicular tumours
- Autonomous ovarian cysts
- Severe long-term untreated primary hypothyroidism
- Genetic causes
  - Testotoxicosis
  - McCune-Albright syndrome
  - Prader-Willi syndrome, Williams syndrome, Temple syndrome
  - Others

Hypogonadism

Hypogonadotropic hypogonadism

- Isolated congenital
  - With olfactory defects: Kallmann’s syndrome
  - Normal olfaction: isolated hypogonadotropic hypogonadism
- Functional hypogonadotropic hypogonadism
  - Hypothalamic amenorrhoea
  - Male functional hypogonadism
- Tumours
- Malformations
- Combined with other pituitary dysfunction

- Congenital hypopituitarism or due to systemic disorders, drugs, or radiation exposure

- Syndromes with hypogonadotropic hypogonadism
  - Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, CHARGE syndrome, Gordon's syndrome, and others

Hypergonadotropic hypogonadism

- Turner's syndrome
- Klinefelter's syndrome
- Bilateral gonadal failure
- Anorchia
- Primary ovarian or testicular failure
- Radiation
- Drugs or chemotherapy
- Trauma
- Infection
- Isolated forms of gonadal failure: LH receptor and FSH receptor gene mutations

LH=luteinising hormone. FSH=follicle-stimulating hormone.

Production of sex steroids independent of the activation of the hypothalamic-pituitary-gonadal axis results in gonadotropin-independent or peripheral precocious puberty. In this form of puberty, sex hormones are usually derived from the gonads or adrenal glands, or from exogenous sources (panel). In patients with peripheral precocious puberty, the sexual characteristics can be appropriate for the child's sex (isosexual) or inappropriate, with virilisation of girls or feminisation of boys (contrasexual).

Delayed puberty

Delayed puberty is defined clinically by the absence or incomplete development of secondary sexual characteristics by age 13 years in girls or age 14 years in boys. Delayed puberty can be a variant of normal development, known as constitutional delay of growth and puberty, when healthy teenagers spontaneously develop puberty after the upper age limit (panel). The absence or incomplete development of secondary sexual characteristics by age 18 years in both sexes is classified as hypogonadism. The absence of activation of the hypothalamic-pituitary-gonadal axis because of a defect in the CNS defines hypogonadotropic hypogonadism. This disorder can be caused by a deficiency in GnRH secretion, action, or both, also known as isolated hypogonadotropic hypogonadism. A genetic defect has been identified in approximately 40% of known cases. Alternatively, hypogonadotropic hypogonadism can have an organic cause such as a tumour, use of drugs,

or inflammatory or systemic disorders (panel). Isolated hypo gonadotropic hypogonadism can be classified as Kallmann's syndrome when associated with absence of smell (anosmia), or isolated hypogonadotropic hypogonadism when there is no effect on olfaction. Kallmann's syndrome typically results from abnormal fetal development of GnRH neurons; both GnRH and olfactory neurons originate from the olfactory placode and migrate together into the CNS during embryogenesis.[32] Impairment of the migration of these neurons is often associated with genetic defects.[33–35] By contrast, isolated hypogonadotropic hypogonadism is more typically associated with normal olfactory and GnRH neuronal development, but impaired regulation of GnRH secretion.[33,35] The absence of pubertal development caused by an intrinsic defect in the gonads results in hypergonadotropic hypogonadism, which can also be caused by genetic or organic disorders.

Normal physiological controls of the timing of onset and progression of puberty

Role of GnRH

In the 1970s, Belchetz and colleagues[36] showed in animal models that intermittent release of GnRH is required for the activation of the pituitary-gonadal axis. Although the mechanism that causes the pulsatility of the GnRH neuronal network can be intrinsic to the GnRH neurons themselves,[37] lesions of the arcuate nucleus have been shown to abolish LH pulsatility, consistent with the idea that there is a higher order input into the network of GnRH neurons regulating GnRH secretion.[38] Puberty is initiated with a sustained increase in pulsatile release of GnRH from the hypothalamus after a quiescent period during childhood. Studies of agonadal human beings have shown that the prepubertal suppression of hypothalamic-pituitary-gonadal function occurs even in the absence of feedback by sex steroids, suggesting that the juvenile pause represents a state of neurally determined functional stasis rather than immaturity of the GnRH neurons.[39] The exact mechanism that leads to the reinstatement of pulsatile GnRH secretion is not known, but evidence suggests that a complex interaction between nutritional, environmental, and genetic factors is involved in the regulation of puberty initiation.[40]

Many neurotransmitters can modify the GnRH secretory pattern, with an excitatory or inhibitory effect on GnRH secretion. During childhood the predominant pathway is believed to be the inhibitory network, which decreases around the time of puberty initiation, along with augmentation of the excitatory tonus. Studies in animal models have identified several of the regulatory components of the GnRH system. Results for these studies suggest that catecholamines and glutamate are components of the excitatory input, whereas -aminobutyric acid (GABA) might be a component of the inhibitory network.[1] Studies in patients with pubertal disorders have not identified genetic defects in the genes encoding these factors, which undermines the evidence for their potential roles, but does not rule them out entirely as important for puberty initiation.

Genes involved in GnRH regulation

Overview—Data showing an association between the ages at which a mother and her children attain pubertal milestones and between the timing of puberty within ethnic groups

are suggestive of genetic modulation of the reproductive endocrine axis.[23,41] These and other data suggest that around 50–80% of the variation in pubertal onset might be genetically determined.[40]

Many studies have been done to investigate candidate mechanisms governing GnRH release; however, the most compelling evidence for specific GnRH neural inputs comes from genetic studies in patients with pubertal disorders. Two of the most important excitatory components of the GnRH network were identified with the demonstration that the genetic loss of such inputs results in failure to initiate the GnRH pulse generator at the expected time of puberty, resulting in isolated hypogonadotropic hypogonadism.[42–45]

Kisspeptin system—The discovery of the kisspeptin system as a crucial component for pubertal activation of the hypothalamic-pituitary-gonadal axis occurred in 2003, when loss-of-function mutations of the *KISS1R* (previously known as *GPR54*) gene were identified in individuals with isolated hypogonadotropic hypogonadism, establishing KISS1R inactivation as a cause of this disorder (table, figure 2).[42,43] Physiological and pharmacological studies have shown that kisspeptin is an essential part of the complex excitatory network that regulates GnRH secretion. Administration of kisspeptin results in increases in plasma LH concentrations in healthy men,[54,55] and in women kisspeptin also induces LH release, although the response varies across the menstrual cycle.[56] Kisspeptin stimulates gonadotropin release less potently but in a more physiologically effective way than do current treatments with GnRH analogues.[57] A non-constitutively activating mutation in *KISS1R* was the first identified genetic cause of central precocious puberty, reported in an adopted girl with breast development with slow progression that had first been noted at birth and that progressed at age 7 years.[49] Mutations in *KISS1* were also identified in patients with isolated hypogonadotropic hypogonadism and central precocious puberty, strengthening the evidence base for the association of this system with pubertal onset.[47,48]

In animal models, the KISS1 neurons appear to mediate sex steroid feedback effects in the hypothalamus.[58,59] These neurons express oestrogen receptor a and receive sex steroid signals from the gonads, which regulate *KISS1* expression and control the release of GnRH.[60] In many mammalian species, *KISS1* expression is negatively regulated in the arcuate nucleus and positively regulated in the anteroventral periventricular nucleus and preoptic area by sex steroids. The *KISS1* positive regulation is believed to be important for the LH surge in females of many mammalian species.[61]

Tachykinins—Neurokinin B (NKB) belongs to a family of closely related peptides called tachykinins. The role of NKB in the control of reproductive function was the subject of investigation for several years because of neuroanatomical evidence for potential NKB inputs to GnRH neurons.[62] It was not until 2009 that Topaloglu and colleagues[44] identified NKB as an important factor for human puberty initiation, studying ten consanguineous families with multiple affected members who had isolated hypogonadotropic hypogonadism. Homozygous loss-of-function mutations in the genes encoding the NKB receptor (*TACR3*) and neurokinin B (*TAC3*) were identified, providing compelling evidence that the NKB system is necessary for the activation of the hypothalamic-pituitary-gonadal axis in puberty (table, figure 2). The report by Gianetti and colleagues[63] of reversibility of isolated

hypogonadotropic hypogonadism in a high proportion of patients with *TACR3* mutations suggested that the NKB system is not absolutely required for GnRH regulation after the maturation of the hypothalamic-pituitary-gonadal axis. However, other studies did not show a similar frequency of reversibility,[45] and it is still not definitively known whether the NKB system is essential for the excitatory GnRH regulatory network after pubertal development.

Although the effect of NKB on GnRH secretion depends on the hormonal context, administration of NKB has been shown to elicit strong stimulation of LH production mediated by GnRH in animal models.[64] Neurons co-expressing kisspeptin and NKB in the human mediobasal hypothalamus often co-express substance P.[65] Substance P belongs to the tachykinin family along with neurokinin B and neurokinin A. Substance P and neurokinin A have been reported to stimulate the gonadotropic axis in men.[66] The regulation of gonadotropin release by the tachykinins and their receptors occurs at least partly through actions on KISS1 neurons in mice.[67]

Makorin ring finger protein 3—The first gene with an inhibitory effect on GnRH secretion with mutations identified in human beings was *MKRN3* (table, figure 2). The identification of this novel factor in the GnRH network arose from whole-exome sequencing analysis of families with central precocious puberty.[52] *MKRN3* is located in the Prader-Willi syndrome critical region on chromosome 15 and before the identification of its role in puberty, the few reports about this gene came from research into Prader-Willi syndrome.[68,69] The maternal *MKRN3* allele is imprinted and only the paternal allele is expressed.[68–70] Following this inheritance pattern, all *MKRN3* mutations identified in patients with central precocious puberty were inherited from their fathers.[52]

MKRN3 is the most common genetic defect associated with central precocious puberty so far; families with central precocious puberty from several different ethnic groups harbour mutations in this gene.[52,71–76] There was no previous association of *MKRN3* with the hypothalamic-pituitary-gonadal axis and the mechanism by which *MKRN3* regulates puberty initiation is not yet completely understood. The mutations identified in patients with central precocious puberty are expected to disrupt protein function. *MKRN3* expression in the arcuate nucleus of mice is high prepubertally and decreases before puberty initiation, reaching very low levels in adult life.[52] Taken together, these findings suggest that the loss of function of MKRN3 results in early puberty, implying an inhibitory role of MKRN3 on GnRH secretion.[77] The very low expression of *MKRN3* in the adult mouse, the similarity of the phenotype of patients with central precocious puberty with and without *MKRN3* mutations, and the absence of an identified phenotype beyond central precocious puberty in patients with *MKRN3* loss-of-function mutations imply that MKRN3 is important for puberty initiation, but not for the maintenance of pulsatile GnRH secretion later in life. However, further studies and larger samples of children with central precocious puberty and *MKRN3* mutations are necessary to more fully clarify whether the clinical course of puberty might differ as compared with idiopathic central precocious puberty and whether there might be any other associated reproductive or non-reproductive phenotypes.

MKRN3 belongs to the Makorin family, a family of E3 ubiquitin ligases.[78] Its protein structure has a ubiquitin ligase domain and it has been postulated that MKRN3 might inhibit

stimulators of GnRH secretion (figure 2).[79] Further research into the mechanism of action of MKRN3 will expand our knowledge of the GnRH inhibitory network.

In a recent meta-analysis of genome-wide association and custom-genotyping array studies of age at menarche in up to 182 416 women of European descent, a variant downstream of *MKRN3* had the largest effect size for association with menarche when the variant was paternally inherited.[80] This finding implicates common variation near *MKRN3* as an important source of variation in pubertal timing in the general population.

LIN33B—In 2009, genome-wide association studies identified an association between the locus 6q21 (in or near the *LIN28B* gene) with age at menarche and height.[81–84] *LIN28B* encodes a regulator of the let-7 class of microRNAs. Although several other human studies replicated the findings from the genome-wide association studies, the mechanism by which this gene is associated with the control of GnRH secretion is unknown.[85] Mutations in *LIN28B* have not been identified in patients with central precocious puberty or constitutional delay of growth and puberty.[86,87]

Many other genes have been identified in association with developmental defects in GnRH neurons. These genes affect GnRH neuronal migration and are associated with hypogonadotropic hypogonadism with anosmia, or Kallmann's syndrome (table).[35,46,47,53,88–90] Other genes have been identified in association with hypogonadotropic hypogonadism in conjunction with syndromic disorders, but are beyond the scope of this Series paper.

Metabolic factors that affect GnRH secretion

Animal and human studies in the 1960s and 1970s showed that the proper function of the hypothalamic-pituitary-gonadal axis is gated by metabolic and nutritional factors.[91,92] A threshold bodyweight is necessary for pubertal development and reproduction.[91] The identification of peripheral hormones (such as leptin, insulin, and ghrelin) that signal the metabolic status to the reproductive axis has expanded our knowledge about the neuroendocrine mechanisms linking metabolism and reproduction (figure 3). Nonetheless, our understanding of how such dynamic interplay occurs remains incomplete.

Leptin, an adipocyte-derived hormone, is a satiety factor secreted in proportion to the amount of body energy stores, and was one of the first factors linking metabolism with the reproductive axis.[93] Serum leptin concentrations and leptin mRNA concentrations in adipose tissue are associated positively and very closely with fat mass.[94] Leptin is a permissive metabolic signal to the reproductive system; its circulating concentrations inform of the actual size of energy reserves not only to the reproductive axis, but to several body systems.[95] As has been shown for bodyweight, the attainment of appropriate leptin concentrations is indispensable for the maturation of the hypothalamic-pituitary-gonadal axis, normal pubertal progression, and maintenance of fertility.[96]

Leptin acts through the leptin receptor, a single-transmembrane-domain receptor of the cytokine receptor family.[97] The finding that homozygous mutations in genes encoding leptin (*LEP*) or leptin receptor (*LEPR*) cause hypogonadotropic hypogonadism in human beings

emphasises the role of leptin in reproduction.[98–100] In addition to the reproductive phenotype, individuals with homozygous mutations in *LEPR* presented with early-onset morbid obesity and reduced growth hormone and thyrotropin secretion.[100] Leptin treatment of patients with hypogonadotropic hypogonadism and a homozygous mutation in *LEP* resulted in the induction of menstrual cycles, development of secondary sexual characteristics, and pulsatile gonadotropin secretion.[101,102] Moreover, leptin administration in women with hypothalamic amenorrhoea (a state of relative leptin deficiency) restored reproductive function, induced ovulation, and increased circulating concentrations of thyroxine, insulin-like growth factor 1 (IGF-1), and bone markers, reinforcing the central role of leptin for normal reproductive and neuroendocrine function.[103]

Another systemic hormone with a major role in the regulation of reproduction is the pancreatic hormone insulin (figure 3).[104] Studies have suggested that insulin acts on the hypothalamic-pituitary-gonadal axis at the level of the hypothalamus to directly or indirectly modulate GnRH secretion (possibly via kisspeptin), as well as at the level of the pituitary gonadotrope.[105] Insulin is a major regulator of leptin production; therefore, some of the positive effects of insulin on the reproductive system might derive from its ability to stimulate leptin secretion.[106] However, the precise site of action of insulin at the hypothalamic level in vivo remains in question.[107] IGF-1 is structurally homologous to insulin and findings suggest that it is also involved in GnRH regulation.[108] Moreover, studies show an increase in IGF-1 expression during puberty in human beings.[109]

Ghrelin, a peptide predominantly secreted by the stomach, has been postulated to be a peripheral signal for energy insufficiency, acting as a potent orexigen (figure 3).[110] Ghrelin has direct actions on the brain and the pituitary, where it has an inhibitory effect on gonadotropin pulsatility and decreases LH responsiveness to GnRH, as well as a stimulatory effect on prolactin secretion, probably involving direct action on somatomammotroph cells.[111]

Conclusions

The triggers of puberty initiation have puzzled scientists for many years. Pubertal development culminates with reproductive competence. Because of its paramount evolutionary importance, the reproductive system is controlled by a complex regulatory network. In this system, a major hierarchical role is held by GnRH neurons. GnRH is secreted in a unique pulsatile manner by neurons located in the hypothalamus to stimulate the pituitary gonadotropins and gonadal sex steroids. The regulation of GnRH secretion is still not completely understood, but we have witnessed a substantial expansion of our understanding of the signals involved in this regulation in the past two decades. The decrease in the average age of puberty initiation between the mid-19th and mid-20th centuries suggested an association of nutrition and environmental factors with reproduction,[20,41] which was substantiated by the identification of leptin as an important link between both systems, together with the characterisation of the effects of the metabolic hormones, insulin and ghrelin, on the reproductive axis. Although studies in animals have led to identification of regulators of GnRH such as catecholamines, GABA, and glutamate, genetic studies of patients with pubertal disorders have resulted in the identification of a major regulatory hub

for the GnRH neurons—ie, the hypothalamic neurons expressing kisspeptin and neurokinin B.[42–44] These findings have important clinical implications, not only to aid in diagnosis and improve genetic counselling, but also to contribute to the development of new therapies for reproductive disorders. For example, kisspeptin has been used in clinical studies to induce ovulation in infertile women.[112]

Search strategy and selection criteria

We searched MEDLINE and PubMed for articles published in English up to June 1, 2015, using the search terms “puberty”, “puberty onset”, or “GnRH regulation”, combined with “regulation”, “puberty onset”, “hypothalamic-pituitary-gonadal axis”, “markers”, “Tanner stages”, “trends”, “metabolism”, “kisspeptin”, “tachykinin”, “MKRN3”, “leptin”, “insulin”, and “GWAS”. We read relevant papers in full, searched their reference lists, and selected the most relevant on the basis of design, findings, and time of publication.

More recently, genetic studies have led to the identification of the most common known genetic cause of central precocious puberty, *MKRN3*.[52] Although the mechanism by which *MKRN3* regulates the hypothalamic-pituitary-gonadal axis is still to be elucidated, the identification of mutations in this gene in patients with different ethnic origins and its expression pattern in the hypothalamus of mice support the association of *MKRN3* with GnRH regulation. Different from the other genetic factors regulating the hypothalamic-pituitary-gonadal axis, *MKRN3* operates in an inhibitory mode. It is the first imprinted gene to be implicated in GnRH regulation. Genomic imprinting hypothetically evolved to control the dosage of developmentally important genes and occurs in about 100 mammalian genes.[113] Increasing evidence implicates epigenetic mechanisms in timing of puberty.[114] After identification of the association of *MKRN3* with puberty regulation, single nucleotide polymorphisms in imprinted gene regions were linked to the age of menarche, supporting puberty timing as a selective trait.[80] The availability of powerful new technologies has contributed to expanding our knowledge of the regulation of puberty and recognising the role of genetic imprinting in the control of the activation of GnRH secretion at the time of puberty initiation.[114] An increased understanding of puberty regulation will help to improve the treatment of reproductive disorders.

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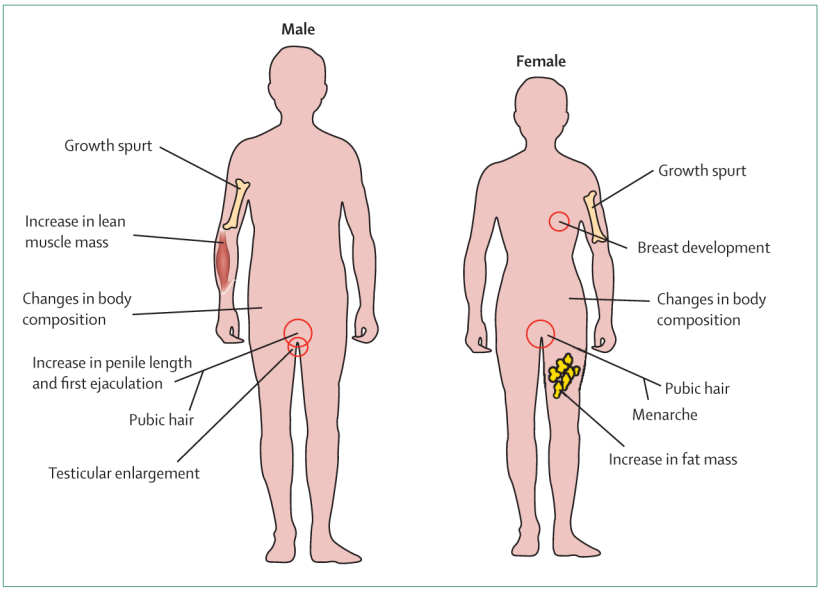

Figure 1. Physical changes and secondary sexual characteristics that appear during pubertal development

Changes in body composition are used to detect pubertal development. The figure shows the physical changes that occur as a result of the activation of the hypothalamic-pituitary-gonadal axis.

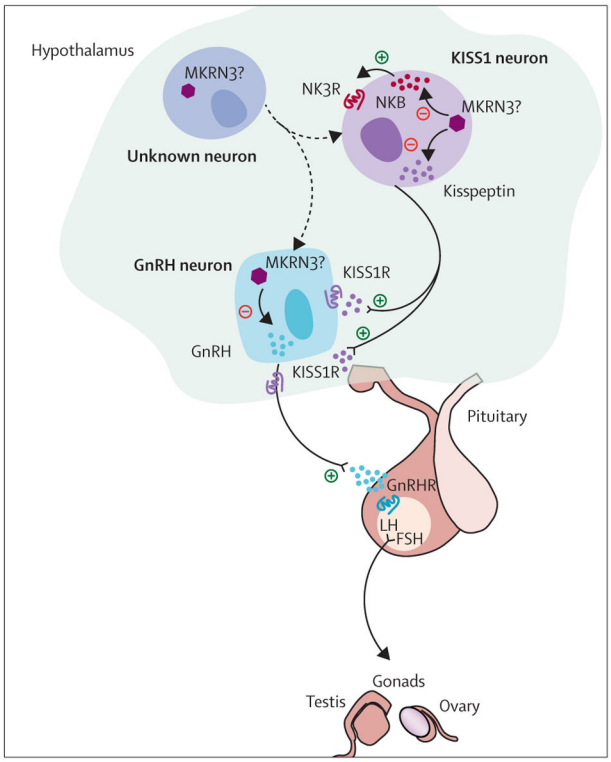

Figure 2. Mechanisms of action of the genetic factors involved in the control of puberty onset

Important regulators of GnRH have been identified in patients with pubertal disorders. The figure depicts essential regulators of GnRH secretion in which mutations have been identified in human beings. Dashed line represents proposed pathway. FSH=follicle-stimulating hormone. GnRH=gonadotropin-releasing hormone. GnRHR=gonadotropin-releasing hormone receptor. KISS1=kisspeptin. KISS1R=kisspeptin receptor. LH=luteinising hormone. MKRN3=makorin ring finger protein 3. NKB=neurokinin B. NK3R=neurokinin B receptor. +=stimulatory effect. –=inhibitory effect. ?=proposed mechanism.

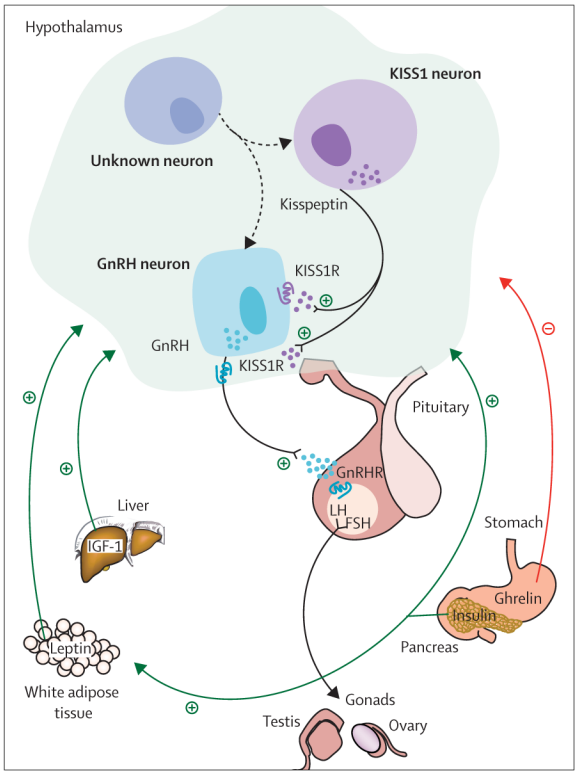

Figure 3.

Tentative model for the metabolic control of GnRH secretion by peripheral metabolic hormones

The peripheral hormones that transmit metabolic signals to GnRH neurons are shown: leptin, a signal for energy abundance, is a permissivefactor for GnRH secretion. Ghrelin, a putative signal of energy insufficiency, is an inhibitory factor for GnRH secretion. Insulin and IGF-1 have stimulatory effects on the reproductive axis. Dashed line represents proposed pathway. FSH=follicle-stimulating hormone. GnRH=gonadotropin-releasing hormone. GnRHR=gonadotropin-releasing hormone receptor. IGF-1=insulin-like growth factor 1. KISS1=kisspeptin. KISS1R=kisspeptin receptor. LH=luteinising hormone. +=stimulatory effect. –=inhibitory effect.

Table

Genes involved in the control of GnRH

	Locus	Protein	Inheritance	Phenotype	References
Stimulation of GnRH synthesis or secretion					
GNRHR	4q13.2	GnRH receptor	Autosomal recessive	Isolated hypogonadotropic hypogonadism	35, 46
KISS3	1q32.1	Kisspeptin	Autosomal recessive	Isolated hypogonadotropic hypogonadism and central precocious puberty	47, 48
KISS3R	19p13.2	Kisspeptin receptor	Autosomal recessive	Isolated hypogonadotropic hypogonadism and central precocious puberty	42, 43, 49
TAC3	12q13.3	Neurokinin B	Autosomal recessive	Isolated hypogonadotropic hypogonadism	44
TACR3	4q24	Neurokinin B receptor	Autosomal recessive	Isolated hypogonadotropic hypogonadism	44
GNRH3	8p21.2	GnRH	Autosomal recessive	Isolated hypogonadotropic hypogonadism	50, 51
Inhibition of GnRH synthesis or secretion					
MKRN3	15q11–13	Makorin ring finger protein 3	Paternally inherited	Central precocious puberty	52
GnRH migration					
KAL3	Xp22.31	Anosmin-1	X-linked	Kallmann’s syndrome	35, 46
FGFR3	8p11.2	Fibroblast growth factor receptor 1	Autosomal dominant	Kallmann’s syndrome or isolated hypogonadotropic hypogonadism	35, 46
FGF3	10q24.32	Fibroblast growth factor 8	Autosomal dominant	Kallmann’s syndrome or isolated hypogonadotropic hypogonadism	35, 46
PROK3	3p13	Prokineticin 2	Autosomal recessive	Kallmann’s syndrome or isolated hypogonadotropic hypogonadism	35, 46
PROKR3	20p12.3	Prokineticin receptor 2	Autosomal recessive	Kallmann’s syndrome or isolated hypogonadotropic hypogonadism	35, 46
CHD3	8p12.1	Chromodomain helicase DNA binding protein 7	Autosomal recessive	Kallmann’s syndrome or isolated hypogonadotropic hypogonadism	35, 46
SEMA3A	7q12.1	Semaphorin-3A	Autosomal dominant	Kallmann’s syndrome	35, 46
WDR33	10q26.12	WD repeat-containing protein 11	Autosomal recessive	Kallmann’s syndrome or isolated hypogonadotropic hypogonadism	35, 46
HS3ST3	2q.21	Heparan sulphate 6-O-sulphotransferase 1	Autosomal dominant	Kallmann’s syndrome or isolated hypogonadotropic hypogonadism	35, 46
FGF33, IL33RD, DUSP3,	··	Genes encoding components of	Autosomal dominant	Kallmann’s syndrome or isolated hypogonadotropic	53
SPRY3, and *FLRT3*		fibroblast growth factor pathway		hypogonadism	

GnRH=gonadotropin-releasing hormone.

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