Philip Kumanov
Ashok Agarwal *Editors*

Puberty

Physiology and Abnormalities

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Preface

'Twas strange that one so young should thus concern
His brain about the action of the sky;
If you think 'twas philosophy that this did,
I can't help thinking puberty assisted.

Lord Byron "*Don Juan*"
Canto the First, XCIII

The exact neuroendocrinological mechanisms that bring childhood to an end still remain unclear, and the subsequent period of puberty represents a sequence of profound hormonal, physical, and psychical changes. The social relationships of maturing individuals are likewise altered. The transition from girl to woman and from boy to man, respectively, is a time of raised concerns: Both parents and children constantly worry about growth and sexual maturation advancing normally. Some diseases, hidden to this point, become apparent. As a complex process of profound changes, puberty is one of the most vulnerable periods of life. No one has represented so skillfully the drama of those who are no longer children but not yet mature, overshadowed by the dark uncertainty of the future, as the Norwegian artist Edvard Munch in his masterpiece, *Puberty*.

With that in mind, the need for a comprehensive textbook on the growth and development of children, as well as on the most important abnormalities and deviations of puberty, is more than imperative. The responsibility of the medical community to growing children is substantial, as this period of transformation from childhood to maturity is crucial for lifelong health. An insufficient or inadequate approach to the mental or physical stability of adolescents may have serious consequences afterwards. The problem has escalated in the last few decades given the aging population and lower worldwide birth rates. Normal reproduction would be impossible without a healthy puberty.

This book is mainly clinically oriented but extends to also cover corresponding theoretical aspects. It will be useful for pediatricians, endocrinologists, gynecologists, andrologists, urologists, family practitioners, child psychologists, and public health specialists—all those who are challenged in their everyday practice with the

problems of puberty. The chapters are prepared by internationally reputed experts, whose contributions are thankfully acknowledged.

Throughout the book, the reader should keep in mind that the second most remarkable phenomenon, after birth of normal child, is its transition to a healthy mature person.

Edvard Munch “Puberty”
The National Museum of Art, Architecture and Design, Oslo
[Reprinted with kind permission from National Museum of Art, Architecture and Design]

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Abbreviations

BMD	Bone mineral density
BMI	Body mass index
BPA	Bisphenol A
CALIPER	Canadian Laboratory Initiative on Pediatric Reference Interval Database
CB1Rs	Cannabinoid-1 receptors
CBG	Cortisol binding globulin
CDGP	Constitutional delay of growth and puberty
CDP	Constitutional delayed puberty
CGIs	CpG islands
CYP19A1	Cytochrome P 450 19 A1
DBCP	Dibromochloropropane
DDT	Dichlorodiphenyltrichloroethane
DHEA	Dehydroepiandrosterone
DHEAS	DHEA-sulfate
DNMTs	DNA methyltransferases
e-cigarette	Electronic cigarette
EDC	Endocrine disrupting chemicals
endo-siRNAs	Endogenous sinus
FSH	Follicle stimulating hormone
GALP	Galanin-like peptide
GC-MS	Gas chromatography-mass spectrometry
GH	Growth hormone
GHBP	Growth hormone binding protein
GHD	GH deficiency
GHRH	GH-releasing hormone
GnRH	Gonadotropin-releasing hormone
GNRH	Gonadotropin-releasing hormone
GNRHR	Gonadotropin-releasing hormone receptor
H	Histone
HDM	Histone demethylases

HPC	Hypothalamic-pituitary-gonadal
HTM	Methyltransferases
IA(s)	Immunoassay(s)
ID-MS	Isotope dilution MS
IGF	Insulin-like growth factor
IGFBP	IGF-binding protein
IGF-I	Insulin-like growth factor-I
IHH	Idiopathic hypogonadotopic hypogonadism
IS	International standard
K	Lysine
KISS-1	Kisspeptin 1
LC-MS	Liquid chromatography coupled to mass spectrometry
LC-MS/MS	Liquid chromatography coupled to tandem mass spectrometry
LH	Luteinizing hormone
miRNAs	MicroRNAs
MS	Mass spectrometry
nAChR	Nicotinic acetylcholine receptor
NHANES	National Health and Nutrition Examination Survey
NIBSC	National Institute of Biological Standards and Control
NPY	Neuropeptide Y
PCBs	Polychlorinated biphenyls
POP	Persistent organic pollutants
QC	Quality control
RISC	RNA-induced silencing complex
SHBG	Sex hormone binding globulin
THC	Δ9-Tetrahydrocannabinol
TPs	Transition proteins
UTR	Untranslated region

Chapter 1
Maturation and Physiology of Hypothalamic Regulation of the Gonadal Axis

Yoshihisa Uenoyama, Naoko Inoue, Nahoko Ieda, Vutha Pheng, Kei-ichiro Maeda, and Hiroko Tsukamura

Introduction

It is well accepted that the hypothalamus plays a pinnacle role in the hierarchical control of the gonadal axis through the anterior lobe of the pituitary gland in mammals. The concept of hypothalamic regulation of the gonadal axis dates back to the late 1940s, when Geoffrey Harris and colleagues [1] predicted the presence of neurohumoral substances, which control the pituitary gland. By this time, two gonadotropins, i.e., follicle-stimulating hormone (FSH) and luteinizing hormone (LH), had already been isolated from the pituitary gland [2]. Intensive studies have been performed to isolate the predicted substance(s) controlling FSH and/or LH release. In the early 1970s, a decapeptide, which stimulates both FSH and LH release [3], was isolated from porcine and ovine hypothalami by two groups, led by Andrew Schally [4] and Roger Guillemin [5], respectively. The discovery of the gonadotropin-releasing hormone (GnRH) facilitated the studies on the involvement of hypothalamic neurotransmitters and neuropeptides in GnRH/gonadotropin release system during the last three decades of the twentieth century. It has become increasingly clear that the activity of GnRH neurons is under a complex influence of afferent inputs, which mediates the feedback action of gonadal steroids, timing of sexual

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maturation at puberty, drives estrous/menstrual cycles, and arrests gonadal activity under the adversity such as lactation, malnutrition, and diseases [6–11].

At the turn of the twenty-first century, discoveries via inactivating mutations of novel neuropeptide signaling, i.e., kisspeptin-GPR54 signaling, in humans suffering the hypogonadotropic hypogonadism, provided a breakthrough in our understanding of the hypothalamic mechanism controlling GnRH/gonadotropin release at the onset of puberty. This review focuses on our current understanding of how the hypothalamus regulates pubertal maturation of gonadal axis in mammals via GnRH/gonadotropin release.

Tonic GnRH/Gonadotropin Release Controls Pubertal Maturation of Gonadal Activity

There are two modes of GnRH/gonadotropin release in mammals. Males exhibit only tonic GnRH/gonadotropin release, whereas females exhibit both tonic and surge-mode GnRH/gonadotropin release. The tonic GnRH/gonadotropin release is characterized by its pulsatile nature, which was originally detected by a combination of frequent blood sampling and radioimmunoassay for LH in primates [12], and controls follicular development and maintenance of corpus luteum in females, and spermatogenesis in males, along with the steroidogenesis in both sexes. The surge-mode GnRH/gonadotropin release is observed at the mid-menstrual cycle in primates [13, 14] and the end of the follicular phase in other animals [15, 16] to trigger ovulation and the corpus luteum formation.

Sexual maturation at the puberty onset seems to be timed by an increase in tonic GnRH/gonadotropin release in several mammals examined to date [17–21]. Experimentally, a pioneer study by Ernst Knobil and colleagues demonstrated that intermittent GnRH stimulation to the pituitary at a physiological frequency observed in adulthood induced puberty onset in immature female rhesus monkeys and that its withdrawal reverted to the immature state [22]. This finding strongly suggests that an increase in tonic GnRH/gonadotropin release is the first step in the pubertal onset. Knobil and colleagues also established a method for electrophysiological recording of multiple unit neuronal activity (MUA) that is synchronized with LH pulses [23] and suggested that the neuronal activity recorded in the mediobasal hypothalamus could be derived from the so-called GnRH pulse generator. The periodic increase in electrical activity, called MUA volleys, is considered as a manifestation of GnRH release and seems to be suppressed in prepubertal animals. The onset of puberty, therefore, is considered to be dependent on the activation of the GnRH pulse generator.

KNDy Neurons as a Master Regulator of Tonic GnRH/Gonadotropin Release

An intrinsic source of the GnRH pulse generator had been deemed as a great enigma of the GnRH/gonadotropin-releasing system before the discovery of kisspeptin (first named metastin [24]). To date, the most plausible interpretation is that

kisspeptin neurons localized in the hypothalamic arcuate nucleus (ARC) (also known as KNDy neurons as described below) serve as a master regulator of tonic GnRH/gonadotropin release in mammals. A critical role of kisspeptin in puberty onset has emerged from clinical studies for familial hypogonadotropic hypogonadism, characterized by pubertal failure due to gonadotropin deficiency. Two years after the deorphanization of GPR54 as a receptor for kisspeptin in 2001 [24, 25], two studies demonstrated that inactivating mutations of *GPR54* gene caused pubertal failure in humans [26, 27]. Subsequently, the phenotype of humans with inactivating mutations of the *GPR54* gene was recapitulated in humans bearing inactivating mutations of the *KISS1* gene (coding kisspeptin) [28] and in rodent models carrying targeted mutations of *Kiss1* or *Gpr54* loci [27, 29–33]. In particular, *Kiss1* knockout rats showed a severe hypogonadotropic hypogonadal phenotype, suggesting an indispensable role of kisspeptin in pubertal maturation of gonadal axis in both sexes [33]. Because *Gpr54* gene expression in GnRH neurons is evident in rodents [29, 34], kisspeptin is thought to directly control GnRH release and thus gonadotropin release. Indeed, increasing evidence indicates that kisspeptin stimulates gonadotropin release via GnRH neurons in several mammals [34–36].

Clinical studies for hypogonadotropic hypogonadism also demonstrated a critical role of neurokinin B (NKB), a member of tachykinin family, in hypothalamic regulation of puberty onset. Inactivating mutations of *TAC3* (coding NKB) or its cognate *TACR3* (coding tachykinin NK3 receptor) gene were found in humans suffering from the hypogonadotropic hypogonadism [37–40]. It should be noted that kisspeptin, NKB, and an endogenous opioid, dynorphin A, are co-localized in a cohort of ARC neurons in mammalian species [41–43], and thus the cohort of neurons has now become known as the KNDy neurons for the names of three neuropeptides, such as kisspeptin, NKB, and dynorphin A. Our previous studies demonstrated that the neuronal activity accompanied with LH pulses is successfully detected in the area near the cluster of KNDy neurons in goats [43, 44], suggesting that KNDy neurons are an intrinsic source of the GnRH pulse generator. Based on the results currently available [43–45], we envision that NKB and dynorphin A regulate the intermittent discharge of KNDy neurons in an autocrine and/or paracrine manner, resulting in pulsatile GnRH/gonadotropin release. Indeed, our recent study indicates the involvement of NKB and dynorphin A in pubertal maturation of GnRH/gonadotropin release [46], i.e., chronic administration of tachykinin NK3 receptor agonist or kappa-opioid receptor antagonist facilitated puberty onset along with the induction of tonic LH release in female rats. This result suggests that a lack of NKB signaling and relatively high dynorphin A tone may play a key role in suppression of the intermittent discharge of KNDy neurons, which drive pulsatile GnRH/gonadotropin release. In other words, it is likely that an increase in NKB stimulation and/or decrease in the inhibitory tone of dynorphin A (#1 in Fig. 1.1) drives intermittent discharge of KNDy neurons and hence GnRH/gonadotropin release (#2 in Fig. 1.1), resulting in puberty onset along with follicular development in the ovary (#3 in Fig. 1.1). Double-labeled immunoelectron microscopic studies indicate that an action site of kisspeptin seems GnRH neuronal terminals in the median eminence, where kisspeptin exerts stimulatory influence on GnRH neurons via volume transmission [47, 48]. Direct evidence for pubertal increase in kisspeptin release was proposed

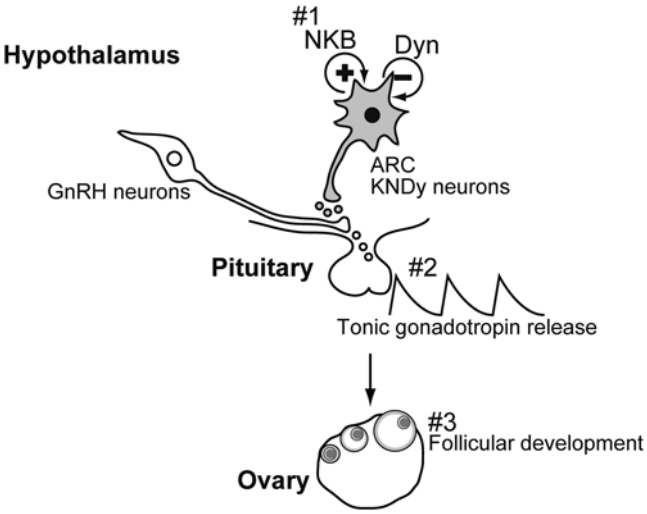

Fig. 1.1 Schematic illustration showing the possible hypothalamic mechanism regulating pubertal increase in GnRH/gonadotropin release in female mammals. KNDy neurons localized in the hypothalamic arcuate nucleus (ARC) play a key role in pubertal increase in GnRH/gonadotropin release in mammals. At the onset of puberty, an increase in neurokinin B stimulation and/or decrease in the inhibitory tone of dynorphin A (#1) may drive the intermittent discharge of KNDy neurons in an autocrine/paracrine manner. Kisspeptin stimulates tonic GnRH release at the median eminence and thus gonadotropin secretion (#2), which times puberty onset along with the follicular development in females (#3)

from a previous study, in which Keen et al. [49] showed a pubertal increase in both kisspeptin and GnRH release and coordinated release of pulsatile kisspeptin and GnRH at the median eminence in rhesus monkeys.

Estrogen-Dependent and Estrogen-Independent Prepubertal Restraint of GnRH/Gonadotropin-Releasing System

The GnRH/gonadotropin-releasing system seems to be already matured before the onset of puberty. Indeed, ARC *Kiss1* gene expression and pulsatile LH release immediately increased after ovariectomy in prepubertal rats [50, 51]. Estrogen replacement restores the prepubertal restraint of the ARC *Kiss1* gene expression and LH pulses in female rats [50, 51], suggesting that the prepubertal suppression of the tonic GnRH/gonadotropin-releasing system is dependent on a circulating estrogen derived from the immature ovaries. A possible mechanism involved in the prepubertal restraint of tonic GnRH/gonadotropin-releasing system is illustrated in Fig. 1.2. Based on the results currently available [50, 51], we envisage that estrogen derived from the immature ovaries (#1 in Fig. 1.2) may play a key role in prepubertal suppression of ARC *Kiss1* gene expression (#2 in Fig. 1.2), resulting

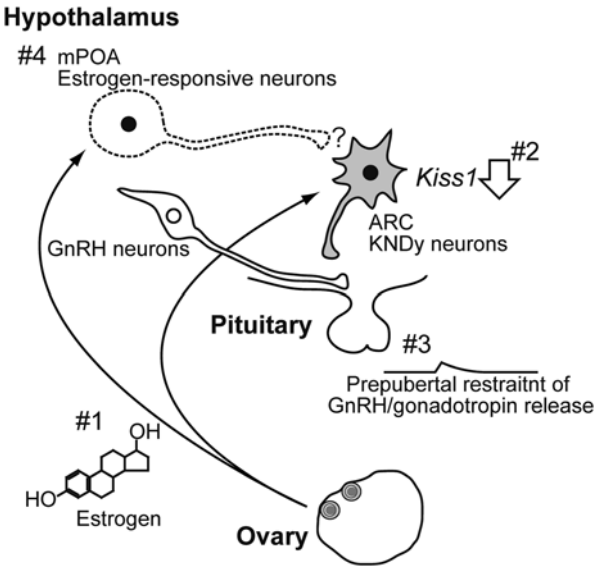

Fig. 1.2 Schematic illustration showing a possible mechanism regulating the pubertal restraint of the GnRH/gonadotropin release system in female mammals. During the prepubertal period, estrogen derived from the immature gonads (#1) strongly suppresses ARC *Kiss1* gene expression in KNDy neurons (#2) and hence GnRH/gonadotropin release (#3). Estrogen may exert an inhibitory influence on ARC *Kiss1* gene expression via direct or indirect pathways (#1). Estrogen-responsive neurons in the medial preoptic area (mPOA) may exert an inhibitory influence on GnRH/gonadotropin release via suppression of ARC *Kiss1* gene expression (#4)

in a restraint of tonic GnRH/gonadotropin release during the prepubertal period (#3 in Fig. 1.2). Since kisspeptin neuron-specific estrogen receptor α (ERα) knockout mice show precocious puberty onset along with a higher ARC *Kiss1* gene expression than wild-type mice [52], estrogen-dependent prepubertal restraint of *Kiss1* gene expression and LH pulses would be directly mediated by ERα in ARC KNDy neurons. Similarly, in males, the prepubertal suppression of the tonic GnRH/gonadotropin-releasing system seems dependent on a circulating testosterone derived from the immature testes, because castration increases plasma LH levels in prepubertal male rats [53].

In addition to the direct inhibitory effect on ARC *Kiss1* gene expression, estrogen may indirectly inhibit *Kiss1* gene expression and/or GnRH/gonadotropin-releasing system during the prepubertal period. Our recent study showed that site-specific micro-implants of estradiol in the medial preoptic area (mPOA) or ARC restored suppression of LH pulses in prepubertal ovariectomized rats [50]. This suggests that estrogen-responsive neurons, at least, in the mPOA and ARC, are involved in the estrogen-dependent prepubertal restraint of GnRH/gonadotropin-releasing system in female rats. Given the critical role of kisspeptin and NKB in pubertal maturation in humans and rodents, KNDy neurons could be a first candidate for the estrogen-responsive neurons in the ARC. Additionally,

estrogen-responsive neurons in the mPOA may exert an inhibitory influence on ARC *Kiss1* gene expression (#4 in Fig. 1.2).

The inhibitory influence of estrogen on ARC *Kiss1* gene expression and GnRH/gonadotropin release appears to decrease during the pubertal transition, resulting in upregulation of ARC *Kiss1* gene expression and GnRH/gonadotropin release [51]. This scenario is consistent with the classical gonadostat hypothesis [54] that changes in hypothalamic sensitivity to negative feedback action of estrogen are associated with pubertal maturation of the GnRH/gonadotropin-releasing system in rodents. We envisage that pubertal decrease in the responsiveness to estrogen in ARC KNDy neurons plays a role in pubertal increase in *Kiss1* gene expression. It is unlikely that changes in responsiveness to estrogen negative feedback action during the pubertal transition are simply caused by a change in the expression of ERα, because our previous study showed that the number of ERα-expressing cells and *Esr1* gene (encoding ERα) expression in the POA and ARC was comparable between pre- and postpubertal periods in female rats [50]. Further studies are warranted to address this issue.

It should be noted that the central mechanism controlling the prepubertal restraint of GnRH/gonadotropin-releasing system in primates appears to differ from other species such as rodents and sheep [10, 11]. In monkeys, gonadectomy induces an increase in gonadotropin release during the neonatal period and after the onset of puberty, but not during the prepubertal period [11]. This indicates that both steroid-dependent and steroid-independent pathways are responsible for restraint of GnRH/gonadotropin-releasing system. Terasawa and Fernandez [10] suggest that the steroid-independent inhibition may be due to the abundant synaptogenesis in primate brain than other species and that the decrease in the number of synapse to the adult levels could lead to pubertal increase in GnRH/gonadotropin release via removal of inhibitory inputs in primates. The characteristic steroid-independent restraint period of GnRH/gonadotropin-releasing system in primates is called the juvenile period [55]. In humans, the juvenile hiatus in GnRH/gonadotropin secretion is seen between the ages of 4–9 years [55], even in girls suffering from Turner syndrome with gonadal dysgenesis [56] and boys with testicular defects [57], both which exhibit elevated plasma gonadotropin levels in infantile and peripubertal period.

Cues Relieving Prepubertal Restraint of GnRH/Gonadotropin-Releasing System

It is well demonstrated that the timing of puberty onset is dependent on body weight rather than chronological age [58]. Epidemiologic studies showed that age of menarche in girls declined from 17 years old in the nineteenth century to 13 years old in the twentieth century in developed countries [58]. This secular trend can be understood in terms of the faster somatic growth in humans in the twentieth century [58].

Thus, nutritional cues are likely to contribute to the regulation of pubertal maturation of GnRH/gonadotropin-releasing system. Energy storage in the body fat has been considered to be a possible determinant for the onset of puberty for a long time [59, 60]. Leptin, the first hormone discovered from fat tissue [61, 62], was then considered as a signal that relays the attainment of energy storage to the brain, because leptin-deficient mice do not show puberty and exogenous leptin restores fertility [63]. In fact, the leptin receptor is expressed in several hypothalamic and extra-hypothalamic nuclei including ARC [64]. Recently, KNDy neurons were found to express leptin receptors [65]. Mice with a leptin deficiency showed decreased ARC *Kiss1* gene expression [65], suggesting that leptin seems to be a nutritional cue relieving the prepubertal restraint of GnRH/gonadotropin-releasing system. Leptin, however, could be a prerequisite of normal puberty, because the increase in leptin secretion is not necessarily synchronized with the onset of puberty [58].

In addition to nutrition, the photoperiod tightly regulates the timing of puberty onset in seasonal breeders such as sheep and Syrian hamsters. Foster et al. [18] clearly showed that the onset of puberty is postponed to the next breeding season in lambs, which achieved critical body size in late winter. Earlier studies showed that *Kiss1* gene expression is higher in the breeding season than in the nonbreeding season in sheep and Syrian hamsters [66, 67]. Taken together, KNDy neurons may integrate multiple external cues, such as nutrition or photoperiod, to control pubertal maturation of the GnRH/gonadotropin-releasing system.

Conclusions and Unanswered Questions

Studies during the last few decades have provided a new framework for the understanding of pubertal maturation of hypothalamic regulation of gonadal axis in mammals. It is now well accepted that KNDy neurons are responsible for the regulation of pubertal increase and GnRH/gonadotropin release in mammals. But, there are still some important unanswered questions. Little is known about the cellular and molecular mechanisms controlling the prepubertal restraint of and pubertal increase in kisspeptin biosynthesis, which is tightly controlled by steroid-dependent and steroid-independent mechanism. In particular, mechanisms underlying the relationship between nutritional statuses and relieving the prepubertal restraint of kisspeptin biosynthesis are still unanswered questions. Further studies, therefore, are needed to fully elucidate the pubertal maturation of hypothalamic mechanism regulating gonadal axis in mammals.

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