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Puberty and Resonance: A Hypothesis

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Abstract

A new mechanism for puberty is proposed. Puberty appears to result from the interaction of two physiologic oscillators within the hypothalamus: the arcuate nucleus, which produces the gonadotropin-releasing hormone, and the suprachiasmatic nucleus, which is a master oscillator that regulates many circadian rhythms. Puberty results when the frequency of the arcuate nucleus has slowed sufficiently to resonate with a harmonic of the suprachiasmatic nucleus rhythm. The onset of puberty is earlier in blind girls and rats reared in darkness because they have circadian rhythms which are more rapid than usual. Therefore, the frequency of the arcuate nucleus does not have to slow as much to resonate with the same harmonic of the suprachiasmatic nucleus rhythm, and puberty can occur at an earlier age. The proposed mechanism also accounts for the occurrence of luteinizing hormone pulses only during sleep in early puberty, and for the elevation of gonadotropins at birth.

Puberty, the transitional period between childhood and adulthood, is accompanied by the appearance of secondary sexual characteristics and the achievement of fertility. In mammals, the central nervous system exercises the only restraint to puberty onset. This neuroendocrine control is mediated by the gonadotropin releasing hormone (GnRH) secreting neurons in the arcuate nucleus of the hypothalamus (1). For many years, a "gonadostat" or feedback mechanism was believed to explain the relatively sudden onset of puberty. Recent evidence, however, has cast doubt on the gonadostat hypothesis; few investigators in the field today still believe that it is correct. This article proposes a new explanation for the onset of puberty, the physical phenomenon of *resonance*.

The Gonadostat Hypothesis

The basis of the gonadostat hypothesis is the pituitary hypertrophy that occurs after castration. This phenomenon was familiar to physiologists at the beginning of this century and is clearly described in a comprehensive article on the pituitary written by Harvey Cushing in the autumn of 1909 (2, 3). In 1936 Hohlweg found that estradiol treatment was more effective suppressing castration hypertrophy in prepubertal rats than in adult rats (4). Hohlweg's observation provided the rationale for the view, later put forward by Ramirez and McCann (5), that puberty is caused by a sudden decrease in sensitivity of the hypothalamic-pituitary unit to sex hormone feedback. The immature gonads were known to produce small amounts of sex steroids, even in very young animals. These hormones were believed to inhibit the hypothalamic-pituitary production of the gonadotropins, follicle stimulating hormone (FSH), and luteinizing hormone (LH). It was hypothesized that around the time of puberty, the hypothalamic-pituitary axis lost its sensitivity to such small amounts of sex steroids, a sudden outpouring of gonadotropins occurred, and puberty was the result. In other words, the "gonadostat" had been reset and would only respond to the feedback effect of much higher levels of sex hormones.

In the past few years, assay techniques that make possible the continuous measurement of gonadotropin levels have cast doubt on the gonadostat hypothesis. These measurements reveal that LH, for example, is elevated not only at puberty but also at birth in both rats and humans (Fig. 1). In humans, LH falls between the ages of two and four, then rises again at puberty. This fluctuation, which corresponds with the period of

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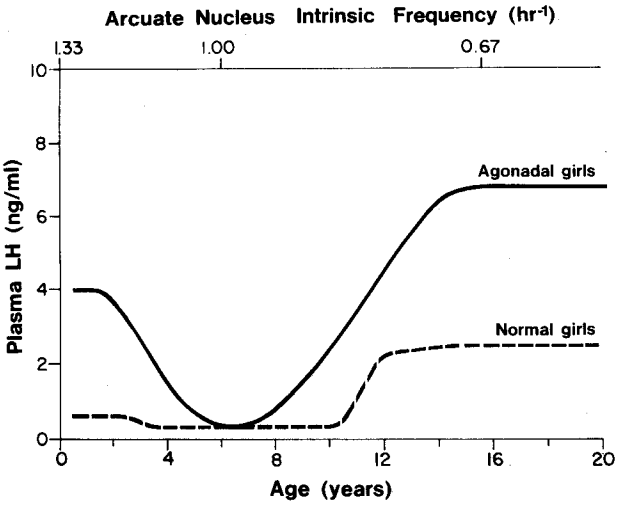

FIG. 1. (Modified from Grumbach, reference no. 1): The high LH levels at birth and puberty, in both normal and agonadal girls, can be accounted for by a continually slowing arcuate nucleus intrinsic frequency after birth.

infant sexuality and subsequent latent period posited by Freud (6), is especially prominent in agonadal children; it cannot be explained adequately on the basis of the gonadostat hypothesis. Further, the sensitivity of the pituitary-hypothalamic axis does not appear to change appreciably during development (7). These observations imply that the phenomenon observed by Hohlweg is a result rather than a cause of puberty onset (8).

Fertility and Circadian Rhythms

The reproductive cycle of mammals is closely related to the 24-hour light : dark cycle and circadian rhythms (9). For example, during long nights and short days or after blinding, gonadal atrophy will occur in the Syrian golden hamster, *Mesocricetus auratus*. This phenomenon has been shown to be mediated by stimulation of the pineal gland (10). Moreover, the four-day estrus cycle of hamsters is closely coupled to the length of the light : dark cycle. A normal hamster living in a 24-hour light : dark cycle has an estrus cycle of 96 hours (4 × 24); whereas a hamster maintained under constant dim illumination with a free running circadian rhythm of 24.5 hours has an estrus cycle of 98 hours, that is, 4 × 24.5 (9).

Puberty, too, is affected by the light:dark cycle. Blind girls have their menarche earlier than sighted girls (11, 12), and rats reared in constant darkness have vaginal opening earlier than rats reared in an eight hour light : sixteen hour dark cycle (13). Other investigators have attributed this acceleration of puberty to a pineal effect. However, such an effect would be paradoxical, since blindness or darkness stimulates the pineal, resulting in gonadal atrophy (10).

A more plausible explanation is that acceleration of the normal 24 hour circadian rhythms has accelerated puberty. These rhythms are generated in rats, hamsters, and probably higher mammals as well by a hypothalamic structure, the suprachiasmatic nucleus or SCN (14). The SCN rhythm is exactly synchronized with the external light-dark cycle by impulses received from the eyes through a retinohypothalamic projection. In a blind animal or an animal kept in constant darkness or constant dim illumination, the SCN rhythm is free running, that is, somewhat greater or less in frequency than one cycle in 24 hours. The SCN is believed to be a master clock or *zeitgeber*, probably driving other physiologic rhythms, including plasma corticosterone levels and pineal N-acetyltransferase levels in rats. In blinded animals these rhythms are also free running, though synchronized with each other (15).

Blind adult human beings are known to have a free running frequency of about one cycle in 25 hours (16), but the free running frequency of children is unknown. One may, therefore, suggest that the free running frequency of a child is greater than one cycle in 24 hours—perhaps one cycle in 21 hours—and slows with age. Such slowing with age has recently been demonstrated in hamsters (17).

There are two possible ways of explaining how accelerated circadian rhythms could accelerate puberty. One way is to postulate that an animal needs a certain critical number of rhythmic stimuli to trigger puberty. In the rat, which has vaginal opening at about 38 days, 38 such stimuli would obviously be necessary. But in a rat on a 21-hour light : dark cycle, 38 stimuli could be given in about 33 days (that is, 21/24 × 38), thus accelerating puberty (Fig. 2), a fact which has been demonstrated experimentally (18). Attractive though this explanation may be, it fails to account for two important facets of the childhood-puberty-adulthood sequence: (a) the elevation of gonadotropins at birth, and (b) the pulses of LH occurring every 1½ hours only during sleep at the onset of puberty in humans; these pulses later occur continuously every 1½ hours throughout the day (19). However, the physical conditions of oscillation and resonance can explain all of these factors.

Oscillation and Resonance

Work by Knobil and others suggests that the gonadotropin-releasing hormone secreting cells of

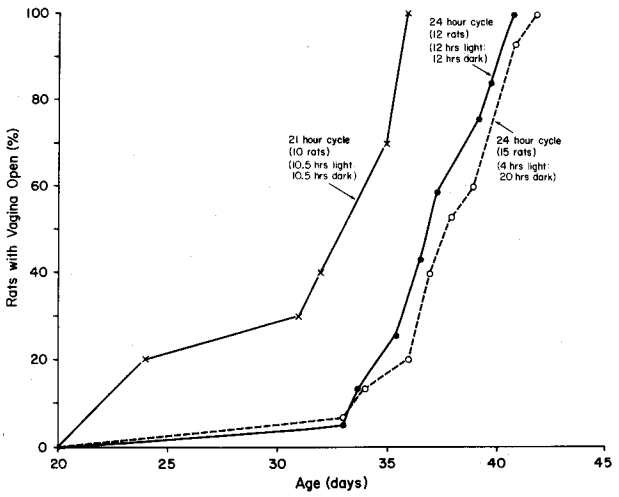

FIG. 2. Rats reared on a 21-hour light : dark cycle (10.5 : 10.5) had vaginal opening significantly ($p < 0.01$) earlier than rats reared on two variants of a 24-hour light : dark cycle (12 : 12 or 4 : 20).

the arcuate nucleus are an independently functioning oscillator with their own intrinsic or free-running frequency (20, 21). But in a normal, intact animal, the oscillation of the arcuate nucleus interacts with the *zeitgeber,* the SCN. As the animal approaches puberty, the frequency of the arcuate nucleus slows and resonance, which is well documented in animals (22), occurs.

Hormonal surges increase in intensity at this time because in any oscillating system, the amplitude of the oscillations surges to a maximum at resonance. This may be likened to the motion of a swing being pushed periodically. When the pushes occur with a frequency other than the intrinsic one of the swing, the displacement of the swing is rather small. But as the frequency of the pushes approaches the intrinsic frequency of the swing, the displacement of the swing becomes larger and larger. Resonance is said to occur when an oscillating system, be it swing or arcuate nucleus, is acted on by a periodic series of impulses (from the SCN in the case of puberty) having a frequency equal or nearly equal to its intrinsic frequency.

This explanation is most satisfactory if the SCN is postulated to be acting on the arcuate nucleus with an ultradian frequency of one cycle in 1½ hours (that is, 0.67 cycle per hour) rather than one cycle in 24 hours. Such an ultradian frequency is possible according to the laws of physics because it is an integral multiple or harmonic of the fundamental frequency of the SCN (that is, 16 × 1/24). Further, ultradian oscillations of this frequency and the existence of more than one intrinsic frequency are well documented in humans and other animals (22, 23).

An animal on a 21-hour light : dark cycle would have an ultradian rhythm more rapid than 0.67 cycle per hour, since this rhythm is a multiple of and coupled to the SCN rhythm. As a result, the arcuate nucleus rhythm would not have to slow as much for resonance to occur, and puberty would take place at an earlier age (Fig. 3).

The high LH level at birth can also be explained. If the frequency of the arcuate nucleus of an infant is very much higher than in an adult, specifically 1.33 cycles per hour, resonance with the ultradian rhythm of the SCN will occur, since 1.33 cycles per hour is an integral multiple (harmonic) of 0.67 cycle per hour (that is, almost 2 × 0.67). As the frequency of the arcuate nucleus slows between four and eight years of age, resonance is lost and LH levels drop. But when the frequency of the arcuate nucleus has slowed to 0.67 cycle per hour, resonance again occurs, resulting in the gonadotropin surge necessary for secondary sexual development (Fig. 1). The surges at puberty may be greater than the neonatal surges because of the growth and maturation of the brain that have taken place during the interval, or because resonance may not occur as readily at the higher fundamental frequency, 1.33 cycles per hour.

An interesting characteristic of the data in Fig. 1 is the apparent logarithmic slowing of the intrinsic frequency of the arcuate nucleus with time, especially evident in the agonadal girls. The peak LH level in infancy occurs at age 1.6, the minimum at age 5, and the peak pubertal level at

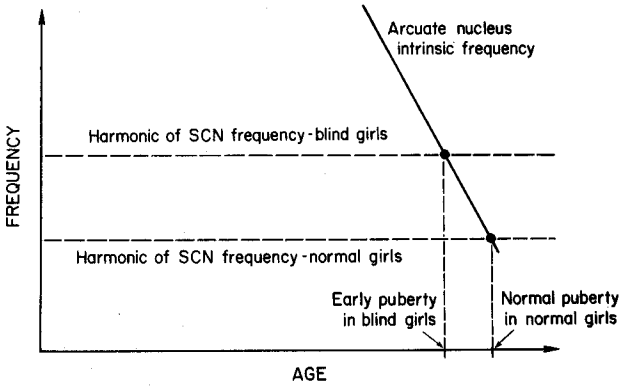

FIG. 3. Blind girls (and rats reared in constant darkness) probably have higher than normal suprachiasmatic nucleus (SCN) frequencies and corresponding harmonics. As a result, the intrinsic frequency of the arcuate nucleus does not have to slow as much for resonance to occur, and puberty can take place at an earlier age.

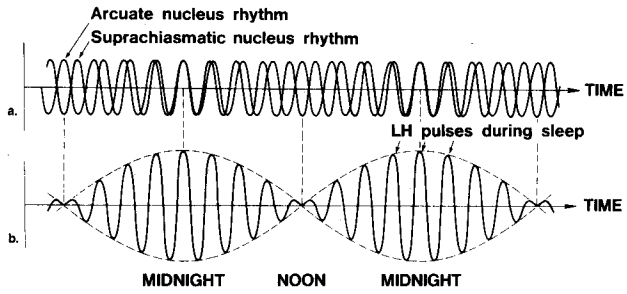

FIG. 4. The beat phenomenon. Two rhythms of slightly different frequencies, shown in (a), combine in (b) to produce a rhythm whose amplitude (broken line) varies periodically with time. This variation may account for the LH pulses which occur only during sleep in early puberty.

age 16 (1); the logarithms for each of these ages are as follows:

age	1.6	5	16	50
log age	0.2	0.7	1.2	1.7

The logarithmic difference between each of these age-points is 0.5. Thus, the next theoretically complete loss of resonance, comparable to that at age 5, would occur at age 50—around the time of menopause.

The mechanism of resonance can account for the LH pulses that occur during sleep in early puberty. At early puberty, the frequency of the arcuate nucleus is very close to the ultradian frequency of the SCN. When two oscillators of very nearly the same frequency interact, the phenomenon known as "beats" will occur (Fig. 4); the rhythms combine to give a rhythm whose amplitude varies periodically with time. Such a mechanism is familiar in mammals, having already been invoked to explain the hormone level variations in the rat estrus cycle (24). In the phenomenon of puberty, the beats correspond with the LH pulses during sleep.

In addition, the beat phenomenon appears to be related to the connection between time of puberty onset in girls and body weight. Very lean girls undergo menarche later than girls with more adipose tissue (25); a specific fat-to-lean mass ratio must be present for the onset of menarche. The resonance mechanism of puberty suggests that extreme leanness increases the frequency of the arcuate nucleus. One would therefore expect that rapid loss of weight in a young postpubertal woman might restore LH "beats" during sleep; this, in fact, has been observed to occur (26).

Thus, as this article attempts to demonstrate, many of the characteristics of puberty can be explained as the simple interaction between two groups of oscillating cells within the brain, the arcuate nucleus and the suprachiasmatic nucleus.

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