

# Continuation of Gradual Weight Gain Necessary for the Onset of Puberty May Be Responsible for Obesity Later in Life

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**Abstract:** A continuation of the gradual weight gain necessary for the onset of puberty may be responsible for obesity later in life. Hypothetically, a group of brain nuclei form components of a single pubertal clock mechanism that drives pre-pubertal weight gain and governs the onset of puberty and fertility. No mechanism evolved to shut off pre-pubertal and pubertal weight and body fat gain after puberty. The weight gain continues unabated throughout life. A better understanding of the mechanism of puberty and pre-pubertal weight gain could provide new insights into obesity and diseases associated with obesity such as type 2 diabetes, dyslipidemia, hypertension, heart disease, depression, etc. [*Discovery Medicine* 20(110):191-196, October 2015]

What causes us to gain weight as we age? Why don't we lose weight as we get older?

Mozaffarian *et al.* (2011) wrote that average long-term weight gain in non-obese populations is gradual but accumulates over time, and can be caused by life style changes, diet, and exercise.

Another cause may be the steady weight and body fat gain required for the onset of puberty. Hypothetically, a group of brain nuclei form components of a single pubertal clock mechanism that drives pre-pubertal weight gain and governs the onset of puberty and fertility. However, no mechanism evolved to shut off the constant weight and body fat gain needed for puberty, after puberty has occurred. The pre-pubertal and puber-

tal weight gain continues throughout life.

## Fertility and the Light:Dark Cycle

The reproductive cycle of mammals is closely related to the 24-hour light:dark cycle and circadian rhythms (Tamarkin *et al.*, 1985). For example, during long nights and short days or after blinding, gonadal atrophy will occur in the Syrian golden hamster, *Mesocricetus auratus*. This phenomenon is mediated by stimulation of the pineal gland (Hoffman and Reiter, 1965; Reiter, 1980; Reiter *et al.*, 2011a; 2011b). 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 x 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 x 24.5 (Zucker, 1980).

It appears that cycle durations are quite similar per one cycle. But over time (weeks or months for animals and years for humans), the small difference per cycle will add up, leading to earlier or later occurrence of puberty or menarche.

## Oscillators (Pulse Generators) in the Brain

The suprachiasmatic nucleus (SCN) of the mammalian hypothalamus has been referred to as the master circadian pacemaker that drives daily rhythms in behavior and physiology (Abe *et al.*, 2002). There is also evidence for extra-SCN circadian oscillators, in particular the arcuate nucleus, which is responsible for the hourly gonadotropin pulses necessary for puberty and fertility (Pohl and Knobil, 1982). Indeed, the brain contains multiple damped circadian oscillators outside the SCN. The phasing of these oscillators to one another may play a critical role in coordinating brain activity and its adjustment to changes in the light:dark cycle (Abe *et al.*, 2002).

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## Mechanism of Puberty

A pivotal event in the onset of puberty in mammals is the resumption of pulsatile release of gonadotropin-releasing hormone (GnRH) from neurons of the hypothalamus. Known influences on the timing of this event in mammals include the light:dark cycle, leptin levels, and the increased expression of neurokinin B, kisspeptin, and their receptors, NK3R and KISS1R (Hughes, 2013).

One familial version of precocious puberty is the result of mutations in a paternally expressed imprinted gene, MKRN3, which encodes makorin RING-finger protein 3 (Abreu *et al.*, 2013). Imprinted genes have a sex bias. They are expressed only from the maternal or the paternal chromosome. Some genes are paternally imprinted, whereas others are maternally imprinted. MKRN3 is maternally imprinted, and expression from the maternally inherited copy of the gene is silenced. MKRN3 protein is synthesized from RNA transcribed only from the paternally inherited copy of the gene. Makorin proteins are prolifically expressed in the developing brain, especially within the arcuate nucleus, the function of which is necessary for puberty and fertility.

Delayed puberty and estrogen resistance have been described in a woman with an estrogen receptor  $\alpha$  variant. This woman had no breast development and distinctly elevated serum levels of estrogens, as well as bilateral multi-cystic ovaries (Quaynor *et al.*, 2013).

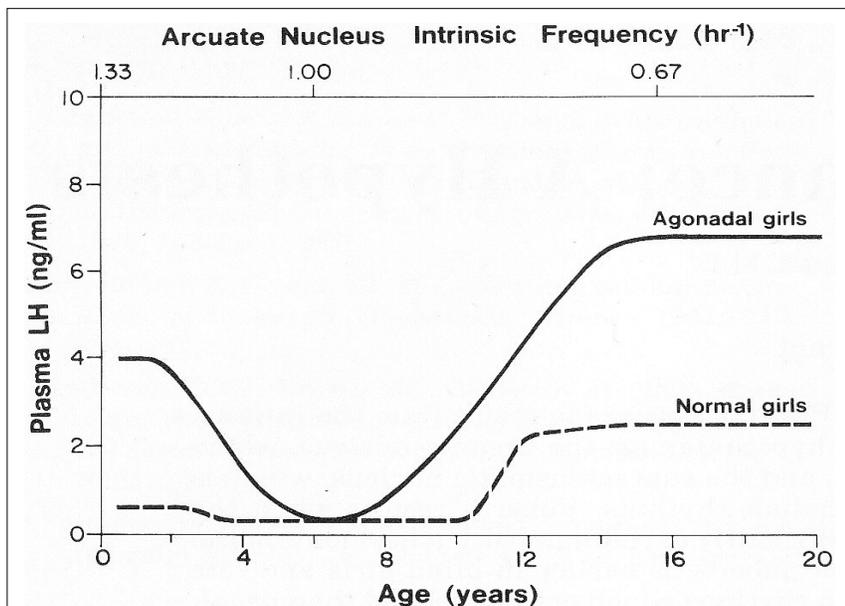
Yet despite many physiologic studies, there is no agreement as to what mechanism or mechanisms may actually trigger the onset of puberty. It is not known why puberty starts at about the age at the junction of the first and second decades of human life.

Lehrer (1983) has proposed that clock genes in the brain (Hastings, 1998) and the resonance of brain oscillators and circadian rhythms cause puberty (Sizonenko, 2000). This resonance mechanism can explain three apparently unrelated characteristics of puberty:

1. The gonadotropins are elevated at birth. Luteinizing hormone (LH), for example, is high not only at puberty but also at birth in both rats and humans (Figure 1). In humans, LH falls between the ages of two and four, then rises again at puberty (Grumbach, 1980). This fluctuation, which corresponds with the period of infant sexuality and subsequent latent period described by Freud (Freud, 1905), is especially prominent in agonal children. The high LH levels at birth and puberty, in both normal and agonal girls, can be accounted for by continual reduction in arcuate nucleus intrinsic frequency after birth, with resonance at birth and puberty, the resonance at birth occurring at twice the intrinsic frequency of the resonance at puberty.

2. Blind girls have their menarche earlier than sighted girls (Zacharias and Wurtman, 1964), and rats reared in constant darkness have vaginal opening earlier than rats reared in an eight hour light:sixteen hour dark cycle (Relkin, 1967). The onset of puberty is probably earlier in blind girls and rats reared in darkness because they have circadian rhythms which are more rapid than usual; the entrainment of these rhythms and the SCN to the daily light:dark cycle does not occur and they free-run. Therefore, the intrinsic frequency of the arcuate nucleus does not have to diminish as much to resonate with the same harmonic (frequency multiple) of the suprachiasmatic nucleus rhythm, and puberty can occur at an earlier age (Figure 2).

3. Hourly LH pulses occur only during sleep in early puberty (Boyar *et al.*, 1972), but occur throughout the day and night in adulthood. At early puberty, the intrinsic frequency of the arcuate nucleus is very close, but not equal to, the frequency of the brain oscillator entrained to the SCN, with which it resonates at sexual maturity. When two



**Figure 1.** The high LH levels at birth and puberty, in both normal and agonal girls, can be accounted for by a continual reduction of arcuate nucleus intrinsic frequency after birth. (Modified from Grumbach, 1980).

oscillators of very nearly the same frequency interact, the “beat” phenomenon occurs (Figure 3). 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 (Yochim and Shirer, 1981). At puberty, the beats correspond with the LH pulses during sleep.

Note that the resonance mechanism for puberty is basically the description of a clock. A mechanical clock has an oscillator (pendulum) and counts pendulum swings (oscillations). When the clock mechanism has counted a specified number of oscillations, it chimes. When the pubertal clock counts a specific number of oscillations, i.e., light:dark cycles, puberty occurs.

### Testable Hypothesis #1

Characteristics 1 and 3 combined provide a testable hypothesis of the resonance mechanism of puberty. As the LH pulsations in early childhood decline in amplitude (Figure 1), at about the age of three years the pulses may occur only during sleep as they do during the increase in amplitude during early puberty. This would be consistent with a common mechanism underlying LH changes in both periods.

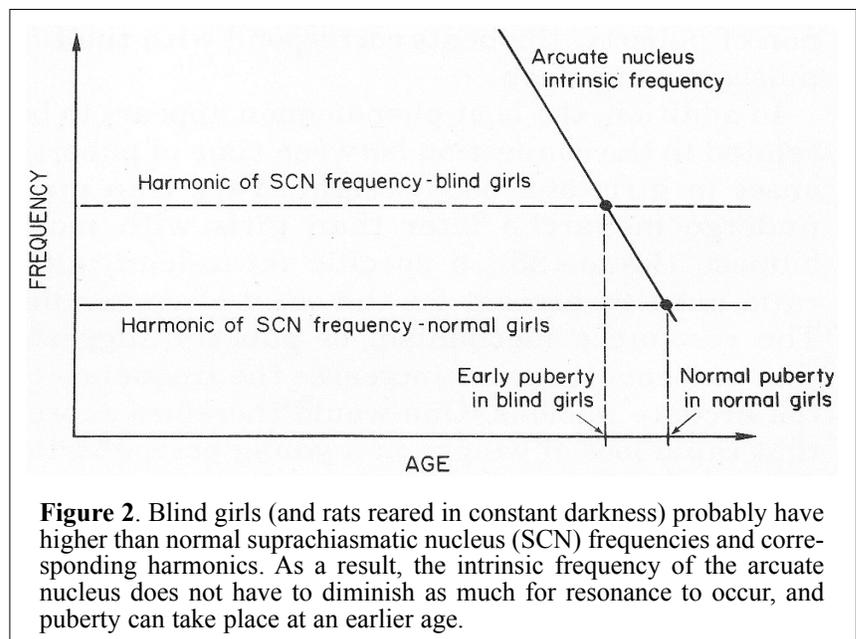
The gonadotropin pulses are present in early childhood, though at significantly diminished amplitude, insufficient to stimulate gonadal activity (Hayes and Crowley, Jr, 1998). But no 24 hour studies of their levels, comparable to the studies of early puberty (Boyar *et al.*, 1972), have been done.

### Body Fat, Weight Gain, Puberty, and the Light: Dark Cycle

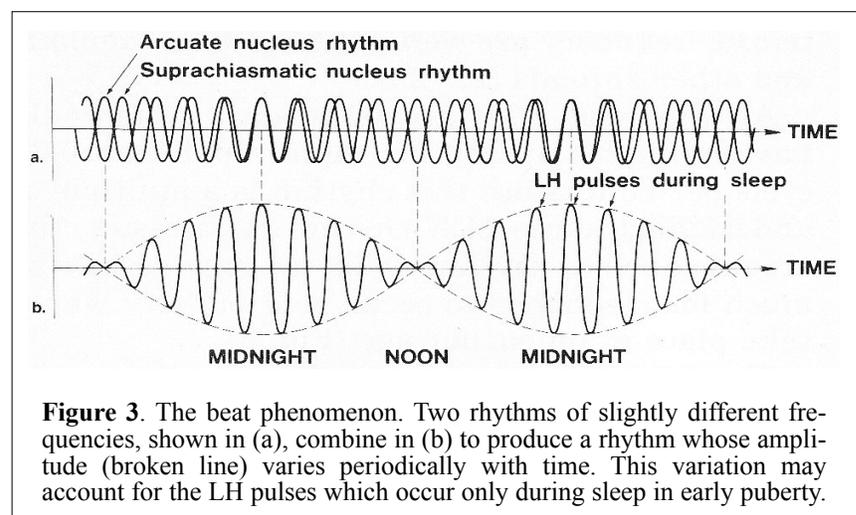
Frisch and colleagues reported that reduction in fat/lean ratio in young ballerinas and college athletes delays onset of menarche (Frisch *et al.*, 1980). Moreover, estrus is simultaneous with vaginal opening in 81% of rats on a high-fat diet, in comparison to 48% on low-fat diets, suggesting that a critical body composition of fatness is essential for fertility of the rat and the human female (Frisch *et al.*, 1975).

Pre-puberty (childhood) obesity is recognized as a major risk factor for adult obesity, and has been rising dramatically in the West (Poskitt and Edmunds, 2008). Analyses from two nationally representative samples of U.S. girls suggest a drop of about 2½ months in the average age of menarche during the time period between 1963-1970 and 1988-1994. This drop was paralleled by a concurrent shift in the population distribution of body mass index toward higher relative weights (Anderson *et al.*, 2003).

Although boys do not have a marker of puberty as distinctive as menarche, their body mass index increases constantly throughout childhood and they too seem to require the same critical fatness for puberty to occur (Mantzoros *et al.*, 1997; Vizmanos and Marti-



**Figure 2.** 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 diminish as much for resonance to occur, and puberty can take place at an earlier age.



**Figure 3.** 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.

Henneberg, 2000).

Pubertal weight gain is related to the length of the daily light:dark cycle. Rats on a 22.5 hour light:dark cycle have early vaginal opening (Lehrer, 1986) and more weight gain than rats on a 25 hour cycle (Vilaplana *et al.*, 1995). The pubertal clock mechanism needs to count a fixed number of light:dark cycles to trigger puberty, and in rats on the 22.5 hour cycle the necessary number occurs sooner (Sizonenko and Aubert, 1986; Sizonenko, 2000).

Hypothetically, gain of body mass and fatness are manifestations of the pubertal clock mechanism within the brain. The pubertal clock, possibly mediated by leptin (Mantzoros *et al.*, 1997), drives the weight gain, as well as the other physiologic and hormonal changes needed for puberty. However, no mechanism evolved to shut off the constant weight and body fat gain needed for puberty, after puberty has occurred, and the pre-pubertal weight gain continues throughout life (Figure 4). The drop in BMI up to age 5 in Figure 4 parallels the fall in plasma LH levels shown in Figure 1. The narrow left segment and widened right segment of the sinusoidal BMI curve in Figure 4 may correspond to the fact that gonadotropin (arcuate nucleus) pulse frequency decreases with aging in post-menopausal women (Hall *et al.*, 2000).

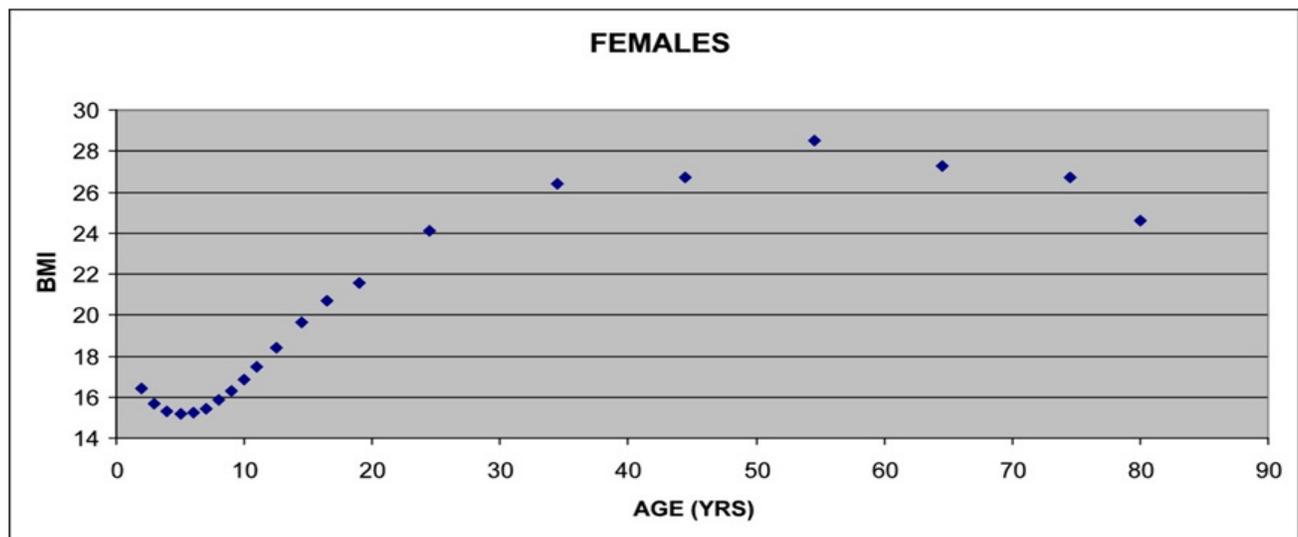
**Testable Hypothesis #2**

Women whose menarche was delayed will have lower BMI in later life than women with normal menarche, controlling for BMI at the age of normal menarche. Since abnormally low BMI at the age of normal menarche has been proposed as a cause of delayed menarche, its effect -- beyond the effect of early BMI on later BMI -- will be examined.

In the course of testing hypothesis 2, the effect of abnormally low BMI at the time of normal menarche on adult BMI will be tested. If there is such an effect in women, the same effect may be present in men. Published studies have examined effects of high, but not low, BMI.

For example, earlier age at menarche is associated with a significantly higher adult BMI. This inverse association of age at menarche with BMI and obesity in middle age is not explained by confounding by early childhood BMI (Pierce and Leon, 2005).

Earlier age at menarche is also associated with a significantly higher risk of diabetes, and specifically type 2 diabetes, in later life. But in one study the effect of age at menarche was reduced by adjustment for adult BMI and was no longer significant (Pierce *et al.*, 2012).



**Figure 4.** BMI vs. age in females. Data from girls in 50th percentile of BMI ages 2 years to 19 years are from Centers For Disease Control, Clinical Growth Charts ([http://www.cdc.gov/growthcharts/clinical\\_charts.htm#Set1](http://www.cdc.gov/growthcharts/clinical_charts.htm#Set1)); data for women above age 20 (7 data points) are from reference Kuczmarski *et al.*, 1994, women in the 50th BMI percentile. The drop in BMI up to age 5 parallels the fall in plasma LH levels shown in Figure 1. The narrow left segment and widened right segment of the sinusoidal BMI curve above may correspond to the fact that gonadotropin (arcuate nucleus) pulse frequency decreases with aging in post-menopausal women (Hall *et al.*, 2000). Note the five points above BMI 25. These women are overweight. 55% of American women fall into this category (Must *et al.*, 1999).

## Conclusion

In centuries past, obesity and continual weight gain after puberty were not of particular concern. Primitive man had to survive long enough only to reproduce, and no natural shutoff mechanism for pre-pubertal weight gain evolved. Until mid-twentieth century, infectious diseases were the major public health problem. Cigarette smoking and resultant cardiovascular disease took their place.

Today, obesity is the major threat to public health. More than 60% of adults in the United States are obese, and the problem has spread to children and adolescents, with dismal consequences. Hypertension, type 2 diabetes, and dyslipidemia have already reduced life expectancy by more than five years among individuals who have these health issues. Depression, another consequence of obesity, is also increasing. The cost of medical care to treat obesity-related illness is spiraling upward, along with diminished productivity and lost income (Wyatt *et al.*, 2006).

The obesity epidemic is a fairly new phenomenon. Before this epidemic, 50 years (or 100 years) ago for example, the same puberty development in human history should also have applied to weight gain during puberty; however, a far smaller proportion of the population had obesity even though no mechanism evolved to shut off the constant weight and body fat gain needed for puberty, after puberty has occurred. From another angle, both before and after the obesity epidemic, a significant number of individuals (a large majority of the population before the epidemic), who had gone through puberty, remained in the normal weight range. These two observations can be explained by the continual extension of the human lifespan.

There has been a striking increase in average life expectancy during the 20th century, which counts as one of society's greatest achievements. Although most babies born in 1900 did not live past age 50, life expectancy at birth now exceeds 83 years in Japan and is at least 81 years in several other countries.

Extension of life expectancy from 50 to 83 has led in many people to obesity resulting from the pubertal weight gain mechanism that is never shut off. As life expectancy continues to increase, so does the prevalence of obesity. A majority of people who have gone through puberty do not have obesity just after puberty because pre-pubertal and pubertal weight gain are gradual and obesity develops over a period of many years. Therefore, more people are obese later in life.

Some people (the majority in many populations) even with today's long lifespan (for example, the majority of Japanese and Chinese people) do not have obesity later in life. Did weight gain during puberty play a role in these non-obese people? The pubertal weight gain occurs irregardless, but obesity is a complex disease with multiple risk factors, in adults (Chou *et al.*, 2004) and children (Reilly *et al.*, 2005). Some of these factors may lessen or suppress the impact of pubertal weight gain on the development of obesity in some individuals.

A better understanding of the mechanism of puberty and pre-pubertal weight gain could provide new insights into obesity and may help to stem an obesity epidemic.

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## Disclosure

The author reports no conflicts of interest.

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