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Review

Developmental variations in environmental influences including endocrine disruptors on pubertal timing and neuroendocrine control: Revision of human observations and mechanistic insight from rodents

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ABSTRACT

Puberty presents remarkable individual differences in timing reaching over 5 years in humans. We put emphasis on the two edges of the age distribution of pubertal signs in humans and point to an extended distribution towards earliness for initial pubertal stages and towards lateness for final pubertal stages. Such distortion of distribution is a recent phenomenon. This suggests changing environmental influences including the possible role of nutrition, stress and endocrine disruptors. Our ability to assess neuroendocrine effects and mechanisms is very limited in humans. Using the rodent as a model, we examine the impact of environmental factors on the individual variations in pubertal timing and the possible underlying mechanisms. The capacity of environmental factors to shape functioning of the neuroendocrine system is thought to be maximal during fetal and early postnatal life and possibly less important when approaching the time of onset of puberty.

1. Introduction

1.1. The classical paradigm of secular advance in human pubertal timing

Fig. 1 summarizes the data on changes in menarcheal age that are used classically to illustrate the secular trend in pubertal timing in various countries. Environmental factors have been thought to account for the reduction in menarcheal age that has been reported since 1850 till 1960 in Scandinavian countries (Tanner, 1962) and further in many European countries and USA (reviewed in Parent et al. (2003)). These findings were interpreted as a result of the improvement in life standards and socio-economical conditions (Biro et al., 2006; Dunger et al., 2006; Ong et al., 2004, 2006; Cheng et al., 2012; Himes, 2006; Roa and Tena-Sempere, 2010). A projection after 1960 of the former reduction seen in Scandinavian countries (Fig. 1) indicates that a sustained secular trend would have led to a mean menarcheal age of less than 12 yrs by the end of the 20th century. This was not the case: after 1960, the secular advancement in female pubertal timing has become less rapid or has even come to an end in countries such as Sweden, Belgium and Hungary (reviewed in Parent et al. (2003)) (Fig. 1). However, menarcheal age has shown a very rapid progression in countries like China and India (reviewed in Parent et al. (2003)) where the standard of life has improved recently. Altogether, those data are consistent with a prominent role of nutrition availability. The "critical weight/fat mass" theory proposed by Frisch and Revelle (1970) and subsequent work (Biro et al., 2006; Dunger et al., 2006; Ong et al., 2004, 2006; Cheng et al., 2012; Himes, 2006; Roa and Tena-Sempere, 2010) have put emphasis on the role of nutritional conditions based on adiposity in puberty, at the time of menarche. The discovery of leptin (Zhang et al., 1994; Campfield et al., 1995) and its prerequisite role in the neuroendocrine control of pubertal maturation and reproduction (reviewed in Sanchez-Garrido and Tena-Sempere (2013)) has added to the importance of energy balance in the prepubertal period to enable onset and progression of puberty.

The secular advancement in pubertal timing has been established following observations about mean or median age at menarche. Implicitly, the whole female pubertal process was thought to undergo similar changes though there were no data available to confirm that. The existence of similar changes for male puberty remains putative. Recent study (Goldstein, 2011) has investigated the secular trend in age at increased mortality in males, assuming

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that mortality at that age is due to adolescent risk taking behaviors presumably depending on pubertal timing. Because that male adolescent mortality hump fell from an average of 21 years in 1850 to 18 years in 1960, the author concluded to a likely secular advancement in pubertal age in males. Few decades ago, the levelling off or arrested secular reduction in average menarcheal age led to the conclusion that stabilization had occurred after resetting pubertal timing to younger ages. Such a conclusion had implications on issues raised by scientists and clinicians: no further changes in pubertal timing could mean that environmental factors were stable and that the previously defined age limits for pubertal disorders were still valid. In 1961, Thamdrup (1961) proposed the age limits of 8 years and 9 years for diagnosis of sexual precocity in girls and boys respectively. Fifty years later, those age limits have not been revised, so far, though as discussed below, the age limits for onset of puberty in the population of many countries have changed in the recent past.

1.2. Pubertal timing and preceding life periods across species

Pubertal neuroendocrine activation or reactivation of the pituitary–gonadal axis is essential for achievement of reproductive capacity. A leading factor in that process is Gonadotropin Releasing Hormone (GnRH) that is released by median eminence terminals of peptidergic neurons in a pulsatile manner showing increased frequency and amplitude at the onset of puberty (Grumbach, 2002; Terasawa and Fernandez, 2001; Plant, 2008; Lomniczi et al., 2013; Ojeda and Lomniczi, 2014). This event occurs at a time in life that varies both among species and within a single species. In Fig. 2 are shown the species-related differences in relative duration of the prepubertal latency (from birth to puberty) when calculated as a percentage of lifespan for comparison purposes. Ewe (Foster et al., 1985), rat (Maeda et al., 2000) and quail (Ottinger et al., 2003) start puberty after a latency accounting for 4.8–5.7% of the lifespan as opposed to 16.3% in humans (Roelants et al., 2009) and 22.5% in baboons (Onyango et al., 2013) that is about 3–4 times longer than in non-primate species. Another less emphasized species-related difference is the variance of pubertal timing among individuals. The timing of puberty shows important differences between human individuals and the physiological range (3rd to 97th centile) of 4.8 years (Roelants et al., 2009) represents 6.25% of the life span. In the laboratory rat with a life expectancy of 2 years, the timing of puberty varies within 4–5 days (Maeda et al., 2000) accounting for an individual variance of 0.55% which is 11 times less than in humans. In sheep (Foster et al., 1985), and quail (Ottinger et al., 2003), the variance of pubertal timing represents 0.87% and 1.9% of lifespan, respectively, that is also less than in humans (Fig. 2). The baboon, a subhuman primate shows a variance of pubertal timing (Onyango et al., 2013) that is even longer than in humans, when expressed relatively to average lifespan (10.0%). These data indicate that inter-individual variations in pubertal timing may be influenced by evolution across species. These data also suggest that not only the timing i.e. the latency between birth and mean or median age at a given pubertal sign is worth being studied but also the variance i.e. the time period between the earliest and latest individuals in a reference population for occurrence of a given pubertal sign. Both parameters (latency and variance) are likely influenced by environmental factors and could even be differentially affected with different mechanisms possibly involved. In the present paper, we will review comparatively the impact of different environmental factors on pubertal timing in humans and in animal models. The variance of pubertal timing has a different magnitude across species (Fig. 2) and may not have the same significance in animals and in humans. Laboratory animals are more homogeneous in term of genetic background and are exposed to a very regulated environment. However, they are unavoidable models when it comes to study the mechanisms of neuroendocrine regulation of pubertal timing.

Since some data obtained in human, non-human primates and rodents will be discussed with emphasis on neuroendocrine maturation, it is important to keep in mind that when birth takes place in rodents, maturation of the brain is less advanced than in human newborns (Clancy et al., 2007). In the rat, the onset of puberty is marked by an increase in testicular weight increase in males and vaginal opening followed by the first estrus in female rodents and (Maeda et al., 2000). The onset of puberty takes place around the time of weaning by the age of 3 weeks as evidenced from onset of increase in serum levels of gonadal hormones (Maeda et al.,

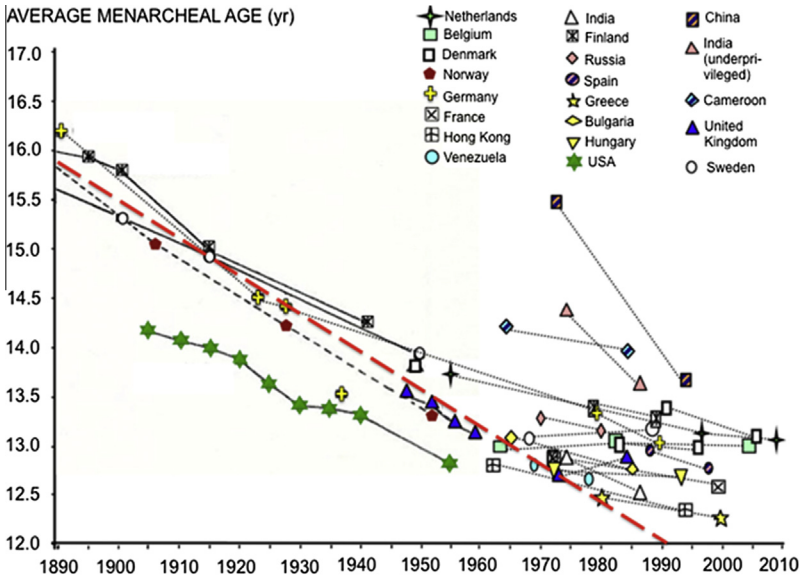

Fig. 1. Evolution of average menarcheal age (year) in the USA and Nordic countries between 1890 and 1960 (data compiled by Tanner (1962) and further, between 1960 and 2010, in different countries in Europe, USA and around the world (updated data compiled by Parent et al. (2003)). The broken red line represents the projected reduction after 1960, based on the former changes in Scandinavian countries as reported by Tanner: mean menarcheal age would have fallen down to below 12 yrs by the end of the 20th century. In fact, after 1960, average menarcheal age has leveled off in many countries while still progressing rapidly in countries such as India or China.