Psychoneuroendocrinology (2010) **35**, 133—140

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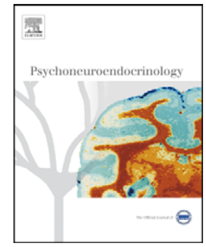

HPG-axis hormones during puberty: A study on the association with hypothalamic and pituitary volumes

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Received 31 March 2009; received in revised form 12 May 2009; accepted 28 May 2009

KEYWORDS
FSH;
Estradiol;
Puberty;
Pituitary gland;
Hypothalamus;
Volumetric MRI

Summary
Objective: During puberty, the hypothalamus—pituitary—gonadal (HPG) axis is activated, leading to increases in luteinizing hormone (LH), follicle stimulating hormone (FSH) and sex steroids (testosterone and estradiol) levels. We aimed to study the association between hypothalamic and pituitary volumes and development of pubertal hormones in healthy pubertal children.
Method: Hormone levels of LH, FSH, estradiol (measured in urine) and testosterone (measured in saliva) were assessed in 85 healthy children (39 boys, 46 girls) between 10 and 15 years of age. Hypothalamic and pituitary gland volumes were segmented on high resolution structural MRI scans. Since sex hormone production is regulated in a sex-specific manner, associations between hormones, hypothalamus and pituitary were analyzed in boys and girls separately.
Results: LH, estradiol and testosterone levels all increased with age in both sexes, whereas FSH level did not. Pituitary volume also increased with age and explained 12%, 10% and 8% of the variance in female estradiol, testosterone and LH levels respectively. Corrected for age, pituitary volume explained 17% of FSH level in girls (not boys). Hypothalamic volume did not change with age and did not significantly explain variance in any hormonal level.
Discussion: Our study suggests that a larger pituitary volume is related to higher FSH production, but this association seems independent of pubertal development. The positive association between estradiol, LH and testosterone and pituitary volume is related to age-related pubertal development. With respect to the hypothalamus, we did not find convincing evidence for a larger structure to be involved in elevated hormonal production.

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doi:10.1016/j.psyneuen.2009.05.025

1. Introduction

The hypothalamus and pituitary gland are key structures involved in mediating responses vital for maintaining homeostasis, including sleep, hunger, thirst, thermoregulation and sexual maturation (Tran et al., 2004). Sexual maturation is referred to as the period of puberty, which is characterized by (re)activation of the hypothalamus—pituitary—gonadal (HPG) axis. In brief, gonadotropin releasing hormone (GnRH) neurons in the hypothalamus induce the secretion of GnRH. GnRH and peripheral factors from the gonads regulate the production of gonadotropins LH and FSH from the pituitary gland (Marshall, 1995). The increase in LH and FSH during puberty induces the maturation of the gonads, leading to marked estradiol and testosterone secretion (Grumbach and Styne, 2003).

Recently, in children between 10 and 15 years of age, we demonstrated associations between age-related increases in female estradiol levels and cortical gray matter: increased gray matter density was observed in prefrontal and occipital areas, whereas decreased gray matter density was found in prefrontal, temporal and parietal areas (Peper et al., 2009a). Other HPG-axis hormones (testosterone, LH (Peper et al., 2009a) or FSH (unpublished data)) did not relate to cortical brain areas in this age group.

Animal studies found that increased levels of sex steroids (either exogenous or endogenous) and gonadotropins are associated with an increased degree of cell proliferation within the pituitary gland (Nolan and Levy, 2006a,b). Attempts have been made to indirectly relate human (sex) hormone production to morphology of the pituitary gland. For example, a more advanced phase of pregnancy (among others accompanied by increased estradiol activity) was associated with an enlarged pituitary (Gonzalez et al., 1988; Dinc et al., 1998). Furthermore, indirect evidence for an association between sex hormones and pituitary volumes comes from studies on sex differences (i.e. males and females display clear sex differences in hormonal profiles): during puberty, pituitary volume shows a growth spurt, which is more pronounced in girls than in boys (Takano et al., 1999). Also, a sex difference in pituitary height (Elster et al., 1990; Denk et al., 1999) and volume was found (MacMaster et al., 2007) which became apparent during adolescence (i.e. girls larger than boys) (Elster et al., 1990). But see (Fink et al., 2005) who did not report a sex difference in pituitary size or volume, although this was reported in pre-pubertal children.

Pituitary volume changes have also been related to increased activity of the hypothalamus—pituitary—adrenal (HPA) axis: for instance, psychosis has been associated with an enlarged pituitary volume (Pariante et al., 2004, 2005). It is suggested that the enlargement is due to an increase in the size and number of pituitary corticotrophin cells caused by the activation of the hormonal stress response (for review see Pariante, 2008).

In humans, the relation between HPG-axis hormones and hypothalamic volumes has been studied less well than pituitary volumes. Treatment with testosterone induced hypothalamic volume increases whereas androgen blocking medication decreased hypothalamic volumes (Hulshoff Pol et al., 2006). In healthy males (who evidently have higher testosterone levels than females), a larger hypothalamus was found (Goldstein et al., 2001), providing indirect evidence for a positive association between testosterone and hypothalamic volume. Moreover, pathological conditions such as hypothalamic hamartoma's (i.e. benign tumors composed of neurons and astroglia located near or on the hypothalamus) have been associated with precocious puberty (Jung et al., 2005). Furthermore, increased hypothalamic volumes were observed in schizophrenia patients compared to healthy controls (Goldstein et al., 2007), a condition characterized by abnormal endocrinological profiling (Walker et al., 2008).

The aim of the current study was to explore the relation between levels of pubertal hormones (i.e. LH, FSH, testosterone and estradiol) and volume of the hypothalamus and pituitary gland. It was hypothesized that larger hypothalamic and pituitary gland volumes are both associated with higher hormonal production in both boys and girls.

2. Subjects and methods

2.1. Participants

The sample consisted of 85 healthy children between 10 and 15 years of age (mean 11.9 (±1.1) years), including 39 boys and 46 girls recruited from the Netherlands Twin Register (Boomsma et al., 2006) (Table 1). These non-twin children and their younger twin-siblings took part in a larger study described elsewhere (Peper et al., 2008, 2009a,b; van Leeuwen et al., 2009). Exclusion criteria consisted of any major medical or psychiatric illness and participation in special education. Physical health and mental health were assessed with a medical history inventory. Parents and the participants themselves gave written informed consent to participate in the study. The study was approved by the Central Committee on Research involving Human Subjects (CCMO) of the Netherlands and was in agreement with the Declaration of Helsinki (Edinburgh amendments).

Table 1 Characteristics of the sample.

	Boys		Girls	
	N	Mean (SD)	*N*	Mean (SD)
Age (y)	39	11.6 (1.0)	46	12.1 (1.2)*
Hypo (ml)	36	1.05 (.12)	40	1.01 (.09)
Pit (ml)	36	.53 (.13)	41	.58 (.14)
TB (ml)	39	1402.9 (92.7)	46	1304.4 (96.8)***
FSH (U/l)	37	.39 (.25)	40	.85 (.44)***
LH (U/l)	30	2.20 (2.19)	36	2.14 (2.30)
T (pmol/l)	29	70.8 (66.1)	38	58.7 (36.3)
E (pmol/l)	37	1027.0 (696.7)	35	2371.6 (1332.2)***
Tan A	38	1.63 (.75)	46	2.85 (.97)***
TanB	38	1.71 (.96)	46	2.83 (1.23)***
TanC	38	1.50 (.60)	—	—

Hypo = hypothalamus volume; Pit = pituitary gland volume; TB = total brain volume; T = testosterone; E/c = estradiol; Tan = Tanner stages.

* $p < .02$.

*** $p < .0001$ (sex differences, corrected for age).