Article

Current Biology

Ovarian Hormones Organize the Maturation of Inhibitory Neurotransmission in the Frontal Cortex at Puberty Onset in Female Mice

Highlights

- Inhibitory neurotransmission increases in the frontal cortex after puberty
- Pre-pubertal, but not post-pubertal, gonadectomy blocks this increase
- Pre-pubertal hormone treatment accelerates maturation of tonic and phasic inhibition
- Hormone treatment, which drives early puberty, impacts behavioral flexibility

Authors

David J. Piekarski, Josiah R. Boivin, Linda Wilbrecht

Correspondence

wilbrecht@berkeley.edu

In Brief

Piekarski et al. find that pubertal hormones play a critical role in the adolescent maturation of inhibitory neurotransmission in the frontal cortex. These data provide a putative mechanism by which the timing of puberty onset, independent of age, may play a role in the development of the frontal lobes and their associated functions.

Piekarski et al., 2017, Current Biology *27*, 1–11
June 19, 2017
http://dx.doi.org/10.1016/j.cub.2017.05.027

CellPress

Please cite this article in press as: Piekarski et al., Ovarian Hormones Organize the Maturation of Inhibitory Neurotransmission in the Frontal Cortex at Puberty Onset in Female Mice, Current Biology (2017), http://dx.doi.org/10.1016/j.cub.2017.05.027

Current Biology
Article

Ovarian Hormones Organize the Maturation of Inhibitory Neurotransmission in the Frontal Cortex at Puberty Onset in Female Mice

David J. Piekarski,[1] Josiah R. Boivin,[2] and Linda Wilbrecht[1,3,4,*]
[1]Department of Psychology, University of California, Berkeley, 16 Barker Hall, Berkeley, CA 94720, USA
[2]Neuroscience Graduate Program, University of California, San Francisco, 1550 4th Street, San Francisco, CA 94158, USA
[3]Helen Wills Neuroscience Institute, University of California, Berkeley, 16 Barker Hall, Berkeley, CA 94720, USA
[4]Lead Contact
*Correspondence: wilbrecht@berkeley.edu
http://dx.doi.org/10.1016/j.cub.2017.05.027

SUMMARY

The frontal cortex matures late in development, showing dramatic changes after puberty onset, yet few experiments have directly tested the role of pubertal hormones in cortical maturation. One mechanism thought to play a primary role in regulating the maturation of the neocortex is an increase in inhibitory neurotransmission, which alters the balance of excitation and inhibition. We hypothesized that pubertal hormones could regulate maturation of the frontal cortex by this mechanism. Here, we report that manipulations of gonadal hormones do significantly alter the maturation of inhibitory neurotransmission in the cingulate region of the mouse medial frontal cortex, an associative region that matures during the pubertal transition and is implicated in decision making, learning, and psychopathology. We find that inhibitory neurotransmission, but not excitatory neurotransmission, increases onto cingulate pyramidal neurons during peri-pubertal development and that this increase can be blocked by pre-pubertal, but not post-pubertal, gonadectomy. We next used pre-pubertal hormone treatment to model early puberty onset, a phenomenon increasingly observed in girls living in developed nations. We find that pre-pubertal hormone treatment drives an early increase in inhibitory neurotransmission in the frontal cortex, but not the somatosensory cortex, suggesting that earlier puberty can advance cortical maturation in a regionally specific manner. Pre-pubertal hormone treatment also accelerates maturation of tonic inhibition and performance in a frontal-cortex-dependent reversal-learning task. These data provide rare evidence of enduring, organizational effects of ovarian hormones at puberty and provide a potential mechanism by which gonadal hormones could regulate the maturation of the associative neocortex.

INTRODUCTION

The onset of adolescence, initiated by the onset of puberty, is increasingly recognized as an inflection point for the development of associative regions of the neocortex [1]. Across mammals, adolescence is characterized by changes to cognitive and executive functions that coincide with large-scale reorganization of associative cortical regions, including the frontal cortex [2–4]. This period of development is also associated with declining plasticity in language-related circuits, declining capacity for recovery from cortical damage [5–11], and increased risk of psychiatric disease [3, 12]. Although it remains unclear whether these developmental changes are caused by the pubertal rise in gonadal hormones or are simply coincident [1], it is clear that early puberty onset exacerbates risk of psychiatric illnesses connected to frontal functions [13–15], suggesting a possible causal link. Gonadal steroid receptors are present across the neocortex [16–18], and a number of anatomical changes in the human cortex correlate with changes in hormone levels during puberty [19–23]. In rodent experiments that manipulate hormones, frontal cortex neuron density is sensitive to gonadectomy in females, but not males [24], but it is still unknown whether puberty onset impacts functional measures of frontal cortex circuit development such as inhibitory and excitatory neurotransmission.

Nuclear estrogen receptors in the associative cortices are expressed almost exclusively in fast-spiking interneurons [17, 25], suggesting that the pubertal rise in gonadal hormones may directly impact inhibitory neurotransmission. Fast-spiking interneurons are implicated in the regulation of cognition, plasticity, and neuropsychiatric illness [26–29], and are thought to play an important regulatory role in brain development by adjusting the balance of excitation and inhibition (E/I) onto cortical pyramidal neurons. This shift in E/I balance is most likely a key mechanism regulating sensitive-period plasticity in primary sensory cortices [30–32]. We have previously demonstrated a striking rise in the strength of inhibitory neurotransmission in deep layers of the frontal cortex during early adolescence [33], which led us to develop a working model in which gonadal steroids drive frontal cortex maturation by increasing the strength of local inhibitory neurotransmission [1].

In the present report, we manipulated exposure to gonadal steroids in mice at peri-pubertal ages and measured the