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Review

A system biology approach to identify regulatory pathways underlying the neuroendocrine control of female puberty in rats and nonhuman primates

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ABSTRACT

This article is part of a Special Issue "Puberty and Adolescence".

Puberty is a major developmental milestone controlled by the interaction of genetic factors and environmental cues of mostly metabolic and circadian nature. An increased pulsatile release of the decapeptide gonadotropin releasing hormone (GnRH) from hypothalamic neurosecretory neurons is required for both the initiation and progression of the pubertal process. This increase is brought about by coordinated changes that occur in neuronal and glial networks associated with GnRH neurons. These changes ultimately result in increased neuronal and glial stimulatory inputs to the GnRH neuronal network and a reduction of transsynaptic inhibitory influences. While some of the major players controlling pubertal GnRH secretion have been identified using gene-centric approaches, much less is known about the system-wide control of the overall process. Because the pubertal activation of GnRH release involves a diversity of cellular phenotypes, and a myriad of intracellular and cell-to-cell signaling molecules, it appears that the overall process is controlled by a highly coordinated and interactive regulatory system involving hundreds, if not thousands, of gene products. In this article we will discuss emerging evidence suggesting that these genes are arranged as functionally connected networks organized, both internally and across sub-networks, in a hierarchical fashion. According to this concept, the core of these networks is composed of transcriptional regulators that, by directing expression of downstream subordinate genes, provide both stability and coordination to the cellular networks involved in initiating the pubertal process. The integrative response of these gene networks to external inputs is postulated to be coordinated by epigenetic mechanisms.

Contents

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The biological underpinnings of the cellular systems controlling puberty

The basic neuroendocrine mechanisms controlling the initiation of female reproductive capacity are well characterized. An increase in pulsatile release of gonadotropin-releasing hormone (GnRH) is ultimately responsible for setting in motion the endocrine manifestations of puberty. This change is, in turn, determined by modifications in transsynaptic (Kordon et al., 1994; Ojeda and Terasawa, 2002) and glial (Ojeda et al., 2008, 2010b) inputs to the GnRH neuronal network. While the transsynaptic changes involve an increase in excitatory inputs and a reduction in inhibitory influences (Ojeda and Terasawa, 2002; Plant and Witchel, 2006; Terasawa and Fernandez, 2001), the glial component is predominantly facilitatory, and exerted by growth factors and small molecules that stimulate GnRH secretion (Lomniczi and Ojeda, 2009; Ojeda and Skinner, 2006).

In the last ten years, significant progress has been made towards identifying neuronal subsets involved in both the excitatory and inhibitory control of GnRH secretion. We now know that the excitatory control of puberty is not only provided by glutamatergic neurons (Ojeda et al., 2006; Plant and Witchel, 2006), but also even more conspicuously by neurons that produce kisspeptin (reviewed in d'Anglemont and Colledge, 2010; Oakley et al., 2009). Kisspeptins are a family of peptides encoded by the *KISS1*/*Kiss1* gene and that act as powerful stimulators of GnRH release (Kauffman et al., 2007; Oakley et al., 2009; Shahab et al., 2005); in their absence or in the absence of its receptor (known as GPR54 or Kiss1R), puberty fails to occur (de Roux et al., 2003; Lapatto et al., 2007; Seminara et al., 2003; Topaloglu et al., 2012). In primates, kisspeptin neurons are mostly located in the arcuate nucleus (ARC) of the medial basal hypothalamus (Shahab et al., 2005). In rodents, there is a second population of kisspeptin neurons located in the periventricular region of the anteroventral periventricular nucleus (AVPV) (Clarkson et al., 2009; Gottsch et al., 2004). It appears clear now that kisspeptin neurons of the ARC are required for pulsatile GnRH release (Navarro et al., 2011; Wakabayashi et al., 2010), and that at least in rodents AVPV kisspeptin neurons are needed for the pre-ovulatory surge of gonadotropins (Khan and Kauffman, 2011; Smith et al., 2006).

In all mammalian species so far studied the first neuroendocrine manifestation of puberty is a diurnal increase in pulsatile LH release (reviewed in Ojeda and Skinner, 2006), which is in all likelihood driven by kisspeptin neurons of the ARC. These cells have been termed KNDy neurons (Lehman et al., 2010; Navarro et al., 2011), because they produce *K*isspeptin, *N*eurokinin B (NKB) and *D*ynorphin (Navarro et al., 2011; Wakabayashi et al., 2010). It is currently believed that KNDy neurons release NKB, which acts on other KNDy neurons *via* specific receptors to stimulate kisspeptin release (Navarro et al., 2011; Wakabayashi et al., 2010) (but see Kinsey-Jones et al., 2012). Like *KISS1* and its receptor, inactivating mutations of *TAC3*/*Tac2* (which encodes NKB) or *TACR3* (the gene encoding the NKB receptor), results in pubertal failure (Topaloglu et al., 2008). NKB and kisspeptin are released periodically, and this oscillatory behavior is thought to be determined by a phase-delayed inhibitory feedback of dynorphin on NKB release (Navarro et al., 2011; Wakabayashi et al., 2010). Dynorphin is an opioid peptide that inhibits GnRH secretion (Kinoshita et al., 1982; Navarro et al., 2009; Schulz et al., 1981). Diagrams describing these interactions have been published (d'Anglemont and Colledge, 2010; Lehman et al., 2010; Wakabayashi et al., 2010).

The inhibitory transsynaptic circuitry controlling GnRH release involves at least three different neuronal subsets. GABAergic and opiatergic neurons have been known for many years to be central players (reviewed in Terasawa and Fernandez, 2001). More recently, evidence has been provided suggesting that RFamide-related peptide (*RFRP*), the mammalian ortholog of the peptide gonadotrophin-inhibiting hormone (GnIH) in birds (Ebling and Luckman, 2008), is a physiological inhibitor of GnRH neurons in mammals (Ducret et al., 2009; Gibson et al., 2008; Tsutsui et al., 2010). As such, RFRP-containing neurons may be significant components of the restraining mechanism that maintains GnRH secretion in check during reproductive maturation. RFRP neurons may use one or two peptides (RFRP1 and RFRP3) for transsynaptic communication; these peptides are recognized by a high-affinity receptor termed GPR147 or NPFFR1 (Hinuma et al., 2000; Tsutsui et al., 2010), and a low-affinity receptor termed GPR74 or NPFFR2 (Fukusumi et al., 2006). Because GPR147 is expressed in GnRH neurons (Ducret et al., 2009; Poling et al., 2012), RFRP-containing neurons can directly repress GnRH neuronal function. In contrast to this simplicity, GABAergic neurons can affect GnRH secretion indirectly, *via* inhibitory effects exerted on neurons connected to the GnRH neuronal network (Ojeda et al., 2006; Terasawa and Fernandez, 2001), or directly using excitatory mechanisms set in motion by the activation of $GABA_A$ receptors located on GnRH neurons themselves (DeFazio et al., 2002; Moenter and DeFazio, 2005). Opiatergic neurons appear to exert a pure inhibitory tone on GnRH neurons, but this input is provided by different peptides acting on different receptors (Kordon et al., 1994); as in the case of GABAergic inputs, opiatergic inhibition may be exerted directly on GnRH neurons (Dudas and Merchenthaler, 2006) or indirectly on neurons involved in the stimulatory control of the GnRH neuronal network, such as KNDy neurons of the ARC (Navarro et al., 2009). Additional components of the regulatory system controlling the onset of female puberty include novel molecules required for glutamate release (Choi et al., 2008; Ha et al., 2008) and GnRH neuron excitability (Garcia-Rudaz et al., 2008).

In addition to neurons, the pubertal activation of GnRH secretion involves the participation of glial cells (Ojeda et al., 2008, 2010b). Astrocytes and tanycytes (ependymoglial cells lining the ventro-lateral surface of the third ventricle) produce signaling molecules that stimulate GnRH release, and contribute to determining the timing of puberty (reviewed in Lomniczi and Ojeda, 2009; Ojeda et al., 2010b). Glial cells facilitate GnRH secretion *via* two complementary mechanisms. One of them involves growth factors of at least four different families (reviewed in Mahesh et al., 2006; Prevot, 2002). Transforming growth factor-beta (TGFβ) is recognized by cell-membrane receptors endowed with serine–threonine kinase; the epidermal growth factor (EGF) family, basic fibroblast growth factor (bFGF), and insulin-like growth factor 1 (IGF-I) are recognized by receptors with tyrosine kinase activity. Genetic disruption of erbB (erythroblastosis B) receptors (which recognize the members of the EGF family) delays female sexual development due, at least in part, to impaired erbB ligand-induced glial prostaglandin E_2 (PGE_2) release (Lomniczi and Ojeda, 2009). Preventing the proteolytic processing of erbB ligands in astrocytes delays puberty (Lomniczi et al., 2006) and disrupting astrocytic PGE_2 production drastically diminishes the electrophysiological activity of GnRH neurons (Clasadonte et al., 2011).

The second mechanism of glia-to-GnRH neuron communication involves plastic rearrangement in cell adhesiveness provided by at least three different cell–cell communication systems: one involves the sialylated form of the neural cell adhesion molecule NCAM (PSA-NCAM) (Parkash and Kaur, 2005; Perera et al., 1993). Another requires the adhesion molecule Synaptic Cell Adhesion Molecule 1 (SynCAM1) (Sandau et al., 2011a, 2011b), and a third one is based on the interaction of neuronal contactin with glial Receptor-like Protein Tyrosine Phosphatase-β (RPTPβ) (Parent et al., 2007). All three systems use adhesive proteins containing intracellular signaling domains, suggesting that the interaction of glial cells with GnRH neurons not only involve secreted bioactive molecules (growth factors, prostaglandins, *etc.*), but also intracellular signaling mechanisms set in motion by adhesive molecules (reviewed in Lomniczi and Ojeda, 2009). A more comprehensive coverage of the mechanisms controlling the onset of puberty can be found in earlier reviews (Ojeda and Urbanski, 1994; Ojeda et al., 2006; Tena-Sempere, 2006; Terasawa and Fernandez, 2001), and in several chapters of this book (Tena-Sempere, Megan Hagenauer/Terri Lee, Dennis Styne).