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Review

Sexual differentiation of the gonadotropin surge release mechanism: A new role for the canonical NfκB signaling pathway

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ABSTRACT

Sex differences in luteinizing hormone (LH) release patterns are controlled by the hypothalamus, established during the perinatal period and required for fertility. Female mammals exhibit a cyclic surge pattern of LH release, while males show a tonic release pattern. In rodents, the LH surge pattern is dictated by the anteroventral periventricular nucleus (AVPV), an estrogen receptor-rich structure that is larger and more cell-dense in females. Sex differences result from mitochondrial cell death triggered in perinatal males by estradiol derived from aromatization of testosterone. Herein we provide an historical perspective and an update describing evidence that molecules important for cell survival and cell death in the immune system also control these processes in the developing AVPV. We conclude with a new model proposing that development of the female AVPV requires constitutive activation of the Tnfα, Tnf receptor 2, NfκB and Bcl2 pathway that is blocked by induction of Tnf receptor-associated factor 2-inhibiting protein (Traip) in the male.

1. Introduction

Sex-specific patterns of luteinizing hormone (LH) release are fundamental to reproduction in mammals. The male pattern is tonic, while the female pattern is cyclic and culminates in a preovulatory surge of LH release. These patterns are controlled by sexually dimorphic neural structures that differentiate perinatally when the testes, but not the ovaries are actively secreting steroid hormones [9]. Mimicking the male hormonal profile in perinatal females leads to a condition characterized by polycystic ovaries and infertility [6,7]. Therefore, to better understand the etiology of polycystic ovarian syndrome and other types of hypothalamic infertility, it is important to determine the mechanisms underlying the process of sexual differentiation of the brain.

In the first section of this paper, we review the pioneering research on sexual differentiation of the neural substrate that controls gonadotropin release. In the second section, we describe research that identified the anteroventral periventricular nucleus (AVPV) as a region critical for the female pattern of cyclic LH release in rodents. The third section focuses on phenotypic characterization of neurons that comprise the AVPV. The fourth section discusses work showing that male-specific apoptosis plays a key role in sexual differentiation of the AVPV. The fifth section provides evidence that a novel protein, tumor necrosis factor receptor associated factor 2-inhibiting protein (Traip), induces apoptosis in the male AVPV by blocking nuclear factor κB (NfκB) activation. In the final section, we present a new model of AVPV sexual differentiation and describe future directions for this research.

2. Sexual differentiation of gonadotropin release patterns: Pioneers of the early frontier

Normal ovarian and testicular functions depend on sex-specific gonadotropin release patterns to such an extent that alterations in these patterns reduce fertility. Sex differences in the mammalian pituitary gonadotropin content were first observed in the early 1900s [21,33,35,94,149]. In 1933 Fevold et al. [37] showed that the pituitary produced two gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH), and that cyclic changes in the release of these hormones was required for ovulation. To test the idea that the ovary imposes a cyclicity on pituitary functions, Goodman transplanted ovaries into the anterior chamber of adult gonadectomized male and female rats [42]. He observed that grafts in females showed cyclic changes with spontaneous formation of follicles and corpora lutea, but in males they produced only follicles that failed to luteinize, suggesting that the ovary was not responsible for sex differences in gonadotropin release patterns [42].

Evidence that sex differences in gonadotropin release patterns in mammals were imprinted early in life came from groundbreaking work of Pfeiffer in 1935–1936. He grafted ovaries into

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females or neonatally castrated males at the time of puberty and observed both follicles and corpora lutea; in contrast, only follicles were seen in ovaries grafted into intact males or females implanted at birth with testes [111]. In addition, he showed that ovaries transplanted into females with testicular grafts produced corpora lutea when injected with LH. Based on these findings, Pfeiffer proposed that the pituitary is bipotential until puberty and that prepubertal exposure to testicular secretions masculinizes the gland such that it releases FSH, but not LH [111]. In 1941, Bradbury provided further support for this hypothesis by showing that ovaries of females treated postnatally with testosterone proprionate (TP) produced both follicles and corpora lutea when transplanted into untreated females. Conversely, ovaries from untreated females transplanted into postnatally androgenized females grew only follicles. In 1954, Barraclough and Leathem demonstrated that TP permanently suppressed ovulation in females when administered on postnatal day 5 (PND5), but not in those treated on PND20 [10]. Together these findings supported the hypothesis that exposure of female rodents to androgen during the early neonatal period permanently abolished the potential for LH surge release and ovulation.

The idea that gonadotropin release was controlled by the hypothalamus rather than the pituitary gland began to gain traction in the late 1940s when Markee et al. [83,84] and Harris [51] showed that electrical stimulation of the hypothalamus, but not the pituitary gland, induced ovulation in rabbits. A few years later, Harris and Jacobsohn [53], as well as Martinez and Bittner [85], demonstrated that male pituitaries transplanted under the median eminence of hypophysectomized female rats restored ovulation in the recipients. Subsequently, Critchlow showed that electrical stimulation of the hypothalamus could induce ovulation in cycling rats in which ovulation was blocked by barbiturates [25], supporting the idea that the hypothalamus controlled the pituitary gland (see Harris [52]). Further evidence for this idea came from Barraclough and Gorski's work showing that stimulation of particular hypothalamic regions induced ovulation in androgenized rats [8]. These findings verified that neonatal androgen exposure masculinizes the pattern of LH release through actions in the hypothalamus, not the pituitary gland.

The hypothalamic regions chosen by Barraclough and Gorski [8] for electrostimulation in the 1960s were based on earlier work by Crtichlow [25] and Everett [36]. Induction of ovulation was achieved by stimulation of the preoptic area (POA) [36] or the more caudal hypothalamic area containing the ventromedial (VMN) and arcuate (Arc) nuclei. In androgenized females, Barraclough and Gorski observed ovulation after VMN/Arc, but not POA stimulation [8]. Based on these results they concluded that the VMN/Arc region controls tonic gonadotropin release sufficient to support estrogen production, but the POA is necessary for the cyclic surge pattern of release that induces ovulation. This idea was supported by Köves and Halász in their 1970 report showing that cuts separating the POA from the more caudal hypothalamus blocked ovulation and produced constant estrus as observed in androgenized rats [73]. Finally, in 1978 Goodman [43] showed that the POA, not the medial basal hypothalamus or pituitary gland, was the primary site in which estradiol (E_2) elicited LH surge release. Together these studies demonstrated that the POA is an important sexually differentiated brain region in which E_2 regulates the female-specific pattern of LH release.

In view of evidence from rodent models that the LH surge release pattern was sexually differentiated by developmental exposure to T, several studies in the 1970s tested whether this was the case in subhuman primates as well. Results of several studies suggest that it is not. Goy and Resko showed that female monkeys exposed to T in utero ovulate when they reach puberty [47]. Subsequent work by Karsch et al. [70], as well as Steiner et al. [136], showed that males orchidectomized as adults show LH surge release after E_2 treatment. Perhaps the most compelling evidence that the LH surge mechanism is not sexually dimorphic in subhuman primates comes from work of Norman and Spies. These researchers showed in 1986 that ovaries transplanted into orchidectomized male monkeys secrete female-typical levels of E_2 and develop functional corpus lutea [103]. It should be noted that although positive feedback regulation of LH release by E_2 is not sexually differentiated, negative feedback mechanisms are masculinized in monkeys by T administered prenatally [136].

3. Localization of sexually differentiated brain nuclei important for ovulation

In the 1980s, research by a number of laboratories focused on more precisely defining the region of the POA required for cyclic LH surge release. Studies of Wiegand and Terasawa showed that small lesions of the medial preoptic nucleus (MPN) produced persistent estrus in rats [146]. In addition, only lesions in this region blocked LH surge release induced by E_2 and progesterone (P_4) in ovariectomized (OVX) rats. Work by Ronnekleiv and Kelly showed that MPN lesions caused accumulation of luteinizing hormone-releasing hormone (LHRH; now termed gonadotropin-releasing hormone; GnRH) rostral, lateral and caudal to the lesions and in the median eminence [118]. This work provided evidence that the MPN directly or indirectly regulates GnRH neurons. In 1989, we reported that microimplants of anti-estrogen blocked E_2-induced LH surge in OVX rats when placed in the MPN region; these implants had no effect on E_2 suppression of basal LH release (negative feedback) [108]. Subsequently we showed that the anti-estrogen microimplants also block changes in GnRH mRNA in neurons rostral to the microimplants and in GnRH concentrations in the median eminence [109]. Thus, either lesions or local E_2 deprivation in a rostral POA region initially termed the MPN blocks the female-typical LH surge release pattern without altering negative feedback actions of the steroid.

The nomenclature of the POA region(s) responsible for the female-typical LH surge release pattern changed over time. In 1982, Bleier et al. described multiple sexually dimorphic areas of the preoptic area (extending from the rostral POA through the region containing the suprachiasmatic nucleus; SCN) in four rodent species [11]. The more caudal of these was termed the anterior hypothalamic nucleus and it contained a subgroup corresponding to the sexually dimorphic nucleus of the POA (SDN-POA) previously identified by Gorski et al. [45,46]. Bleier called the rostral-most sex-specific nucleus the medial preoptic nucleus (abbreviated as MP), a term consistent with that of a stereotaxic atlas used at that time [72]. She showed that in the rat, the MP was distributed over a greater rostral–caudal extent and was more cell-dense in females than in males [11]. The MP described by Bleier is similar to the area we identified as a site in which E_2 action is required for the LH surge [108]. Simerly et al. later refined the medial POA nomenclature [129], and changed the designation of the region previously called the MPN (MP by Bleier) to the anteroventral periventricular nucleus (AVPV). The AVPV structure is now defined as depicted on plates 17–19 of the Swanson atlas [137].

Bleier and colleagues also observed a sexually dimorphic region, the periventricular area (Pea; more recently termed PePOA [77], PePo [133], PVpo [55] or PeN [121]) just caudal to the MP (AVPV) in the rat [11]. They described this region as a narrow periventricular space densely packed with cells in females, but sparsely cellular in the male. This region seems likely to be that described by Wiegand and Terasawa as "a small periventricular column of cells