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Minireview: Synthesis and Function of Hypothalamic Neuroprogesterone in Reproduction

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The physiology and regulation of steroid synthesis in the brain have emerged as important for understanding brain function. Neurosteroids, those steroids synthesized *de novo* in nervous tissue, have been associated with numerous central nervous system functions, including myelination, mental retardation, and epilepsy. Central regulation of reproduction was thought to depend on steroids of peripheral origin. Only recently has the role of neurosteroids in reproduction been appreciated. This minireview describes our work trying to understand how circulating estradiol modulates the synthesis of neuroprogesterone. The synthesis of neuroprogesterone occurs primarily in astrocytes, and requires the interaction of membrane-associated estrogen receptor with metabotropic glutamate receptor and the release of intracellular calcium stores. The newly synthesized neuroprogesterone acts on estradiol-induced progesterone receptors in nearby neurons to initiate the LH surge. (*Endocrinology* 149: 2739–2742, 2008)

IT IS DIFFICULT to overstate the importance of steroid hormones. These compounds are critical mediators of homeostasis, and an organism's response to various stressors and injury. In addition to the massive quantities of steroid hormones produced by peripheral steroidogenic organs, the gonads and the adrenal glands, it is now well accepted that the brain synthesizes steroids *de novo* (neurosteroids), and converts circulating steroids to neuroactive steroids (*e.g.* dehydroepiandrosterone, estradiol, allopregnanolone). Both neurosteroid and neuroactive steroids affect brain function through actions at their cognate receptors, estrogen receptor (ER), progesterone receptor (PR), or by modulating receptors whose primary transmitter is not a steroid (*e.g.* the $GABA_A$ receptor).

A distinction based on the origin of the steroids is useful. Steroids of peripheral origin are hormones, released into the circulation to act on distal target sites, including nervous tissue. Thus, the actions of these steroid hormones affect a wide variety of tissues and influence numerous physiological properties. Neurosteroids, more properly could be considered neurotransmitters. They are made in the brain, their release is regulated, and they are neuroactive as demonstrated by their modulation of intracellular signaling pathways, channels, and transcription.

Neurosteroids are not isolated from peripheral steroids. Mutual interactions modulate levels in the brain and periphery. In mammalian species, levels of neurosteroids are very low and do not appear to "spill" into circulating pools of hormonal steroids. Peripheral, hormonal, or circulating steroids are made in large concentrations by both the gonads and adrenal cortex. One of the hallmarks of steroid hormones is that they are carried in the blood, either free or bound to a carrier protein. Free steroids are capable of diffusing across the blood-brain barrier into cells of the nervous system to encounter both membrane-associated steroid receptors and intracellular receptors. Thus, the concentration of steroids in the brain is a mixture of peripherally derived steroids, converted peripheral steroids, and neurosteroids. Intracellular steroid receptors are either ligand-activated transcription factors, or they stabilize other transcription factors such as fos and jun (1–3). These transcriptional actions of steroids are very dramatic and have been extensively studied (4, 5). Membrane steroid receptors are either coupled to intracellular pathways directly or interact with growth factor receptors (*e.g.* IGF-I receptor) or G protein-coupled receptors (*e.g.* glutamate receptors).

In addition to providing a reservoir of steroids, circulating hormonal steroids also modulate the site-specific synthesis of neurosteroids (6, 7) and their cognate receptors (8–10). This dual regulation of neurosteroidogenesis and postsynaptic receptor expression has profound implications for neurosteroid function (Fig. 1). Interactions of peripheral steroids with neurosteroid synthesis are involved in regulating reproduction in the hypothalamus.

Neurosteroidogenesis

The knowledge that the brain makes steroids *de novo* (*i.e.* neurosteroids) dates back over a quarter century (11). Studies indicate that astrocytes are the primary steroidogenic cells, and their primary steroid product is neuroprogesterone, but oligodendrocytes and neurons are also steroidogenic (12–23). Steroidogenesis begins when the C-27 cholesterol side chain

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Abbreviations: AGT, Aminoglutethimide; ER, estrogen receptor; $[Ca^{2+}]_i$, free cytoplasmic calcium; 3β-HSD, 3β-hydroxysteroid dehydrogenase/Δ^5-Δ^4-isomerase; IP_3, inositol 1,4,5-trisphosphate; mGluR, metabotropic glutamate receptor; PLC, phospholipase C; PR, progesterone receptor; StAR, steroid acute regulatory protein.

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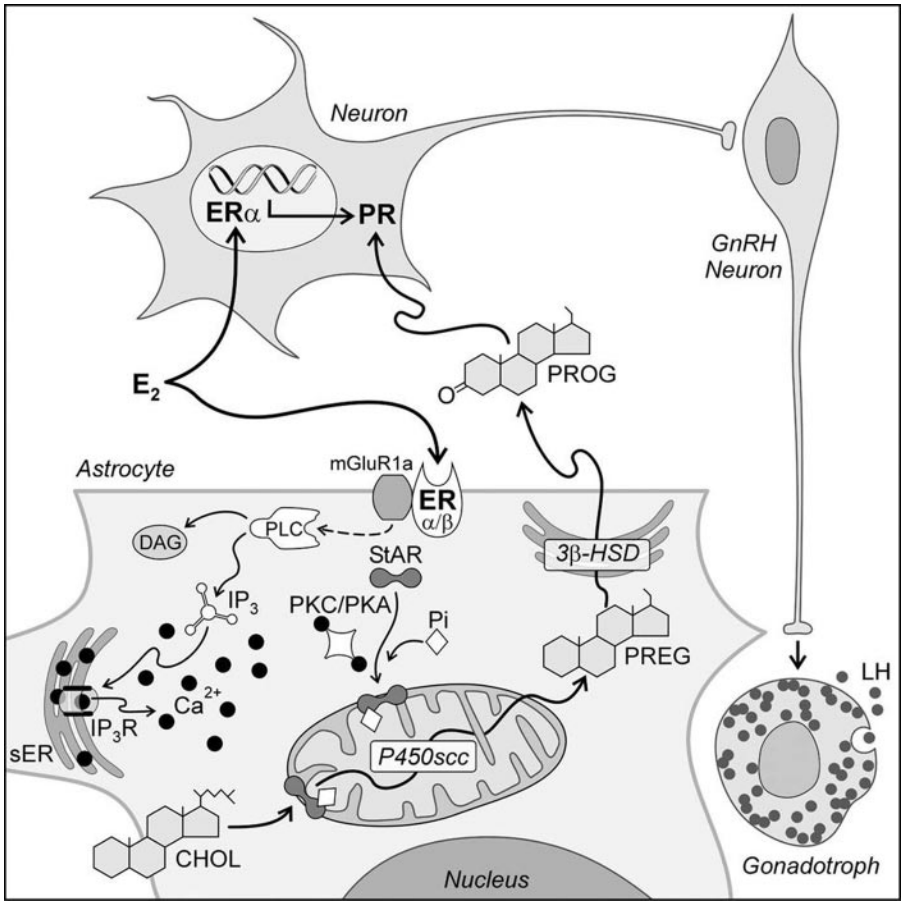

FIG. 1. A model of proposed estradiol (E_2) actions on hypothalamic cells. In astrocytes, circulating estradiol acts on a membrane-associated ER to increase $[Ca^{2+}]_i$ through the mGluR1a, which activates the PLC/IP_3 pathway, releasing Ca^{2+} from the smooth endoplasmic reticulum (sER). Protein kinase C (PKC) or protein kinase A (PKA) mediates StAR phosphorylation, activating the rate-limiting step of neurosteroidogenesis. In the mitochondrion, P450scc converts cholesterol (CHOL) to pregnenolone (PREG), which is further converted to progesterone (PROG) by 3β-HSD. Progesterone activates estradiol-induced PR in neurons that project to and stimulate GnRH neurons initiating the LH surge (60). DAG, Diacylglycerol; Pi, inorganic phosphate.

is removed by the cytochrome side chain cleavage enzyme P450 (P450scc; Fig. 1) along the inner mitochondrial membrane. 3β-Hydroxysteroid dehydrogenase/Δ^5-Δ^4-isomerase (3β-HSD) converts pregnenolone to progesterone (for review, see Refs. 24 and 25). The overall rate-limiting step in steroidogenesis is the delivery of cholesterol to the inner mitochondrial membrane. At least three proteins mediate the transport of cholesterol from the outer to the inner mitochondrial membrane: steroid acute regulatory protein (StAR); peripheral type benzodiazepine receptor; and its endogenous ligand endozepine, also called diazepam binding inhibitor (26–30) (for review, see Refs. 31 and 32). Both StAR and peripheral type benzodiazepine receptor have been localized in astrocytes (33–35).

Circulating estradiol stimulates neuroprogesterone synthesis in the adult female brain by regulating the levels of steroidogenic proteins and their activity (6). *In vivo*, estradiol significantly increased hypothalamic 3β-HSD mRNA levels and 3β-HSD enzyme activity with a time course that accounts for the increase in hypothalamic neuroprogesterone seen before the LH surge (6, 10). *In vitro*, estradiol rapidly stimulates the synthesis of neuroprogesterone in cultured female astrocytes (19, 20). Estradiol acts through membrane ERs to rapidly increase free cytoplasmic calcium ($[Ca^{2+}]_i$), leading to increase in progesterone synthesis (19, 36).

Rapid estradiol signaling in astrocytes is mediated by metabotropic glutamate receptor (mGluR) 1a

In peripheral steroidogenic tissues, steroid production is regulated by G protein-coupled receptors that induce the phosphorylation of protein kinases (37–40). In the brain, estradiol stimulates neuroprogesterone synthesis that involves the phospholipase C (PLC)-inositol 1,4,5-trisphosphate (IP_3)-$[Ca^{2+}]_i$ pathway (Fig. 1). Membrane ERs activate the PLC-IP_3 pathway through an interaction with mGluRs (41). Moreover, ERα-mGluR interactions have regulated sexual receptivity (42) and mediated antinociceptive estradiol actions in dorsal root ganglion neurons (43, 44). In our astrocyte culture system, antagonizing mGluR1a prevents the estradiol-induced $[Ca^{2+}]_i$ flux (Kuo, J., O. Hariri, G. Bondar, J. Ogi, and P. Micevych, submitted for publication). These data are consistent with the hypothesis that estradiol can act via a membrane-associated ERα that signals through mGluR1a and the PLC/IP_3 pathway, releasing $[Ca^{2+}]_i$ in astrocytes to increase neuroprogesterone synthesis (Fig. 1).

Neuroprogesterone and the LH Surge

During each estrous cycle, FSH stimulates the growth, maturation of, and steroidogenesis in ovarian follicles that produce a rapid increase in circulating, hormonal estradiol. When the circulating concentration of estradiol reaches a critical level, the negative feedback onto the hypothalamus

and anterior pituitary becomes positive. This estrogen-positive feedback initiates the surge release of GnRH and stimulates the release of LH from the anterior pituitary. Under the influence of LH, ovulation is stimulated, the ruptured follicle forms a corpus luteum and secretes progesterone.

In addition to estradiol (45–47), preovulatory progesterone is essential for the LH surge (6, 48–51). For example, ovariectomized rats treated with only estradiol show a physiological but blunted LH surge. Progesterone treatment increases the magnitude and duration of the surge (52). Although the ovary and adrenal have been proposed as sources of preovulatory progesterone (53–56), ovariectomized and adrenalectomized rats continue to produce an LH surge in response to estradiol priming (6, 57). The estradiol-induced LH surge is blocked by RU486, a PR antagonist, or progesterone synthesis inhibitors (trilostane or epostane) (6, 48, 50, 51, 58, 59).

Estradiol induction of neuroprogesterone synthesis

In the adult brain, neuroprogesterone is synthesized by astrocytes (15, 19, 20). Thus, neuroprogesterone needed to trigger the LH surge can be produced locally in the hypothalamus (6). Moreover, hypothalamic neuroprogesterone concentrations were correlated with surge levels of plasma LH ($r^2 = 0.77$), indicating that an LH surge is triggered by hypothalamic neuroprogesterone. Blocking hypothalamic neurosteroidogenesis prevents estrogen positive feedback. Intact animals injected with aminoglutethimide (AGT) (a P450scc inhibitor) into the third ventricle on the morning of proestrus had significantly reduced hypothalamic neuroprogesterone levels (49.8 ± 16.7 *vs.* 18.4 ± 12.2 pg/mg; $P < 0.05$). Although plasma levels of estradiol were similar between control and AGT rats (28.4 ± 12.3 *vs.* 17.7 ± 5.0 pg/ml), progesterone levels (27.9 ± 7.6 *vs.* 10.4 ± 4.4 ng/ml; $P < 0.05$) were attenuated. These data demonstrate that peripheral steroidogenesis was not blocked but suggested that the LH surge did not occur. This was confirmed by low LH levels on the day of the expected LH surge in AGT rats, and by a lack of a cornified vaginal cytology (estrus), and corpora lutea. AGT rats had atrophied fluid-filled uteri demonstrating the importance of neuroprogesterone for initiating the LH surge.

Summary

The idea that neurosteroids and, in particular, neuroprogesterone are important components of normal central nervous system functions is emerging. We reviewed the mechanisms of neuroprogesterone synthesis, its relationship to peripheral steroids, and the importance of neuroprogesterone to estrogen positive feedback and reproduction (Fig. 1). Initiation of the LH surge requires that circulating estradiol stimulates neuroprogesterone synthesis and induces PR in the hypothalamus. The locally synthesized neuroprogesterone acts on these PRs to initiate the release of GnRH and stimulates the surge release of LH needed for ovulation.

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