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Estradiol Promotes Purkinje Dendritic Growth, Spinogenesis, and Synaptogenesis During Neonatal Life by Inducing the Expression of BDNF

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Abstract Neurosteroids are synthesized de novo from cholesterol in the brain. In rodents, the Purkinje cell actively produces several kinds of neurosteroids including estradiol during neonatal life, when cerebellar neuronal circuit formation occurs. Estradiol may be involved in cerebellar neuronal circuit formation through promoting neuronal growth and synaptic contact, because the Purkinje cell expresses estrogen receptor-β. To test this hypothesis, in this study we examined the effect of estradiol on dendritic growth, spinogenesis, and synaptogenesis in the Purkinje cell using neonatal wild-type (WT) mice or cytochrome P450 aromatase knock-out (ArKO) mice. Administration of estradiol to neonatal WT or ArKO mice increased dendritic growth, spinogenesis, and synaptogenesis in the Purkinje cell. In contrast, WT mice treated with tamoxifen, an ER antagonist, or ArKO mice exhibited decreased Purkinje dendritic growth, spinogenesis, and synaptogenesis at the same neonatal period. Estrogen administration to neonatal WT or ArKO mice increased the expression of brain-derived neurotrophic factor (BDNF) in the cerebellum, whereas tamoxifen decreased the BDNF level in WT mice similar to ArKO mice. BDNF administration to tamoxifen-treated WT mice increased Purkinje dendritic growth. These results indicate that estradiol induces dendritic growth, spinogenesis, and synaptogenesis in the developing Purkinje cell via BDNF action during neonatal life.

Keywords Purkinje cell · Estradiol · Brain-derived neurotrophic factor · Dendritic growth · Spinogenesis · Synaptogenesis

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It is well established that neurosteroids are synthesized de novo from cholesterol in the central and peripheral nervous systems of vertebrates [for reviews, see 1, 2]. To analyze neurosteroid action in the brain, data on the regio- and temporal-specific synthesis of neurosteroids are needed. We have demonstrated that the Purkinje cell is a major site for neurosteroid formation in various vertebrates including rodents [for reviews, see 2, 3]. The rat Purkinje cell possesses several kinds of steroidogenic enzymes, such as cytochrome P450 side-chain cleavage enzyme (P450scc) and 3β-hydroxysteroid dehydrogenase/Δ^5-Δ^4-isomerase (3β-HSD), and actively produces progesterone de novo from cholesterol as a product of an increase of 3β-HSD activity during neonatal life [4, 5]. Recently, we have further demonstrated that the rat Purkinje cell expresses a key enzyme of estrogen formation, cytochrome P450 aromatase (P450arom), and produces estradiol during neonatal life [6].

Because the Purkinje cell produces several kinds of neurosteroids at particular period, this neuron is considered to serve as an excellent cellular model for the study of neurosteroid actions. It is well-known that, in the rat, marked morphological changes occur in the cerebellum after birth during neonatal life [7, 8]. Purkinje cell differentiation in

rodents occurs around embryonic day 15. After cellular fate is determined, major developmental processes of Purkinje cell, such as dendritic growth and synaptogenesis, start around birth, and the formation of the cerebellar neuronal circuit completes in the neonate, when the formation of estradiol is high [6]. Therefore, estradiol may be involved in dendritic growth, spinogenesis, and synaptogenesis in the Purkinje cell, because the Purkinje cell expresses estrogen receptor-β (ERβ) [9]. To test this hypothesis, this study investigated estrogen actions on dendritic growth, spinogenesis, and synaptogenesis in the Purkinje cell using normal wild-type (WT) mice or cytochrome P450arom knockout (ArKO) mice in the neonate.

In vivo administration of estradiol benzoate (EB), a stable form of estradiol, to newborn WT mice increased the dendritic growth of Purkinje cells and the formation of Purkinje dendritic spines and axospinous synapses. In contrast, the ER antagonist tamoxifen decreased the dendritic growth of Purkinje cells and the formation of Purkinje dendritic spines and axospinous synapses. These results indicate that estradiol is involved in cerebellar neuronal circuit formation during neonatal life by promoting dendritic growth, spinogenesis, and synaptogenesis in the Purkinje cell. The observation by estradiol administration to newborn WT mice was confirmed by the study with ArKO mice. Estradiol deficiency in ArKO mice decreased dendritic growth, spinogenesis, and synaptogenesis in Purkinje cells in the neonate. In addition, administration of estradiol to ArKO mice increased Purkinje dendritic growth, spinogenesis, and synaptogenesis. These findings suggest physiological actions of endogenous estrogen on the promotion of dendritic growth, spinogenesis, and synaptogenesis in the developing Purkinje cell.

Because it has been reported that neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), are highly expressed in the developing cerebellum [10], estradiol may induce the expression of BDNF. Administration of estrogen to newborn WT mice increased the expression of BDNF in the cerebellum. In contrast, ArKO mice decreased the level of BDNF in the cerebellum, compared with WT mice. Estrogen administration to ArKO mice restored the level of BDNF to WT mice. In addition, BDNF administration to tamoxifen-treated WT mice increased Purkinje dendritic growth. Taken together, it is considered that BDNF mediates estrogen actions on the promotion of dendritic growth, spinogenesis, and synaptogenesis in the developing Purkinje cell.

In conclusion, estradiol promotes Purkinje dendritic growth, spinogenesis, and synaptogenesis during neonatal life by inducing the expression of BDNF. These estrogen actions may be essential for cerebellar neuronal circuit formation.

Conflicts of Interest We declare that we have no conflict of interest.

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