AROMATASE AND NEUROREGENERATION

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Aromatase (*cyp19a1*) is a converting enzyme for estrogen biosynthesis. A single gene of *cyp19a1* identified in mammals and specific promoter differentially regulates E₂ produce in the brain. Interestingly, teleost fish having two isoforms of *cyp19a1*, *cyp19a1a* and *cyp19a1b*, encoding ovarian and brain aromatase, respectively. In addition, teleost fish are characterized by having highly aromatase activity and neuroregenerative response. In contrast with fish, neuroregeneration process is limited in mammals. Therefore, understanding molecular mechanism of estradiol signaling in neural injury in fish may give a new insight for the development of novel treatment in mammals, particularly in neurodegenerative diseases. Here, the author briefly reviews and discusses the potential role of neural estrogen for regeneration process.

Keywords: Aromatase, regeneration, teleost

Introduction

Estrogen is catalyzed from testosterone by aromatase enzyme.¹ It is widely known the action of estrogen on reproductive system.² However, it has been reported that estrogen receptor (ER) is highly expressed across the brain area during development,^{3,4} indicating the role of estrogen for brain development. Several line of evidences show that estradiol (E₂) is de novo catalyzed in the brain,⁵ suggesting E₂ is locally produced in the brain. Though it is difficult to distinguish the source of E₂ production to understand the role of brain estrogen in mammals, several approaches technique used to elucidate the role of brain estrogen, such as aromatase knock out (KO),⁶ Yet, the function of estrogen produced in the brain is not completely understood.

Teleost fish, including zebrafish, characterized by having two aromatase (*cyp19a1*) isoforms, *cyp19a1a* and *cyp19a1b* expressed predominantly in ovary and brain, respectively.⁷ Moreover, brain aromatase (AroB) is highly expressed in early development,⁷ suggesting the important of brain estrogen for brain development. Furthermore, zebrafish showing high neurogenic activity in the brain compared with mammals,⁸ implying a close relationship between aromatase and neurogenesis. Recent study indicate that AroB regulates serotonergic neuron in embryonic zebrafish, which possibly one of the mechanisms of AroB in modulating brain neurogenesis.⁹ Thus, zebrafish makes a good model to understand the role of brain estrogen.

Glial Aromatization

In mammals, aromatase is expressed in glia and neuronal cells in the brain.¹⁰ Interestingly, AroB expression is restricted to radial glial cells (RGCs) in zebrafish, acting as neural progenitor.¹¹ To evaluate the role of brain aromatase in neuroregeneration, several studies performed brain

injury. Following brain injury, aromatase level is increase and starts to express in the astrocyte.¹²⁻¹⁴ Indeed, aromatase is exhibited proliferative activity in RGCs.¹⁵ Similar to that observed in mammals, induction of AroB⁺ RGCs in fish concurrence with the increase of proliferating cell nuclear antigen (PCNA⁺) cells.¹⁶ These results support that upregulation of E₂ biosynthesis is necessary as a response to neural injury, possibly to promote regeneration and repair.

Spinal cord is a part of central nervous system. Recent study showed that zebrafish connective tissue growth factor a (ctgfa) together with radial glia accelerated the bridging process in spinal cord injury.²³ Aromatase expressions are known shifted from neuron to reactive astrocyte and might exerts its neuroprotective effect in the end stage of amyotrophic lateral sclerosis (ALS).²⁴ Indeed, the inflammatory mediators stimulate the activation of *cyp19a1* gene during neural injury (Fig. 1)¹⁸ and AroB is expressed in fish spinal cord.¹⁶ Hence, it is possible to hypothesize that AroB radial glia of spinal cord might be contributes as one of the important factors in stimulating neural regeneration. Furthermore, several evidences indicates that additional of E₂ speed up the recovery time in spinal cord injury.^{25,26} Taken together, this review emphasized the importance of brain-formed estrogen for neural regeneration and repair. Thus, E₂ might be useful as treatment for neurodegenerative diseases in mammals.

Conclusion

Highly expression of brain aromatase and neuroregenerative capability in fish makes a zebrafish a useful model for evaluating the function of brain aromatase in neurogenesis. Estradiol produce in the brain is involved in regulating brain repair and plasticity in fish.

Figure 1. Possible mechanism of aromatase induces spinal cord regeneration. Pro-inflammatory mediators induce the upregulation of *cyp19a1b* and *gfap* in glial cells¹⁷⁻¹⁹. As a result, there is an increase of E2 biosynthesis by the activation of AroB, and create a positive loop between E2-AroB. Through genomic (nuclear ER) signaling, E2 stimulate brain-derived neurotrophic factor (BDNF), a neurotrophic factor, to promote cell proliferation²⁰. Interestingly, BDNF auto-regulation bring a positive feedback loop to increase its production, indicating that this mechanism is important to obtain BDNF levels in modulating physiological outcome in neuron²¹. In addition to genomic action, it is well established that non-genomic (membrane ER, GPER/GPR30) signaling is important for rapid action of E2 in the brain. Binding of E2-GPER initiates the activation of *ctgf* gene to further stimulates cell proliferation²², which possibly speed up neural repair in fish.

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