Special Article

Modulation of Brain Synaptic Plasticity by Steroid Hormones

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Brain Synaptic plasticity has been studied extensively in the past decade. Alterations in synaptic plasticity are implicated in both normal brain functions and disorders. The molecular events leading to synaptogenesis or neurogenesis are being delineated. Several neurotransmitter receptors may be involved, but direct relation to NMDA receptors and BDNF peptides are suggested. Both genomic and non-genomic actions of steroid hormone on brain neurotransmission have been demonstrated. The direct action of neurosteroids to modulate neurotransmitter receptor binding and responses can be one of the mechanisms in the regulation of brain synaptic plasticity. Several lines of evidence in support of this hypothesis are reviewed in the present article.

Keywords: *Brain, Synaptic plasticity, Steroid, Neurotransmission*

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The concept of brain plasticity has gained general acceptance for decades and its functional implications have been explored extensively[1-5]. These included learning and memory[1-3], reward and reinforcement[2,3], stress response[4,5], aging and psychiatric disorders such as depression and Alzheimer's dementia[4,5]. The roles of steroid hormones on brain functions have also been well documented[6-10]. For example, corticosteroids have a pivotal role in stress responses[6] while sex steroid hormones are involved in a variety of behavioral development and psychological alterations[7-10]. The molecular mechanisms for both synaptic plasticity and parts of neurosteroid actions on brain functions are related to neurotransmitter receptors and the consequent steps of signal transduction. The present article reviews some of the significant findings in brain synaptic plasticity and in the actions of neurosteroids on brain neurotransmission. The potential relevance of neurosteroid actions to synaptic plasticity will be discussed.

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Synaptic plasticity

Synaptic plasticity is the nervous systems ability to modify the number, nature, and level of activity of its synapses. These changes include synaptogenesis and synaptic remodeling which can occur both in a developing and in an adult brain. One model that is extensively used in the study of brain plasticity is the seasonal morphological and functional changes in song bird brain. The volumes of entire brain regions that control song increase dramatically in anticipation of the breeding season[11].

From the studies in all models of synaptic plasticity both in vitro and in vivo, the alterations may involve regulation of signal transduction, gene expression and structural changes of neuronal spines and dendritic tree. The molecular mechanisms of these changes have been under intensive investigation in recent years. These include the studies on calcium signaling[12], $GABA_A$ receptor[13-14], cholinergic synapses[15], dopamine[16], serotonin[17], brain-derived neurotrophic factor (BDNF)[17,18], and most recently on glutamate receptors[19-21]. Several protein mediators and genes are found to be involved in the signal transduction cascades, and the alterations at these steps result in new protein synthesis, new membrane formation and finally synaptogenesis or neurogenesis[22-26].

Nongenomic action of steroid hormones

Steroid hormones are recognized as producing effects via intracellular receptors, activating gene transcription to mRNA that encodes many enzymes and receptor protein syntheses. These genomic and long-term effects of steroids are involved in a variety of physiological functions from fetal development, learning, sexual and other behaviors, aggressiveness, and psychological alterations in the menstrual cycle or other disorders[6-10]. However, several lines of evidence suggest that many effects of steroids may not involve genomic action. These effects are rapid (within seconds or minutes), insensitive to inhibitors of protein synthesis, and are membrane-mediated action. The term nongenomic action is later generally accepted for this membrane action[27-30]. Several proliferative and electrophysiological effects of steroids are clearly mediated by membrane actions. Examples of nongenomic steroid actions include rapid aldosterone effects in lymphocytes and vascular smooth muscle, vitamin D3 effects in epithelial cells, progesterone action in human sperm, neurosteroid effects on neuronal functions and vascular effects of estrogen[30]. Apparently, both genomic and nongenomic actions are responsible for a wide range of steroid effects. Examples of recent findings are summarized in the present review.

Cortisol

The roles of cortisol in physiological functions and the pathology of brain have been extensively reviewed by several authors[6] and will not be emphasized in the present review. Its relation to the aging process, however, has recently received much attention. The quantitative and qualitative changes of hypothalamus-pituitary-adrenal (HPA) axis are good examples of age-related modifications of neuroendocrine secretions[31]. The consequences of alterations in the integrative activities of HPA axis may promote and amplify many aging phenomena. The dampening of cortisol and dehydroepiandrosterone (DHEA) circadian fluctuation and the reduced DHEA/cortisol ratio are implicated in several clinical disorders such as atherosclerosis, abnormal immune responses, and impairment of cognitive and affective performance[31,32]. The relationships between cortisol-stress responses and brain synaptic plasticity will be discussed in the next section.

Testosterone

The physiological roles of testosterone on sexual behaviors are well documented[10]. Nongenomic actions of testosterone, however, are implicated from the later findings on its membrane actions. Testosterone acetate and other steroids inhibited ^{3}H-QNB binding to muscarinic receptors at hypothalamic membranes with clear structural activity relationships and stereospecificity[33]. Castrated rats exhibited low electrical activity at the preoptic area which can be activated directly by testosterone[34]. Moreover, testosterone was found to antagonize the amphetamine effects on dopamine release from mesolimbic structures[35]. Both genomic

and nongenomic actions, however, may be involved in the effects of testosterone on neurotransmitter regulation. These include the elevation of tyrosine hydroxylase activity and the down-regulation at serotonin-3 receptor[36], enhancing in choline acetyltransferase and monoamine oxidase activities and increasing ϒ-aminobutyric acid (GABA) turnover[34]. Recent studies have found that testosterone, acting through its androgenic metabolite 5α-dihydrotestosterone (DHT), can increase dendritic spine density in CA1 region of the male rat hippocampus[37]. This effect may be mediated by the increased in N-methyl-D-aspartate (NMDA) receptors[37]. The roles of testosterone in cognitive function and possible relation of andropause to Alzheimer's disease have been recently reviewed[38].

Estrogen

The roles of estrogens in coordinated regulation of complex physiological process to maintain homeostasis have been well documented in both animals and human studies[7,8,39]. These include functions in reproduction, stress responses, feeding, sleep cycles, temperature regulation, and motivated behaviors. The nongenomic mechanisms in these rapid responses to estrogen have been proposed. For example, estrogen induced proliferation of breast cell lines and dilatation of blood vessels[40] are believed to involve plasma membrane-associated estrogen receptors leading to rapid activation of endothelial NO synthase[41,42].

Several studies have demonstrated the direct actions of estrogen on neurons. Effect of estrogen on hypothalamic electrical activity can be found shortly after intravenous injection[43]. Also in hypothalamus, estrogen alters the responses to μ-opioid, GABA, proopiomelanocortin (POMC), and dopamine receptors[44]. The coupling of membrane estrogen receptors to G-protein-mediated phosphorylase C leading to the regulation of protein kinase activies in hypothalamic neurons has been characterized[44]. This action of estrogen may be responsible for the rapid modulation of GnRH neurons in the hypothalamus through opioid and GABA systems. The rapid modulation of prolactin released by dopaminergic neurons may also be affected by estrogenic action.

Evidence for direct feedback of neurosteroids on GnRH neurons was also obtained from the study by voltage-clamp recording of the GnRH responses in brain slices. Allopregnanolone increased while dehydroandrosterone sulfate decreased the responses of GnRH neurons to activation at GABA receptors[45].

Estrogen exerts effects on brain neurotransmission in several other brain areas; for example, forebrain cholinergic system, hippocampus, cerebral cortex, caudate putamen, raphe nucleus, and locus coeruleus[7,8,46,47]. Extensive studies were emphasized on the effects of estrogen at hippocampal synapses. It has been confirmed that estrogen increases synaptogenesis in this brain area[39,48,49]. This effect may be mediated by reducing GABA interneuron activity and/or increasing NMDA receptors[48-51]. The role of estrogen in cognitive function and its uses in prevention of Alzheimer's dementia have been reviewed elsewhere[52]. Its possible mechanism in modulating neurotransmission and synaptic plasticity will be discussed.

Progesterone

The nongenomic actions of progesterone are supported by the evidence that they are rapid, insensitive to inhibitors of transcription, mimicked by steroids coupled to cell membrane-impermeant molecules, and demonstrable in cells that do not express the classic genomic progesterone receptor[9,27,53]. Nongenomic action of progesterone has been demonstrated on the activation of acrosomal reaction in sperm[54]. Two proteins representing the possible surface progesterone

receptors were indentified by using antibody directed against progesterone receptor. Another cell that has been extensively studied for rapid nongenomic action of progesterone is the Xenopus oocyte[53]. This action is mediated by a G-protein-coupled receptors distinct from the classic intracellular progesterone receptor. Progesterone binding at membrane receptor may activate cytoplasmic tyrosine kinase and mitogen-activated kinase (MAPK) pathway[53,54].

The direct action of progesterone derivatives on brain activity was reported more than 60 years ago[55]. Structure-activity relationships and stereospecificity for these effects are confirmed[56]. Later membrane receptor binding studies revealed that progesterone potently modulates ligand binding at GABA[57-59] and muscarinic receptors[33,60]. Actions of progesterone derivatives on GABA and muscarinic receptors were later demonstrated in several other tissues[61-63]. Actions of several groups of drugs are now postulated to involve neurosteroids modulation at a number of neurotransmitter receptors[61,62].

Steroid hormones and synaptic plasticity

The best example of evidence to demonstrate the roles of steroid hormones in synaptic plasticity may be the studies on hippocampal dendritic spine density under the influence of estradiol[48,64]. NMDA receptors may be the major target which was altered in animals treated with estradiol[49,50,64]. The same action and effects are also possible for androgens[65]. Progesterone also reduces neuronal cell death but may involve different mechanisms on apoptotic protein[66].

Other lines of evidence are the studies on the effects of stress and adrenal steroids on the structural changes in neurons in hippocampus, amygdala, prefrontal cortex, and piriform cortex which can be prevented by certain psychotherapeutic drugs[67-69]. In these studies, stress given to animals in different models can cause neuronal dendritic spine shrinkage which can be reversed or prevented by an antidepressant such as tianeptine[69].

As has been reviewed earlier, cortisol, testosterone, estrogen, and progesterone can modulate neurotransmitters receptor binding and possibly signal transduction cascades. Receptor function and signal transduction from several mediators are related to the transcription and protein synthesis, which result in synaptic plasticity. The future questions for research into this area should not be what is related to, but how the sequences of events lead to brain synaptic plasticity. Many investigators are working to elucidate signaling pathways after steroid membrane binding[70], and this should be promising for our better understanding on their relations to muscarinic, GABA, glutamate and BDNF responses.

Conclusion

Multiple factors and mechanisms are involved in brain synaptic plasticity. Cellular adaptations are detected at all levels including regulation of neurotransmitter receptors, signal transduction cascades, and gene transcription. These neurochemical adaptations can lead to alterations in synaptic strength, dendritic spine, cell morphology and cell number. Several neurotransmitter receptors may be involved, including acetylcholine, GABA, dopamine, and serotonin, but recent studies point to BDNF and NMDA receptors as critical key steps in these regulations. Signal transduction cascades from these receptors leading to alterations on gene transcription have been the subject of wide interest in recent years, and certainly will help in better understanding on the mechanism of synaptic plasticity.

Steroid hormones, i.e., cortisol, testosterone, estradiol, progesterone as reviewed in the present article, exert effects on brain by both genomic and nongenomic mechanisms. There is no doubt about the roles of these neurosteroids on brain synaptic

plasticity, but the question is how. Membrane actions of steroids have been demonstrated by several study methods including membrane receptor binding and electrophysiological responses. They can modulate the action at a number of neurotransmitter receptors such as opioid, GABA, dopamine and muscarinic cholinergic receptors. Estradiol and testosterone may induce synaptogenesis by increasing the responses at NMDA receptors, while progesterone is potent at GABA and muscarinic receptors. Steroid membrane receptor signaling pathways are the subject under extensive study now, and their relations to BDNF and NMDA receptors are worthwhile for future study.

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บทบาทของสเตียรอยด์ฮอร์โมนในการปรับภาวะยืดหยุ่นที่จุดประสานประสาทในสมอง

บพิตร กลางกัลยา

ภาวะยืดหยุ่นที่จุดประสานประสาท (synapse) ในสมอง เป็นเรื่องที่มีผู้ศึกษามากในปัจจุบัน และสามารถนำไปอธิบายกลไกการเรียนรู้ การจำ การตอบสนองต่อความเครียด และการเกิดพยาธิสภาพของสมอง ซึ่งเกิดโดยมีการปรับระดับการทำงานหรือปรับรูปร่างที่รอยประสานที่ปลายเซลล์ประสาท กลไกระดับโมเลกุลที่เกิดขึ้นเป็นเรื่องที่กำลังวิจัยกันอยู่อย่างกว้างขวาง โดยมีเรื่องการตอบสนองที่เปปไทด์ BDNF และตัวรับของกลูตาเมตชนิด NMDA เป็นข้อมูลที่เกี่ยวข้องโดยตรง ในอีกด้านหนึ่งการศึกษาเรื่องการออกฤทธิ์ต่อสมองของสเตียรอยด์ฮอร์โมนมีข้อมูลชัดเจนว่าฮอร์โมนเหล่านี้มีการออกฤทธิ์ที่ผนังหุ้มเซลล์โดยมีผลต่อการออกฤทธิ์ของสารส่งผ่านประสาทหลายชนิด รวมทั้ง GABA, glutamate, dopamine, acetylcholine ผลจากการออกฤทธิ์ปรับระดับการทำงานของสารส่งผ่านประสาทเหล่านี้ น่าจะเป็นเหตุผลที่อธิบายบทบาทของสเตียรอยด์ฮอร์โมนต่อการพัฒนาการของเด็ก ต่อพฤติกรรมการตอบสนองต่อความเครียดและการเปลี่ยนแปลงทางจิตประสาทที่เกิดขึ้นเมื่อมีการเปลี่ยนระดับของฮอร์โมน และมีความเป็นไปได้ที่ผลเหล่านี้ส่วนหนึ่งน่าจะเกิดจากการออกฤทธิ์ปรับภาวะยืดหยุ่นที่จุดประสานประสาทในสมอง