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Recent Advances in Neurosteroids: A Review

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Abstract

A progressive decline of cognitive and memory functions, compared to the average young-life performance, characterize brain aging. A crucial event for the activation of protein kinase C is its translocation from the cytosol to different intracellular sites and recent studies have demonstrated the key role played by several anchoring proteins in this mechanism. The defective activation of PKC-dependent pathways during aging is due to a defective mechanism of translocation of the kinase because of reduced levels of the major anchoring protein RACK-1 (receptor for activated C kinase). Pharmacological strategies aimed at the correction of age-associated memory deficits have been mostly focused on neurotransmitters using direct or indirect agonists. Among these the activities of dehydroepiandrosterone (DHEA), pregnenolone (PREG) and their sulfates, have been extensively studied. Some steroids are synthesized within the central and peripheral nervous system, mostly by glial cells. These are known as neurosteroids. In the brain, certain neurosteroids have been shown to act directly on the function of membrane receptors for neurotransmitters. Neurosteroids also regulate important glial functions such as the synthesis of myelin proteins. An important role for neurosteroids in myelin repair has been demonstrated in the rodent sciatic nerve, where progesterone and its direct precursor pregnenolone are synthesized by Schwann cells.

Keywords: Aging; Memory; Protein kinase C; Dehydroepiandrosterone; Pregnenolone

Introduction

In 1981, Corpéchot [1] introduced the term "neurosteroid" (NS) to name, dehydroepiandrosterone sulfate (DHEAS), a steroid compound. DHEAS was found at high levels in the brain long after gonadectomy and adrenalectomy, and later shown to be synthesized by the brain. Androstenedione, pregnenolone, their sulfates and lipid derivatives as well as tetrahydro metabolites of progesterone and deoxycorticosterone (DOC) were reported to be neurosteroids. The term "neuroactive steroid" (NAS) refers to steroids that may modify the neural activities [2]. Pregnenolone sulfate (PREGS) is reported to be the most potent memory-enhancing neurosteroids, as it acts as a potent positive modulator of N-methyl-d-aspartate receptors (NMDARs) and a negative modulator of gamma-aminobutyric acid receptors (GABA (A) R) [3].

Neurosteroids are produced within the brain. Neurosteroids are cholesterol-derived molecules and they exert trophic and protective actions. Neuroinflammation and neurodegeneration is caused by Infection of human and feline immunodeficiency viruses (HIV and FIV, respectively) which may ultimately cause neurological deficits. Secretion of neuroinflammatory host and viral factors by glia and infiltrating leukocytes mediates the principal neuropathogenic mechanisms during lentivirus infections. Virus or inflammation-mediated neurodegeneration can be treated by Neurosteroids [3].

Steroid hormones exert their effects by binding to intracellular receptors that act as transcriptional regulators of gene expression. Investigations have reported that some steroids also bind to specific neurotransmitter receptors and alter neuronal excitability which may produce nongenomic effects. Steroids possessing these properties have been named as "neuroactive steroids". The neuroactive steroids include pregnenolone and pregnenolone sulfate, dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEA-S), and progesterone, as well as some 3-reduced neurosteroids, including allopregnenolone and tetrahydrodeoxycorticosterone (THDOC). Neuroactive steroids can exist as circulating steroid hormones or they may be produced within the brain from cholesterol. If they produced in the brain, then they are referred to be neurosteroids. Enzyme P450 side-chain cleavage catalyzes the conversion of cholesterol to pregnenolone. Several enzymes are involved for the conversion of pregnenolone to a number of other neurosteroids. Neuroactive steroids act as allosteric modulators at several neurotransmitter receptors, like Gamma amino butyric acid (GABA), NMDA, glutamate and 5-HT3 receptors. It has been reported that NASs play important role in the pathophysiology and/or pharmacotherapy of a number of neuropsychiatric conditions. The immunosuppressive lentiviruses, including human, simian, and feline immunodeficiency viruses (HIV, SIV, and FIV, respectively) are reported by systemic immune disruption followed by immunosuppression, which leads to the acquired immunodeficiency syndrome (AIDS) with the concurrent development of neurological disorders, termed neurovirulence [4].

Vitamin D (calciferol) is a fat-soluble seco-steroid synthesized in skin (as hormone) or ingested with food (as vitamin). Vitamin D is biologically inactive but it undergoes bioactivation by double hydroxylation in liver and kidney and forms 1, 25-dihydroxyvitamin D (1, 25-D, calcitriol, soltriol) which are the biologically active form of vitamin D. Vitamin D functions by regulating mineral homeostasis, tissue proliferation, differentiation and apoptosis, as well as the cardiovascular and immune systems. 1, 25-D regulates the expression of numerous target genes through the nuclear vitamin D receptor (VDR), belonging to a common family of steroid receptors that also includes steroid, glucocorticoid and retinoic acid receptors. The mechanism of vitamin D includes the binding 1, 25-D, the VDR undergoes a conformational change and binds

to vitamin D response DNA elements in the promoter regions of target genes, controlling their transcription. VDR autoradiography can be used to study vitamin D brain targets and its in-vivo histopharmacology with high resolution and sensitivity. It has been reported there is high-affinity of vitamin D binding to the brain. Mounting evidence for the presence of vitamin D, its receptors (VDR), and enzymes of bioactivation/metabolism in brain neurons, glial cells, brain macrophages, spinal cord and the peripheral nervous system confirms its role as an autocrine or paracrine neuroactive steroid [5].

Endocannabinoids in the CNS regulate the information flow in neuronal networks associated with sensory integration and memory processing. A role of endocannabinoids in cognitive functions has been reported in behavioral studies using SR141716A, the selective antagonist of the cannabinoid receptor 1 (CB1R) that is the main cannabinoid receptor in the CNS. A high density of CB1Rs and high endocannabinoid levels is present in the hippocampus. Exogenous cannabinoids also modulate memory, hippocampal neuronal activity, and synaptic plasticity. Cannabinoid agonists decrease long-term potentiation and depression and stop the neurotransmitter release, especially acetylcholine (ACh). The septohippocampal cholinergic projection is reported to be the main neurotransmitter system in encoding learning and memory. It has been reported that low doses of cannabinoids stimulate, whereas high doses inhibit, these functions [6].

Steroid synthesized from cholesterol in the central nervous system but not from gonads and adrenal glands has been defined as neurosteroids. Neurosteroids play a protective role on the neurons. Neurosteroids cures the disorders of nervous system like neurodegenerative diseases. Neurosteroids are synthesized in central nervous system and they modulate brain cell properties and functions. Pregnenolone and pregnenolone sulphate play an important role in memory and learning. The 3-alpha-hydroxy metabolites of progesterone have anaesthetic effects.

It has also been reported that progesterone prevents depression-like behavior. The antidepressant and neuroprotective effects of dehydroepiandrosterone have also been reported. Testosterone and estradiol also acts as neuroprotective agents.

Neurotransmitters and Growth Factors involved in Learning

A number of neurotransmitter receptors and growth factors influence synaptic plasticity and memory. CaMKII is activated by calcium *via* phosphorylation, which in turn phosphorylates AMPA receptors and increases their number in the postsynaptic membrane. A change in the number and activity of AMPA receptors in synapses is the proposed mechanism for up- or down-regulating synaptic function in LTP or LTD. CaMKII is required for LTP in the hippocampus and this kinase plays an important role in the local storage of memory in individual synapses. Neurotransmitter receptors like metabotropic glutamate, muscarinic cholinergic, dopamine, and adrenergic receptors are linked to MAPK activation through PKA or PKC. Linkages between these receptor pathways and the MAPK cascade and transcriptional activation may be responsible for effects of commonly prescribed drugs on cognition. For example, anticholinergic or glutamate blocking drugs can impair memory, whereas stimulants or antidepressants that enhance effects of serotonin, dopamine, or norepinephrine can enhance cognition.

The Central nervous system (CNS) process information with the help of chemical messenger like neurotransmitter, neuromediators, neuromodulators, neuroregulators, and neurotropic factor which act specifically to mediate neurotransmission. Some examples of neurotransmitter are nor adrenaline, adrenaline, dopamine, Gamma Amino Butyric Acid (GABA), glutamate, acetylcholine, 5-hydroxytryptamine (5-HT), peptides: endorphins, seretonin, glycogen and vasoactive intestinal polypeptides (VIP) etc. Some examples of neuromodulator are prostaglandins (PGs), purines and neuropeptides which interact with their receptors and regulate the CNS functioning [7]. Nitric oxide (NO) is also an important neurotransmitter of the brain. NO induces cognitive behavior in experimental animals. Learning and memory impairment occurring in man and animals due to defect in NO activity in the brain is also reported. It occurs as a consequence of pathological conditions such as epilepsy, stress, diabetes and side effects of therapeutic agents [8].

Acetylcholine: Sleep and Thermoregulation

Neurosteroids are cholesterol-derived molecules synthesized within the brain, which exert trophic and protective actions. neuroinflammation and neurodegeneration is caused by infection by human and feline immunodeficiency viruses (HIV and FIV, respectively) causes, leading to neurological deficits. Neuroactive steroids can act as allosteric modulators at several neurotransmitter receptors, including-aminobutyric acid (GABA), NMDA glutamate, 5-HT3, GABA-A receptor and the NMDA receptor being the most crucial [4].

The term neurosteroid does not signify a particular class of steroids, but only refers to their site of synthesis the nervous system. Progesterone, for example, which is a hormone produced and secreted by the ovaries and adrenal glands, is considered to be a neurosteroid if it is synthesized within the brain or peripheral nerves. Steroidogenesis starts with the transformation of cholesterol to pregnenolone by the cytochrome P450scc. This step is characteristic of the steroidogenic cells of endocrine glands, including the testes, ovaries, and adrenal glands. The pregnenolone levels are much higher in the brain than in blood. This may be due to the cerebral retention of circulating hormone, as pregnenolone persisted in the brain days after castration and adrenalectomy. It was also reported that the cytochrome P450scc is expressed in the white matter throughout the brain.

Neurosteroids: Biological Significance

They are essential for nervous functioning and they also protect the brain from reduction in circulating steroid levels. The blood levels of pregnenolone and progesterone are very low in males and their nervous system may depend on a local production of these steroids. Progesterone synthesized by glial cells plays an important role during nerve regeneration in male rodents. It has been also reported that progesterone inhibits the neuronal nicotinic acetylcholine receptor and activates hypothalamic oxytocin receptors, whereas its 5a, 3cc-reduced metabolite, 3a, 5ocTH-progesterone, activates the chloride channel of the GABA-A receptor complex. On experimentation on rats, it was noticed that the local infusion of sulphated pregnenolone, an inhibitor of the GABAA receptor, into the *nucleus basalis magnocellularis* improves memory performance. Infusion of 3a, 5a,-tetrahydroprogesterone, an activator of the GABAA receptor, has the opposite effect. Pregnenolone and steroids metabolically derived from it also have memory enhancing effects in mice [9].

Biosynthesis of Neurosteroids in Central Nervous System

Neurosteroids are syntehsized from cholesterol *de novo* by neurons and glial cells. The steroidogenic enzymes including P450scc, 3β-hydroxysteroid dehydrogenase/Δ5-Δ4-isomerase (3β-HSD), P450 17α-liyase, 17-β-hydroxysteroid dehydrogenase (17β-HSD) and P450 aromatase are expressed in the central nervous system of mammalian and non-mammalian vertebrates. Pregnenolone which is a precusor of dehydroepiandrosterone is formed from cholesterol in the presence of P450scc. Progesterone is formed from pregnenolone by the 3β-HSD. Testosterone is formed by both progesterone and DHEA. Estradiol is formed from testosterone in the presence of P450 aromatase [2].

The changes of Neurosteroids in Neurodegenerative Diseases

Changes in neurosteroid levels and their steroidogenic enzyme expressions are responsible for physiopathological conditions. Aromatase expression is increased during the brain injury in mamalian and birds. It has been reported that in the patients of affective depression the concentration of cerebrospinal fluid pregnenolone is decreased. The local impairment of progesterone synthesis is linked with the initiation and progression of cerebellar lesions [10].

Preventive and Therapeutic Use of Neurosteroids in Neurodegenerative Diseases

It has been reported that neurosteriods exhibit neuroprotective, myelinating, antiapoptotic and antiinflammatory effects. The use of 17β-estradiol and progesterone protects the brain from demyelination and stimulate remyelination. Progesterone plays an important role in myelin formation. Estriol and progesterone inhibits the microglial production of nitric oxide which is toxic to oligodendrocytes. It has also been reported that progesterone prevents depression-like behavior in a model of Parkinson's disease rats. Progesterone and allopregnanolone administrations reduce the cell death, gliosis, and functional deficits after traumatic brain injury. Allopregnanolone exerts an analgesic effect in the experimental pain model. On the neonatal administration, estradiol promotes myelin formation. The estradiol treatment is useful to enhance recovery after ischemic injury. Hormonal alterations during gestation have a protective effect on multiple sclerosis. Additionally, estriol treatment with the pregnancy doses has been found to be effective in treatment of non-pregnant female multiple sclerosis patients. Administration of 17-beta-estradiol protects oligodendrocytes from cytotoxicity in a dose-dependent manner. Dehydroepiandrosterone protects hippocampal neurons against neurotoxication [10].

Discovery of the Purkinje cell as a Major Site for Neurosteroidogenesis

Neurosteroids are formed from cholesterol in the Purkinje cell. Pregnenolone, a 3-hydroxy-5-steroid, is a main precursor of steroid hormones secreted by peripheral steroidogenic glands, such as gonads and adrenals. Pregnenolone is formed by the cleavage of the cholesterol side-chain by P450scc, a rate-limiting mitochondrial enzyme originally found in peripheral steroidogenic glandular cells. Therefore, it is essential to demonstrate the presence of P450scc in the Purkinje cell. The distribution of immunoreactive cell bodies and fibers was coincident with the location of somata and dendrites of Purkinje cells. The presence of P450scc in Purkinje cells was confirmed by the Western immunoblot analysis. This showed the neuronal location of P450scc [10].

Conclusion

The neurosteroids are synthesized in the central nervous system in mammalian and non-mammalian vertebrates have been reported. Neurosteroids mediates brain cell properties and functions. Neurosteroids have many actions including myelinating, antiapoptotic, anti-inflammatory and antidepressant. The neuroactive steroids are utilized for the prevention and therapy of various neurodegenerative diseases like multiple sclerosis, Parkinson's disease, autoimmune encephalomyelitis, traumatic brain injury and ischemic injury [11].

It has been reported that brain neurosteroids are the 4th generation neuromessengers, synthesized within the neurons. These neurosteroids cause acute modulation of neuron–neuron communication through neurotransmitter receptors. First generation neuromessengers are neurotransmitters such as glutamate, GABA and acetylcholine. Second generation neuromessengers are catecholamines such as dopamine and serotonin. Third generation neuromessengers are neuropeptides such as Enkephalin, vasoactive intestinal peptide, and substance P. Although 1st–3rd generation neuromessengers are stored in synaptic vesicles, and are rapidly exocytosed from presynapses, neurosteroids are produced in mitochondria and microsomes driven by Ca^{2+} signals, and released by passive diffusion as paracrine messengers. DHEA potentiates the GABA–induced Cl^- current but DHEA sulfate (DHEAS) suppresses it Neurosteroids are reported to be effective in learning and memory of animals [12].

A progressive decline of cognitive and memory functions, compared to the average young-life performance, characterize brain aging. The changes in performance may depend upon altered activity of neurotransmitters acting on attention and memory trace formation (acetylcholine, catecholamines, glutamate) or the failure of the transduction mechanisms linked to receptor activation. One of the fundamental cellular changes associated with brain aging is the alteration of mechanisms involving the activity of the calcium phospholipid-dependent protein kinase C (PKC). Recently, attention has been paid to the memory enhancing properties of some steroid hormones, namely 'neurosteroids'. Among these the activities of dehydroepiandrosterone (DHEA), pregnenolone (PREG) and their sulfates, have been carefully studied. These neuroactive steroids can regulate neuronal function through their concurrent influence on transmitter-gated ion channels and gene expression. There is the possibility that DHEA, among other neurosteroids, could modulate directly the age-associated impairment of PKC signal transduction and provide experimental evidence that DHEA can revert the alteration of RACK-1 anchoring protein expression [13].

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