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The Role of Pregnenolone in Inflammatory Degenerative Brain Disease

Ferri C[1] and Fioranelli M[1,2*]

[1]Marconi University, Rome, Italy

[2]University B.I.S. Group of institutions, Punjab Technical University, Punjab, India

***Corresponding Author :** Massimo Fioranelli
Professor, Marconi University
Rome, Italy
Tel: +61 74 9232008 **E-mail:** massimo.fioranelli@gmail.com

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Abstract

Pregnenolone is a steroid hormon that is directly produced by the brain as well, that is why it is defined neurosteroid. Pregnenolone carries out several cerebral functions, such as neuroprotection, neuroplasticity and neurogenesis; moreover, it regulates the mood and the memory. All of these functions are possible thanks to the relationships pregnenolone establishes with some of the most important neurotransmitters. As a matter of fact, it connects to GABA receptors, NMDA receptors and sigma-1 receptors. It has been proved that pregnenolone is concerned with some important neurological and psychiatric diseases. Actually, some scientists hypothesize that it could also be useful to these diseases' pharmacotherapy. This article illustrates the ways pregnenolone may be used and the ways it is concerned with neurological and neuropsychiatric diseases.

Keywords

Pregnenolone; Inflammatory; Brain Disease

Introduction

Pregnenolone is a neurosteroid, a hormone produced by the central nervous system. Moreover, it is synthesized by other organs like the liver, the adrenal glands, the testicles, the ovaries and the skin. Pregnenolone's chemical structure is 3-alfa-idrossi-5-beta-pregnen-20–one [1] and it is synthetized in this way: adenohypophysis secretes ACTH hormone, which reaches arenal glands' cortical region and stimulates to produce cortisol. The latter binds to StAR protein in the outer membrane of mitochondria and gets inside; there, cytochrome enzyme P450scc cuts the cortisol chain, so that pregnenolone is product [1,2].

Recently, this neurosteroid has shown interesting cerebral properties. As a matter of fact pregnenolone, binding to some neurotransmitters [3], can have a sort of propeties regarding neuroprotection, neuroplasticity and neurogenesis and can also regulate memory and mood [1].

Before considering how pregnenolone may be used to treat some important neurologic or psychiatric diseases we must evaluate pregnenolone's influence over some neurotransmitters:

GABA

GABA is an inhibitory neurotransmitter, which means that it slow mental functions and produces relaxation and torpidity. Pregnenolone binds to GABA receptor called GABA A [3], then it can exercise two opposite functions: if it is simple pregnenolone it will act as an agonist, encouraging neurotransmitter recaptation; on the other side, pregnenolone sulfate acts as an antagonist, which means that it inhibits the recaptation and GABA's consequent action [4,5].

NMDA

There is an important relationship between pregnenolone and glutamate receptors [1]. Pregnenolone sulfate acts as an antagonist upon NMDA receptors; as a consequence, it favor calcium ions to enter the postsynaptic compartment and improves memory fixation [6,7]. Furthermore, pregnenolone keeps the balance between GABA and glutamate because of the influence it has on them, favouring the neuroprotection.

SIGMA 1

This receptor is involved in calcium release process and it can influence psychiatric phenomena such as schizophrenia and depression, because of its action on dopamine. Several neurologic functions pregnenolone exercises in the central nervous system are mediated by the stimulation of these receptors [1].

Some studies demonstrate that SIGMA 1 receptors could have an antipsychotic function [8]. This would be due to the fact that these receptors are antagonist over dopamine, which is the responsible of schizophrenia positive symptoms [9].

The aim of this paper is to understand the way pregnenolone is involved in neurotoxicity, examining mainly the relationship between this neurosteroid and neuroprotection. It is reasonable to observe how pregnenolone can be useful in pharmacological therapies for some important neurological diseases whose onset, advancement and exacerbation are heavily influenced by neurotoxicity and neurodegeneration processes.

Alzheimer's Disease

Recently, very interesting studies have been carried out about Alzheimer's disease. Patients suffering from this disease present particular anatomical irregularities; actually, the sulci of the cerebral cortex are much deeper in these patients than in normal people, meanings that this disease implies loss of cerebral tissue [10]. In Alzheimer there is the presence of amyloid plaques which contain beta-amyloid proteins and neurofibrillar tangles [10]. Both of these structures have a primary toxic action on cerebral neurons and are partially responsible for the degeneration of the disease.

Scientific researches demonstrated that pregnenolone can be fundamental to reduce the production of beta-amyloid proteins [1,11]. In fact, it has been found out that the first physiological reaction central nervous system carries out against these toxic structures is to raise the quantity of the neurosteroid in the brain. Such a reaction demonstrates that pregnenolone is involved in the neurodegenration of these cerebral anomalies.

Unfortunately, experimental data we have at disposal are not enough to prove the precise way pregnenolone influence amyloid plaques. Nevertheless, it is verisimilar that such an action can be made through the influence pregnenolone exerts on glutamate receptors, particularly on NMDA, or on GABA receptors, even if it is not possible to show the way it happens yet.

Pregnenolone also possesses one more feature that makes it useful in the treatment of Alzheimer's disease and of other diseases as well. It has been observed that the administration of pregnenolone sulfate sigma in old rats' hippocampus increases hippocampal neurons production by 55%. This experiment proves that pregnenolone, thanks to his sulfate's action, is involved in neurogenesis process. Since almost all neurological diseases imply the loss of cerebral tissue, pregnenolone would be of primary importance to assure the regular replacement of damaged or degenerated neurons.

Parkinson's Disease

At the present time, we only dispose of a small quantity of information about the relationship between pregnenolone and Parkinson's disease; such a situation is due to the fact that a possible relation between them had never been taken into consideration until a few years ago.

Nevertheless, it has been noticed that also in Parkinson's disease pregnenolone levels are lower than usual [12], which means that the neurosteroid is involved in the pathology we are dealing with. As well as Alzheimer, Parkinson's disease is characterized by anomalous anatomic structures, which lead dopamine neural circuitries to degeneration. In the matter of Parkinson, it is known that the damaged area is the substantia nigra.

The way pregnenolone positively works on Parkinson's symptoms is not clear yet, although we can advance some hypothesis about it: the neurosteroid could act on the pathology through its neuroprotective and neurogenic properties besides the influence it has on sigma 1 receptors, which are responsible for the regulation of dopamine release. As a consequence, it is clear that pregnenolone could not only relieve the symptoms, but also slow the disease's advancement.

Conclusion

Pregnenolone-sulphate show an interesting antinflammatory propertie, and, secreted locally into the brain by microglia cells, may play a promising role in neurodegenerative disease.

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