Published in final edited form as:

Front Neuroendocrinol. 2009 July ; 30(2): v–ix. doi:10.1016/j.yfrne.2009.04.006.

Steroids and neuroprotection: new advances

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Abstract

Gonadal hormones exert neuroprotective actions. In addition, it has become evident that the local synthesis of these molecules in the central nervous system may prevent or reduce neurodegeneration. The neuroprotective actions of steroids involve neurons, glial cells and blood vessels, are exerted via steroid receptor signaling initiated at the nuclear or membrane level and steroid receptor independent mechanisms. They include the regulation of phosphatases and kinases and the regulation of the expression of molecules controlling inflammation and apoptosis. In addition, mitochondria have emerged as new central targets for neuroprotective actions of steroids. These neuroprotective actions have been documented in different experimental models of neurological alterations, including motoneuron injury, Parkinson's disease, traumatic brain injury, multiple sclerosis, stroke and Alzheimer's disease. In addition, steroids promote serotonergic neuronal function and protect against affective disorders. This special issue of *Frontiers in Neuroendocrinology* contains a collection of reviews of the most recent ideas and findings on these various aspects of sex steroid-dependent neuroprotection.

Keywords

allopregnanolone; apoptosis; aromatase; astroglia; estradiol; microglia; mitochondria; progesterone; testosterone; vitamin-D

Introduction

The behavioral effects of gonadal hormones are known since the demonstration in 1849 by Arnold A. Berthold (1803–1861) that a product of the testes activates sexual behavior in roosters. The steroid nature of gonadal hormones was characterized in the beginning of 20th Century and soon thereafter, they were synthesized and became available for experimentation. Consequently most work focused for 50–70 years on the effects of gonadal steroids on reproduction. During last quarter of the 20th century, several findings have however slowly broadened this research and it is now widely accepted that besides their effects on reproduction, sex steroids are implicated in the control of a broad variety of brain events and mechanisms including changes in cognitive abilities, pain control, neuroplasticity and neuroprotection. In this issue of *Frontiers in Neuroendocrinology* several experts review the latest available information on neuroprotection by steroids, in particular estrogens, progestins and androgens.

Abundant experimental evidence indicating that ovarian hormones exert neuroprotective actions has accumulated over the last two decades. In addition, it has become evident that

the local synthesis of these molecules in the central nervous system may prevent or reduce neurodegeneration. Although some clinical studies, such as the Women's Health Initiative Memory Study (WHIMS), have questioned the efficacy of ovarian hormones to prevent brain neurodegeneration and cognitive decline in women aged 65 years and older (for example, see [8,11] in this issue), other epidemiological and clinical data in younger women support the experimental findings in animals. In addition, new experimental data, showing that a prolonged period of hypoestrogenicity disrupts both neuroprotective and anti-inflammatory actions of estradiol [11], may help to reconcile the results of animal studies with those of the WHIMS. Some clinical evidence also supports the potential cognitive benefit of testosterone therapy in men [8] and several experimental studies have identified neuroprotective actions of adrenal and testicular androgens [5,8]. However, it is clear that we need more basic information on the mechanisms involved in the neuroprotective actions of steroids to predict the conditions in which hormone treatments may have positive outcomes for brain function in humans and design the best possible therapeutic approaches.

New advances in the identification of molecular mechanisms involved in the neuroprotective actions of steroids

In this volume, recent research on the multiple molecular mechanisms involved in the neuroprotective actions of estradiol and other estrogenic molecules are reviewed by Simpkins et al [10]. These include the regulation of the levels of protein phosphatases, of the phosphorylation of signaling kinases and of the expression of molecules regulating apoptosis. Mitochondria have emerged as new central targets for the neuroprotective actions of estrogens. Both steroid receptor signaling initiated at the nuclear or at the membrane level, as well as estrogen receptor independent antioxidant effects, and, perhaps, estrogen receptor mediated regulation of mitochondrial genome, contribute to the final neuroprotective outcome. Examples of these mechanisms, which in part also apply for progesterone and testosterone, are reviewed by other authors in this issue when referring to the neuroprotective actions of sex steroids on specific pathologies.

Role of local steroid synthesis and metabolism in the brain

It is important to consider that the same molecules used by the body as endocrine signals, such as estradiol, progesterone and testosterone, may also be locally synthesized in different tissues to act as paracrine or autocrine factors. There is now evidence that the central nervous system, at least in some species, is able to produce progesterone, testosterone and estradiol from cholesterol. Therefore, local synthesis of steroids by the brain may provide an endogenous neuroprotective tone. In addition, hormonal steroids may be metabolized within the brain and spinal cord, and the resulting metabolites may actually be the active neuroprotective agents. For instance, progesterone is locally synthesized from pregnenolone in the nervous system and should thus be considered, in part, as an autocrine or paracrine neuroprotective steroid. In addition, progesterone, either from local or gonadal origin, is metabolized in the nervous system to reduced derivatives, such as allopregnanolone (tetrahydroprogesterone), that may activate complementary neuroprotective mechanisms [3,4,6].

Saldanha et al [9] review the role of testosterone metabolism resulting namely in the local synthesis of estradiol in the nervous system. This local production of estradiol represents an endogenous mechanism of neuroprotection after different brain insults. Multiple studies demonstrate that estradiol produced by astroglia after brain injury is neuroprotective in songbirds and mammals. For instance, the inhibition of local estradiol synthesis within the brain results in the exacerbation of damage after brain injury and aromatase inhibition prevents neuroprotective actions of several estrogen precursors, including testosterone [9].

Additionally, the transformation of testosterone into 5 α -dihydrotestosterone, which is catalyzed by the enzyme 5 α -reductase, may also participate in the neuroprotective effects of the hormone [9]. Therefore, it is important to determine the mechanisms regulating aromatase and 5 α -reductase in the brain and to understand the interaction of local versus peripheral androgens and estrogens on neuroprotection.

In this context, the newly discovered *seladin-1* gene seems to play a key role in the neuroprotective mechanisms of estradiol. In 2000, *seladin-1* (SElective Alzheimer's Disease Indicator-1) was found to be overexpressed in vulnerable brain regions of Alzheimer's disease patients. This gene encodes the enzyme 3-beta-hydroxysterol delta-24-reductase, involved in the cholesterol biosynthetic pathway. Peri et al [7] discuss evidence indicating that *seladin-1* may be involved in the neuroprotective effects of estradiol and of selective estrogen receptor modulators. The neuroprotective actions of these molecules against β -amyloid and oxidative stress in fetal neuroepithelial cells is associated to an increase in the expression of *seladin-1*. Conversely, silencing of *seladin-1* abolishes the neuroprotective actions of estradiol [7]. Estradiol may increase *seladin-1* expression by promoting the release of insulin-like growth factor-1 (IGF-1), which enhances *seladin-1* synthesis. Thus, *seladin-1* may represent an important link between the neuroprotective actions of estradiol and IGF-1. Peri et al [7] propose that the neuroprotective mechanism of *seladin-1* may involve an increased synthesis of cholesterol and its consequent metabolism to neuroprotective steroids.

Motor neuron diseases

Neuroprotective actions of androgens have been characterized in different experimental models of neurodegeneration, including oxidative stress, serum deprivation, beta-amyloid toxicity, heat shock-induced cell death and excitotoxicity [5,8]. In addition, androgens exert trophic actions on motoneurons, maintaining the integrity of their dendrites and synaptic contacts [5]. Developmental actions of androgens, promoting motoneuron survival, result in the generation of sex differences in the number of motoneurons in specific spinal cord regions innervating the muscles of the penis [5]. In addition, androgens are neuroprotective for adult motoneurons, protecting against motoneuron death, preventing dendritic atrophy, preserving presynaptic innervation and enhancing axonal regeneration in different paradigms of motoneuron injury [5]. All these protective and reparative actions of androgens, which are reviewed by Fargo et al [5], result in functional recovery of motor function and are of particular relevance for amyotrophic lateral sclerosis and other human diseases characterized by progressive loss of motoneurons.

Parkinson's disease

Bourque et al [2] specifically address the molecular mechanisms involved in the protective effects of estradiol and progesterone on Parkinson's disease. Steroid signaling mechanisms initiated in the plasma membrane and in the cell nucleus seem to converge to promote neuroprotection by estradiol and progesterone. In particular Bourque et al [2] review new evidence indicating that the phosphatidylinositol-3 kinase/Akt and the mitogen-activated protein kinase pathways are involved in the neuroprotective action of estradiol in experimental animal models of Parkinson's disease. Estradiol neuroprotective effects are also associated to an increased ratio of antiapoptotic Bcl-2 versus proapoptotic Bad in the striatum. Growth factors, such as brain derived neurotrophic factor (BDNF) and IGF-1 may interact with estradiol in the promotion of neuroprotection.

Traumatic brain injury

Experimental animal studies have shown that progesterone is an effective treatment to reduce neural damage after traumatic brain injury. Cekic et al [3] argue that one of the reasons why progesterone shows a better therapeutic outcome than other drugs for the treatment of traumatic brain injury is because the hormone has multiple mechanisms of action. For instance, progesterone maintains mitochondrial function, enhances the expression of pro-survival genes, such as bcl-2, and reduces pro-apoptotic signaling after brain injury. In addition, progesterone reduces brain inflammation, lipid peroxidation and brain edema, promotes neuronal survival and increases the levels of trophic factors such as BDNF [3,4].

Cekic et al [3] also discuss the advantages of the combination of vitamin D and progesterone for the treatment of traumatic brain injury. Vitamin D is a steroid that acts via the activation of the nuclear steroid vitamin D receptor as well as by membrane initiated steroid signaling. Vitamin D deficiency, a common condition in older people, can exacerbate brain damage after injury and may decrease the neuroprotective efficacy of other therapeutic strategies for the treatment of traumatic brain injury, including the neuroprotective actions of progesterone. Vitamin D exerts neuroprotective and anti-inflammatory actions by mechanisms that are different but compatible with the neuroprotective mechanisms of progesterone. Cekic et al [3] propose that the combination of progesterone and vitamin D may overcome the effects of vitamin D deficiency in patients with traumatic brain injury and may enhance the neuroprotective effects of progesterone in non-vitamin D deficient patients.

Control of inflammation

In addition to their direct action on neurons, sex steroids also display neuroprotective effects by an action on glial cells. Suzuki et al [11] address the role of astrocytes and microglia in the control by estradiol of brain inflammation after stroke. Cekic et al [3], De Nicola et al [4] and Kipp and Beyer [6] also show the importance of glial cells as targets for the neuroprotective and anti-inflammatory actions of progesterone. These hormones reduce brain inflammation by downregulating the expression of pro-inflammatory cytokines by microglia and astroglia. In addition, progesterone reduces brain edema at least in part by regulating the expression of aquaporin 4, a water channel present in astrocytes, that probably plays a key role in the regulation of water balance in damaged brain tissue. These anti-inflammatory actions of sex steroids are not only relevant for the protection of neurons, but also essential for the protection of myelin.

Multiple sclerosis and other demyelinating diseases

De Nicola et al [4] also emphasize the importance of oligodendrocytes and myelin for the neural repair promoted by progesterone. This hormone indeed promotes the differentiation of oligodendrocyte precursors into myelin-forming mature oligodendrocytes and promotes myelin repair [4]. Kipp and Beyer [6] also address the interaction of progesterone and estradiol in the control of multiple sclerosis associated processes, showing that estradiol and progesterone have complementary effects to enhance remyelination after experimental demyelination. Estradiol prevents apoptotic cell death of oligodendrocytes and promotes myelin sheet formation, while progesterone induces cell branching of oligodendrocytes and regulates expression of myelin proteins. In addition, estradiol may reduce excitotoxic damage by increasing the uptake of glutamate by astrocytes and promote the synthesis of IGF-1 by astrocytes, a factor that enhances the proliferation and differentiation of oligodendrocytes [6].

Stroke

Suzuki et al [11] review new findings on the neuroprotective actions of estradiol against neurodegenerative events associated to cerebrovascular stroke and emphasize the importance of adequate timing for estrogen therapy after stroke to obtain adequate benefits. This is because estradiol protects against stroke damage by decreasing apoptosis during the initial 24 hours and by enhancing the generation of new neurons within the first 96 hours after the insult. The role of neurogenesis in the neuroprotective effect of estradiol is a new and interesting development. The hormone enhances neurogenesis in the subventricular zone following stroke by a mechanism that requires both α and β subtypes of estrogen receptors. In addition, estradiol promotes the migration of newly generated neurons towards the damaged brain region, probably contributing to the repair of altered neuronal circuits. Another important aspect of the mechanisms involved in the neuroprotective action of estradiol in stroke is the control of inflammation and the protection of the neurovascular unit. Astrocytes and microglia play an essential role on this process. Since an increased inflammation reduces proliferation, estradiol may contribute to enhance neurogenesis after stroke by reducing inflammation.

Protection of serotonergic neurons: implications for cognitive and affective disorders

An important aspect to consider within the global neuroprotective spectrum of gonadal hormones is their role as modulators of mood and affection. There is considerable evidence that gonadal steroids exert pro-cognitive and anti-depressive actions and that reduced levels of these hormones with menopause, with aging and by other causes may represent a risk factor for the onset of cognitive and affective disorders. Serotonin neurons in the dorsal raphe are key regulators of cognition and affection. These neurons are a direct target of ovarian steroids. Bethea et al [1] in this issue present evidence that gonadal steroids not only regulate the function of dorsal raphe serotonergic neurons but also promote their survival. Using a monkey model of surgical menopause with hormone replacement, Bethea et al [1] have shown that ovarian hormones protect serotonin neurons by decreasing the expression of genes involved in the caspase-independent pathway and in the cell cycle.

Alzheimer's disease

Neuroprotective actions of gonadal hormones for Alzheimer's disease are reviewed by Pike et al [8]. Although results of clinical studies are highly controversial, the authors present a critical analysis of the findings in the light of new evidence suggesting that hormone therapy has preventive effect on the pathology and that early initiation of the therapy is essential to obtain positive clinical outcomes. Experimental findings indicate that estradiol is able to target several important landmarks of the pathology. For instance, estradiol regulates β -amyloid accumulation in the brain and protects neurons against β -amyloid damage via a variety of mechanisms, including regulation of the expression of proteins involved in the control of apoptosis and inhibition of excitotoxic neuronal death. Estradiol is also able to inhibit the pathological hyperphosphorylation of Tau characteristic of Alzheimer's disease brains. Therefore, experimental findings support a protective role for estradiol in Alzheimer's disease. Still, new studies are needed to determine whether the neuroprotective action of estradiol against Alzheimer's disease related alterations in experimental animals is impaired in older individuals or after a long period of deprivation of ovarian hormones, to reconcile the experimental findings with the results of some clinical trials.

Another important topic is the role of progesterone for the prevention of Alzheimer's disease. Pike et al [8] analyze data indicating that progesterone may antagonize the

neuroprotective effect of estradiol, and for instance block the beneficial effect of estradiol in lowering β -amyloid accumulation. In contrast, progesterone may also have beneficial effects and the combination of estradiol and progesterone is able to reduce the levels of hyperphosphorylated Tau. The pattern of administration of progesterone, cyclic rather than continuous, may be essential for the neuroprotective actions of the hormone.

Pike et al [8] also addresses the role of androgens for the prevention of Alzheimer's disease in men. Experimental data indicate that androgens, like estradiol, decrease β amyloid levels and reduce β amyloid damage. Finally, Pike et al [8] discuss the possible development of new selective estrogen and androgen receptor modulators, lacking undesirable peripheral effects, for the prevention of neurodegenerative disorders.

Conclusions

In conclusion, the papers gathered in this special issue of Frontiers in Neuroendocrinology highlight multiple mechanisms (Figure 1) through which sex steroids reduce brain damage and promote brain regeneration. Figure 1 shows that steroid brain concentrations depend of both their systemic levels and their local synthesis and metabolism by neurons and glial cells. Thus, the protection of the nervous system exerted by steroids may change depending on sex, reproductive status, aging and other physiological conditions.

Steroids activate in the nervous system several mechanisms that impact on neuronal survival (Fig. 1): (i), regulation of transcriptional activity by steroid receptor signaling initiated in the cell nucleus; (ii), regulation of transcriptional activity via the regulation of kinases and phosphatases by steroid receptor signaling initiated at the plasma membrane; (iii), regulation of cell survival and metabolism by steroid receptor signaling initiated in the mitochondria and (iv), regulation of the activity of ion channels associated to neurotransmitter receptors and of antioxidant effects via steroid receptor independent mechanisms. All these mechanisms interact to finally result in the promotion of neuronal survival by decreased apoptosis, decreased excitotoxicity and decreased cell oxidation.

The following articles also demonstrate that the neuroprotective mechanisms of steroids involve multiple cell types in the nervous system: neurons, glial cells and blood vessels (Fig. 2). By acting on microglia and astroglia, steroids reduce reactive gliosis and the release of pro-inflammatory cytokines. Actions of steroids on astrocytes and endothelial cells are also important to control the function of the neurovascular unit and to reduce brain edema. By promoting the differentiation of oligodendrocyte precursors, the survival of oligodendrocytes and the expression of myelin proteins, steroids enhance myelin formation and repair. All these actions, that contribute to maintain neuronal function and survival, may be in part mediated by the synthesis and release of growth factors by neurons and glial cells in response to steroids. In addition, steroids promote neuronal survival by a direct action, via mechanisms analyzed in figure 1. Finally, steroids may also be able to promote neurogenesis in the injured brain and to facilitate the migration of newly generated neurons to the damaged brain regions, contributing, together with the control of gliosis, myelin formation and the vascular system, to the reorganization and repair of the neural tissue.

The present volume dedicated to these neuroprotective actions of steroids clearly demonstrates the pervasive effects of these molecules on brain structure and function. It is hoped that this collection of papers will attract attention to these important effects and promote further research on this clinically relevant topic.

Acknowledgments

The authors acknowledge support from Ministerio de Ciencia e Innovación, Spain (BFU2008-02950-C03-01/BFI to LMG-S) and of the National Institute of Mental Health (MH50388 to JB).

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Fig. 1.

Multiple neuroprotective mechanisms of steroids. Steroid brain concentrations depend of both their systemic levels and their local synthesis and metabolism. Steroids activate in the brain both steroid receptor dependent and steroid receptor independent mechanisms that involve the cell nucleus, the plasma membrane and the mitochondria. By these mechanisms, steroids regulate the transcription of genes involved in the control of neuronal survival, decrease excitotoxicity and exert anti-oxidant effects.

Fig. 2.

Besides promoting neuronal survival by a direct action on neurons, steroids also exert complementary and interrelated actions that result in the reduction of brain damage and in the repair of the injured brain tissue. Steroids reduce reactive gliosis and inflammation, promote the remyelination of injured axons, control the function of the neurovascular unit, reduce brain edema, and promote neurogenesis in the injured brain.