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Neuroprotective Role of Steroidal Sex Hormones: An Overview

Ali Nasir Siddiqui,[1] Nahida Siddiqui,[2] Rashid Ali Khan,[1] Abul Kalam,[3] Nasimudeen R. Jabir,[4] Mohammad Amjad Kamal,[4,5] Chelapram Kandy Firoz[4] & Shams Tabrez[4]

1 Department of Pharmaceutical Medicine, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India
2 Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India
3 Department of Pharmacology, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India
4 King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia
5 Enzymoics, 7 Peterlee Place, Hebersham, NSW, Australia

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Correspondence
S. Tabrez, King Fahd Medical Research Center, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia.
Tel.: +966-126401000 Ext. 25185;
Fax: +966-126952076;
E-mail: shamstabrez1@gmail.com
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SUMMARY

Progesterone, estrogens, and testosterone are the well-known steroidal sex hormones, which have been reported to have "nonreproductive "effects in the brain, specifically in the neuroprotection and neurotrophy. In the last one decade, there has been a surge in the research on the role of these hormones in neuroprotection and their positive impact on different brain injuries. The said interest has been sparked by a desire to understand the action and mechanisms of these steroidal sex hormones throughout the body. The aim of this article was to highlight the potential outcome of the steroidal hormones, viz. progesterone, estrogens, and testosterone in terms of their role in neuroprotection and other brain injuries. Their possible mechanism of action at both genomic and nongenomic level will be also discussed. As far as our knowledge goes, we are for the first time reporting neuroprotective effect and possible mechanism of action of these hormones in a single article.

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Introduction

The best-known steroidal sex hormones secreted primarily by the ovaries in females are progesterone, estrogens, and testosterone, from the testicles in males. The hypothalamus releases the peptide gonadotropin-releasing hormone (GnRH) which ultimately controls the release of the peptides follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary [1]. These hormones control the development of follicular growth and corpus luteum in females, which ultimately results in the production of progesterone and estrogen [2]. Several studies revealed that apart from reproductive roles, progesterone, estrogens, and testosterone have protective actions against different brain injuries [3–5].

There is growing evidence that suggests progesterone and its metabolite (allopregnanolone) could exert neuroprotective effects on the injured central nervous system (CNS). Over the last several years, preclinical studies around the world also suggested that progesterone, given in the acute stage of injury, could limit tissue damage and improves functional outcome after blunt traumatic brain injury (TBI), spinal cord injury, stroke, diabetic neuropathies, and other types of acute neural injury [6–11]. Progesterone has been reported for their role in brain neurogenesis regulation and regeneration, convulsions, myelination, TBI, cognition, mood alteration, inflammation, and mitochondrial function in different animal models [12–17]. Several clinical studies also highlighted their role in neuroprotection [18,19]. The neuroprotective mechanism of action of progesterone is still at the speculative stage because of vast complexity of the brain. Some scientific literature supports the involvement of progesterone receptors (PR) that include the classic nuclear progesterone receptors A (PRA), progesterone receptors B (PRB) and their spliced variants and seven transmembrane progesterone receptors β [20,21]. Scientific literature also suggested activation of different CNS signaling cascade pathways, viz. mitogen-activated protein kinase (MAPK), extracellular-regulated kinase (ERK), and up-regulation of brain-derived neurotrophic factor (BDNF) by progesterone [22–27]. All of these signaling cascades have been reported for their role in neuroprotection.

On the other hand, several studies reported the role of estrogen in stimulation, neuroprotection, and beneficial for cell survival [28,29]. The mechanism of action of estrogens also remains obscure, because of the complexity of the brain. Like progesterone, the data related to estrogens also suggest that estrogen receptor-α (ERα) and estrogen receptor-β (ERβ) may exert neuroprotection in the brain. At genomic level, estrogen has been reported to increase the expression of the

anti-apoptotic gene, B-cell lymphoma 2 (*bcl-2*), and inhibits the expression of the pro-apoptotic gene. *In vitro* study also highlighted their role in the activation of extracellular signal-regulated kinases (ERK) and phosphoinositol-3-kinase (PI3K)-Akt pathways [30]. The enhanced release of transforming growth factor (TGF)-β1 is an important step of neuroprotection by estrogen [28]. Some researchers also support the notion that testosterone could act against neurodegenerative disorders including Alzheimer's disease (AD), mild cognitive impairment (MCI), or depression [31]. In the following section, we will try to cover these steroidal sex hormones at the individual level based on their neuroprotective action along with their mechanistic insight.

Progesterone and Their Neuroprotective Action

Progesterone has been reported for their neuroprotective action in various *in vitro* and *in vivo* models [27,32–34]. Several clinical studies also highlighted the neuroprotective potential of progesterone [18,19,35–37]. Moreover, progesterone could target several regions of the brain particularly hypothalamus, hippocampus, and cortex. In most of the studies, progesterone has been suggested to have neuroprotective and/or regenerative effects in the hippocampal and cortical region [32,33]. It can be synthesized by both central and peripheral nervous system and can act not only on the brain but also on peripheral nerves. Baulieu et al. (1996) reported that progesterone promotes the formation of the myelin sheath in rat Schwann cells and increases the number of myelinated axons [38]. In another study, the same group reported that blocking the action of progesterone impairs myelination in regenerating axons [39]. Progesterone has been also reported to stimulate myelination in organotypic slice cultures of rats and mouse cerebellum [40]. Several pieces of evidence in scientific literature also suggest that depletion in sex steroidal hormones, estrogen, and progesterone at menopause stage is a significant risk factor for the development of AD in women, which could be overcome by hormonal therapy [41,42]. Gonzalez et al. (2004) showed higher expression of BDNF at both mRNA and protein level in response to progesterone treatment in rats with spinal cord injury [43]. Progesterone enhancement of endogenous neuronal BDNF could also provide a trophic environment within the lesioned spinal cord and might be part of progesterone-activated pathways to provide neuroprotection [43]. Moreover, progesterone treatment also significantly reduces the neuropathological and behavioral abnormalities associated with TBI in the rodent model [44]. The antioxidant effect of progesterone also supports its potential in the treatment of brain injury [45]. Progesterone has been reported for its neuroprotective action in symptomatic wobbler mice with spinal cord motor neuron degeneration, which could be mediated by the regulation of expression of some specific genes in neurons and glial cells [43]. The therapeutic outcome associated with progesterone in the management of acute spinal cord injury was also reported to be good [46]. Progesterone also acts on other brain region such as nucleus tractus solitarius (NTS), reverses the hypoxic injury in rats, and restores the normal respiratory rhythm [47]. Progesterone and its derivatives (dihydroprogesterone [DHP] and tetrahydroprogesterone [THP]) have been reported to have the protective effect against diabetic neuropathy in experimental animal models [48]. Scientific literature suggests the profound effect of progesterone on seizure processes [49,50]. Antiseizure effects of progesterone and its metabolite have been also reported in various animal models [51,52]. Progesterone has also shown to decrease epileptiform activity in mice [53], maximal electroshock (MES)-induced seizures in rat [54], kainic acid-induced seizures in rat [55], and amygdala-kindled seizures in rats [56]. Along with earlier mentioned studies, some clinical studies also reported a decrease in catamenial epilepsy in women in response to progesterone, which points antiseizure potential of progesterone [57].

Collectively, all these mechanisms might be important in protecting the brain against various neurodegenerative diseases and brain-related dysfunctions.

In view of encouraging results of the preclinical studies, progesterone had been taken into the clinical trials for its neuroprotective effects especially against TBI, ischemic stroke, multiple sclerosis and even for the treatment of AD. Interestingly, the neuroprotective efficacy of progesterone was found to be remarkable at the earliest phase of animal models for TBI, traumatic spinal cord injury, middle cerebral artery occlusion, and neurodegeneration [58–62]. The above-mentioned reports enable progesterone to enter four phase II trials to test its protective efficacy after TBI including ProTECT II and SyNAPSe. It also came out with consistent and encouraging outcome [18,19,63,64]. However, the results of the large multicenter randomized and placebo-controlled phase III trials were disappointing [65–67]. Phase III trial in women with intractable partial epilepsy also did not show much effect by progesterone, but the *post hoc* analysis identified a subset of women with higher levels of perimenstrual seizure exacerbation that were responsive to treatment [68]. Progesterone as a neuroprotective agent offers great promises still it failed at phase III clinical trials. The reason behind the failure of progesterone at phase III trial was believed to be due to faulty extrapolation of preclinical animal studies data and use of subjective items measures that neither reflects nature of deficits or long-term quantitative recovery. In one of the report, Ioannidis (2005) suggested that clinical research in general typically fails because of the laboratory studies on which trials are based often do not replicate one another and have too many false-positive findings [69]. These published papers then lead to unwarranted and overenthusiastic estimations of effect sizes and are uncritically reported in the peer-review literature and accepted and used by the clinical community to go forward with clinical trials. Future problems can be avoided by pooling preclinical data, require more coordinated and sequential phase II trials using standardized outcomes to replicate potential findings [70]. Recently, Menon and Maas (2015) suggested that precise definitions of injury, better trial design, better patient selection procedures, better outcome measures, and better options for when to take them and how often are needed to get positive outcome during phase III clinical trials [71]. It is also suggested to test the potential of these hormones in nonhuman primates so that a high number of model animal could be involved.

Mechanism of Neuroprotection by Progesterone

Nuclear progesterone receptor (PR) has been localized in several regions of the brain including hippocampus, hypothalamus, cortex, and cerebellum [20,72–74]. Typically, the steroid hormones such as progesterone, estrogen, and testosterone had been maintained inactive under hypotonic conditions due to the association with heat-shock proteins (hsps). The interaction between PR and chaperons molecule (hsp70, hsp90, hsp40) is prerequisite for hormonal binding which further express their action by dissociation from the chaperons molecule, then dimerize and finally interact with progesterone response element at the promoter region of the target genes [75,76]. Two major isoforms of PR, a full length PR-B and N-terminal truncated PR-A isoform, have been reported to exist [77,78]. Although PR is expressed in hippocampus and frontal cortex, progesterone shows its effect in PR knockout mice as well, indicating the involvement of some other receptor [79]. A novel progesterone binding protein (distinct from conventional PR), exclusively localized in neural tissue including the cerebral cortex, cerebellum, caudate nucleus, thalamus, pituitary gland, and spinal cord, has been also reported [80]. Overall, progesterone has established neuroprotective action that takes place via several mechanisms. They could cause a reduction in both IL-β and TNF-α level in post-TBI [43]. Progesterone has been also reported to inhibit the inflammatory cytokines in the medial frontal cortex of TBI [81,82]. They reduce cerebral edema by stabilizing the blood–brain barrier, thus preventing the flow of water, ions, and inflammatory molecule across the membrane [43,45]. In fact, progesterone, estrogen, and testosterone had been known to activate MAPK, ERK, and Akt signaling pathways, which are reported to be associated with neuroprotection [83]. Earlier studies suggested the co-regulation between BDNF and steroid hormones, viz. progesterone, estrogens, and testosterone. BDNF is a neurotrophin, abundantly expressed in several areas of the CNS and known to enhance specific learning and memory processes [84]. Neuroprotection by progesterone is associated with up-regulation of BDNF, a rise in the activity of choline acetyltransferase, and reduction in the mitochondrial dysfunction [85–88]. Progesterone has been also reported to suppress inflammatory response and expression of nitric oxide synthase-2 in cerebral ischemia model [89]. On the other hand, it is noteworthy that progesterone could block the estrogen-induced increase in spine density in hippocampus and reverses the estrogen-induced enhancement of spatial memory in rodents indicating its antagonistic relationship with estrogen [90–92].

Estrogens and Their Neuroprotective Action

Apart from the reproductive role, estrogens have been reported to exert complex and diverse action against neurodegenerative disease and injuries. In addition, estrogens have shown to have protective effect on the stroke in animal models [93,94]. Furthermore, it also improves histological, physiological, and behavioral outcomes after transient middle cerebral artery occlusion, global forebrain ischemia, and subarachnoid hemorrhage and may be beneficial in reducing the risk of cognitive decline in women with normal function [95]. Wise et al. (2005) reported that 17-beta-estradiol (estrogen) slows down the progression of injury, diminishes the extent of cell death by suppressing apoptotic pathways, and enhances the expression of cell survival genes [96]. Administration of this estrogen to male rats significantly reduces brain edema and neurological deficits [97]. Brain edema was reported to be less significant in female compared with male rats. The estrogen receptor (ER) antagonist ICI182, 780 was found to be exacerbated in an intracerebral hemorrhage (ICH)-induced brain edema in female but not in male rats, suggesting protective ER activation during ICH in female rats [97]. Estrogens and related drugs (selective estrogen receptor modulator, ERα, and Erβ) agonist produce neuroprotection of focal and global ischemia induced in the rat, mice, and gerbils [98], Moreover, estrogen treatment protects the dorsal hippocampal neurons CA1 regions, which are susceptible to ischemic injury [98]. Goodman et al. (1996) reported that pretreatment of estrogens could protect cultured hippocampal neurons against oxidative stress injury, glucose deprivation, glutamate, FeSO4, and amyloid beta-peptide toxicities and promote cell survival [99]. Despite several reports on neuroprotection, some contradictory results of worsening of neuropathology by estrogen have also been reported. However, it is generally believed that estrogen increases neuronal excitability and mediates proconvulsant effects [100]. There are also clinical and animal data that show that estrogen has anticonvulsant effects [101]. However, conflicting data also exist on the association between estrogen and epileptic seizures.

Promising preclinical studies on estrogen enable it to test in clinical trials for its neuroprotective potential. A pilot clinical trial with estriol administration in women with multiple sclerosis showed promising results with significant reduction in pathological lesions [102]. Subsequent phase II study had been enrolled, and one study published with encouraging results as the estriol combined with glatiramer acetate in women with relapsing-remitting multiple sclerosis and treatment was well tolerated over 24 months [103]. Even though several phase II and phase III clinical trials have been registered for estrogen to investigate the protective effects on neurodegeneration, the results are yet to be released.

Mechanism of Neuroprotection by Estrogen

Along with the well-recognized reproductive effect, estrogens could also influence numerous nonreproductive functions such as bone and mineral metabolism, cardiac and vascular function, memory and cognition, mood alterations, and progression of age-related disease [104]. Several studies have explored the role of different estrogen receptors (ER) in the neuroprotection [94,95,105–111]. Two isoforms of estrogen receptor ERα and ERβ are expressed in adult brain. ER antagonist ICI 182780 increases infract size in middle cerebral artery occlusion of cerebral ischemia in female rats [112,113]. Estrogen could also block estrogen-induced neuroprotection in global ischemia and cortical explants studies [114]. The neuroprotective potential of estrogen was found to be lost in OVX estrogen receptor-α knockout (ERKO) mice but at the same time, it protects the brain of OVX estrogen

receptor-β knockout (BERKO) mice, suggesting the involvement of ERα in neuroprotection [106,109]. Interestingly, few studies reported the involvement of only ERβ isoform and/or both ERα and ERβ in the protection of CA1 neurons from global ischemia-induced death [115]. Under the genomic level, estrogen is known to overexpress anti-apoptotic gene *bcl-2* in ischemic part following global ischemia [105,116,117]. Furthermore, it also inhibits the expression of BAD gene, which is the antagonist of *bcl-2* gene [105,116–118]. Estrogen also induces certain pathways such as rapid activation of extracellular signal-regulated kinases (ERK) and phosphoinositol-3-kinase (PI3K)-Akt pathways in cortical and hippocampal cells *in vitro*, which also play a role in the neuroprotective action [22,119,120]. ER antagonist ICI182, 780 has been reported to block estradiol benzoate treatment-induced phosphorylation of Akt in the CA1 region of the hippocampus following cerebral ischemia, which is associated with inhibition of pro-apoptotic MLK3-MKK4/7-JNK1/2 (mixed lineage kinase-3/MAP kinase kinase-4-7/c-jun-N-terminal kinase) pathway [22]. The interaction of ERα with cytoskeleton protein, $p130^{Cas}$ (a complex containing Src and PI3K), could lead to the activation of ERK and Akt pathways [121]. In addition, ERα has also been reported to interact with the calmodulin binding protein (striatin), in vascular cells, which facilitates cell membrane targeting and is critical for estrogen-mediated Akt and eNOS [endothelial nitric oxide synthase] activation [122]. The neuroprotective roles of TGF-β to cortical, hippocampal neurons, and cerebral ischemia have been also reported in scientific literature [123,124]. Moreover, specific PI3K inhibitors or Akt inhibitor could directly prevent Akt activation and completely block the induction of TGF-β1 release by estrogen [125].

Androgens/Testosterone and Their Neuroprotective Action

Testosterone, the gonadal hormone, has been reported for its various effects on numerous body tissues, including CNS [31]. One of the less known actions of testosterone is neuroprotection that takes place via activation of androgen pathways. Because of its lipophilic nature, testosterone could cross the blood–brain barrier and influence neuronal cells [126]. Moreover, testosterone has also been reported to have antioxidant and anti-apoptotic potential, which provides neuroprotective effect [127–129]. Testosterone acts via androgen receptors, which are present in neurons throughout the CNS [31,129,130]. Many of the therapeutic effects of testosterone, viz. libido, cognition, and mood alterations, are mediated through CNS [131]. The decrease in testosterone level in men may lead to neurological disorders like AD, in which β amyloid (Aβ) protein is directly related to testosterone level [132,133].

Table 1 Neuroprotective action and proposed mechanism of action of progesterone, estrogens, and testosterone

Hormone	Neuroprotective effects	Mechanism of action	References
Progesterone	Promotes formation of myelin sheath	Interact with heat-shock protein	Baulieu et al. 1996
	Increases the number of myelinated axons	[hsp70, hsp90, and hsp40]	Ghoumari et al., 2003
		↓IL-β and TNF-α in post-TBI	Gaichino et al., 2003
	Modifies glial tube organization	↑MAPK, ERK, and Akt signaling pathways	Baulieu and Schumacher, 2000
	Stabilizing the blood–brain barrier	↓ Inflammatory response	Evans et al. 2004
		↓Expression of nitric oxide synthase-2	Wali et al. 2007
			Gruenbaum et al. 2011
Estrogens	Enhances the expression of genes that optimizes cell survival	↑Expression of anti-apoptotic gene *bcl-2*	Sampei et al., 2000; Hurn and Macrae, 2000
	Protection from stroke in experimental animal models	↓Expression of BAD gene	Simpkins et al., 1997
		↑Extracellular signal-regulated kinases (ERK)	Catherine et al., 2005
	Reduces the risk of cognitive decline brain edema and neurological deficits in women	↑ Phosphoinositol-3-kinase (PI3K)-Akt activation	Wise et al., 2005
			Nakamura et al., 1996
			Goodman et al., 1996
	Protect neurons against oxidative stress injury, glutamate toxicity, glucose deprivation, FeSO4 toxicity, and amyloid beta-peptide toxicity	↑Interaction with $p130^{Cas}$	Veliskiova et al., 2007
		↑Interaction with striatin	Gloria et al., 2006
		↑Transforming growth factor-β (TGF-β)	
	Anticonvulsant effects		
Testosterone	Neuronal plasticity in the spinal nucleus	↑Expression of hsp 70	Nguyen et al., 2010
		↓Apoptotic and rapid cell signaling pathways	Tehranipour and Moghimi, 2010
	Excitability in the CA1 region of hippocampus	↑Signal transduction pathways that have relevance to cell viability in both neuronal and non-neuronal cells	Spritzer and Galea, 2007
	Prevents retraction or increase the length of neuritis from motor neurons		Zhang et al., 2010
			Ottem et al., 2007
			Marron et al., 2005
	Antioxidant and anti-apoptotic effects	↑MAPK/ERK signaling	Nguyen et al., 2005
			Yao et al., 2015

Androgens are also positive regulators of neuronal plasticity in the spinal nucleus of the bulbocavernosus [134], excitability in the CA1 region of the hippocampus [135], and spine density in the hippocampus [136]. Moreover, androgens also prevent retraction [137] or increases the length [138] and size [139] of neuritis from motor neurons. Other neurotrophic effects of testosterone include cell differentiation [140], neurogenesis [141,142], development of neurons in the hippocampus [143], motor [144,145], and autonomic systems [146].

Regulation of neuronal viability is one of the important actions of androgens. During development, androgen metabolites determine neuron number in specific sexual dimorphic nuclei via apoptosis regulation [147,148]. Androgens could also regulate central and peripheral motor neurons survival following injury [149,150]. As far as our knowledge goes from the available scientific literature, we did not come across any clinical trial study on testosterone that might be currently undergoing. We have summarized the neuroprotective effects and their proposed mechanism of action of progesterone, estrogen, and testosterone in Table 1.

Mechanism of Neuroprotection by Testosterone

The activation of gene pathways that increase or decrease the expression with cell survival is the general mechanism for androgen receptor (AR)-dependent neuroprotection. Androgen neuroprotection could be blocked by anti-androgen flutamide, which antagonizes AR-dependent neuroprotection. The genomic androgen pathway includes members of heat-shock protein family that could provide cellular protection during stress [151]. Zhang et al. (2004) reported neuroprotection by androgen via increased expression of hsp70 [152]. Moreover, Pike (2001) suggested AR-dependent neuroprotection through inhibition of apoptotic and rapid cell signaling pathways [153]. Additionally, androgen could also activate signal transduction pathways that have relevance to cell viability in both neuronal and non-neuronal cells. In one study, Lin et al. (1999) reported increased cell survival of human prostate LNCaP cell following treatment with dihydro-testosterone via P13K/Akt signaling [154]. Similar result was also reported by Yao et al. (2015) in the C6 glial cells [155].

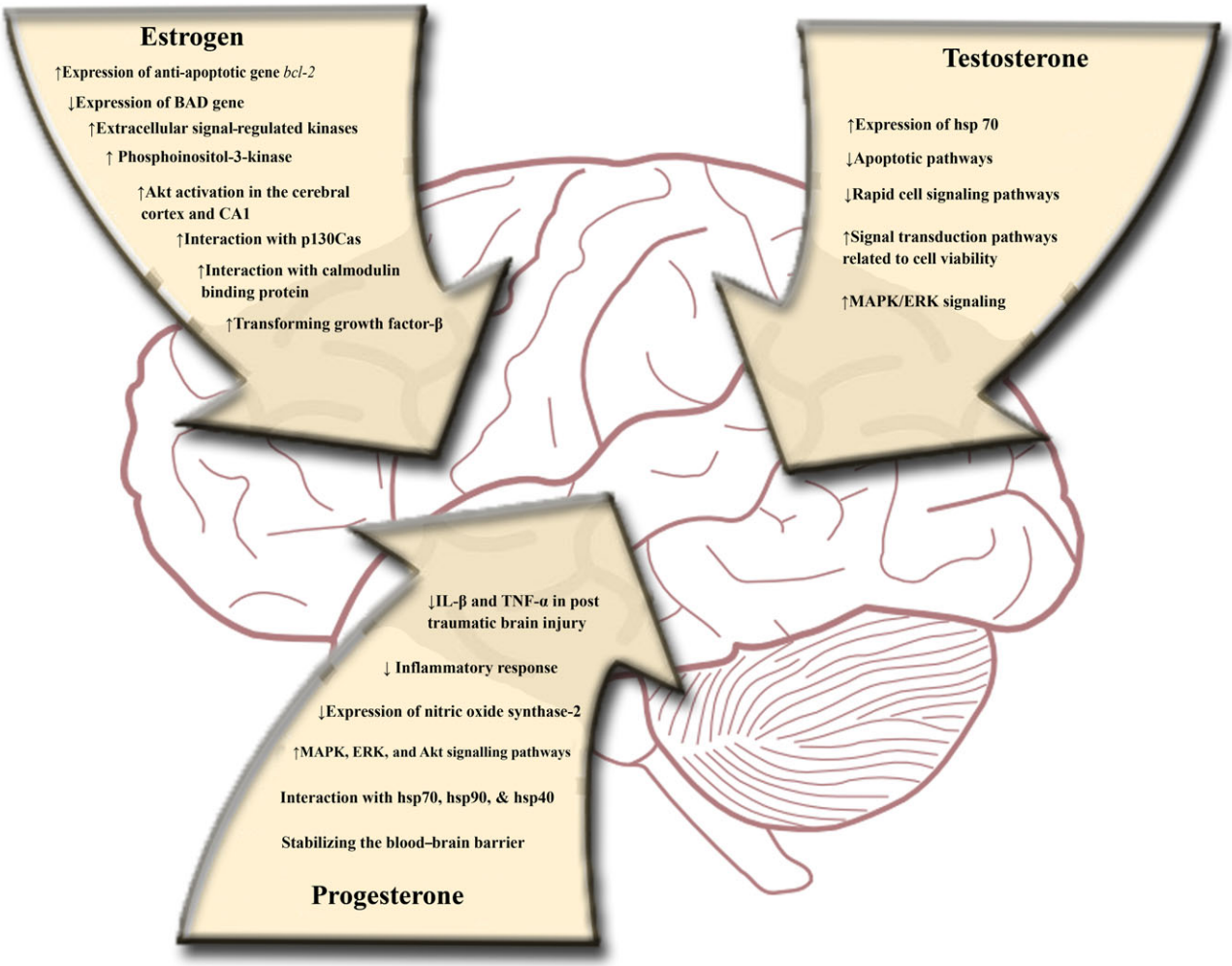

Figure 1 Neuroprotective mechanism of action of progesterone, estrogen, and testosterone.

Some researchers explored the activation of MAPK/ERK signaling cascade by androgens in neurons that are believed to contribute neuroprotection. Their role was confirmed by inhibiting MAPK/ERK signaling by MEK inhibitors, which blocked both androgen-induced ERK phosphorylation and neuroprotection. Nguyen et al. (2005) also reported androgen-activated neuroprotection via MAPK/ERK signaling in PC12 cells [156]. They also reported that activation of MAPK/ERK cascade led to the Rsk-1 activation and ultimately phosphorylation of BAD gene at Ser112 region. It is also believed by the neuroscientist that MAPK/ERK-Rsk signaling in androgen neuroprotection might regulate neuronal viability. A schematic diagram showing the various mechanistic action of progesterone, estrogen, and testosterone has been also provided in Figure 1.

Conclusion

Based on our review article, it is quite clear that progesterone, estrogen, and testosterone possess neuroprotective potential. Their possible mechanisms of action have been also reported in scientific literature. However, some of the contradictory reports are also available in the literature. We believe more research is required to pinpoint certain mechanism of action of these individual sex steroids.

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Conflict of Interest

None to declare.

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