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Review

Neuroprotection by gonadal steroid hormones in acute brain damage requires cooperation with astroglia and microglia

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ABSTRACT

The neuroactive steroids 17β-estradiol and progesterone control a broad spectrum of neural functions. Besides their roles in the regulation of classical neuroendocrine loops, they strongly influence motor and cognitive systems, behavior, and modulate brain performance at almost every level. Such a statement is underpinned by the widespread and lifelong expression pattern of all types of classical and non-classical estrogen and progesterone receptors in the CNS. The life-sustaining power of neurosteroids for tattered or seriously damaged neurons aroused interest in the scientific community in the past years to study their ability for therapeutic use under neuropathological challenges. Documented by excellent studies either performed *in vitro* or in adequate animal models mimicking acute toxic or chronic neurodegenerative brain disorders, both hormones revealed a high potency to protect neurons from damage and saved neural systems from collapse. Unfortunately, neurons, astroglia, microglia, and oligodendrocytes are comparably target cells for both steroid hormones. This hampers the precise assignment and understanding of neuroprotective cellular mechanisms activated by both steroids.

In this article, we strive for a better comprehension of the mutual reaction between these steroid hormones and the two major glial cell types involved in the maintenance of brain homeostasis, astroglia and microglia, during acute traumatic brain injuries such as stroke and hypoxia. In particular, we attempt to summarize steroid-activated cellular signaling pathways and molecular responses in these cells and their contribution to dampening neuroinflammation and neural destruction.

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Contents

Abbreviations: AD, Alzheimer's disease; AQP, aquaporin; ATP, adenosine triphosphate; BBB, blood–brain barrier; BSA, bovine serum albumin; CaMK, Ca^{2+}/calmodulin-dependent protein kinases; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; ER, estrogen receptor; ERK, extracellular signal-related kinase; GFAP, glial fibrillary acidic protein; GLAST, gutamate–aspartate transporter; GLT-1, glutamate transporter-1; GPR30, G-protein coupled receptor 30; ICI, ICI 182,780; IGF, insulin-like growth factor-1; IL, interleukin; iNOS, inducible nitric oxide synthase; Ko, knockout; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MNAR, modulator of nongenomic activity of ER; NF-κB, nuclear factor-kappa B; PELP1, proline, glutamate and leucine rich protein1; PI3K, phosphatidylinositol 3-kinases; PKA, protein kinase A; PKC, protein kinase C; RCEs, respiratory chain enzymes; ROS, radical oxygen species; SERM, selective estrogen receptor modulator; siRNA, small interfering RNA; Src, sarcoma; TGF-β, transforming growth factor-beta; tMCAO, transient middle cerebral artery occlusion; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor.

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1. Neuroactive steroids as neuroprotective agents – a short preface

The two steroid hormones, 17β-estradiol and progesterone or derivatives of these steroids, either of gonadal source reaching the brain via the peripheral circulation or being intrinsically synthesized within the brain compartment by glial or nerve cells control brain development, neural function, including motor and cognitive performance, as well as homeostasis of various physiological parameters [1–7]. Besides their classical "housekeeping" roles, it is well-accepted that these steroids provide robust neuroprotection in a variety of experimental brain injury models [8–11] and under neurodegenerative conditions [12–14]. Often, acute neurological and chronic neurodegenerative diseases reveal striking or subtle sex differences with respect to the male-to-female incidence ratio, gender-specific differences in the severity of brain failure, ethiopathology, mortality, and responsiveness to therapeutic treatments. Clinical and experimental literature highlights such gender aspects of neurological disorders in ischemic stroke, traumatic brain injury, multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis and others [10,15–22]. Likewise, disturbance of endogenous steroid levels and availability by menopause, disease-related changes, or in relevant knockout animal models are associated with a worse prognostic course in distinct neurological disorders [23–26].

Defensive protective steroid hormone actions in the nervous system include the stabilization of the blood–brain barrier (BBB), alleviating brain edema, dampening pro-inflammatory and supporting anti-inflammatory processes, activating anti-apoptotic pathways, stimulating survival-promoting factors, counteracting oxidative stress, promoting respiratory chain function, and reducing glutamate excitotoxicity [10,27–32]. This list provides insight into the complexity of steroid action in the brain under pathological circumstances and the multifaceted way to counteract a toxic environment and come to the aid of neurons [33]. To which extent the different steroid effects contribute to the overall neuroprotective action is largely unknown. Just as well might a selective action dominate and the others are only secondary sustentative. One also has to keep in mind that these steroids not only act at the damaged site but regulate and modulate brain systems not primarily affected during a specific disease. These effects, we refer herein as "positive side effects", are often underestimated in experimental brain studies and may indirectly contribute to the stabilization of neural circuits badly afflicted with pathophysiological processes. Thus, such indirect action might be particularly supportive for compensatory mechanisms in the CNS and coping with behavioral deficits.

Both steroid hormones often reveal a chameleonic manner of cellular signaling in the brain as reported in other organs and tissues comprising different classical nuclear estrogen and progesterone receptors (ERalpha, ERbeta, PR) which are also found at extranuclear sites. Besides direct binding to responsive elements in the promoter region of genes thereby regulating gene transcription, steroid receptors can form multi-protein units outside the nuclear compartment or be coupled to other effectors within a cell. In both cases, these receptors are typically linked to non-classical or unconventional steroid signaling pathways [4]. These steroid receptors are implicated in rapid cytoplasmic steroid signaling via regulation of different protein kinase systems including the extracellular signal-related kinase (ERK) pathways, sarcoma (Src) family kinases, cAMP/protein kinase A (PKA) signaling, Ca^{2+}/calmodulin-dependent protein kinases (CaMK), phosphatidylinositol 3-kinases (PI3 K) and other signal transduction cascades [4,6,10,34–39]. In addition, neurotransmitter receptors and other membrane-associated proteins are targeted by these steroids. Progesterone and its metabolites, act directly on the GABA-A receptor and modulate the receptor physiology-kinetics as well as on sigma receptors [40,41]. Estrogens alone or estrogen-classical estrogen receptor complexes execute their function within the mitochondrial compartment by regulating the function and expression of mitochondrial proteins, *i.e.* proton channels and subunits of key enzymes of the respiratory chain, as well as by eliminating radical oxygen species (ROS) [35,36,42–45,30]. Alternatively, estrogens can interact with a G-protein coupled receptor 30 (GPR30) which, as classical extranuclear estrogen receptors also do, interacts with scaffold proteins such as modulator of nongenomic activity of ER (MNAR)/proline, glutamate and leucine rich protein 1 (PELP1), striatin, and p130Cas, thus cascading again to intracellular kinase systems [41,45]. We might assume that classical genomic- and non-classical steroid signaling pathways are intertwined in mediating neuroprotective and life-supporting effects in the brain and, due to their time and spatial resolution in signaling, affect early and late protective as well as cell compartment-related processes in a spatiotemporal fashion. As presented in Fig. 1, classical and non-classical receptors are present in astroglia throughout the brain and during different stages of development, and the activation of respective downstream signaling cascade can be monitored.

In the following chapters, we concentrate on the two major cell types of brain glia which play a decisive role during repair processes in the CNS and are part of the brain-intrinsic immune system and neuroinflammatory cascade, *i.e.* astroglia and microglia. Special attention is given to their roles as estrogen and progesterone target cells and integration of steroid-mediated neuroprotective action.

2. Astroglia as presumed target to convey steroid-mediated neuroprotection

There is convincing evidence that astrocytes from different brain regions and in different phases of life contain all relevant types of receptors (see above) for both steroid hormones, although it is not fully clear whether these receptors are always expressed constitutively or rather on demand when astrocytes become activated under pathological conditions [13,14,23,33,36,38,39,46–48]. There are a few reports which substantiate the latter statement. Beta-amyloid toxicity to cortical neurons is reduced and corresponds with increased estrogen receptor-α expression in reactive astrocytes which is supposed to limit neuronal damage [49]. Knockdown of estrogen receptor-α by siRNA experiments contrariwise increased the sensitivity of nerve cells to this toxin. Excitotoxic injury and physical-stab wounds cause an increased expression of estrogen receptor-α in reactive cerebral cortical astroglia, whereas data for estrogen receptor-β are more inconsistent [50]. Similar observations were made in microglia (described *in extenso* in the next chapter) [50]. To make a short detour to another neurological disease model, there comes direct evidence from the experimental autoimmune encephalomyelitis (EAE) mouse model which mimics in part the neuroinflammatory component of multiple sclerosis that estrogen receptor-a deletion in astroglia but not in neurons is indeed essential for the observed protective estrogenic effects on CNS inflammation and axonal loss [51]. Fig. 1 shows a set of confocal images which demonstrate the expression of classical estrogen receptors in glial fibrillary acidic protein (GFAP)-positive astrocytes and the different intracellular location of these receptors. Additionally, non-classical estrogen action on intracellular calcium signaling and the activation of distinct signal transduction pathways are presented. Less evident are data concerning the presence and turnover of progesterone receptors in normal and disease-affected brain tissue. In a recent transient stroke study in male rats, we could demonstrate that the expression of both estrogen receptor subtypes (α and β) is massively boosted in the ipsilateral infarcted cerebral cortex compared to the non-struck contralateral side, whereas no changes in progesterone

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