Neuroprotection by Ovarian Hormones in Animal Models of Neurological Disease

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Ovarian hormones can protect against brain injury, neurodegeneration, and cognitive decline. Most attention has focused on estrogens and accumulating data demonstrate that estrogen seems to specifically protect cortical and hippocampal neurons from ischemic injury and from damage due to seizures. Although multiple studies demonstrate protection by estrogen, in only a few instances is the issue of how the steroid confers protection observed. Here, we first review data evaluating the neuroprotective effects of estrogens, a selective estrogen receptor modulator (SERM), and estrogen receptor α- and β-selective ligands in animal models of focal and global ischemia. Using focal ischemia in ovariectomized ERαKO, ERβKO, and wild-type mice, we clearly established that the ERα subtype is the critical ER mediating neuroprotection in mouse focal ischemia. In rats and mice, the middle cerebral artery occlusion (MCAO) model was used to represent cerebrovascular stroke, while in gerbils the two-vessel occlusion model, representing global ischemia, was used. The gerbil global ischemia model was used to evaluate the neuroprotective effects of estrogen, SERMs, and ERα- and ERβ-selective compounds in the hippocampus. Analysis of neurogranin mRNA, a marker of viability of hippocampal neurons, with in situ hybridization, revealed that estrogen treatment protected the dorsal CA1 regions not only when administered before, but also when given 1 h after occlusion. Estrogen rarely is secreted alone and studies of neuroprotection have been less extensive for a second key ovarian hormone progesterone. In the second half of this review, we present data on neuroprotection by estrogen and progesterone in animal model of epilepsy followed by exploration into ovarian steroid effects on neuronal damage in models of multiple sclerosis and traumatic brain injury.

Key Words: Animal model; stroke; ischemia; epilepsy; trauma; allergic encephalitis.

Introduction

Although the ovarian hormones, estrogen and progesterone, primarily regulate reproductive functions in the brain and periphery, they also influence the development, growth, differentiation, maturation, and function of the peripheral and central nervous systems. Estrogen functions as a neurotrophic molecule that supports neuronal viability and, under certain conditions, prevents neuronal cell death. Recent evidence suggests that progesterone may also contribute to these events, albeit to a lesser extent. Estrogen may act via three mechanisms: (i) it may function as a factor that regulates gene transcription after binding to its receptor (estrogen receptor-α [ERα] or ERβ) and interacting with an estrogen response element(s) present in the promoter region of estrogen-regulated genes; (ii) estrogen may bind to ERα and/or ERβ and interact with proteins in the cell membrane or the cytoplasm to activate second messenger systems, and (iii) estrogen may act via receptor independent mechanism(s) as a free-radical scavenger. Progesterone’s actions too have been ascribed to (i) transcriptional mechanisms via progesterin receptors (PR), (ii) rapid signaling events, (iii) binding of progesterone metabolites to GABA receptors, or (iv) antioxidant actions much like those of estrogen. In viewing hormonal influences on models of neuronal injury, it is critical to appreciate that steroidal actions can be exerted on multiple processes that will ultimately affect whether a neuron lives or dies (Fig. 1), and that these processes have defined temporal patterns (Fig. 2). Thus, when the steroid is administered it will determine on which process it acts and whether or not treatment will be successful.

A large body of evidence indicates that estrogen protects against brain injury, neurodegeneration associated with Alzheimer’s disease (AD) and Parkinson’s disease (PD), as well as aging-related cognitive decline (for reviews see refs. 1–3). Recent evidence further implicates estrogen as a neuroprotective factor against neuronal damage from epilepsy (4,5), despite its reputation as a proconvulsant (6–11), and against cytokine damage in animal models of multiple scler-
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Endocrine

osis. Progesterone is used clinically to suppress seizure activity and to reduce edema following head injury; experimentally only low doses of progesterone are effective. Unfortunately, the mechanism by which the steroids mediate these effects is still uncertain. Understanding how these steroids act in brain injury becomes crucial as an increasing segment of the female population will spend a significant proportion of their lifespan in a hypoestrogenic, hypoprogesteronemic postmenopausal state. Unraveling the cellular and molecular mechanisms that underlie the protective actions of steroidal hormones may lead to new therapies for disorders/dysfunctions associated with loss of ovarian steroids.

In this review, we describe the use of a variety of animal paradigms that model stroke, epilepsy, autoimmune conditions similar to multiple sclerosis, and brain trauma. Through the use of these models and the investigation of different steroidal compounds, distinctly different roles for ovarian hormones in neurological diseases are emerging: estrogen is a potent neuroprotective agent that likely acts via both receptor-mediated and receptor-independent mechanisms to protect neurons from injury; whereas progesterone can dampen neuronal excitability but may have complex and dose-dependent interactions with molecules provoking cell death and processes affecting inflammation.