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Introduction to *Reproductive Hormones and Neurodegenerative Disease*

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This special section was inspired by the ongoing controversy regarding steroid hormone therapy in the menopause and andropause. Will it cure us or kill us? Does the answer lie in the choice of whom to treat, when to treat, or how to treat? There is a large body of basic scientific evidence that steroid hormones can have beneficial effects on neuronal injury and neurodegeneration. Yet clinical trials have not been uniformly positive.

The articles in this section address the relationship between gonadal and reproductive hormones, and neurodegeneration. Many of the papers deal mainly with estradiol, which has been most extensively studied. However, compelling evidence exists that other steroids, including progesterone and testosterone, as well as the pituitary and gonadal peptides can also affect neuronal function and survival.

The paper by DeLacalle focuses on the effects of estrogen on neuronal morphology, illustrating that estrogen is a potent structural signal that can drive developmental as well as adult neuronal plasticity. Correlation of changes in neuronal morphology with physiological and behavioral effects can provide new insights into how plasticity of neuronal structure leads to functional plasticity.

Sohrabji and Bake discuss the age-related effects of estrogen on the blood–brain barrier and inflammatory cytokine expression, and how these may impact the response to estrogen therapy (ET). Age-related changes in response may determine whether the effects of ET are beneficial or deleterious.

Bryant et al. summarize the signaling pathways that transmit the neuroprotective effects of gonadal steroids, particularly estrogen. They make the important point that understanding the mechanisms of estrogen-mediated neuroprotection will guide the development of safe, effective, related therapeutic interventions.

Suzuki et al. review the evidence that estradiol can exert a protective effect in an animal model of ischemic stroke-like injury and enhance the ability of the adult brain to undergo repair. Effects may be mediated through estrogen receptor-α and involve both reduction of apoptosis and increased neurogenesis.

Hoffman et al. review the neuroprotective effects of estrogen, selective estrogen receptor modulators (SERMs), and estrogen receptor subtype-selective ligands in animal models of focal and global ischemia. Data are also presented on the neuroprotective effects of estrogen and progesterone in animal models of epilepsy, multiple sclerosis, and brain trauma.

The article by Pike et al. discusses the evidence that testosterone depletion with age in men increases the risk for Alzheimer's disease (AD) through decreased regulation of β-amyloid accumulation and loss of testosterone's neurotrophic and neuroprotective functions. They argue that these findings support initiation of clinical trials to evaluate testosterone therapy for the prevention of AD.

Czlonkowska et al. review the current clinical and experimental evidence that the modulation of inflammatory mediators, including cytokines, by estrogen explains the sexual dimorphism in the prevalence of a number of neurological diseases with an inflammatory component, including AD, Parkinson's disease (PD), multiple sclerosis, and amyotrophic lateral sclerosis. Inhibition of neuroinflammation correlates with less neuronal degeneration making anti-inflammatory agents candidates for therapeutic intervention in a number of neurodegenerative disorders.

Barron et al. review the role of gonadotropins in the brain and the potential direct neuropathological effects of elevated gonadotropin levels. They provide compelling evidence that luteinizing hormone is involved in several key biochemical and cellular processes, including β-amyloid metabolism, CNS cholesterol homeostasis, and pro-inflammatory effects, that contribute to the pathogenesis of AD.

Singh's review discusses the data that support the neuroprotective role of progesterone and describes the mechanisms whereby progesterone elicits its protection. Progesterone may reduce cell death, induce remyelination, and act as an antioxidant.

Tamás et al. discuss the effects of age and gender on the neurochemical and behavioral outcome of 6-hydroxydopamine treatment in an animal model of PD. They describe intriguing new data that age, gender, and gonadectomy can affect loss of dopaminergic neurons, and the behavioral consequences.

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The article by Wilson et al. discusses the anti-inflammatory properties of estrogen that may have particular relevance in chronic neuroimmune disorders such as HIV dementia. They hypothesize that estrogen may be able to decrease the incidence of HIV dementia and other AIDS-related neurological disorders in HIV-1 positive women.

It is clear that multiple hormones of the reproductive axis profoundly affect CNS metabolism and function in a variety of ways. The task ahead is to determine how this knowledge can be used to design new therapeutic strategies that prevent neurodegeneration secondary to aging and disease and enhance repair after CNS injury.