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Review

Sex differences and the effect of hormonal therapy on ischemic brain injury

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Abstract

Epidemiological data emphasize the importance of sex differences in the mortality and morbidity of stroke and cardiovascular disease. The importance of hormonal influences on stroke outcome has pointed out the importance of gender, age, and presence of neural hormones. This clinical data has been substantiated by various experimental studies using clinically relevant models of cerebral ischemia and stroke. Published findings emphasize that male and female animals respond differently to periods of cerebral ischemia and that various combinations of hormonal treatments can provide protection, both histopathological and behavioral. Mechanisms underlying the hormonal effects on ischemic outcome are multifactorial. These include effects on vascular integrity and cerebral blood flow, excitotoxicity, oxidation pathways, inflammation, and apoptosis. Although many studies have shown positive results with hormonal treatments, negative findings have also been presented. Explanations for the limitations of hormonal treatment include uncertainties regarding therapeutic window, specific therapeutic dose range, as well as the specific pathophysiological processes being targeted. Additional studies are therefore required to clarify under what conditions hormonal therapy is most protective or not warranted. Experimental studies utilizing a variety of cerebral ischemia and stroke models are reviewed to indicate under what conditions sex differences and hormonal therapy are most important in terms of functional outcome.

Keywords: Hormones; Ischemia; Mechanisms of action; Estrogen; Progesterone

Contents

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1. Introduction

The use of sex hormones to prevent or treat neurological/vascular disease has become a highly debated topic because of the recent clinical findings using hormone replacement therapy (HRT) [1,2]. These clinical studies were initially begun because of the overwhelming experimental evidence on the efficacy of hormones in treating injury via targeting multiple pathomechanisms along with strong epidemiological data reporting sex differences in morbidity and mortality of stroke and cardiovascular disease. In a recent update published by the American Heart Association, the prevalence of cardiovascular disease (CVD) in women was lower than men until the post-menopausal (over 55) age [3]. When age is adjusted, the incidence of stroke is also lower in women than men. The percentage of those individuals having a transient ischemic attack (TIA) or mini-stroke is lower in women than men. However, these numbers can be somewhat misleading when differentiating between different types of stroke. For example, mortality from subarachnoid hemorrhage is higher in women than men. Nevertheless, the overwhelming evidence reported from the epidemiological studies and the preclinical data point to a real effect of hormonal influence on outcome.

The question is how to balance the findings from the experimental work with the findings from the HRT studies in order to develop a therapeutic plan that will provide prevention as well as neuroprotection in patients at risk for CVD and stroke. Several reasons may underlie the discrepancy in the HRT studies from the preclinical work. Among these are, route of administration of hormones, dosage of hormones, age at which HRT is started, pharmacological composition of the hormone, and target population [4]. Since the majority of preclinical data in animal models of ischemia demonstrate an improvement with hormonal therapy, it is important that new clinical trials are designed based on these data rather than just a preventative strategy in those individuals who already have some incidence of cardiovascular disease in their medical history. Wise [5] has discussed this problem extensively in a review on whether or not estrogen therapy can be protective or an increased risk for disease. The purpose of this paper is to provide the reader with a general summary of reported sex differences in models of cerebral ischemia and stroke, how hormonal treatment can affect outcome and what pathways and mechanisms of action may be influenced by each hormone.

2. Sex differences in cerebral ischemic animal models

Sex differences in ischemic animal model outcomes have been reported [6–9]. These findings quickly led to studies on specific interactions of hormones in these models, which are discussed further below. Hall et al. [8] were one of the first groups to demonstrate smaller infarct volumes in female animals compared to males after 3 h of unilateral carotid occlusion in gerbils. These results also extended to an improvement in other measures such as cortical extracellular calcium and Vitamin E levels. Female animals have shown an improvement in cerebral blood flow (CBF) along with decreased infarct volume compared to males in a suture model of middle cerebral artery occlusion (MCAO) [6]. In contrast to these studies in young animals, Alkayed et al. [7] reported no difference in cortical and striatal infarct volumes after 2-h MCAO in older male and senescent female rats. The findings from the young and older animal studies parallel what has been observed clinically after stroke in terms of epidemiology and whether or not the presence of circulating endogenous hormones are able to provide neuroprotection. This in turn, spawned new investigations into what affect hormones could be having on ischemic outcome in ovariectomized rats. The predominant hormone that has been studied in the ischemia field is estrogen. This is most likely due to initial studies showing estrogens ability to affect vascular function. However, more recently, there has been an increase in the number of ischemic studies reporting on the results of progesterone or testosterone treatment.

3. Hormones and histological outcome after ischemia

The characterization of hormone receptors and the local production of hormones within the brain have spearheaded an increased interest in this research area as a potential treatment strategy after injury (see Table 1). In addition, both in vitro and in vivo studies have demonstrated multiple pathways that hormones affect, many of which are involved in ischemic injury. Therefore, numerous studies have reported on the selective use of estrogen [7,9–24], progesterone [7,25–29] or a combined [30] approach as a treatment strategy in an ovariectomized female (OVX), female or male animal before or after an ischemic insult and demonstrated the efficacy of this treatment strategy in improving histological outcome.

Several different models of cerebral ischemia and stroke have been utilized for hormone neuroprotection studies. These include transient middle cerebral artery occlusion, permanent MCAO, transient global ischemia and photothrombosis. These models produce similar injury cascades along with development of cerebral infarction and neuronal cell loss. The transient MCAO estrogen treatment studies were performed in OVX rats with a pre- [11,14,21] or post-treatment [9] strategy to target infarct volume. Rusa et al. [11] reported a decrease in ischemic brain damage as measured by cortical and caudate-putamen infarction volumes with a prolonged estrogen (25 μg) treatment protocol of 7–16 days prior to MCAO. In that study, estrogen treatment did not affect local cerebral blood flow (LCBF) in the ischemic areas, which indicated that estrogen is reducing infarct volumes via a flow-independent mechanism. This hemodynamic finding has been confirmed using magnetic resonance imaging (MRI) of OVX estrogen pretreated MCAO animals compared to ovariectomized control rats [21]. These investigators reported reduced lesion size in diffusion-weighted and T2-weighted