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Review

Astrocytic response to cerebral ischemia is influenced by sex differences and impaired by aging

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ABSTRACT

Ischemic stroke occurs more often among the elderly, and within this demographic, women are at an increased risk for stroke and have poorer functional recovery than men. This is also well replicated in animal studies where aging females are shown to have more extensive brain tissue loss as compared to adult females. Astrocytes provide nutrients for neurons, regulate glutamate levels, and release neurotrophins and thus play a key role in the events that occur following ischemia. In addition, astrocytes express receptors for gonadal hormones and synthesize several neurosteroids suggesting that the sex differences in stroke outcome may be mediated through astrocytes. This review discusses key astrocytic responses to ischemia including, reactive gliosis, excitotoxicity, and neuroinflammation. In light of the age and sex differences in stroke outcomes, this review highlights how aging and gonadal hormones influence these responses. Lastly, astrocyte specific changes in gene expression and epigenetic modifications during aging and following ischemia are discussed as possible molecular mechanisms for impaired astrocytic functioning.

Contents

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Background

By 2030, it is estimated that 19% of the population will be greater than 65 years of age. As the world's population ages, the prevalence of age-related neurological diseases will increase. Specifically, the prevalence of stroke increases during aging. The average age of ischemic stroke patients is 71 and 17.8% of the population over 45 years of age showed at least one stroke-related symptom (Ovbiagele et al., 2013; Fonarow et al., 2010). The increased risk for stroke during aging is accompanied with poorer stroke outcomes and the cost associated with treating stroke totals more than 36 billion dollars annually in the United States (Go et al., 2014). In addition, elderly patients are less likely to be discharged home and more likely to die in the hospital (Copen et al., 2001; Fonarow et al., 2010).

Given the effects of normal aging on the brain (reviewed in Juraska and Lowry, 2012) it is not surprising that the aged brain responds differently to stroke than the adult brain. Ischemia leads to a series of events including increased intracellular calcium levels and increased glutamate release resulting in excitotoxicity, upregulation of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, and loss of normal protein structure and function (Yenari and Han, 2012). Excessive calcium levels can trigger activation of signaling pathways that cause an overproduction of free radicals and dysfunction of mitochondria, which leads to oxidative stress and cell death (Starkov et al., 2004). In astrocytes, higher levels of mitochondrial calcium can also enhance neuroprotection due to increased in ATP production (Zheng et al, 2010; Zheng et al., 2013). Furthermore, ischemic injury induces a cascade of events that lead to disruption of the blood–brain barrier (Yang and Rosenberg, 2011). The blood–brain barrier is composed of specialized brain microvascular endothelial cells interconnected by tight junction proteins, surrounded by pericytes, and a defined basement membrane. Astrocytic end feet located on the outer side of the basement membrane further regulate blood–brain barrier function and deliver nutrients to nearby neurons (Figley and Stroman, 2011; Abbott et al., 2006). The blood–brain barrier is designed to maintain homeostasis of the brain microenvironment and the known disruption after ischemia may make changes during aging particularly important. In humans, normal aging results in increased blood–brain barrier permeability (Farrall and Wardlaw, 2009; Montagne et al., 2015) and decreased microvessel density (Brown and Thore, 2011). Furthermore, studies in a senescence-accelerated mouse model have shown that the passage of cytokines through the blood–brain barrier is altered (Banks et al., 2001; McLay et al., 2000), the expression of the glucose transporter GLUT-1 is reduced (Vorbrodt et al., 1999) and there is increased permeability of the blood–brain barrier (Ueno et al., 1993; Pelegri et al., 2007). This increased permeability in the blood–brain barrier may exacerbate cell loss following ischemia. Although the blood–brain barrier consists of several different cell types that are susceptible to age-related changes, this review will highlight the importance of astrocytes in stroke outcomes during aging with an emphasis on the influence of sex since both are risk factors for stroke.

There are well documented sex differences in stroke risk and stroke outcomes. According to the Framingham Heart Study, women had an overall lower risk of stroke than men (Petrea et al., 2009), however although men and women had a similar prevalence of stroke at age 35 to 44 years, between the ages of 45 and 54 women were more than twice as likely to have had a stroke than men (Towfighi et al., 2007). In addition, partially due to longer life-spans and age of stroke, women are discharged to long term care facilities more often, have poorer functional outcomes, and a lower probability of achieving independence in activities of daily living after discharge (Appelros et al., 2009; Fukuda et al., 2009; Kapral et al., 2005; Gargano et al., 2011). A recent study found that even though acute stroke care was similar between males and females, women had poorer functional outcomes and increased dependence on nursing care three months after ischemia (Gattringer et al., 2014).

Preclinical studies have historically examined stroke severity and recovery in young animals; however, in agreement with the human data, more recent animal studies have shown that the aged brain responds differently to experimental stroke than the young brain. For example, following cerebral ischemia adult females (3–7 months) have smaller infarcts than middle-aged females (rats: 9–12 months, mice: 12–15 months) (Selvamani and Sohrabji, 2010b; Manwani et al., 2011; Selvamani et al., 2014) and aged females (>16 months) (Rosen et al., 2005; DiNapoli et al., 2008; Liu et al., 2009). However, studies examining the outcome of ischemia and the effects of aging in male animals have produced varying results. Similar to the results observed in females, several studies have shown that aged male rodents exhibit larger infarcts, increased edema, and worse neurological functional deficits compared to adult males (Dong et al., 2014; Miao et al., 2013; Tennant et al., 2014). The accelerated development of degenerating neurons and apoptotic cells following ischemia in males may contribute to the poorer outcomes (Popa-Wagner et al., 2007). There is also evidence that chronic infection resulting in pre-existing inflammation, a condition known to influence stroke outcome, results in increased infarct size in aged male mice but not in young mice 24 h post stroke (Dhungana et al., 2013). Importantly, some studies have found opposite effects of aging or no effects of aging in male mice following ischemia. For example, 16 month old male mice have smaller infarcts and less atrophy than adult male mice following transient focal ischemia (Liu et al., 2009; Manwani et al., 2011), and adult rats had more extensive neurological damage than aged rats following occlusion of the external carotid artery (Shapira et al., 2002). In contrast, other studies have shown no differences in infarct volumes following ischemia between adult and middle-aged males (Selvamani et al., 2014). These differences suggest that several factors may influence the outcome of ischemia during aging, including the type of occlusion, inclusion of middle-aged versus aged animals, and the time point examined following stroke. Irrespective of infarct size, several studies have found more severe behavioral deficits and poorer functional recovery in aging animals following stroke than adult animals. Whereas adult males began to recover sensorimotor functioning 1–2 days after stroke and fully recovered within 15 days, this was delayed in aged rats and functionality only returned to 70% of pre-stroke levels at day 15 (Popa-Wagner et al., 2007). Although rehabilitative training on a novel task following ischemia resulted in behavioral improvement in adult males, improvement was only observed in aged males with a previously learned task (Tennant et al., 2014).

Sex has been identified as an important variable for stroke outcome in animal models of stroke as well. In particular, adult females have smaller infarcts and better cerebral blood flow than adult males (Hall et al., 1991; Alkayed et al., 1998; Selvamani et al., 2014), however the sex difference is reversed in aging and middle-aged females have larger infarct volumes than middle-aged males (Manwani et al., 2013). In a direct comparison of adult and middle-aged male and female rats, adult females displayed smaller infarct volumes as