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Review

Interactions between age, sex, and hormones in experimental ischemic stroke

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ABSTRACT

Age, sex, and gonadal hormones have profound effects on ischemic stroke outcomes, although how these factors impact basic stroke pathophysiology remains unclear. There is a plethora of inconsistent data reported throughout the literature, primarily due to differences in the species examined, the timing and methods used to evaluate injury, the models used, and confusion regarding differences in stroke incidence as seen in clinical populations vs. effects on acute neuroprotection or neurorepair in experimental stroke models. Sex and gonadal hormone exposure have considerable independent impact on stroke outcome, but these factors also interact with each other, and the contribution of each differs throughout the lifespan. The contribution of sex and hormones to experimental stroke will be the focus of this review. Recent advances and our current understanding of age, sex, and hormone interactions in ischemic stroke with a focus on inflammation will be discussed.

1. Introduction

Stroke is a major cause of mortality and the leading cause of long-term disability in the USA. Ischemic stroke accounts for 87% of all strokes (Rojas et al., 2007; Roger et al., 2011). To date only one FDA approved therapy is available for patients with acute ischemic stroke, the thrombolytic tissue plasminogen activator (tPA) (Maestre-Moreno et al., 2005). Unfortunately, despite our best efforts, only a small number of patients are eligible for tPA therapy. Thrombolytic therapy, although extremely efficacious, has a very short time window of treatment, ranging to 3 h in the USA to 4.5 h in Europe (Hacke et al., 2008) after which decreasing efficacy and increased risk of hemorrhagic complications occur. Basic scientists have identified numerous potential "neuroprotective" agents that reduce stroke injury in experimental models, but attempts to bring these therapies into the clinic has met with limited success. Numerous promising agents have failed to show protective effects in clinical trials (Ginsberg, 2008). This has led to the questions (1) are we utilizing the most appropriate animal models in our preclinical studies? and (2) are we designing our clinical trials with guidance from emerging experimental data? These concepts must be considered if we hope to develop efficacious neuroprotective candidates.

Young, male animals are the invariable favorite for use by most stroke researchers in experimental studies. However, clinical stroke is a disease that mainly affects the elderly (Rojas et al., 2007; Roger et al., 2011). In fact, age is the most important independent risk factor for stroke (Rosamond et al., 2008) with stroke rates doubling every decade after the age of 55 (Rojas et al., 2007). The aged brain undergoes numerous neurochemical and physiological changes over the lifespan that change the responsiveness to a variety of therapies compared with young brains (Anyanwu, 2007). Acetylcholinesterase (AChE) and Na^+K^+ATPase activity in synaptosomes decreased with age resulting in neuronal vulnerability changes to excitotoxic insults (Mantha et al., 2006).

Abbreviations: AChE, acetylcholinesterase; AIF, apoptosis inducing factor; AMP, adenosine monophosphate; ATP, adenosine-5′-triphosphate; AVPV, anteroventral periventricular nucleus; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; BTK, Bruton tyrosine kinase; CBF, cerebral blood flow; CSF, cerebrospinal fluid; CHD, coronary heart disease; DAPI, 4′,6-diamidino-2-phenylindole; DHT, dihydrotestosterone; eNOS, endothelial nitric oxide synthase; E2, 17β-estrodial; ERT, estrogen replacement therapy; ER, estrogen receptor; ERE, estrogen-responsive element; GABA, γ-aminobutyric acid; GM-CSF, granulocyte-macrophage colony-stimulating factor; HIE, hypoxic–ischemic encephalopathy; HRT, hormone replacement therapy; 5-HT, 5-hydroxytryptamine; IL, interleukin; IRAK-1, interleukin 1 receptor-associated kinase 1; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MIP-1, macrophage inflammatory protein-1; MCP-1, monocyte chemotactic protein-1; MCAO, middle cerebral artery occlusion; MRI, magnetic resonance imaging; MAPK-1, mitogen-activated protein kinase 1; NADPH, nicotinamide adenine dinucleotide phosphate; NeuN, Neuronal Nucleus protein; NHANES, National Health and Nutrition Examination Surveys; NKCC, Na^+–K^+–Cl^- co-transporter; NFs, neurofilaments; NF-κB, nuclear factor-κB; NEMO, NF-κB essential modulator; OPC, oligodendrocyte progenitor cell; Ovx, ovariectomy; pAMPK, phosphorylated adenosine monophosphate-activated protein kinase; PARP, poly(ADP-ribose) polymerase; TNF, tumor necrosis factor; tPA, thrombolytic tissue plasminogen activator; WHI, Women's Health Initiative; WEST, Women Estrogen Stroke Trial; XCI, X-chromosome inactivation; XIAP, X-linked inhibitor apoptosis protein.

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Simvastatin, a hypolipidemic drug for the treatment of dyslipidemia, fully restored short- and long-term memory in adult, but not in aged mice of Alzheimer's disease model (Tong et al., 2012). Sex differences are also seen in the epidemiology of ischemic stroke (Turtzo and McCullough, 2010). In neonates, male sex is a risk factor for poor outcome, whereas increased incidence and morbidity is seen in elderly females. Childhood ischemic stroke appears to be more common in boys regardless of age, stroke subtype, or history of trauma (Golomb et al., 2009; Cheong and Cowan, 2009). Elderly women not only have higher stroke incidence than age-matched men, but also have poorer recovery, higher morbidity and mortality once a stroke occurs (Glader et al., 2003; Appelros et al., 2009; Niewada et al., 2005; Fukuda et al., 2009; Roquer et al., 2003). These clinical data remind us that age and sex are important impact factors which should be fully taken into account in experimental stroke studies. This review discusses age- and sex-related differences in stroke phenotypes and the possible underlying mechanisms, aiming to shed light on the discrepancies between experimental and clinical data of stroke studies.

2. Impact of age and sex on normal brains

2.1. Aging effects on the brain

Both global and regionally specific changes in brain tissue volume occur with aging (Killiany et al., 2004) (Table 1). Studies with magnetic resonance imaging (MRI) revealed that in the elderly white matter volume loss predominates over that seen in the gray matter (Double et al., 1996; Guttmann et al., 1998; Resnick et al., 2000). The frontal lobes show the greatest decline in the volume with age (approximately 12%), followed by the temporal lobe (9%) and the occipital and parietal lobes which only showed modest change (DeCarli et al., 2005). Apart from the age related changes in the brain volume, neurochemical and physiological changes also occur with aging (Anyanwu, 2007) (Table 1). Cerebral blood-flow (CBF) is regionally reduced with aging in the fronto- and temporocortical area and in the subcortical region, and age negatively correlates with perfusion in both the left and right fronto-cortical regions (Peremans et al., 2002). Recent studies showed that in aging tissues from female and male animals, markers of oxidative stress increase due to decreased activity of antioxidant enzymes. In addition, proteolysis increases due to decreased activity of aminotransferase (Sinha et al., 2005; Bala et al., 2006). Significant alterations in neurotransmitters and enzyme activity are seen with advancing age in the non-demented elderly. These include well documented changes in levels of choline acetyltransferase, and an increase in vasoactive intestinal peptide immunoreactivity (Perry et al., 1981). Age-related changes are also seen by the relatively robust decrease in brain nutritional factors, including carbohydrates, proteins, and fat (Solfrizzi et al., 2006), and by the loss of key enzymes of the respiratory chain involving cytochrome oxidase and succinic dehydrogenase (Bertoni-Freddari et al., 2006).

2.2. Sex differences in the brain

Numerous sex differences in human brain structure have been described demonstrating that the brain is a sexually dimorphic organ (Table 2). *In vivo* imaging and postmortem studies report that the cerebrum is larger in men than women by 8–10% (Filipek et al., 1994; Witelson, 1989; Passe et al., 1997; Rabinowicz et al., 1999; Nopoulos et al., 2000), a finding that is not wholly attributed to body size. Regionally specific sex differences relative to size of cerebrum have also been reported. Goldstein et al. (2001) reported that sexual dimorphisms of adult brain volumes were more evident in the cortex, with women having larger volumes, relative to cerebrum size, particularly in frontal and medial paralimbic cortices. Men had larger volumes, relative to cerebrum size, in the frontomedial cortex, the amygdala and hypothalamus. Other studies showed that relative to cerebrum size, women have larger volumes in cortical gray matter (Gur et al., 1999), in regions associated with language functions, e.g. Broca's area (Harasty et al., 1997), in the hippocampus, caudate, and thalamic nuclei (Filipek et al., 1994; Giedd et al., 1996; Murphy et al., 1996) than men. In contrast, men have been found to have larger volumes,

Table 1
Impact of aging on brain anatomy and physiology.

	Parameters	Changes with aging	Species	References
Tissue volume	Amount of CSF	Increase	Human	Pfefferbaum et al. (1994) and Matsumae et al. (1996)
	Overall brain volumes	Decrease	Human	Pfefferbaum et al. (1994) and Matsumae et al. (1996)
	White matter	Decrease	Human	Double et al. (1996), Guttmann et al. (1998) and Resnick et al. (2000)
	Gray matter	Small decrease	Human	Double et al. (1996), Guttmann et al. (1998) and Resnick et al. (2000)
	Frontal lobe	Decrease	Human	DeCarli et al. (2005)
	Temporal lobe	Decrease	Human	DeCarli et al. (2005)
	Occipital and parietal lobe	Decrease	Human	DeCarli et al., 2005
	Hippocampus	Decrease	Human	Raz (2000)
Physiology and neurochemistry	Oxidative stress	Increase	Rat	Sinha et al. (2005) and Bala et al. (2006)
	Glutathione peroxidase and NADPH generation	Increase	Rat	Hothersall et al. (1981)
	Glucose-6-phosphate dehydrogenase activity	Increase	Rat	Baquer et al., 2009
	Malic enzyme	Increase	Rat	Baquer et al. (2009)
	Vasoactive intestinal peptide immunoreactivity	Increase	Human	Perry et al. (1981)
	CBF	Decrease	Dog	Peremans et al. (2002)
	ATP citrate-lyase	Decrease	Rat	Baquer et al. (2009)
	Acetyl Co-A carboxylase	Decrease	Rat	Baquer et al. (2009)
	Fatty acid synthetase	Decrease	Rat	Baquer et al. (2009)
	Carbohydrates	Decrease	Human	Solfrizzi et al. (2006)
	Tryptophan and tyrosine	Decrease	Human	Solfrizzi et al. (2006)
	Unsaturated fatty acids	Decrease	Human	Solfrizzi et al. (2006)
	GABA	Decrease	Rat	Caspary et al. (1999)