



The effect of aging on brain injury and recovery after stroke



This special issue of *Neurobiology of Disease* focuses on the effects of aging on brain injury and recovery after ischemic and hemorrhagic stroke. Multiple reasons have been proposed as to why preclinical neuroprotective therapies for stroke have failed to translate to the clinic (Fisher et al., 2009; Ginsberg, 2008). One potential contributory factor has been that most preclinical studies have been performed in young healthy animals (primarily rodents), whereas stroke in humans is predominantly a disease of the elderly. For example, in the USA, the prevalence of stroke is ~7-fold greater in patients older than 80, than in patients aged 40–59 years (Benjamin et al., 2018). The impact of aging on different components of the brain, how it affects stroke injury and recovery, as well as therapeutic efficacy are the major focuses of this special issue.

White matter injury, including demyelination, and recovery has been relatively understudied compared to grey matter injury. Subcortical white matter stroke accounts for ~30% of all strokes (Rosenzweig and Carmichael, 2013) and white matter tracts can also be affected by other stroke subtypes. Most preclinical studies are performed in rodents that have much less white matter than humans and white matter injury studies are underrepresented. Marin and Carmichael (2019) and Xu et al. (2019) review the impact of aging on white matter and myelin damage after stroke. Marin and Carmichael (2019) review data on demyelination after human and animal white matter strokes, the mechanisms involved and what limits remyelination and how that may be enhanced. Xu et al. (2019) reviews the impact of aging and another major stroke co-morbidity, hypertension, on white matter injury and repair after ischemic stroke. Both of these reviews serve to reinforce the growing understanding of the importance of white matter injury in stroke, the mechanisms involved and the potential for enhancing white matter repair to promote rehabilitation after stroke.

One consequence of white matter injury is altered connectivity between areas of the brain. Major technical advances are being made in assessing brain connectivity in patients and animals (Bauer et al., 2018; Glasser et al., 2016). Straathof et al. (2019) examined the impact of aging on neural networks within the rat brain and modeled the effects of different types of stroke (location/size) on those networks. They found that strokes induced both local and global changes in neural networks (efficiency and hub locations) and that aging impacts those changes. Using such modeling in patients may help inform specific rehabilitation strategies to limit stroke impact.

The ability of the brain to recover from a stroke depends on factors such as stroke size and location as well as comorbidities such as aging, hypertension and diabetes. However, it is also influenced by genetic polymorphisms. Balkaya and Cho (2019) review data on the prevalent Val66Met polymorphism in brain derived neurotrophic factor in humans that alters post-stroke plasticity. The Val66Met polymorphism impairs

cortical plasticity particularly in the aged. It has been widely thought of as being maladaptive but that may depend on a variety of factors including stroke location.

A major issue in stroke research is whether therapies that are efficacious in young animals will also show benefit in old animals? This has led to the emphasis on including stroke studies in aged animals in STAIR guidelines (Fisher et al., 2009). This special issue includes four studies determining the effects of potential stroke therapies in aged animals. Continuing the theme of the importance of stroke-induced white matter injury, Bastian et al. (2019) examined casein kinase 2 (CK2) inhibition as a method for reducing such injury. They found that targeting CK2, or its downstream signaling, protected against white matter injury irrespective of age. Given that CK2 inhibitors are currently in clinical trials for cancer, this is a promising therapeutic approach. Jiang et al. (2019) examined the effects of omega-3 polyunsaturated fatty acids (n-3 PUFAs) on ischemic brain injury in young and old mice. Those long-term studies (out to 35 days) found that n-3 PUFAs reduced brain injury and enhanced angiogenesis and oligodendrogenesis as well as white matter restoration. Such protection with n-3 PUFAs was, however, greater in young mice. In hemorrhagic stroke, there has been interest in the use of minocycline as a therapy as it may reduce brain injury due to inflammation and iron overload. Dai et al. (2019) found that minocycline could reduce intracerebral hemorrhage-induced brain injury in aged (18 months) female rats complementing prior studies in young animals (Zhao et al., 2011). There have been recent Phase I clinical trials of minocycline showing safety (Chang et al., 2017; Fouda et al., 2017) and another iron chelator, deferoxamine, in intracerebral hemorrhage is in Phase II clinical trial (iDEF; NCT02175225). Another potential therapeutic approach for ischemic and hemorrhagic stroke is the use of stem cells. Nguyen et al. (2019) reviews studies using stem cells to treat stroke and other neurological diseases. It particularly focuses on how aging impacts such studies not only by impacting the underlying disease but also by affecting endogenous stem cells that might be involved in injury repair.

Understanding the mechanisms by which aging impacts stroke-induced brain injury and repair may help identify new ‘specific’ therapeutic targets for the elderly. Thus, for example, Stamatovic et al. (2019) found that aging in mice causes an increase in blood-brain barrier permeability that is linked to reduced expression of a NAD dependent deacetylase, sirtuin-1 (Sirt1). Overexpressing Sirt1 or a Sirt1 agonist protected against age-related barrier hyperpermeability.

While the Stamatovic et al. (2019) paper examines the effects of aging on the blood-brain barrier and brain endothelial tight junction protein regulation, Guo et al. (2019) used microarrays to examine the effects of aging, hypertension and diabetes on mouse brain and heart vasculomes. They generally found very different effects of these stroke co-morbidities on the brain vasculome, although there were common

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pathway effects related to the suppression of immune response. Interestingly, the effects of aging on gene expression in the brain and heart microvascular endothelial cells were quite disparate. There is growing evidence on the importance of cerebrovascular injury on not only stroke incidence but also stroke outcome (Jiang et al., 2018; Shi et al., 2016). Understanding how the cerebrovascular changes with comorbidities, such as aging and hypertension, described by Guo et al. (2019) and Stamatovic et al. (2019) influence stroke-induced cerebrovascular injury is an important area for future research and may identify novel therapeutic targets. In addition, aging and hypertension are risk factors for vascular cognitive impairment. Raz et al. (2019) here report on cerebrovascular and parenchymal changes in spontaneously hypertensive stroke prone rats fed a high salt/low protein diet, a model of vascular cognitive impairment, as well as changes in patients with subcortical ischemic vascular disease. They provide evidence of a link between hypertension-induced vascular dysfunction and parenchymal injury.

This Special Issue reflects a number of ‘hot topics’ in stroke research. (1) The importance of preclinical stroke studies including aged animals. (2) The impact of aging on therapeutic strategies. (3) The importance of white matter injury in stroke outcome. (4) How to enhance behavioral recovery via white matter restoration or manipulating neural networks. (5) The importance of ‘brain’ rather than just ‘neuronal’ protection, including preventing cerebrovascular injury. Hopefully, studies addressing these issues will help in translating preclinical data (on neuroprotection and neurorehabilitation) to the clinic.

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