Commentary on “Age-Dependent Increase in Infarct Volume Following Photochemically Induced Cerebral Infarction: Putative Role of Astroglia”

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Khramlov, Kharlamov, and Armstrong (1) describe a method for producing precise, focal lesions in the cerebral cortex of rats (Fischer 344) that can be used to evaluate age differences in neurodegenerative processes. The method involved a photochemically induced infarct in the parietal sensorimotor cortex. The main result of their efforts was to establish that the aged brain was more damaged as the result (infarct volume was greater) and that the response of astroglia to the injury was muted compared to younger animals. Astroglia are upregulated in the area of neural injury. As the authors point out, astroglia activation is associated with repair of brain injury as these cells secrete basement membrane and neurotrophic proteins; however, depending upon a number of factors, their presence can either promote or deter recovery.

Although previous investigators have described how to utilize this method for producing a photothrombotic infarct (2) with functional effects (3), Kharlamov and colleagues relate how the use of this procedure in aging studies can present several advantages over other commonly applied methods for producing specific brain lesions. Unlike stroke models in which arteries are occluded, the photothrombotic model is relatively noninvasive with only the scalp being opened. Other brain lesion methods require invasion of the brain with a probe to deliver a neurotoxic agent or electrolytic lesion. The photothrombotic lesion is well defined and is reproducible in size when used in the same rodent model. Additionally, Kharlamov and colleagues showed functional deficits, as measured in a rotarod task, that improved with recovery from the stroke but at a slower rate among aged rats.

While acknowledging these advantages of the photothrombotic stroke model, it should also be recognized that the model has less appeal as a physiologically relevant model of stroke than other models. For example, middle cerebral artery occlusion is clearly more relevant since such occlusions occur naturally in humans and account for a large percentage of strokes suffered (4).

In addition, there are potential confounds to the method for use in aging studies, several of which the authors acknowledge and evaluate carefully. Specifically, the skull of the aged rats (27 mo) was twice as thick as that of younger rats (4 mo). This morphological difference resulted in less light reaching the surface of the aged cortex and should have predicted a reduced infarct size compared to young rats. Just the opposite was reported, which was an intriguing observation. Because of this difference in skull thickness, the authors also acknowledged the possibility of temperature differences on the cortical surface generated by the light source, but they found none. There is one possible confound that the authors did not consider, which was differences in body weight among the age groups. The dye was given intravenously at 80 mg/kg. Although no body weight data were provided, it is likely that the older rats weighed more than the young rats, probably 10−20% more. Although it is conventional to use body weight-adjusted doses because of differences in pharmakinetetic properties of the agent being examined, in this case the intention was to have the agent remain within the circulation. Thus, if the volume of blood did not differ across the age groups to the same extent as body weight differed, then the aged rats would have had a higher concentration (mg/ml blood) of the dye in circulation and thus a greater production of oxyradicals produced. This possible confound should be investigated.

There are other technical issues regarding the results of the study that should be addressed as well. The authors do not acknowledge the value of stereological analysis for use in studies of aged brain (5–7). The issue of differential tissue shrinkage with age is critical to consider when making age comparisons of neural parameters (6). Although it would appear that Kharlamov and colleagues used a volumetric analysis to evaluate lesion size, the analysis of astroglia responses in selected samples based upon densitometric estimates (cells per unit area) could have been biased because of greater shrinkage of tissue in the aged brain samples. While acknowledging this possibility, we must also acknowledge that the age difference in vimentin-positive cells was so substantial (twice as many cells counted in 4-mo-old brains compared to 27-mo-old brains) that this possible analytical bias would not likely obscure such a big difference in cellular response.

What the authors could not address with great clarity are the differential results regarding astroglia responses following brain injury reported in similar studies. Several previous reports have noted increased astroglia response in brains of aged mice (8,9) and rats (10) following specific brain lesions. Other studies have agreed with results of Kharlamov and colleagues in observing a reduced astrocytic response following brain (11) or spinal cord (12) injury in aged rats. The authors provide an interesting discussion regarding hypothesized mechanisms effecting neurodegeneration in the immediate vicinity of the
lesion through the activity of cytokines secreted by macrophages invading the damaged area, while glutamate toxicity appears to be involved in the later occurring damage observed at more distal sites. However, it remains of great importance to determine under what circumstances and experimental conditions (strain, species, type of injury, location) one would predict an age-related increase or decrease in astrocytic response.

One area that the authors did not address regarding mechanistic explanations of the greater damage observed in the aged brain is the involvement of oxyradicals generated by photosensitive dye in producing the damage. Since oxidative stress is a major hypothesis of brain aging (13), the paper could have acknowledged that an age-related reduction in protection against oxidative stress may have been responsible for the greater damage observed in the aged brain. More interesting would have been a test of this hypothesis in which an antioxidant would have been given to demonstrate protection of the aged brain against this insult.

With these relatively few shortcomings aside, Kharlamov and colleagues have described a highly useful model for examining a number of hypotheses related to the increased vulnerability of the aged brain to insult. In addition, they have documented evidence of this greater vulnerability and offered several intriguing hypotheses that their group is pursuing. This model, together with successful confirmation of the hypotheses, offers a valuable means of assessing potential interventions to prevent stroke-induced neurodegeneration.

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**References**


