Letters to the Editor

Response to Letter by Parkkinen et al

Response:

We thank Dr Parkkinen and colleagues for their interesting and provocative observations. In our view, there is strong reason to believe that the substantial neuroprotective efficacy of human albumin in acute ischemic stroke demonstrated preclinically\(^1,2\) and suggested in our ALIAS Pilot Clinical Trial\(^3\) is probably the result of multiple protective actions of the albumin molecule rather than attributable to a single factor. Although our present knowledge does not permit prioritization of the relative importance of albumin’s multiple biological activities, we can nonetheless enumerate the universe of possible candidate mechanisms of this ingenious molecule: fatty-acid binding and transport; antioxidant functions; binding of redox-active transition metals, notably, copper ions; intravascular antagonism of red-cell aggregation and sedimentation and of activated-neutrophil binding to endothelium in the ischemic microcirculation; salutary actions on astrocytes; the reaction of albumin with nitric oxide to form an S-nitrosothiol with endothelial-relaxing–factor-like properties; and, lastly, albumin-induced hemodilution.\(^4\)

Dr Parkkinen et al presents in vivo evidence, consistent with our own view,\(^5\) that \(\alpha_1\)-acid glycoprotein (AGP) present in albumin solutions does not account for albumin-neuroprotection.

Moreover, however important, they call attention to the fact that the binding of circulating albumin to lysophosphatidylcholine (lysoPC) may serve to scavenge the lysoPC otherwise present in ischemia and thereby prevent its injurious proinflammatory and oxidative actions; and that administration of exogenous high-dose albumin, by implication, offers increased lysoPC-binding capacity once endogenous albumin has become saturated. This hypothesis is amenable to direct experimental testing in vivo, by attempting to demonstrate that the albumin traversing the ischemic brain undergoes an increase in its lysoPC content, and that brain lysoPC levels in the ischemic brain decline after albumin treatment. The authors are encouraged to pursue these and other studies.

It is of interest, as well, that lysoPC has been reported to be a preferred physiological carrier of the polyunsaturated fatty acid, docosahexaenoic acid (DHA), to the brain.\(^6\) DHA, which is vital to synaptic function, is depleted from the ischemic brain. We have shown that a component of albumin-neuroprotection in ischemia may be its ability to transport fatty acids, including DHA, back into the ischemic brain.\(^7\) A metabolite of DHA, 10,17\(\alpha\)-docosatriene, is highly neuroprotective in ischemia.\(^8\)

Finally, the complexing of lower-dose albumin to DHA enhances its neuroprotective efficacy in ischemia, compared with the equivalent dose native albumin.\(^9\)

Thus, the plot thickens!

Disclosures

None.

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