Response to Letter by Hadjiev and Mineva

Response:
We appreciate the kind comments from Drs Hadjiev and Mineva in their Letter to the Editor regarding our article on the beneficial effect of normobaric hyperoxia (NBO) in reducing the neurovascular complications associated with delayed tPA treatment.1

Animal and human studies have suggested that MMP-9 induction is closely linked to tPA-induced intracerebral hemorrhage in ischemic stroke, the most feared neurovascular complication in tPA thrombolysis. In our article, we demonstrated that early NBO treatment significantly reduced tPA-associated hemorrhage and mortality in ischemic stroke rats. To clarify the mechanisms for the observed protection, we examined the effect of NBO on MMP-9 induction in the BBB microvasculature. Our data showed that NBO treatment reduced MMP-9 induction in tPA-treated rats but not in saline-treated rats, suggesting NBO may inhibit tPA-augmented, but not ischemia-triggered, MMP-9 induction. We speculate that prolonged ischemia may change the response of cerebral microvessels (mainly endothelial cells) to tPA in terms of MMP-9 production. This idea is currently under investigation in our laboratory. Because we did not provide direct experimental evidence supporting such a mechanism, we were careful to state in the article that the interference of the tPA–MMP-9 pathway may be part of the mechanism for the neurovascular protection by NBO, and further studies are required to ascertain this mechanism. As such, we agree with Hadjiev and Mineva’s comments that it is still questionable whether NBO protects the BBB microvasculature through interfering with the tPA–MMP-9 pathway. In the past several years, several groups including us have provided substantial experimental evidence supporting the neuroprotective effect of early NBO treatment in experimental stroke.2–5 Besides neuroprotection, we have recently shown that NBO can also reduce ischemic BBB damage by inhibiting MMP-9–induced tight junction disruption.6 These observed neuro- and vasoprotective effects of NBO greatly encourage us to share the enthusiasm by Hadjiev and Mineva that NBO treatment, if initiated early, may represent a promising therapeutic strategy for ischemic stroke. Obviously, more thorough studies, including using modern neuroimaging approaches, will be needed in further evaluating the therapeutic potential of NBO in ischemic stroke.

Disclosures
None.

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