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POTENTIAL BENEFIT OF PHARMACOLOGICAL INDUCTION OF BETA COMMON RECEPTOR

Reply to the Editor:

We thank Grasso and colleagues for their thoughtful letter in response to our recent publication and would like to express our gratitude for their work.

Erythropoietin (EPO) is widely known to attenuate ischemic reperfusion injury in a variety of organs, including the brain, heart, kidney, and spinal cord. However, large clinical trials in myocardial infarction, heart failure, stroke, acute kidney injury, and chronic renal disease have failed to show improved outcomes.¹⁻⁵ To obtain the maximum protective efficacy of EPO, we have focused on the beta common receptor subunit of EPO receptor (bcR), which is distinct from the hematopoietic receptor. The bcR expression in normal tissue is generally low, but it is significantly upregulated by metabolic stressors such as ischemia and chemokines.⁶ Bohr and colleagues⁷ reported that lipopolysaccharide and heat shock promote the expression of bcR. We previously reported that ischemic reperfusion injury induces bcR expression in spinal cords in both in vivo and

in vitro models.⁸ Furthermore, we found that bcR expression was significantly induced by diazoxide (DZ) (ATP-dependent potassium channel opener) and that optimized induction of bcR prepared protective signaling pathways before ischemia (Figure 1).⁹

On the other hand, although the hematopoietic receptor is a high affinity for EPO, bcR is characterized by a lower affinity. Therefore, high-dose EPO is required to activate the bcR.⁶ Taking into consideration side effects of EPO such as thrombosis, the use of nonhematopoietic derivatives such as carbamylated erythropoietin is expected in the future, and targeted specific therapy is necessary.

It goes without saying that it is important to demonstrate the mechanism of induction of bcR. We strongly believe that optimized pharmacologic induction of bcR can expand the possibilities of EPO in clinical work. We successfully induced bcR expression using the administration of DZ without ischemia. The combination treatment of DZ and EPO significantly attenuated ischemic reperfusion injury in the spinal cord via upregulation of bcR expression. Further research into this synergetic mechanism may allow for development of target-specific therapy that can ameliorate ischemic complications following aortic interventions.

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FIGURE 1. A time trial about beta common receptor (bcR) expression was carried out using diazoxide (DZ) given to mice by oral gavage. The expression of bcR was evaluated by western blot analysis. The expression of bcR was significantly upregulated 12 hours after administration of DZ and it peaked at 36 hours after administration of DZ.

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