PERSPECTIVES

Targeting red cell-derived ATP signalling to improve the aged muscle circulation

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The circulating red blood cells (RBCs) are the most abundant cells in the body (accounting for 84% of all body cells; Sender *et al.* 2016) and can function as an important signalling source for regulating the integrated, multilevel processes adjusting the flow of oxygen to meet the oxygen demand of contracting skeletal muscle (Ellsworth & Sprague 2012). RBCs contribute to the regulation of skeletal muscle oxygen delivery in part by releasing the vasoactive and sympatholytic substance ATP at the level of the microcirculation. ATP is released from the RBCs through signalling pathways that are activated by reduced oxygen-haemoglobin binding and other metabolic and haemodynamic stimuli such as hyperthermia, reduced pH, hypercapnia, elevated shear stress and augmented mechanical deformation (Ellsworth & Sprague 2012; González-Alonso 2012). Conditions that reduce blood oxygenation such as hypoxia and exercise are therefore expected to increase RBC ATP release, thereby augmenting skeletal muscle hyperaemia to regulate oxygen supply according to demand. There is, however, evidence that the deoxygenation-activated signalling pathway is impaired in isolated RBCs from healthy older adults, a finding that may explain the lower circulating ATP and diminished functional hyperaemia in the exercising muscle of older people (Kirby *et al.* 2012). Evidence from the literature indeed indicates that skeletal muscle blood flow during moderate-to-severe hypoxia and moderate intensity exercise are reduced with age and that blunted increases in circulating ATP are associated with age-related restrictions in haemodynamics. Shedding new light into how to remedy this impairment, a recent study revealed that treating isolated RBCs with the Rho-kinase inhibitor fasudil improves the age-related blunting in deoxygenation-induced RBC ATP release (Racine & Dinneno 2019). Pharmacologically targeting the RBC ATP release pathway is therefore an attractive investigative approach to improve blood perfusion and thus

the flow of oxygen through the circulation of healthy older adults and those with circulatory diseases.

In this issue of the *Journal of Physiology*, Racine *et al.* (2022) provide the first experimental evidence in the human forearm model that systemic Rho-kinase inhibition (induced via venous infusion of fasudil) leads to improvements in age-related reductions in limb blood flow during moderate hypoxia and moderate intensity rhythmic handgrip exercise. In that study, the forearm haemodynamic responses to venous fasudil infusion were compared to those during placebo saline infusion when older and young adults were exposed to control normoxia and moderate hypoxia at rest and when they performed graded rhythmic handgrip exercise (i.e., 5, 15 and 25% maximal voluntary contraction, MVC). A key finding linking red cell signalling and circulatory control is that the improvement in forearm blood flow with fasudil infusion in the older participants was associated with elevations in the plasma concentration of ATP. Strengthening this mechanistic link, the study also revealed that the age-related reductions in deoxygenation-induced RBC ATP release tended to improve when treating isolated RBCs with the Rho-kinase inhibitor. Taken together, the findings support the idea that systemic Rho-kinase inhibition improves limb blood flow responses to hypoxia and moderate intensity rhythmic handgrip exercise by enhancing circulating ATP.

An important consideration in determining the effectiveness of systemic Rho-kinase inhibition as a therapeutic intervention to treat underperfused limbs is the consistency and the magnitude of its hyperaemic effects. In this light, the reasons why systemic fasudil infusion did not alter forearm blood flow at rest or during mild intensity rhythmic handgrip exercise (i.e., 5 and 15% MVC) in either young or older adults cannot be directly addressed in this study. Nor can the research reveal the root cause for the opposite effects of systemic fasudil infusion on forearm blood flow at 25% MVC (i.e., 7.4±2.5 vs 8.1±2.5 kg workload in the old and young groups, respectively). The older adults displayed a ~20% increase and the young cohort a ~10% decline, such that the ~18% lower forearm blood flow observed in the older adults under control conditions was no longer evident (~300 ml min^{-1} in both groups). Notwithstanding these unknowns, Racine and collaborators' outstanding integrative physiology investigation provides strong foundations for future translational studies that establish whether

pharmacological activation of the RBC ATP release pathway improves aged muscle circulation, metabolism and exercise tolerance during other essential exercise modalities for human beings like walking.

References

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Additional information

Competing interests

None declared