

RBCs Contribute to Vascular Dysfunction in Diabetes - Can we fix that?



Prof. Randy S. Sprague

**Departments of Pharmacological and
Physiological Science and Internal Medicine
M.D., Saint Louis University**

Saint Louis, USA

Erythrocytes (RBCs) play an important role in the regulation of the microcirculation via the release of the potent vasodilator, adenosine triphosphate (ATP) when these cells are exposed to reduced oxygen tension. In skeletal muscle, the release of ATP from RBCs in areas of the muscle in which oxygen need increased ensures that blood flow (oxygen delivery) is accurately matched with tissue oxygen need.

In type two diabetes this mechanism is defective, that is, low oxygen-induced ATP release is severely impaired. In this talk I will present evidence in support of the use of insulin and C-peptide to correct this defect in erythrocyte physiology. In addition a role for phosphodiesterase 5 inhibitors in the therapy of the peripheral vascular disease of type 2 diabetes will be suggested. Both approaches suggest new approaches to the treatment of peripheral vascular disease as well as delayed wound healing in humans with type 2 diabetes.

Recent relevant publications:

1. Sprague RS, Stephenson AH, Bowles EA, Stumpf MS and Lonigro AJ: Reduced Expression of Gi in Erythrocytes of Humans with Diabetes Type 2 is Associated with Impairment of both cAMP Generation and ATP Release. *Diabetes* 55:3588-3593, 2006.
2. Sprague RS and Ellsworth ML: Vascular disease in pre-diabetes: New insights derived from systems biology. *Mo Med.* 107:265-269, 2010. PMID: 20806839.
3. Sridharan M, Adderley SP, Bowles EA, Egan TM, Stephenson AH, Ellsworth ML and Sprague RS: Pannexin 1 is the conduit for low oxygen tension-induced ATP release from human erythrocytes. *Am J Physiol (Heart and Circ):*299:H1146-52, 2010 (PMC2957350).
4. Sprague RS, Bowles EA, Achilles D and Ellsworth ML: Erythrocytes as controllers of perfusion distribution in the microvasculature of skeletal muscle. *Acta Physiol* 202:285-92, 2011 (PMC3021763).
5. Richards JP, Stephenson AH, Ellsworth ML and Sprague RS: Synergistic effect of C-peptide and insulin on low O₂-induced ATP release from human erythrocytes. *Am J Physiol* 305: R1331–R1336, 2013.
6. Richards JP, Yosten GLC, Kolar GR, Jones CW, Stephenson AH, Ellsworth ML, and Sprague RS: Low O₂-induced ATP release from erythrocytes of humans with type 2 diabetes is restored by physiological ratios of C-peptide and insulin. *Am J Physiol* 307: R862–R868, 2014.
7. Bowles EA, Moody GN, Yeragunta Y, Stephenson AH, Ellsworth ML and Sprague RS: Phosphodiesterase 5 inhibitors augment UT-15C-stimulated ATP release from erythrocytes of humans with pulmonary arterial hypertension, *Exp Biol & Med* 240:121-127, 2015.
8. Richards JP, Bowles EA, Gordon WR, Ellsworth ML, Stephenson AH and Sprague RS: Mechanisms of C-peptide-mediated rescue of low O₂-induced ATP release from erythrocytes of humans with type 2 diabetes. *Am J Physiol* 308:R411-R418, 2015.
9. Ellsworth ML, Ellis CG and Sprague RS: Role of Erythrocyte-released ATP in the Regulation of Microvascular O₂ Supply in Skeletal Muscle. *Acta Physiologica* (in press) doi: 10.1111/apha.12596, 2015.
10. Richards JP, Bowles EA, Ellsworth ML, Stephenson AH and Sprague RS: Signaling Mechanisms involved in C-peptide-mediated inhibition of low O₂ induced ATP release from human erythrocytes. *ISBT Science Series* 11:325 331, 2016.