PERSPECTIVES

Redundancy reflects versatility of blood flow regulation mechanisms

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Despite a century of focused experimental study on the regulation of muscle hyperaemia, including the robust response to voluntary exercise in mammals, the precise mechanisms of the phenomenon remain unclear. Today it is recognized that the nature of the blood flow response to exercise is complex and includes multiple intrinsic and extrinsic signals integrated from the level of the heart to the capillary, including molecular-receptor processes. Autonomic, endocrine and skeletal muscle input, which are categorized as autocrine, endocrine and paracrine signalling, regulate hyperaemic responses. Such complex regulatory interaction underscores the versatile nature of this system for ensuring adequate muscle nutritive supply, especially oxygen, under a variety of conditions.

Since the mid-twentieth century, physiologists have focused on discovering 'the signal' controlling muscle blood flow. That is, what specific factor is released (*and from where*) during muscle contraction, or conditions of a mismatch between oxygen delivery and demand, to vasodilate the muscle and increase blood flow? In both animals and humans a plethora of studies have been undertaken with pharmacological blockade of specific factors, infusion of substances known to be endogenously produced, or tracking the magnitude or time course of a substance in relation to changes in blood flow. Vasoactive candidates from muscle have been studied on the premise that skeletal muscle releases signals that feed back the magnitude of its nutritive needs. Among others, factors such as potassium, CO_2, H^+, H_2PO_4, PO_4^{--}, and adenosine have been considered potential vasodilator candidates. Similarly, another major area of inquiry has focused on potential vasoactive substances released from motor and/or autonomic nerves such as ACh, ATP and neuropeptide Y, representing feed-forward control. In 1980 Furchgott & Zawadzki highlighted the role of the vascular endothelium for regulating vasodilatation, which led to further work elucidated the importance of endothelial-derived factors such as nitric oxide (NO), prostaglandins (PG), and endothelial-derived hyperpolarization factor (EDHF) on muscle vasodilatation. Recent research has also explored how oxygen sensing is linked to the vasodilator signal. In this regard, the role of Hb–NO binding and release and alternatively ATP release by the red blood cell are attractive hypotheses.

Studies which have employed selective pharmacological blockades of various substances have yielded conflicting results, thereby precluding a precise link of the magnitude of the hyperaemic response to muscle contraction. However, what has emerged out of this vast body of work is the recognition of redundancy. That is, there are multiple vasodilatory substances that can contribute to muscle vasodilatation. System redundancy is not particularly new and has been shown to exist during exercise in other regulatory processes such as hepatic glucose release and control of ventilation. Yet, until recently, there has been a lack of concrete experimental evidence to support redundancy of circulatory control. In the last few years several papers have emerged from animal studies, and to a limited extent in humans, suggesting vasodilator interactions between NO, PG, EDHF and adenosine, which contribute to a portion of the increase in muscle blood flow during exercise.

In this issue of *The Journal of Physiology*, a paper by Schrage *et al.* (2004) represents a step forward in experimental approaches to unravelling the nature of blood flow regulation during voluntary exercise in humans. The authors measured forearm blood flow with Doppler ultrasound during light, rhythmic wrist flexion (10% MVC) under control conditions and during selective blockade of PG and NO, as well as combined blockade of NO + PG. The authors also examined the influence of the order of drug administration as well as the route and timing of blockade on blood flow at rest and during contraction. The results support previous work on the combined influence of NO and PG, and extend to several new findings. First, increases in blood flow from rest to exercise were reduced when pharmacological blockade was administered during contraction compared to administration prior to exercise onset. Second, NO and PG independently contributed to exercise hyperaemia, but the influence of PG was transient. Third, when PG was blocked during contraction redundant mechanisms restored blood flow over time, which clarifies previous discrepant findings of the independent roles of PG and NO. That is, both factors independently contribute and interact to increase blood flow during exercise, but their effects are resting *versus* contraction, as well as time and intensity, dependent. Finally, in the case of PG blockade, redundant mechanisms other than NO restored a transient decrease in blood flow during exercise.

The current study is noteworthy for its example of the creativity of study design needed for exploring the complexity of the redundancy of blood flow regulation and sets the stage for future experimental work in humans. For example, what are the specific factors responsible for redundancy? How do various dilators interact and under what conditions do they operate? Are the responses to different contraction modes different? Is the regulation and vasodilator sensitivity similar in different muscle groups, fibre types and other tissues? And in what manner do muscle types account for flow heterogeneity? Integration of analytical chemistry, molecular biology, tissue culture, isolated tissue preparations and animal studies will help compose a picture of the intact, situational response involving the interaction of the muscular, nervous and endocrine systems with that of the vasculature. Paraphrasing words by respiration physiologist Julius Comroe, if there is an important task to be taken care of in the human body, there is more than one way to do it.

Furchgott RF & Zawadski JV (1980). *Nature* **288**, 373–376.

Schrage WG, Joyner MJ & Dinenno FA (2004). *J Physiol* **557**, 599–611.

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