Skeletal muscle hyperemia during exercise: do we have all the answers now?

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(Introduced by Mark Hargreaves)

Blood flow to exercising skeletal muscles increases. This increase is generally proportional to the metabolic demands associated with the level of exercise, and under some circumstances blood flow to the active muscles can rise 50- to 100-fold above resting values. Mechanical, neural, humoral, and so-called metabolic factors may or may not contribute to this hyperaemic response. For almost 150 years efforts to isolate a single factor that is responsible for most or all of the hyperaemic responses to exercise have uniformly failed. Additionally, interest in various mechanisms seems to come and go in waves, as has been the case for both mechanical and neural factors along with ATP and adenosine. From time to time new candidate dilator substances are identified such as nitric oxide, but these newer dilating mechanisms typically join a list of factors that make only modest contributions to the hyperaemic responses to exercise. Taken together, these observations suggest that either the regulation of skeletal muscle blood flow during exercise is an example of biological “uber-redundancy,” that there are one or more unknown substances or mechanisms that will in fact explain a high fraction of dilator responses to exercise, or that numerous substances with small effect sizes acted synergistically. They also raise questions about experimental paradigms which are clearly adequate to describe the magnitude of the increase in flow but may not be adequate to pharmacologically and physiologically dissect the mechanisms responsible for it. The current state of the art on mechanisms of dilation and their relative contributions to exercise hyperaemia lead to ideas about new approaches including: 1) the best ways to deliver pharmacological agents to blood vessels, 2) the use of rare patients as experiments in nature, and 3) advanced imaging techniques to address these fundamental issues.