The following is the abstract of the article discussed in the subsequent letter:

Richardson, RS, H Wagner, SR Mudaliar, R Henry, EA Noyeszewski, and PD Wagner. Human VEGF gene expression in skeletal muscle: effect of acute normoxic and hypoxic exercise. Am. J. Physiol. 277 (Heart Circ. Physiol. 46): H2247–H2252, 1999. Vascular endothelial growth factor (VEGF) is involved in extracellular matrix changes and endothelial cell proliferation, both of which are precursors to new capillary growth. Angiogenesis is a vital adaptation to exercise training, and the exercise-induced reduction in intracellular PO2 has been proposed as a stimulus for this process. Thus we studied muscle cell PO2 [myoglobin PO2 (MbPO2)] during exercise in normoxia and in hypoxia (12% O2) and studied the mRNA levels of VEGF in six untrained subjects after a single bout of exercise by quantitative Northern analysis. Single-leg knee extension provided the acute exercise stimulus: a maximal test followed by 30 min at 50% of the peak work rate achieved in this graded test. Because peak work rate was not affected by hypoxia, the absolute and relative work rates were identical in hypoxia and normoxia. Three percutaneous needle biopsies were collected from the vastus lateralis muscle, one at rest and then the others at 1 h after exercise in normoxia or hypoxia. At rest (control), VEGF mRNA levels were very low (0.38 ± 0.04 VEGF/18S). After exercise in normoxia or hypoxia, VEGF mRNA levels were much greater (16.9 ± 6.7 or 7.1 ± 1.8 VEGF/18S, respectively). In contrast, there was no measurable basic fibroblast growth factor mRNA response to exercise at this 1-h postexercise time point. Magnetic resonance spectroscopy of myoglobin confirmed a reduction in MbPO2 in hypoxia (3.8 ± 0.3 mmHg) compared with normoxia (7.2 ± 0.6 mmHg) but failed to reveal a relationship between MbPO2 during exercise and VEGF expression. This VEGF mRNA increase in response to acute exercise supports the concept that VEGF is involved in exercise-induced skeletal muscle angiogenesis but questions the importance of a reduced cellular PO2 as a stimulus for this response.

Expression of angiogenic growth factors in human skeletal muscle in response to a singular bout of exercise

To the Editor: Our group published in the American Journal of Physiology an article about vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2) mRNA response to acute exercise in human skeletal muscle. Recently, another paper was published in the same journal dealing with the same question. I would like to take this opportunity to point out the similarities and differences in our work.

In our study, VEGF and FGF-2 mRNA were measured by skeletal muscle biopsies before and after one-legged exercise performed under conditions of nonrestricted and restricted blood flows at the same absolute workload (1). The VEGF mRNA increased in contrast to FGF-2 mRNA expression in response to exercise. However, no difference in VEGF mRNA response was found between the two conditions, but a trend to greater increase existed after exercise with restricted blood flow. We argued that the lack of further increase in VEGF mRNA with flow restriction might be explained by a smaller further reduction in oxygen saturation and oxygen tension in the femoral vein between nonrestricted and restricted exercise than in the rest-to-exercise transition. A correlation was observed between exercise-induced lactate and the exercise increase in VEGF mRNA expression, which indicates a graded response in VEGF mRNA expression to metabolic stress. In addition, the exercise-induced mRNA expression of VEGF was also correlated at the mRNA level to the two subunits of hypoxia-inducible factor 1, HIF-1α and HIF-1β (ARNT), a crucial transcription factor for the hypoxic regulation of VEGF. Recently, a similar study involving one-legged knee-extension exercise during normal and reduced oxygen delivery was published by Richardson et al. (2). One difference between the two studies was that lowered oxygen delivery in the latter study was achieved through hypoxic air breathing and not through blood flow reduction, as in our study (1). Even if hypoxic and ischemic exercise differ in blood flow from the skeletal muscle, and thereby metabolite trapping, the results from Richardson et al. (2) confirmed the data from our study. The VEGF mRNA increased, but not FGF-2 mRNA, in response to one-legged exercise, and no further increase was found during exercise under hypoxic condition similar to the ischemic situation (1, 2). However, Richardson et al. (2) did not rule out the possibility for a hypoxic angiogenic switch point, i.e., the further decrease in oxygen tissue levels during hypoxic condition produced no further angiogenic stimulus, which resembles the discussion from our earlier study (1, 2).

Available data therefore indicate that the major angiogenic factor VEGF seems to increase to a greater extent and more consistently at the mRNA level than other measured angiogenic factors, such as FGF-2, in response to increased muscle activity. These findings are also supported by earlier observations from a study in exercising rats (3). However, the regulating mechanisms in this response are not clear, but the present data cannot exclude changed oxygen tension in the skeletal muscle as one possible stimulus.
REFERENCES


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