Letters to the Editor

Protein Synthesis in Cardiac Hypertrophy

It is with some discomfort that I must draw your attention to an erroneous citation and to misinformation concerning our perfusion system presented by Morkin et al. to explain some disagreement between our earlier data and those they report (Circ Res 30:690-702, 1972).

On page 702, the authors state, “In attempting to relate the present results to those obtained by Schreiber et al. it should be borne in mind that the perfusion pressures used by these workers even during overload were lower than those found normally in the rat heart. Hence, the validity of direct comparison with values obtained in vivo is uncertain.” Earlier on the same page, the authors cited our work “in perfused rat hearts.”

At the outset, let me point out that we have never published data concerning cardiac perfusion in the rat heart. Our perfusion model has consistently been the baby guinea pig heart, which was specifically selected because it responds rapidly and is a low-pressure system. The normal systolic blood pressure in the fully grown guinea pig (weight about 1 kg or more) is approximately 70 mm Hg and that in the very young guinea pig (weight 250-300 g) is much lower. The baby guinea pig heart functions at the lower systolic blood pressures which we have used for more than 5 hours without any decrease in contractility. Overload is achieved by raising the aortic blood pressure to a level short of blowing out the young guinea pig hearts, usually a level twice that in the controls. It is of interest that perfusion of this model at an aortic blood pressure equivalent to that in the adult rat almost always results in cardiac rupture and leaking.

Thus, the citation by Morkin et al. is incorrect, and the use of the argument that our perfusion system with pressures lower than those normally found in the rat makes comparison of data uncertain is also incorrect.

There may be many reasons besides species differences for discrepancies in data found in in vivo and in vitro models. However, increased adenyl cyclase activity, nuclear polymerase activity, microsomal protein synthesis, mRNA synthesis, rRNA synthesis, total protein synthesis, and myosin synthesis found in our perfusion model have also been reported in different in vivo models, although usually at later times following onset of increased aortic blood pressure. The earlier occurrences found in our model may be due to the rapid response of baby hearts.

In vivo measurements of protein synthesis usually involve single-pulse injections of amino acid tracers: the specific activities of the precursor pools are either unknown or variable, the effects of reutilization of amino acids on measurements of protein synthesis are difficult to assess, and in general, the increase in aortic blood pressure following banding is not known and the effects on coronary flows are not reported. Furthermore, the body’s homeostatic mechanisms come into play, and there are data to show that hormones, such as thyroid hormone and steroids, affect protein synthesis. Despite the drawbacks of any in vitro perfusion system, the model we have used has distinct advantages: the aortic blood pressure can be accurately controlled and measured, the coronary flows are known, the ventricular loads can be controlled and measured, the perfusion solution contains a constant specific activity of the tracer amino acid and, hence, there is a relatively constant specific activity in the precursor pool, and there is no effect of neurological or humoral homeostatic mechanisms, since the loading is done after the heart is removed from the body.

In view of the differences in models, discrepancies in data are, therefore, not unexpected. Whatever the cause of discrepancy between the two groups of data, it is not, as the authors cited, due to our using a rat heart at lower than normal pressures. It would be unfortunate if future readers of the article by
Morkin, Kimata, and Skillman would discount our earlier data because of the misinformation presented concerning our perfusion system.

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REPLY TO THE ABOVE LETTER

We thank Dr. Schreiber for calling to our attention that guinea pig hearts rather than rat hearts were used for their perfusion experiments. Regardless of the species used, we believe it would be helpful to state precisely what pressure levels are found in vivo. Our point is to draw attention to the importance of relating changes in myosin synthesis observed in vitro to the synthesis rate in normal animals. Conceivably, myosin synthesis might be depressed under control conditions in vitro and more nearly normal when perfusion pressure is raised. Also, the increase in myosin synthesis in the perfused heart might be related to accelerated myosin degradation or even to some in vitro abnormality in the myofibrillar assembly process.

As we have shown, when the heart is subjected to overload in vivo, myosin synthesis does not increase for several days above the level in animals that have not been operated on and closely corresponds to the increase in myosin content. In contrast, the increase in myosin synthesis observed after pressure overload in vitro occurs in a few hours, and there are no data to indicate that a net increase in myosin content occurs or that myosin degradation has not been altered. Hence, we think it fair to question whether the increase in synthesis that is observed in the isolated heart is related to the process of compensatory growth.

We agree that when using intact animals for measurements of protein metabolism it is important to consider possible effects of amino acid reutilization and changes in amino acid pools, and we have attempted to carefully evaluate these variables. It should be borne in mind, however, that the in vitro model is subject to the same general problems. Even when coronary flow and the specific activity of amino acids in the perfusate are kept constant, it cannot be assumed that intracellular pools of amino acids are the same in control and overloaded hearts. Careful measurements of tissue amino acid pools are needed in both model systems.

It would seem to us that the value of data on myosin metabolism from in vitro and in vivo experiments can be greatly enhanced by making appropriate comparisons.

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