Letter to the Editor

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Protective Role of Fatty Acid–Binding Protein in Ischemic and Reperfused Heart

In their recent paper Srirmani et al1 have described a series of interesting experiments aimed at disclosing the earlier suggested2,3 possible protective role of cytoplasmic fatty acid–binding protein (FABPc) in ischemic and reperfused myocardium. The authors hypothesized that if FABPc can bind the fatty acids and thioesters accumulating intracellularly during ischemia and reperfusion, thereby preventing these compounds from exerting deleterious effects, an increase of the cellular content of FABPc might provide additional protection for ischemic and reperfusion injury. It was found that isolated rat hearts preperfused with liposome-incorporated heart-type FABPc, and subsequently subjected to ischemia and reperfusion developed less tissue injury than did hearts preperfused with liposomes only. This finding led the authors to conclude that in the ischemic and reperfused myocardium, FABPC exerts a protective role by the above-mentioned mechanism. However, it is our opinion that this conclusion cannot be drawn from the data presented in their article.

Perfusion with liposome-incorporated FABPc would be an elegant method to elevate the content of this protein in the myocytes. In this approach it is assumed that a substantial amount of the FABPc supplied is indeed taken up by the myocytes. Unfortunately, the authors failed to demonstrate this because tissue and perfusion buffer were not analyzed for changes in FABPc content after administration of this protein. Measurement of FABPc in tissue and perfusion medium is of particular importance in the experiments described in their article, because of the substantial loss of FABPc from the myocardium after ischemia and reperfusion,4 a loss similar to that of creatine kinase and lactate dehydrogenase,5 which challenges the fatty acid buffering role of FABPc under these circumstances.

An important finding in their study is that during the reperfusion phase coronary flow was consistently higher in FABPc-treated than in control hearts, reaching a statistically significant difference of 60% after 30 minutes of reperfusion. These differences in flow suggest that the liposome-FABPc complex exerts a vasodilating effect on the coronary vasculature. If this dilatation results in enlargement of the capillary permeability surface area, it could largely explain the observed higher rate of disappearance of [1,14C] arachidonic acid from the recirculating perfusion medium of the FABPc-treated, as compared with the untreated, hearts. Indeed, arachidonic acid uptake showed a maximal difference of 50% after 30 minutes of reperfusion. Therefore, these differences in fatty acid uptake do not necessarily reflect differences in tissue FABPc content, as stated by the authors.6

An additional difficulty in assessing the true physiological value of the study is the lack of appropriate control experiments. First, no data are provided to show that the beneficial effect of FABPc is specific for this myocardial protein or that other proteins capable of non–covalent binding of long-chain fatty acids, such as albumin, would display similar protection. Second, preperfusing the hearts with non–protein-containing liposomes might already alter cardiac biochemical properties and, hence, influence the consequences of subsequent ischemia and reperfusion.

Duan and Karmazyn,6 after all, have shown that addition of phosphatidylcholine to the perfusion medium enhanced the recovery of ventricular contractility of isolated rat hearts subjected to ischemia and reperfusion from about 15% to about 60% of the preischemic values. Interestingly, phosphatidylcholine was effective only when administered before the ischemic insult and in concentrations up to about 100 μM. At higher concentrations vasoconstriction was noted.6 These authors have provided evidence that the beneficial effect of exogenous phosphatidylcholine is related to better preservation of subsarcolemmal mitochondrial function and to reduction of the toxic effect of accumulating lysophosphatidylcholine in ischemic reperfused hearts.6 Srirmani et al7 also used phosphatidylcholine liposomes but did not mention their concentration in the perfusion medium. Therefore, it cannot be inferred whether in their experiments phosphatidylcholine exerted a protective or a coronary vasoconstricting effect on the ischemic reperfused heart. However, the marked reduction in coronary flow (25–35%) observed in both FABPc-treated and untreated hearts during the first 15 minutes of perfusion (i.e., in the presence of liposomes) indicates that coronary vasoconstriction occurred. In the case of FABPc-containing liposomes it is conceivable that the vasoconstricting effect was partially blocked. In other words, it cannot be excluded that liposome-incorporated FABPc influences the effects of constituents of the liposomal membrane on myocardium. The fact that Srirmani et al7 found an effect only when FABPc was used before the ischemic insult is in favor of this concept.

In conclusion, the possible role of cytoplasmic FABPc, in sequestering excess fatty acids and esters is an interesting concept because the accumulation of these substances has been suggested to play an important role in the pathogenesis of ischemic and reperfusion injury.7 However, the study of Srirmani et al7 provides no evidence to support or disprove the feasibility of this intriguing hypothesis.

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