British Journal of Pharmacology (2002) 135, 1345–1346
www.nature.com/bjp

COMMENTARY

Cyclo-oxygenase-2 inhibition and exacerbation of myocardial dysfunction – protection with nitric oxide?

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The role of arachidonic acid products on myocardial function have been the focus of numerous studies over the past 30 years, since it was first published that NSAID efficacy is a result of inhibition of the cyclo-oxygenase enzyme (Smith & Willis, 1971; Vane, 1971). Many of these studies have since reported that the arachidonate products, including prostacyclin, can have significant modulator roles both in the preservation of basal organ function and during defense following pathological insult or disease. More recently and following the discovery of an inducible form of the cyclo-oxygenase enzyme (COX-2), which has been hypothesized and subsequently shown to be upregulated by either inflammatory insult or ischaemic related disturbances, a new class of selective inhibitors of the inducible cyclo-oxygenase enzyme has been developed (see reviews: Katori & Majima, 2000; Fitzgerald & Patrono, 2001).

It is probably too early to define the consequences of COX-2 inhibition in clinical situations in which myocardial function is compromised. Whereas the recent introduction of selective inhibitors of COX-2, whose use is directed toward the treatment of inflammation and pain, has provided chemical tools to help further elucidate arachidonate products in cardiac diseases (e.g., Dowd *et al*., 2001), the ultimate resolution resides in future clinical studies.

In this issue Rossoni *et al*. (2002) have raised a question whether these studies should receive more immediate attention. They report that in blood-free perfused rabbit hearts there appears to be a relationship between the degree of ischaemic-related myocardial dysfunction and extent of inhibition of COX-2. They show that these selective inhibitors reduce the ability of the ischemic heart to rapidly respond with vasodilatation (due to prostacyclin release?) during reperfusion immediately after an acute ischaemic event. The reduction of prostacyclin production by selective COX-2 inhibitors would seem at odds to the hypothesis that endothelial generated prostacyclin is a constitutive mediator and primarily a product of COX-1 (see Katori & Majima, 2000). Indeed, if it is solely a product of COX-2 and if its inhibition prevents the ischaemic organ compensating *via* vasorelaxant mechanisms, it is easily possible to devise a scenario with a potential damaging outcome.

During reperfusion following myocardial ischaemia the endothelial lining of coronary vessels become an important layer of cell defense. The endothelium becomes a resource for mediators whose release and function is to preserve perfusion-dependent performance of the affected organ. In this context, along with prostacyclin, both endothelin-1 and nitric oxide can play equally important roles in maintenance of organ perfusion. It has been shown that endothelial cells are capable of generating nitric oxide whose vasodilator and antiplatelet properties can compliment those of prostacyclin. Is it possible that nitric oxide can supplement for any loss of prostacyclin generation? In this same manuscript Rossoni *et al*. (2002) argue that the effects of a nitric oxide releasing NSAID (see review: Fiorucci *et al*., 2001) can overcome, and even partially preserve myocardial function following ischaemic reperfusion. Although they did not monitor NO production they rationalize that the addition of nitric oxide donor functionality (*via* nitrate incorporation) can best explain their findings since the parent NSAID, aspirin, did not display this activity. This is a provocative observation and explanation. It also implies that endogenous endothelial nitric oxide production cannot compensate for a diminished prostacyclin release (especially when the endothelial cell is dysfunctional following hypoxia). Indeed, it has been reported that the primary role of endothelial NO is not as a vasodilator but as a modulator or inhibitor of endothelin-1 mediated vasoconstriction (Banting *et al*., 1996).

If there is an endothelin-1 responsive increase in the perfusion pressure following ischaemia/reperfusion then it may also reflect an inability of endogenous endothelial nitric oxide production to rapidly increase and compensate during acute insult. Further, it has been shown that an exogenous nitric oxide donor such as nitrosylated tPA, when added immediately prior to insult can prevent coronary endothelial dysfunction and is cardioprotective against myocardial ischaemia/reperfusion (Delyani *et al*., 1996), suggesting maintenance of nitric oxide levels within the endothelium can indeed modulate the endothelial response.

The relative contributions of endothelial released mediators such as protacyclin and nitric oxide in situations involving cardiac disease (or other cardiovascular diseases in general) may be critical to outcome. There appears to be an association between vascular nitric oxide deficiency, endothelial dysfunction and arterial thrombosis (Loscalzo, 2001). Further, if nitric oxide is primarily a potent modulator capable of existing in different redox states and exhibiting different biologies depending upon the redox state (Stamler *et al*., 1992) there are potentially many complex outcomes.

Whereas recent preclinical and clinical reports raise questions of an increased risk of adverse cardiovascular

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events in essentially normal individuals in which COX-2 is selectively inhibited (Hennan *et al*., 2001; Mukherjee *et al*., 2001), this study by Rossoni also raises the question of effects in people who have disease, especially if it is associated with a nitric oxide deficiency. The outcome of acute cardiovascular events (such as platelet aggregation or coronary spasm) involving the combination of a drug-induced inhibition of prostacyclin production in a nitric oxide deficient individual could be unfavorable.

In summary, basic research is conducted to challenge hypotheses, provoke discussion and provide future direction for study. The observation by Rossoni *et al*. (2002) that there is an exacerbation of myocardial dysfunction with acute reperfusion following a selective COX-2 dependent loss of endothelial prostacyclin production and that supplementation with nitric oxide functionality is beneficial in these circumstances is provocative and certainly worthy of further investigation.

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