British Journal of Pharmacology (2002) 137, 941–942
www.nature.com/bjp

COMMENTARY

Unravelling mechanisms underlying ischaemic arrhythmias – the importance of models

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A new model of regional ischaemia using blood-perfused isolated rat hearts is reported in this issue. This model has potential value in pharmacology to test the actions of drugs against the arrhythmias that arise early period (0–30 min) after induction of ischaemia. Unfortunately, the severity of arrhythmias in this new model is reduced, when compared to other models, in both the early and the late period (1–4 h) of coronary artery occlusion. This commentary compares the new model with previous models, and comments on the possible mechanisms of arrhythmias induced by ischaemia. *British Journal of Pharmacology* (2002) **137,** 941–942. doi:10.1038/sj.bjp.0704976

Keywords: Arrhythmias; isolated hearts; ischaemia; blood perfused; ischaemia models

Clements-Jewery *et al*. (2002b) in this issue describe a new model of ischaemia-dependent arrhythmias in rat hearts that raises as many questions as it answers. In this model, isolated rat hearts, perfused with blood from donor animals, were subjected to regional ischaemia by occluding a coronary artery. In the model, arrhythmias were reduced in both the early (0–30 min) and late (1–4 h) arrhythmic periods following coronary occlusion, when compared with other models of regional ischaemia in rats (see Table 1). The early period corresponds to when ischaemic tissue can be rescued by reperfusion, the late period to infarct development. In other models, *in vitro* or *in vivo*, the same temporal and intensity patterns for early arrhythmias are seen and differences arise only in the later period. Thus, the present results raise interesting questions.

The findings of Clements-Jewery *et al*. (2002b) have to be viewed within the context of extensive literature on arrhythmic responses in rat hearts following coronary artery occlusion in intact animals, or in isolated buffer-perfused hearts. In some models the nature and extent of ischaemia-induced arrhythmias have been described with great precision and accuracy. For example, the Cardiome Pharma Corporation data-base contains data from 2000 anaesthetized rats. Such a wealth of information should make it easy to use rat models to ask specific questions, and attempt answers, with data that are reliable and well-controlled. Thus, apart from this latest model early arrhythmic responses, *in vivo* and *in vitro*, are similar and may involve the same mechanism. Many interventions (drugs, surgery, transplantation) have been applied *in vivo* and *in vitro* in attempts to determine the factors and mechanisms responsible for these early arrhythmias. Results from most studies indicate that the major factor responsible for early arrhythmias arise directly as a result of myocytes being made ischaemic, and not from exogenous factors such as nerves, other cell types, blood, arrhythmogenic mediators, etc. Importantly, the same mechanism seems to be involved *in vivo* and *in vitro*. Why then does the presence of blood reduce such arrhythmias? Is the blood providing a protective factor?

With respect to the late-phase arrhythmias less is known. As shown in Table 1, they vary with the model used. For example, in the *in vivo* model of heterologous cardiac transplantation (Guo *et al*., 1999), late arrhythmias were fewer in transplanted hearts (regardless of the duration of transplant) than in recipients. Is this model an analogue of the isolated blood-perfused heart described by Clements-Jewery *et al*. (2002b) in this issue? If so, can we explain the similarity regarding late arrhythmias? One factor common to both isolated blood-perfused and transplanted hearts is the absence of an intact nervous system. If the authors of the present study had occluded a coronary artery in their 'support' rats we may have gained further insight.

A major objective now is confirmation of the findings of Clements-Jewery *et al*. (2002b), and in other models in which the data-base is limited, to ensure that the facts, as provisionally provided in Table 1, are correct. In the presence of established facts we can attempt to provide answers using the careful logic of Clements-Jewery *et al*. (2002b). In our opinion, the best model for assessing antiarrhythmic drug actions against early arrhythmias could be the blood-perfused model. In this model *in vivo* plasma concentrations could be easily reproduced and many experimental interventions assessed. However, we do need to know the reasons for the reduced arrhythmias.

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Table 1 Occurrence and severity of ischaemia-induced arrhythmias in various rat models after coronary ligation

Treatment	*Early**	*Late**	*Refs*
Conscious chronically prepared	Normal	Normal	Johnston *et al*., 1983
Conscious acutely prepared	Normal	Slightly reduced	MacLeod *et al*., 1983
Anaesthetized chronically prepared	Normal	Normal	Curtis *et al*., 1985 Botting *et al*., 1986
Aaesthetized acutely prepared	Normal	Slightly reduced	Clarke *et al*., 1980 Curtis *et al*., 1985
Isolated buffer perfused	Normal	Relative absence	Clements-Jewery *et al*., 2002a
Isolated blood perfused	Reduced	Relative absence	Clements-Jewery *et al*., 2002b
Recipient animal 2–10 days	Normal	Reduced	Guo *et al*., 1999
Transplanted heart 2–10 days	Normal	Greatly reduced	Guo *et al*., 1999

*The table represents a qualitative assessment of early and late arrhythmias in various rat models. For comparative purposes arrhythmias seen in conscious chronically prepared rats are regarded as the norm.

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(Received August 2, 2002
Accepted September 10, 2002)