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COMMENTARY

Endocannabinoids as mediators in the heart: a potential target for therapy of remodelling after myocardial infarction?

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Endocannabinoid production by platelets and macrophages is increased in circulatory shock. This may be protective of the cardiovascular system as blockade of CB_1 cannabinoid receptors exacerbates endothelial dysfunction in haemorrhagic and endotoxin shock and reduces survival. Now evidence suggests that blockade of CB_1 receptors starting 24 h after myocardial infarction in rats has a deleterious effect on cardiac performance, while use of a nonselective cannabinoid receptor agonist prevents hypotension and reduces endothelial dysfunction, although left ventricular end diastolic pressure is elevated. Cannabinoids and endocannabinoid systems may therefore present useful targets for therapy following myocardial infarction.
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Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; 2-AG, 2-arachidonylglycerol; AM-251, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; BK_{Ca}, large conductance Ca^{2+}-sensitive K^+ channels; HU-210, 11-hydroxy-Δ^8-tetrahydrocannabinol-dimethylheptyl; IRI, ischaemia/reperfusion injury; SR 141716A, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride

It is widely accepted that there are endocannabinoid systems within the central nervous system (Di Marzo, 1999), but cannabinoid receptors are also found in peripheral tissues, with both CB_1 and CB_2 receptors being reported in functional and molecular studies of the cardiovascular system (see review by Randall *et al.*, 2002). Several ligands have been proposed as physiological endocannabinoids, with anandamide (2-arachidonylethanolamide) and 2-arachidonylglycerol (2-AG) the most commonly favoured candidates (Di Marzo, 1999). Although no definitive physiological role has been discovered for endocannabinoids in the heart and circulation, in a series of studies, Wagner and his co-workers have put forward evidence that the endocannabinoid system might be activated in cardiovascular pathology. They have reported that hypotension is reduced by the CB_1 receptor antagonist SR 141716A in both haemorrhagic and endotoxic shock and that platelets and monocytes from rats in endotoxic shock can lower blood pressure in normal rats in a way that is sensitive to the cannabinoid antagonist (Wagner *et al.*, 1998). They also showed that the platelets and monocytes from the rats with shock were generating anandamide and 2-AG.

Now, in this issue, Wagner *et al.* (2003) report an approach to see if exogenous or endogenous cannabinoids can modify cardiac remodelling after myocardial infarction. Myocardial ischaemia occurs when the coronary circulation is impaired. Although reperfusion is the best method to salvage ischaemic myocardium, it is associated with additional damage known as reperfusion injury. Collectively, ischaemia/reperfusion injury (IRI) can, in the short-term, result in one or more of irreversible cellular damage (infarct), reversible contractile dysfunction (stunning) and arrhythmogenesis. In the longer term, mycardial infarction and IRI can trigger a process by which the morphology and size of the heart is affected in a process known as remodelling. Current therapies are targeted at limiting remodelling because the process is well correlated with mortality and morbidity (Jugdutt, 1993). Despite its importance, other than agents used to enhance reperfusion, there are no treatments currently available specifically to limit the consequences of IRI and myocardial infarction. Although early treatment with angiotensin-converting enzyme inhibitors (ACEI) is effective in reducing the early phase of remodelling, there is still a significant incidence of mortality (Pfeffer *et al.*, 1997). Therefore, there is a need to develop therapies designed to limit myocardial damage and act as complementary or alternative treatments to ACEI in the early phases of remodelling. In light of this need, it is interesting to note that a number of recent reports have highlighted a potentially important role for endocannabinoids in modifying the recovery from, or the severity of, IRI.

Endocannabinoids may be involved in the mechanisms by which lipopolysaccharide endotoxin limits infarct size (Lagneux & Lamontagne, 2001) and they might limit mortality after coronary artery occlusion (Wagner *et al.*, 2001). Although the CB_1 receptor antagonist SR 141716A increased blood pressure in animals suffering cardiogenic shock after myocardial infarction relative to infarcted animals not given the drug, it increased the mortality rate and enhanced endothelial dysfunction; this suggests that endocannabinoids might be protective in cardiogenic shock (Wagner *et al.,* 2001). In their latest paper, Wagner *et al.* (2003) report that early remodelling in a model in which there is no reperfusion after coronary artery occlusion is limited by the nonselective cannabinoid agonist HU-210. Interestingly, the CB_1-receptor

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antagonist, AM-251 had no effect on survival in contrast to the effects of the very closely related SR 141716A (Wagner *et al.*, 2001); the two antagonists differ only in an iodine for chlorine substitution on one phenyl ring. Although caution needs to be exercised in interpretation, as CB_1-receptor independent actions of SR 141716A have been reported when used at higher concentrations (White & Hiley, 1998), this finding correlates well with our recent findings that cardiac responses to the endocannabinoid, anandamide, are mediated via a novel site that is sensitive to SR 141716A (at a concentration below that causing nonspecific effects such as inhibition of BK_{Ca}) and insensitive to AM-251 (Ford *et al.,* 2002).

In their new study, Wagner *et al.* (2003) used the relatively nonselective cannabinoid agonist HU-210. This agent appeared to be of benefit only if the infarct size was less than 40% of the area at risk, suggesting that the potential utility of cannabinoid intervention might be limited by severity of the insult. The target receptor for HU-210 is unknown as antagonist studies were not conducted and, unfortunately, little is known of its ability of HU-210 to activate the novel cardiac site that mediates responses to anandamide. However, the lack of receptor desensitisation to chronic agonist treatment bodes well for the use of pharmacological tools targeting this potentially protective pathway. The adverse effects of chronic treatment with HU-210 reported by the authors appear to be mediated at the level of the CNS and could be circumvented by using drugs that are excluded by the blood – brain barrier. Alternatively, as it is known that after myocardial infarction circulating levels of endocannabinoids are elevated (Wagner *et al.*, 2001), a cannabinoid uptake inhibitor could be used to increase the time that they would be active at cannabinoid receptors. Unfortunately, the best known uptake inhibitor, AM404, also activates vanilloid VR1 receptors. Therefore, the effects of VR1 receptor activation after myocardial infarction would need to be clarified.

Although at a very early stage, and limited by a lack of highly selective pharmacological tools, evidence is accumulating that endocannabinoids are able to ameliorate IRI, limit mortality and reduce the early phase of remodelling. Further work is needed to clarify the pharmacology and mechanism of action of cannabinoids in the setting of IRI as well as of nonreperfused, infarcted myocardium, as used by Wagner *et al.* (2003).

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