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COMMENTARY

Cirrhotic cardiomyopathy: an endocannabinoid connection?

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It has been known for over half a century that liver cirrhosis is associated with abnormal cardiovascular function (Ma & Lee, 1996; Moller & Henriksen, 2002). Portal hypertension caused by tissue scarring is associated with hyperdynamic circulation, manifested by increased heart rate and cardiac output and reduced splanchnic and systemic vascular resistance with low normal or decreased arterial blood pressure. Although the mechanism of peripheral vasodilation in liver cirrhosis, including the possible role of nitric oxide and other endothelium-dependent factors, has been intensively investigated during the past decades, the results have been disappointingly inconclusive (Ma & Lee, 1996; Moller & Henriksen, 2002).

Recent studies have suggested that endocannabinoids and their receptors could play an important role in the hypotension associated with various pathologic states including cardiogenic, haemorrhagic and endotoxic shock (reviewed in Pacher *et al*., 2005), as well as advanced liver cirrhosis (Bátkai *et al*., 2001; Ros *et al*., 2002). In these latter studies, intravenous administration of the CB_1 antagonist SR141716 increased arterial blood pressure in cirrhotic rats primarily through a vascular mechanism, as suggested by the parallel increase in total peripheral resistance (Ros *et al*., 2002) and decreased mesenteric blood flow (Bátkai *et al*., 2001). The involvement of vascular CB_1 receptors was further indicated by the increased expression of CB_1 receptors in vascular endothelial cells from cirrhotic compared to normal livers (Bátkai *et al*., 2001) and the increased relaxation of mesenteric arteries from cirrhotic compared to normal rats in response to the endocannabinoid anandamide (arachidonoyl ethanolamide, AEA) (Domenicali *et al*., 2005). Also, circulating macrophages and platelets from cirrhotic animals and patients have elevated levels of endocannabinoids and, when isolated and injected into normal rats, these cells elicit SR141716-sensitive hypotension (Bátkai *et al*., 2001; Ros *et al*., 2002). Patients with cirrhosis often have endotoxemia as lipopolysaccharide generated by normal intestinal bacteria, which is known to stimulate the synthesis of AEA in macrophages (Di Marzo *et al*., 1999; Liu *et al*., 2003), gains access to the systemic circulation as a result of its impaired hepatic elimination.

On the basis of previous *in vitro* and *in vivo* studies of the effects of AEA on blood pressure, it was widely held that the predominant haemodynamic effect *in vivo* is vascular. However, in these earlier studies the direct cardiac effects were not evaluated. More recent detailed *in vivo* haemodynamic analyses clearly indicate, however, that AEA-induced hypotension is of predominantly cardiac origin due to a CB_1-mediated decrease in cardiac contractility (Bátkai *et al*., 2004; Pacher *et al*., 2005), which has also been documented in isolated cardiac preparations *in vitro* (Bonz *et al*., 2003). The results presented by Gaskari *et al*. (2005) in this issue implicate a similar endocannabinoid and CB_1 receptor-mediated mechanism in the abnormal myocardial contractility associated with liver cirrhosis.

Experimental and clinical studies during the past decades have strongly suggested the existence of latent heart failure with impaired responsiveness to standardized pharmacological or physiological stress, termed 'cirrhotic cardiomyopathy' or CCMP, with pathophysiologic and clinical features distinct from alcoholic cardiomyopathy (Ma & Lee, 1996; Moller & Henriksen, 2002). CCMP is characterized by decreased β-adrenergic responsiveness, defective excitation-contraction coupling and conductance abnormalities, despite the increased baseline cardiac output. This is an important clinical problem, because the marked peripheral vasodilation in cirrhosis often masks the cardiomyopathy, but when patients are challenged by physical or mental stress or pharmacological stimulation, the symptoms of impaired cardiac function could become manifest leading to heart failure (Ma & Lee, 1996; Moller & Henriksen, 2002).

In their very interesting study, Gaskari *et al*. (2005) have used isolated left ventricular papillary muscles from normal rats and rats with bile-duct ligation-induced liver cirrhosis to explore the possible role of endocannabinoids in the reduced cardiac contractile responsiveness to β-adrenergic stimulation in the cirrhotic rats. They found that papillary muscles from cirrhotic rats had a blunted contractile response to isoproterenol as compared to controls, which could be effectively restored by incubation with the selective CB_1 receptor antagonist AM251. Furthermore, preincubation of control papillary muscles with AEA resulted in a blunted contractile response to isoproterenol similar to that seen in cirrhotic preparations, and this effect could be also prevented by AM251. These novel findings suggest that increased endocannabinoid signalling *via* CB_1 receptors may be responsible for the blunted ventricular responsiveness to β-adrenergic stimulation. Control and cirrhotic preparations did not differ in their sensitivity to exogenous AEA or in the level of expression of CB_1 receptors and of the AEA-degrading enzyme, fatty acid amide hydrolase. However, at higher stimulation frequencies the AEA reuptake inhibitors VDM11 and AM404 significantly enhanced papillary muscle relaxation in cirrhotic but not in control preparations, and this effect was completely blocked by AM251 and pertussis toxin and partially blocked by

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tetrodotoxin. These findings suggest that local endocannabinoid production may be increased in cirrhosis, mostly in neural elements, which could account for the CB_1 receptor-mediated effects of the uptake inhibitors. On the basis of these findings, the authors propose that increased local endocannabinoid synthesis in cirrhotic hearts in response to stress, such as increased heart rate and haemodynamic overload, can play an important role in the blunted contractile responsiveness associated with CCMP.

Although increased endocannabinoid production in the cirrhotic myocardium has not been directly documented, this exciting new study provides the first evidence for the existence of a CB_1 receptor-mediated tonic inhibition of β-adrenergic responsiveness of isolated cardiac ventricular muscle in a rat model of biliary cirrhosis. Further studies should establish the role of the endocannabinoid system in the pathophysiology of cardiac dysfunction associated with liver cirrhosis of various origin *in vivo* and also investigate the potential effects of endocannabinoids and CB_1 antagonists on calcium homeostasis in cardiac myocytes. It is well accepted that the vasodilated state and impaired myocardial contractility in advanced liver cirrhosis contribute to mortality through increasing the risk of ascites formation and variceal haemorrhage (Gines *et al*., 1987). Therefore, it may be worthwhile to consider a clinical trial of the safety and effectiveness of a CB_1 receptor antagonist in preventing or reversing the adverse haemodynamic consequences of cirrhosis, which could extend life until a suitable liver becomes available for transplantation. Recent findings that the progression of liver fibrosis induced by carbon tetrachloride can be slowed down by inactivation of CB_1 receptors (Grenard *et al*., 2004) suggest a broader role of CB_1 receptors in the pathogenesis of cirrhosis and forecast additional potential benefits from the therapeutic use of a CB_1 antagonist.

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