Endothelin Receptors in Normal and Cirrhotic Human Liver

Lowell Ling[1], Rhoda Kuc[1], Janet Maguire[1], Neil Davie[2], Paul Gibbs[3], Graeme Alexander[4], Anthony Davenport[1]. [1]University of Cambridge, Clinical Pharmacology, Department of Medicine, CB2 0QQ, United Kingdom, [2]Pfizer Ltd, Pulmonary vascular disease specialty care, Europe, KT20 7NS, United Kingdom, [3]University of Cambridge, Department of Surgery, CB2 2QQ, United Kingdom, [4]University of Cambridge, Department of Medicine, CB2 0QQ, United Kingdom.

Medical treatment of portal hypertension (PH) is currently limited with current drug interventions such as prophylactic propranolol which is only effective in 60% of patients.[1] PH is often a consequence of cirrhosis, and acute variceal bleed contributes to the high mortality. Endothelin (ET) axis dysfunction has been implicated in the pathogenesis of cirrhosis and PH with elevated plasma ET reported in patients with the disease.[2, 3] Animal studies show that treatment with selective ET_A or mixed antagonists can reduce portal vein pressure in normal and CCl_4 induced cirrhosis.[4] These results suggest significant translational potential as clinical meta-analysis showed that reduction of hepatic vein pressure gradient results in reduced rates of primary and recurrent variceal bleeds.[5] ET antagonists are currently used for the treatment of pulmonary hypertension, therefore these drugs have the advantage that they could be quickly repurposed to treat PH. The challenge is to confirm and translate the therapeutic benefits seen in animal studies to humans.

Our aim was to identify the distribution of the ET receptor subtypes in normal or cirrhotic hepatic artery and portal vein by immunohistochemistry and to characterise ET pharmacology in the liver parenchyma using autoradiography and radioligand binding assays. Human tissue was obtained with informed consent and ethical approval. Using confocal microscopy, both ET_A-like and ET_B-like immunoreactivity localised to the endothelium, smooth muscle and adventitia of normal and diseased hepatic artery (n=3) and portal vein (n=5). Using [^{125}I]ET-1, competition binding experiments with BQ788 (ET_B selective) and sitaxentan (ET_A selective) revealed that ET_B is the predominant receptor subtype expressed in both normal and cirrhotic liver parenchyma. Expression of receptor subtypes determined by autoradiography showed that ET_B is the main receptor subtype in liver lobules in normal and cirrhotic tissue. Our results are consistent with animal studies and quantify the relative expression of ET_A and ET_B in normal and cirrhotic liver and vessels.

		% ET_A	% ET_B	n
BQ788				
	Normal	22.3 ± 2.7	77.7 ± 2.7	5
	Cirrhosis	7.2	92.8	2
Sitaxentan				
	Normal	18.6 ± 5.6	81.3 ± 5.6	5
	Cirrhosis	7.2	92.8	2

Table 1. Percentage of ET_A:ET_B receptors in liver parenchyma determined using subtype selective antagonists.

These results show that normal human liver contains one of the highest densities of ET_B receptors when compared with other organs, with a further increase in the ET_B:ET_A ratio in cirrhosis. Our data provides evidence that blockade of beneficial ET_B receptors may account for the hepatic toxicity of mixed ET antagonists. Localization of ET receptors within the human liver and *in vitro* pharmacology of hepatic artery and portal vein are needed to translate and validate ET receptor antagonists as a potential drug therapy for PH.

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