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Short Communication

Correction of Oxygen-Nutrient Mismatch Might Account for the Beneficial Effect of Obeticholic Acid in NASH

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DESCRIPTION

The Farnesoid X Receptor (FXR) is a nuclear bile acid receptor involved in bile acid homeostasis, hepatic and intestinal inflammation, liver fibrosis, and cardiovascular disease. Obeticholic Acid (OCA), a potent, selective FXR agonist decreases portal hypertension in animal models of cirrhosis [1,2]. The drug is also effective in the treatment of non-alcoholic steatohepatitis, NASH [3-5]. The two disparate findings might be reconciled by an effect of OCA on hepatic artery flow.

The liver has a unique dual blood supply comprising both a Portal Vein (PV) and a Hepatic Artery (HA). PV blood is nutrient rich and deoxygenated. It lacks myogenic elements for flow control, which is unregulated but accounts for over 80 percent of liver blood supply. By contrast, HA blood is well oxygenated and accounts for 20 percent of liver blood flow. The liver has no mechanisms for matching nutrient delivery *via* the PV with oxygen supply from the HA.

Thus, chronic excess nutrient delivery *via* the PV may fail to be matched by oxygen supply from the HA, resulting in relative tissue hypoxia and damage. This potential link between oxygen-nutrient mismatch and liver disease pathology was first proposed for alcoholic steatohepatitis, ASH by Lautt [6] with chronic excess alcohol exposure. It is of interest that maximum damage in both NASH [7] and ASH [8] is found in zone 3 of the hepatic lobule, where the partial pressure of oxygen is lowest [7]. Furthermore, NASH has been associated with chronic obstructive sleep apnea and intermittent hypoxia. Treatment of intermittent hypoxia in obstructive sleep apnea improves NASH severity [9-11].

The liver also plays a dramatic role as a blood volume reservoir. Although liver mass constitutes only 2.5 percent of total body weight, combined PV and HA blood flow accounts for nearly 25 percent of cardiac output [12]. Maintaining total hepatic blood flow at a constant level, is essential for the integrity of the cardiovascular and circulatory system. Total hepatic blood flow is controlled by a unique interaction between PV and HA blood flow, an observation first described by Burton-Opitz in 1911 [13] and termed the Hepatic Arterial Buffering Response (HABR) [14,15]. The mechanism of this powerful reflex has been attributed to adenosine washout [16].

In this *ex vivo* liver perfused model, devoid of a splanchnic circulation, OCA dose-responsively increases HA blood flow. This is associated with an inverse reduction in PV flow, while HV outflow remains relatively constant [17], suggesting that HABR might be a powerful mechanism for inducing changes in portal vein flow, independent of the splanchnic circulation.

Studies of portal hypertension have hithertofore been in whole animal models that included the splanchnic circulation [1-2]. Drug induced changes in portal pressure have been assumed due primarily to the degree of splanchnic vasoconstriction or vasodilation as well as intrahepatic resistance. A highly significant finding from this study is that portal pressure can be modulated by drugs that directly affect HA vasoconstriction or vasodilation, rather then mesenteric and splanchnic arteriolar constriction or dilatation. The direct effects of cardio-selective and non-selective beta-blockers as well as drugs like terlipressin and octreotide on HA blood flow in the isolated perfused liver model will need to be addressed.

CONCLUSION

The study highlights the potential for drugs that could directly affect blood flow in the HA on ASH, NASH and portal hypertension. Pharmacologically induced increase in HA blood flow will simultaneously increase oxygen delivery to the liver, which could reduce liver damage in ASH and NASH. Similarly, increased HA flow inversely reduces PV flow and pressure *via* HABR, which might prove an effective way to reduce portal hypertension.

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