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Editorial

Dual organ beneficial effects of metformin in cirrhotic rats with hepatopulmonary syndrome

Liver fibrosis causes portal hypertension which dilates collateral vasculature and enhances extra-hepatic angiogenesis including intrapulmonary shunts, which subsequently complicates with hepatopulmonary syndrome (HPS). Metformin is an anti-diabetic agent which has anti-inflammation and anti-angiogenesis properties.[1−3] HPS is a severe complication of liver cirrhosis which is characterized by deoxygenation in cirrhotic patients.[4] In this issue of the *Journal of the Chinese Medical Association*, Chen and his colleagues comprehensively evaluated the hemodynamic and biochemistry parameters, and a blood-gas analysis of a 21-day regimen of metformin 150 mg/kg/day treatment on common bile duct ligated (CBDL)-cirrhotic rats.[5] The study revealed that metformin treatment neither induced obvious hypoglycemic event nor altered hemodynamics in cirrhotic rats.[5] The plasma levels of alanine aminotransferase, hepatic inflammation and fibrosis were significantly reduced by chronic metformin treatment. Metformin did not modify the cirrhotic-HPS-related hypoxia and intrapulmonary angiogenesis; however, it significantly reduced intrapulmonary shunts. Furthermore, metformin reduced the protein expressions of COX-2 and PI3K in the liver and COX-1 in the lung.

In the Chan et al. study, the plasma level of ALT and hepatic inflammation and fibrosis were significantly attenuated by chronic metformin treatment in common bile duct-ligated (BDL)-cirrhotic rats.[5] Consistent with the current study finding, metformin have been proven to enhance liver function in HCV-related cirrhotic patients.[6] In an animal model, metformin protects galactosamin-induced liver injury by way of the AMPK-dependent pathway.[7] In vitro studies with human hepatocytes also suggested that anti-inflammatory action of metformin comes from AMPK activation.[8,9] Notably, the metformin-related amelioration of BDL-induced hepatic inflammation and fibrosis was independent of hepatic AMPK pathway, but through the PIK-3 pathway.[1] Interestingly, plasminogen activator inhibitor-1 (PAI-1), an acute phase protein, has been known to correlate with hepatic fibrosis. Early liver injury and inflammation due to bile duct ligation was significantly blunted in PAI-1 (−/−) mice compared to wild-type mice.[10] The hepatic protective effects of PAI-1 in cholestatic liver injury and inflammation come from an elevation in hepatic activities of urokinase-type plasminogen activator, and activation of hepatocyte growth factor receptor c-Met.[10]

Hepatocytes apoptosis plays an important role in the pathogenesis of cholestatic liver injury. An *in vitro* study reported that metformin dose-dependently reduces bile acid glycochenodeoxycholic acid (GCDCA)-induced hepatocyte apoptosis.[11] This study reported that the AMPK-independent protective effect of metformin is mainly dependent on an intact PI3-kinase pathway in GCDCA-exposed hepatocytes.[11] Although the hepatic PAI-1 signals were not evaluated in BDL-cirrhotic rats, both hepatic PAI-1 and PI3-kinase pathways are crucial for the beneficial effects of chronic metformin treatment in cirrhotic rats.[5]

This study is characterized by the use of a well-established animal model of intrapulmonary vasodilatation and macrophage infiltration in BDL-cirrhotic rats with HPS.[5,12] The dose and duration of metformin use in this study suppress the pulmonary COX-1 expression and intrapulmonary shunt amount.[5] The lack of chronic metformin treatment on pulmonary angiogenesis of cirrhotic rats might be due to the complication anti-angiogenesis and pro-angiogenesis of metformin.[13,14] Taking into consideration the complicated and multifaceted pathogenesis of cirrhotic HPS, more than one therapeutic strategy may be necessary to effectively improve hepatic fibrosis, cirrhosis as well as HPS.

In patients with diabetes, continuation of metformin use after the diagnosis of cirrhosis significantly improved survival durations.[15] Overall, this study first established the mechanism and effects of chronic metformin treatment in cirrhotic rats with dual organ beneficial effects. On the other hand, this study also reported that it is safe to use metformin in cirrhotic animals with glucose intolerance and mild renal impairment.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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