# Contribution of Transient Receptor Potential Canonical 5 (TRPC5) to hepatic dyslipidemia in a model of diet induced cholestasis

**Introduction:** Cholestasis, defined as the accumulation of bile in the hepatic systemis a condition common in pregnancy or is a secondary complication to other diseases such as hepatitis and primary biliary cirrhosis[1]. A non-selective cation channel, transient receptor potential canonical 5 (TRPC5), was shown to be modulated by a number of endogenous and exogenous lipids[2], highlighting a role in lipid metabolism. Hepatic bile acids includingcholic acid(CA) play an important physiological role in lipid metabolism and are also involved in the pathogenesis of cholestasis[3]. We examined the roleofTRPC5 in the pathogenesis of cholestasis, specifically the inflammation and metabolic dysfunction component, *in vivo*, using a dietary model[3].

**Methods:** Male TRPC5 wild-type (WT) and knockout(KO) mice (129/SvImJ background, 25-30g, ≥8 weeks; Howard Hughes Medical Institute, Boston)were fed control (RM3) or 0.5% CA supplemented diet for 3 weeks (n=5-7 for each group). Whole livers were weighed to determine hepatomegaly. *Ex vivo* analysis included: plasma alanine transaminase (ALT) and aspartate transaminase (AST) levels indicative of liver damage, myeloperoxidase (MPO)activity indicative of neutrophils accumulation and inflammation, and triglycerides (TG)/ cholesterol levels. Results were normalised to protein content, expressed as the mean ± Standard Error of the Mean (SEM), and analysed by2-way analysis of variance with Bonferroni *post hoc* tests. P<0.05 were considered to be statistically significant.

**Results:** CA-induced hepatomegaly was confirmed in the WT compared with WT control mice; this was absent in TRPC5 KO mice. Plasma markers for liver injury were increased in CA-fed WT mice for ALT and AST, but less so in CA-fed KO mice. ALT was significantly increased in WT CA-fed mice and this was abolished in KO CA-fed mice.MPO activity in the liver was increased in WT mice on high-CA diet that was abolished in the KO CA mice and significantly attenuated compared to WT CA mice. The increased hepatic triglycerides (TG) accumulation in the WT mice was not observed in the KO mice. TG accumulation was significantly attenuated in KO CA compared to WT CA. Cholesterol levels were increased in both WT and KO mice but was significantly attenuated in TRPC5 KO mice.

**Table 1: Role of TRPC5 in CA-induced liver pathology**

| | WT Control | WT CA | KO Control | KO CA |
|---|---|---|---|---|
| Liver: Body weight ratio | 4.0 ±0.1 | 4.8 ±0.1$^{***}$ | 4.1 ± 0.3 | 4.6 ±0.1 |
| ALT (Units/L) | 163.0± 13.5 | 363.5±52.8$^{***}$ | 158.2± 11.7 | 234.2± 45.4$^{\#}$ |
| AST (Units/L) | 286.3± 47.5 | 463.1±29.3$^{*}$ | 309.2± 36.7 | 380.1 ±64.8 |
| MPO (Units/g protein) | 72.5±6.4 | 130.4±11.7$^{***}$ | 71.4±6.2 | 90.9±6.6$^{\#\#}$ |
| Hepatic TG (mmol/g protein) | 19.7 ±1.8 | 44.9 ±5.6$^{***}$ | 20.2 ±3.4 | 25.9 ±2.4$^{\#\#}$ |
| Cholesterol (mmol/g protein) | 0.04±0.005 | 0.25 ± 0.04$^{***}$ | 0.05 ± 0.01 | 0.18 ±0.03$^{**/\#}$ |

$^{*}$p<0.05, $^{**}$<0.01, $^{***}$p<0.001 vs WT/KO control, $^{\#}$p<0.05, $^{\#\#}$p<0.01 vs WT CA

**Conclusion:** In conclusion, this study presented a novel role for TRPC5 in contributing to the liver pathology observed in a model of diet-induced cholestasis. This raises the possibility that suppressing its function will lessen the liver injury observed in cholestasis.

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(1) Beuers*et al.* (2009). *J Hepatol.* **51(2):** 237-67.

(2) Bon and Beech (2013). *Br J Pharmacol.***170(3)**: 459-74

(3) Papacleovoulou*et al.* (2013). *J Clin Invest*. **123(7)**: 3172-81.