

Abstract

Background. Hypertension a significant risk factor for cardiovascular diseases and organ failure. Recent studies have shown associations between the gut microbiome and hypertension marked by a low species abundance and diversity of the gut microbiome in hypertension. Furthermore, the eradication of *Helicobacter pylori* resulted in significant blood pressure reductions. This data links the role of the gut microbiome and the presence of *H. pylori* to hypertension. However, the proposed mechanism is not understood. This study hypothesised that endogenous cardiotonic steroids (CTS) which modify $\text{Na}^+\text{-K}^+$ ATPase activity and affect arterial pressure, are formed from bile acids, and mediated by the gut microbiome by a presently unknown pathway.

Aim. To demonstrate the conversion of ^{14}C -(C4)-cholesterol to bile acids and CTSs in rat models of hypertension.

Methods. Ethics approval was obtained for the study (AREC Clearance: 2018/09/42/C). Radioactively labelled ^{14}C -(C4)-cholesterol was administered once-off through oral gavage in Spontaneous Hypertensive Rats (SHR) and Wistar Kyoto rat models of hypertension and blood pressure was monitored for 21 days. Faecal samples were collected daily. Bile acids and CTS were extracted with methyl-tert-butyl ether and separated by Ultra-High Performance Liquid Chromatography with mass-spectrometry used for their identification. Standards were available for only a few primary, secondary and CTS compounds.

Results. The findings of this study were 1) that the ^{14}C -(C4)-label was poorly incorporated into primary and secondary bile acids and was not detected in CTS compounds; 2) bufalin was detected in some, not all, of the SHR samples but was absent in the WKY rat samples; 2) digitoxin was detected in both WKY and SHR samples; and 3) correlation of blood pressure increase in WKY, not SHR rats, and in female rats, with the total proportion of measured hydrodeoxycholic acid and lithocholic acid.

Conclusion. Other ^{14}C - or preferably ^{13}C -primary bile acids should be tested to improve conversion to secondary bile acids and CTSs. Measurement of the full bile acid and CTS profiles will elucidate the spectrum of CTSs present in faecal material and will suggest important pathways in the biosynthesis of these compounds. However, this study provides a valuable platform on which future studies can be based when determining the importance of the microbiome in hypertension.