European Journal of Pharmacology 774 (2016) 118–126

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Cardiovascular pharmacology

Taurochenodeoxycholate relaxes rat mesenteric arteries through activating eNOS: Comparing with glycochenodeoxycholate and tauroursodeoxycholate

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ARTICLE INFO

Article history:
Received 31 August 2015
Received in revised form
3 February 2016
Accepted 3 February 2016
Available online 4 February 2016

Keywords:
Taurochenodeoxycholate
Glycochenodeoxycholate
Tauroursodeoxycholate
eNOS
Vasorelaxation

ABSTRACT

The bile acids (BAs) and their conjugates have vascular activities and the serum levels of BAs and their conjugates are increased in liver diseases. In the present study, we examined the in vitro vasoactivities of BAs conjugates taurochenodeoxycholate (TCDC) (5–80 μM), glycochenodeoxycholate (GCDC) (20–150 μM) and tauroursodeoxycholate (TUDC) (20–150 μM) in rat mesenteric arteries and thoracic aorta. The isometric tension of rat mesenteric arteries and thoracic aorta was recorded by using multi-wire myograph systems. TCDC induced significant concentration-dependent relaxation in endothelium-intact but not endothelium-denuded rat mesenteric arteries pre-contracted with phenylephrine (PE). TCDC also showed vasorelaxant effects on high K^+ induced contraction in rat mesenteric arteries. L-NAME treatment inhibited TCDC-induced relaxation in mesenteric arteries pre-contracted with PE. Acute treatment with TCDC increased protein expression of P-eNOS (ser1177) in human umbilical vein endothelial cells. GCDC dose-dependently relaxed PE-induced vasoconstriction in both endotheium-intact and endothelium-denuded rat mesenteric arteries, but GCDC showed no effect on high K^+-induced vasoconstriction. Both GCDC and TCDC showed no apparent relaxation on PE and high K^+-induced vasoconstriction in rat thoracic aorta. TUDC showed no effect on PE and high K^+-induced vasoconstriction in rat mesenteric arteries and thoracic aorta. The study demonstrates that TCDC relaxes rat mesenteric arteries through activating eNOS. TCDC might be the major BAs conjugate for vasorelaxation in vivo.

1. Introduction

Bile acids (BAs) are synthesized in the liver from cholesterol metabolism. The principal BAs include the primary BAs cholic acid and chenodeoxycholic acid (CDCA), their conjugates with glycine and taurine, and the secondary BAs deoxycholic acid and lithocholic acid (Houten et al., 2006). These bile acids show multiple biological activities, such as regulating triglyceride, cholesterol, energy, and glucose homeostasis, thus, the BA-controlled signaling pathways are regarded as targets for common metabolic diseases (Houten et al., 2006). It is interesting that some bile acids even show contrasting effects each other, for instance, the taurine-conjugate of UDCA (tauroursodeoxycholic acid, TUDCA) protects against glycochenodeoxycholic acid (GCDCA)-induced apoptosis in primary cultures of rat hepatocytes (Schoemaker et al., 2004). Because BAs are considered as signaling molecules with systemic endocrine functions, their biological activities need further elucidating.

Previous studies had reported that bile acids as well as their glycine- and taurine-conjugates were vasoactive. Pak et al. reported that tauroursodeoxycholate, taurochenodeoxycholate and taurodeoxycholate caused vasorelaxation in the isolated perfused rat mesentery (Pak et al., 1994). Sandeep et al. reported that deoxycholyltaurine induced vasorelaxation of phenylephrine-constricted rings of rat thoracic aorta (Khurana et al., 2005). Recently, Khurana et al. found that deoxycholylglycine reduces pressure- and agonist-induced vasoconstriction independent of muscarinic receptor, NO or K^+ channel activation (Khurana et al., 2012). Although the vasorelaxant effects of BAs and their conjugates have been proved, a question should be noted that, whether the concentrations of these BAs and their conjugates could match the concentrations in vivo in physiological or pathophysiological states.

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http://dx.doi.org/10.1016/j.ejphar.2016.02.011
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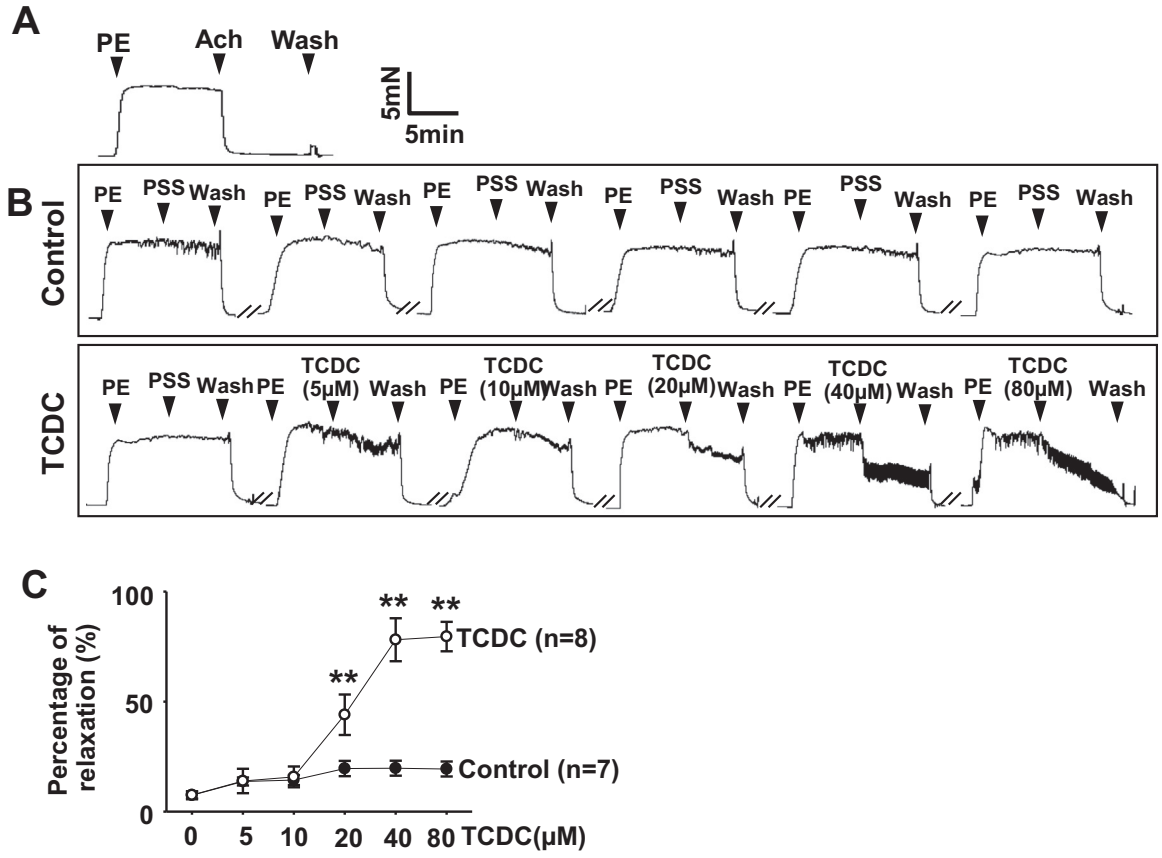

Fig. 1. TCDC relaxed PE-induced constriction of rat mesenteric arteries with intact endothelium. (A) The intact-endothelium of mesenteric arteries was confirmed by Ach-induced relaxation. PE, phenylephrine; Ach, acetylcholine. (B) The representative original recordings of TCDC induced relaxation in PE-evoked constriction in rat mesenteric arteries with intact endothelium. (C) The summarized data showed that TCDC relaxed PE-induced constriction of rat mesenteric arteries with intact endothelium.$^{**}P < 0.01$ vs control. TCDC, taurochenodeoxycholate. The concentrations of PE and Ach were 5 μM and 1 μM respectively.

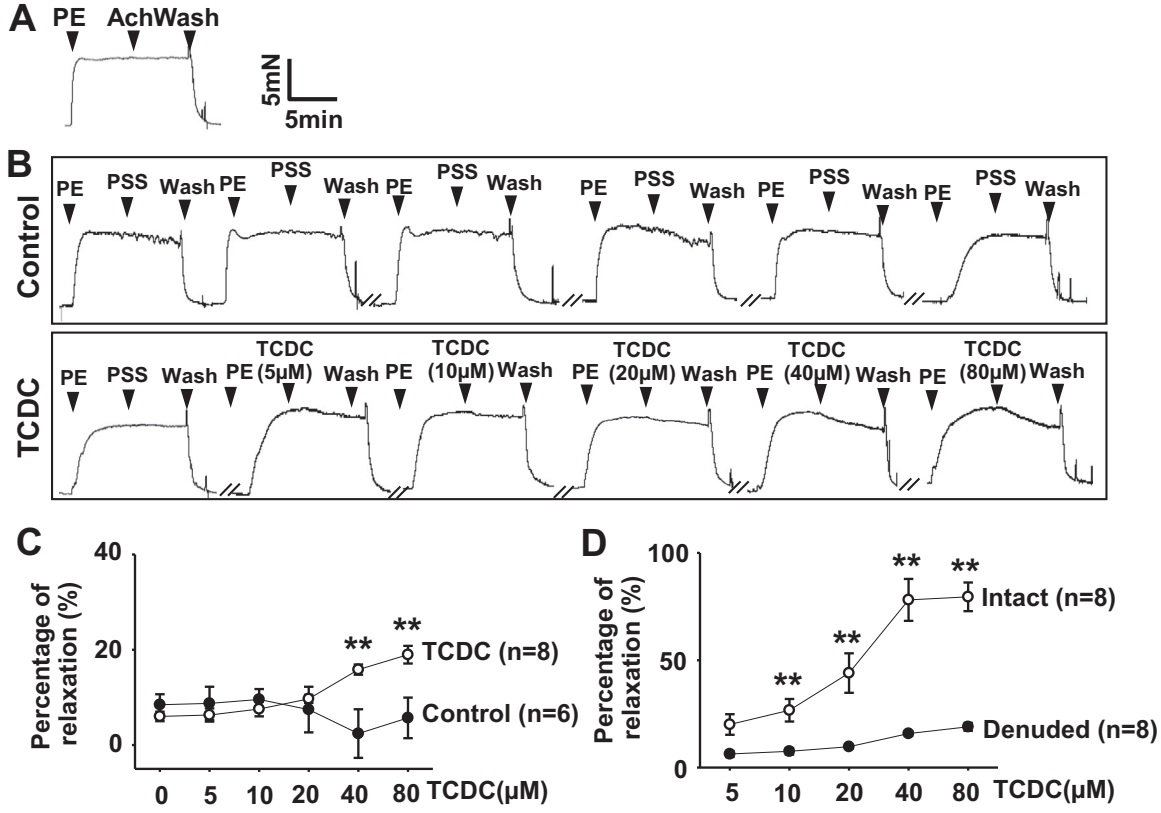

Fig. 2. TCDC relaxed PE-induced constriction of rat mesenteric arteries with denuded endothelium. (A) The endothelium denudation was confirmed by absence of Ach-induced relaxation. PE, phenylephrine; Ach, acetylcholine. (B) The representative original recordings of TCDC-induced relaxation in PE-evoked constriction in rat mesenteric arteries with denuded endothelium. (C) The summarized data of TCDC induced vasorelaxation in rat mesenteric arteries with denuded endothelium.$^{**}P < 0.01$ vs control. (D) TCDC-induced vasorelaxation was endothelium-dependent.$^{**}P < 0.01$ vs denuded. TCDC, taurochenodeoxycholate. The concentrations of PE and Ach were 5 μM and 1 μM respectively.