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Pseudoephedrine/ephedrine shows potent anti-inflammatory activity against TNF-α-mediated acute liver failure induced by lipopolysaccharide/D-galactosamine ☆

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ABSTRACT

The anti-inflammatory effects of pseudoephedrine/ephedrine were investigated using the experimental model of lipopolysaccharide (LPS)-induced acute liver failure in D-galactosamine (D-GalN)-sensitised male rats in order to elucidate effects other than sympathomimetic effects. Rats were intraperitoneally injected with D-GalN (400 mg/kg) and LPS (40 μg/kg) to induce acute liver failure. The treatment groups were then intraperitoneally administered pseudoephedrine/ephedrine at 0 h and 4 h after induction and the activation induced by treatment with pseudoephedrine and/or LPS on the primary Kupffer cells (KCs) was monitored. Compared with controls induced by GalN/LPS alone, pseudoephedrine dramatically reduced the infiltration of inflammatory cells and bile ductular hyperplasia and hepatic necrosis observed in liver sections. It inhibited both hepatocellular apoptosis and the expression of monocyte chemotactic protein-1. It lowered the production of tumour necrosis factor-α (TNF-α) in the beginning of acute liver failure induced by D-GalN/LPS. Correspondingly, levels of alanine aminotransferase (ALT), total bilirubin (TBIL) and malondialdehyde were attenuated. Ephedrine demonstrated all these identical protective effects as well. In addition, pseudoephedrine significantly suppressed the production of p-IκB-α, reducing the degradation of sequestered nuclear factor kappa B (NF-κB) in the cytoplasm, and inhibited the translocation of NF-κB/p65 to the nucleus, the transcription of TNF-α mRNA and the production of TNF-α in primary KCs. These results suggest that pseudoephedrine and ephedrine have a potent anti-inflammatory activity against D-GalN/LPS-induced acute liver failure in rats, and this comprehensive anti-inflammatory effect may result from the inhibition of TNF-α production.

1. Introduction

Pseudoephedrine and ephedrine are a pair of naturally occurring epimers (Fig. 1A) and are the main active components isolated from well-known Ephedra species (*ma huang*). Ephedrine/pseudoephedrine have long been used as drugs. As early as 1924, Chen and Schemidt published the first pharmacological study on ephedrine (Chen and Schemidt, 1924), and since then ephedrine and its epimer pseudoephedrine have been widely investigated due to their sympathomimetic effects. These compounds are used clinically as treatments for diseases of the respiratory system such as colds, influenza and rhinitis, or as weight loss supplements (Lee, 2011). Pseudoephedrine is gradually replacing ephedrine to treat infections of the upper respiratory tract because of the stronger side effects of ephedrine, such as stimulation of the central nervous system and cardiovascular systems (Haller and Benowitz, 2000).

We conducted an extensive literature search for screens of anti-inflammatory drugs obtained from herbs. Ephedra contains pseudoephedrine/ephedrine which might have excellent anti-inflammatory effects and has been used in ancient Chinese traditional medicine for treatment of icterus (Zhang, 1999; Zhang, 1995; Wang et al., 2011; Fiebich et al., 2012). However, articles have been published concerning the hepatotoxicity associated with ephedra (*ma huang*) (Nadir et al., 1996; Borum, 2001). Therefore, we speculated whether pseudoephedrine/ephedrine, the major ingredient of ephedra, could treat icterus resulting from acute liver injury induced by TNF-α.

In this study, we established an experimental model of apoptotic liver injury in rats induced by TNF-α produced by intraperitoneally injecting D-galactosamine (D-GalN) and a low dose of lipopolysaccharide (LPS) (Josephs et al., 2000; Olleros et al., 2010;

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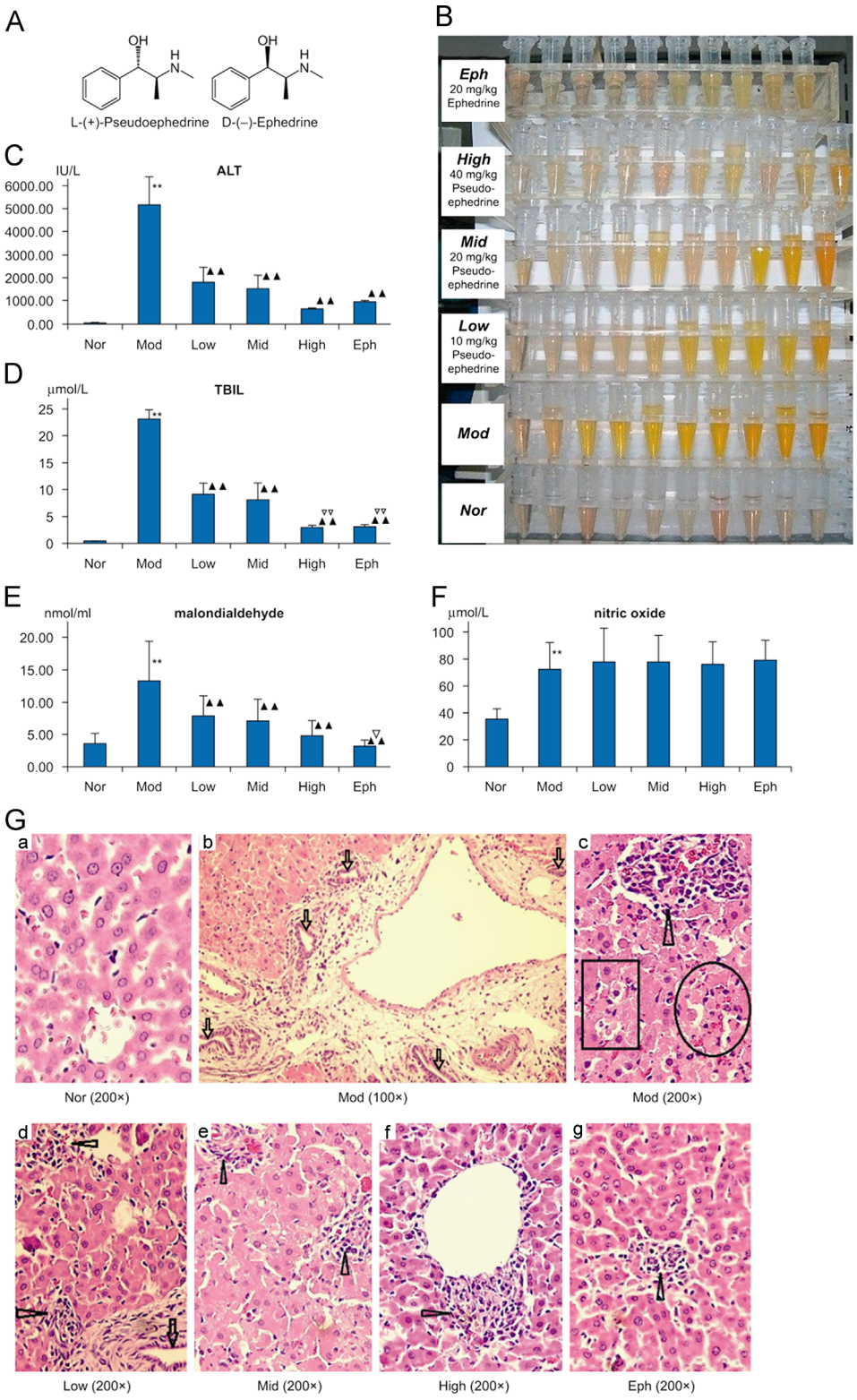

Fig. 1. Effects of pseudoephedrine and ephedrine treatment on D-GalN/LPS-induced acute liver failure at 24 h. Blood samples were withdrawn via the abdominal aorta. At 0 h and 4 h after the injection of 400 mg/kg D-GalN and 40 μg/kg LPS or saline, the rats were intraperitoneally administered either drugs or saline. Nor: saline+saline; Mod: D-GalN/LPS+saline; Low: D-GalN/LPS+10 mg/kg pseudoephedrine; Mid: D-GalN/LPS+20 mg/kg pseudoephedrine; High: D-GalN/LPS+40 mg/kg pseudoephedrine; Eph: D-GalN/LPS+20 mg/kg ephedrine (body weight, $n=10$ per group). (A) Epimer structure of pseudoephedrine and ephedrine; (B) images of serum colour; levels of (C) ALT; (D) TBIL; (E) malondialdehyde; and (F) nitric oxide; (G) H&E staining of morphological sections of the liver: (a) normal lobular architecture and cell structure, (b) significant bile ductular hyperplasia (arrows), (c) cellular vacuolar degeneration, hydropic degeneration (rectangle) and haemorrhage, focal necrosis, infiltration of inflammatory cells (circle). In G-(c–g), the triangles show focal necrosis, and the arrows show bile ductular hyperplasia. $^{**}P<0.01$ compared to Nor; $\blacktriangle\blacktriangle P<0.01$ compared to Mod; $\triangledown P<0.05$, $\triangledown\triangledown P<0.01$ compared to Low.