4 - 59 Endothelium-independent Vasorelaxant Effect of 20(S)-protopanaxadiol on Isolated Rat Thoracic Aorta*

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Ginseng (Panax ginseng C.A. Mey) has been widely used in traditional Chinese medicine for over a thousand years to improve health and vigor. The beneficial effects of ginseng have been investigated in disorders of the central nervous system, cardiovascular system, endocrine system and immune system[1]. To date, more than 40 ginsenosides, which are the main bioactive chemical constituents of ginseng, have been reported[2]. These ginsenosides are classified as protopanaxadiols or protopanaxatriols. Orally administered protopanaxadiol-type and protopanaxatriol-type ginsenosides are metabolized to 20(S)-protopanaxadiol (PPD) via compound K and 20(S)-protopanaxatriol (PPT) via ginsenoside Rh1, respectively, by gut microbiota[3]. These metabolites have better bioavailability, owing to their crossing of the intestine-blood and blood-brain barriers[4]. These compounds exhibit many pharmacological activities similar to those of ginseng. In addition, 20(S)-PPD exhibits anticancer effects in experimental animals and cultured cells. At present, 20(S)-PPD has been developed into a Chinese medicine to assist in radiotherapy and chemotherapy, which is currently being assessed in clinical stage III trials[5]. As an important active ingredient, 20(S)-PPD exhibits numerous pharmacological effects *in vitro* or *in vivo*; however, it remains unknown whether 20(S)-PPD has vasorelaxant effects in rat thoracic aortas. Therefore, the present study was designed to investigate the vasoactivity of 20(S)-PPD and its possible mechanisms in isolated rat aortic rings with or without endothelium.

Aortic rings with or without endothelium was prepared from Wistar rats and suspended in organ-chambers. The changes in tension of the preparations were recorded through isometric transducers connected to a data acquisition system. The aortic rings were precontracted with phenylephrine (PE, 1 μmol/L) or high K^+(80 mmol/L). Application of 20(S)-PPD (21.5∼108.5 μmol/L) caused concentration-dependent vasodilation of endothelium-intact aortic rings precontracted with PE or highK^+, which resulted in the EC_{50}values of 90.4 or 46.5 μmol/L, respectively. The removal of endothelium had no effect on 20(S)-PPD-induced relaxation. The vasorelaxant effect of 20(S)-PPD was also not influenced by the preincubation with β-adrenergic receptor antagonist propranolol, or with ATP-sensitive K^+channel blocker glibenclamide, voltage-dependent K^+ channel blocker 4-AP and inward rectifier K^+ channel blocker $BaCl_2$, whereas it was significantly attenuated by the preincubation with Ca^{2+}-activated K+ (BK_{Ca}) channel blocker TEA (1 mmol/L). Furthermore, the inhibition of NO synthesis, cGMP and prostacyclin pathways did not affect the vasorelaxant effect of 20(S)-PPD (Fig. 1) In Ca^{2+}-free solution, 20(S)-PPD (108.5 μmol/L) markedly decreased the extracellular Ca^{2+}induced contraction in aortic rings precontracted with PE or high K^+ and reduced PE-induced transient contraction. Voltage-dependent Ca^{2+} channel antagonist nifedipine inhibited PE-induced contraction; further inhibition was observed after the application of receptor-operated Ca^{2+} channel inhibitor SK&F 96365 or 20(S)-PPD (Fig. 2).

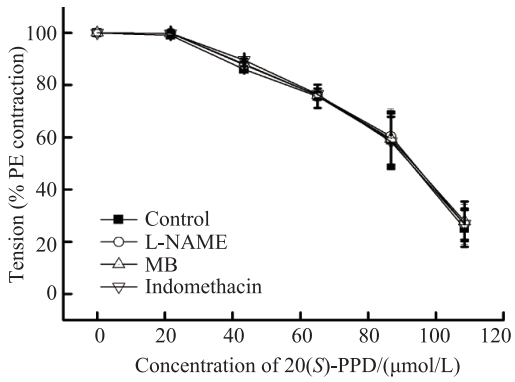

Fig. 1 The relaxant effect of 20(S)-PPD on PE (1 μmol/L)-pre-contracted aortic rings in the presence or absence (control) of L-NAME (10 μmol/L), MB (10 μmol/L) and indomethacin (1 μmol/L). Values are expressed as the mean±SEM. n=8.

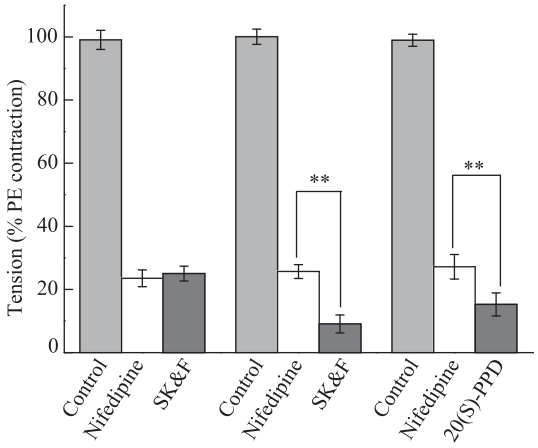

Fig. 2 The effects of 20(S)-PPD (108.5 μmol/L) and SK&F 96365 (SK&F 50 μmol/L) in the presence of nifedipine (Nif 10 μmol/L) on PE-induced contraction in endothelium-denuded aortic rings. Values are expressed as the mean±SEM. n=8. $^{**}P < 0.01$.

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20(S)-PPD induces vasorelaxation via an endothelium-independent pathway. The inhibition of voltage-dependent Ca^{2+} channels and receptor-operated Ca^{2+} channels and the activation of Ca^{2+}-activated K^{+} channels are probably involved in the relaxation.

References

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4 - 60 Study on Protein Marker of Hepatotoxicity Induced by Iron Ion Radiation in Mice

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It is important to determine whether exposure to cosmic radiation induces disease or toxicity in astronauts and space travellers[1]. In this investigation, we used a comparative proteomics approach based on a 2-DE reference map to detect alterations in protein expression in the serum of Swiss–Webster mice following exposure to iron ion radiation (IIR), and to identify biomarkers of liver toxicity. The results reveal the underlying molecular mechanisms of liver disease or toxicity following exposure to IIR.

Compared with the control (Fig. 1), the irradiated mice showed inflammatory cell in filtration, blood vessel congestion and dilatation, hepatic necrosis in the liver lob-ules, and the hepatic portal vein had obvious pathological changes. The pathological evidence demonstrated that IIR resulted in long-term liver injury in mice. Differential serum protein spots between irradiated mice and controls were screened using 2-DE and the differentially expressed protein spots detected by PDQuest 8.0 software based on the ± over 1.5-fold difference in the protein quantities (normalized spot volume) was used as the standard to determine differential spots. A total of 11 differentially expressed spots were enlarged to show in Fig. 2. We profiled serum proteome alterations in mice after IIR exposure using 2-DE, and identified potential biomarkers of toxicity in liver tissues. To the best of our knowledge, this is the first study to demonstrate the serum proteomic profiles underlying liver toxicity in mice after IIR.

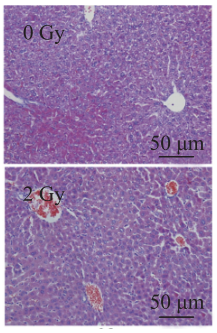

Fig. 1 (color online) Hepatic histological examination in male mice at 3 months after IIR. Photomicrographs of sections stained with H&E (magnification 200 ×), bar= 50 μm.

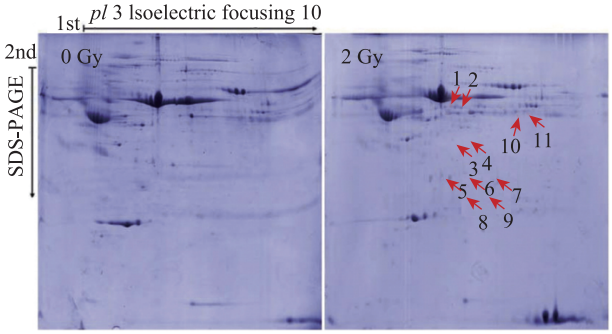

Fig. 2 (color online) The protein profiles and differentially expressed spots of mice serum at 3 months after IIR. 10 μL serum were separated using IEF of pH 3∼10, followed by 12% SDS-PAGE and visualized by CBB-R 250 staining. Red arrows represent increased expression.

Reference

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