BETULINIC ACID AMELIORATES ENDOTHELIOUM-DEPENDENT RELAXATION IN L-NAME-INDUCED HYPERTENSIVE RATS BY REDUCING OXIDATIVE STRESS

Lin-Bo Qian1, Jia-Yin Fu2, Xin Cai2, Hui-Ping Wang2, Jan-An Wang3, Qiang Xia2 1Department of Physiology, Zhejiang University School of Medicine, Hangzhou, China Clinical Research Center, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 2Department of Physiology, Zhejiang University School of Medicine, Hangzhou, China; 3Department of Cardiology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Objective Modern pharmacological studies reveal that betulinic acid (BA), the key active constituent of traditional Chinese cardiovascular herbs Zizyphi Spinosi semen, up-regulated endothelial nitric oxide synthase (NOS) and down-regulated NADPH oxidase, and our previous study shows that BA ameliorated the impairment of endothelium-dependent relaxation (EDR) induced by H2O2 in rat aortas. Here, we hypothesised that BA may attenuate endothelial dysfunction in hypertensive rats via its modulation of the oxidative stress and vascular NO pathway.

Methods Male Sprague–Dawley rats were injected with Nω-nitro-L-arginine methyl ester hydrochloride (L-NAME) (15 mg/kg/day, intraperitoneal) for four weeks to induce...
Abstracts

hypertension. After treatment with L-NAME for two weeks,
rats with mean blood pressure >120 mm Hg measured by tail-
cuff method were considered hypertensive and then injected
with BA (0.8, 4, 20 mg/kg/day, intraperitoneal) for the last
two weeks. The effect of BA on the tension of rat thoracic aor-
tic rings was measured in an organ bath system. The levels
of nitric oxide (NO), reactive oxygen species (ROS), and the
activity of superoxide dismutase (SOD) and NOS in aortas
were assayed.

Results (1) BA (0.1 to 100 μM) evoked a concentration-depen-
dent relaxation in endothelium-intact normal rat aortic rings
(the E_max reached 74.06±6.18%, and EC50 was 1.67 μM), which
was significantly attenuated by pretreatment with L-NAME
(100 μM) or methylene blue (MB, 10 μM), but not by indo-
methacin (10 μM). (2) Pretreatment with EC50 concentration
of BA enhanced the acetylcholine (ACh)-induced EDR, the
E_max increased from 70.74±6.66% to 85.39±7.16% (p<0.01),
which was also markedly reversed by both L-NAME and MB.
(3) The blood pressure in hypertensive rats induced increased
to 135.22±5.38 mm Hg (p<0.01 vs control group), which was
markedly attenuated by high dose of BA (106.49±7.28 mm Hg).
(4) The ACh-induced EDR in hypertensive rat aortic rings was
impaired, and the E_max fell to 23.65±6.0% (p<0.01 vs control
group), which was markedly improved by chronic treatment
with BA (0.8, 4 and 20 mg/kg/d) for two weeks (the E_max
reaching 31.53±4.41%, 36.60±9.16% and 46.47±6.87%). (5)
The increase of ROS level and the decrease of NO level, SOD
and eNOS activities in hypertensive rat aortas were markedly
inhibited by BA.

Conclusion BA decreased blood pressure and improved ACh-
induced EDR in L-NAME-induced hypertension rats, which
may be mediated by reducing oxidative stress and retaining
the bioavailability of NO.