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The drug was provided by Tianjin Zhong wei Pharmaceutical Company Ltd. Blood samples for pharmacokinetic analyses were collected pre-dose and then at 0.17, 0.33, 0.67, 1, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 h after dosing for single dosage groups. For multiple dosage group, on d 5, d 6, and d 7 pre-dose and at 4 h after dosing and on d 8 the times for blood collection were the same as that of single dosage groups. HPLC was used to determine the blood concentration of ibudilast. **RESULTS:** The pharmacokinetic parameters of 5 mg and 10 mg groups were: T_{max} (1.6±1.2) h and (1.6±0.8) h, C_{max} (17±5) µg/L and (25±7) µg/L, AUC (103±24) µg·L⁻¹·h and (144±65) µg·L⁻¹·h, $T_{1/2}$ (5.4±2.1) h and (4.4±2.2) h, respectively. For 20 mg group: T_{max} (3.3±1.6) h, C_{max} (56±22) µg/L, AUC (623±185) µg·L⁻¹·h, $T_{1/2}$ (31±15) h. Following multiple dosing of 10 mg, steady state C_{max} was (45±18) µg/L and steady state C_{min} was (19±9) µg/L, the peak to trough fluctuation index (DF) was 85 %±9 %, and AUC_{ss} (768±340) µg·L⁻¹·h. Following the last dosing of 10 mg, the pharmacokinetic parameters were: T_{max} (2.7±1.6) h, C_{max} (48±21) µg/L, AUC (658±278) µg·L⁻¹·h, and $T_{1/2}$ (33±13) h. **CONCLUSION:** After multiple dosing of 10 mg ibudilast sustained release capsule, the peak to trough blood concentration fluctuation keeps stable, and the recommended dosage is 10 mg twice daily.

S-04 Gastric oxidative stress and hemorrhagic ulcer in *Salmonella typhimurium*-infected rats

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AIM: The infection of *Salmonella typhimurium* (*S typhimurium*) may lead to various organ diseases. This research was to propose that the infection of *S typhimurium* caused gastric oxidative stress and disruption of gastric mucosal barriers, and thus resulted in gastric hemorrhagic ulcer in rats. **METHODS:** Male pathogen-free Wistar rats were deprived of food for 24 h. Single injection of live culture of *S typhimurium* (1×10⁶-1×10⁹ CFU/rat in 1.0 mL of sterilized phosphate buffer saline (PBS) was challenged iv to rat 5 h after withdrawal of food. Age-matched control rats received PBS only. After gastric surgery and vagotomy, rat stomachs were irrigated for 3 h with either normal saline or a simulated rat gastric juice con-

taining HCl 100 mmol/L, pepsin 600 mg/L, and NaCl 54 mmol/L. Gastric parameters, including mucosal glutathione and lipid peroxide generation as well as luminal hemoglobin content and mucosal damage were determined. **RESULTS:** The production of gastric hemorrhagic ulcer and various gastric parameters was dependent on the concentration of *S typhimurium* injected. The maximal response was obtained at the concentration of 1×10⁹ CFU/rat. The presence of luminal gastric juice produced gastric hemorrhagic damage. High relation of ulcer formation to mucosal lipid peroxide generation and glutathione levels was also observed in those *S typhimurium*-infected rats. This exacerbation of ulcerogenic parameters was dose-dependently inhibited by pretreatment of ofloxacin. Pretreatment of antioxidants, such as reduced glutathione, allopurinol and dimethylsulfoxide, also caused amelioration of gastric hemorrhagic damage in *S typhimurium*-infected rats. **CONCLUSION:** Infection of *S typhimurium* may produce gastric hemorrhage and mucosal ulceration via aggravation of gastric oxidative stress that can be effectively ameliorated by antioxidants or antibiotics.

S-05 Effects of prouision on scavenging free radicals

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AIM: To detect the effects of prouision on hydroxyl free radicals and superoxide free radicals *in vitro*. **METHODS:** Prouision, natural porous ore material with some biological functions found in Japan, Japan Patent Application Number: BFC4j (B2002-52397). Prouision-A, B, C (P-A, P-B, P-C), offered by Dr M Hashimoto, were the powders mixed of these porous ore in different proportions (grey powder, d ≤3 µm). The effects of prouision on hydroxyl free radical and superoxide free radicals were determined by the assays of deoxyribose and xanthine oxidase, respectively. Their direct effects on these free radicals were also performed with the Electron spin resonance (ESR). **RESULTS:** 1) IC₅₀ for P-A, P-B, and P-C on scaveng-

ing hydroxyl free radicals by the assay of deoxyribose was 0.2209, 0.2962, and 0.2183 g/L, respectively, the order for their actions was C>A>B. The 95 % confidence limit was 0.0909-0.5367, 0.1302-0.6741 g/L, and 0.0895-0.5322 g/L, respectively. 2) The inhibition produced by P-A, P-B, and P-C at the concentration of 1.4 mg/L on hydroxide free radicals detected by ESR was 35.24 %, 36.92 %, and 55.14 %, respectively. This action was in a dose-dependent manner and the order for their actions was C>B≈A, confirming the results obtained by the assay of deoxyribose. 3) IC₅₀ for P-A, P-B, and P-C on scavenging superoxide free radicals by the assay of xanthine oxidase was 0.4025, 0.3854, and 0.3626 g/L, respectively, the order was C>B>A. The 95 % confidence limit was 0.2065-0.7847, 0.2041-0.7276, and 0.1823-0.7213 g/L, respectively. 4) The inhibition by P-A, P-B, and P-C at the concentration of 0.34 mg/L on superoxide free radicals detected by ESR was 5.99 %, 9.15 %, and 9.15 %, respectively, also confirming the results of xanthine oxidase assay. **CONCLUSION:** Prouson has the properties scavenging hydroxide and superoxide free radicals.

S-06 Steroids modulate placental CRH gene transcriptional activity through cAMP regulatory element

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AIM: To explore the regulation of corticotropin-releasing hormone (CRH) gene expression by steroid hormones in placenta and its molecular mechanism. **METHODS:** Human primary cultured placental trophoblasts were transfected with CRH-luciferase reporter genes and treated with estrogen, progesterone, and their antagonists. **RESULTS:** Estradiol (E2) inhibited basal and cAMP-stimulated CRH promoter activity. A pure estrogen antagonist ICI182, 780 not only blocked repression of CRH gene expression by E2, but up-regulated CRH promoter activity. This effect appeared to occur specifically through ER α -mediated mechanism, as similar effects were found in the ER α over-expression trophoblasts. Through deletion and mutagenesis

analyses we found that estradiol inhibition of the CRH gene required cAMP regulatory element (CRE). Progesterone (P4) treatment resulted in a decrease in CRH promoter activity. Addition of Ru486 or inhibition of endogenous P4 production by placental cells, led to an increase of promoter activity. It was also found that the repression of CRH gene expression by P4 also required CRE. This CRE sequence conferred E2 and P4 inhibitions upon a heterologous promoter (rabbit β -globin). **CONCLUSION:** Estrogen and progesterone play inhibitory roles in the regulation of CRH gene transcription in human placental trophoblasts. These effects occurred through CRE of CRH gene.

S-07 Soluble protein of a novel costimulatory molecule, Dectin-2, breaks ultraviolet B-induced immune tolerance in contact hypersensitivity in mice

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AIM: One of hazardous adverse effects of ultraviolet B light (UV) exposure to skin may be best exemplified with its immunosuppressive property on contact hypersensitivity (CHS) and the subsequent induction of tolerance. Bearing in mind thoughts that artificial break of impaired cutaneous immune response may lead to regain host's immune competence, we focused on a novel costimulatory molecule, Dectin (Dec)-2, shown to be selectively expressed on antigen presenting cells, such as epidermal Langerhans cells (LC). **METHODS & RESULTS:** Mice exposed to low doses of UV and sensitized thereafter with hapten, dinitrofluorobenzene (DNFB) through the exposed skin area showed markedly ameliorated CHS upon resensitization and rechallenge to the same animals. When soluble Dec-2 (sol-Dec2), an inhibitor of cognate Dec-2, was injected iv before resensitization, following rechallenge led to full occurrence of CHS, indicating that sol-Dec2 breaks UV-induced tolerance. This is the first demonstration that functional neutralization of costimulatory molecule restores impaired cutaneous immune response. To fur-

cardiomyocytes. **METHODS:** The supernatant lactate dehydrogenase (LDH), superoxide dismutase (SOD) activity and malondialdehyde (MDA) content were determined in the cultured cardiomyocytes subjected to hypoxia induced by incubation in a 3 % O₂-5 % CO₂ hypoxic atmosphere for 12 h at 37 °C with or without ET-1 pretreatment. [Ca²⁺]_i were measured with Ca²⁺-sensitive fluorescent probe fluo-3/AM under laser scanning confocal microscope. Fluorescence intensity emitted from fluo-3/AM-loaded cells reflected the concentration of [Ca²⁺]_i. The hypoxia model used in [Ca²⁺]_i measurement was established by constant perfusing cardiomyocytes for 30 min with hypoxic DMEM solution containing Na₂S₂O₄ 1mmol/L and equilibrated with 95% N₂-5 % CO₂. Pretreatment with ET-1 consisted of three cycles of ET-1 perfusion (5 min for each) followed by ET-1-free DMEM solution (10 min for each) prior to hypoxia. **RESULTS:** (1) Under pretreatment with ET-1 0.01-1 nmol/L, LDH release and supernatant MDA content were decreased, but SOD activity was enhanced dose-dependently, as compared with the hypoxia group (*P*<0.01). (2) The spontaneous calcium transient in cultured cardiomyocytes was terminated in 30 s, and then [Ca²⁺]_i was increased markedly after perfusion with hypoxic solution. (3) ET-1 0.01-1 nmol/L increased the frequency of [Ca²⁺]_i transient in cultured cardiomyocytes in a dose-dependent manner. The termination of [Ca²⁺]_i transient and the elevation of [Ca²⁺]_i caused by hypoxia were postponed under pretreatment with ET 0.01-1 nmol/L. **CONCLUSION:** Pretreatment with ET-1 0.01-1 nmol/L attenuated hypoxia-induced injury partially due to improving SOD activity, decreasing in MDA production, and inhibiting [Ca²⁺]_i elevation. ET-1 pretreatment possibly protected rather than injured cultured neonatal rat cardiomyocytes under the condition of hypoxia.

P-04 Animal models of rhinorrhea induced by carbamylcholine

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AIM: To set up the rabbit and rat models of rhinorrhea induced by carbamylcholine (Car), a parasympathomimetic agent. **METHODS:** The rhinorrhea animal models induced by Car were produced on rabbit and rat.

The revised method of filter paper strips was used to collect the nasal mucosal secretion and monitor the nasal response. Ipratropium bromide (IB), a typical anticholinergic agent, was used to check the effects on hypersecretion induced by Car. **RESULTS:** 1) Nasal secretion was obviously increased by Car in a dose-dependent manner. Car 86 µg/kg and 30-min challenge were adopted for the rabbit model, and Car 0.64 mg/kg and 30-min challenge were used for the rat model. 2) The rabbit nasal secretory kinetics induced by Car was in a prolonged pattern, quite different from the quick pattern induced by methacholine. The rabbit nasal secretion induced by Car was increased slowly and reached the peak with the amount of (54±32) mg per 2 min at about the 13th min, and then decreased to near the basic level 30 min later. The rat nasal secretory kinetics induced by Car was a little different from that of rabbits, in which it was increased quickly, reached the peak at about the 7th minute with the amount of (8.2±2.7) mg per 2 min, and went back to the basic level after 31 min. 3) IB effectively inhibited the hypersecretion on both rabbit and rat models challenged by Car in a dose-dependent manner. **CONCLUSION:** The rabbit and rat rhinorrhea models were successfully produced by Car. Their nasal secretory kinetics proved to be the prolonged patterns and the nasal hypersecretion induced by Car was obviously inhibited by ipratropium bromide.

P-05 Effects of prousion on rabbit models with high plasma lipid

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AIM: To check the toxicity of prousion-B and detect its effects on the rabbit models with high plasma lipid. **METHODS:** Prousion-B (P-B): one kind of prousion powder (grey powder, d_s≤3 µm) made of natural porous ore found in Japan, Japan Patent Application Number: BFC4j (B2002-52397), offered by Dr M Hashimoto. 1) The acute toxicity of P-B suspended with 0.2 % CMC was performed on the mice of Kunming species. 2) The rabbit models with high plasma lipid

were used to determine the effects of P-B *in vivo*, ie, the rabbits were divided into 6 groups: blank control, model, positive control (nicotinic acid), P-B in different dosage (0.1, 0.2, and 0.4 g/kg). The rabbits were given ig with the above drugs once a day at the same time with high lipid food for 6 weeks. 3) The blood lipid levels were checked in 2 weeks and the blood samples were taken for the examination of some enzyme activities reflecting the heart and liver functions. **RESULTS:** 1) The dosage of P-B in the largest suspension concentration (3 g/kg) did not induce death of the mice, showing that the toxicity of P-B was low. 2) Although there was no significant difference between the rabbit groups given with P-B and the control in statistics, P-B showed a tendency to decrease blood total cholesterol (TC), low-density lipoprotein (LDL), and apolipoprotein B (apB) levels in the rabbits. 3) P-B obviously inhibited the increase of total creatine kinase (TCK) activity and glutamic-pyruvic transaminase (GPT) and glutamic-oxaloacetic transaminase (GOT) levels induced by high plasma lipids in the rabbit models, reflecting that P-B had certain protective functions on the rabbit model with high plasma lipid. 4) P-B showed no obvious effects on kidney function, blood electrolyte levels, and erythrocyte index in rabbit models. **CONCLUSION:** Prouson-B had certain protective functions on the rabbit model with high plasma lipid.

P-06 Role of the caudal ventrolateral medulla I₁-imidazoline receptors in controlling the cardiovascular activities

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AIM: Many papers showed that the I₁-imidazoline receptors within the center nerve system played an important role in controlling the cardiovascular activities. The purpose of the present study was to explore the possible role of I₁-imidazoline receptors within the caudal ventrolateral medulla (CVLM) in regulation of cardiovascular activities in anesthetized rats. **METHODS and RESULTS:** Unilateral microinjection of 2 nmol of idazoxan, a mixed antagonist of I₁-imidazoline receptors and α_2 -adrenoceptors, into the CVLM significantly ($P < 0.01$) decreased blood pressure (BP), heart rate (HR), and the firing rate of presympathetic neurons in

the rostral ventrolateral medulla (RVLM). Moreover, the CVLM unilateral injection of idazoxan significantly ($P < 0.01$) reduced the inhibitory responses of the ipsilateral RVLM presympathetic neurons evoked by stimulation of aortic nerve and elevation of BP, and partially inhibited the neuronal cardiac cycle-related rhythm. Depressor responses evoked by aortic nerve stimulation were significantly ($P < 0.01$) attenuated 10 and 20 min after bilateral microinjection of idazoxan 2 nmol (each side) into the CVLM. However, injection of 500 pmol of yohimbine, a selective α_2 -adrenoceptor antagonist, into the CVLM did not affect the resting cardiovascular activities and baroreceptor reflex. **CONCLUSION:** the CVLM I₁-imidazoline receptors played an important role in tonic and reflex control of peripheral cardiovascular activities.

P-07 Stimulating endothelin synthesis and secretion of rat aorta by rat urotensin II

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AIM: To investigate the effect and signal transduction pathways of urotensin II (UII) on endothelin production in cultured aortic tissues of rat. **METHODS:** Aortic slices were incubated with different concentration of UII. Contents of endothelin (ET) both in medium and tissues were measured with radioimmunal assay. Different inhibitors were added to the medium to study the roles of different signal transduction pathways in the stimulating effect of UII on production of ET. **RESULTS:** UII significantly stimulated ET secretion (ET in medium) and production (ET both in medium and tissues) from rat aortic slices. After 3-h incubation, ET production (including secretion) were increased significantly in 10 nmol/L of UII group than control group (pg/mg, wet weight: 4.5 ± 0.7 vs 1.83 ± 0.20 , $P < 0.01$). After 6 h incubation, it was shown that UII induced ET secretion and production in a time and concentration-dependent manner, which were increased by 59.2 %, 108.0 %, 159.6 %, and 178.0 % in secretion ($P < 0.01$), and 40.6 %, 68.4 %, 103.1 %, 105.7 % in production (P