Effects of ginsenosides on sympathetic neurotransmitter release in pithed rats[1]

ZHANG Feng-Luan, CHEN Xiu

(Dept Pharmacology, Hunan Medical College, Changsha 410008)

ABSTRACT In order to elucidate the mechanism of biphasic action of ginsenosides (G) on blood pressure, the effects of G on the sympathetic neurotransmitter release was examined in pithed rats. G 30 mg/kg iv did not affect the pressor response of exogenous NE. However, G significantly attenuated the pressor action of NE released by electric stimulation on spinal T_{7-13}. Since yohimbine is a selective prejunctional α_2-receptor blocker, it inhibits the presynaptic negative feedback on NE release. It was demonstrated that yohimbine 0.05 mg/kg iv augmented the pressor response of spinal electric stimulation, and G blunted significantly the augmentation. It is proposed that G serves as a presynaptic α_2-receptor agonist, and its hypotensive effect is attributed to the reduction of transmitter release of sympathetic nerves. Its hypertensive effect is explained as a result of less selective action on postsynaptic α_1-and possibly α_2-receptors in vascular muscles.

KEY WORDS blood pressure; electric stimulation; ginsenosides; norepinephrine; pithed rats; spinal cord; yohimbine

Ginsenosides (G) produced a biphasic action on blood pressure in dogs and rats[1]. This was explained by different responses of contraction and relaxation in different blood vessels[2]. However, drug effects on blood pressure can also be mediated by affecting neurotransmitter release. The purpose of the present study is to elucidate the mechanism of the biphasic action of G based on the possibility of action on presynaptic regulation of adrenergic neurotransmitter release in pithed rats.

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MATERIALS AND METHODS

Experimental procedure Male rats (214 ±SD 22 g), under ether anesthesia and artificial respiration, were pithed via the orbit with a metal rod with a partially noninsulated tip as an active electrode coupled with an indifferent electrode inserted subcutaneously to one leg, to deliver sympathetic stimulation on spinal T_{7-13} and to elicite selective pressor response[3]. The parameters of electric stimulations were: 60 V, wave width 0.4 ms, frequency 1.2, 2.4, 4.8, 9.6 and 19.2 Hz, produced by square wave stimulator (Type YSD-4, Bangbu Electronic Inc)

Experimental design In the 1st experiment effect of G on the pressor response of exogenous NE was observed. 14 pithed rats were equally and randomly allocated into 2 groups. Effects of G 30 mg/kg iv on the pressor responses of iv NE (0.5, 1, 2, 4, 8 μg/kg) were observed, and compared with normal saline (control group) on the pressor response of NE.

In the 2nd experiment, effects of iv G 30 mg/kg (n = 7) on the pressor response induced by electric stimulation for 15 s on the spinal sympathetic nerves were compared with saline control group (n = 6).

The 3rd experiment was designed to examine G effect on the yohimbine-induced pressor response via negative feedback blockade. The difference of pressor responses (ΔBP) elicited by electric spinal stimulation before and after yohimbine 0.05 μg/kg iv

was compared between G 30 mg/kg and normal saline iv (5 rats/group) 10 min before yohimbine.

Group comparisons by *t* test were calculated to estimate the differences between action of G and normal saline.

Chemicals Ginsenosides were extracted[4] from *Panax ginseng* C A Meyer. Yohimbine and norepinephrine were purchased from Sigma.

RESULTS

Effect of G on the pressor responses of NE As shown in Fig 1, the pressor actions of NE in different doses were dose-dependent and there was no significant difference between G and saline. This suggests that the pressor responses of exogenous NE are not affected by G.

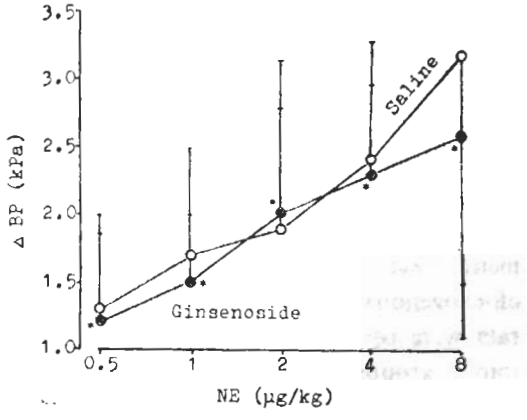

Fig 1. Effect of ginsenosides on pressor response of iv norepinephrine. n=7, $\bar{x}\pm$SD. *p>0.05

Effect of G on the pressor responses to spinal sympathetic stimulation As shown in Fig 2, the pressor responses (ΔBP) by all different frequencies of electric stimulation were not significantly affected by normal saline ($p>0.05$). While G attenuated significantly the pressor responses of spinal sympathetic stimulation ($p<0.05$ or $p<0.01$ in most frequencies of stimulation), and the ΔBP became more negative as the frequencies of stimulation increased. These findings suggest that the pressor responses to sympathetic transmitter release induced by spinal electric stimulation are significantly inhibited by G.

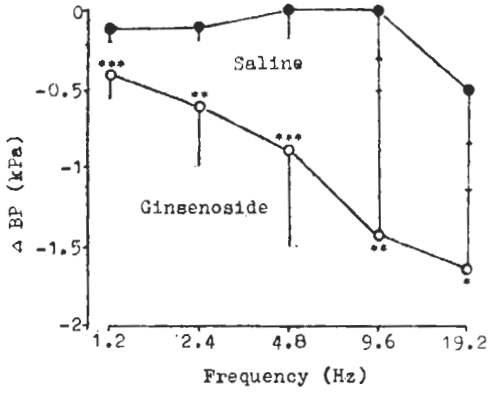

Fig 2. Effect of ginsenosides on pressor response induced by spinal electrical stimulation in pithed rats. $\bar{x}\pm$SD. *p>0.05, **p<0.05, ***p<0.01

Effect of G on yohimbine induced pressor response As shown in Fig 3, yohimbine 0.05 μg/kg enhanced the pressor responses (ΔBP) of electric stimulation at 2.4, 4.8, and 9.6 Hz to 0.4 ± 0.6, 0.3 ± 1.0 and 0.5 ± 1.0 kPa, respectively, via blocking the negative feedback initiated by presynaptic α_2-receptor. Pretreatment by G reversed the pressor potentiation action on

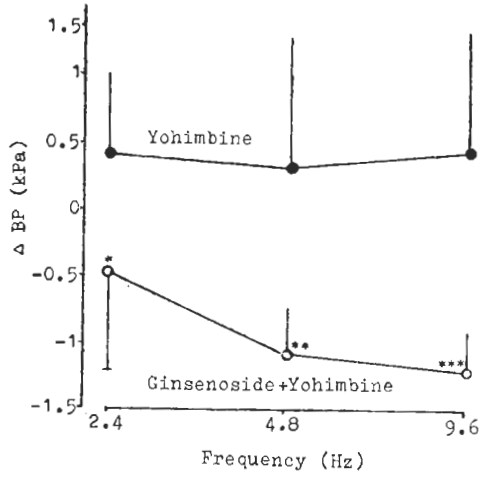

Fig 3. Effect of ginsenosides on pressor response of sympathetic stimulation enhanced by yohimbine. n=5, $\bar{x}\pm$SD. *p>0.05, **p<0.05, ***p<0.01

ΔBP to -1.0 ± 0.4 ($p<0.05$) and -1.2 ± 0.3 ($p<0.01$) kPa by 4.8 and 9.6 Hz, respectively. These data indicate that G can antagonize the blocking action of yohimbine on presynaptic negative feedback regulation of blood pressure.

DISCUSSION

The present experiment showed that pressor responses on exogenous NE were not affected by G in pithed rats. However, pressor responses to sympathetic stimulation were reduced significantly by G. This indicates that G neither antagonizes directly the effect of NE, nor blocks post-junctional α_1-receptors. It has been well documented that yohimbine[5], as α_2-receptor blocker, blocks selectively prejunctional α_2-receptors and inhibits negative feedback loop and thus expresses as increasing the pressor responses induced by electronic stimulation.

In our experimental condition, iv yohimbine 0.05 mg/kg augmented the pressor responses of spinal electronic stimulation at 4.8 and 9.6 Hz, whereas G blunted significantly the augmentation. It is concluded that G may serve as a presynaptic α_2-receptor agonist and its hypotensive effect may be attributed to the reduction of transmitter release of sympathetic nerves. The transient hypertensive component of biphasic effect of G is explained as a result of less selective action on postsynaptic α_1-receptors in vascular muscles. The α_2-receptors in the vascular muscles can be reactivated by catecholamine in the circulation and can produce pressor response[6]. It is speculated that G may also stimulate the postsynaptic α_2-receptor and produce hypertensive action.

Our experiment may bring some clues to clarify the experience of traditional Chinese medicine considering *Panax ginseng* possesses modulating action on blood pressure: increases blood pressure in hypotensive state and lowers blood pressure in hypertension.

The present experiment proposes a new idea that G may stimulate presynaptic α_2-receptor supported by its antagonistic action on the pressor effect of yohimbine.

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人参皂甙对破坏脊髓大鼠交感神经递质释放的作用[1]

张凤鸾、陈　修　（湖南医学院药理教研室，长沙 410008）

提要　破坏脊髓大鼠实验显示，iv 人参皂甙 30 mg/kg，不影响外源性去甲肾上腺素(NE)的升压反应，但显著减弱电刺激胸段的升压反应，又能拮抗突触前膜 α_2 受体阻滞剂育亨宾加强电刺激引起的升压反应．结果表明，人参皂甙的降压作用不是直接对抗 NE 的作用，可能是通过兴奋突触前膜 α_2 受体减少交感神经递质释放．

关键词　血压；　电刺激；　人参 皂甙；　去甲肾上腺素；　损毁脊髓大鼠；　脊髓；　育亨宾

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