

18b-glycyrrhetic acid increases blood pressure in rats through the action on myoendothelial gap junctions

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18b-glycyrrhetic acid (GA), a pentacyclic triterpenoid found in the roots of licorice plants (Glycyrrhiza glabra), possesses high biological activity, including anti-inflammatory and antimicrobial properties. Additionally, it effectively blocks myoendothelial gap junctions. Our experiments on adult Wistar rats have shown that GA administration via gavage in the dose 0.015 g per 100 g of body weight caused a significant increase in arterial blood pressure measured both invasively and non-invasively as early as on the 7th day after beginning of the treatment. Further administration of GA up to 21 days did not change blood pressure significantly. Thoracic aortic rings obtained from GA-treated animals demonstrated a decreased ability to relax in response to acetylcholine (ACh): the maximal dilatory response and the sensitivity of the vascular preparations to ACh measured as pD_2 ($-\log EC_{50}$) were significantly suppressed compared to the relaxant responses of rings from untreated rats. GA externally applied to intact tissues at a concentration of 2×10^{-5} M inhibited the ACh-induced relaxation. The inhibition was more pronounced than that observed in vascular rings obtained from the GA-treated animals. Nevertheless, it was smaller than that observed under combined action of the nitric oxide synthase inhibitor, L-NAME, and indomethacin, indicating that GA affects preferentially EDHF-dependent component of the ACh-induced relaxation. These results may suggest that damage of myoendothelial gap junctions that provide electrical communication between the endothelium and the smooth muscle layers may, at least partially, cause the development of arterial hypertension under GA treatment.

Key words: 18b-glycyrrhetic acid; myoendothelial gap junctions; NO; EDHF; arterial hypertension.

INTRODUCTION

Over the centuries, licorice root has been widely used as a food ingredient and even as a component in drug therapy. The development of arterial hypertension under the influence of licorice was first described in 1953 [1]. During the last years, new experimental and clinical data indicate that excessive use of licorice leads to the development of arterial hypertension [2–11]. It is clear now that consumption of licorice (liquorice) can lead to dangerously high blood pressure and low potassium levels (hypokalemia).

To create an experimental model of arterial hypertension, for many years we have used *in vivo* treatment with glycyrrhetic acid, the active component in licorice. Until now, we

could not find a clear explanation of the cellular mechanisms for this phenomenon, except that proposed elsewhere [12], where it was suggested that an excess of licorice leads to development of pseudohyperaldosteronism due to glycyrrhizin binding to the mineralocorticoid receptor, since glycyrrhetic acid has structural similarity to aldosterone.

This point of view undoubtedly has a right to exist. Nevertheless, we would like to test a hypothesis suggesting other cellular mechanisms that determine the development of hypertension with the consumption of active ingredients of licorice root, based on modern concepts of myoendothelial relations in the vascular wall.

It is well known that vascular endothelial cells play an important role in the control of vascular tone. Nitric oxide (NO) is a vasoactive

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mediator released from endothelial cells and it is an important component in the regulation of vascular tone by inhibiting vascular smooth muscle contraction. It has been also found that direct connections exist between smooth muscle cells and endothelial cells. These connections, called gap junction, allow various signal molecules, ions and electrical impulses to directly pass between the cells [13–17]. The myoendothelial gap junctions provide an electrical communication between endothelial and smooth muscle cells, and may be involved in endothelium-dependent vasorelaxation mechanisms associated with the release of endothelium-derived hyperpolarizing factor (EDHF) [18].

The important role of gap junctions in cellular functions was confirmed in experiments with heptanol, octanol or halotane – gap junction blockers in cardiac muscle [19]. It has also been shown that 18b-glycyrrhetic acids (GA) is an effective blocker of gap junctions in guinea-pig mesenteric arterioles [15].

Our previous studies demonstrated that gap junctions are a critical point of signaling pathways involved in Rho kinase-dependent Ca^{2+} sensitization during sustained hypoxic pulmonary vasoconstriction [16].

Licorice roots (*Glycyrriza glabra* L.) and its products, in turn, are often used in therapy as anti-inflammatory, antispasmodic, antibacterial and expectorant drugs. Since GA is one of its physiologically active components, it may cause some unwanted side effects.

The aim of present study was to estimate possible effect of GA on the vascular tone and blood pressure level in the laboratory animals, as well as to identify the mechanisms underlying the side effects under GA treatment.

METHODS

All experimental procedures followed the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (Strasbourg, 1986)

and approved by the local Bioethics Committee of the SI “Institute of Pharmacology and Toxicology National Academy of Medical Sciences of Ukraine” (Kyiv, Ukraine). The experiments were performed on 17 adult Wistar rats weighing 240 ± 10 g. Animals were divided into 2 groups: control and experimental. 18 β -glycyrrhetic acid as 3% water suspension was administered via gavage, in dose 0.015 g per 100 g of body weight (b.w.) once a day for 21 days. The control animals received distilled water, 0.5 ml/100 g b.w.

Systolic blood pressure (BPs) was measured using rat tail sphygmomanometer S-2 (HSE, Germany) just before administration of the tested substance and on the 7th, 14th and 21st day of the treatment. After 21st day of the GA treatment, the animals were anesthetized with ketamine/xylazine (1 ml/kg b.w.) and surgical preparations consisted in tracheotomy and catheterization of carotid artery was made. BP measurements were performed with the module DBA Type 660 (“HSE”, Germany) using polygraph RB-85 (“Nihon Kohden”, Japan) and Isotec transducer (“HSE”, Germany). The data were digitized with an analog-to-digital converter (ADC; “HSE”, Germany), accumulated and further processed using the Haemodyn software (“HSE”, Germany).

To estimate the endothelium-dependent responses in isolated aortic rings, endothelium-dependent vasodilator, acetylcholine (ACh) was used at concentrations 10^{-9} – 10^{-5} M.

Experiments were performed on ring preparations (1 mm wide) isolated from rat thoracic aorta. Aortas were obtained from rats sacrificed by cervical dislocation after anesthesia with ketamine/xylazine (1 ml/kg b.w.). The rings were prepared with care to avoid damage to the endothelial layer. Aortic rings were mounted isometrically under a resting tension of 10 mN in a flowing tissue bath, between a stationary stainless steel hook and an isometric force transducer (AE 801, SensoNor A/S, Norten, Norway) coupled to an AD converter Lab-Trax-4/16 (“World Precision Instruments, Inc.”,

USA). Vascular rings were maintained at 37°C and superfused continuously at a rate of 2 ml/min with modified Krebs-bicarbonate buffer solution (see Chemicals and Solutions). They were allowed to equilibrate for 1 h under resting tension of 3 g before starting the experiments. All experiments were carried out in the presence of indomethacin (10^{-5} M) to exclude any possible involvement of prostacyclin in the endothelium-dependent relaxation response to ACh.

Chemicals and solutions. All chemicals were obtained from “Sigma” (USA). Experiments with isolated vascular preparations were performed at 37°C in modified Krebs-bicarbonate buffer solution of the following composition (in mM): NaCl - 133; KCl - 4.7; NaHCO₃ - 16.3; NaH₂PO₄ - 1.38; CaCl₂ - 2.5; MgCl₂ - 1.2; glucose - 7.8; pH 7.4.

Statistical analysis. All data are mean \pm s.e.m; *n* indicates blood pressure measurements or the number of preparations tested. Curves were fitted to Hill equation. Half-maximal effective concentration (EC₅₀) values were expressed as pD₂ ($-\log EC_{50}$, where EC₅₀ is half-maximum effective concentration). The distribution normality was evaluated with Shapiro-Wilk test. EC₅₀ values and maximal relaxation were compared by the Student’s *t*-test for unpaired data. Comparison of variables obtained by different treatments with basic values were made by one-way ANOVA with a repeated measurements design, and if any significant difference was found, the Scheffe’s multiple comparison test was applied. Data were statistically analyzed with MS Excel (“Microsoft”, USA) and Origin 9.7 (“OriginLab Corp.”, USA).

RESULTS AND DISCUSSION

In vivo experiments. Systolic blood pressure measured by a non-invasive method in animals treated with GA (day 21) increased significantly on the 7th day and reached its maximum values on the 21st day of GA administration (Tables 1).

Measurements of systolic and diastolic

pressure in the acute experiment showed higher values of blood pressure increase compared to the non-invasive method (Table 2).

Blood pressure measurements in anesthetized and awake rats clearly indicate that GA administration promoted an increase in both systolic and diastolic blood pressure. Systolic and diastolic blood pressure in GA-treated animals on the 21st day of the treatment was 28% and 33% higher, respectively, compared to control animals. It is important to note that blood pressure levels in the control group of animals did not change significantly throughout the experimental period (up to the 21st day).

In vitro contractile recordings experiments. Experiments using aortic rings obtained from rats chronically treated with GA. Initially, we examined the responses to ACh in the thoracic aortic rings isolated from rats subjected to chronic oral GA administration. Aortic rings isolated from GA-treated animals demonstrated an impaired endothelial-dependent relaxation to ACh. As shown in Fig. 1, ACh at concentration 10^{-9} – 10^{-5} M caused well expressed dose-dependent relaxation after phenylephrine (PhE, 10^{-6} M) induced contraction in thoracic rings isolated from intact animals. Aortic rings obtained from the GA-treated animals demonstrated a significant reduction in endothelial-dependent relaxation to ACh compared to the control rings. The amplitude of maximal relaxation responses to ACh (10^{-5} M) decreased from $90.3 \pm 2.1\%$ in control rings to $60.5 \pm 5.1\%$ in rings obtained

Table 1. Dynamics of systolic blood pressure (BPs) measured non-invasively in rats following the course of 18 β -glycyrrhetic acid administration ($M \pm m$, $n = 9$)

| Treatment duration | Relative changes in BPs (mm Hg) |
|--------------------|---------------------------------|
| Initial level | 119.0 \pm 2.2 |
| 7 days | 138.0 \pm 5.3* |
| 14 days | 132.5 \pm 2.2* |
| 21 days | 136.7 \pm 3.8* |

Note: *The data statistically differ from the initial level, $P < 0.01$.

Table 2. Effect of the 3 weeks course of 18 β -glycyrrhetic acid administration on systolic and diastolic blood pressure measured invasively in rats (M \pm m)

| Treatment | BP (mm Hg) | | |
|-------------------------|-------------------|------------------|--------------------|
| | Systolic | diastolic | mean |
| Control group (n = 8) | 138.0 \pm 4.4 | 89.8 \pm 7.1 | 105.9 \pm 7.2 |
| GA-treated rats (n = 9) | 176.9 \pm 10.0* | 119.5 \pm 8.9* | 143.7 \pm 10.2** |

Note: *The data statistically differ from the control group, $P < 0.01$. **The data statistically differ from the control group, $P < 0.05$.

from GA-treated rats ($P < 0.01$, $n = 14$). The pD_2 for control and experimental groups were also significantly different (-7.8 ± 0.14) and (-7.3 ± 0.06), ($P < 0.05$, $n = 14$), respectively, supporting that sensitivity of vascular tissues to ACh had significantly decreased following GA treatment.

Nitric oxide synthase inhibitor, L-N^o-nitroarginine methyl ester (L-NAME, 3×10^{-4} M) additionally suppressed ACh-induced relaxation up to $12 \pm 1.3\%$ of the maximal amplitude of contraction evoked by PhE ($P < 0.01$, $n = 14$).

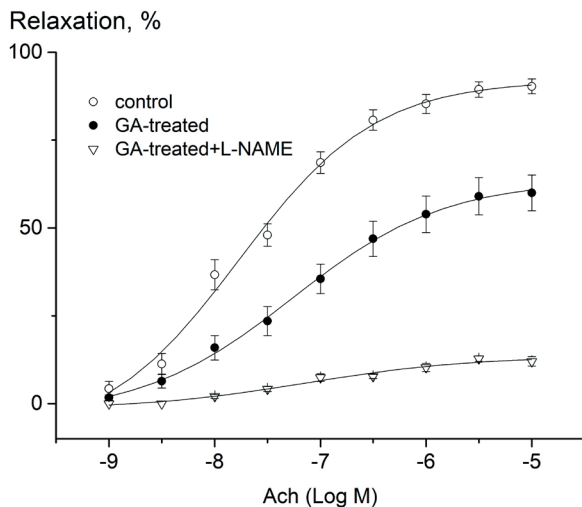


Fig. 1. Cumulative concentration-response curves to acetylcholine obtained in aortic rings from GA-treated rats: \circ – intact preparations; \bullet – vascular rings obtained from the rats treated with GA (18b-glycyrrhetic acid, 0.015g per 100 g b.w.) for 21 days; ∇ – rings obtained from GA-treated rats and incubated in the presence of N-nitro-L-arginine methyl ester (L-NAME, 3×10^{-4} M). All rings were pre-contracted with phenylephrine (10^{-6} M). Results are expressed in percent of the contraction evoked by phenylephrine. All experiments were performed in the presence of indomethacin (10^{-5} M). Concentration-response curves were fitted by the Hill equation

Experiments using intact tissues with direct addition of GA to the organ bath. To clarify the GA effect further, we performed the experiments with intact vascular tissues. GA at a concentration 2×10^{-5} M, being added to the organ bath directly for 7 min before ACh application, caused a prominent inhibition of the response to ACh in control rat rings (from 90.3 ± 2.1 to $45.9 \pm 2.8\%$ of maximal ACh-induced relaxation in contraction caused by PhE, $n = 14$, Fig. 2).

L-NAME (3×10^{-4} M) decreased the relaxant response to ACh up to $18.9 \pm 0.5\%$, but did

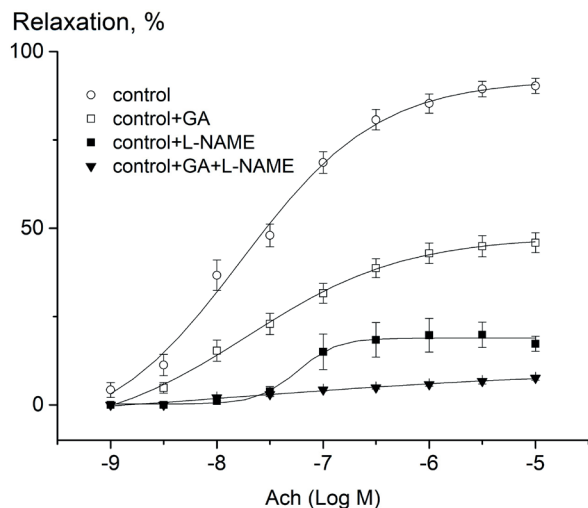


Fig. 2. Cumulative concentration-response curves to acetylcholine performed on intact aortic ring from healthy rats obtained before (\circ) and after 7 min of GA application (\square); GA plus L-NAME (\blacktriangledown) and L-NAME alone (\blacksquare). All rings were pre-contracted with phenylephrine (10^{-6} M). Results are expressed in percent of the contraction evoked by phenylephrine. All experiments were performed in the presence of indomethacin (10^{-5} M). Concentration-response curves were fitted by the Hill equation

not cause a complete block of ACh-induced relaxation in intact aortic rings, suggesting a significant endothelium-derived hyperpolarizing factor (EDHF)-mediated component. The addition of L-NAME (3×10^{-4} M) in combination with GA (2×10^{-5} M) to the bath solution dramatically reduced endothelium-dependent relaxation of rings obtained from healthy animals (from 90.3 ± 2.1 to $7.6 \pm 0.6\%$ of maximal relaxation amplitude to ACh, $n = 14$).

It is interesting to note that the similar effects of L-NAME were observed in tissues obtained from GA-treated animals (Fig. 1).

The endothelium-dependent vascular responses in hypertension are well known to be markedly depressed in both animals and humans [20–23]. The main finding of present study is that orally administered GA or drugs that contain this active compound in a sizable concentration may lead to unwanted vascular malfunction and development of arterial hypertension. To shed light on possible mechanisms of GA side effects, we have compared the effects of GA on endothelium-dependent vascular responses in intact tissues and in tissues isolated from GA-treated animals.

It is known that the ACh-induced relaxation of blood vessels can be attributed to the release of three main components: endothelium-derived relaxing factor (EDRF/NO), prostacyclin and endothelium-derived hyperpolarizing factor (EDHF). It is generally accepted that these components can be separated in experiment using nitric oxide synthase blockers (e. g., L-NAME) and inhibitors of prostacyclin synthesis, such as indomethacin.

We performed experiments that evaluated of ACh-induced endothelium-dependent responses using isolated vascular preparations. It is important to note that indomethacin was present in all isolated tissue experiments to block prostacyclin production.

It has been shown that at least in some vascular beds the EDHF phenomenon is accounted by transmission of a hyperpolarizing electrical signal from the endothelium to

the underlying smooth muscle cells through intercellular gap junction [17, 18, 24]. We suppose that GA affects mainly the mechanisms associated with the transmission of EDHF signal from the endothelium to the underlying smooth muscles.

Our results showed that L-NAME plus indomethacin reduced the amplitude of ACh-induced relaxation in intact aortic tissues by about 80%, indicating rather small degree of expression of the EDHF component in ACh-induced relaxation in the aortas from healthy rats. At the same time, the maximum amplitude of ACh relaxation in the aorta of GA-treated rats was reduced by about 30%. This indicates that GA can act on the regulatory mechanisms of vascular tone not only through the pathway associated with the EDHF component, but also partially (by about 10%) through the EDRF/NO component. Thus, the studies with L-NAME applied on intact and GA-treated vascular preparations suggest that GA selectively inhibits stable EDHF-dependent component of ACh-induced vascular relaxations, while the NO-dependent component of relaxation is less affected.

The addition of GA to the organ bath with intact aortic preparations decreased the relaxation amplitude more strongly compared to the effect achieved following chronic in vivo GA-treatment. Therefore, GA may be considered as an inhibitor of EDHF signal propagation as a result of uncoupling of the connection between the endothelium and smooth muscle cell layers in the vascular wall [25]. It is likely that long-term GA administration resulted in inhibition of both EDHF (preferentially) and EDRF/NO component (in a lesser degree) of ACh-induced dilatation, leading to development of endothelial dysfunction that, in turn, causes an increase in arterial blood pressure level.

Our results indicated that EDHF-dependent component of ACh-stimulated relaxation of rat thoracic aorta is relatively small and averages about 20% of the total dilator response. However, it is an important mechanism for

normal vascular function. In particular, EDHF is a rather stable component of ACh-induced relaxation under oxidative stress since g-radiation selectively inhibits the NO-dependent pathway, while EDHF-dependent component of the relaxation remains resistant and maintains low endothelium-dependent responses [26]. Interestingly, non-invasive measurement of systolic blood pressure in irradiated (6 Gy) rats showed that on the 9th day of the post-irradiation period, blood pressure also increased significantly due to dysfunction of endothelial-dependent mechanisms of vascular tone regulation [27].

CONCLUSIONS

Our results suggest that a significant increase in blood pressure in rats treated with 18 β -glycyrrhetic acid could be caused by a disruption of electrical connection between endothelial and smooth muscle layers in the vascular wall, specifically damage to myoendothelial gap junctions that leads to the development of unwanted blood pressure.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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18 β -ГЛИЦИРРЕТИНОВА КИСЛОТА ПІДВИЩУЄ ТИСК КРОВІ У ЩУРІВ, ВПЛИВАЮЧИ НА МІОЕНДОТЕЛІАЛЬНІ КОНТАКТИ

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18 β -глицирретинова кислота (GA) – пентациклічний три-терпеноїд, що міститься в коренях солодки (*Glycyrrhiza glabra*), має високу біологічну активність, включаючи протизапальну та протимікробну дію, а також здатність блокувати міоендоделіальні контакти. Наші експерименти

на дорослих щурах лінії Вістар показали, що внутрішньошлункове введення раз на добу GA в дозі 0,015 г на 100 г маси тіла спричинює значне підвищення артеріального тиску, вимірюваного неінвазивно з 119,0 \pm 2,2 до 138,0 \pm 5,3 мм рт. ст. вже на 7-й день після початку курсу. Подальше її введення до 21-го дня не призводило до істотних змін цього показника. Кільця грудної аорти тварин, які отримували GA, демонстрували знижену здатність розслаблюватись у відповідь на дію ацетилхоліну. Максимальна дилатаційна реакція і чутливість судинних препаратів до ацетилхоліну, виражена як pD₂ (-log EC₅₀), були значно пригнічені (60,5 \pm 5,1% і 7,3 \pm 0,06) порівняно з відповіддю на релаксанти тканин інтактних тварин (90,3 \pm 2,1% та -7,8 \pm 0,14) відповідно. GA при застосуванні для інкубації тканин інтактних щурів у концентрації 2 \cdot 10⁻⁵ ммоль/л пригнічувала індуковану ацетилхоліном релаксацію більшою мірою, ніж це спостерігалось на кільцях судин тварин, які отримували лише GA. Однак таке зменшення було менш вираженим, ніж за умов дії інгібітора синтази оксиду азоту L-NAME та індометацину. Це вказує на те, що GA впливає переважно на EDHF-залежний компонент релаксації, викликаной дією ацетилхоліну. Наші результати вказують на те, що пошкодження міоендоделіальних щілинних контактів, які забезпечують електричний зв'язок між ендотелієм і шаром гладеньких м'язів, може, принаймні частково, брати участь у розвитку артеріальної гіпертензії, викликаной введенням GA.

Ключові слова: 18 β -глицирретинова кислота; міоендоделіальні контакти; NO; EDHF; артеріальна гіпертензія.

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18 β -ГЛИЦИРРЕТИНОВАЯ КИСЛОТА ПОВЫШАЕТ ДАВЛЕНИЕ КРОВИ У КРЫС, ДЕЙСТВУЯ НА МИОЭНДОТЕЛИАЛЬНЫЕ КОНТАКТЫ

18 β -глицирретинова кислота (GA) – пентациклічний три-терпеноїд, що міститься в корнях солодки (*Glycyrrhiza glabra*), має високу біологічну активність, включаючи протизапальну та протимікробну дію, а також здатність блокувати міоендоделіальні контакти. Наші експерименти на дорослих щурах лінії Вістар показали, що внутрішньошлункове введення один раз в сутки GA в дозі 0,015 г на 100 г маси тіла викликало значительное підвищення артеріального тиску, вимірюваного неінвазивним методом з 119,0 \pm 2,2 до 138,0 \pm 5,3 мм рт. ст. уже на 7-й день після початку курсу. Подальше її введення до 21-го дня експеримента не приводило до суттєвих змін цього показника. Кільця грудної аорти тварин, які отримували GA, демонстрували знижену здатність розслаблюватись у відповідь на дію ацетилхоліну. Максимальна дилатаційна реакція і чутливість судинних препаратів до ацетилхоліну, виражена як

pD_2 ($-\log EC_{50}$), были значительно подавлены ($60,5 \pm 5,1\%$ и $7,3 \pm 0,06$) по сравнению с ответом на релаксант тканей интактных животных ($90,3 \pm 2,1\%$ и $-7,8 \pm 0,14$) соответственно. GA при использовании для инкубации тканей здоровых крыс в концентрации $2 \cdot 10^{-5}$ ммоль/л подавляла индуцированную ацетилхолином релаксацию в большей степени, чем это наблюдалось на кольцах сосудов животных, получавших только GA. Однако это подавление было менее выраженным, чем при действии ингибитора синтазы оксида азота L-NAME и индометацина, что указывает на преимущественное влияние GA на EDHF-зависимый компонент релаксации, вызванной ацетилхолином. Наши результаты могут указывать на то, что повреждения миоэндотелиальных щелевых контактов, обеспечивающих электрическую связь между эндотелием и слоем гладких мышц, по крайней мере, частично, вовлечены в развитие артериальной гипертензии под влиянием GA.

Ключевые слова: 18β -глицирретиновая кислота; миоэндотелиальные контакты; NO; EDHF; артериальная гипертензия.

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Received 04.06.2021