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Original Article

The features of reserpine-induced gastric mucosal lesions

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Aim: To reinvestigate the characteristics of reserpine-induced gastric mucosal lesions (GMLs).
Methods: The GML-inducing effect of reserpine and the time-course of recovery from reserpine-induced GMLs were examined in Sprague-Dawley (SD) rats. The GML-inducing and blood pressure-decreasing effects of Compound Hypotensive Tablets (CHTs) were investigated in spontaneously hypertensive rats (SHRs). Intracerebroventricular (icv) injection and vagotomy were performed to verify the central vagal mechanism in reserpine-induced GMLs.
Results: Single intraperitoneal (ip) injections of reserpine (0.25, 0.5, 1, 2, 4, and 6 mg/kg) dose-dependently induced GMLs in SD rats. Both single and repeated (2 weeks) oral administrations of reserpine led to slight GMLs at doses of 24 mg/kg and 10 mg/kg, respectively. Blood pressure was significantly decreased in SHRs after 2 months of CHT administration (0.01 and 0.03 mg/kg; doses were expressed as the amount of reserpine in the CHT). CHT doses of 0.3 mg/kg induced GMLs, but 0.1 mg/kg did not. Examining the time course of recovery from GMLs, severe GMLs occurred 18 h after ip reserpine (4 mg/kg), obviously lessened at 1 week and healed spontaneously at 3 weeks. Intracerebroventricular injections of reserpine caused GMLs at much lower doses (0.08 and 0.4 mg/kg), and reserpine-induced GMLs were greatly inhibited by vagotomy, suggesting the involvement of a central vagal mechanism.
Conclusion: Reserpine-induced GMLs were dose-dependent, and the lesions healed spontaneously within 3 weeks. Long-term treatment with CHT at doses adequate to decrease blood pressure will not induce GMLs. A central vagal mechanism was involved in reserpine-induced GMLs.

Keywords: reserpine; gastric mucosal lesions; vagotomy; time course of recovery from gastric lesions; compound hypotensive tablets

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Introduction

Hypertension is one of the major risk factors for the leading causes of death in adult populations worldwide. If not properly treated, hypertension can lead to stroke, heart attack, heart failure and kidney disease[1–5]. Hypertension often requires lifelong treatment with one or more antihypertensive medications. Treatment with medication for hypertension can reduce the incidence of stroke (by about 35%–40%), heart attack (by 20%–25%), and heart failure (by more than 50%)[6].

Sixty years ago, people suffered from hypertension because of a lack of antihypertensive drugs. Reserpine, first isolated from the root of the medicinal plant *Rauvolfia serpentina* in 1952, revolutionized the treatment of hypertension. In the following two decades, reserpine was used extensively to manage hypertension[7, 8]. However, overdose and long-term use of reserpine can produce adverse effects, such as gastric mucosal lesions (GMLs), depression and sexual dysfunction[9–11]. These side effects restricted its clinical use. At present, reserpine is not the first-line antihypertensive drug and is seldom used alone. However, many antihypertensive compounds containing reserpine, such as Compound Hypotensive Tablets (CHTs) and Compound Reserpine Tablets are still widely used in China because of their effectiveness and low cost. The doses of reserpine used in the antihypertensive compounds are very low compared with the doses of reserpine that were used 40 years ago. Therefore, it is necessary to re-evaluate the side effects of different doses of reserpine. The present work focused mainly on the GMLs induced by reserpine and CHT.

It is considered that reserpine induces gastric damage by reducing sympathetic tone and increasing cholinergic tone,

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which leads to excessive acid secretion[12–14]. In this study, vagotomy and intracerebroventricular (icv) injection of reserpine were performed to further demonstrate the role of a central vagal mechanism in reserpine-induced GMLs. In addition, to investigate the characteristics of reserpine-induced GMLs in detail, the dose-effect of reserpine in causing GMLs was examined in two administration routes: intraperitoneal (ip) and oral. The time course of recovery from reserpine-induced GMLs was also studied. Finally, the blood pressure-reducing and GML-inducing effect of CHT, a combination drug that includes reserpine, were evaluated to determine its clinical safety.

Materials and methods

Animals and drugs

Male Sprague-Dawley (SD) rats (weighing 200–240 g) were purchased from Sino-British SIPPR/BK Lab Animal Ltd. Male spontaneously hypertensive rats (SHRs, 4–5 months old) were provided by the Animal Center of the Second Military Medical University (Shanghai, China). The animals were housed under controlled conditions (temperature, 23–25 °C; in light from 8:00 to 20:00) and received standard animal chow and tap water *ad libitum*. All animals used in this study received humane care in compliance with the Institutional Guidelines for the Health and Care of Experimental Animals.

Reserpine and CHT were provided by Beijing Shuanghe Pharmaceutical Co, Ltd (Beijing, China). The composition (mg/tablet) of CHT is as follows: hydrochlorothiazide 12.5, triamterene 12.5, hydralazine 12.5, and reserpine 0.1. In this study, the CHT dose is expressed as the amount of reserpine in the tablet.

GML evaluation

Animal was sacrificed and the stomach was removed from the abdomen after the pyloric sphincter was tied with a surgical suture. From the esophagus side, 5 mL of 10% formalin solution was injected into the stomach. The distended stomach was then immediately tied on the esophagus side with another surgical suture to prevent formalin leakage. The stomach was immersed in 10% formalin solution to fix the outer layer. 24 h later, each stomach was dissected along the greater curvature and rinsed with tap water to remove the gastric contents. The ulcerative lesion index of each rat was calculated by adding the values in Table 1, according to methodology described by Gamberini *et al*[15].

Intracerebroventricular injection

The rats were anesthetized intraperitoneally with a combination of ketamine (40 mg/kg) and diazepam (6 mg/kg) and fixed with a stereotaxic frame. The scalp skin was incised, and the periosteum was separated from the cranium. A single dose of reserpine (5 μL, 4 mg/mL, or 20 mg/mL) was stereotaxically injected into the lateral cerebral ventricle of the rat. In control rats, vehicle (dimethyl sulfoxide, 5 μL) was injected into the lateral cerebral ventricle. The coordinates were 0.9 mm posterior to bregma, 1.6 mm lateral from the midline and 3.7 mm below the surface of the skull[16–20].

Table 1. The diagnostic categories of GML in rats.

GML	GML index
Loss of normal morphology	1
Discoloration of mucosa	1
Mucosal edema	1
Hemorrhages	1
Petechial points (until 9)	2
Petechial points (≥10)	3
Ulcers up to 1 mm	*n*×2
Ulcers >1 mm	*n*×3
Perforated ulcers	*n*×4

n: number of ulcer.

Vagotomy

The rats were anesthetized intraperitoneally with a combination of ketamine (40 mg/kg) and diazepam (6 mg/kg). A midline abdominal incision was made, and the stomach was exposed. The gastric branches of the vagus nerve were resected at the esophagus, just above the stomach. The area was also covered with 5% phenol to destroy nerves that were overlooked in the surgery[21]. In control rats, a sham operation was performed with the midline abdominal incision and the exposure of stomach, but the vagus nerve was not resected.

Blood pressure measurement

Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were measured in conscious rats by the indirect tail-cuff method. The rats were warmed for 10 min at 37 °C in a thermostatically controlled heating cabinet for better detection of the tail artery pulse. A cuff was placed around the tail, and the ventral surface of the tail was contacted to a pulse transducer, through which the waves of the tail artery were converted into impulses and then visualized through an amplifier as rhythmic waves. SBP, DBP and HR were digitized automatically by the system after the tails were pressurized through the cuff. The final values were obtained by averaging 5 or 6 successful readings[22, 23].

Experimental protocols

Experiment 1: GMLs induced by a single dose of reserpine, administered intraperitoneally in SD rats

Sixty rats were randomly divided into 6 groups and fasted for 24 h with free access to water. A single dose of reserpine (0.25, 0.5, 1, 2, 4, or 6 mg/kg) was then injected intraperitoneally, and GMLs were evaluated 18 h later.

Experiment 2: GMLs induced by a single dose of reserpine, administered intragastrically in SD rats

Thirty rats were randomly divided into 3 groups and fasted for 24 h with free access to water. A single dose of reserpine (12, 24, or 48 mg/kg) was administered intragastrically, and

GMLs were evaluated 18 h later.

Experiment 3: GMLs induced by reserpine administered intragastrically for 2 weeks in SD rats

Twenty-four rats were randomly divided into 3 groups and fasted for 24 h before the first administration of reserpine. Reserpine was administered intragastrically (1, 3, or 10 mg/kg) daily for 2 weeks. The rats were then killed and GMLs were evaluated.

Experiment 4: Evaluation of the blood pressure-reducing effect and the GML-inducing effect of CHT in SHRs

Blood pressure levels were assessed in 14 SHRs. They were divided into 2 groups on the basis of SBP level and received rat chow containing 0.01 and 0.03 mg/kg of CHT, respectively, for 2 months. At the end of treatment, SBP, DBP, and HR values were determined in conscious rats to examine the effect of CHT on blood pressure. In addition, 14 other SHRs were divided into two groups. These animals received rat chow containing 0.1 and 0.3 mg/kg of CHT, respectively, for 2 months, after which the GML-inducing effect of CHT was evaluated.

Experiment 5: Time course of recovery from GMLs in SD rats

Forty-one rats were fasted for 24 h, and a single dose of reserpine (4 mg/kg) was injected intraperitoneally to induce GMLs. Seven rats were sacrificed 18 h later and evaluated for GMLs. The remaining rats were killed 1, 2, or 3 weeks later and evaluated for GMLs.

Experiment 6: GMLs induced by icv injection of reserpine in SD rats

Twenty rats were divided into 3 groups and fasted for 24 h with free access to water. They were given an icv injection of reserpine (0.08 or 0.4 mg/kg; n=7) or dimethyl sulfoxide (n=6) and sacrificed 18 h later, after which they were evaluated for GMLs.

Experiment 7: Effect of vagotomy on reserpine-induced GMLs in SD rats

Rats were randomly divided into 2 groups and fasted for 24 h. Vagotomy was performed in one group; the other served as a control group. Reserpine (ip, 4 mg/kg) was injected 6 h after vagotomy. Rats were sacrificed 18 h later and evaluated for GMLs.

Statistical analysis

All data were expressed as mean±SEM. A statistical analysis was performed with Student's t-test. P<0.05 was considered statistically significant.

Results

GMLs induced by ip and oral administration of reserpine in SD rats

The GML-inducing effect of reserpine was evaluated for two different drug administration methods. The results indicated that GMLs were induced dose-dependently by a single ip injection of 0.5 mg/kg to 6 mg/kg of reserpine, and no effects were observed in rats given 0.25 mg/kg of reserpine (Figure 1A). The GML-inducing effect of orally administered reserpine was much weaker. A single oral administration of 12 mg/kg of reserpine did not induce GMLs. Reserpine doses of 24 mg/kg and 48 mg/kg induced only slight GMLs (Figure 1B). When reserpine was orally administered at a dose of 10 mg/kg for 2 weeks, GMLs was caused; however, at lower doses (1 mg/kg or 3 mg/kg daily), reserpine did not induce gastric lesions (Figure 1C).

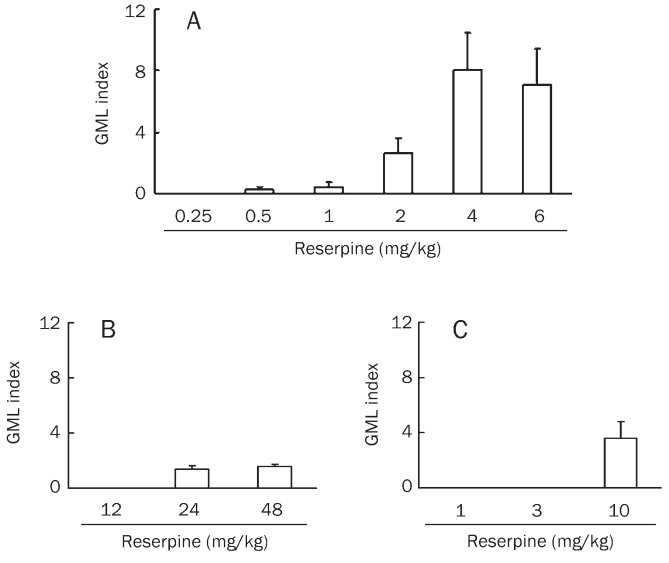

Figure 1. GML induced by a single ip administration (A), a single (B) and repeated (C, 2 weeks) oral administration of reserpine in SD rats. All values are expressed as means±SEM. n=10 in A and B, n=8 in C.

Evaluation of the bloodpressure-reducing and the GML-inducing effects of CHT

Long-term (2 months) treatment with CHT significantly decreased blood pressure in conscious SHRs. SBP/DBP decreased by 16/11 mmHg in rats treated with CHT 0.01 mg/kg daily and by 21/22 mmHg in rats treated with CHT 0.03 mg/kg daily. In the GML experiment, lesions developed only with a large dose of CHT (0.3 mg/kg daily for 2 months), resulting in a GML index of 4.6±0.8. In rats treated with 0.1 mg/kg of CHT, the stomachs were intact and no GMLs were found (Figure 2, Table 2).

Time course of recovery from reserpine-induced GMLs

Severe GMLs were found 18 h after reserpine injection (4 mg/kg ip). Of the seven sacrificed rats, six had large ulcers and petechial points in the stomach. The GML index was 6.4±1.8. One week after reserpine injection, GMLs were noticeably diminished. The GML indexes were 0.44±0.17 on day 8 and 0.29±0.13 on day 15. No ulcers or petechial points were observed in the stomach, but slight mucosal edema and hype-

Table 2. Effect of CHT administered intragastrically for 2 months on SBP, DBP, HR, and GML in SHRs. $^{b}P<0.05$, $^{c}P<0.01$ *vs* Pre-drug.

Dose (mg/kg)	SBP (mmHg) pre-drug	SBP (mmHg) post-drug	DBP (mmHg) pre-drug	DBP (mmHg) post-drug	HR (mmHg) pre-drug	HR (mmHg) post-drug	GML index
0.01	173±3.1	157±3.1^{c}	129±3.9	118±2.4^{b}	355±12	349±10	
0.03	170±2.5	149±2.8^{c}	130±4.1	108±2.2^{c}	354±11	338±5.4	
0.1							0
0.3							4.6±0.8

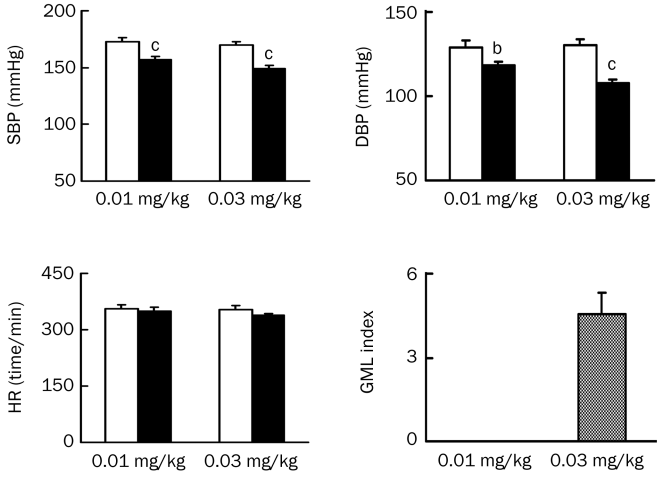

Figure 2. Effect of CHT administered intragastrically for 2 months on SBP, DBP, HR, and GML in SHRs. Open bars, pre-drug administration; solid bars, post-drug administration. Data are expressed as means±SEM. *n*=7 in each group. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. $^{b}P<0.05$, $^{c}P<0.01$ *vs* pre-drug administration.

remia were found in some rats at these time points. Three weeks later, the rats had completely recovered from reserpine-induced GMLs. Their stomachs were intact and no injuries were found (Figure 3).

GMLs induced by icv injection of reserpine

Intracerebroventricular injection of vehicle did not induce GMLs in rats, and icv reserpine produced GMLs similar to those found after ip injection, but at much lower doses (Figure 4). The GML index of 0.08 mg/kg of icv reserpine was comparable to that of 2 mg/kg of ip reserpine (2.1±0.14 and 2.6±0.98, respectively). The GML index of 0.4 mg/kg of icv reserpine was 9.1±1.4, slightly higher than that of 4 mg/kg of ip reserpine (8.0±2.4). These results indicate that a central mechanism is involved in the GML-inducing effect of reserpine. Typical lesions resulting from icv reserpine are shown in Figure 4A and 4B.

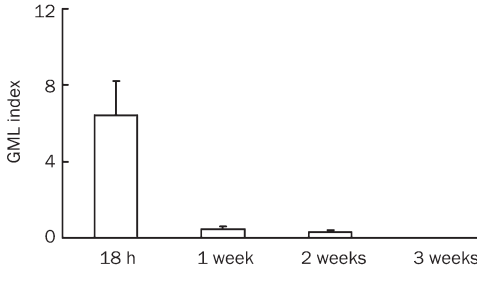

Figure 3. Time-course of recovery from GML induced by reserpine (4 mg/kg) administered intraperitoneally in SD rats. Data are expressed as means±SEM. *n*=7 at 18 h, *n*=9 at 1 week, *n*=14 at 2 weeks, *n*=11 at 3 weeks.

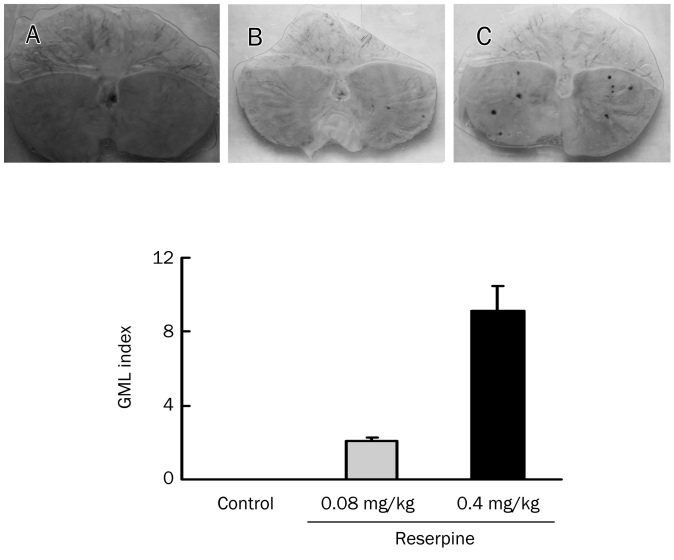

Figure 4. GML induced by intracerebroventricular injection of reserpine in SD rats. A, B, and C, representative samples of GML inducd by vehicle, 0.08 mg/kg of reserpine and 0.4 mg/kg of reserpine. Data are expressed as means±SEM. *n*=6 in control group; *n*=7 in reserpine groups.

Effect of vagotomy on reserpine-induced GMLs

Reserpine-induced GMLs were partly inhibited by gastric vagotomy (Figure 5). After the gastric vagus was resected, the reserpine-induced GML index was reduced to 20% of that of the control group. Figure 5A and 5B show the typical lesions observed in control rats and vagotomized rats.

Discussion

The main findings of the present work can be summarized as follows: (1) reserpine-induced GMLs were highly dependent on the dose, route and duration of the drug administration, as

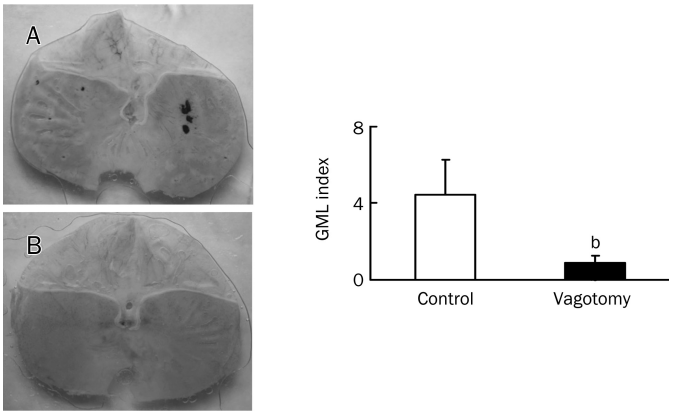

Figure 5. Effect of vagotomy on reserpine-induced GML in SD rats. A and B, representative samples of GML in control and vagotomized rats. Data are expressed as means±SEM. n=7 in control group. n=9 in vagotomized group, $^bP<0.05$ *vs* Control.

well as on the individual's gastric status. The small dose of reserpine in CHT did not induce GMLs during the treatment of hypertension. (2) Reserpine-induced GMLs healed spontaneously within 3 weeks. (3) The effect of reserpine on GMLs was mediated by the central vagal nervous system.

NSAIDs are the primary cause of drug-induced GMLs. Recently, *Helicobacter pylori* has been proven to play an important role in the pathogenesis of GMLs. At present, reserpine is seldom used alone. However, because many antihypertensive compounds contain reserpine, it is important to understand the nature of reserpine-induced GMLs.

Given the low bioavailability of reserpine, the doses that inducing GMLs with ip and intragastric administration were very different. GMLs were induced with single doses of 0.5 mg/kg of ip reserpine and 24 mg/kg of intragastric reserpine. This represents a 48-fold difference between these two administration routes. In both administration routes, a close dose-effect relationship existed in terms of inducing GMLs. In this study, rats were fasted for 24 h before the reserpine administration, and a single oral dose of reserpine 24 mg/kg produced GMLs. However, in our preliminary experiment, this dose of reserpine did not induce GMLs when the rats were not fasted before drug administration (data not shown). These results confirm the clinical necessity of taking the drug after meals.

CHT, a compound drug containing a small dose of reserpine, has been one of the most widely used antihypertensive drugs in China for more than 30 years. An estimated 900 million CHTs were consumed in each of the past 5 years. In this study, we found that blood pressure significantly decreased with 0.01 mg/kg of CHT. When rats were treated with 0.1 mg/kg of CHT for 2 months, no gastric injury was detected. GMLs occurred in the rats treated with 0.3 mg/kg of CHT for 2 months. Thus, the dose of CHT required to induce GMLs is 30 times higher than is necessary to decrease blood pressure. Generally, the dose of CHT (mainly reserpine) used to treat hypertension is not enough to induce GMLs. However, CHT should be avoided to be used in hypertensive patients with histories of gastric ulcers.

We also found that reserpine-induced gastric injury consisted mostly of mucosal lesions. As many other drug-induced side effects, this gastric injury can heal spontaneously after the drug withdrawal. It was found that this injury decreased significantly 1 week after the drug was administered and completely disappeared within 3 weeks. It should be noted that in this study, a single large dose of reserpine (4 mg/kg) was used to induce GMLs. The resulting injuries may be different from the GMLs induced by long-term treatment. Clinically, if gastric injury occurs during CHT treatment, we should withdraw the drug and give anti-ulcer treatment when necessary. The prognosis of this gastric injury is generally good.

Yamaguchi *et al* reported that reserpine increased acid secretion in rats[13], which was a possible mechanism leading to mucosal lesions. However, the exact mechanism is not yet clear. Reserpine was believed to exhaust the monoamines at the ends of sympathetic nerves, leading to overactivity of the vagal nervous system at the peripheral level. This may lead to an oversecretion of gastric acid. On the other hand, reserpine may exhaust the monoamines in the central nervous system, resulting in inhibition of sympathetic nerve outflow and the activation of the vagus. In this study, we found that gastric mucosal injury was partially inhibited by vagotomy. This result was consistent with Kim's report that reserpine-induced gastric acid secretion was greatly reduced, but not completely blocked, by vagotomy[14]. In addition, we found that icv reserpine 0.08 mg/kg produced gastric lesions in SD rats. This dose was much lower than the ip dose (0.25 mg/kg) that did not induce GMLs. We can deduce from these results that reserpine centrally inhibits the sympathetic nervous system, leading to an activation of vagal nerves and other factors that regulate gastric-acid secretion and inducing GMLs.

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Author contribution

Ding-feng SU designed the research; Xiu-juan MA, Xiang ZHENG, Zhi-peng WEN, Shu-wei SONG, Wei LIU, and Qian-zhou LÜ performed the research; and Xiu-juan MA and Guo-cai LU wrote the paper.

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