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Protective effect of centrally-injected glucagon-like peptide-1 on reserpine-induced gastric mucosal lesions in rat: Possible mechanisms

Santral olarak enjekte edilen "glucagon-like peptide-1"in sıçanda reserpin ile oluşturulan gastrik mukozal hasar üzerine koruyucu etkisi: Olası mekanizmalar

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Background/aims: *Intracerebroventricular glucagon-like peptide-1 (GLP-1) has been shown to prevent the gastric mucosal lesions induced by reserpine. In the present study, we aimed to investigate the contribution of 1- the cholinergic pathway, 2- the sympathetic pathway, 3- somatostatin and 4- endogenous nitric oxide to this gastroprotective effect.* ***Methods:*** *Rats were equipped with intravenous and intracerebroventricular cannulas under ether anesthesia for drug delivery. Rats were pretreated with mecamylamine (5 mg/kg; i.p.) and atropine sulfate (1 mg/kg; i.p.), yohimbine (1 mg/kg; i.p.), cysteamine (280 mg/kg; s.c.), and N^G-nitro-L-arginine methyl ester (3 mg/kg; i.v.) to investigate the role of the cholinergic pathway, sympathetic pathway, somatostatin and endogenous nitric oxide, respectively, in the gastroprotective effect of GLP-1. To produce gastric mucosal lesions, reserpine was administered intraperitoneally at a dose of 25 mg/kg in 10 ml/kg of 0.5% acetic acid solution. Four hours later, the animals were decapitated, and their stomachs were removed and scored for mucosal damage.* ***Results:*** *Glucagon-like peptide-1 (100 ng/10 µl; i.c.v.) inhibited the reserpine-induced gastric mucosal damage by 90% ($p<0.01$). Neither the nicotinic receptor antagonist mecamylamine (5 mg/kg; i.p.) nor the muscarinic receptor antagonist atropine sulfate (1 mg/kg; i.p) affected the gastroprotective activity of GLP-1. On the other hand, pretreatment with yohimbine, an α_2-adrenergic receptor antagonist (1 mg/kg; i.p.), cysteamine, a somatostatin depletor (280 mg/kg; s.c.), and N^G-nitro-L-arginine methyl ester, a nitric oxide synthase inhibitor (3 mg/kg; i.v.), significantly abolished the protective effect of GLP-1 on reserpine-induced gastric mucosal lesions ($p<0.001$, $p<0.01$ and $p<0.01$, respectively).* ***Conclusions:*** *We conclude that the sympathetic pathway, somatostatin and nitric oxide, but not the cholinergic pathway, contribute to the gastroprotective effect of intra-cerebroventricular GLP-1 on reserpine-induced gastric mucosal lesions.*

Key words: Glucagon-like peptide-1, intracerebroventricular, stomach, cholinergic system, sympathetic system, somatostatin, nitric oxide, rat

Amaç: *Sıçanlarda reserpin ile oluşturulan gastrik mukozal lezyonları önlediği gösterilmiş olan intraserebroventriküler "glucagon-like peptide-1" (GLP-1)'in gastroprotektif etkisinde 1- kolinerjik yolun, 2- sempatik yolun, 3- somatostatinin ve 4- endojen nitrik oksitin rolünün araştırılması amaçlandı.* ***Yöntem:*** *Sıçanlara uygulanacak ilaçlar için, eter anestezisi altında intravenöz ve intraserebroventriküler kanül yerleştirildi. İntraserebroventriküler GLP-1'in gastroprotektif etkisinde kolinerjik yolun, sempatik yolun, somatostatinin ve nitrik oksitin rolünü araştırmak amacıyla sıçanlara sırasıyla mekamilamin (5mg/kg; i.p.) ve atropin sülfat (1mg/kg; i.p.), yohimbin (1mg/kg; i.p.), cysteamin (280mg/kg; s.c.) ve N^G-nitro-L-arginine methyl ester (3mg/kg; i.v.) enjeksiyonu yapıldı. Gastrik mukozal hasar oluşturmak için 10 ml/kg %'lik 5 asetik asit solusyonunda 25 mg/kg dozda reserpin intraperitoneal olarak enjekte edildi. Dört saat sonra sıçanlar dekapite edilerek mideleri çıkartıldı ve mukozal hasarlar skorlandırıldı.* ***Bulgular:*** *"Glucagon-like peptide-1" (100 ng/10 µl; i.c.v.) reserpin ile oluşturulan gastrik mukozal hasarı %90 oranında inhibe etti ($p<0.01$). Ne nikotinik reseptör antagonisti mekamilamin, ne de muskarinik reseptör antagonisti atropin sülfat "glucagon-like peptide-1"in gastroprotektif aktivitesini etkilemedi. Ancak, α_2-adrenerjik reseptör antagonisti yohimbin, somatostatin deplesyonuna neden olan cysteamin ve nitrik oksit sentaz inhibitörü olan N^G-nitro-L-arginine methyl ester, intraserebroventriküler olarak enjekte edilen "glucagon-like peptide-1"in reserpinle oluşturulan gastrik mukozal hasarı önleyici etkisini büyük oranda ortadan kaldırdı (sırasıyla; $p<0.001$, $p<0.01$ ve $p<0.01$).* ***Sonuç:*** *İntraserebroventriküler olarak uygulanan "glucagon-like peptide-1"in reserpin ile oluşturulan gastrik mukozal hasarlardaki gastroprotektif etkisinde sempatik yolun, somatostatin ve nitrik oksitin rolünün olduğu, kolinerjik yolun ise bu etkide rol oynamadığı düşünülmektedir.*

Anahtar kelimeler: Glucagon-like peptide-1, intraserebroventriküler, mide, kolinerjik sistem, sempatik sistemsomatostatin, nitrik oksit, sıçan

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INTRODUCTION

Experimental ulcer models are frequently used not only for the investigation of peptide pathophysiology but also for the evaluation of the antiulcer activity of various agents. The etiology of gastric ulcer is multifactorial, and gastric acidity, pepsin secretion, gastric motility and gastric mucosal blood flow are all important factors in the development of ulcers (1). Therefore, various experimental models have been designed to induce gastric lesions using aspirin, indomethacin, ethanol, reserpine, pylorus ligation and stress. Each ulcer model has its own pathophysiological mechanism. Reserpine, used in this study, is thought to induce gastric ulcers mainly via the depression of adrenergic activity with an increase in the cholinergic tone (2). Although the reserpine-induced ulcer model has been considered to be acid-dependent (3), Kagoshima and Suguro (4) have suggested that hypermotility seems to be more important than hypersecretion for the induction of gastric mucosal lesions by reserpine.

A number of brain-gut peptides and neuropeptides have been shown to exert protective effects on gastric lesions induced by several experimental models, including the reserpine model (5-9). Among these, glucagon-like peptide-1 (GLP-1) has gained attention because of its multisystemic effects. GLP-1 is a bioactive peptide encoded in the preproglucagon gene (10). It is secreted by the enteroendocrine L-cells in response to food ingestion (11, 12). It stimulates insulin secretion and inhibits glucagon secretion, which is why it is under investigation as a potential treatment of diabetes mellitus (13, 14). Apart from these, GLP-1 has important effects on the motor and secretory functions of the proximal gastrointestinal tract (15, 16). It inhibits gastric emptying and proximal intestinal motility (15, 17-19), as well as gastric acid and pancreatic exocrine secretions (16, 20). The brain is a potential target organ for the actions of GLP-1, and it has been shown that several well-known effects of the peptide are mediated by central mechanisms (16, 18). We have previously observed that intra-cerebroventricular (i.c.v.) GLP-1 prevents the gastric mucosal lesions induced by reserpine (21). Although the mediators of this effect are as yet unknown, a number of modulatory systems may be involved, including the cholinergic and the sympathetic systems, somatostatin and nitric oxide (NO). In fact, all the mentioned systems and transmitters also have direct effects on gastric mucosal lesions in relevant doses. For example, cholinergic activation induces gastric ulcers by increasing gastric acid secretion (22). On the other hand, stimulation of cholinergic afferent fibers exerts gastroprotective effects, mediated by calcitonin gene-related peptide (CGRP), NO and various other peptides (23). The sympathetic system is also involved in gastric acid secretion and in the pathogenesis of gastric mucosal lesions, mainly through presynaptic α_2-adrenoceptors. Stimulation of these receptors mediates both the antisecretory action and the mucosal protective effect (24, 25). Somatostatin exerts inhibitory effects on gastric acid secretion and gastrointestinal motility and also mediates the effects of various brain-gut peptides (26). Finally, although there are contradictory data about the effect of NO on gastric acid secretion (27, 28), it is a well-known mediator that regulates several components of gastrointestinal mucosal defense (29). In the present study, we aimed to investigate the possible involvement of these pathways in the gastroprotective effect of GLP-1 on reserpine-induced gastric mucosal lesions.

MATERIALS AND METHODS

Animals

Female Sprague Dawley rats (Experimental Animals Breeding and Research Centre, Uludağ University Medical Faculty, Bursa, Turkey), weighing 200-250 g were used in this study. Rats were housed 4-6 in a cage under constant environmental conditions (20-24°C; 12-h light-dark cycle). The animals were fasted for 24-26 h before the experiments with free access to tap water until 1 h before testing (n=78). The surgical and experimental protocols used were approved by the Animals Care and Use Committee of Uludağ University.

Surgical Procedures

Ether anesthesia was used during surgery. For i.v. injections, rats were implanted through the right femoral vein with a PE 50 tubing filled with heparinized saline (100 U/ml). For i.c.v. injections, a burr hole was drilled through the skull 1.5 mm lateral to the midline and 1-1.5 mm posterior to the bregma on the right side. Through this hole, a 10 mm length of 20 gauge stainless steel hypodermic tubing (prepared by S. Aydin) was directed toward the right lateral ventricle. The cannula was lowered 4.2-4.5 mm below the surface of the skull perpendicularly and was fixed to the skull with acrylic cement. Animals were housed individually and

allowed to recover for five days. At the end of the experiments, 5 µl of a methylene blue solution was injected into the cerebral ventricle through the cannula, and the placement of the inner end of the cannula was verified for each rat. After decapitation, the brains were removed and sections were observed macroscopically to ascertain whether the cannula had been correctly placed into the lateral cerebral ventricle.

Induction and Evaluation of Gastric Mucosal Lesions

In order to produce reserpine-induced gastric lesions, reserpine was administered intraperitoneally at a dose of 25 mg/kg in 10 ml/kg of 0.5% acetic acid solution (30). Four hours later, the animals were decapitated, and the stomachs were removed and opened along the greater curvature. The number and severity of gastric lesions were evaluated according to the following rating scale:

0: no lesion

1: mucosal edema and petechiae

2: 1-5 small lesions (1-2 mm)

3: more than 5 small lesions or 1 intermediate lesion (3-4 mm)

4: two or more intermediate lesions or 1 gross le sion (greater than 4 mm)

5: perforated ulcers

Experimental Protocols

Effect of i.c.v. GLP-1 on reserpine-induced gastric lesions

GLP-1 (100 ng/10 µl) or saline (10 µl) was injected intracerebroventricularly 5 min before reserpine administration. We used 100 ng i.c.v. GLP-1 throughout the experiments, since we have recently shown that this is the most effective dose in this model, inhibiting the gastric mucosal lesions by 85% (21). Gastric lesions were evaluated 4 h later.

Role of the cholinergic system in the gastroprotective effect of i.c.v. GLP-1

Rats were pretreated with a nicotinic receptor antagonist, mecamylamine (5 mg/kg; i.p.), and a muscarinic receptor antagonist, atropine sulfate (1 mg/kg; i.p.), 10 min before GLP-1 (100 ng/10 µl; i.c.v.) or saline (10 µl; i.c.v.) injection. Reserpine was administered 5 min later.

Involvement of the α_2-adrenergic receptors in the gastroprotective effect of i.c.v. GLP-1

Rats received yohimbine, an α_2-adrenergic receptor antagonist (1 mg/kg; i.p.), 10 min before GLP-1 (100 ng/10 µl; i.c.v.) or saline (10 µl; i.c.v.) injection. Reserpine was administered 5 min later.

Effect of somatostatin depletion on the gastroprotective effect of i.c.v. GLP-1

Rats received cysteamine, a somatostatin depletor (280 mg/kg; s.c.), 4 h before GLP-1 (100 ng/10 µl; i.c.v.) or saline (10 µl; i.c.v.) injection. Reserpine was administered 5 min later.

Involvement of the NO pathway in the gastroprotective effect of i.c.v. GLP-1

Rats received N^G-nitro-L-arginine methyl ester (L-NAME), a NO synthase inhibitor (3 mg/kg; i.v.), 1 min before GLP-1 (100 ng/10 µl; i.c.v.) or saline (10 µl; i.c.v.) injection. Reserpine was administered 5 min later.

Drugs

GLP-1, reserpine, mecamylamine chloride, atropine sulfate, cysteamine, L-NAME and yohimbine were purchased from Sigma (Sigma Chemical Co., MO, USA) and dissolved in saline. I.c.v. injections were performed using a Hamilton microsyringe.

Statistical Analysis

Data are presented as means ± SE. Non-parametric Mann-Whitney U test was used to determine statistical significance. Differences were considered to be significant at $p<0.05$.

RESULTS

Effect of i.c.v. GLP-1 on reserpine-induced gastric lesions

In the saline + reserpine group, the average ulcer score was 3.1 ± 0.3 versus 0.3 ± 0.2 in the GLP-1 (100 ng/10 µl) + reserpine group. Thus, this dose of GLP-1 inhibited the reserpine-induced gastric mucosal lesions by 90% ($p<0.01$) (Figure 1).

Role of the cholinergic system in the gastroprotective effect of i.c.v. GLP-1

Neither the nicotinic receptor antagonist mecamylamine (5 mg/kg; i.p.) nor the muscarinic receptor antagonist atropine sulfate (1 mg/kg; i.p) changed the effect of GLP-1 on reserpine-induced gastric mucosal lesions (ulcer scores: 1.1 ± 0.3 and 1.1 ± 0.3, respectively) (Figure 1). None of the agents alone had any significant effect on gastric lesions.

Involvement of the α_2-adrenergic receptors in the gastroprotective effect of i.c.v. GLP-1

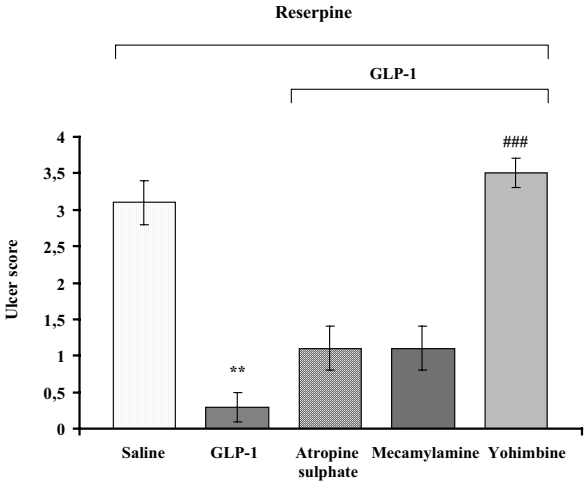

Figure 1. Role of the central cholinergic and sympathetic systems in the protective effect of i.c.v. GLP-1 on reserpine-induced gastric mucosal lesions. Rats received a nicotinic receptor antagonist mecamylamine (5 mg/kg; i.p.), a muscarinic receptor antagonist atropine sulfate (1 mg/kg; i.p.) or an α_2-adrenergic receptor antagonist yohimbine (1 mg/kg; i.p.) 10 min before GLP-1 (100 ng/10 μl; i.c.v.) or saline (10 μl; i.c.v.) injection. Reserpine was administered 5 min later and gastric lesions were scored 4 h later. Results were presented as means± SE. Each group consisted of 6-7 rats.
**: p<0.01 with respect to the saline group.
###: p<0.001 with respect to the GLP-1 group

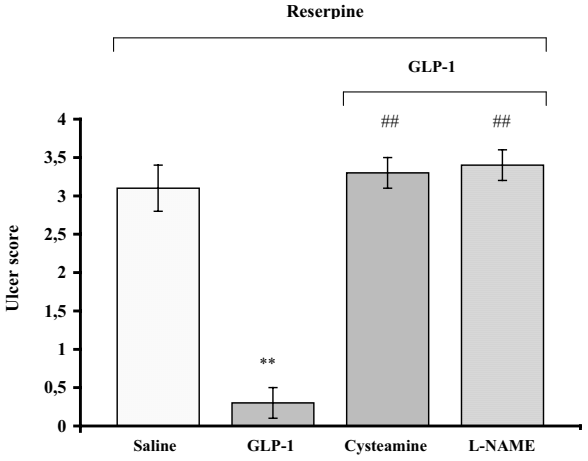

Figure 2. Role of somatostatin and NO in the protective effect of i.c.v. GLP-1 on reserpine-induced gastric mucosal lesions. Rats received a somatostatin depletor cysteamine (280 mg/kg; s.c.) 4 h before or a NO synthase inhibitor L-NAME (3 mg/kg; i.v.) 1 min before GLP-1 (100 ng/10 μl; i.c.v.) or saline (10 μl; i.c.v.) injection. Reserpine was administered 5 min later and gastric lesions were scored 4 h later. Results were presented as means±SE. Each group consisted of 6-7 rats.
**: p<0.01 with respect to the saline group.
##: p<0.01 with respect to the GLP-1 group

The gastric ulcer scores of the rats which were pretreated with yohimbine, an α_2-adrenergic receptor antagonist (1 mg/kg;i.p.), were significantly higher (ulcer score: 3.5 ± 0.2) than those of the reserpine + GLP-1 group (p<0.001) (Figure 1). Yohimbine alone did not have any effect on gastric lesions.

Effect of somatostatin depletion on the gastroprotective effect of i.c.v. GLP-1

Injection of cysteamine, a somatostatin depletor (280 mg/kg; s.c.), 4 h before GLP-1 prevented the protective activity of GLP-1 against reserpine-induced gastric mucosal lesions (ulcer score: 3.3 ± 0.2) (p<0.01) (Figure 2). Cysteamine alone did not have any effect on gastric lesions.

Involvement of the NO pathway in the gastroprotective effect of i.c.v. GLP-1

Inhibition of NO synthesis by L-NAME (3 mg/kg; i.v.) significantly abolished the protective effect of GLP-1 on reserpine-induced gastric mucosal lesions (ulcer score: 3.4 ± 0.2) (p<0.01) (Figure 2). L-NAME alone did not have any effect on gastric lesions.

DISCUSSION

GLP-1 is a peptide known to exert a wide range of effects on various systems. Recently, we have observed the gastroprotective effect of GLP-1 in various gastric ulcer models (21), which led us to further investigate the mechanisms involved in this effect. We have reported that GLP-1 prevents ethanol-induced gastric mucosal lesions when injected intra-cerebroventricularly, and central muscarinic and peripheral nicotinic cholinergic receptors and NO contribute to this protective effect (31). However, since gastric ulcer models have different pathogenetic mechanisms, the gastroprotective effect of GLP-1 in each model may not involve the same mechanism, and therefore should be investigated separately. Here, we investigated the contribution of 1- the cholinergic pathway, 2- the sympathetic pathway, 3- somatostatin and 4- endogenous NO in the gastroprotective effect of i.c.v. GLP-1.

Wettergren (32) has suggested that the inhibitory action of GLP-1 involves the vagus nerves, although neither efferent transmission of vagal impulse to the ganglia of the stomach and the pancreas nor the function of their intrinsic excitatory neurons seems to play a role. Imeryuz et al. (18) have also reported that central and peripheral effects

of GLP-1 on gastric emptying are abolished following vagal afferent denervation, while neither cholinergic nor adrenergic blockade had any effects. Similarly, we found that neither mecamylamine nor atropine sulfate influenced the gastroprotective effect of GLP-1 on reserpine-induced gastric mucosal lesions, suggesting that nicotinic and muscarinic cholinergic receptors do not mediate this effect.

Yohimbine, an α_2-adrenergic receptor antagonist, significantly prevented the gastroprotective effect of GLP-1 on reserpine-induced gastric mucosal lesions. It has been reported that activation of presynaptic α_2-adrenoceptors on the vagus nerve not only inhibits gastric acid secretion and gastric motility (25, 33), but also stimulates mucosal protective effect (24). Thus, stimulation of α_2-adrenergic receptors by GLP-1 may lead to gastroprotection via the mentioned effects.

The contribution of somatostatin in the gastrointestinal effects of GLP-1 is not clear and seems to depend on the species. Eissele et al. (34) have reported that GLP-1 stimulates somatostatin secretion in the perfused rat stomach, suggesting that the inhibitory effect of GLP-1 on acid secretion may be mediated by somatostatin. On the other hand, Orskov et al. (35) did not observe an effect of GLP-1 on somatostatin release in the isolated perfused pig stomach. Similarly, it has been shown that GLP-1 has no effects on the circulating concentrations of somatostatin, although it effectively inhibits sham-feeding induced acid secretion (36).

It has been reported that centrally-injected GLP-1 also inhibits gastric acid secretion (18, 21), but the role of somatostatin in this effect is not clear. In the present study, we used a somatostatin depletor, cysteamine, to investigate the possible role of somatostatin in the gastroprotective effect of GLP-1 in reserpine-induced gastric mucosal lesions. Cysteamine prevented the gastroprotective effect of GLP-1, indicating that somatostatin is involved in this effect. Cysteamine-induced somatostatin depletion occurs both in the periphery and the central nervous system and therefore we cannot discriminate whether central or peripheral somatostatin mediates the gastroprotective effect of i.c.v. GLP-1. Furthermore, this effect may be due to somatostatin-induced inhibition in gastric acid secretion or increase in gastric mucosal blood flow, or both, since it has been suggested that somatostatin may cause vasodilation directly via a mechanism which involves endothelial NO (37).

NO was another candidate which could participate in the gastroprotective effect of GLP-1. L-NAME, a NO synthase inhibitor, significantly abolished the effect of GLP-1. We have previously obtained similar results in the ethanol model of gastric mucosal damage (31). Since the major cause of gastric mucosal lesions in the ethanol model is the decrease in gastric mucosal blood flow, the involvement of NO in the gastroprotective activity is not surprising. On the other hand, reserpine induces gastric mucosal lesions mainly by causing hypermotility, although its hypersecretory and vasoconstrictor effects cannot be neglected. GLP-1 may modulate most of the reserpine-induced effects. Although there is no data at present about the effect of GLP-1 on gastric mucosal blood flow, it has been shown that it causes vasodilation in pulmonary arteries and this effect is mediated by NO (38). The vasodilator effect of GLP-1 in the pulmonary arteries seems to endothelium-dependent (38, 39), while the vasorelaxant effect of GLP-1 in the rat femoral artery has been shown to be NO- and endothelium-independent (40). We have observed that NO is involved in the gastroprotective effect of GLP-1 in both ethanol and reserpine models. GLP-1 may prevent gastric mucosal lesions by increasing gastric mucosal blood flow and/or decreasing gastric motility, and both effects may be mediated by NO. In addition, stimulation of α_2- adrenoceptors on endothelial cells leads to the release of vasodilator substances like NO (41). Thus, the data we obtained from both L-NAME and yohimbine trials seem to support each other.

In conclusion, we can put forward that the sympathetic pathway, somatostatin and NO, but not the cholinergic pathway, contribute to the gastroprotective effect of i.c.v. GLP-1 on reserpine-induced gastric mucosal lesions.

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