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Full Length Research Paper

Effects of salmon calcitonin and calcitonin gene related peptide (CGRP) on gastric mucosal barrier in stress induced rats

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The aim of this investigation was to examine and compare the effects of calcitonin gene related peptide (CGRP) and salmon calcitonin (sCT) on gastric lesions and mucosal barrier components such as mucus and phospholipids in rats exposed to cold + restraint stress (CRS). Twenty-eight Wistar albino rats (150 – 200 g) used for this study were provided by the Animal Health and Research Center of Dicle University Diyarbakir/Turkey (DUSAM). The rats were withheld from feeds for 24 h; then, they were divided into four groups - each of which consisted of seven rats such as: control, stress, and CGRP + CRS and sCT + CRS groups. CGRP and sCT were administered 10 µg/kg intravenously 30 min prior to stress induction. After scarification of the rats, stomachs were examined macroscopically for ulcerative lesions. The amounts of mucus and phospholipids, which are important components of the gastric mucosal barrier, were then measured according to Corne and Baur methods. It was found that cold + restraining stress caused gastric lesions to increase, and that the application of CGRP and sCT decreased the lesions (P = 0.002, P = 0.001 respectively). Moreover, at the same time, it was determined that the decrease in the amount of mucus and phospholipids, due to the stress, was prevented significantly by administration of CGRP and sCT; for mucus as P = 0.002 and P = 0.002 respectively, for phospholipids as P = 0.002 and P = 0.002, respectively. According to our findings, CGRP and sCT were found to be effective in preventing acute hemorrhagic gastric lesions caused by stress, and in maintaining gastric mucosal barrier parameters.

Key words: Calcitonin gene related peptide, gastric mucosal barrier, salmon calcitonin.

INTRODUCTION

The integrity of gastric mucosa depends on a variety of different factors. Among these factors, surface-active phospholipids (Kao et al., 1987), mucosal blood flow (Stein, 1989; Wallace, 1996) and mucus secretion play central roles (Allen, 2005). Cold-restraint stress is a commonly used and clinically relevant experimental model for acute gastric damage (Senay, 1967; Baki, 2000).Stress ulceration represents a serious complication in patients under stress conditions. Experimental studies have demonstrated that the exposure of rat gastric mucosa to stress produces gastric mucosal lesions (Konturek et al., 1999).

Cold restraint stress produces a sudden reduction of blood flow and acute hemorrhagic lesions in the gastric mucosa of experimental animals (Duan et al., 2004). Maintenance of gastric blood flow is important to protect the mucosa from endogenous and exogenous damage factors (Wallace et al., 1996).

Calcitonin (CT) and calcitonin gene-related peptide (CGRP) are derived from CT/CGRP gene. This alternative tissue-specific processing of primary mRNA from the CT/CGRP gene in rats generates two distinct peptides,

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CT and CGRP. CT, a calcium-lowering hormone, is a 32 amino acid single chain peptide expressed mainly in the thyroid gland. CGRP is a 37 amino acid vasoactive neuropeptide that is widely distributed in the central and peripheral nervous systems in mammals (Rosenfeld, 1983; Wimalawansa, 1996). CGRP is a sensory neuropeptide that has wide distribution within the mammalian gastrointestinal tract. The highest concentration of CGRP in the gut is found in the stomach and it is presumed that CGRP might participate in a restorating mechanism of the ulcer (Tani, 1999; Sternini, 1987).

Exogenous CGRP has been reported to exert a potent antiulcer activity in some experimentally-induced gastric ulcers (Evangelista, 1997; Gray 1994). The actions of CGRP in the stomach include inhibition of acid, pepsin and gastrin secretion (Clementi, 1993; Kraenzlin, 1985), inhibition of motility (Katsoulis and Conlon, 1989), stimulation of blood flow (Bauerfeind et al., 1989) and release of somatostatin (Bunnett et al., 1990).

Calcitonin is a polypeptide hormone that causes hypochalcemia by inhibition of calcium, releasing from bone (Talmage et al., 1983) without affecting serum calcium levels. High amounts of salmon calcitonin injected parenterally have been shown to suppress serum gastrin levels and gastric acid secretion (Becker et al., 1973). CT has a high index of protection against ulcers induced by CRS (Guidobono et al., 1991).

The aim of this study is to compare the effects of CT and CGRP caused by the same gene and the anti ulcerative effect on the mucus and phospholipids levels of gastric mucosal barrier components against ulcerative stress and macroscopic gastric mucosal changes.

MATERIALS AND METHODS

Twenty-eight Wistar albino rats, weighing 150 – 200 g, were used in this study. Animals were housed under standard conditions (21 ± 2°C) in the Animal Health and Research Center of Dicle University (DUSAM). The study protocol was approved by the Animal Research Committee (DEHEK) of Dicle University/Turkey. Animals were maintained in a 12 h light/dark cycle with tap water and food freely available.

Experimental studies were designed to evaluate that CGRP and sCT effective in preventing acute hemorrhagic gastric lesions caused by stress in maintaining gastric mucosal barrier parameters. The twenty-eight animals were randomly divided into four groups. Each group consisted of seven rats; the normal control group, the stress group, the sCT + CRS and the CGRP + CRS groups. sCT and CGRP (10 µg/kg) were dissolved in sterile distilled water and injected intravenously 30 min before stress via tail vein (Kaneko et al.,1998). sCT and CGRP were purchased from Sigma (T–3660, C-0292. Sigma Chemical Co., St. Louis).

Rats were starved for 24 h, and the drinking water was removed 1 h before starting experiments. For CRS, the rats were restrained in individual close-fitting tubular wire-mesh cages at 4°C for 3 h (Senay et al., 1967). At the end of 3 h, the CRS applied animals were removed from the restraining devices. Maintenance of anesthesia was confirmed by inhalation with ether and all the rats were sacrificed by cervical dislocation.

Stomachs were removed, opened along the greater curvature, and examined macroscopically for gastric mucosal damage. Each lesion was measured along its greatest diameter (mm). When assessing the size of petechia, five such lesions were considered equivalent to 1 mm ulcer. The sum of the lesions lengths in each group was divided by number of rats in that group and expressed as the mean ulcer index (Ogle et al., 1985).

The amount of stomach mucus was determined by the Corne's method (Corne et al., 1974). The glandular portion of the stomach was excised, weighed and immersed for 2 h in Alcian blue solution. The excess dye was removed by 2 successive rinses of 15 min each in sucrose solution. The mucus bound dye was extracted by immersing the gastric tissue in $MgCl_2$ solution, which was intermittently shaken for 1 min at 30 min intervals over a 2 h period. The blue extract thus obtained was shaken with diethyl ether. The resulting emulsion was centrifuged and the optical density of the aqueous phase was measured at 600 nm in a Shimadzu-UV 1601 spectrophotometer. The quantity of Alcian blue extracted per gram of wet glandular tissue was then calculated from standard curves.

The amount of phospholipids was measured by the method of Baur (Baur et al., 1974). In order to determine the concentration of phospholipids, 0.2 g mucosal extract was placed in the tubes. 1 ml of nitric acid was added to each tube and heated by flame until no more nitric acid fumes were observed and then cooled. To each tube was added 1 ml of ascorbic acid–trichloroacetic acid, 0.5 ml of ammonium molybdate (1%) and 1 ml of arsenite citrate and mixed. After 15 min, absorption of the mixture was measured at 700 nm against a blank. The amount of phospholipids was calculated from standard curves.

Stomach tissue samples which were collected from the rats were fixed in 10% formaldehyde for 24 h. Subsequently they were rinsed by streaming water for one day in order to remove formaldehyde pigment. The samples were dehydrated by treatment in absolute alcohol series of 70, 80 and 96% for 1 h in each following rinsing. After polishing process by treatment with methyl benzoate and benzene series the tissues were blocked in paraplast. Series of 5 µ thick cross-sections were taken from the prepared blocks. The cross-sections were dyed with Crossman's triple dye. The cross-sections were inspected in research microscope attached Nikon E400 Eclipse digital camera.

Mean and standard deviation (SD) for continuous and median value for discrete variables were calculated. Categorical data were evaluated by Kruskal Wallis test for groups, and Mann Whitney test for two groups. Two-sided P values were considered statistically significant at $P<0.05$. Statistical analyses were carried out by using the statistical packages for SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

The effects of CGRP and sCT on CRS caused gastric lesions demonstrated in Table 1. Ulceration index was 16.78 ± 1.35 in CRS group; 6.39 ± 0.90 in CGRP + CRS group and 8.71 ± 0.91 in sCT + CRS group. Thus, it was observed that CGRP and sCT decreased the gastric lesions and ulcerations caused by CRS ($P = 0.002$ and $P = 0.001$, respectively).

The effect of CGRP and sCT on mucus which is a component of gastric mucosal barrier was demonstrated in Table 2. Mucus quantity was 158 ± 2.17 µg/g wet tissues in the group which was not subjected to CRS. The mucus level of stomach mucosal barrier was decreased in CRS group ($P = 0.002$). The mucus quantity in the trial groups subjected to CGRP and SCT was determined as 116.08 ± 6.98, 105.09 ± 8.59 µg/g wet tissue ($P = 0.002$ and $P = 0.002$, respectively).

Table 1. The effects of CGRP and sCT on stomach ulceration index in rats subjected to CRS (ulceration index: mm).

Group	n	Mean ± SD	Median	KruskallWallis	P
CRS	7	16.78 ± 1.35	17.4000		
CGRP+ CRS	7	6.39 ± 0.90*	8.2000	17.81	P<0.001
sCT+ CRS	7	8.71 ± 0.91**	6.4900		

*P = 0.002; **P = 0.001.

Table 2. The effects of CGRP and sCT on stomach mucosal mucus level in rats subjected to CRS.

Group	n	Mean±SD	Median	KruskallWallis	P
Control	7	158 ± 2.17	159.01		
CRS	7	71.61 ± 3.17 *	71.73		
CGRP+ CRS	7	116.08 ± 6.98**	118.00	23.98	P<0.001
sCT+ CRS	7	105.09 ± 8.59***	101.7		

*P = 0.002, **P = 0.002, ***P = 0.002.

Table 3. The effects of CGRP and sCT on stomach mucosal phospholipids levels in rats subjected to CRS.

Group	n	Mean ± SD	Median	KruskallWallis	P
I-Control	7	6.03 ± 0.55	5.90		
II- CRS	7	2.08 ± 0.43	2.08	22.86	P<0.001
III-CGRP+ CRS	7	3.28 ± 0.53	3.08		
IV-sCT+ CRS	7	3.67 ± 0.48	3.88		

I-II groups = (P = 0.002), I-III groups = (P = 0.002), II-IV groups = (P = 0.002).

The effect of CGRP and sCT on phospholipids levels which is a component of gastric mucosal barrier caused by CRS was demonstrated in Table 3.

Phospholipids quantity was calculated as 6.03 ± 0.55 mg/g wet tissue in the group which was not subjected to CRS. Phospholipids level of stomach mucosal barrier was decreased in the rats subjected to CRS (P = 0.002). Its levels were 3.28 ± 0.53 and 3.67 ± 0.48 mg/g wet tissue, respectively, in the groups subjected to CGRP + CRS and sCT + CRS and, the phospholipids levels in those groups increased as compared to those of control group (P = 0.002 and P = 0.002, respectively).

Histological findings

Control group

Tunica mucosa and submucosa of the stomachs of the rats in control group was normal in histological examination (Figure 1).

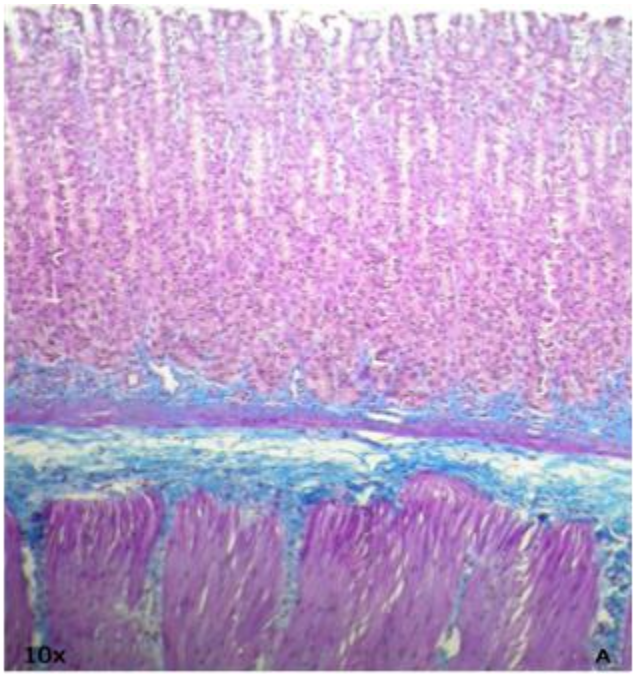

Figure 1. The histological view of the stomach of the control group (Stain: Crossman's triple X100).

Stress group

There were histological differentiations in tunica mucosa

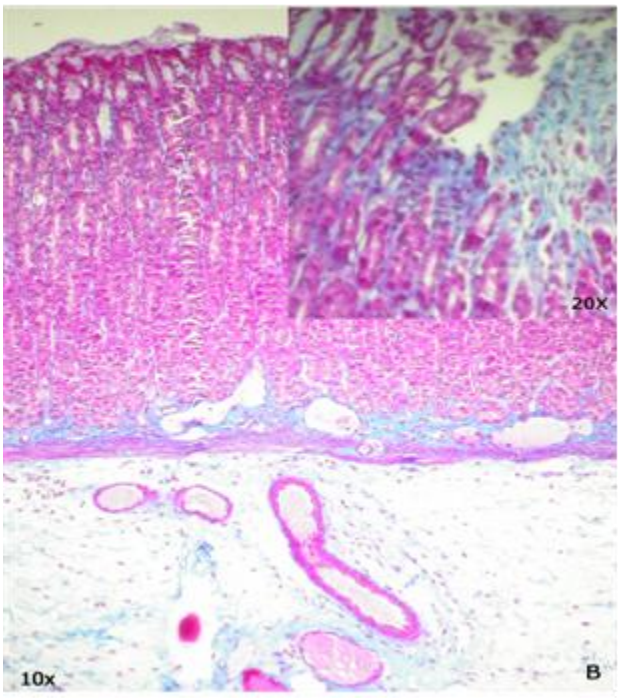

Figure 2. Histological view of the stomach of stress group (Stain: Crossman's triple X100).

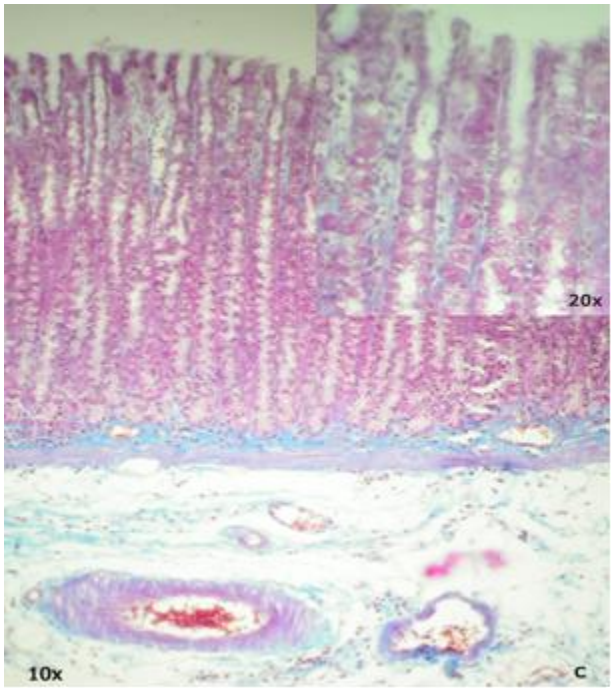

Figure 3. Histological view of the stomach of the stress + sCT group (Stain: Crossman's triple X100).

and submucosa layers of the stomachs of this group. Lamina epithelialis layer of tunica mucosa lost its integrity and were dilatations observed in capillary vessels in lamina propria. There was obvious dilatation and edema in blood vessels of tunica mucosa. A diffuse lymphocyte infiltration was observed in this level (Figure 2).

Stress + sCT group

Histological differentiations were observed to begin to improve and there were signs of regeneration in lamina epitelialis of tunica mucosa. The basal cells of gastric glandules were increased obviously. Dilatation of vessels in lamina propria was regressed but lymphocyte infiltration was continued. Besides, edema and lymphocyte infiltration in tunica submucosa was also continued (Figure 3).

Stress + CGRP group

Lamina epithelialis of the tunica mucosa of the rats in this group improved. The dilatation and edema of the vessels in lamina propria and submucosa disappeared and no lymphocyte infiltration was observed (Figure 4)

DISCUSSION

Our results demonstrate that exogenous injection of CGRP and sCT decreases the number of ulcerations, increases mucus and phospholipids level produced by CRS, protecting the gastric mucosa from stress-induced injury. Increase in gastric acid secretion, gastric mucosal irrigation, prostaglandin synthesis, bicarbonate secretion, decrease in mucus production and corruption of gastric mucosal barrier are all considered as pathologic mechanisms caused by gastric lesions due to stress (Wow and Turnberg, 1982).

Calcitonin (CT) is a polypeptide hormone that causes hypocalcaemia by inhibition of calcium release from bone. Without affecting serum calcium levels, high amounts of salmon CT injected parenterally is able to stimulate the secretion of somatostatin from the gastrointestinal tract and does reduce gastrin secretion, possibly via the stimulation of somatostatin secretion (Becker, 1973; Woloszczuk, 1986).

In researches, commonly used sCT was determined to have multiple effects. It was observed that 75% of sCT treated patients were healed in 4 weeks who were suffering from arthritis and osteoporosis accompanied peptic and/or duodenal ulceration (Badurski, 1993). sCT was determined to have a protective effect against the experimentally induced stress ulceration (Erin et al., 1996). And have the possible protective effects due to its effects on somatostatin (Guidobono et al., 1991). Tache et al. (1988) reported that the protective effect of sCT is via regulating gastric secretion and motor functions independent from prostaglandins.

We did not encounter a publication demonstrating the

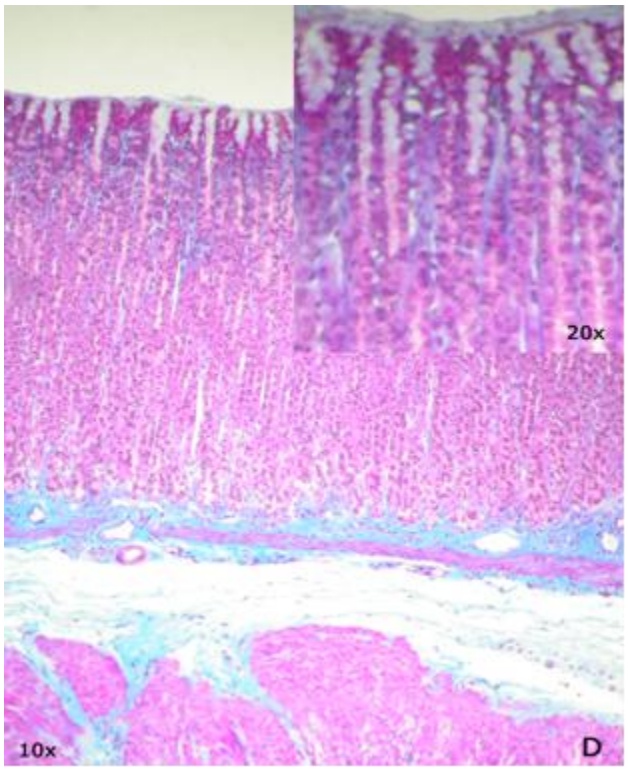

Figure 4. Histological view of the stomach of the stress+ CGRP group (Stain: Crossman's triple X100).

relation of sCT with mucus and phospholipids. But the possible reasons of sCT caused increase in mucus and phospholipids levels may be linked to its effects causing decreased gastric acid level and besides increase in somatostatin.

Evangelista et al. (1997) reported that exogenous CGRP application showed a strong anti-ulcerative effect on animals with experimental ulcer. According to results of this study it was observed that CGRP and sCT significantly prevented CRS caused decrease in levels of mucus and phospholipids which are important components of gastric mucosal barrier. Moreover it was observed that CGRP and sCT decreased the formation of acute hemorrhagic ulceration due to CRS.

Harada et al. (2003), demonstrated that CGRP increased the stress caused decrease in mucosal irrigation via prostaglandins while Holzer et al. (1991), demonstrated that CGRP increased mucosal irrigation directly. Increase in gastric mucosal irrigation is one of the most important factors in production of phospholipids and mucus. Ichikawa et al. (2000), suggest that age linked gastric mucus biosynthesis is regulated by CGRP, and fibers are intensely present in mucosal propria, and age linked decrease in NOs activity may be responsible of decrease in mucin regulated by CGRP. The versatile effect of CGRP in regulation of irrigation is a strong evidence of its direct and indirect protective effect on gastric barrier.

Ichikawa et al. (2000), demonstrated that exogenous CGRP treatment affects mucus biosynthesis positively via stimulating specific receptors in gastric mucus cells Kawabata et al. (2001), suggested that mucus increasing effect of CGRP is its main gastro protective effect and, its irrigation increasing effect is a less effective protective factor. Akiba et al. (2001) linked the duodenal mucus thickness increasing effect of CGRP treatment to irrigation in their research. In this study it is parallel with effect of CGRP on mucus increase.

Okumura et al. (2000), demonstrated that CGRP and adrenomedulin, which are members of calcitonin family, increased phosphatidylcholine secretion in lungs. Phosphtidyl choline is the most common component among gastric phospholipids. Hence, although there is no sufficient data showing that calcitonins causes increase in mucosal irrigation but they probably cause increase in phospholipids synthesis.

CGRP causes increase in synthesis of prostaglandins (PG) (Harada et al., 2003), Kao and Lichtenberger (1993) reported that prostaglandins cause a huge increase in intrinsic gastric mucosal phospholipids. It was revealed that PG is one of the possible reasons which cause increase of phospholipids.

Kawashima et al. (2002) reported that CGRP controls somatostatin production by affecting D cells in gastric mucosa. Guzel et al. (1999) reported that somatostatin has protective effects against stress by increasing the quantity of phospholipids and mucus. Hence, it suggests that CGRP possibly has indirect strong gastro protective effects on somatostatins as well.

In conclusion, CGRP and sCT have parallel effects on inhibition of gastric secretions and increase in somatostatin secretion while CGRP is distinguished from sCT by its direct and indirect - via PG and nitric oxide - protective effects due to increasing gastric microdilatation. CGRP and sCT protect gastric mucosal barrier against CRS through some partially similar mechanisms but further researches are needed in order to evaluate their synergistic effects.

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