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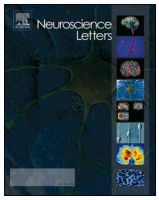

Peripheral administration of neuropeptide W inhibits gastric emptying in rats: The role of small diameter afferent fibers and cholecystokinin receptors

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ABSTRACT

Neuropeptide W (NPW), a novel hypothalamic peptide, contributes to the central regulation of food intake and energy balance, and suppresses feeding behavior when administered centrally. The aim of our study was to investigate the role of peripherally administered NPW in the modulation of gastric emptying, and to evaluate the participation of afferent fibers, cholecystokinin (CCK) receptors and gastric smooth muscle contractility in the regulatory effects of NPW on gastric motility. In Sprague-Dawley male rats equipped with gastric fistula, gastric emptying rate of the saline and peptone solutions was measured following subcutaneous administration of NPW (0.1 or 5 μg/kg) preceded by subcutaneous injections of saline, CCK-1 or CCK-2 receptor antagonists. Another group of rats with cannulas were injected subcutaneously with capsaicin for afferent denervation before commencing emptying trials. The effect of NPW on carbachol-induced gastric contractility and the role of CCK receptors in gastric smooth muscle contractility were also assessed in gastric strips. Peripheral injection of NPW delayed gastric emptying rate of both caloric and non-caloric liquid test meals, while administration of CCK-1 or CCK-2 receptor antagonists or denervation of small diameter afferents reversed NPW–induced delay in gastric emptying. Moreover, NPW inhibited antrum contractility in the organ bath. Our results revealed that peripherally administered NPW delayed liquid emptying from the stomach via the involvement of small diameter afferent neurons and CCK receptors, and thereby this regulatory role may contribute to its central regulatory role in controlling food intake and energy balance.

1. Introduction

Gastric motility, which is critical in the regulation of appetite, digestion, satiety and body weight [23], is accomplished by the integrated action of the central nervous system, enteric nervous system and gastrointestinal hormones. The gastrointestinal peptide hormones released from the pancreas and intestines in response to physical and chemical nature of the food actively modulate gastric emptying, and they are also involved in the regulation of satiety signals, food intake and energy metabolism [18,21,35]. When released during digestion, a large number of peptide hormones including cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and leptin inhibit the gastric emptying rate [3,20,33,47], while the orexigenic hormones ghrelin and motilin accelerate gastric emptying in the inter-digestive period [40]. Neuropeptide W (NPW), which is produced extensively in the hypothalamus as well as in the gastric antral G cells [16,31], regulates food intake and energy homeostasis both centrally and peripherally [42,43] but its role in the regulation of gastric functions was not identified yet. Since it is common that gastrointestinal peptides released in response to food ingestion are also involved in the short-term regulation of gastric functions [35], NPW is expected to modulate gastric emptying.

NPW, which exists in two endogenous molecular isoforms with 23 (NPW23) or 30 (NPW30) amino acids, is the endogenous ligand for the orphan G-protein coupled receptors GPR7 (NPBWR1) and GPR8 (NPBWR2) [16,41]. In parallel to its intense distribution in the hypothalamus, NPW acts as a central regulatory molecule for the regulation of feeding [13]. Intracerebroventricular administration of NPW exerts a diurnal biphasic effect on food intake [32,41,46], while plasma NPW

Abbreviations: CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; NPW, neuropeptide W; CCh, carbachol.

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levels and expression of NPW in the gastric mucosa were shown to fluctuate by feeding and fasting [6,31], indicating the central and peripheral role of NPW in appetite regulation. Since NPW released from G cells in the gastric antrum was demonstrated to inhibit adjacent gastric vagal afferents stimulated by mechanical stimuli [30], it is possible that NPW could be involved in the regulation of gastric emptying via the gastric vagal afferents. Moreover, we have recently shown that peripherally administered NPW protects against stress-induced gastric injury [44], which further necessitates to study the role of NPW in gastric motility control.

The first aim of our study was to investigate whether peripheral administration of NPW would change gastric emptying rate in rats equipped with gastric cannula. Secondly, it was aimed to evaluate the participation of small diameter afferents and CCK receptors in the NPW-induced control of gastric motility. Moreover, the direct effect of NPW on gastric smooth muscle contractility and the possible involvement of CCK receptors were investigated in gastric muscle strips.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (250–320 g, 12-week-old) were supplied from the Marmara University Animal Center (DEHAMER) and housed in a light- (12/12 h), humidity- (65–70 %) and temperature- (22 ± 2 °C) controlled room. The animals were fed with standard rat pellets and water *ad libitum*. Experiments were planned and performed in compliance with the Turkish law on the use of animals in experiments and with the guidelines of the New York Academy of Sciences. All experimental protocols were approved by the Marmara University Animal Care and Use Committee (approval code: 54.2018.mar; date: 04.06.2018).

2.2. Surgery and the measurement of gastric emptying rate

Rats (n = 16) were fasted for 18 h with free access to water, and were anesthetized with the intraperitoneal injections of ketamine (100 mg/kg) and chlorpromazine (0.75 mg/kg). Through a paramedian incision, a small stainless steel Gregory cannula was implanted in the gastric body, and the fitted cannula was then exteriorized through a midline stab incision [10]. The incisions were closed in layers, and the rats were returned to their home-cages to be housed individually. The rats were then allowed to recover for 3 weeks during which they were accustomed to light restraint in Bollman-type cages for 1– 2 h each day. At the end of the 3-week period, rats were placed in Bollman cages to measure the gastric emptying of test solutions every other day. The stomach of the overnight fasted rat was flushed with warm saline (0.9 % NaCl; 300 mOsm/kg H_2O) until clean and was allowed to drain freely for 45 min. Then, mixed with a nonabsorbable dilution marker (phenol red, 60 mg/L) liquid test meals containing either saline or peptone (4.5 % meat peptone II, w/v; Sigma) solutions at 37 °C were instilled into the gastric cannula in a 3-ml volume. Following a 5-min emptying time, the remaining solution in the stomach was then collected from the cannula into the petri dishes. The gastric emptying rate was calculated from the volume and phenol red concentration, which was determined spectrophotometrically at 550 nm [49]. Gastric emptying rate (GER) in 5 min was calculated with the following formula: GER = [(volume of instilled solution X absorbance of instilled solution) − (volume of collected fluid X absorbance of collected fluid)] / (average of both absorbances).

2.3. Assessment of the effect of NPW on gastric emptying rate and the role of CCK receptors

Based on the results of our earlier study [44], in which peripherally administered NPW was shown to protect against stress-induced gastric injury, we used the effective doses (0.1 μg/kg and 5 μg/kg) to investigate the effect of NPW on gastric emptying rate. In half of the rats equipped with cannula (n = 8), GERs of "non-caloric" saline and "caloric" peptone solutions instilled into the stomach were determined following subcutaneous (sc) injection of saline or NPW-30 (Phoenix Pharmaceuticals, 005–64, USA) at 5 min before the gastric emptying experiment. To study the effect of CCK receptors, CCK-1 receptor antagonist devazepide (1 mg/kg; Sigma; sc) or gastrin/CCK-2 receptor antagonist YM022 (1 mg/kg; Sigma; sc) was administered at five minutes before NPW (0.1 or 5 μg/kg; sc) injection. The emptying of physiological saline or peptone following the injections of different combinations of NPW and CCK receptor antagonists was studied in a random order on different days. At least 30 min was allowed between successive emptying tests. Each emptying trial with different agents was repeated at least 3 times in each animal, and the average of repeated tests was taken as the emptying result for each rat.

2.4. Assessment of the effect of afferent denervation on NPW-induced change in gastric emptying rate

At the fourth week following gastric surgery, half of the rats fitted with gastric cannula (n = 8) were injected with capsaicin for the denervation of small diameter afferent fibers. Freshly prepared capsaicin (Sigma) in 10 % Tween-80, 10 % absolute ethanol and 80 % saline was injected over a 3-day period [45]. Under light ether anesthesia, capsaicin doses were intraperitoneally (ip) injected as 25 mg/kg on the 1st day, 50 mg/kg on the 2nd day, and 50 mg/kg on the 3rd day, reaching a total of 125 mg/kg. Before the first capsaicin injection, rats also received atropine (2 mg/kg; ip) to decrease the acute effects of capsaicin on the respiratory and cardiovascular systems. Gastric emptying experiments were initiated 10 days after the last capsaicin injection. On the 9th day, in order to verify the effectiveness of capsaicin application on afferent innervation, a drop of 0.001 % capsaicin in saline was instilled into one eye of each rat to observe any wiping movements. None of the cannulated rats showed any wiping movements. Then, gastric emptying of saline or peptone following injections of NPW (5 μg/kg; sc) and CCK receptor antagonists was studied in a random order, as done in the non-capsaicin-treated rats.

2.5. Assessment of the effect of NPW on carbachol-induced gastric contractility and the role of CCK receptors

Additional male rats (n = 20) were fasted overnight and decapitated to remove their stomachs. Gastric antrum and corpus strips (~3 mm) were cut along the longitudinal axis. The strips were mounted vertically with 3.0 silk between 2 curved hooks and placed into 20-mL organ baths, which were aerated with a mixture of 95 % O_2 and 5 % CO_2 containing Krebs–Henseleit buffer solution (pH 7.4, 37℃, composition in mmol/L: NaCl, 118; $CaCI_2$, 1.8; KCl, 4.8;$MgS0_4$, 1.2; $NaHCO_3$, 25; KH_2PO_4, 1.2; glucose, 11). The continuous dynamic curves were recorded using isometric force transducers (IOBS 99 isolated tissue bath stand sets; Commat ltd, Ankara, Turkey) and visualized with MP 35 data acquisition system (BIOPAC Systems, Inc, Goleta, CA, USA). An equilibration period of 60 min was given, which included washouts at every 20 min, and the strip was then pre-loaded at an initial stretch of 1 g. At the beginning of each experiment, maximum contractile response to KCl (80 mM) was obtained. Following a washout, submaximal dose (3×10^{-6} mM) of carbachol (CCh), which was determined by a dose–response study, was added to the bath to get the contractile response to CCh. After refreshing the Krebs solution, NPW (0.1, 1, 3 or 5 nmol/L; corresponding to 0.3, 3.3, 10 and 17.8 μg/L, respectively) and submaximal dose of CCh were added in the organ bath at the same time. Then, the lower and higher doses of NPW were selected to investigate the involvement of CCK receptors in the contractile effects of NPW. The strips were pre-incubated for 5 min with devazepide (30 nmol/L) or YM022 (30 nmol/L), after which NPW (0.1 or 5 nmol/L) plus CCh were added to record the contractile responses. For each of the combinations with CCh and NPW in the organ bath, the average amplitude of contractions

within a 0.1 *sec* period (including the maximum amplitude) was recorded. At the end of each experiment, tissue wet weights were measured and the contractile responses were defined as g/100 mg wet tissue weight. The doses of the CCK antagonists were chosen based on the results of our previous research [37].

2.6. Statistical analysis

GraphPad Prism 9.3.0 (GraphPad Software, San Diego, CA, USA) was used for statistical analyses. In the gastric emptying experiments, one-way ANOVA followed by the Kruskal-Wallis test was used to determine the level of statistical significance between experimental groups, while Mann-Whitney test was used to compare the data of in vitro experiments. All data were presented as mean ± standard error of mean. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Effect of NPW on gastric emptying rate of saline and peptone solutions

Compared with the gastric emptying measurements preceded by saline injection, administration of NPW either at 0.1 μg/kg (NPW-0.1) or 5 μg/kg (NPW-5) dose significantly delayed the gastric emptying of liquid test meals ($p < 0.01$–0.001), showing the inhibitory effect of NPW on the gastric emptying of both the non-nutrient saline and meat peptone (Fig. 1). On the other hand, the CCK-1 receptor antagonist devazepide or the CCK-2 receptor antagonist YM022 abolished the NPW-0.1-induced delay in saline and peptone emptying ($p < 0.05$), while delayed peptone emptying due to NPW-5 was also abolished by both CCK receptor antagonists ($p < 0.01$–0.001). The inhibitory effect of NPW-5 on saline emptying was also reversed by the CCK-1 receptor antagonist ($p < 0.05$), but the CCK-2 receptor antagonist YM022 did not alter NPW-5-induced delay in saline emptying.

In order to evaluate the involvement of capsaicin-sensitive afferent fibers in the control of NPW-induced inhibition of gastric emptying, the higher NPW-5 dose was chosen. As compared to rats with intact afferents, NPW-5 was not capable of inhibiting saline emptying in capsaicin-treated rats, while NPW-5-induced delay in peptone emptying was abolished ($p < 0.001$; Fig. 2), implicating that NPW delays gastric emptying via the involvement of afferent neurons. Furthermore, when devazepide plus NPW-5 were injected in capsaicin-treated rats, both saline ($p < 0.001$) and peptone ($p < 0.05$) emptying were facilitated as compared to the corresponding emptying rates measured following only NPW-5 injection in rats with intact afferent fibers, suggesting that CCK-1 receptors may also mediate the NPW-induced delay in gastric emptying even in the absence of afferent fibers. On the other hand, YM022 in capsaicin-treated rats had no significant effect on NPW-induced delay in the gastric emptying of either saline or peptone.

3.2. Effect of NPW on CCh-induced contractility of corpus and antrum muscle strips

Since NPW resulted in delayed gastric emptying of both the non-caloric saline and the caloric peptone meal, we further investigated the direct effect of NPW on the contractile function of the gastric corpus and antrum. Accordingly, strips of corpus and antrum were placed in isolated organ baths and NPW was added (0.1, 1, 3, and 5 nM) along with the submaximal dose (3×10^{-6} mM) of CCh. CCh-induced contractile responses in the corpus strips were not altered with the addition of NPW (Fig. 3). Similarly, addition of NPW in lower concentrations did not change antral contractility, but NPW at the 5 nM concentration decreased the contractile response of the antrum strips to submaximal CCh ($p < 0.05$).

Addition of either of the CCK receptor antagonists to the organ bath containing NPW, which had no impact on cholinergic contraction of the

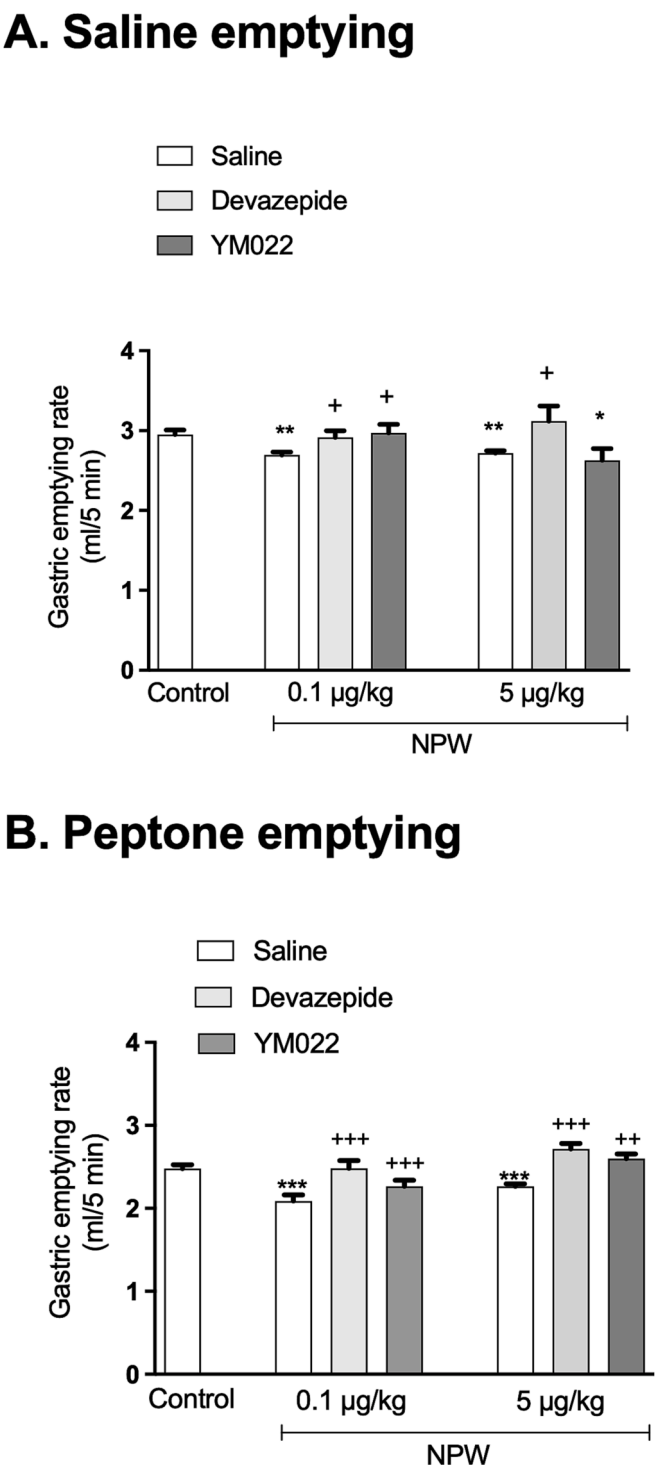

Fig. 1. Gastric emptying rate (GER) following intragastric instillation of either saline (A) or peptone (B) in conscious rats equipped with gastric cannulas ($n = 8$). GER was determined at 5 min after the subcutaneous injection of saline (control) or neuropeptide W (NPW; 0.1 or 5 μg/kg; corresponding to 0.03 and 1.66 nmol/kg, respectively). NPW injections were preceded by subcutaneous injection of either saline, cholecystokinin (CCK)-1 or CCK-2 receptor antagonist (Devazepide, 1 mg/kg or YM022, 1 mg/kg; respectively). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, compared to GER measured following only saline injection. +$p < 0.05$, ++$p < 0.01$, +++$p < 0.001$; compared to GER measured following saline plus NPW injection.

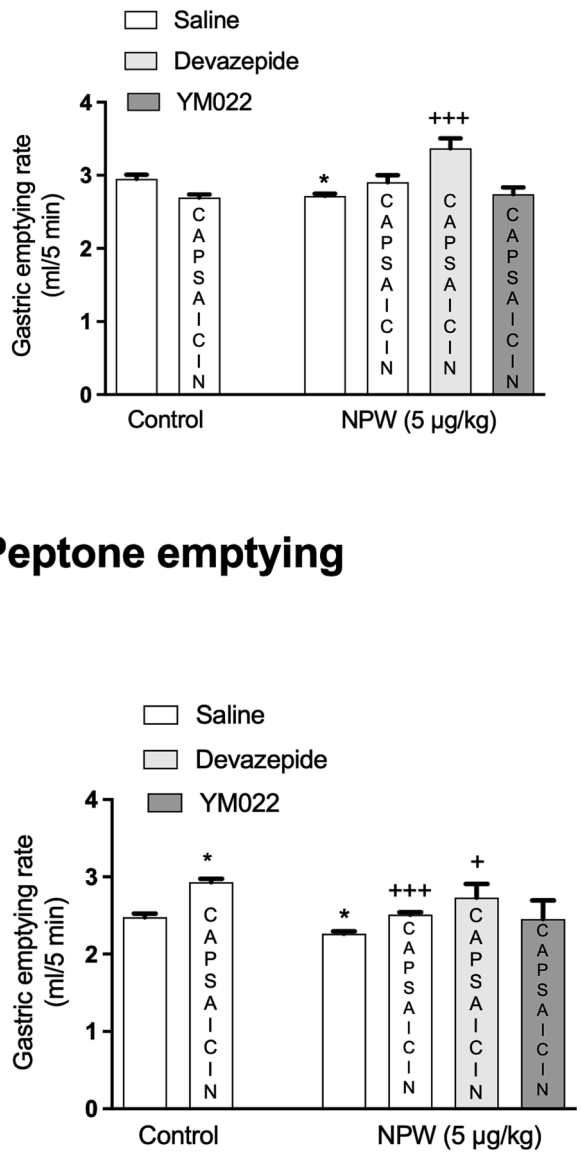

Fig. 2. Gastric emptying rate (GER) in conscious rats with gastric cannulas that were treated with capsaicin for afferent denervation (n = 8), as compared to non-capsaicin-treated rats (n = 8). GER was determined following intragastric instillation of either saline (A) or peptone (B) after the subcutaneous injection of saline (control) or neuropeptide W (NPW; 5 µg/kg; corresponding to 1.66 nmol/kg) preceded by subcutaneous injection of either saline, cholecystokinin (CCK)-1 or CCK-2 receptor antagonist (Devazepide, 1 mg/kg or YM022, 1 mg/kg; respectively). *p < 0.05, compared to GER measured following only saline injection. +p < 0.05, +++p < 0.001; compared to GER measured following saline plus NPW injection.

corpus strip, did not alter the contractile responses of the corpus strips (Fig. 4). Similarly, addition of devazepide or YM022 to organ bath containing the low dose of NPW did not have a significant effect on CCh-induced contraction of the antrum strips. On the other hand, the inhibition of CCh-induced contractile response of the antrum strips due to 5 nM NPW was not evident when the CCK-1 receptor antagonist was added to the organ bath, but inhibition of contraction by 5 nM NPW was not affected by the CCK-2 receptor antagonist, implicating that the inhibitory effect of the high dose of NPW on antrum muscle contraction involves the interaction of CCK-1 receptors.

4. Discussion

The results of the present study revealed that peripheral administration of NPW delayed gastric emptying rate of both non-caloric and caloric solutions, while both CCK-1 and CCK-2 receptor antagonists as well as afferent denervation by capsaicin reversed the NPW–induced inhibition of gastric emptying. Moreover, NPW directly suppressed the cholinergic contractility of antral smooth muscle, suggesting a direct effect of NPW in delaying the emptying rate of stomach. These findings suggest that NPW is involved in the physiological control of gastric motility that may include the activation of CCK receptors and small diameter afferent fibers, as well as its putative receptors on the gastric smooth muscle cells.

Understanding of the physiological mechanisms that control gastric motility and gastric emptying is essential in the management and treatment of gastric dysmotility, which ranges from delayed gastric emptying to abnormally rapid gastric transit [12,17,39,48]. Gastric emptying is regulated by neurohormonal control mechanisms that are activated by the physical composition (solid or liquid) and chemical nature (nutrients, caloric density) of the food [18]. Vagal preganglionic cholinergic neurons as well as postganglionic cholinergic or non-cholinergic neurons arising from the myenteric plexus coordinate the gastric emptying, while intestinal and pancreatic hormones released during digestion inhibit gastric motility by modulating the activity of these neurons. The gastrointestinal peptide hormones that regulate food intake and gastric motility were shown to act through their receptors expressed on vagal afferent neurons located in the nodose ganglia [11]. The orexigenic hormone ghrelin affects the feeding behavior and accelerates gastric emptying via its receptor on gut-innervating vagal afferent fibers [8]. On the other hand, CCK and GLP-1 were reported to delay gastric emptying and thereby cause satiety via the stimulation of their receptors on vagal afferent fibers [11,14,15,19]. Activation of the CCK-1 or CCK-2 receptors, which are both expressed on smooth muscle cells and on the neurons of the central and peripheral nervous systems, delays gastric emptying by relaxing the lower esophageal sphincter and increasing the tone of the pyloric sphincter [25]. Our findings revealed that gastric emptying rate of both the caloric and non-caloric liquid meals was delayed by NPW, while afferent denervation by capsaicin abolished the NPW-induced delay in gastric emptying, suggesting that modulation of gastric emptying by NPW is mediated by small diameter afferent fibers, which include the vagal afferents. Moreover, the gastric inhibitory effect of exogenous NPW was also reversed by both CCK-1 or CCK-2 receptor antagonists, implicating the involvement of CCK receptors in the regulation of gastric emptying by NPW. Moreover, antral smooth muscle contractility was depressed by the higher dose of NPW, showing an inhibitory effect of NPW on the major driving force of gastric emptying. Although it was previously reported that the NPW receptor GPR7 and L-type calcium channels are co-expressed in vascular smooth muscle to regulate contractility [24], the presence of NPW receptors on the gastric smooth muscle is not described yet. However, our present findings show that NPW induces the reflex inhibition of gastric emptying via the involvement of small diameter afferent fibers and CCK receptors, while contractility of antral muscle is directly suppressed by NPW to inhibit the antral motor pump.

The chemical and physical properties of a liquid test meal, including its acidity, viscosity, osmolarity, protein, and fat content, determine its gastric emptying rate [15]. Peptone delays gastric emptying via the CCK-1 receptors and capsaicin-sensitive small diameter afferent neurons, and the inhibitory effect of peptone on gastric emptying in the rat coincides with the release of endogenous CCK [15]. In the present study, gastric emptying of peptone was slower than saline emptying, showing the well-known inhibitory role of peptone on gastric emptying rate. Our results

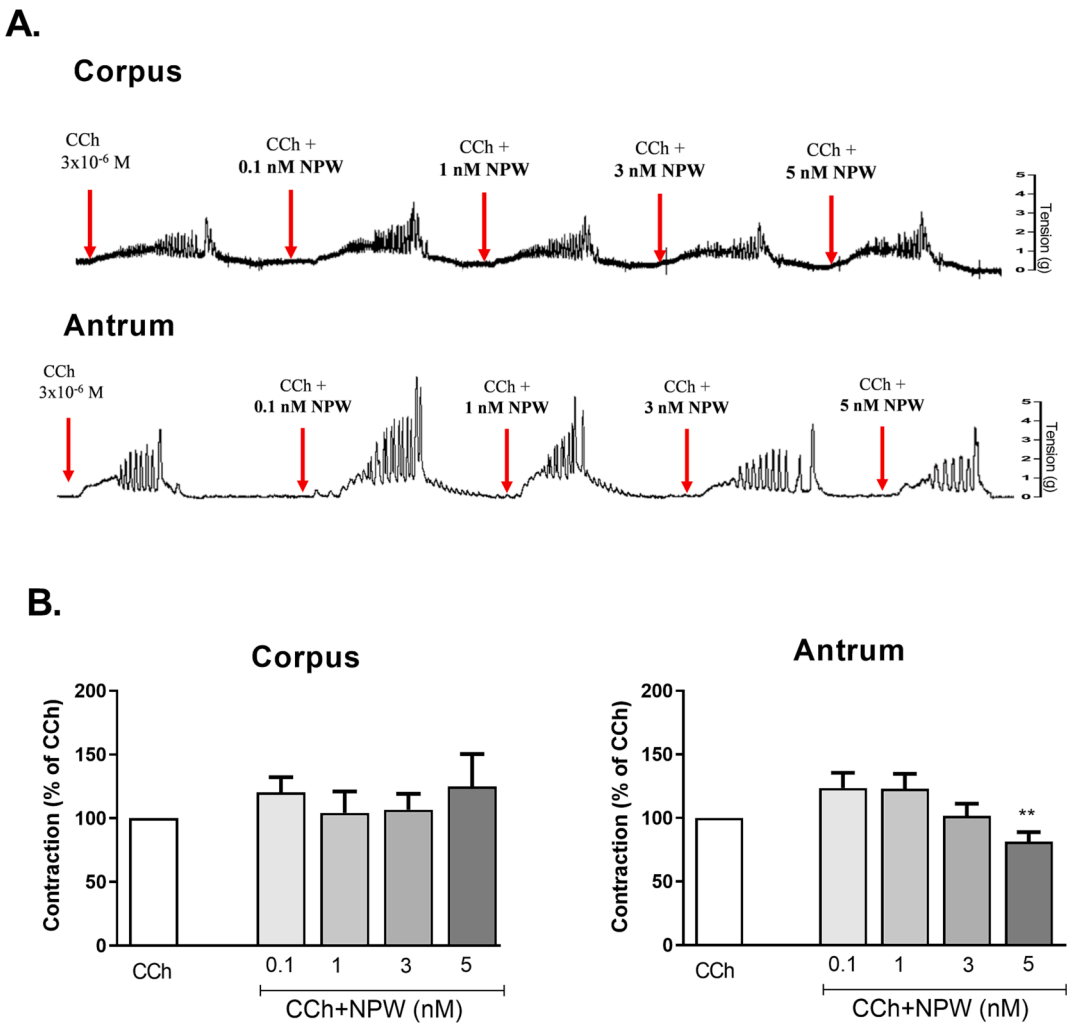

Fig. 3. Representative peak contractions (A) and the average peak (%) contractions of the corpus (B) and antrum (C) strips mounted in organ baths that were contracted with the submaximal dose of carbachol (CCh, 3×10^{-6} mM) either in the absence or presence of neuropeptide W (NPW; 0.1, 1, 3 and 5 nM; corresponding to 0.3, 3.3, 10 and 17.8 μg/L, respectively) in the bath (n = 5–8). The average amplitude of contractions within a 0.1 *sec* period (including the maximum amplitude) was recorded and defined as g/100 mg wet tissue weight. *$p < 0.05$; compared to % contraction of CCh in the absence of NPW.

also demonstrated that peripheral administration of NPW delayed saline emptying and further delayed peptone-induced slower gastric emptying rate, while afferent denervation by capsaicin as well as CCK receptor antagonists abolished NPW-induced delay in peptone emptying. These results suggest that the inhibitory effect of NPW on gastric emptying could be associated with the endogenous release of CCK and dependent on CCK receptors. On the other hand, high-dose NPW-induced delay in saline emptying was not reversed by CCK-2 antagonist, suggesting a non-CCK-2-receptor dependent mechanism of NPW in inhibiting gastric emptying. Li et al. [29] have shown that gastric vagal afferents originating from the gastric mucosa express GPR7 and are located close to NPW-containing G cells, suggesting that NPW released from these cells could modulate the activity of neighboring gastric vagal afferents. They have also reported that exogenous administration of NPW following food intake selectively modulates the mechanosensitivity of gastric vagal afferents. Although they have shown that the gastric emptying of liquid and solid test meals measured by breath testing ($^{13}CO_2$) in mice was not changed with peripheral administration of NPW, we demonstrated the inhibitory effect of NPW on the gastric emptying of liquid test meals in cannulated rats. The discrepancy in results may be related with the dose of NPW or the method of gastric emptying. Nevertheless, based on the aforementioned studies, our findings implicate that the gastric inhibitory effect of NPW could be mediated by the small diameter afferents that express NPW receptors or NPW could inhibit gastric emptying by stimulating the release of CCK, which binds to its receptors on small diameter afferents [34]. Regarding that PYY, leptin and GLP-1 interact with CCK-expressing vagal afferents in modulating food intake and gastric emptying [5,9,26], it is possible that CCK receptor activation on the vagal afferents is also involved in NPW-induced regulation of gastric motility.

Several satiety-inducing peptide hormones such as CCK, GLP-1, peptide YY and leptin are also known to inhibit gastric emptying [3,18,20,33]. When given exogenously, CCK and PYY slow down the gastric emptying rate by the relaxation of the proximal stomach, inhibition of antral motor activity and pyloric contraction, while they also inhibit the energy intake [2,4,27,36,38]. Although central administration of NPW was suggested to have an orexigenic effect during the light phase, it has an opposing anorexigenic effect on energy expenditure and feeding behavior during the dark phase, when feeding normally takes place [1,32,41,46]. In accordance with that, plasma NPW concentrations were lower in the gastric antral vein of the fasted rats, but the plasma levels were increased after *ad libitum* refeeding [31]. Central administration of NPW has increased c-Fos expression as an indicator of neuronal activation in several brain sites, which are associated with the hypothalamic control of food intake [28]. Research on the distribution and localization of NPW in the brain has proven that NPW is involved in

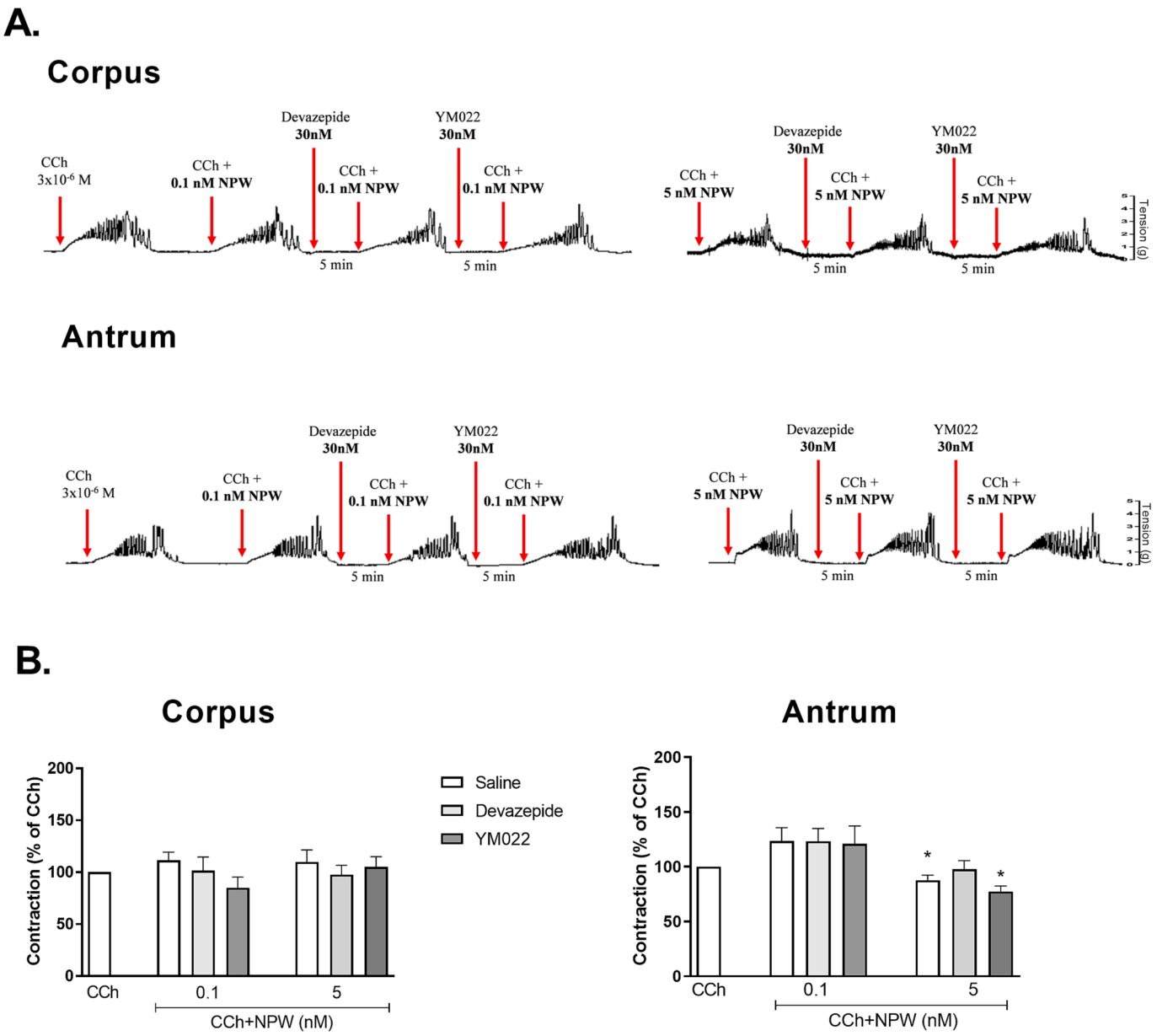

Fig. 4. Representative peak contractions (A) and the average peak contractions of the corpus (B) and antrum (C) strips mounted in organ baths that were contracted with the submaximal dose of carbachol (CCh, 3×10^{-6} mM) in the absence or presence of neuropeptide W (NPW; 0.1 and 5 nM), CCK-1 receptor antagonist (Devazepide) or CCK-2 receptor antagonist (YM; YM022) in the bath (n = 5–8). The average amplitude of contractions within a 0.1 *sec* period (including the maximum amplitude) was recorded and defined as g/100 mg wet tissue weight. *$p < 0.05$; compared to % contraction of CCh in the absence of NPW.

feeding-regulating neuronal circuitry along with other neurons that release peptides related with feeding behavior, such as neuropeptide Y (NPY), orexin, melanin-concentrating hormone (MCH), and proopiomelanocortin (POMC) [43]. In male knock-out mice lacking the genes encoding GPR7 receptor, hyperphagia, decreased energy consumption, reduced locomotor activity, increased body weight with late-onset obesity were observed, and it was suggested that the NPW receptor may have a distinct role in the regulation of energy homeostasis independent of leptin or melanocortin signaling pathways [22]. On the other hand, based on the upregulation of NPW expression in both leptin- or leptin receptor-deficient mice, it was reported that the role of NPW in the regulation of feeding and energy metabolism could be critical in the presence of leptin insufficiency, during which NPW may suppress feeding via the melanocortin-4-receptor signaling pathway [7]. In addition to the central anorexigenic effects of NPW, our present findings show that peripheral administration of NPW delays gastric emptying and thereby it is expected to contribute to satiety and reduced energy intake, because gastric accommodation and gastric emptying regulate intestinal exposure of nutrients and thereby participate in the control of appetite and satiety [23].

5. Conclusion

Our results demonstrate for the first time that peripherally administered NPW delayed liquid emptying from the stomach via the involvement of small diameter afferent neurons and CCK receptors. Thus, this peripheral inhibitory effect of NPW on gastric emptying may contribute to its central regulatory role in controlling food intake and energy balance. Our results also suggest that putative NPW receptor agonists/antagonists or agents that modulate the GPR7 signaling pathway might have a beneficial potential in the management and treatment of gastric dysmotility.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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