Rebound Contraction by Nitric Oxide in the Longitudinal Muscle of Porcine Gastric Fundus

Junho La, Taewan Kim, Taesik Sung, Jeongwoo Kang, Hyunju Song, Hyunju Kim and Ilsuk Yang*

Department of Veterinary Physiology, College of Veterinary Medicine, Seoul National University, Suwon 441-744, Republic of Korea

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ABSTRACT—The rebound contraction induced by electrical field stimulation (EFS) and nitric oxide (NO) donor, S-nitroso-L-cysteine (cysNO), were investigated in the longitudinal muscle of porcine gastric fundus (LM-PGF). Under the presence of atropine and guanethidine, cysNO and EFS produced sequential relaxation-contraction in LM-PGF. Tetrodotoxin abolished the EFS-induced response, while leaving the cysNO-induced one unaffected. A soluble guanylate cyclase inhibitor, lH-[1,2,4]-oxadiazolo-[4,3-a]-quinoxalin-1-one, inhibited both cysNO and EFS-induced biphasic response. A cGMP analogue only relaxed LM-PGF. A phosphodiesterase V inhibitor, zaprinast, prolonged the cysNO and the EFS-induced relaxation and inhibited the rebound contraction. The rebound contraction was inhibited by verapamil, an L-type Ca\(^{2+}\) channel blocker. The cysNO and the EFS-induced biphasic response were inhibited by ryanodine plus cyclopiazonic acid or by ruthenium red, a ryanodine-receptor blocker. LM-PGF was relaxed on exposure to caffeine and then produced a verapamil-sensitive rebound contraction during the washout period. CysNO and EFS did not induce the rebound contraction in the presence of caffeine. These results suggest that the NO-induced rebound contraction involves both Ca\(^{2+}\)-release from the ryanodine-sensitive store and Ca\(^{2+}\)-influx through L-type channels. Although the NO-induced biphasic response is dependent on cGMP, rapid removal of cGMP seems necessary for the rebound contraction.

Keywords: L-type Ca\(^{2+}\) channel, Longitudinal muscle of porcine gastric fundus, Ryanodine-sensitive Ca\(^{2+}\) channel, S-Nitroso-L-cysteine, Soluble guanylate cyclase

Nitric oxide (NO), derived from L-arginine by NO synthase (NOS), is considered as an inhibitory nonadrenergic-noncholinergic (NANC) neurotransmitter that relaxes smooth muscles by activating soluble guanylate cyclase (sGC) (1). However, NO-induced contraction or excitation was also reported in many types of smooth muscles, yet there is not a consensus about the exact mechanism (2 – 7). In opossum esophagus, methylene blue inhibits NO-induced contraction, and a membrane permeable cGMP analogue mimics this contractile effect of NO (4). In contrast, methylene blue has no effect on NO-induced contraction in rat ileum, and the cGMP content of this tissue hardly increases during contraction (3). In the guinea pig ileum, NO-induced contraction is blocked by tetrodotoxin (TTX) and inhibited by atropine and substance P antagonist, which suggests that the contraction by NO is a neurogenic response (2).

The Ca\(^{2+}\) source for NO-induced contraction also seems to be different among tissues. For example, NO-induced contraction is reduced slightly by nifedipine but suppressed strongly by ryanodine in sheep urinary bladder neck (5). Comparatively, it is unaffected by ryanodine but reduced by nifedipine in rat ileum (3).

In our previous study, the longitudinal muscle of porcine gastric fundus (LM-PGF) showed a sequential relaxation-contraction response in a NOS inhibitor-sensitive manner upon electrical field stimulation (EFS) (8). In the present study, our aim was to investigate the involvement of a TTX-sensitive mechanism, the participation of cGMP, and the Ca\(^{2+}\) sources utilized in the NO-induced rebound contraction of LM-PGF.

MATERIALS AND METHODS

Preparation of smooth muscle strips and Recording of muscle tension

Porcine gastric fundus muscle was obtained from local...
slaughterhouse and transported in refrigerated Krebs solution to the laboratory for dissection. Longitudinal muscle was carefully dissected to a muscle strip with approximate dimension of 2 × 10 mm. The muscle strip was suspended in the tissue holder and placed between two platinum plates, which were located in 20-ml chamber filled with warmed (37 ± 1°C) and aerated (95% O₂ and 5% CO₂) Krebs solution. The upper end of the strip was connected to an isometric force transducer (FT-03; Grass-Telefactor, West Warwick, RI, USA). The output of the transducer was processed through MacLab 2/e (AD Instruments, Castlehill, Australia) and recorded on a Macintosh LC III computer. Two platinum plates were connected to the electrical stimulator (S88, Grass-Telefactor).

For the experiment using caffeine, the muscle strip was incubated in a 2-ml chamber into which the oxygenated and pre-warmed Krebs solution was continuously perfused at a rate of 1.6-ml/min. The temperature of the solution in the bath was maintained at 37.0 ± 0.5°C.

An initial tension of 1 g was loaded on each muscle strip during the 60-min equilibration period with rinsing every 15 min. The muscarinic antagonist atropine (1 μM) and adrenergic transmission blocker guanethidine (30 μM) were administered to set up the NANC condition. Muscle tone was not raised by any contractile agent to exclude the possible interference with a contractile mechanism except for the experiment using ryanodine and CPA. Since these two drugs significantly elevated the muscle tone by themselves, the control experiment was performed in the condition where the muscle tone was raised to a similar extent by carbachol (0.3 μM). As a NO donor, we chose S-nitroso-L-cysteine (cysNO) because the response of LM-PGF to cysNO most closely resembled that to EFS (see results).

Data analyses
A rebound contraction was defined as the contraction that overshot the initial tone after recovery from relaxation. The amplitude of cysNO-induced rebound contraction (cysNO-RC) was calculated from the difference between the tension just before the cysNO administration and the peak tension of rebound contraction. When required, the duration of cysNO-induced relaxation was measured as the time taken to fully restore the initial tone from the beginning of relaxation. The effect of each drug was evaluated by comparing the amplitude of cysNO-RC before drug treatment with that after. The magnitude of cysNO-induced relaxation was measured by the difference between the tension just prior to cysNO administration and the nadir tension of relaxation and calculated as a percentage of the pre-stimulus tension level.

CysNO preparation
CysNO was prepared according to the modified method of Barbier and Lefevbre (9). Briefly, the same volume of acidified NaNO₂ (200 mM in 1 N HCl, pH<2) and L-cysteine (200 mM in distilled water) were mixed together under 4°C. The solution turned bright red as cysNO was formed. CysNO solution was prepared immediately before use and kept in ice pot under the protection from light.

Solution and drugs
The Krebs solution used in these experiments contained 118.4 mM NaCl, 4.7 mM KCl, 1.2 mM KH₂PO₄, 1.2 mM MgSO₄, 25 mM NaHCO₃, 2.5 mM CaCl₂ and 11.7 mM glucose. 1H-[1,2,4]-Oxadiazolo-[4,3-a]quinoxalin-1-one (ODQ) and (±)-S-Nitroso-N-acetylpenicillamine (SNAP) were purchased from Biomol (Plymouth Meeting, PA, USA). Zaprinast was from Calbiochem (San Diego, CA, USA). The following drugs were purchased from Sigma (St. Louis, MO, USA): sodium nitrite, L-cysteine, sodium nitroprusside dihydrate (SNP), guanethidine sulfate, atropine sulfate, charbamylcholine chloride (carbachol, CCh), phenolamine hydrochloride, (±) epinephrine, tetrodotoxin, cyclopiazonic acid, 8-bromoguanosine 3’-5’-cyclic monophosphate (8-Br-cGMP), ruthenium red, verapamil, caffeine, and dimethylsulfoxide (DMSO).

Statistical analyses
Data are expressed as means ± S.E.M. with n, the number of muscle strips. Statistical comparisons were made by the paired Student’s t-test, considering the P values of 0.05 or less to be statistically significant.

RESULTS

Effects of EFS and NO donors on LM-PGF
As reported in our previous study (8), muscle strips of LM-PGF maintained tone at rest (1.63 ± 0.08 g, n = 48) and showed a sequential relaxation-contraction in response to EFS (80-V, 1 – 16-Hz train pulse with 0.5-ms duration for 10-s) under the presence of atropine (1 μM) and guanethidine (30 μM). Figure 1 shows representative examples of various relaxant stimuli in the same experimental condition. Acidified NaNO₂, cysNO, SNAP and SNP all relaxed the LM-PGF in a concentration-dependent manner. However, the relaxation induced by SNAP and SNP were more sustained and not followed by complete tone recovery. Only acidified NaNO₂ and cysNO could mimic the EFS-induced transient biphasic response. Upon the administration of an equivalent amount (equal volume and concentration) of HCl, the pH of the bathing fluid rapidly dropped by 0.22 ± 0.02 (n = 6) and was restored to the initial pH within 7 min. However, LM-PGF did not respond to HCl, indicating that the biphasic response induced by acidified NaNO₂ or cysNO was not due to the pH change. Since all the relaxant stimuli that could induce a biphasic
response had a short relaxation period, it was examined whether the biphasic response could be induced by any other ‘short-acting’ relaxant activating a different intracellular pathway. Among several relaxants, epinephrine (10 μM) induced a relaxation comparable with that by acidified NaNO$_2$ or cysNO and yet it did not produce the rebound contraction under the presence of α-adrenoceptor blocker phentolamine (Fig. 1F). This result implied the rebound contraction was a specific response to the endogenous NO and the highly unstable NO donors.

CysNO was more potent than acidified NaNO$_2$. The cysNO-induced relaxation was readily observable at 0.1 μM and usually reached 100% before 100 μM. Comparatively, an apparent cysNO-RC began to emerge around 3 μM, and the maximal contraction was observed at 100 μM; its relative amplitude was 43.5 ± 8.9% (n = 9) of carbachol (1 μM)-induced tonic contraction, and the EC$_{50}$ value of cysNO-RC was 14.1 ± 3.0 μM (n = 9).

The rebound contraction induced by 100 μM cysNO was reproducible. Taking the amplitude of the first administration-induced cysNO-RC as 100%, that of the second and the third were 101 ± 2% and 100 ± 2%, respectively (n = 25). Therefore, we used 100 μM cysNO as an exogenous NO donor throughout this study. As shown in Fig. 2, the biphasic response induced by 100 μM cysNO was not affected by TTX (1 μM) that could completely abolish the EFS-induced response.

**Involvement of cGMP in the NO-induced rebound contraction**

A specific sGC inhibitor, ODQ, raised the resting tension from 2.23 ± 0.82 to 3.15 ± 0.31 g at 1 μM (n = 12), and no further elevation of resting tone was observed above that concentration, which implied that tonically active sGC was adequately inhibited by 1 μM ODQ. As represented in Fig. 3A and B, ODQ (1 – 10 μM) significantly inhibited the cysNO-induced biphasic response in a concentration-dependent manner. The inhibitory effect of ODQ was con-
firmed in the experiment in which EFS was used as a relaxant stimulus (Fig. 3C). These results indicated that the NO-induced rebound contraction as well as relaxation was dependent on cGMP production.

We examined whether a cGMP analogue could mimic the biphasic response. The membrane permeable cGMP analogue 8-Br-cGMP (1–10 μM) failed to induce a biphasic response, but only produced sustained relaxation in a concentration-dependent manner (Fig. 4). This result raised the possibility that the persistent presence of cGMP might interfere with the rebound contraction in LM-PGF. We tested this hypothesis by using zaprinast, an inhibitor of cGMP-specific phosphodiesterase (PDE5), to suppress the hydrolysis of cGMP. Upon administration, zaprinast

![Fig. 2. Effects of TTX on the EFS and the cysNO-induced response in LM-PGF. TTX (1 μM) did not affect the cysNO (100 μM)-induced biphasic response, while it abolished the EFS-induced one (80-V, 16-Hz train pulse with 0.5-ms duration for 10 s). Note the small contraction instead of relaxation during EFS application under the presence of TTX. Dots and asterisks represent the time of cysNO and EFS application, respectively.](image1)

![Fig. 3. Effect of sGC inhibitor on the cysNO and the EFS-induced response in LM-PGF. A: Original traces superimposed to represent the inhibitory effect of ODQ (10 μM) on the cysNO (100 μM)-induced biphasic response (arrows: control, arrowheads: ODQ). B: Summarized graph showing the concentration-dependent inhibitory action of ODQ on the cysNO (100 μM)-RC (n = 12). **: significantly different from the control value (P<0.01). C: ODQ also inhibited the EFS-induced biphasic response. The numbers at the bottom of the trace indicate the frequency of EFS.](image2)

![Fig. 4. Effect of cGMP on LM-PGF. A membrane-permeable cGMP analogue 8-Br-cGMP did not induce the rebound contraction but only produced the sustained relaxation.](image3)
transiently relaxed LM-PGF and lowered the resting tone from 1.86 ± 0.34 to 1.32 ± 0.17 g (n = 6) at 30 μM. It increased the duration of cysNO-induced relaxation to 263 ± 19% (n = 6, P<0.01) and inhibited cysNO-RC by 97.4 ± 1.9% (n = 6) at 30 μM (Fig. 5: A and B). Zaprinast had a similar effect on the EFS-induced biphasic response (Fig. 5C). Zaprinast enhanced the rebound contraction induced by low frequencies of EFS (1 – 8 Hz), while it prolonged the relaxation but significantly reduced the rebound contraction induced by high frequencies of EFS (16 – 50 Hz).

Dependency of the NO-induced rebound contraction on the Ca^{2+}-influx through L-type channel

Verapamil, an L-type Ca^{2+} channel blocker, decreased the resting tone, and significantly reduced the amplitude of cysNO-RC by 81.9 ± 6.2% (n = 6) at 10 μM, but did not produce any notable change in tension-recovery from relaxation (Fig. 6: A and B). The duration of the cysNO-induced relaxation was 113 ± 8% of control value (n = 6, P>0.3) at 10 μM verapamil. As represented in Fig. 6C, the EFS-induced rebound contraction (EFS-RC) was also inhibited by 10 μM verapamil.

Dependency of the NO-induced rebound contraction on the Ca^{2+}-release from ryanodine-sensitive store

Both the Ca^{2+}-influx through voltage-operated Ca^{2+} channel and the Ca^{2+}-release from the ryanodine-sensitive internal store are involved in the contraction of gastrointestinal longitudinal muscles, and these two events are linked with each other (10). Therefore, the participation of ryanodine-sensitive Ca^{2+} store in cysNO-RC and EFS-RC could not be excluded.

To investigate this issue, we tried to inhibit Ca^{2+}-mobilization from the ryanodine-sensitive store by using a high concentration of ryanodine (30 μM). In combination with ryanodine, we administered cyclopiazonic acid (CPA, 10 μM) to inhibit the store-refilling. This combined treat-
ment induced tonic contraction (5.42 ± 0.65 g, n = 5) that reached plateau within 30 min. Verapamil (10 μM) significantly inhibited this tonic contraction, which indicated that the combined treatment activated Ca\(^{2+}\)-influx through L-type channels (Fig. 7A).

In the presence of ryanodine and CPA, LM-PGF showed gradual decrease of cysNO-induced biphasic response as cysNO was administered every 20 min (Fig. 7: B and C). In comparison, the time-matched experiment showed that cysNO-induced biphasic response was not altered by the repeated cysNO administration in the muscle strips whose tension had been raised from 2.26 ± 0.36 to 7.06 ± 0.93 g (n = 4) by CCh (0.3 μM). This combined treatment also affected the EFS-induced biphasic response. As shown in Fig. 7D, the EFS-induced relaxation was significantly inhibited, and the EFS-RC was abolished in the presence of ryanodine and CPA.

To verify that cysNO-RC and EFS-RC involve Ca\(^{2+}\)-release from the ryanodine-sensitive store, we examined whether an antagonist and an agonist of the ryanodine receptor (RyR) could affect the rebound contraction. The RyR antagonist ruthenium red decreased the resting tone, and significantly inhibited cysNO-RC in a concentration-dependent manner (20 – 200 μM). Moreover, it suppressed the cysNO-induced relaxation as ryanodine plus CPA did (Fig. 8: A and B). The inhibitory effect of ruthenium red was also observed in the EFS-induced biphasic response. The potent RyR agonist caffeine (1 – 10 mM) relaxed the LM-PGF by itself, and LM-PGF produced a verapamil-sensitive rebound contraction during the washout period (Fig. 9A). This response was similar in pattern to the cysNO-induced biphasic response. The effect of caffeine was not affected by ODQ (10 μM), indicating that it was not related to the cGMP production (data not shown). In addition, both cysNO and EFS did not produce the rebound contraction when LM-PGF had been relaxed in the presence of caffeine (Fig. 9: B and C).

**DISCUSSION**

In the present study, we observed that cysNO, a NO donor, mimicked the EFS-induced biphasic response in
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LM-PGF under an NANC experimental condition. Upon cysNO administration, LM-PGF rapidly relaxed and then restored its initial tone to progressively produce a prominent rebound contraction. This contraction was not affected by TTX. Therefore, the mechanism of NO-induced contraction in LM-PGF seems different from that in the guinea pig ileum where NO-induced contraction is blocked by TTX (2).

**Involvement of cGMP in the NO-induced rebound contraction**

It is well known that cGMP mainly mediates NO-induced relaxation in smooth muscle cells (11). To inspect whether cGMP also mediates the cysNO and the EFS-
induced rebound contraction in LM-PGF, we examined the effects of ODQ, 8-Br-cGMP, and zaprinast. ODQ significantly inhibited the cysNO and the EFS-induced biphasic response. It indicates that the NO-induced biphasic response is dependent on cGMP production in LM-PGF. The sequential relaxation-contraction may be due to that i) cGMP activates both the relaxation and the contraction mechanism but the latter is late in onset, or ii) cGMP is responsible only for relaxation but a cGMP-activated mechanism in turn induces contraction when [cGMP] is decreased. Two sets of our experimental evidence oppose the former supposition. First, a PDE-resistant cGMP analogue, 8-Br-cGMP (12), only induced relaxation in LM-PGF. Second, an inhibitor of PDE5, zaprinast, increased the duration of the cysNO and the EFS-induced relaxation but significantly inhibited the rebound contraction. These results imply that the rebound contraction cannot occur if cGMP is not rapidly removed. This notion is supported by the observation that the rebound contraction was induced only by NO donors which are known to be highly unstable and expected to be ‘short-acting’ (13). Therefore, it seems more plausible that cGMP primarily mediates relaxation in LM-PGF, and the rebound contraction is produced in the absence of cGMP by a mechanism that had been activated via a cGMP-dependent pathway. However, our conclusion is tentative until studies are done to compare the [cGMP] in the relaxation phase with that in the rebound contraction phase. Work of this nature was beyond the scope of present study.

Ca\textsuperscript{2+} for the NO-induced rebound contraction

We found that verapamil inhibited both cysNO-RC and EFS-RC in LM-PGF, which indicates that the rebound contraction is dependent on the Ca\textsuperscript{2+}-influx through L-type channels. It was reported that Ca\textsuperscript{2+}-influx through L-type channels could activate the RyR to trigger Ca\textsuperscript{2+}-induced Ca\textsuperscript{2+} release in smooth muscle cells (14, 10). Reversely, it was also suggested that Ca\textsuperscript{2+}-release from the ryanodine-sensitive store could induce Ca\textsuperscript{2+}-influx through voltage-operated Ca\textsuperscript{2+} channels (15). These reports raised the possibility that together with the Ca\textsuperscript{2+}-influx through L-type channels, Ca\textsuperscript{2+}-release from the ryanodine-sensitive store might be involved in the NO-induced rebound contraction.

We tested this possibility by inhibiting the Ca\textsuperscript{2+}-mobili-
zation from the ryanodine-sensitive store and observed that cysNO-RC was gradually reduced after the combined treatment of ryanodine and CPA. This result is a complicated one to analyze since the gradual reduction of cysNO-RC indicates that store was ‘gradually depleted’, while the significant contraction after the combined treatment implies that store was ‘already depleted’ and the refilling signal was activated. The basis of this discrepancy remains unclear, but it can be supposed that in our experimental condition, the store was refilled partially via a CPA-insensitive pathway after the combined treatment. It was suggested that in some smooth muscle, part of the refilling of internal calcium stores was not sensitive to CPA (16). In this case, if the CPA-insensitive refilling process cannot fully compensate for the Ca\(^{2+}\)-release by agonist, then the agonist-induced response will gradually decline. Thornbury et al. also reported that muscle tone increased and the sharp rebound contraction gradually decreased on exposure to CPA in the urinary bladder neck muscle of sheep (5).

While the effect of the combined treatment on the cysNO-RC is complicated, that on the EFS-RC is clear. As represented in Fig. 7D, EFS-RC was abolished by the combined treatment. This result may be due to that EFS is different from cysNO in its ability to release NO. It should be noted that 100 \(\mu\)M cysNO usually induced a larger response than EFS used in our experiment (Fig. 1: A and C). Therefore, it seems likely that the EFS-released NO was insufficient to mobilize enough calcium for inducing the rebound contraction in the presence of ryanodine and CPA. However, it is also possible that ryanodine and CPA act prejunctionally to reduce the EFS-induced NO release.

Because the combined treatment induced a verapamil-sensitive tonic contraction by itself, it can be argued that the decrease of the rebound contraction might have resulted from the reduction of L-type channel availability. However, this assumption withstands our observation that the rebound contraction was reproducible in the CCh-precontracted LM-PGF. In addition, in the experiment using the antagonist and agonist of RyR, we found both cysNO and EFS could not induce the rebound contraction when the RyR was inhibited by ruthenium red or when it was already activated by caffeine. The above pieces of experimental evidence suggest that the NO-induced rebound contraction require the Ca\(^{2+}\)-release from the ryanodine-sensitive store. However, the Ca\(^{2+}\)-release itself seems not to directly evoke muscle contraction; rather, it seems to be linked to a relaxing mechanism and to act as a signal to induce Ca\(^{2+}\)-influx through L-type channels in LM-PGF (discussed in detail in the following section). These findings are distinct from the observations in sheep bladder neck and rat ileum where only one Ca\(^{2+}\) source is necessary for NO-induced contraction (3, 5).

**The NO-induced relaxation in LM-PGF**

We found that the NO-induced relaxation was also inhibited by ryanodine plus CPA and by ruthenium red. It suggests that the NO-induced relaxation in LM-PGF involve the Ca\(^{2+}\)-release from the ryanodine-sensitive Ca\(^{2+}\) pool. Other investigators have reported similar results. In isolated guinea pig gastric smooth muscle, ruthenium red blocks the cGMP-induced hyperpolarizing outward Ca\(^{2+}\)-dependent K\(^+\) (K\(_{ca}\)) current (17). In opossum esophageal muscle, NO-induced relaxation is produced by Ca\(^{2+}\)-release and subsequent activation of hyperpolarizing K\(_{ca}\) currents.
tion developed during washout of caffeine in a concentration mechanism case, cGMP indirectly activates the Ca$^{2+}$ release induces relaxation and then causes Ca$^{2+}$ releases Ca$^{2+}$ as follows: NO activates sGC to produce cGMP that the NO-induced rebound contraction in LM-PGF would be of interest to explore the exact mechanism of NO-induced relaxation in LM-PGF in future studies.

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REFERENCES
1 Sanders KM and Ward SM: Nitric oxide as a mediator of nonadrenergic noncholinergic neurotransmission. Am J Physiol 262, G379 – G393 (1992)
2 Bartho L and Lefebvre RA: Nitric oxide mediated contraction in enteric smooth muscle. Arch Int Pharmacodyn 329, 53 – 66 (1995)
3 Lefebvre RA and Bartho L: Mechanism of nitric oxide-induced contraction in the rat isolated small intestine. Br J Pharmacol 120, 975 – 981 (1997)
4 Saha JK, Hirano I and Goyal RK: Biphasic effect of SNP on opossum esophageal longitudinal muscle: involvement of cGMP and eicosanoids. Am J Physiol 265, G403 – G407 (1993)
5 Thornbury KD, Donaghy KM and Peake J: Characteristics of the NANC post-stimulus (‘rebound’) contraction of the urinary bladder neck muscle in sheep. Br J Pharmacol 116, 2451 – 2456 (1995)
6 Venkova K and Krier J: A nitric oxide and prostaglandin dependent component of NANC off-contractions in cat colon. Am J Physiol 266, G40 – G47 (1994)
7 Ward SM, Dalziel HH, Thornbury KD, Westfall DP and Sanders KM: Nonadrenergic, noncholinergic inhibition and rebound excitation in canine colon depend on nitric oxide. Am J Physiol 262, G237 – G243 (1992)
8 Kim TW, Na JH, Lee JH and Yang IS: A study on the nonadrenergic noncholinergic neurotransmitters in porcine gastric fundus. Korean J Vet Res 37, 119 – 128 (1997)
9 Barbier AJ and Lefebvre RA: Influence of S-nitrosothiols and nitrate tolerance in the rat gastric fundus. Br J Pharmacol 111, 1280 – 1286 (1994)
10 Makhlof GM and Murthy KS: Signal transduction in gastrointestinal smooth muscle. Cell Signal 9, 269 – 276 (1997)
11 Ignarro LJ: Signal transduction mechanisms involving nitric oxide. Biochem Pharmacol 41, 485 – 490 (1991)
12 Zimmerman AL, Yamanaka G, Eckstein F, Baylor DA and Stryer L: Interaction of hydrolysis-resistant analogs of cyclic GMP with the phosphodiesterase and light-sensitive channel of retinal rod outer segments. Proc Natl Acad Sci USA 82, 8813 – 8817 (1985)
13 Feilisich M and Stamler JS: Donors of nitrogen oxides. In Methods in Nitric Oxide Research, Edited by Feelisch M and Stamler JS, Vol 102, pp 83 – 86, John Wiley & Sons Ltd, West Sussex (1996)
14 Collier ML, Ji G, Wang Y and Kotlikoff MI: Calcium-induced calcium release in smooth muscle: loose coupling between the action potential and calcium release. J Gen Physiol 115, 653 – 662 (2000)
15 Ohta T, Ito S and Nakazato Y: Chloride currents activated by caffeine in rat intestinal smooth muscle cells. J Physiol (Lond) 465, 149 – 163 (1993)
16 Qian Y and Bourreau JP: Two distinct pathways for refilling Ca$^{2+}$ stores in permeabilized bovine trachealis muscle. Life Sci 64, 2049 – 2059 (1999)
17 Duridanova DB, Gagog HS and Boev KK: Ca$^{2+}$-induced Ca$^{2+}$ release activates K$^+$ currents by a cyclic GMP-dependent mechanism in single gastric smooth muscle cells. Eur J Pharmaco 298, 159 – 163 (1996)
18 Cayabys FS and Daniel EE: Role of sarcoplasmic reticulum in inhibitory junction potentials and hyperpolarizations by nitric oxide donors in opossum oesophagus. Br J Pharmacol 118, 2185 – 2191 (1996)
19 Selermidis S and Cocks TM: Nitrogic relaxation of the mouse gastric fundus is mediated by cyclic GMP-dependent and ryanodine-sensitive mechanisms. Br J Pharmacol 129, 1315 – 1322 (2000)
20 Twort CH and van Bremmen C: Cyclic guanosine monophosphate-enhanced sequestration of Ca$^{2+}$ by sarcoplasmic reticulum in vascular smooth muscle. Circ Res 62, 961 – 964 (1988)
21 Takeuchi T, Sugimoto K, Morimoto H, Fujita A and Hata F: Mechanism of a nitric oxide donor NOE 1-induced relaxation in longitudinal muscle of rat proximal colon. Jpn J Pharmaco 86, 390 – 398 (2001)