Comparison of the Effects of YC-1, DEA/NO, Sodium Nitroprusside and Theophylline on the Sheep Sphincter of Oddi

KOYUN ODDİ SFİNKTERİ ÜZERİNDE YC-1, DEA/NO, SODYUM NİTROPRUSİYAT VE TEOFİLİNİN ETKİLERİNİN KARŞILAŞTIRILMASI

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Abstract

Objective: It has been demonstrated that nitric oxide (NO) plays an important physiological role in various parts of the gastrointestinal (GI) tract. This study was designed to show the existence of NO system in the sheep sphincters of Oddi (SO) and to compare the effects of drugs that affect NO system by different mechanisms.

Material and Methods: SO rings were mounted in tissue baths with modified Krebs-Henseleit solution and aerated with 95% oxygen and 5% carbon dioxide. Electrical field stimulation (EFS) responses and concentration-response curves for 3-(5'-hydroxymethyl-2'-furyl)-1-benzyl indazole (YC-1, 10^{-10}-10^{-5} M), diethylamine/NO complex (DEA/NO, 10^{-8}-10^{-4} M), sodium nitroprusside (SNP, 10^{-8}-3 x 10^{-4} M) and theophylline (10^{-8}-10^{-4} M) on SO rings precontracted with carbachol (10^{-6} M) were recorded isometrically with a Grass polygraph. We also evaluated the effect of YC-1 (10^{-6} and 10^{-5} M) and DEA/NO (10^{-5} and 10^{-4} M) on the levels cyclic GMP (cGMP) in isolated SO rings.

Results: EFS-induced contractile responses was decreased by atropine (10^{-6} M) and guanethidine (10^{-5} M), but potentiated by L-NAME (3 x 10^{-5} M). YC-1 (10^{-10}-10^{-5} M), DEA/NO (10^{-8}-10^{-4} M), SNP (10^{-8}-3 x 10^{-4} M) and theophylline (10^{-8}-10^{-4} M) induced concentration-dependent relaxation of isolated SO rings precontracted with carbachol (10^{-6} M). In carbachol-precontracted SO rings the order of potency was YC-1>DEA/NO>SNP= theophylline. YC-1 and DEA/NO increased cGMP levels more than control and carbachol groups ($p > 0.05$).

Conclusion: These results show that NO system exists in the sheep SO. YC-1, DEA/NO, SNP and theophylline induce quantitatively different relaxation of SO rings. YC-1 is a more potent relaxant than other drugs and causes more elevation of cGMP levels in isolated SO rings.

Key Words: Sphincter of Oddi, nitric oxide, YC-1 [3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole], nitroprusside, theophylline

Özet

Amaç: Nitrik oksit (NO)'in gastrointestinal kanalın değişik bölümlerinde önemli bir fizyolojik rol oynadığı gösterilmiştir. Bu çalışma, koyun Oddi sfinkteri (SO)'nde NO sisteminin varlığını göstermek ve farklı mekanizmalarla NO sistemini etkileyen ilaçların etkilerini karşılaştırmak için planlandı.

Gereç ve Yöntemler: SO halkaları modifiye Krebs-Henseleit solüsyonu ile doldurulmuş ve %95 oksijen %5 CO_2 ile gazlandırılan doku banyolarına asıldı. Elektriksel alan stimülasyonu (EFS) cevapları ve karbakol (10^{-6} M) ile kastırılmış dokularda 3-(5'-hidroksimetil-2'-furil)-1-benzil indazol (YC-1, 10^{-10}-10^{-5} M), dietilamin/NO kompleksi (DEA/NO, 10^{-8}-10^{-4} M), sodyum nitroprusiyat (SNP, 10^{-8}-3 x 10^{-4} M) ve teofilin (10^{-8}-10^{-4} M) konsantrasyon-cevap eğrileri izometrik olarak Grass poligrafa kaydedildi. Ayrıca, YC-1 (10^{-6} ve 10^{-5} M) ve DEA/NO (10^{-5} ve 10^{-4} M)'nun siklik GMP (sGMP) düzeyleri üzerindeki etkileri ölçüldü.

Bulgular: EFS ile oluşturulan kasılma cevapları atropine (10^{-6} M) ve guanethidine (10^{-5} M) ile azaldı, ama L-NAME (3 x 10^{-5} M) ile güçlendi. YC-1 (10^{-10}-10^{-5} M), DEA/NO (10^{-8}-10^{-4} M), SNP (10^{-8}-3 x 10^{-4} M) ve teofilin (10^{-8}-10^{-4} M) karbakol (10^{-6} M) ile kastırılmış SO halkalarında konsantrasyona-bağımlı gevşemeler oluşturdu. Karbakol ile kastırılmış SO halkalarında potens sırası YC-1>DEA/NO>SNP= teofilin idi. YC-1 ve DEA/NO sGMP düzeylerini control ve karbakol guplarından daha fazla arttırdı ($p > 0.05$).

Sonuç: Bu bulgular, koyun SO'da NO sisteminin bulunduğunu, YC-1, DEA/NO, SNP ve teofilinin SO halkalarında faklı ölçüde gevşemeler oluşturduğunu göstermektedir. YC-1 diğer ilaçlardan daha potent bir gevşeticidir ve sGMP düzeylerinde daha fazla artışa neden olur.

Anahtar Kelimeler: Oddi sfinkteri, nitrik oksit, YC-1 [3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole], sodyum nitroprusiyat, teofilin

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The sphincter of Oddi (SO), which is a valve that regulates the flow of bile and pancreatic secretions into the duedonal lumen, is innervated by a ganglionated plexus that lies within its wall.[1] Anatomical and immunohistochemical

investigations have demonstrated that the SO is richly innervated by cholinergic, adrenergic and nonadrenergic-noncholinergic (NANC) nerves.[2,3] These nerves in addition to hormones are important in the control of SO motility and function.[4,5]

Nitric oxide (NO) is synthesized by the activation of neuronal NO synthase (nNOS) in the myenteric plexus.[6] NO released in response to nerve stimulation of the myenteric plexus regulates the muscle tone of the sphincter in the lower esophagus, pylorus, SO, and anus.[7] Competitive inhibitors of NOS increase the strength of sphincter contractions, and L-arginine, the substrate for NOS, antagonizes this effect.[8] Hemoglobin, a potent scavenger of NO, increases the contractile frequency, strength of contractions, and baseline tone of the opossum SO.[9] Thus, both the inhibition of NO production and prevention of its action alter SO motility.

Topical application of NO donors, such as S-nitroso-N-acetylcysteine (SNAC), glyceryl trinitrate (GTN) and sodium nitroprusside (SNP), decrease SO motility.[10-12] Theophylline, a nonselective phosphodiesterase (PDE) inhibitors, inhibits morphine-induced spasm of Oddi's sphincter in man.[13] YC-1 ([3-(5'-hydroxymethyl-2'-furyl)-1-benzyl indazole]), a novel NO-independent soluble guanylyl cyclase (sGC) activator, and diethylamine/nitric oxide (DEA/NO), a recently developed NO donor, are induced concentration-dependent relaxations in various smooth muscles, such as myometrium, corpus cavernosum and carotid artery.[14-18] There is no available data in the literature related to the compared relaxant effect of YC-1, DEA/NO, SNP and theophylline in isolated sheep SO rings.

The structure of the SO and the effects of drugs that affect NO system varies in different species. Therefore, the aims of this study were to determine the existence of NO system in the sheep SO and, to compare the effects of YC-1, DEA/NO, SNP and theophylline.

Material and Methods Ethics

The present experiments conformed to the Guiding Principles for Care and Use of Experimental Animals. In addition, the experimental protocol applied was approved by the local ethical boards of the Cumhuriyet University Medical Faculty.

Experimental Design and Tissue Preparation

Adults male Anatolian Akkaraman sheeps (n= 26), weighing 38-45 kg and aging 12-14 mounths, were used throughout the study. The sheeps were killed by cervical sheers in the slaughterhouse. The abdomen was opened with a midline incision and the SO was rapidly removed and transferred to laboratory in previously aerated (95% O_2 and 5% CO_2) Krebs' bicarbonate solution (composition in mmol/L: NaCl, 120; KCl, 4.6; $CaCl_2$, 2.5; $MgCl_2$, 1.2; $NaHCO_3$, 22; NaH_2PO_4 and glucose 11.5). SO muscle rings were placed in a 10 mL muscle bath, filled with pre-aerated Krebs' bicarbonate solution at 37°C. The upper end of the preparation was tied to an isometric transducer (Grass FT 03, Quincy, MA, USA) and preloaded with 1.5 g. SO muscle rings were washed in every 15 min and allowed to equilibrate for 60-90 min until a stable baseline was attained.

Isometric Measurements

Some of SO rings were placed between stimulating electrodes. Contractions were elicited with electrical field stimulation (EFS). Stimulation was provided by two parallel platinum electrodes and was applied at sequential frequencies of 2, 4, 8, 16 and 32 Hz, as square-wave pulses of 50 V (0.1 ms) delivered at 10-s intervals by a current amplifier and a stimulator (S88, Grass Instruments, Quincy, MA, USA). After control EFS responses, the SO rings were treated with 10^{-6} M atropine (a muscarinic receptor blocker) and 10^{-5} M guanethidine (adrenergic nerve blocker) or 3 x 10^{-5} M L-NAME (an inhibitor of NOS) for 20 min, to eliminate the adrenergic and cholinergic components or nitrergic component, and to determine the relaxation responses to the stimulation of NANC nerves.

Submaximal contraction was obtained with 10^{-6} M carbachol in some of SO rings. Following contraction by carbachol (10^{-6} M), the relaxation responses to YC-1 (10^{-10}-10^{-5} M), DEA/NO (10^{-8}-10^{-4} M), SNP (10^{-8}-3 x 10^{-4} M) and theophylline (10^{-8}-10^{-4} M) were obtained in a cumulative manner. After the addition of each concentration, we waited

until a plateau response was obtained before adding the next one.

Measurement of cGMP Levels in SO Rings

SO rings were obtained from male sheeps and equilibrated in Krebs solution (composition as above) continuously gassed with a mixture of 95% oxygen and 5% carbon dioxide at 37ºC (pH= 7.40) for 60 min. Five sets of experimental studies were performed except for control group. Tissues were exposed to 10^{-6} M carbachol for 15 min in the first set. In the 2nd, 3rd, 4th and 5th sets tissues were separately exposed to 10^{-6} M YC-1, 10^{-5} M YC-1, 10^{-5} M DEA/NO and 10^{-4} M DEA/NO after incubation with 10^{-6} M carbachol for 15 min in organ bath. As a control group, experiments without studied drugs were used. At the end of a total incubation period, the samples were immediately transferred into liquid nitrogen and homogenized with ethanol and incubated for 30 min at 0-4ºC. Then, the homogenate was centrifuged at 4ºC for 10 min at 12 000 x g. The supernatants poured into a clean test tube and dried in a vacuum at 50ºC to remove ethanol. Aliquots of the supernatant were tested for cyclic GMP (cGMP) by radioimmunoassay (RE 110 21 and RE 290 71 respectively; IBL, Hamburg, Germany). The samples were then processed according to the instructions provided with the kits for determination of cGMP levels. Sampling data were divided according to the weight of the SO rings, and the results were expressed in pmol/mg SO.

Data Analysis

EFS responses were expressed as a percentage of precontraction by KCl (80 mM). The relaxation responses induced by YC-1, DEA/NO, SNP and theophylline were expressed as a percentage of precontraction by carbachol (10^{-6} M). Maximum relaxant effect (E_{max}) and concentrations of YC-1, DEA/NO, SNP and theophylline producing 50% of the E_{max} (EC_{50}) were calculated for each concentration-response curve. The pEC_{50} was calculated as the negative logarithm to base 10 of the EC_{50} for statistical analysis.[19] Experimental values were presented as means ± SEM and analysed by repeated measures of analysis of variance (ANOVA) with the Newman-Keuls test, and Student's t test when appropriate. A p value of < 0.05 was considered significant. All statistical analyses were performed using Statistica for Windows 6.0. (Statsoft, Inc., Tusla, USA).

Drugs

Chemicals used in the current experiments were atropine, guanethidine, L-NAME, carbachol, DEA/NO, SNP and theophylline from Sigma (St. Louis, MO, USA), YC-1 from A.G. Scientific, Inc. (San Diego, CA, USA). All chemicals were dissolved in distilled water except for YC-1, which was dissolved in dimethylsulfoxide (DMSO) and then diluted with distilled water for preparation of decreasing concentrations of this drug. The amount of DMSO used to dissolve the drugs had no effect on sheep SO smooth muscle. Drugs-containing solutions were freshly prepared on the day of the experiments.

Results

EFS (2, 4, 8, 16 and 32 Hz, 50 V, 0.1 ms, 10 s) caused contractile responses on basal tension of sheep SO rings. Preincubation (20 min) of SO rings by atropine (10^{-6} M, n= 10) and guanethidine (10^{-5} M, n= 10) combination significantly decreased the contractile responses induced by EFS, whereas preincubation (20 min) by L-NAME (3 x 10^{-5} M, n= 10) significantly increased the contractile responses elicited by EFS ($p< 0.05$) (Figure 1).

YC-1 (10^{-10}-10^{-5} M, n= 10), DEA/NO (10^{-8}-10^{-4} M, n= 10), SNP (10^{-8}-10^{-4} M, n= 10) and theophylline (10^{-8}-10^{-4} M, n= 10) induced concentration-dependent relaxations on SO rings precontracted by carbachol (10^{-6} M) (Figure 2). In carbachol-precontracted SO rings the order of potency (pEC_{50}) was YC-1>DEA/NO>SNP= theophylline ($p< 0.05$). In carbachol-precontracted SO rings the order of efficacy (E_{max}) was YC-1= DEA/NO>SNP= theophylline ($p< 0.05$) (Table 1).

Carbachol (10^{-6} M, n= 6), YC-1 (10^{-6} and 10^{-5} M, n= 6) and DEA/NO (10^{-5} and 10^{-4} M, n= 6) significantly increased the cGMP levels compared with the control on SO rings ($p< 0.05$) (Table 2). In SO rings, the order of increase in cGMP levels was 10^{-5}

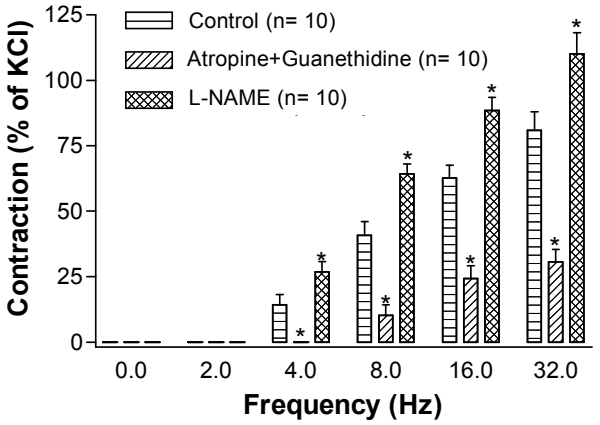

Figure 1. Changes in isometric tension induced by EFS (2, 4, 8, 16 and 32 Hz, 50 V, 0.1 ms, 10 s) in the presence of atropine (10^{-6} M) and guanethidine (10^{-5} M) or L-NAME (3 x 10^{-5} M) in the isolated sheep sphincter of Oddi. The data are expressed as a percent of KCl (80 mM)-induced contraction and showed as means ± SEM.
* $p< 0.05$, statistically different from control.

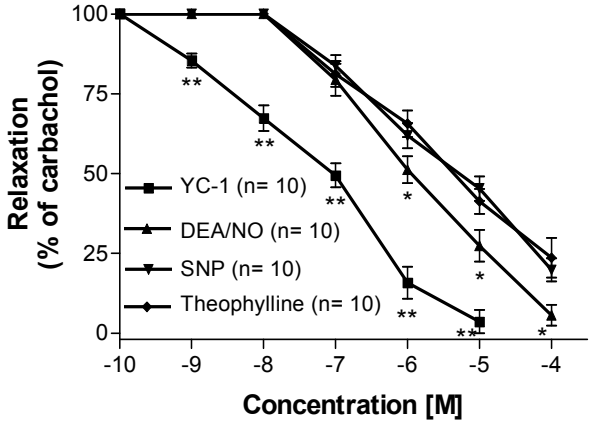

Figure 2. The relaxation responses induced by YC-1 (10^{-10}-10^{-5} M), DEA/NO (10^{-8}-10^{-4} M), SNP (10^{-8}-10^{-4} M) and theophylline (10^{-8}-10^{-4} M) in the isolated sheep sphincter of Oddi. Relaxations are expressed as a percent of carbachol (10^{-6} M)-induced precontraction and showed as means ± SEM.
* $p< 0.05$, statistically different from SNP and theophylline relaxation responses.
** $p< 0.05$, statistically different from all relaxation responses.

M YC-1>10^{-6} M YC-1>10^{-4} M DEA/NO= 10^{-5} M DEA/NO>10^{-6} M carbachol ($p< 0.05$) (Table 2).

Discussion

In gastrointestinal tract, NANK innervation is important in nerve mediated relaxation and membrane hyperpolarisation and present evidence indicates that NO is a NANK neurotransmitter.[20,21] It is widely accepted that NO, through cGMP synthesis, induces a sequence of protein phosphorylation that leads to smooth muscle relaxation.[22] It has been shown that nitrergic relaxation of the rabbit SO is accompanied by an increase in both cGMP and cAMP concentration.[23] Theoretically, an increase in tissue cAMP concentration secondary to cGMP-increase might result from an inhibition of cAMP metabolism through inhibition of the enzyme type III (cGMP-inhibited cyclic nucleotide phosphodiesterase: PDE3) phosphodiesterase.[24] Moreover, in addition to its smooth muscle relaxing effect, NO has been proposed to stimulate the release of vasoactive intestinal polypeptide (VIP) or calcitonin gene-related peptide (CGRP) from enteric nerve terminals through presynaptic mechanisms. VIP or CGRP, once released, facilitates further NO

Table 1. pEC_{50} and E_{max} values for the relaxant effects of YC-1, DEA/NO, SNP and theophylline in sheep SO rings precontracted by carbachol (10^{-6} M). Data are expressed as means ± SEM.

	pEC_{50}	E_{max}
YC-1 (n= 10)	7.16 ± 0.10[a] (0.03)	96.4 ± 3.6[b] (0.02)
DEA/NO (n= 10)	6.08 ± 0.08	94.4 ± 3.2[b] (0.03)
SNP (n= 10)	5.80 ± 0.07	80.2 ± 3.6
Theophylline (n= 10)	5.84 ± 0.08	76.4 ± 6.2

[a] Statistically different from all other drugs for YC-1 ($p< 0.05$),
[b] Statistically different from SNP and theophylline for YC-1 and DEA/NO ($p< 0.05$).

Table 2. Increase of the cGMP levels by carbachol, YC-1 and DEA/NO compared with the control on sheep sphincter of Oddi rings. Data are expressed as means ± SEM.

	cGMP levels (fmol/mg)
Control	3.51 ± 0.42
Carbachol (10^{-6} M, n=6)	11.25 ± 1.80[a] (0.03)
Carbachol + YC-1 (10^{-6} M, n=6)	25.32 ± 4.23[a] (0.02)
Carbachol + YC-1 (10^{-5} M, n=6)	47.62 ± 5.12[a,b] (0.01) (0.03)
Carbachol + DEA/NO (10^{-5} M, n=6)	18.22 ± 2.42[a] (0.03)
Carbachol + DEA/NO (10^{-4} M, n=6)	23.81 ± 3.04[a] (0.02)

[a] Statistically different from control ($p< 0.05$),
[b] Statistically different from all other groups ($p< 0.05$).

synthesis/release through cAMP-dependent pathways, thus, an interplay between NO and these NANC peptides underlie the increase in cGMP and cAMP in the SO.[25]

Our results have shown that in vitro inhibition of NOS by the L-arginine analogue L-NAME increases the contractile response induced by EFS, whereas in vitro blockage of muscarinic receptors and adrenergic nerves by atropine and guanethidine combination decreases the contractile responses induced by EFS. The augmentation of the contractile response induced by EFS with L-NAME suggests the involvement of the nitrergic system on the regulation of the sheep SO.

YC-1 is a NO-independent sGC activator that provides an about 10-fold increase of enzyme activity. Apart from an increase in the formation of cGMP via the stimulation of sGC, the substance also prevents cGMP degradation.[14] In the previously study, we shown that YC-1 inhibits spontaneous contractile activity in a concentration-dependent manner in myometrial smooth muscle from pregnant rat.[16] SNP and DEA/NO are NO donors, but SNP and recently developed DEA/NO do not share the same mechanism for NO release. With regard to SNP, it is thought to produce relaxation, at least in part, by NO-induced guanylyl cyclase activation related to formation of S-nitrosothiol intermediates.[26] In addition to the thiol requirement, it has been shown that SNP undergoes metabolic activation in smooth muscle by a SNP-directed, membrane-associated, NO-generating activity.[27] NO/nucleophile adducts DEA/NO complex, differ from SNP in that it spontaneously releases NO in simple aqueous buffer.[15] Salom et al. demonstrated that SNP and DEA/NO induce relaxation of rabbit carotid artery with different potencies.[18] Theophylline is a nonselective PDE inhibitors. cGMP is catabolized by phosphodiesterases (PDEs), a large family of enzymes that also hydrolyze other cyclic nucleotides (such as cAMP).[28] At least 50 different PDEs are described in mammalian cells.[29] Increased intracellular cGMP inhibits smooth muscle contraction. Vedernikov et al. demonstrated in vitro that nonselective PDE inhibition was more effective in relaxing rat myometrium at term, whereas zaprinast (a selective cGMP PDE-5 inhibitor) was less effective.[30] In previous studies, it has been indicated that YC-1, DEA/NO, SNP and theophylline are induced concentration-dependent relaxations in various smooth muscles.[16,18,30]

In this study, we have compared the relaxant effect of YC-1, DEA/NO, SNP and theophylline in isolated sheep SO rings, precontracted by carbachol. YC-1, DEA/NO, SNP and theophylline induced concentration-dependent relaxation of SO rings, with the following order of potency: YC-1>DEA/NO>SNP= theophylline in carbachol-precontracted rings. The pEC_{50} values for YC-1 were significantly greater than those calculated for DEA/NO, SNP and theophylline. This indicates that the actual EC_{50} value (i.e., concentration resulting in 50% of maximal effect) for YC-1 is significantly less than that measured for DEA/NO, SNP and theophylline, and hence, YC-1 is more potent relaxant agents in SO. In carbachol-precontracted rings, the order of efficacy: YC-1=DEA/NO>SNP= theophylline. The E_{max} values for YC-1 and DEA/NO were significantly greater than those calculated for SNP and theophylline. This shows that the efficacy of YC-1 and DEA/NO is significantly greater than that of SNP and theophylline, but the efficacy for the YC-1 and DEA/NO or SNP and theophylline was not significantly different in SO rings.

In this study, carbachol, YC-1 and DEA/NO were responsible for a significant increase in cGMP levels of sheep SO rings in a concentration-dependent manner. YC-1 caused high increase in the cGMP levels compared to the other drugs. These increased levels of cGMP by YC-1 and DEA/NO indicate the mediation of cGMP formation in the relaxant effects of these drugs in SO.

In conclusion, results of this study show that NO system exist in the sheep SO. In vitro application of YC-1, DEA/NO, SNP and theophylline induce relaxation of SO rings with different potencies. YC-1 is a more potent relaxant agent and causes more increase in cGMP levels of

SO rings. YC-1 may be suitable choice in the conscious relaxation of the ERCP and help the ERCP procedures. Since our study was performed on sheep SO in vitro, controlled clinical studies are required to determine if the results obtained can be transferred to humans.

REFERENCES

1. Mawe GM. Oddi: The structure of Oddi's sphincter. In: Daniel EE, Tsuchida S, Tomita T, eds. Sphincter: Normal Function-Changes in Diseases, Boca Raton, FL: CRC Press; 1992. p.175-7.
2. Toouli J, Baker RA. Innervation of the sphincter of Oddi: Physiology and considerations of pharmacological intervention in biliary dyskinesia. Pharmacol Ther 1991;49:269-81.
3. Padbury RT, Furness JB, Baker RA, Toouli J, Messenger JP. Projections of nerve cells from the duodenum to the sphincter of Oddi and gallbladder of the Australian possum. Gastroenterology 1993;104:130-6.
4. Saccone GT, Harvey JR, Baker RA, Toouli J. Intramural neural pathways between the duodenum and sphincter of Oddi in the Australian brush-tailed possum in vivo. J Physiol 1994;481:447-56.
5. Simula ME, Harvey JR, Costi D, Baker RA, Toouli J, Saccone GT. In vitro characterisation of intramural neural pathways between the duodenum and the sphincter of Oddi of the brush-tailed possum. J Auton Nerv Syst 1997;63:77-84.
6. Baker RA, Saccone GT, Brookes SJ, Toouli J. Nitric oxide mediates nonadrenergic, noncholinergic neural relaxation in the Australian possum. Gastroenterology 1993;105:1746-53.
7. Takahashi T. Pathophysiological significance of neuronal nitric oxide synthase in the gastrointestinal tract. J Gastroenterol 2003;38:421-30.
8. Kaufmann HS, Shermak MA, May CA, Pitt HA. Nitric oxide inhibits resting sphincter of Oddi activity. Am J Surg 1993;165:74-80.
9. Cullen JJ, Conklin JL, Murray J, Ledlow A, Rosenthal G. Effects of recombinant human hemoglobin on opossum sphincter of Oddi motor function in vivo and in vitro. Dig Dis Sci 1996;41:289-94.
10. Slivka A, Chuttani R, Carr-Locke DL, et al. Inhibition of sphincter of Oddi function by the nitric oxide carrier S-nitroso-N-acetylcysteine in rabbits and humans. J Clin Invest 1994;94:1792-98.
11. Luman W, Pryde A, Heading RC, Palmer KR. Topical glyceryl trinitrate relaxes the sphincter of Oddi. Gut 1997;40:541-3.
12. Niiyama H, Jagannath S, Kantsevoy S, Cruz-Correa M, Magee C, Kalloo AN. Intrasphincteric nitric oxide reduces sphincter of Oddi motility in an endoscopic porcine model. Dig Dis Sci 2003;48:2187-90.
13. Pap A, Forro G. The effect of theophylline preparations on morphine-induced spasm of Oddi's sphincter in man. Orv Hetil 1998;139:1411-4.
14. Koesling D, Friebe A. Structure and regulation of soluble guanyl cyclase. Rev Physiol Biochem Pharmacol 1999; 135:35-41.
15. Morley D, Keefer LK. Nitric oxide/nucleophile complexes: A unique class of nitric oxide-based vasodilators. J Cardiovasc Pharmacol 1993;22:3-9.
16. Cetin A, Kaya T, Demirkoprulu N, Karadas B, Duran B, Cetin M. YC-1, a nitric oxide-independent activator of soluble guanylate cyclase, inhibits the spontaneous contractions of isolated pregnant rat myometrium. J Pharmacol Sci 2004;94:19-24.
17. Hsieh GC, O'Neill AB, Moreland RB, Sullivan JP, Brioni JD. YC-1 potentiates the nitric oxide/cyclic GMP pathway in corpus cavernosum and facilitates penile erection in rats. Eur J Pharmacol 2003;458:183-9.
18. Salom JB, Barbera MD, Centeno JM, Orti M, Torregrosa G, Alborch E. Comparative relaxant effects of the NO donors sodium nitroprusside, DEA/NO and SPER/NO in rabbit carotid arteries. Gen Pharmacol 1999;32:75-9.
19. Jenkinson DH, Barnard EA, Hoyer D, Humphrey PP, Leff P, Shankley NP. International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification. IX. Recommendations on terms and symbols in quantitative pharmacology. Pharmacol Rev 1995;47:255-66.
20. Bult H, Boeckxstaens GE, Pelckmans PA, Jordaens FH, Van Maercke YM, Herman AG. Nitric oxide as an inhibitory non-adrenergic non-cholinergic neurotransmitter. Nature 1990;345:346-7.
21. Stark ME, Szurszewski JH. The role of nitric oxide in gastrointestinal and hepatic function and disease. Gastroenterology 1991;103:1928-49.
22. Moncada S, Palmer RM, Higgs EA. Nitric oxide: Physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991;43:109-42.
23. Szilvassy Z, Nagy I, Madacsy L, et al Beneficial effect of lovastatin on sphincter of Oddi dyskinesia in hypercholesterolemia and hypertriglyceridemia. Am J Gastroenterol 1997;92:900-2.
24. Walter U. Cyclic GMP-regulated enzymes and their physiological functions. In: Greengard P, Robinson AG, eds. Advances in Cyclic Nucleotide Research and Protein Phosphorylation Research. New York: Raven Press; 1999. p.249-58.
25. Allescher HD, Kurjak M, Huber A, Trudrung P, Schusdziarra V. Regulation of VIP release from rat enteric nerve terminals: Evidence for a stimulatory effect of NO. Am J Physiol 1996;271:568-74.
26. Ignarro LJ, Barry BK, Gruetter DY, et al Guanylate cyclase activation of nitroprusside and nitrosoguanidine is related to formation of S-nitrosothiol intermediates. Biochem Biophys Res Commun 1980;14:93-100.
27. Kowaluk EA, Seth P, Fung HL. Metabolic activation of sodium nitroprusside to nitric oxide in vascular smooth muscle. J Pharmacol Exp Ther 1992;262:916-22.
28. Miyahara M, Ito M, Itoh H, Shiraishi T, Isaka N, Konishi T. Iso-enzymes of cyclic nucleotide phosphodiesterase in the human aorta: Characterization and the effects of E4021. Eur J Pharmacol 1995;284:25-33.
29. Leroy MJ, Pichard AL, Cabrol D, Ferre F. Cyclic 3':5'-nucleotide phosphodiesterase in human myometrium at the end of pregnancy: Partial purification and characterization of the different soluble isoenzymes. Gynecol Obstet Investig 1985;20:27-36.
30. Vedernikov YP, Syal AS, Okawa T, Jain V, Saade GR, Garfield RE. The role of cyclic nucleotides in the spontaneous contractility and responsiveness to nitric oxide of the rat uterus at midgestation and term. Am J Obstet Gynecol 2000;182:612-9.