JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 1994, 45, 2, 285—298

M. MĄCZKA, P. THOR, J. BILSKI, S. J. KONTUREK

NITRIC OXIDE AND THE INTERRELATION BETWEEN INTESTINAL MOTILITY AND PANCREATIC SECRETION IN FASTED AND FED DOGS

Institute of Physiology, Faculty of Medicine, Jagiellonian University, Cracow, Poland

Intestinal motility and pancreatic secretion show synchronous cyclic changes (MMC) that are interrupted by feeding. The aim of this study was to determine the possible implication of nitric oxide (NO) (that was proposed as nonadrenergic noncholinergic neurotransmitter) in the motor and secretory components of MMC in 5 conscious dogs equipped with monopolar electrodes implanted along the small bowel and pancreatic fistulas. In fasted dogs with typical MMCs, L-NNA (an inhibitor of NO synthase) (5 mg/kg-h i. v.) decreased the MMC interval from control value of 80 ± 7 to 60 ± 4 min while increasing significantly the slow waves with spikes and suppressing the phase III-related increase in pancreatic secretion. Infusion of L-arginine (L-Arg) (a substrate of NO synthase) (10 mg/kg-h i. v.) increased the MMC interval from control 79 ± 7 to 96 ± 8 min and reduced the slow waves spikes by about 25%. Pancreatic secretion showed significant increase to about 20%. CCK maximum. Similar but transient effects were observed when glyceryl trinitrate (GTN) (a donor of NO) (1 mg/kg-h) was administered. After ingestion of meal, the MMC cycles were replaced by irregular spike activity with an average of about 35% slow waves with spikes and pancreatic secretion rose to about 70% of CCK maximum. Infusion of L-Arg (10 mg/kg-h) reduced by about 90% the postprandial spike activity but failed to affect significantly the pancreatic secretion. Also, injection of GTN (1 mg/kg-h) reduced the spike activity but did not influence pancreatic secretion. L-NNA in fed dogs caused an initial increase in spike activity followed by phase III and about 60% inhibition of pancreatic secretion. L-NNA added to L-Arg infusion reversed in part both intestinal motility and pancreatic secretory effects of L-Arg infusion. We conclude that NO system exerts a tonic inhibitory influence on intestinal myoelectric activity by reducing the frequency of MMC pacesetter and by suppressing the postprandial activity but stimulates pancreatic secretion.

Key words: *Intestinal motility, pancreatic secretion, nitric oxide, MMC*

INTRODUCTION

It is well established that the fasting digestive tract in dogs and other species is governed by a regular rhythm that modulates its motor pattern and secretory activity (1). Boldyreff (2) was first who recognized the interdigestive cycles of synchronous intestinal motor activity and exocrine pancreatic

secretion. Fasting pancreatic secretion of enzymes reaches peak during phase II and III of the interdigestive migrating motor complex (MMC) cycle and this is accompanied by concomitant rise in plasma motilin, pancreatic polypeptide (PP) and gastrin (3, 4). Although motilin given in physiological dose induced motility patterns and the rise in pancreatic secretion similar to those observed during phase III (3), it is not clear whether the increment in plasma motilin is the cause or just a result of phase III contractile activity of the duodenum (5).

Ordinary feeding interrupts both the motor complex and secretory MMC cycle (1, 6) and stimulates the pancreatic secretion to about 40–60% of the maximal secretory capacity (3). These changes are accompanied by significant increments in plasma gastrin, cholecystokinin (CCK), secretin and PP but none of these hormones applied alone in physiological doses is capable to reproduce the postprandial inhibition of MMC cycles and the stimulation of pancreatic secretion (3).

Recently, an evidence was provided that nitric oxide (NO) acts as an inhibitory noncholinergic nonadrenergic (NANC) neurotransmitter in the stomach (7), the gut (8) and the pancreas (9, 10). Furthermore, the release of NO-like factor in response to stimulation of NANC nerves was demonstrated (11). Because of close relation between the intestinal motility and the pancreatic secretion (3), we investigated the possible implication of NO in the control of both intestinal motility and exocrine pancreatic secretion in fasted and fed conscious dogs equipped with monopolar electrodes in the small bowel to measure myoelectric activity and pancreatic fistula to examine simultaneously pancreatic secretion.

MATERIAL AND METHODS

The studies were carried out on five mongrel dogs that weighed 15–18 kg and were prepared surgically with intestinal electrodes, gastric gistulas (GF) and pancreatic fistulas (PF) as described previously (3, 12). Briefly, eight monopolar silver electrodes were implanted at 30 cm intervals along the entire small intestine to record the myoelectric activity of the gut as described previously (6). The recorded electrical changes represented potential differences between individual electrodes and the reference electrode, a coil of silver wire placed subcutaneously. Recordings were made with a type R-611 Beckmann recorder starting about 1 mo after surgery. The animals remained in good health throughout the period of study. In all tests, except these with feeding the GF and PF were opened and gastric and pancreatic juices were collected by gravity drainage. The gastric juice, usually contaminated with bile, was discarded, whereas the pancreatic juice collected in 15-min aliquots was examined and its volume, HCO_3^- and protein were determined and expressed as outputs per 30 min (12).

All experiments were carried out in the morning, about 18 h after the dogs last meal; the interval between tests was at least 4 days.

In tests conducted under basal conditions at least two control MMC cycles were first recorded, and the pancreatic volume and protein outputs were measured in each 15 min collection sample. Intravenous (i. v.) infusion of saline was given at a rate of 40 ml/h from the start of all experiments

and during recording of the control MMC cycles. After about 2 h examination basal conditions, N-nitro-L-arginine (L-NNA), an arginine analogue that under antagonizes NO synthase (13), L-arginine (L-Arg), a substrate for NO synthase (14, 15), or their combination was infused i. v. for about two hours. In separate experiments glyceryl trinitrate (GTN) was infused i.v. for 1–2 h period. For the comparison, maximal pancreatic protein secretion was examined using i.v. infusion of CCK-8 at a dose of 200 pmol/kg-h for 1 h period.

In tests with feeding, each dog was offered about 500 g of cooked homogenized ground beef that was usually completely consumed. When the myoelectric activity and secretory responses to a meal reached a well sustained plateau, L-NNA, L-Arg or their combination, or GTN was added in a constant dose to i.v. infusion for about 1 h.

In some experiments carried out under basal conditions and after meat feeding, blood samples were taken from the peripheral vein at 15–30 min intervals for the determination of plasma gastrin, CCK, PP, insulin and glucagon as presented previously (3, 12, 16).

Results are expressed as means ± SEM. In tests that compared various stimulants with and without L-NNA, L-Arg, L-NNA plus Lp-Arg or GTN, the changes in myoelectric activity and pancreatic secretion or plasma hormone concentrations were calculated and averaged to provide myoelectric, secretory and hormonal changes for the experimental period. The significance of these differences between means was evaluated by analysis of variance followed by Student's test. Differences were considered significant if $P < 0.05$.

RESULTS

Effect of L-NNA, L-Arg and GTN on fasted pattern of myoelectric activity and pancreatic secretion.

In fasted dogs, four typical phases of the MMC were defined in the small intestine (*Fig. 1*). Pancreatic volume flow and outputs of protein showed periodic fluctuations with the nadir observed at phase I and the peak occurring during late phase II and phase III MMC in the duodenum (*Fig. 2*).

L-NNA infused i.v. (5 mg/kg-h) did not affect the periodic alterations in myoelectric activity of the intestine but caused significant shortening of the MMC interval from control value of 80 ± 7 min to 60 ± 4 min mainly due to the reduction in timing of phase I and II (*Fig. 1*). Pancreatic protein outputs in fasted dogs infused with L-NNA were significantly reduced and showed only a small and insignificant rise during phase II and III of the shortened MMC cycle (*Fig. 2*).

In contrast, infusion of L-Arg (10 mg/kg-h) caused a significant prolongation of the MMC interval (to 96 ± 8 min) (*Fig. 3*) and this was accompanied by a significant increase in pancreatic protein secretion reaching about 20% of CCK maximum (*Fig. 2*). When the infusion of L-Arg was combined with L-NNA, the first phase III appeared in duodenum almost immediately after injection of L-NNA and the second III occurred after about 60 min later (*Fig. 4*). Neither of these phases III were preceded by an increased myoelectric activity (phase II) of the small bowel.

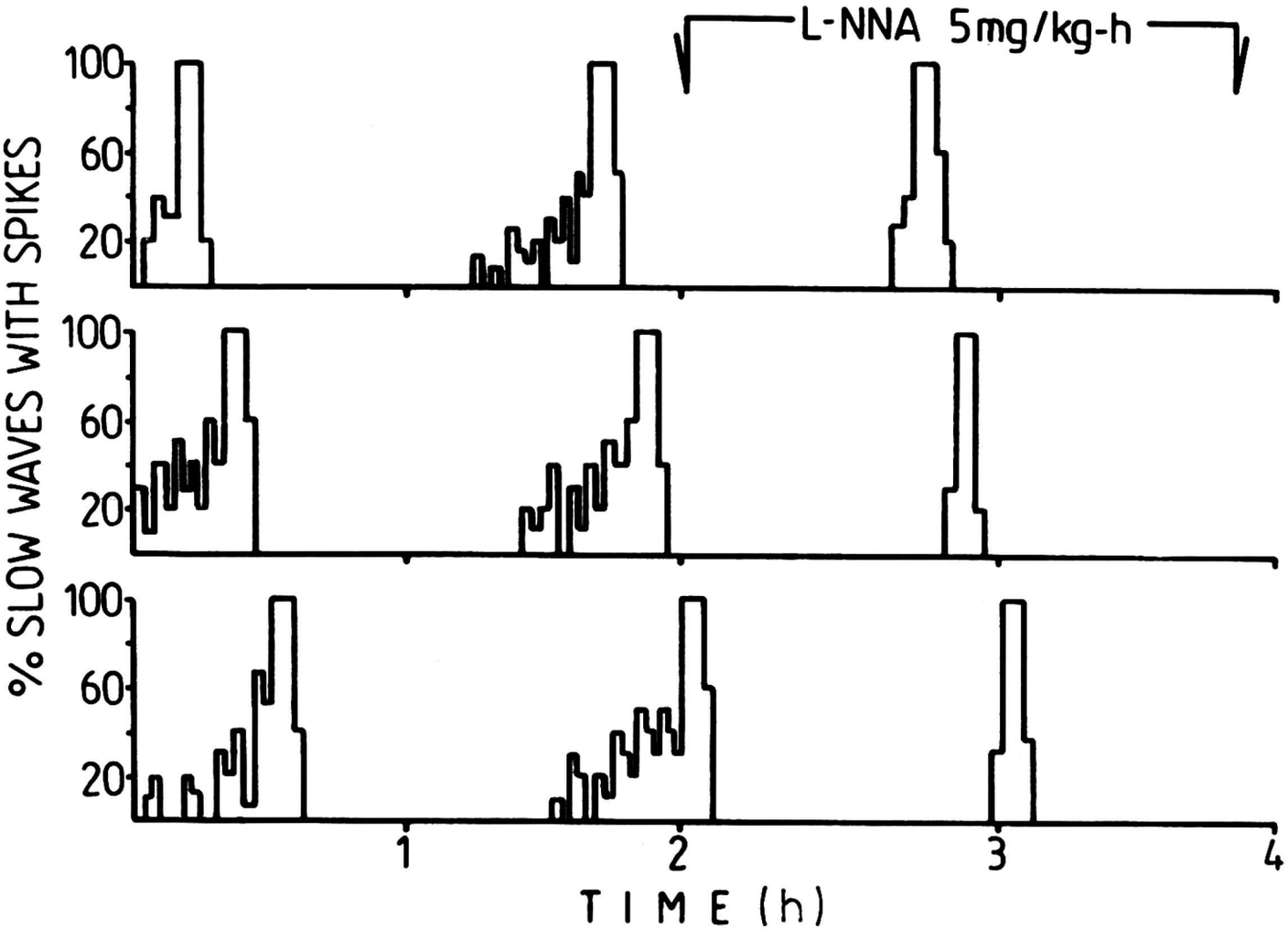

Fig. 1. Effect of i.v. infusion of L-NNA (5 mg/kg-h) on myoelectric activity of small intestine in fasted dogs. Similar results were obtained in other dogs.

Pancreatic protein secretion obtained during i.v. infusion of L-Arg plus L-NNA was significantly lower than that obtained with L-Arg alone (*Fig. 2*).

GTN infused i.v. (0.5 – 1 mg/kg-h) caused a marked delay in the occurrence of MMC and reduced the spike activity. Pancreatic secretion showed an increase reaching about 15% of CCK maximum in the animals. The increased protein secretion was well sustained for the period of infusion (*Table 1*).

Effects of L-NNA, L-Arg, L-NNA + L-Arg and GTN on fed patterns of myoelectric activity and pancreatic secretion

Feeding of a meat meal interrupted the MMC cycle and resulted in a prolong period of low level of irregularly occurring spike potentials (about 35% of slow waves with spikes) in the entire small intestine. It was accompanied by a significant increase in pancreatic protein secretion reaching about 70% of CCK maximum in these animals (*Figs. 2* and *3*). Infusion of L-NNA (5 mg/kg-h) in fed dogs resulted in an initial increase of slow waves with spikes reaching 80 – 100% followed by typical phase III that occurred in

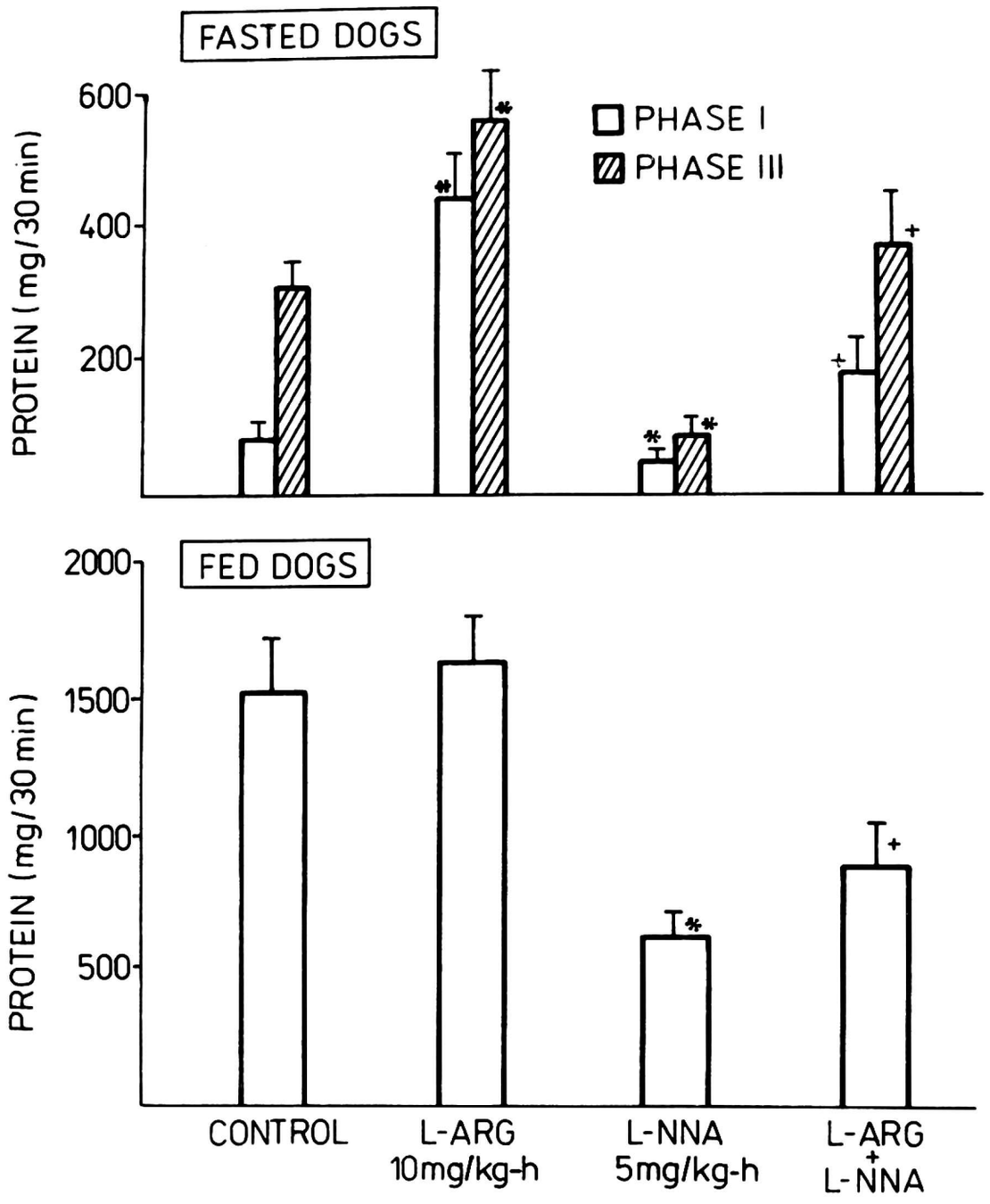

Fig. 2. Pancreatic protein secretion in fasted dogs in phase I and II/III and in fed dogs without or with i.v. infusion of L-Arg (10 mg/kg-h), L-NNA (5 mg/kg-h) and the combination of L-Arg (10 mg/kg-h plus L-NNA (5 mg/kg). Means ± SEM of 5 tests on five dogs. Asterisk indicates significant change as compared to the control value without infusion of L-Arg or L-NNA. Cross indicates significant increase above the value obtained with L-NNA alone.

duodenum and proceeded in usual way along the jejunum and ileum (*Fig. 5*). Infusion of L-NNA resulted in a prompt and marked reduction (by about 60%) in protein output (*Fig. 2*). L-Arg (10 mg/kg-h) infused i.v. almost completely abolished the postprandial spike activity for the period of infusion (*Fig. 6*) but the postprandial pancreatic protein secretion was not significantly affected by L-Arg administration (*Fig. 2*). The addition of L-NNA to L-Arg infusion resulted in a significant increase in the intestinal spike activity with the occurrence of phase III migrating along the small bowel (*Fig. 7*).

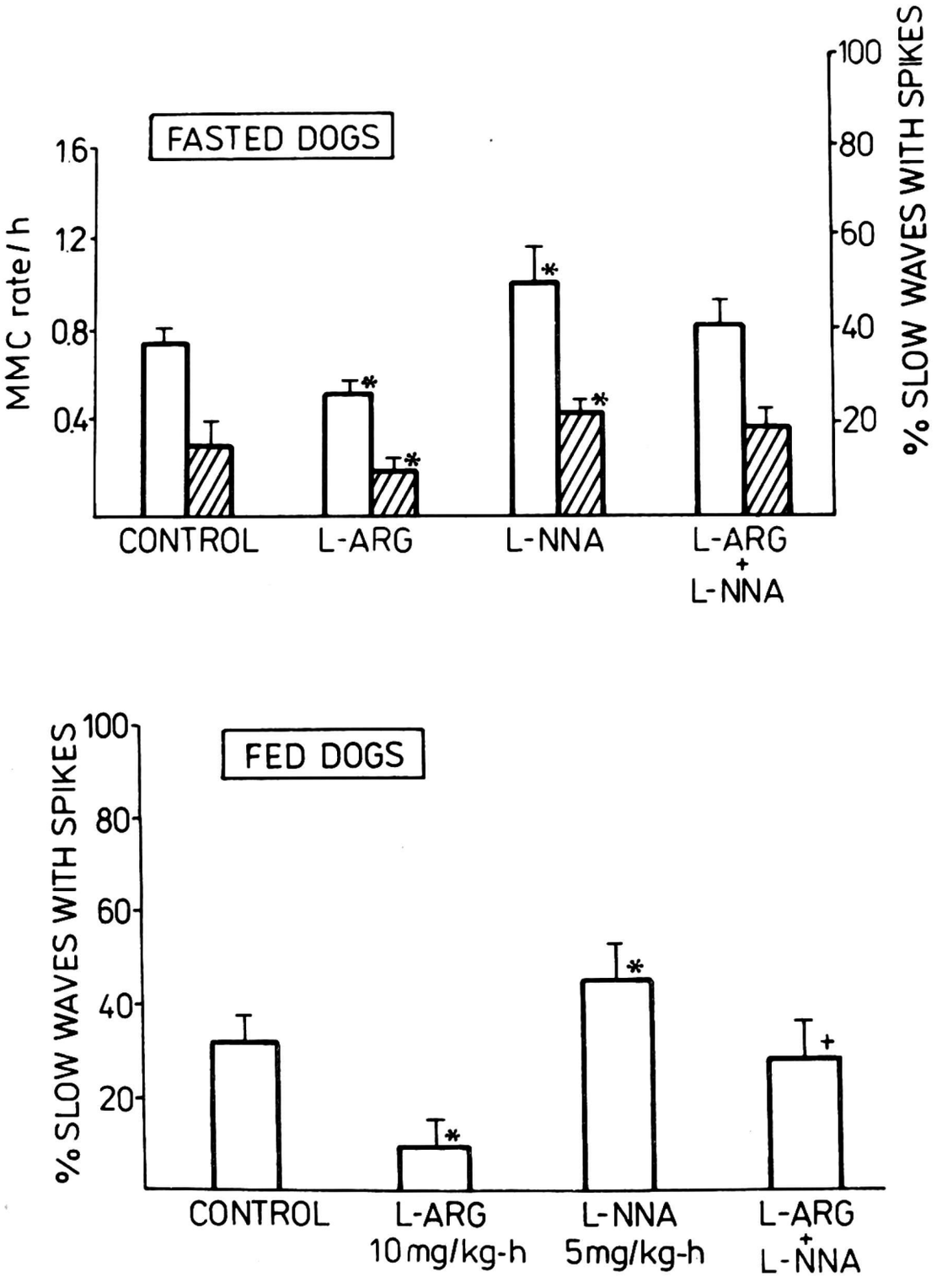

Fig. 3. MMC rate and percent of slow waves spikes in fasted and fed dogs without and with i.v. infusion of L-Arg, L-NNA or their combination as in *Fig. 2.*

When L-NNA was added to L-Arg, the postprandial pancreatic protein secretion was not changed initially (during first 0.5 h) but then was reduced by about 30%. This reduction was significantly smaller than that observed when L-NNA alone without L-Arg was administered in the postprandial period. Administration of GTN (0.5 – 1 mg/kg-h i.v.) caused almost complete suppression of the fed-like activity for about 30 min but then typical low rate postprandial spike activity was observed despite the administration of GTN (*Table 1*).

Table 1. Effects of glyceryl trinitrate (GTN) infused i.v. at a dose of 0.5 or 1 mg/kg-h on myoelectric activity of the small intestine as determined in duodenum, midjejunum and ileum and on pancreatic protein secretion in fasted and fed dogs. Means ± SEM of 5 tests on 5 dogs. Asterisk indicates significant difference ($P < 0.05$) as compared to saline control.

Type of test	MMC Interval (min)	% Slow waves with spikes			Pancreatic Protein (mg/30 min)
		Duodenum	Jejunum	Ileum	
Fasted dogs					
CONTROL (SALINE)	82 ± 8	14 ± 3	14 ± 4	13 ± 4	54 ± 12
GTN 0.5 mg/kg-h	112 ± 15*	9 ± 4	11 ± 3	9 ± 3	220 ± 42*
GTN 1.0 mg/kg/h	132 ± 24*	7 ± 2*	8 ± 2*	8 ± 3*	310 ± 56*
CCK 0.5 μg/kg-h	Interrupted	37 ± 5*	34 ± 5*	29 ± 59*	2160 ± 180*
Fed dogs					
CONTROL (SALINE)	Interrupted	35 ± 8	36 ± 9	32 ± 8	840 ± 94
GTN 0.5 mg/kg-h	Interrupted	17 ± 5*	19 ± 4*	18 ± 6*	920 ± 140
GTN 1.0 mg/kg-h	Interrupted	13 ± 5*	15 ± 4*	16 ± 4*	980 ± 110

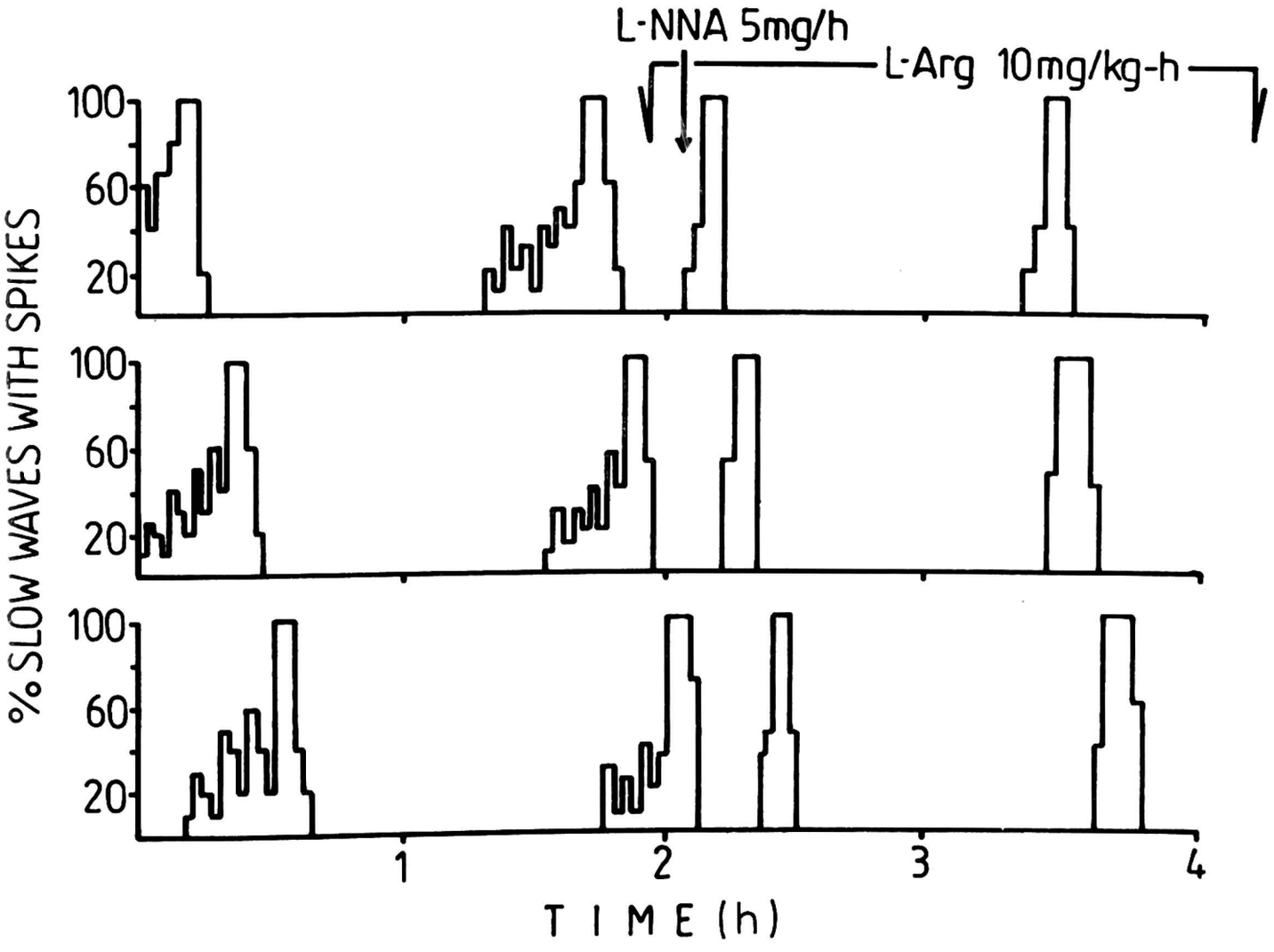

Fig. 4. Effect of i.v. infusion of L-Arg (10 mg/kg-h) combined with injection of L-NNA (5 mg/kg) on myoelectric activity of the small intestine in fasted dogs. Similar results were obtained in other dogs.

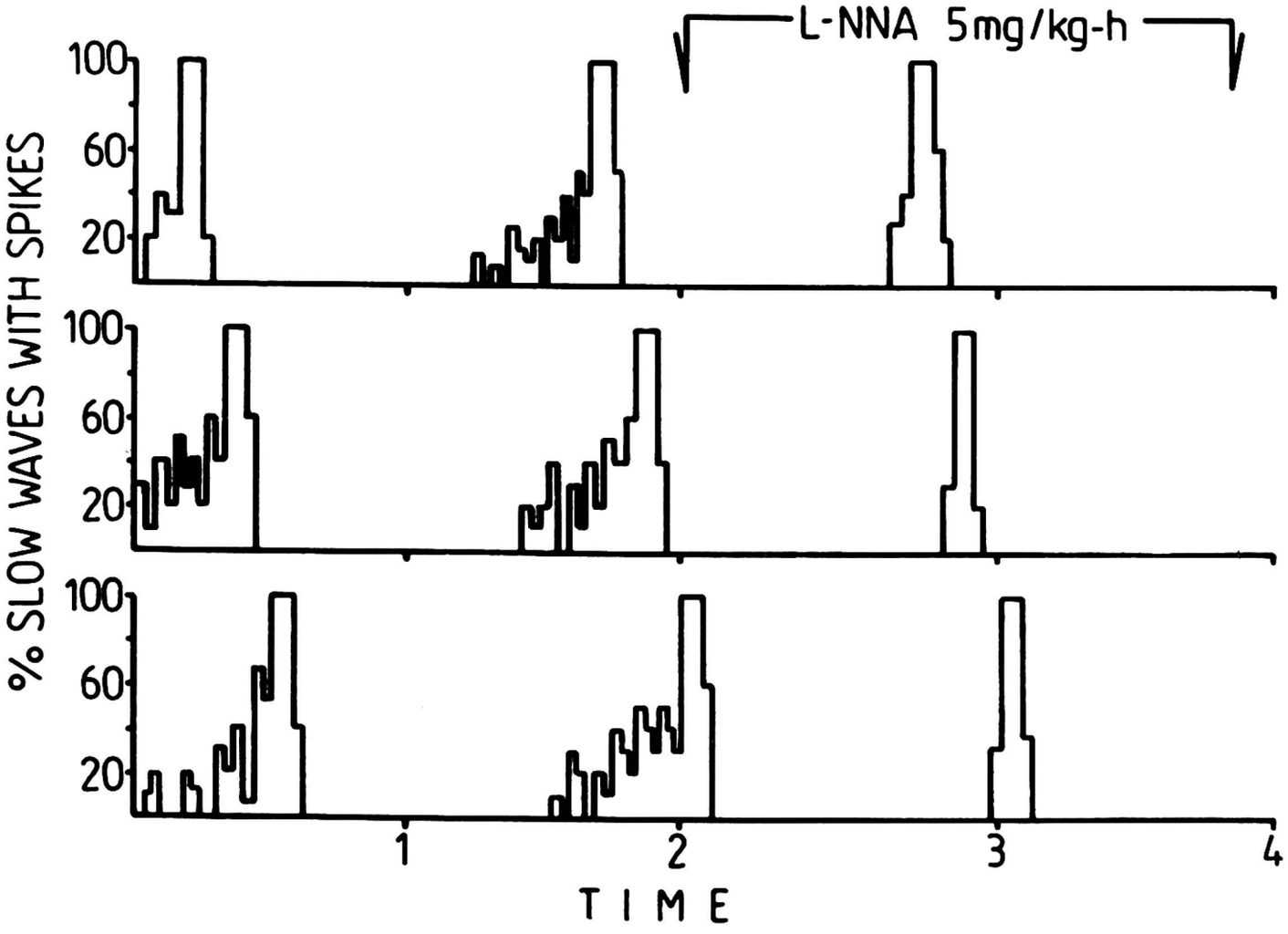

Fig. 5. The myoelectric activity of the small intestine in fed dogs before and during i.v. infusion of L-NNA (5 mg/kg-h). Similar results were obtained in other dogs.

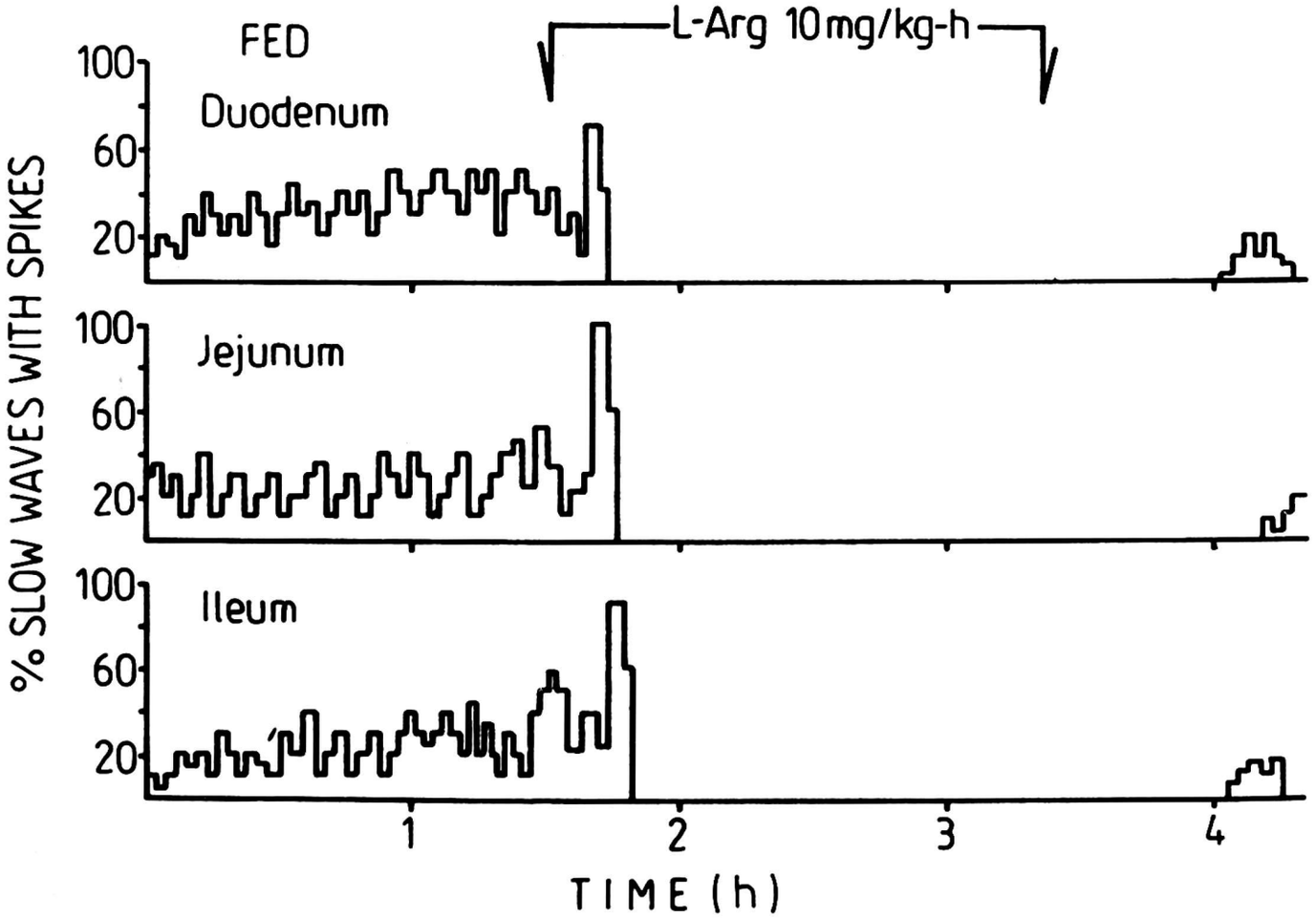

Fig. 6. Effect of i.v. infusion of L-Arg (10 mg/kg-h) on the postprandial myoelectric activity in fed dogs. Similar results were obtained in other dogs.

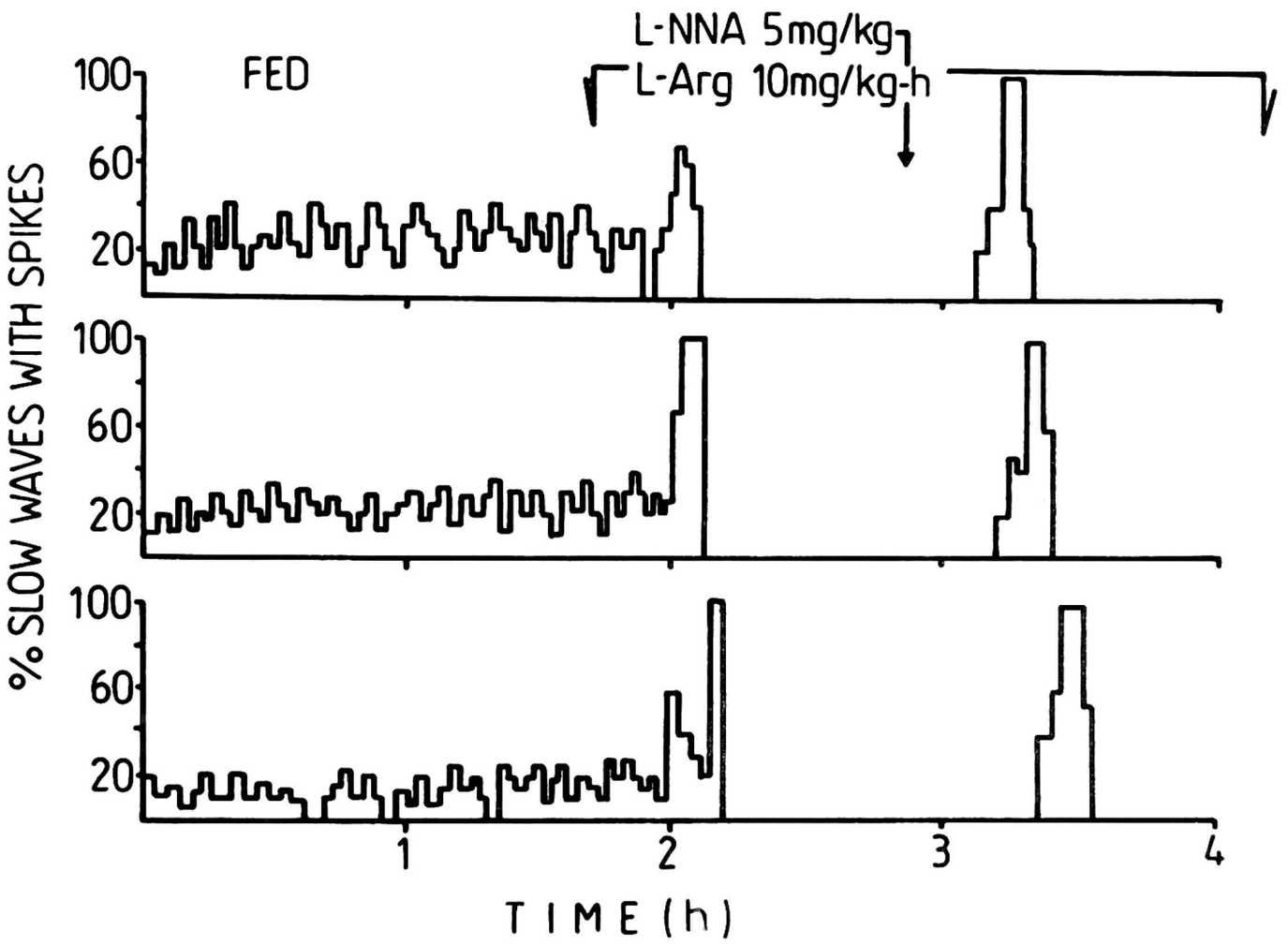

Fig. 7. Effect of i.v. infusion of L-Arg (10 mg/kg-h) plus L-NNA (5 mg/kg) on myoelectric activity of the small intestine in fed dogs. Similar results were obtained in other dogs.

Table 2. Effects of L-NNA (5 mg/kg), L-arginine (10 mg/kg-h) or their combination on the postprandial plasma gastrin, CCK, PP, insulin and glucagon levels in tests as on *Figs. 1* and 2. Mean ± SEM of 5 tests on 5 dogs. Asterisk indicates significant ($P < 0.05$) change as compared to the values obtained with meat feeding alone. Cross indicates significant ($P < 0.05$) increase above the value obtained with L-NNA alone.

Type of test	GASTRIN (pM/l)	CCK (pM/l)	PP (pM/l)	INSULIN (μU/ml)	GLUCAGON (pM/l)
BASAL	26±4	1.2±0.4	18±3	5.5±1.2	36±5
FEEDING (CONTROL)	61±9	4.7±1.3	106±9	15.4±2.6	56±7
FEEDING+L-NNA	38±6*	2.6±0.7*	42±5*	7.1±2.0*	39±2*
FEEDING+L-ARG	58±8	5.1±0.5	168±23	17.6±2.2	72±11
FEEDING+L-ARG+L-NNA	52±6+	3.6±0.5	72±10+	13.1±1.4	53±8+

Effects of L-NNA, L-Arg and L-Arg plus L-NNA on plasma gastrin, CCK, PP, insulin and glucagon levels

The mean values of basal plasma concentrations of gastrin, CCK, PP, insulin and glucagon are shown on *Table 2*. Meat feeding resulted in significat increments in plasma gastrin, CCK, PP, insulin and glucagon. These increments were significantly reduced by the administration of L-NNA alone but not when L-NNA was combined with L-Arg.

DISCUSSION

The results of this study demonstrate that endogenous production of NO is an important pathway that exerts a potent inhibitory effect on intestinal motility but has stimulatory influence on exocrine pancreatic secretion.

Under basal conditions, our dogs showed usual fluctuations in spontaneous pancreatic secretion with typical periodicity in phase with the myoelectric activity of the duodenum reaching the nadir during phase I and the peak at phase II and III. This secretory component of MMC described previously in dogs (17) and humans (18) was quantified and showed to attain 4–9% of the maximal CCK-induced secretory capacity in these animals (3). Although the cyclic pattern of intestinal motility and its secretory components have been first described over 80 years ago by Boldyreff (2) and reconfirmed more recently by several investigators (1), the mechanism underlaying this interesting phenomenon remains obscure. Both autonomic neural system and gut hormones, especially motilin, have been implicated in the mechanism underlaying generation and progression of MMC and accompanying secretory changes of the pancreas (3).

NO has been originally considered as an unstable vasodilator secreted from the endothelial cells to act as a local hormone in the immediate vicinity of these cells (14, 15). Then, Bult et al. (11) using a superfusion bioassay cascade demonstrated that NO-like factor may be released upon stimulation of the NANC nerves. A better understanding of the physiological action of NO derives from the studies on the effect of substances which suppress the NO system and prevent the release of NO such as L-Arg analogues, N^G-monomethyl-L-arginine (L-NMMA) or N^G-nitro-L-arginine (L-NNA) (12). Studies using these inhibitors of NO system showed that NO plays an important role in the control of systemic arterial blood pressure by actively dilatig the blood vessels (19). The effects of endogenously generated NO have been mimicked by the use of agents such as GTN which spontaneously release NO and which serve as "donors" of NO (19). Studies in animals revealed that the inhibition of NO synthase by L-NNA antagonizes NANC nerve-mediated

relaxation of lower esophageal sphincter and reduces the latency of the contraction in the caudad esophagus (20). These data provided a support for the hypothesis that NO is a transmitter of NANC nerve-mediated responses of circular muscle of esophagus and its sphincter. Similar studies using the rat gastric fundus showed that NO is formed and released upon NANC nerve stimulation to induce relaxation mimicked by exogenously applied NO (GTN) (7). NO has been also implicated in the reflex relaxation of the stomach to accomodate food and fluid (19).

In the small intestine, exogenous NO was found to induce dose-dependent membrane hyperpolarization accompanied by the relaxation of the muscle. The electrical stimulation of NANC nerves induced inhibitory junctional potential (IJP) and muscle relaxation but the pretreatment with NO synthases inhibitor, L-NMMA, did not affect the initial large amplitude of rapid hyperpolarization but abolished the following smaller and more sustained amplitude of hyperpolarization of IJP in the muscle (21, 22). Furthermore, such an inactivation of NO synthase abolished or reversed the inhibitory effect of electrical field stimulation of smooth muscle. These results indicate that NO mediates neural descending relaxation of circular smooth muscle of the gut (23). The action of NO released from NANC nerves is limited to a local region and is of very brief duration probably bacause of rapid inactivation of NO by oxygen, superoxide anion and hemoglobin present in the tissue. The presence of an inhibitory NANC innervation that involves the release of NO was also found in canine ileum and ileo-colonic junction (8).

The major question is whether there is any on-going or spontaneous release of NO in the gut that could affect the gastrointestinal tone of the smooth muscle and the peristalsis of the gastrointestinal tract. Studies *in vivo* in acute model of an anesthetized rat showed that L-NAME caused a dose-dependent increase in the intraluminal pressure and initiated phasic intestinal contractions accompanied by an increase in arterial blood pressure (24). These intestinal motor responses as well as the rise in the systemic blood pressure were inhibited by concurrent administration of L-Arg. Our previous studies on anesthetized dogs (25) confirmed that the inhibition of NO synthase enhanced the intestinal myoelectric activity and this was accompanied by the increase in arterial pressure. Both these effects were attenuated by L-Arg infusion. These observations suggested that endogenous NO plays an important role in the modulation of intestinal motility *in vivo*.

No study so far has been published, however, supporting the role of NO in the control of intestinal motility pattern in conscious animals.

As the major part of the enteric innervation of the gut is provided by NANC nerves (26), we assumed that also motor and secretory components of MMC cycles may involve the release and action of NO. Indeed, the suppression of NO synthase by L-NNA in fasted dogs accelerated the

occurrence of successive MMC cycles and strongly suppressed the accompanying fluctuations in pancreatic secretion. This indicates that NO affects the frequency of pacesetter MMC and is required for the progression of phase III along the small bowel as well as for the stimulation of pancreatic secretion at phase II and III. The implication of endogenous NO in the transit of phase III MMC along the gut has also been confirmed using both L-Arg, an endogenous substrate for NO synthesis (14), and GTN, an exogenous donor of NO. Infusion of L-Arg in fasted dogs significantly delayed the occurrence of consecutive phase III MMC and resulted in a significant stimulation in pancreatic secretion. Following administration of GTN, similar prolongation of the MMC interval and the increase in pancreatic secretion was observed to that obtained with L-Arg infusion. Feeding immediately interrupted the cyclic motor pattern of the gut and caused several fold increase in the pancreatic secretion. Infusion of L-Arg had no significant influence on pancreatic secretory activities but caused a remarkable reduction in the postprandial spike activity in the small bowel similar to that observed with GTN, a donor of NO. Moreover, L-NNA injected during the infusion of L-Arg enhanced the spike activity and initiated phase III in the dog duodenum. The combination of L-Arg with L-NNA also caused a marked reduction in the postprandial pancreatic secretion but this reduction was significantly less pronounced than that observed in fed dogs infused with L-NNA alone. Thus, the described changes of the intestinal myoelectric activity and the pancreatic secretion induced by activation or suppression of NO system suggest that NO acts through different pathways on intestinal smooth muscle and pancreatic secretory cells. The action of NO on the intestinal smooth muscle is inhibitory in nature and it could account for the reduction in the frequency of MMC pacessetter potential and for the suppression of the postprandial spike activity. This is in keeping with the previous proposal that NO plays a role as inhibitory neurotransmitter released by NANC nerves in the muscle layer of the gut (7, 8).

In contrast, NO in the pancreas appears to stimulate its secretory activity as evidenced by the increase in exocrine pancreatic secretion following administration of NO released spontaneously from GTN or enzymatically (by NO synthase) from L-Arg (14, 15). The inhibition of NO synthase by L-NNA resulted in a marked reduction in pancreatic secretory activity that was reversed, at least in part, when L-NNA was combined with L-Arg. This inhibitory effect of L-NNA on the postprandial pancreatic secretion was accompanied by the reduction in the release of major gut hormones stimulating the exocrine pancreas such as gastrin and CCK suggesting that NO may also affect the release of gut hormones. Since L-NNA is also capable of suppressing the pancreatic secretion in response to exogenous hormones such as CCK and secretin (9) it is unlikely that NO acts on exocrine pancreas mainly *via* affecting the release of gut hormones. The fact that NO does not influence the secretory

activity of the isolated pancreatic acinar cells (8, 10) suggests that the *in vivo* changes in exocrine pancreas observed after the inhibition of NO synthase with L-NNA or following administration of NO donor such as GTN could be attributed to the alteration in pancreatic blood flow. Previous studies demonstrated that the limitation of the blood flow to the pancreas strongly reduces its secretory activity (27) and L-NNA might cause pancreatic ischemia by removal of the vasorelaxing action of endogenous NO (5). In the stomach, NO synthesized from L-arginine, was also found to enhance mucosal vasodilation associated with the stimulation of gastric acid secretory but failed to affect the secretory activity of oxyntic glands (28). Studies on anesthetized dogs confirmed that also in the pancreas, NO greatly enhances the tissue perfusion (9) and that this could contribute to the stimulatory effect of NO on exocrine pancreas observed in conscious animals.

REFERENCES

1. Weisbrodt NW. Motility of the small intestine. In Physiology of the Gastrointestinal Tract (2nd ed.), LR Johnson (ed), New York, Raven, 1987, pp. 631–663.
2. Boldyreff W. Einige neue Seiten der Tatigkeit des Pankreas. *Ergebn Physiol* 1911; 11: 121–217.
3. Konturek SJ, Thor P, Bilski J, Bielański W, Laskiewicz J. Relationship between duodenal motility and pancreatic secretion in fasted and fed dogs. *Am J Physiol* 1986; 250: G570–574.
4. Magee DF, Naruse S. Neural control of periodic secretion of the pancreas and the stomach in fasting dog. *J Physiol (Lond)* 1983; 344: 153–160.
5. Sarna S, Chey WY, Chey Y et al. Cause and effect relationship between motilin and migrating myoelectric complexes. *Am J Physiol (Gastrointest Liver Physiol 8)* 1983; 245: G277–G285.
6. Weisbrodt NW, Copeland EM, Thor PJ. The myoelectric activity of the small intestine of the dog during total parenteral nutrition. *Proc Exp Biol Med* 1976; 153: 121–124.
7. Boeckxstaens GE, Pelckmans PA, Bogers JJ et al. Release in nitric oxide upon stimulation of nonadrenergic noncholinergic nerves in the rat gastric fundus. *J Pharmacol Exp Therap* 1991; 256: 441–447.
8. Boeckxstaens GE, Pelckmans PA, Bult H, Man JGD, Herman AG, Maercke YMV. Evidence for nitric oxide as mediator of non-adrenergic non-cholinergic relaxations induced by ATP and GABA in the canine gut. *Br J Pharmacol* 1991; 102: 434–438.
9. Konturek SJ, Bilski J, Pawlik WW, Czarnobilski K, Gustaw P, Sendur R. Release of nitric oxide upon vagal and meal-induced stimulation of exocrine pancreatic secretion in dogs. *Digestion* 1992; 52: 97.
10. Molero X, Salas A, Guarner L, Malagelada RJ. Nitric oxide modulates pancreatic response to caerulein. Histological and biochemical improvement in acute pancreatic. *Digestion* 1992; 52: 67–137.
11. Bult H, Boeckxstaens GE, Pelckmans PA, Jordaens FH, Maercke YMF, Herman AG. Nitric oxide as an inhibitory non-adrenergic noncholinergic neurotransmitter. *Nature (Lond)* 1990; 345: 346–347.
12. Thor P, Laskiewicz J, Konturek P, Konturek SJ. Cholecystokinin in the regulation of intestinal motility and pancreatic secretion dogs. *Am J Physiol* 1988; 255: G498–504.

13. Mulsch A, Busse R. N^G-nitro-L-arginine (N^5-[imino(nitroamino)methyl]-L-ornithine) impairs endothelium-dependent dilations by inhibiting cytosolic nitric oxide synthesis from L-arginine. *Naunym-Schmiedeberg's Arch Pharmacol* 1990; 341: 143–147.
14. Palmer RMJ, Ashton DS, Moncada S. Vascular endothelial cells synthesize nitric oxide from L-arginine. *Nature (Lond)* 1988: 333; 664–666.
15. Palmer RMJ, Rees DD, Ashton DS, Moncada S. L-arginine as the physiological precursor from the formation of nitric oxide in endothelium-dependent relaxation. *Biochem Biophys Res Commun* 1988; 153: 1251–1256.
16. Konturek SJ, Tasler J, Bilski J, De Jong AJ, Jansen BJ, Lamers CB. Physiological role and localization of cholecystokinin release in dogs. *Am J Physiol* 1986; 250: G391–395.
17. Keane FB, DiMagno EP, Dezois RR, Go VL. Relationship among canine interdigestive exocrine pancreatic and biliary flow, duodenal motor activity, plasma pancreatic polypeptide and motilin. *Gastroenterology* 1983; 78: 310–316.
18. Vantrappen GR, Peeters TL, Janssens J. The secretory component of the interdigestive migrating motor complex in man. *Scand J Gastroenterol* 1979; 14: 663–667.
19. Vane JR, Botting RM. Secretory functions of the vascular endothelium. *J Physiol Pharmacol* 1992; 43: 195–207.
20. Murray J, Du C, Ledlow A, Bates JN, Conklin JL. Nitric oxide: mediator of nonadrenergic noncholinergic responses of opossum esophageal muscle. *Am J Physiol* 1991; 261: G401–406.
21. Stark ME, Bauer AJ, Szurszewski JH. Effect of nitric oxide on circular muscle of the canine small intestine. *J Physiol* (London) 1991; 444: 743–761.
22. Stark ME, Bauer AJ, Sarr MG, Szurszewski JH. Nitric oxide mediates inhibitory nerve input in human and canine jejunum. *Gastroenterology* 1993; 104: 398–409.
23. Grider JR. Interplay of VIP and nitric oxide in the regulation of the descdending relaxing phase of peristalsis. *Am J Physiol* 1993; 264: G334–340.
24. Calignano A, Whittle BJR, DiRossa M, Moncada S. Involvement of endogenous nitric oxide in the regulation of rat intestinal motility in vivo. *Eur J Pharmacol* 1992; 229: 27–278.
25. Pawlik WW, Gustaw P, Thor P, Sendur R, Czarnobilski K, Hottenstein OD, Konturek SJ. Microcirculatory and motor effects of endogenous nitric oxide in the rat gut. *J Physiol Pharmacol* 1993; 44: 139–146.
26. Abrahamsson H. Non-adrenergic non-cholinergic nervous control of gastrointestinal motility patterns. *Arch Int Pharmacodyn* Ther 1986; 28: 50–61.
27. Konturek SJ, Pawlik W, Czarnobilski K et al. Effects of leukotriene C_4 on pancreatic secretion and circulation. *Am J Physiol* 1988; 254: G849–855.
28. Pique JM, Esplugues JV, Whittle BJR. Endogenous nitric oxide as a mediator of gastric mucosal vasodilation during acid secretion. *Gastroenterology* 1992; 102: 168–174.

Received: February 2, 1994
Accepted: March 15, 1994

Author's address: S. J. Konturek, Institute of Physiology, Faculty of Medicine, Jagiellonian University, ul. Grzegórzecka 16, 31-531 Cracow, Poland