Effect of L-dopa with and without inhibition of extra cerebral dopa decarboxylase on gastric acid secretion and gastrin release in man

R CALDARA, C BARBIERI, V PIEPOLI, M BORZIO, AND E MASCI

From the Second Department of Medicine, Fatebenefratelli Hospital and Third Medical Clinic, University of Milan, Milan, Italy

SUMMARY The present study was undertaken to investigate the possibility that central nervous system monoaminergic pathways may play a role in the control of gastric acid and gastrin secretion in man. Submaximal pentagastrin stimulated ($0.25 \mu\text{g/kg/h}$) gastric acid secretion, as well as basal gastrin concentrations were studied in two groups of subjects. The first group received oral administration of placebo and the catecholamine precursor L-dopa (500 mg); the second group was treated with placebo and the association of L-dopa (100 mg) plus carbidopa (35 mg) after pretreatment with carbidopa (50 mg every six hours for four doses), a schedule which is known to increase brain catecholamine concentrations. In comparison with placebo, stimulated gastric acid secretion was reduced by L-dopa alone, whereas was not modified by L-dopa plus carbidopa. Basal gastrin concentrations were increased after L-dopa and after L-dopa plus carbidopa. These data show that basal gastrin concentration is raised by central catecholamine augmentation; but gastric acid secretion seems to be influenced by changes of peripheral catecholamine concentrations. It is suggested that dopamine and perhaps noradrenaline, but not adrenaline, are important in these effects.

Several recent studies show that catecholamines may play a role in the regulation of gastric acid secretion and gastrin release in man.¹⁻⁸ As the tools used act either at central as well as at peripheral level or only outside the central nervous system, it is not yet clear the specific role of catecholaminergic receptors in the brain. The present study was carried out to evaluate whether an increase in central nervous system catecholamine concentration may affect gastric acid secretion and gastrin release in healthy man.

Methods

PATIENTS

Twenty four non-obese healthy subjects, divided in three groups of eight, without history of gastrointestinal disease (20 men and four women aged 34-58 years) volunteered for this study. Informed consent was obtained from all subjects and the research was carried out according to the Declaration of Helsinki.

Address for correspondence: Dr R Caldara, Second Department of Medicine, Fatebenefratelli Hospital, C.so di Porta Nuova, 23, 20121, Milano, Italy.

Received for publication 21 November 1984

In two groups of eight individuals, after an overnight fast, a nasogastric tube was passed into the stomach and its position was checked by using the water recovery technique.⁹ Gastric juice was collected by continuous aspiration and pooled in 15 minute fractions. After the first 30 minute portion had been discarded, gastric acid secretion was evaluated for two hours during the infusion of a submaximal dose of pentagastrin ($0.25 \mu\text{g/kg/h}$). The study was carried out in two different sessions (placebo and active treatment) at three day intervals in randomised order. Thirty minutes before the introduction of the nasogastric tube, the first group of subjects was orally administered placebo and L-dopa alone (500 mg) and the second group received placebo and L-dopa plus carbidopa (35 mg) after pretreatment with carbidopa (50 mg) every six hours for four doses.

L-dopa (Roche SpA, Milan) is the precursor of catecholamines used to increase their pool both in the brain and in the periphery. Carbidopa (Merck Sharp and Dohme SpA, Rome) is the inhibitor of dopa decarboxylase, which is the enzyme responsible for the conversion of L-dopa into dopamine.

The experiments were carried out in two different groups of subjects on proposal of the ethical committee of the hospital, who suggested no more than two endogastric evaluations in each individual were carried out. In the other eight subjects serum gastrin concentration was measured at the times reported in Figure 1 on three different sessions, at three day intervals in randomised order, after placebo as well as the two drug treatments previously reported. Gastric acid concentration was measured by titration with 0.1 M NaOH to pH 7.0 using a semi-automatic titrimeter. Serum gastrin concentration was determined by radioimmunoassay⁵ using a gastrin antibody in a final dilution of 1:200,000. The interassay and intra-assay variation is <8%. The antibody used detects little (G-17) and big (G-34) gastrin with G-34 about two thirds as potent as G-17 on a molar basis.

The cross reactivity with porcine cholecystokinin is <2%. The samples from each subject were run in the same assay and determined in triplicate. Statistical assessment of data was performed by the two-tailed Student's *t* test for paired data and analysis of variance followed by Duncan's test for

multiple comparisons. Data are mean±SEM and *p* values of <0.05 were considered significant.

Results

In comparison with placebo the administration of L-dopa alone significantly reduced both the gastric acid output and juice volume ($p<0.05$ at the first hour; $p<0.01$ at the second hour) during submaximal pentagastrin stimulation. No significant changes in these variables were observed after L-dopa plus carbidopa (Fig. 2).

A significant increase of gastrin concentration *versus* placebo study was shown after L-dopa ($p<0.05$ at 90 and 120 min) as well as after L-dopa plus carbidopa ($p<0.01$ at 90 and 120 min; $p<0.05$ at 150 min) (Fig. 1). The between treatments comparison revealed a greater stimulation of gastrin release after L-dopa plus carbidopa from 30 to 150 min, which attained statistical significance at 150 min ($p<0.05$).

No side effects were reported by any subject except mild nausea in two subjects after L-dopa administration.

Fig. 1 Effect of placebo, L-dopa and L-dopa plus carbidopa on basal serum gastrin concentration in eight healthy subjects. Mean±SEM. * $p<0.05$; ** $p<0.01$.

Fig. 2 Effect of placebo or L-dopa ($n=8$) and placebo or L-dopa plus carbidopa ($n=8$) on submaximal pentagastrin-stimulated ($0.25 \mu\text{g/kg/h}$) gastric acid output and juice volume in healthy subjects. Mean±SEM. * $p<0.05$; ** $p<0.01$.

Discussion

Systemic administration of L-dopa is followed by its conversion into catecholamines not only in the central nervous system, but also in the periphery. When the conversion of L-dopa into dopamine outside the brain is prevented, it is possible to discriminate between centrally and peripherally mediated L-dopa effects. Carbidopa is a dopa decarboxylase inhibitor which at a low dose does not cross the blood brain barrier¹⁰ and thus inhibits extracerebral, but not cerebral, dopa decarboxylase activity.¹¹ Therefore, the concomitant administration of L-dopa and carbidopa increases the brain catecholamine concentration. In order to obtain increases of catecholamines both outside and inside the brain, we administered L-dopa as well as L-dopa plus carbidopa at a schedule proposed by Fine and Frohman¹² and subsequently used as a classical endocrinological test to differentiate central *versus* peripheral monoaminergic stimulation.

The present data show that the administration of L-dopa with the consequent increase of catecholamines reduces gastric acid secretion. On the contrary, L-dopa plus carbidopa administration is devoid of effect on gastric acid output as well as juice volume (Fig. 2).

Because of the known relationship between gastrin concentrations and gastric acidity, however, the difference shown by the two regimens might be of minor weight in the light of the observed increase in serum gastrin concentrations after both treatments. Although the results obtained in two different groups of subjects for the reasons stated in Methods cannot be directly compared, the present data suggest that this effect is mainly produced in the periphery.

The present study does not elucidate the neurotransmitter involved in this action, because augmented L-dopa concentrations increase dopamine, noradrenaline and adrenaline concentration.¹³ Also dopamine, which does not cross the blood brain barrier,¹⁴ is known to decrease gastric acid secretion both in man^{5,6} and in the experimental animal.¹⁵ Noradrenaline might also play a role as it is devoid of effect at low doses both in animal¹⁶ and in man.⁴ On the contrary, it is unlikely an involvement of adrenaline, as suggested by studies showing that direct⁴ as well as indirect⁷ augmentation of adrenaline blood levels stimulate acid secretion.

The lack of effects observed after L-dopa plus carbidopa is in general agreement with previous data in rats, which show that intracerebroventricular administration of dopamine is ineffective on gastric acidity¹⁶ and central injection of noradrenaline does not possess clear cut effects.¹⁷

The administration of L-dopa with and without inhibition of extracerebral dopa decarboxylase increased serum gastrin concentrations (Fig. 2). The between studies analysis revealed a greater increase after L-dopa plus carbidopa. These data suggest that the increase in gastrin secretion is because of central catecholamine augmentation. This hypothesis is in general agreement with previous findings which show that gastrin secretion in man is not significantly modified by dopamine,^{5,8} which does not cross blood brain barrier, whereas is increased by bromocriptine in man¹⁸ and in animal¹⁹ and by apomorphine in animal,²⁰ which stimulate dopaminergic receptors also inside the central nervous system.

In other catecholamines, basal gastrin concentrations are not changed by noradrenaline administration in man,⁴ but are reduced in cats after sympathetic nerve stimulation to the stomach, a condition associated with an increase of noradrenaline in the antral mucosa.²¹ On the contrary, adrenaline has been shown to increase gastrin release during circumstances with high class plasma catecholamine concentrations, such as severe stress.^{2,3,7} It might be possible, however, that the observed gastrin augmentation be dependent on the reduction in gastric acidity, but it has been reported that acute increase in intragastric pH does not raise serum gastrin concentration in humans.²² Moreover, the lack of changes in gastrin release observed after dopamine infusion, despite a marked inhibition of acid output⁵ of the same magnitude observed in the present study, seems also to exclude such possibility.

In any case, it is possible that the role of catecholamines in the regulation of gastric acidity and gastrin secretion may be primarily of pharmacological than physiological significance. Alternatively, it has to be considered that the observed effect may be because of the intrinsic activity of the drugs.

We are indebted to Merck Sharp and Dohme SpA, Roma, Italy, and to Roche SpA, Milano, Italy, for the supply of carbidopa and L-dopa.

References

- 1 Hayes JR, Ardill J, Kennedy TL, Shanks RG, Buchanan KD. Stimulation of gastrin release by catecholamines. *Lancet* 1972; **1**: 819-21.
- 2 Stadil F, Rehfeld JF. Release of gastrin by epinephrine in man. *Gastroenterology* 1973; **65**: 210-5.
- 3 Brandsborg O, Brandsborg M, Christensen NJ. Plasma adrenaline and serum gastrin: studies in insulin-induced hypoglycemia and after adrenaline infusion. *Gastroenterology* 1975; **68**: 455-60.

- 4 Christensen KC, Stadil F. Effect of epinephrine and norepinephrine on gastrin release and gastric secretion of acid in man. *Scand J Gastroenterol* 1976; suppl: 37: 87-92.
- 5 Caldara R, Ferrari C, Romussi M, Bierti L, Gandini S, Curtarelli G. Effect of dopamine infusion on gastric and pancreatic secretion and on gastrin release in man. *Gut* 1978; 19: 724-8.
- 6 Valenzuela JE, Defilippi C, Diaz G, Navia E, Merino Y. Effect of dopamine on human gastric and pancreatic secretion. *Gastroenterology* 1979; 76: 323-6.
- 7 Jarhult J, Hamberger B, Lanthén G, Ors M, Uvnäs-Wallensten K. The role of catecholamines in the control of gastrin and acid secretion during insulin hypoglycemia in man. *Digestion* 1981; 21: 92-7.
- 8 Schrumpf E, Linnestad P. Effect of cholinergic, adrenergic and dopaminergic blockade on gastrin secretion in healthy subjects. *Scand J Gastroenterol* 1982; 17: 29-31.
- 9 Findlay G, Prescott R, Sircus W. Comparative evaluation of water recovery test and fluoroscopic screening in positioning a nasogastric tube during gastric secretory studies. *Br Med J* 1972; 4: 458-61.
- 10 Clark WC, Oldendorf WH, Dewhurst WG. Blood brain barrier to carbidopa (MK-486) and Ro 4-4602, peripheral dopa decarboxylase inhibitors. *J Pharm Pharmacol* 1973; 25: 416-8.
- 11 Bartholini G, Pletscher A. Effect of various decarboxylase inhibitors on the central metabolism of dihydroxyphenylalanine. *J Pharm Pharmacol* 1969; 21: 323-4.
- 12 Fine SA, Frohman LA. Loss of central nervous system component of dopaminergic inhibition of prolactin secretion in patients with prolactin-secreting pituitary tumours. *J Clin Invest* 1978; 61: 973-80.
- 13 Bartholini G, Da Prada M, Pletscher A. Decrease of cerebral 5-hydroxytryptamine by 3,4-dihydroxyphenylalanine after inhibition of extracerebral decarboxylase. *J Pharm Pharmacol* 1968; 20: 228-9.
- 14 Oldendorf WH. Brain uptake of radiolabeled amino acids, amines and hexoses after arterial injection. *Am J Physiol* 1971; 221: 1629-39.
- 15 Valenzuela JE, Grossman MI. Dopamine stimulates pancreatic secretion and inhibits gastric secretion in dogs. [Abstract] *Clin Res* 1976; 24: 292A.
- 16 Osumi Y, Aibara S, Sakae K, Fujiwara M. Central noradrenergic inhibition of gastric mucosal blood flow and acid secretion in rats. *Life Sci* 1977; 20: 1407-16.
- 17 Morley JE, Levine AS, Silvis SE. Central regulation of gastric acid secretion: the role of neuropeptides. *Life Sci* 1982; 31: 399-410.
- 18 Reding P, De Graef J, Barbier P. Bromocriptine and gastrin secretion. *Lancet* 1978; 1: 1202-3.
- 19 Hirst BH, Lund PK, Reed JD, Sanders DJ. Bromocriptine, gastric acid output, and gastrin secretion. *Lancet* 1977; 1: 902-3.
- 20 Uvnäs-Wallensten K, Gojny M. Effect of apomorphine on peripheral venous gastrin and insulin levels in conscious dogs. *Acta Physiol Scand* 1981; 112: 155-60.
- 21 Blair EL, Grund ER, Reed JD, Sanders DJ, Sanger G, Shaw B. The effect of sympathetic nerve stimulation on serum gastrin, gastric acid secretion and mucosal blood flow responses to meat extract stimulation in anaesthetized cats. *J Physiol* 1975; 253: 493-504.
- 22 Peters MN, Feldman M, Walsh JH, Richardson Ct. Effect of gastric alkalinization on serum gastrin concentrations in humans. *Gastroenterology* 1983; 85: 35-9.