

Effects of Physiological Increases of Plasma Noradrenaline on Gastric Acid Secretion and Gastrointestinal Hormones

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It is not known if the increased plasma concentration of noradrenaline in patients with chronic duodenal ulcer disease is a pathogenetic factor or not. The aim of the present study was to investigate if physiologic changes of noradrenaline would evoke any alterations in gastric acid secretion or in the plasma concentration of some gastrointestinal hormones (gastrin, secretin, PP, PYY, and GIP) known to affect gastric physiology. The results show that basal plasma noradrenaline concentration was 1.8 nM and after infusion with noradrenaline at 0.04 or 0.2 nmol/kg/min plasma levels of 2.5 and 4.4 nM were obtained. No appreciable changes could be found in basal or pentagastrin stimulated acid secretion or in any of the gastrointestinal peptides studied. If the elevated plasma noradrenaline concentration observed in duodenal ulcer patients is a pathogenetic factor; it is probable that it interferes with other variables such as blood flow, bicarbonate secretion, or prostaglandin synthesis.

KEY WORDS: catecholamines; duodenal ulcer; gastric acid; G-1 hormones; noradrenaline; sympathoadrenal system.

It has been reported recently that patients with chronic duodenal ulcer disease (DU) have an increased plasma concentration of noradrenaline (1-3). However, it is not known whether or not this noradrenaline level is sufficiently high to evoke alterations in gastric acid secretion. Leonsins and Waddell (4) found a decrease in histamine-stimulated gastric acid secretion during infusion of a high

dose (0.5 µg/kg/min) of noradrenaline and Christensen and Stadil (5) observed a depressant effect on basal acid output at a dose of 50 ng/kg/min but not at 5 ng/kg/min. It has also been claimed that the serum gastrin concentration rises in response to noradrenaline (5). However, these studies are hampered by the fact that the dose of noradrenaline used has been "supraphysiological" and that no analyses of the resultant plasma noradrenaline concentration have been performed.

The aim of the present investigation was therefore to investigate whether an infusion of noradrenaline, producing plasma noradrenaline levels similar to those observed during insulin hypoglycemia (6-8) or mild exercise (9), would change gastric acid secretion during basal and stim-

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ulated conditions. Due to the proposed link between the sympathetic and peptidergic nervous systems (10) and due to the fact that gastrointestinal hormones might be influenced by the sympathoadrenal system (11–13), we also studied the evoked "physiological" increments in plasma noradrenaline effect on some of the gastrointestinal hormones known to influence acid secretion or gastric function.

MATERIALS AND METHODS

Nine patients (four males and five females, median age 52 years; range 43–65 years) with a history of chronic duodenal ulcer disease for more than one year gave their informed consent to participate in this study. All patients had earlier had endoscopic evidence of duodenal ulcer, but at the time of the investigation they were without symptoms suggestive of active ulceration. The study was approved by the Ethical Committee at the University of Lund.

All tests were performed the morning after an overnight fast and tobacco abstinence. The subjects rested comfortably in an armchair throughout the experiments. Polyethylene cannulas were inserted into the antecubital veins to permit infusion of noradrenaline and for collection of blood samples. A nasogastric tube was positioned in the stomach and residual gastric juice aspirated. By intermittent pump suction, gastric aspirates were collected at 15-min intervals over a period of 225 min. After a 45-min baseline period, noradrenaline (ACO, Sweden) at a dose of 0.04 nmol/kg/min was infused during 30 min followed by a new 45-min control period. Noradrenaline, at a dose of 0.2 nmol/kg/min, was then infused for 75 min and 30 min after the start of this second noradrenaline infusion pentagastrin (Peptavlon®, ICI) was injected subcutaneously in a dosage of 6 µg/kg body wt.

The noradrenaline solution was freshly prepared, diluted in ice-cold isotonic saline containing 20 µg/ml of ascorbic acid, and infused at a rate of 1 ml/min. During the control periods saline was infused at the same rate. The patients were unaware of when noradrenaline or saline was infused. Blood samples for determination of gastrointestinal hormones and catecholamines in plasma were withdrawn every 15 min. Heart rate and blood pressure were also recorded every 15 min.

On a second occasion, separated by at least one week from the first test, a regular pentagastrin test with the same dosage was performed in seven of the nine patients.

The volume of gastric juice in each 15-min sample was recorded and a 5-ml aliquot titrated to pH 7.0 using 0.1 N NaOH in an automatic titrator (Radiometer, Copenhagen, Denmark). Plasma adrenaline, noradrenaline, and dopamine concentrations were measured using high-pressure liquid chromatography with electrochemical detection (14). Plasma concentrations of gastrin, secretin, pancreatic polypeptide (PP), peptide YY (PYY), and gastric inhibitory peptide (GIP) were analyzed as previously described (15, 16). Statistical significances of differences between variables were tested with the Wilcoxon's

matched-pairs signed-ranks test. Data are expressed as median values and interquartile (IQ) ranges. When calculating differences the basal 30-min period immediately before the first noradrenaline infusion was compared to the 30-min infusion of the two noradrenaline solutions and the 30-min period after pentagastrin injection.

RESULTS

Except for slight nausea immediately after the pentagastrin injection, no patient experienced any adverse symptom during the tests.

Median basal plasma noradrenaline concentration was 1.80 nM (1.6–1.94), and it rose to 2.5 nM (2.08–2.72; $P < 0.02$) in response to infusion of noradrenaline at a dose of 0.04 nmol/kg/min and to 4.40 nM (4.2–5.6; $P < 0.01$) in response to a dose of 0.2 nmol/kg/min (Figure 1). The higher dose of noradrenaline induced a significantly ($P < 0.01$) higher plasma concentration than did the lower dose. No changes occurred in the plasma concentration of adrenaline or dopamine during the infusion of noradrenaline.

Heart rate and systolic blood pressure remained unchanged during the noradrenaline infusions, whereas diastolic blood pressure was significantly ($P < 0.05$) higher during infusion of the high dose of noradrenaline (80 mm Hg; IQ range 70–90 mm Hg) compared to 75 mm Hg (IQ range 65–80 mm Hg) during the baseline period.

Basal acid output showed no changes during noradrenaline infusion. There was a significant ($P < 0.01$) rise in acid secretion after pentagastrin both in the absence and presence of noradrenaline (Figure 2). This rise was slightly more pronounced ($P <$

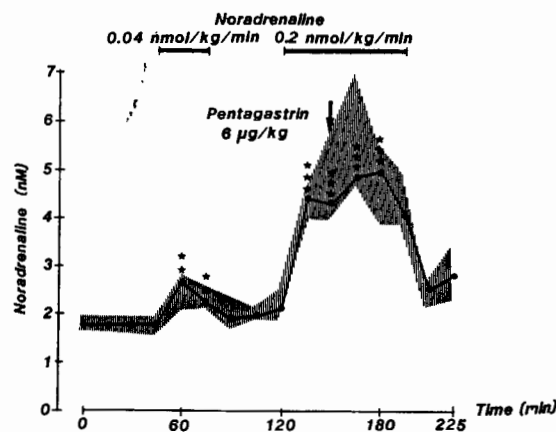


Fig 1. Plasma noradrenaline concentration in the basal state, during infusion of noradrenaline and during pentagastrin. Median and interquartile range shown. ** $P < 0.02$; *** $P < 0.01$.

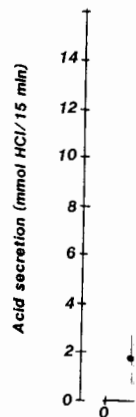


Fig 2. Gastric noradrenaline median and intersecretion during noradrenaline

0.05) during noradrenaline with noradrenaline. Noradrenaline concentrations studied in the presence of noradrenaline (Figure 3). A co

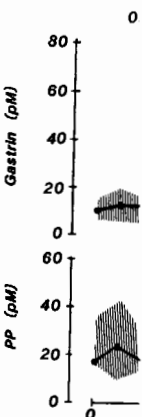


Fig 3. Plasma concentrations of gastrin and pancreatic polypeptide during noradrenaline infusion. Median and interquartile range shown.

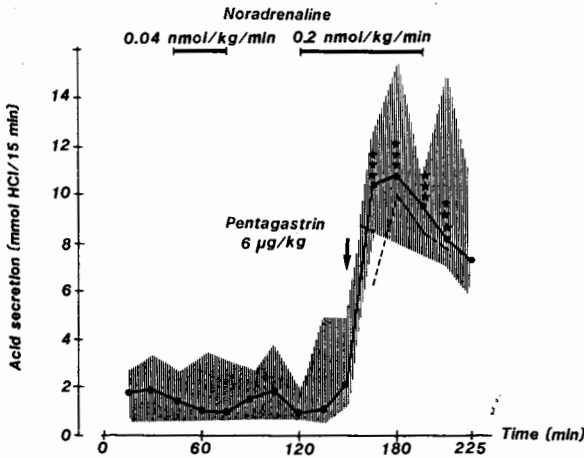


Fig 2. Gastric acid output during basal state, during infusion of noradrenaline, and in response to pentagastrin stimulation. Median and interquartile range shown. Broken line indicates acid secretion during pentagastrin stimulation without concomitant noradrenaline infusion. *** $P < 0.01$.

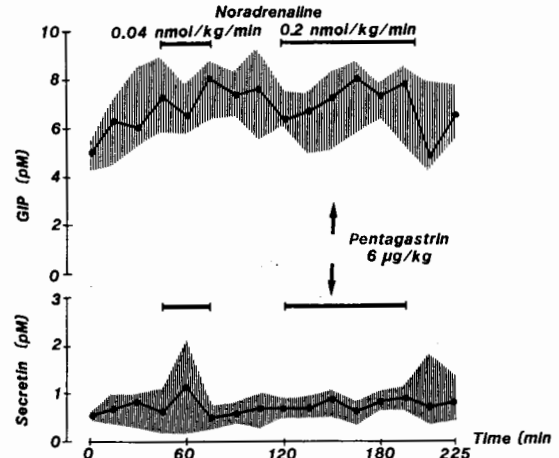


Fig 4. Plasma concentrations of secretin and GIP during basal state, during noradrenaline infusion, and after pentagastrin stimulation. Median and interquartile range shown.

0.05) during the background infusion of noradrenaline (peak acid output 18.2 mmol/30 min with noradrenaline vs 15.3 mmol/30 min without noradrenaline).

Noradrenaline infusion did not change the plasma concentration of the various gastrointestinal peptides studied (Figures 3-5). The serum concentrations of immunoreactive gastrin and PP rose significantly ($P < 0.01$) in response to pentagastrin (Figure 3). A continuous slow decrease of plasma PYY concentration occurred during the tests (Figure 5).

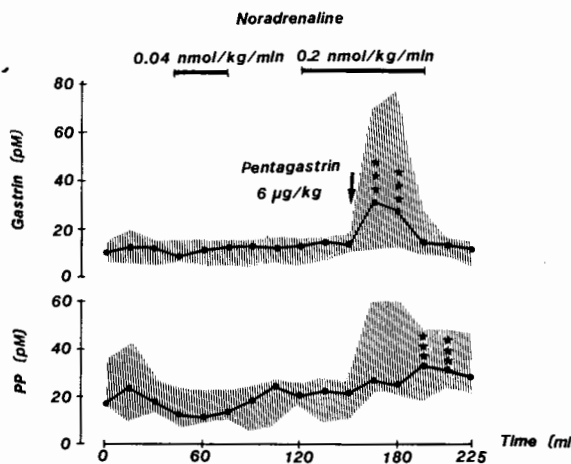


Fig 3. Plasma concentrations of gastrin and PP during basal state, during noradrenaline infusion, and after pentagastrin stimulation. Median and interquartile range shown. *** $P < 0.01$.

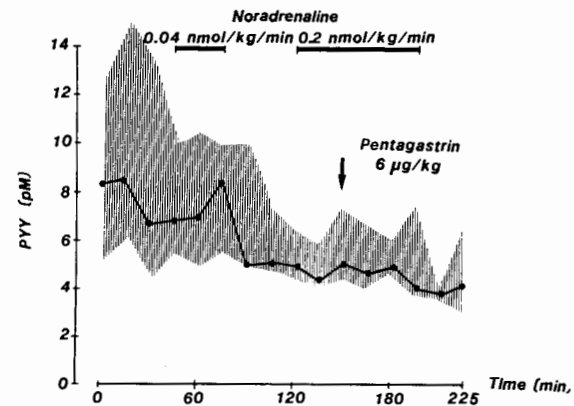


Fig 5. Plasma concentrations of PYY during basal state, during noradrenaline infusion, and after pentagastrin stimulation. Median and interquartile range shown.

DISCUSSION

In the present investigation on the effect of noradrenaline on gastric acid secretion and related gastrointestinal peptides, an attempt was made to select doses which would change the plasma noradrenaline concentration within the physiological range. This was achieved by infusing a dose of 0.04 or 0.2 nmol/kg/min which caused plasma noradrenaline increments up to three times the basal value. These plasma noradrenaline concentrations occur during physical exercise (9), mental stress (17), or during insulin hypoglycemia (6-8). The effect of this physiological noradrenaline con-

centration on basal and pentagastrin-stimulated acid secretion was negligible.

Our findings are thus contradictory to those reported in two previous studies in which gastric acid secretion has been measured during infusion of noradrenaline in man. In the study by Leonsins and Waddell (4) a high dose of 0.5 $\mu\text{g}/\text{kg}/\text{min}$ (equivalent to 3 nmol/kg/min) inhibited gastric acid secretion during basal states and after stimulation with peptone broth, histamine and insulin hypoglycemia. A similar inhibitory effect on basal acid secretion was reported by Christensen and Stadil (5), who infused noradrenaline at a dose of 50 ng/kg/min (0.3 nmol/kg/min). On the other hand, infusion of 5 ng/kg/min noradrenaline solution (equivalent to 0.03 nmol/kg/min) was without effect on the acid secretion. We conclude that blood-borne noradrenaline does not importantly regulate acid secretion under normal circumstances in man, whereas an inhibitory influence of noradrenaline on acid secretion might occur when the amine is released locally in high concentrations upon activation of the sympathetic nerves to the stomach. This inhibition of acid secretion is possibly a result of vasoconstriction (18).

Much data has been accumulated about the role of circulating catecholamines in regulating serum gastrin concentrations. Elevated serum gastrin levels are found concomitant to increased plasma catecholamine concentrations during insulin hypoglycemia (8, 19), during exercise (20), and during respiratory acidosis (21). Furthermore, infusion of noradrenaline in man has generally been reported to increase serum gastrin levels (5) but, again, the doses of noradrenaline infused have probably been pharmacological. In the present study, serum gastrin levels were not changed during elevation of plasma noradrenaline within the physiological range. The rise in serum gastrin after pentagastrin stimulation probably represents a cross-reaction in the radioimmunoassay (22).

The release of pancreatic polypeptide (PP) is mainly controlled by cholinergic mechanisms (23, 24), although the sympathoadrenal system seems to be involved in PP release as well (6, 11, 25, 26). In the present study PP levels were unchanged during the noradrenaline infusions. The rise in PP concentration observed after stimulation with pentagastrin is probably due to the increased acid load (27).

Secretin is capable of inhibiting gastric acid secretion (28), but whether this occurs during physiological conditions is still unknown. During insulin

hypoglycemia, secretin concentrations are unchanged (29), and in the present study noradrenaline did not change serum secretin concentrations. Thus, secretin seems to be neither stimulated nor inhibited by cholinergic or adrenergic influences directly.

The involvement of the sympathoadrenal system in the regulation of GIP release is controversial. In dogs, the GIP response to intraduodenal glucose was unaffected by intravenous infusion of adrenaline (30), but in man, Salera et al (12) found that alpha-adrenergic stimulation suppressed the GIP response to oral glucose. In the present study basal GIP concentrations were unchanged during noradrenaline infusion, suggesting that there is no noradrenergic tone modulating basal GIP secretion under normal conditions.

PYY belongs to the pancreatic polypeptide family known to coexist with catecholamines in the sympathetic nervous system (31). The physiologic role of PYY has not yet been elucidated (16), but infusion of low doses of PYY has been reported to have significant inhibitory effects on gastric acid secretion (32). The slow decline in PYY concentrations in our experiments (Figure 5) are probably due to prolonged fasting (unpublished data). Infusion of noradrenaline did not change serum PYY concentrations.

In summary, an increase in plasma noradrenaline concentrations up to three times the basal values did not influence gastric acid secretion and the various gastrointestinal peptides studied. If the elevated plasma noradrenaline concentration observed in duodenal ulcer patients (1-3) is a pathogenic factor; it is probable that it interferes with other variables such as blood flow (18), bicarbonate secretion (33), or prostaglandin synthesis (34).

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