

Inhibition of gastric acid secretion by intracerebroventricularly administered prostaglandin E₂ in anaesthetized rats

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- 1 The effect of intracerebroventricularly (i.c.v.) administered prostaglandin E₂ (PGE₂) on gastric acid secretion was studied in anaesthetized rats.
- 2 Intracerebroventricular injections of 1 and 3 µg of PGE₂ inhibited gastric acid secretion induced by insulin, electrical vagal stimulation and acetylcholine in a dose-dependent manner.
- 3 Intravenous injections of 1, 3 and 10 µg of PGE₂ had no effect on insulin-stimulated gastric acid output.
- 4 The results indicate that upon i.c.v. administration PGE₂ inhibits gastric acid secretion by acting centrally and not peripherally after leakage from the central nervous system.

Introduction

It is well accepted that the central nervous system is involved in the control of gastric acid secretion, and several brain structures and neural pathways participating in this process have been identified (Grijalva, Lindholm & Novin, 1980). In addition, biochemical signals in the brain initiating or modulating neural and humoral impulses for gastric acid secretion have also been investigated in recent years. Thus it has been proposed that cholinergic (Brodie, Lotti & Bauer, 1970), noradrenergic (Osumi, Aibara, Sakae & Fujiwara, 1977), 5-hydroxytryptaminergic (Hiero, Sánchez-Barriga, Solana & Peña, 1980) and GABA-ergic (Levine, Morley, Kneip, Grace & Silvis, 1981) systems, as well as several neuropeptides (Taché, Vale, Rivier & Brown, 1981), may be involved in the central regulation of gastric acid secretion.

Various prostaglandins, including prostaglandin E₂ (PGE₂), are found in the central nervous system (Wolfe, 1982), and when administered to experimental animals they modify a number of physiological functions by a central action. There is now evidence that prostaglandins have centrally-mediated effects on thermoregulation, cardiovascular system, respiration, hypothalamic and pituitary hormone release, and behaviour (Behrman, 1975; Wolfe & Coceani, 1979; Wolfe, 1982). However, the physiological role of prostaglandins in the central nervous system is still obscure.

Because there is no information on the central actions of prostaglandins on gastric secretion the effects of intracerebroventricularly (i.c.v.) adminis-

tered PGE₂ on the output of gastric acid were studied in anaesthetized rats.

Methods

Measurement of gastric acid secretion

Male Wistar rats weighing 250–300 g were used after a fast of about 20 h. The animals were anaesthetized with urethane, 1.2 g/kg, intraperitoneally and prepared for the measurement of gastric acid output as described previously (Puurunen & Karppanen, 1975). Briefly, the trachea was cannulated and the rat was allowed to breathe spontaneously. A polyethylene cannula was introduced into the stomach through an incision in the duodenum and ligated about 0.5 cm from the pylorus. The stomach was irrigated through the duodenal cannula during the experiments with 4 ml portions of prewarmed (37°C) saline (pH 5.5–6.0). The volume of the solution recovered from the stomach was measured and the concentration of hydrogen ions determined with an automatic potentiometric titrator (TTT 2, Radiometer, Copenhagen, Denmark).

The left femoral vein was cannulated for the intravenous injections which were given in a volume of 1 ml/kg. Mean arterial pressure was recorded continuously via a cannula inserted into the left femoral artery, and any rat in which it was lower than 80 mmHg before any treatment was discarded. The rectal temperature of the animals was kept at 37°C during the experiment.

Intracerebroventricular administration

I.c.v. administration was performed by the stereotaxic method described in detail by Paakkari (1980). Briefly, an injection needle was introduced into the right lateral ventricle and a polyethylene tube filled with the PGE₂ solution or vehicle was attached to it. The solution was allowed to flow into the ventricle by means of hydrostatic pressure in 10 μ l portions at 1 min intervals, the total volume being 30 μ l.

Electrical vagal stimulation

Both vagus nerves were exposed in the neck and ligated. A platinum electrode was applied to the left vagus distal to the ligature. The rats were subjected to artificial respiration via the tracheal cannula by using a Harvard Apparatus Rodent Respirator, Model 681 (Harvard Apparatus, Millis, MA, USA). Impulses of 2 ms duration at a strength of 5 V and a frequency of 5 Hz were delivered with a Harvard Apparatus Stimulator, Model 345.

Drugs

PGE₂ (Ujohn Companies, Kalamazoo, USA) was dissolved in absolute ethanol (10 mg/ml) and stored at -20°C. Further dilutions were made weekly with 0.9% w/v NaCl solution (saline) and stored at 4°C. Insulin solutions (Insulin Actrapid, Novo Industri, Copenhagen, Denmark) were made freshly each day in saline. Acetylcholine chloride (Koch-Light Laboratories, Colnbrook, Bucks) was dissolved in saline and infused intravenously in a volume of 15 μ l/min by means of a Braun infusion pump (B. Braun, Melsungen, W. Germany).

Statistical analysis

The results are expressed as means \pm s.e. Statistical analysis was performed using Student's paired *t* test. *P* values less than 0.05 were taken as significant.

Results

Effect of i.c.v. administration of prostaglandin E₂ on insulin-stimulated gastric acid secretion.

I.v. injection of 1 iu/kg of insulin increased the low basal output of acid within an hour, the maximal stimulation being observed after approximately 2 h. I.c.v. administration of 1 or 3 μ g of PGE₂ performed 40 min after insulin inhibited this stimulation in a dose-dependent manner (Figure. 1). The inhibitory effect of 1 μ g of PGE₂ lasted less than 80 min, whereas in the rats which received 3 μ g PGE₂, acid output remained significantly lower than in the control rats

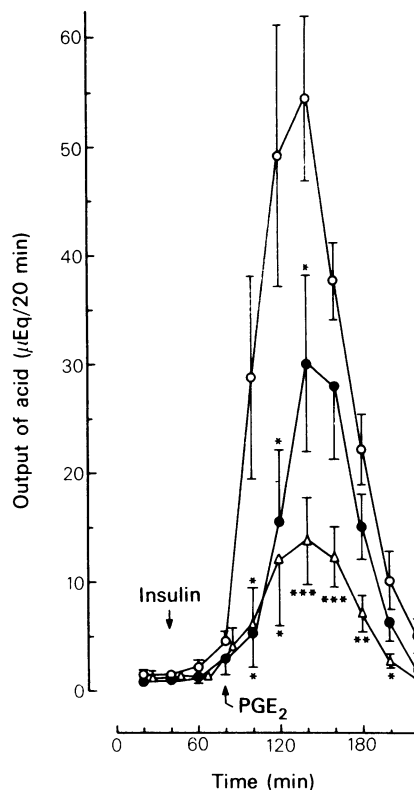


Figure 1 Effect of i.c.v. administration of prostaglandin E₂ (PGE₂) on insulin-stimulated gastric acid secretion in anaesthetized rats. Vehicle (○), 1 μ g (●) or 3 μ g (△) of PGE₂ was administered into the cerebral ventricle 40 min after an i.v. injection of 1 iu/kg of insulin. Means from 7 experiments are given, vertical bars show s.e. mean. **P* < 0.05, ***P* < 0.01 and ****P* < 0.001 indicate the statistical significance (Student's *t* test) as compared to the corresponding values in the vehicle group.

for the remaining 140 min of the experiment (see Figure. 1).

Total acid output over the 3 h period after insulin was 219 ± 35 μ Eq in the control rats (*n* = 7); 1 μ g of PGE₂ decreased it by 52% (to 105 ± 26 μ Eq, *n* = 7, *P* < 0.05) and 3 μ g of PGE₂ by 72% (to 62 ± 21 μ Eq, *n* = 7, *P* < 0.01).

Effect of i.v. injection of prostaglandin E₂ on insulin-stimulated gastric acid secretion

I.v. injection of 1, 3 or 10 μ g doses of PGE₂ given 40 and 80 min after insulin did not affect the insulin-induced stimulation of gastric acid secretion. Overall acid output over the 3 h period after insulin administration was 178 ± 57 μ Eq (*n* = 6) in the control rats and 228 ± 52 μ Eq (*n* = 6), 142 ± 48 μ Eq (*n* = 6) and 157 ± 43 μ Eq (*n* = 6), respectively, in the rats that

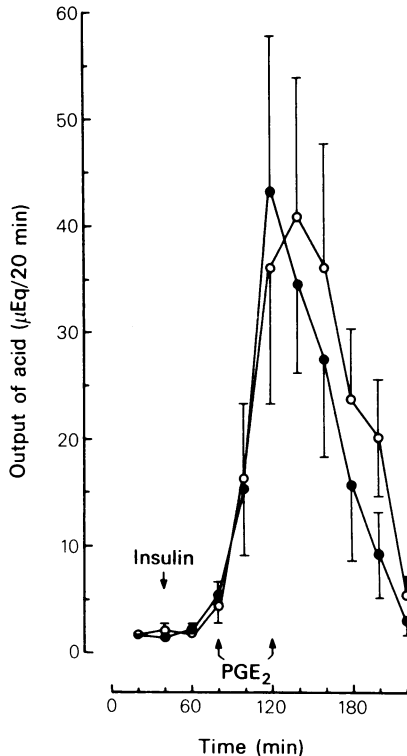


Figure 2 Effect of i.v. injection of prostaglandin E₂ (PGE₂) on insulin-stimulated gastric acid secretion in anaesthetized rats. Vehicle (○) or 10 μg of PGE₂ (●) was administered i.v. 40 and 80 min after an i.v. injection of 1 iu/kg of insulin. Means from 6 experiments are given; vertical bars show s.e.mean.

received 1, 3 or 10 μg of PGE₂. The time-course of the insulin-induced stimulation of gastric acid secretion in the rats treated with two 10 μg doses of PGE₂ or its vehicle is shown in Figure 2.

Effect of i.c.v. administration of prostaglandin E₂ on electrical vagal stimulation of gastric acid secretion

Electrical vagal stimulation (using impulses of 2 ms duration, 5 V strength at 5 Hz frequency) caused an increase in acid output of about the same magnitude as insulin. The increase in acid secretion was inhibited by 1 and 3 μg of PGE₂ administered i.c.v. at the start of the stimulation of the vagus nerve (Figure 3). The inhibitory effect of 1 μg of PGE₂ was transient, the inhibition only being observed at the first 20 min sample after PGE₂ administration, whereas 3 μg of PGE₂ was effective for at least 80 min.

Total acid secretion during the 2 h period of the vagal stimulation, which in the control group was 156 ± 40 μEq ($n = 5$), was not significantly affected by 1 μg of PGE₂ (119 ± 65 μEq, $n = 5$), whereas 3 μg

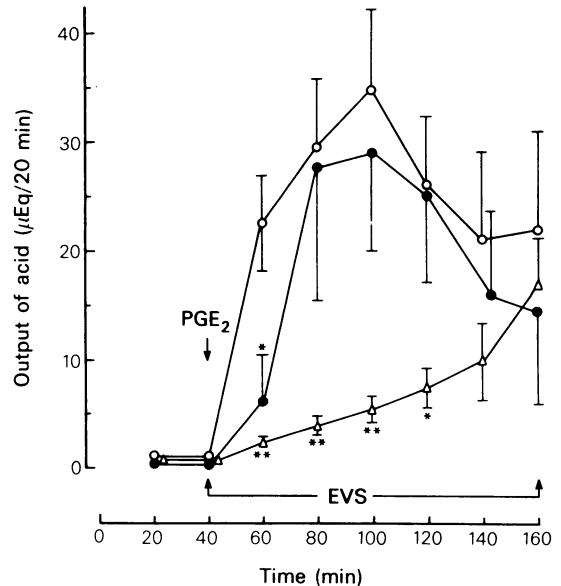


Figure 3 Effect of i.c.v. administration of prostaglandin E₂ (PGE₂) on gastric acid secretion induced by electrical vagal stimulation (EVS) in anaesthetized rats. Vehicle (○), 1 μg (●) or 3 μg (△) of PGE₂ was administered i.c.v. at the start of the vagal stimulation (2 ms, 5 V, 5 Hz). Means from 5 experiments are given; vertical bars show s.e.mean. * $P < 0.05$ and ** $P < 0.01$ versus the vehicle group.

of PGE₂ decreased it by 73% (to 42 ± 11 μEq, $n = 5$, $P < 0.05$).

Effect of i.c.v. administration of prostaglandin E₂ on gastric acid secretion induced by acetylcholine

The stimulation of gastric acid secretion by an i.v. infusion of acetylcholine ($20 \mu\text{g kg}^{-1} \text{ min}^{-1}$) and the effect of i.c.v. administration of PGE₂ on it are depicted in Figure 4. Administration of 1 μg of PGE₂ at the beginning of the acetylcholine infusion did not affect the secretory response to acetylcholine whereas 3 μg of PGE₂ caused an inhibition lasting for at least 80 min.

Overall acid output over the 2 h period of the acetylcholine infusion (200 ± 36 μEq, $n = 5$) was not affected by 1 μg of PGE₂ (157 ± 29 μEq, $n = 5$) whereas 3 μg of PGE₂ decreased it by 59% (to 82 ± 22 μEq, $n = 5$, $P < 0.05$).

Discussion

Prostaglandins of A, E and I type are potent inhibitors of gastric acid secretion in animals and man. It is widely accepted that they have a peripheral site

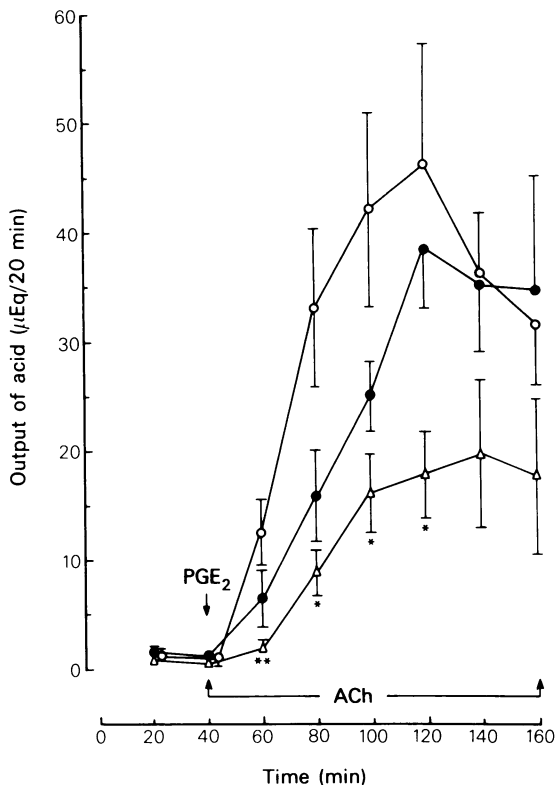


Figure 4 Effect of i.c.v. administration of prostaglandin E₂ (PGE₂) on acetylcholine-induced gastric acid secretion in anaesthetized rats. Vehicle (○), 1 μg (●) or 3 μg (Δ) of PGE₂ was administered i.c.v. at the beginning of an i.v. infusion of acetylcholine (ACh, 20 μg kg⁻¹ min⁻¹). Means from 5 experiments are given; vertical bars show s.e. mean. **P* < 0.05 and ***P* < 0.01 versus the vehicle group.

of action, most probably at the level of the acid-secreting parietal cell. (Robert, 1981). However in the present study, PGE₂ strongly inhibited gastric acid secretion induced by insulin, electrical vagal stimulation or acetylcholine in anaesthetized rats when administered into the cerebral ventricle.

The fact that the same or even higher intravenous doses did not affect gastric acid output indicates that upon i.c.v. administration PGE₂ exerted its action in the brain and not peripherally after leakage from the central nervous system. The lack of effect of the i.v. injection of PGE₂ doses used here is not in disagreement with the findings in the literature. According to Main & Whittle (1973, 1975), a continuous i.v. infusion of PGE₂ at the rate of 2 μg kg⁻¹ min⁻¹ is needed to inhibit slight histamine or pentagastrin stimulation in anaesthetized rats. This would correspond to a dose of 280 μg/kg over 140 min, at which time 3 μg of

PGE₂ after i.c.v. administration still effectively inhibited gastric acid output induced by insulin (Figure 1). Similarly, in conscious gastric fistula rats in which the spontaneous output of acid approximately corresponds to the insulin stimulation of the present work, only very high subcutaneous doses (125 to 250 μg/kg) decrease gastric acid secretion (Main & Whittle, 1975).

The stimulation of gastric acid secretion by insulin is due to a central activation of the vagus nerve through hypoglycaemia (Brooks, 1954). Electrical vagal stimulation increases acid output by release of acetylcholine from the postganglionic nerve fibres, whereas exogenous acetylcholine exerts its action directly on parietal cells. I.c.v. administration of PGE₂ inhibited all these stimulations. Therefore although originating from the brain, the final site of the inhibitory action of PGE₂ is not central, but instead it must initiate neuronal or hormonal impulses in the brain which then act peripherally to inhibit gastric acid secretion.

The present results do not make clear the mechanism by which centrally administered PGE₂ inhibits gastric acid secretion. However, the involvement of the sympathetic nervous system should be considered. In agreement with the previous reports (Hoffman & Schmid, 1979; Sirén, 1981), i.c.v. administration of PGE₂ caused prompt increases in blood pressure and heart rate. Recently, Feuerstein, Adelberg, Kopin & Jacobowitz (1982) have found that centrally administered PGE₂ increases plasma levels of catecholamines, especially of noradrenaline. These findings strongly suggest that central administration of PGE₂ causes activation of the sympathetic nervous system. On the other hand, sympathomimetic compounds have an inhibitory effect on gastric acid secretion (Taylor & Nabi Mir, 1982). Accordingly, the possibility that the inhibition of gastric acid secretion by i.c.v. administration of PGE₂ is mediated by an activation of the sympathetic nervous system cannot be excluded.

Taken together, the present results indicate that PGE₂ has a central inhibitory action on gastric acid secretion in anaesthetized rats. The possibility that PGE₂ participates in the central control of gastric acid secretion therefore deserves further investigation.

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