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Role of putative neurotransmitters in the central gastric antisecretory effect of prostaglandin E_2 in rats

Juhani Puurunen

Department of Pharmacology, University of Oulu, SF-90220 Oulu 22, Finland

1 The role of putative neurotransmitters of the central nervous system in the central gastric antisecretory effect of prostaglandin E_2 (PGE_2) was investigated in pylorus-ligated rats.

2 Pretreatment of the rats with an intracerebroventricular (i.c.v.) injection of 6-hydroxydopamine (6-OHDA) prevented the antisecretory effect of the i.c.v. administration of PGE_2, whereas pretreatment with 5,6-dihydroxytryptamine (5,6-DHT) plus *p*-chlorophenylalanine (PCPA) had no effect.

3 I.c.v.-administered phentolamine and idazoxan antagonized the inhibition of gastric secretion induced by i.c.v. PGE_2, whereas prazosin, propranolol and sulpiride injected via the same route were ineffective.

4 Diphenhydramine, cimetidine, naloxone and theophylline, all administered i.c.v., did not modify the antisecretory effect of i.c.v. PGE_2.

5 The results suggest that an activation of α_2-adrenoceptors in the brain is involved in the central gastric antisecretory effect of PGE_2, whereas neither central 5-hydroxytryptamine receptors, α_1- or β-adrenoceptors, D_2-dopamine receptors, histamine or opioid receptors nor adenosine seem to play any role here.

Introduction

It is well known that the central nervous system participates in the regulation of gastric secretion, and a number of brain structures and neural pathways involved have been identified (Grijalva *et al.*, 1980). In addition, a number of endogenous brain compounds, including noradrenaline, acetylcholine, γ-aminobutyric acid and certain neuropeptides in particular, have been proposed as being of significance in the central nervous system control of gastric secretion (Taché *et al.*, 1981; Morley *et al.*, 1982).

Prostaglandins of types A, E and I are inhibitors of gastric secretion in various species including man, and until just recently it was accepted that they act peripherally, most probably at the level of the acid-secreting parietal cell (Robert, 1981). An additional, central site of action is indicated, however, by our recent findings that prostaglandin E_2 (PGE_2) and $PGF_{2\alpha}$ (but not PGD_2 or PGI_2) inhibit gastric secretion in rats upon intracerebroventricular (i.c.v.) administration at doses which are ineffective when given peripherally (Puurunen, 1983a,b). More recent results nevertheless suggest that although i.c.v.-administered PGE_2 initially acts within the central nervous system to inhibit gastric secretion, its final site of action is peripheral and that vasopressin released from the pituitary gland probably mediates this effect on the stomach (Puurunen, 1984; Puurunen & Leppäluoto, 1984). The present work investigates the interaction of PGE_2 with putative neurotransmitters of the central nervous system in PGE_2-induced central inhibition of gastric secretion.

Methods

Animals

Sprague-Dawley rats (200–250 g) of either sex were used. They were housed under conditions of controlled temperature (22 ± 1°C), relative humidity (40%) and illumination (light on from 06 h 00 min to 18 h 00 min) and had free access to standard rat pellets (Hankkija Oy, Helsinki, Finland) and tap water. Each group consisted of an approximately equal number of males and females.

Intracerebroventricular (i.c.v.) administration

The rats were anaesthetized with chloral hydrate, 0.3 g kg^{-1} intraperitoneally, combined with ether in-

halation when necessary. The skull was exposed with a midline incision from between the eyes to the level of the ears and the rat mounted in a stereotaxic apparatus. A hole was drilled through the skull with a dental drill 5.3 mm posterior to the bragma and 4 mm lateral (right) to the sagittal suture, after which the skin incision was closed. Next morning, after a fast of about 20 h, the rats were lightly anaesthetized with ether and again mounted in the stereotaxic apparatus. For the i.c.v. administrations, a 26 gauge steel cannula was introduced through the hole in the skull at a depth of 2 mm from the dura surface. A polyethylene catheter filled with the solution to be administered was attached to the needle and the desired amount of solution allowed to flow into the lateral cerebral ventricle by hydrostatic pressure at the rate of $10\,\mu l\,min^{-1}$. The correct position of the needle inside the lateral cerebral ventricle was ascertained by the commencement of the inflow of the solution at a hydrostatic pressure of about 25 cmH_2O or lower, which has been found to indicate the proper position of the needle in the ventricular space (Paakkari, 1980).

Measurement of gastric secretion

Immediately after i.c.v. administration of PGE_2 the abdomen was opened and the stomach rinsed with 20 ml of 0.9% w/v NaCl solution (saline) through a polyethylene tube introduced via an incision in the duodenum to remove food residues. After the administration of 2 ml of saline into the stomach, the cannula was taken away and the pylorus ligated. The abdominal wound was closed and protected with a colloid (Nobecutan spray, Astra, Meditec, Askim, Sweden) in order to prevent sucking of blood. Due to neutralization, any sample contaminated with an appreciable amount of blood was discarded. The rats regained the righting reflex 5–10 min after surgery. They were killed with an overdose of ether 1 h after the i.c.v. injection of PGE_2 and the stomach removed. The contents were centrifuged for 5 min at 3,000 *g* and the volume of the supernatant measured; 2 ml was subtracted from this figure to give the net fluid output. The concentration of hydrogen ions was determined with an automatic potentiometric titrator (TTT 2, Radiometer, Copenhagen, Denmark). Peptic activity was measured by the method of Anson & Mirsky (1932) with the modifications described previously (Puurunen & Westermann, 1978).

Depletion of brain biogenic amines

6-Hydroxydopamine hydrobromide (6-OHDA), 250 μg, was injected i.c.v. 9 days before the experiments to ensure depletion of the catecholamines in the brain, and 120 μg of 5,6-dihydroxytryptamine creatinine sulphate (5,6-DHT) was injected i.c.v. 11 days before the experiments and $300\,mg\,kg^{-1}$ of DL-*p*-chlorophenylalanine methyl ester hydrochloride (PCPA) intraperitoneally 3 and 2 days before the experiments for depletion of brain 5-hydroxytryptamine. I.c.v. administrations were made under chloral hydrate anaesthesia in a volume of 20 μl, the controls receiving the same volume of the vehicle (0.9% w/v NaCl solution containing $1\,mg\,ml^{-1}$ of ascorbic acid).

Drugs

PGE_2 (Sigma Chemical Co., St. Louis, U.S.A.) was dissolved in absolute ethanol ($10\,mg\,ml^{-1}$) and stored at −20°C; dilutions were made daily with saline. The following drugs were also used: cimetidine and propranolol hydrochloride (Medipolar, Oulu, Finland); diphenhydramine hydrochloride (Parke-Davis & Co., Pontypool, U.K.); naloxone hydrochloride, theophylline, 6-hydroxydopamine hydrobromide, 5,6-dihydroxytryptamine creatinine sulphate and DL-*p*-chlorophenylalanine methyl ester hydrochloride (Sigma); idazoxan hydrochloride (Reckitt and Colman, Hull, U.K.); prazosin hydrochloride and sulpiride (Suprium injekt., Orion Pharmaceuticals Ltd, Helsinki, Finland). Cimetidine, 25 mg, was dissolved in 0.1 ml of 1 N HCl, then neutralized with 0.2 ml of 1 N NaOH and made up to 1 ml with distilled water. Theophylline was dissolved in fresh 5% $NaHCO_3$ solution and prazosin in distilled water. All the other drugs in powder form were freshly dissolved in saline. The drugs in solution were further diluted with saline. The drug doses refer to the above-mentioned salts.

Statistical analysis

The results are expressed as means ± s.e. Statistical analysis was performed using the one-way analysis of variance and the Tukey's procedure as an *a posteriori* test. *P* values less than 0.05 were taken as significant.

Results

It has previously been found that the i.c.v. administration of 1–10 μg of PGE_2 to conscious, pylorus-ligated rats inhibits the gastric output of acid, pepsin and fluid in a dose-dependent manner (Puurunen, 1983b). In these experiments 3 μg of PGE_2 i.c.v. induced a submaximal inhibition of gastric secretion, as measured 1 h after administration, whereas no change was observed after 2 h. Hence a 3 μg dose of PGE_2 (i.c.v.) with an observation period of 1 h was used in the present study. Since no differences had been noted between male and female rats in their spontaneous gastric secretion or antisecretory response to PGE_2 (Puurunen, 1983b), both sexes were used here. Recep-

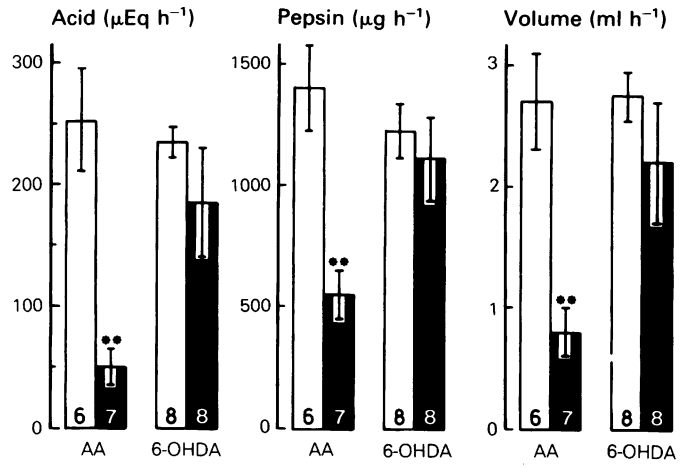

Figure 1 Effect of pretreatment with 6-hydroxydopamine (6-OHDA) on the inhibition of gastric secretion induced by i.c.v.-administered prostaglandin E_2 (PGE_2) in pylorus-ligated rats. 6-OHDA, 250 μg, or 20 μl of the diluent (AA; 0.1% ascorbic acid in 0.9% w/v NaCl solution) was injected i.c.v. 9 days before the experimentation. PGE_2, 3 μg, (filled columns) or 10 μl of its vehicle (open columns) was injected i.c.v. and the pylorus ligated. One hour after the PGE_2 injection the rats were killed and the gastric contents analysed. Each column is the mean for the number of animals indicated by the number in the column; s.e.mean depicted by vertical lines.
** $P<0.01$ indicates the statistical significance as compared with the corresponding group treated with the vehicle used for PGE_2.

tor antagonists were always injected i.c.v. 10 min before PGE_2 and the compounds depleting brain biogenic amines administered as described under Methods.

6-Hydroxydopamine (Figure 1)

Pretreatment with 6-hydroxydopamine (6-OHDA) had no significant effect on the gastric secretion of acid, pepsin and fluid, as measured 1 h after pylorus ligation. I.c.v. administration of 3 μg of PGE_2 markedly reduced all the secretory parameters in the control rats, but had no significant effect in the animals pretreated with 6-OHDA. All the secretory parameters after the injection of PGE_2 were significantly higher ($P<0.01$) in the rats pretreated with 6-OHDA than in the control animals.

5,6-Dihydroxytryptamine plus p-chlorophenylalanine (Table 1)

Pretreatment with 5,6-dihydroxytryptamine (5,6-DHT) and *p*-chlorophenylalanine (PCPA) caused decreases in all the secretory parameters ($P<0.01$), but PGE_2 still produced a significant inhibition of gastric secretion after pretreatment with 5,6-DHT plus PCPA. The percentage decreases in the output of acid, pepsin and fluid were 82, 53 and 71% in the control group and 88, 59 and 73% respectively in the rats pretreated with 5,6-DHT plus PCPA.

Table 1 Effect of pretreatment with 5,6-dihydroxytryptamine (5,6-DHT) and *p*-chlorophenylalanine (PCPA) on the inhibitory effect of i.c.v.-administered prostaglandin E_2 (PGE_2) on gastric secretion in pylorus-ligated rats

Treatment	*No. of rats*	*Acid* (μEq h^{-1})	*Pepsin* (μg h^{-1})	*Volume* (ml h^{-1})
Diluents + vehicle	7	247 ± 46	1208 ± 150	2.1 ± 0.3
Diluents + PGE_2	8	44 ± 12[a]	569 ± 100[a]	0.6 ± 0.1[a]
5,6-DHT + PCPA + vehicle	8	117 ± 26	668 ± 74	1.1 ± 0.2
5,6-DHT + PCPA + PGE_2	8	14 ± 4[a]	275 ± 21[a]	0.3 ± 0.1[a]

The animals were killed 1 h after i.c.v. administration of 3 μg of PGE_2 or the vehicle and the gastric contents analysed. For the 5,6-DHT and PCPA pretreatment, see Methods. The results are means ± s.e.mean.
[a] $P<0.01$ vs the corresponding group treated with the vehicle used for PGE_2.

α-Adrenoceptor antagonists (Figure 2)

Phentolamine An i.c.v. injection of 100 μg of phentolamine did not affect gastric secretion, but totally antagonized the inhibitory effect of 3 μg of PGE_2 administered i.c.v. 10 min later. The secretory parameters after the administration of PGE_2 were significantly higher (acid and volume, $P<0.01$; pepsin, $P<0.05$) in the rats treated with phentolamine than in the control animals.

Idazoxan I.c.v. treatment with 100 μg of idazoxan did not significantly change the spontaneous gastric secretion but, like phentolamine, prevented the antisecretory effect of i.c.v. PGE_2. All the secretory values after PGE_2 were significantly higher ($P<0.01$) in the

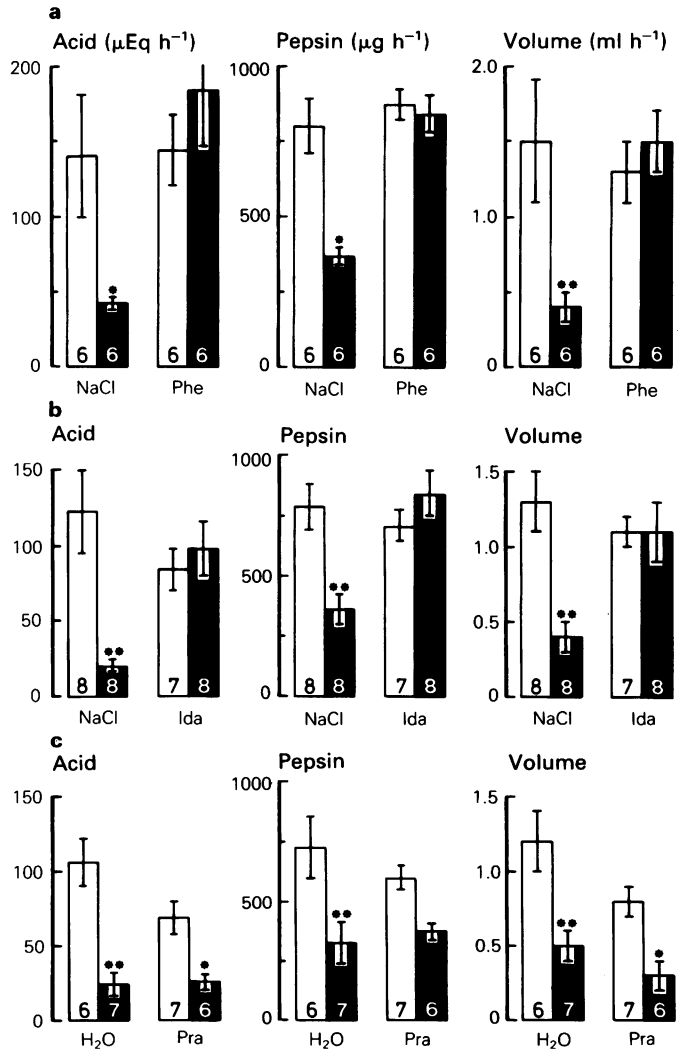

Figure 2 Effect of (a) phentolamine (Phe), (b) idazoxan (Ida) and (c) prazosin (Pra) on the inhibition of gastric secretion induced by i.c.v. administration of prostaglandin E_2 (PGE_2) to pylorus-ligated rats. I.c.v. injections of 100 μg of phentolamine, 100 μg of idazoxan or 50 μg of prazosin or the corresponding vehicle were given 10 min before i.c.v. administration of 3 μg of PGE_2 (filled columns) or its vehicle (open columns) and the animals were killed 1 h later. Each column is the mean for the number of animals indicated by the number in the column; s.e.mean depicted by vertical lines.

* $P<0.05$ and ** $P<0.01$ as compared with the corresponding group treated with the vehicle used for PGE_2.

idazoxan-treated group than in the controls injected with the vehicle for idazoxan.

Prazosin An i.c.v. injection of prazosin itself reduced the output of acid and fluid ($P<0.05$), but not that of pepsin. I.c.v. administration of PGE_2 significantly inhibited the output of acid and fluid in the rats treated with prazosin, but the inhibition of pepsin secretion failed to reach any statistical significance. The percentage decreases in the output of acid and fluid were 77 and 58% in the control group and 62 and 63% respectively in the prazosin-treated group.

Propranolol (Table 2)

I.c.v. administration of 100 μg of propranolol had no effect on the gastric secretory parameters measured, and i.c.v. administration of PGE_2 reduced the secretion of acid and fluid in the rats treated in this way to the same degree as in the controls, whereas no

Table 2 Effect of propranolol (Pro) on the gastric antisecretory action of i.c.v.-administered prostaglandin E_2 (PGE_2) in pylorus-ligated rats

Treatment	*No. of rats*	*Acid* ($\mu Eq\ h^{-1}$)	*Pepsin* ($\mu g\ h^{-1}$)	*Volume* ($ml\ h^{-1}$)
Saline + vehicle	6	118 ± 28	648 ± 142	1.3 ± 0.2
Saline + PGE_2	7	38 ± 8[a]	312 ± 44[a]	0.5 ± 0.1[a]
Pro + vehicle	6	130 ± 21	557 ± 57	1.4 ± 0.1
Pro + PGE_2	8	51 ± 10[a]	340 ± 50	0.6 ± 0.1[a]

Propranolol, 100 μg, or 10 μl of 0.9% w/v NaCl solution (saline) was injected i.c.v. 10 min before an i.c.v. administration of 3 μg of PGE_2 or 10 μl of its vehicle and the animals killed 1 h later. The results are means ± s.e.mean.
[a] $P<0.01$ vs the corresponding group treated with the vehicle used for PGE_2.

Table 3 Effect of sulpiride (Sul; 100 μg i.c.v.) on the inhibition of gastric secretion induced by i.c.v. administration of prostaglandin E_2 (PGE_2)

Treatment	*No. of rats*	*Acid* ($\mu Eq\ h^{-1}$)	*Pepsin* ($\mu g\ h^{-1}$)	*Volume* ($ml\ h^{-1}$)
Saline + vehicle	5	111 ± 23	655 ± 64	1.2 ± 0.1
Saline + PGE_2	5	21 ± 13[a]	288 ± 77[a]	0.5 ± 0.1[a]
Sul + vehicle	5	97 ± 10	663 ± 78	1.0 ± 0.1
Sul + PGE_2	5	20 ± 5[a]	385 ± 24[a]	0.5 ± 0.1[a]

For further details, see Table 2.
[a] $P<0.01$.

Table 4 Effect of diphenhydramine (Dip; 50 μg i.c.v.) and cimetidine (Cim; 100 μg i.c.v.) on the inhibition of gastric secretion by i.c.v.-administered prostaglandin E_2 (PGE_2)

Treatment	*No. of rats*	*Acid* ($\mu Eq\ h^{-1}$)	*Pepsin* ($\mu g\ h^{-1}$)	*Volume* ($ml\ h^{-1}$)
Saline + vehicle	5	117 ± 36	744 ± 143	1.4 ± 0.4
Saline + PGE_2	5	11 ± 2[b]	265 ± 50[b]	0.4 ± 0.1[b]
Dip + vehicle	5	74 ± 20	867 ± 88	1.1 ± 0.2
Dip + PGE_2	6	13 ± 2[a]	406 ± 74[b]	0.5 ± 0.1[a]
Saline + vehicle	5	95 ± 29	697 ± 115	1.2 ± 0.2
Saline + PGE_2	5	11 ± 3[b]	242 ± 43[b]	0.4 ± 0.1[b]
Cim + vehicle	5	84 ± 22	772 ± 114	0.9 ± 0.1
Cim + PGE_2	7	18 ± 6[a]	424 ± 72[a]	0.5 ± 0.1[a]

For further details, see Table 2.
[a] $P<0.05$ and [b] $P<0.01$.

Table 5 Effect of naloxone (Nal; 100 μg i.c.v.) on the gastric antisecretory action of i.c.v.-administered prostaglandin E_2 (PGE_2)

Treatment	*No. of rats*	*Acid* ($\mu Eq\ h^{-1}$)	*Pepsin* ($\mu g\ h^{-1}$)	*Volume* ($ml\ h^{-1}$)
Saline + vehicle	6	165 ± 36	1130 ± 223	1.8 ± 0.3
Saline + PGE_2	6	39 ± 21[b]	420 ± 112[b]	0.6 ± 0.3[b]
Nal + vehicle	6	121 ± 25	999 ± 77	1.2 ± 0.2
Nal + PGE_2	6	29 ± 13[a]	423 ± 107[b]	0.5 ± 0.1[a]

For further details, see Table 2.
[a] $P<0.05$ and [b] $P<0.01$.

Table 6 Effect of theophylline (The; 300 μg i.c.v.) on the inhibitory effect of i.c.v.-administered protaglandin E_2 (PGE_2) on gastric secretion

Treatment	*No. of rats*	*Acid* ($\mu Eq\ h^{-1}$)	*Pepsin* ($\mu g\ h^{-1}$)	*Volume* ($ml\ h^{-1}$)
5% $NaHCO_3$ + vehicle	5	136 ± 44	718 ± 94	1.2 ± 0.2
5% $NaHCO_3$ + PGE_2	5	16 ± 8[b]	306 ± 99[b]	0.5 ± 0.1[b]
The + vehicle	5	90 ± 16	875 ± 114	1.0 ± 0.1
The + PGE_2	6	9 ± 2[a]	401 ± 67[b]	0.5 ± 0.1[a]

For further details, see Table 2.
[a] $P<0.05$ and [b] $P<0.01$.

statistically significant change in the output of pepsin was observed in the propranolol-treated group.

Sulpiride (Table 3)

Treatment with 100 μg of sulpiride i.c.v. had no effect on gastric secretion. I.c.v. administration of 3 μg of PGE_2 decreased the gastric output of acid, pepsin and fluid both in the control and sulpiride treated rats.

Histamine antagonists (Table 4)

I.c.v. administration of diphenhydramine 50 μg, or cimetidine 100 μg, did not significantly affect basal gastric secretion, and in both cases 3 μg of PGE_2 administered i.c.v. inhibited gastric secretion to the same extent as it did in the control rats.

Naloxone (Table 5)

I.c.v. administration of 100 μg of naloxone did not significantly alter gastric secretion as compared with the saline-treated animals. Both in the naloxone- and saline-treated groups i.c.v. PGE_2 induced an inhibition of about the same magnitude.

Theophylline (Table 6)

I.c.v. administration of theophylline 300 μg did not significantly change the spontaneous secretion, and PGE_2 inhibited gastric secretion in these rats to the same extent as in the controls treated with the vehicle for theophylline.

Discussion

Growing attention has been focused in recent years on the identification of chemical transmitters acting in the central nervous system to regulate gastric secretion. As a result, several stimulatory (acetylcholine, thyrotropin-releasing hormone, γ-aminobutyric acid and gastrin) and inhibitory factors (bombesin, gastrin releasing peptide (GRP), calcitonin, somatostatin, neurotensin, opioid peptides, corticotropin-releasing factor (CRF), calcitonin gene related peptide (CGRP), 5-hydroxytryptamine and noradrenaline) affecting gastric secretion upon central administration have been described (Bugajski *et al.*, 1977; Taché *et al.*, 1981; 1983; 1984; Morley *et al.*, 1982). The interactions between these endogenous factors affecting gastric secretion are still poorly understood.

As mentioned in the introduction, PGE_2 and $PGF_{2\alpha}$ can now be added to the list of endogenous compounds of the central nervous system which affect gastric secretion by a central mechanism. As in the case of bombesin, GRP, CRF and CGRP, the final site of action of centrally-administered PGE_2 is peripheral and thus not related to a decreased output of stimulatory vagal impulses. The inhibitory effect of

i.c.v.-administered PGE_2 on gastric secretion in rats is antagonized by hypophysectomy, but not by vagotomy or gastric sympathectomy (extirpation of the ganglion coeliacum and the mesentericus superius), suggesting that the pituitary gland is involved, but not changes in the autonomic nervous system (Puurunen, 1984). In contrast, the gastric antisecretory action of bombesin is not affected by any of these procedures (Taché *et al.*, 1981; Taché & Collu, 1982), whereas both vagotomy and adrenalectomy attenuate the antisecretory response to centrally-administered CRF (Taché *et al.*, 1983) and vagotomy that to CGRP (Taché *et al.*, 1984). In fact, our recent findings strongly suggest that vasopressin released from the pituitary gland mediates the inhibitory action of centrally-administered PGE_2 upon gastric secretion (Puurunen & Leppäluoto, 1984).

Prostaglandins of the E and F series affect a number of the putative central neurotransmitters which have been found to modify gastric secretion (*vide supra*) and/or the release of vasopressin from the pituitary gland (Sklar & Schrier, 1983). According to Hedqvist (1977), prostaglandins of the E series attenuate noradrenergic neurotransmission in the peripheral autonomic nerves, suggesting that they may have a neuromodulatory role in synaptic transmission. As reviewed by Wolfe (1982), studies on the effects of PGE_2 on noradrenaline and dopamine (metabolism) in the brain have given inconsistent results, and it is therefore not clear whether the Hedqvist hypothesis would also operate in the central nervous system. $PGF_{2\alpha}$ increases the level of 5-hydroxytryptamine and the total acetylcholine content in the rat brain (Poddubiuk & Kleirok, 1976), while PGE_1 reduces the release of acetylcholine in rat cerebral slices and the release of this neurotransmitter into the cerebrospinal fluid of the cat (Hársing *et al.*, 1979). Both PGE_2 and $PGF_{2\alpha}$ have been shown to inhibit the activity of brain acetylcholinesterase upon i.c.v. administration to cats (Grbovic & Radmanovic, 1981). Rosenkranz *et al.*, (1980) have found that PGE_2 increases the level of γ-aminobutyric acid in mouse brain, and it is also known to potentiate the histamine-induced formation of cyclic AMP in brain slices from the rat (Berti *et al.*, 1972). Many other observations similarly indicate that prostaglandins, including those of the E and F series, affect the metabolism of cyclic AMP and cyclic GMP in the brain (Wolfe & Coceani, 1979).

Pretreatment of rats with i.c.v.-administered 6-OHDA almost totally prevented the inhibition of gastric secretion induced by an i.c.v. administration of PGE_2. Central administration of 6-OHDA has been widely used to achieve depletion of catecholamines, especially noradrenaline, in the brain. Recent findings of Reader & Gauthier (1984) indicate, however, that an i.c.v. injection of 6-OHDA to rats at the dose used here ensures not only depletion of all the catecholamines, viz. adrenaline, noradrenaline and dopamine, but also that of 5-hydroxytryptamine in various brain regions. This lack of specificity means that the modification of the antisecretory response to PGE_2 by this neurotoxic compound should be interpreted with some caution. The observation that the pretreatment of rats with 5,6-DHT plus PCPA, which has been shown to induce about an 80% depletion of 5-hydroxtryptamine in the rat brain (Collu *et al.*, 1979), did not modify the antisecretory response to PGE_2 suggests that there is no 5-hydroxytryptaminergic mechanism involved here. Put together, these findings obtained with depletors of biogenic amines strongly suggest that a central catecholaminergic mechanism plays a role in the central antisecretory action of PGE_2. They do not, however, give any hint as to which catecholamine is involved.

I.c.v. administration of phentolamine, a non-selective antagonist of α-adrenoceptors, prevented the inhibition of gastric secretion induced by i.c.v.-administered PGE_2, as did idazoxan, a preferential α_2-adrenoceptor antagonist (Doxey *et al.*, 1984), whereas prazosin, which is a selective α_1-adrenoceptor antagonist (Marwaha & Aghajanian, 1982), was ineffective. It is possible, and even likely, that i.c.v.-administered α-adrenoceptor antagonists may be released into the circulation to such an extent that they also block peripheral receptors, although this may not contribute to their antagonistic effect on the action of PGE_2, since no peripheral sympatho-adrenal mechanism seems to be involved in the antisecretory response to i.c.v. PGE_2 (Puurunen, 1984). These findings therefore strongly suggest that an activation of α_2-adrenoceptors in the brain is involved in the central antisecretory action of PGE_2. This is in agreement with the finding that the antisecretory effect of i.c.v.-administered α-adrenoceptor agonists correlates well with their selectivity for α_2-adrenoceptors (Nakadate *et al.*, 1982). Furthermore, there is evidence that adrenergic mechanisms participate in the regulation of the release of pituitary vasopressin (Sklar & Schrier, 1983), which, as mentioned earlier, probably mediates the action of i.c.v.-administered PGE_2 on the secretory apparatus. I.c.v. administration of propranolol, which is an antagonist of β-adrenoceptors, did not modify the inhibitory effect of i.c.v. PGE_2, suggesting that central β-adrenoceptors are not involved. Sulpiride is an antagonist of dopamine D_2-receptors (Kebabian & Calne, 1979), which does not have antagonistic properties at α-adrenoceptors as do the 'classical' dopamine antagonists (Dubocovich & Langer, 1980), and therefore its lack of effect on the antisecretory action of PGE_2 suggests that no mechanisms involving D_2-dopamine receptors are implicated in this effect.

It has been reported that central administration of histamine increases the release of vasopressin from the pituitary gland, an effect which seems to be mediated

via histamine H_2-receptors (Schwartz, 1979; Tuomisto *et al.*, 1984). The treatment of rats with an i.c.v.-administered H_1-receptor antagonist, diphenhydramine, or H_2-receptor antagonist, cimetidine, failed here to modify the central antisecretory activity of PGE_2, suggesting that central histaminergic mechanisms are not involved. According to Rozé *et al.* (1980), β-endorphin is a potent inhibitor of gastric acid secretion in rats upon i.c.v. administration, while there is also evidence that opioid mechanisms may participate in the regulation of vasopressin release (Sklar & Schrier, 1983). However, PGE_2 may not have any interaction with endogenous opiates in the central nervous system inhibition of gastric secretion since treatment with naloxone was ineffective. We have recently found that (−)-N^6-(R-phenyl-isopropyl)-adenosine (L-PIA), which is a widely used metabolically stable analogue of adenosine, is a potent inhibitor of gastric secretion in rats upon i.c.v. administration (Puurunen, unpublished), and therefore it is possible that PGE_2 could interact with brain adenosine while inhibiting gastric secretion. However, this does not seem to be the case since i.c.v. treatment with theophylline, which antagonizes the action of adenosine in various tissues, including brain (Daly, 1982), was ineffective.

When administered to experimental animals, prostaglandins have a centrally-mediated effect not only on gastric secretion, but also on thermoregulation, the cardiovascular and respiratory systems, hypothalamic and pituitary hormone release, behaviour and food intake, as well as an anticonvulsant action (Behrman, 1979; Wolfe & Coceani, 1979; Levine & Morley, 1981; Wolfe, 1982; Sirén, 1982). The available information on the brain mechanisms of these actions is scarce and somewhat conflicting. The thermal, but not the central cardiovascular, effects of PGI_2 may be mediated via a mechanism involving H_2-histamine receptors in the brain (Kandasamy *et al.*, 1981; Sirén, 1981), while according to Brus & Zabawska (1976), central catecholaminergic and cholinergic mechanisms participate in the central hypertensive and tachycardiac effects of $PGF_{2\alpha}$. Furthermore, Brus *et al.*, (1979) also propose that a central 5-hydroxytryptaminergic mechanism is involved in the central thermal and hypertensive effects of $PGF_{2\alpha}$, but not in those of PGE_2. These results were nevertheless obtained using the depletors of biogenic amines 6-OHDA and 5,6-DHT, which, as mentioned earlier, lack specificity in lowering adrenaline, noradrenaline, dopamine and 5-hydroxytryptamine in the rat brain (Reader & Gauthier, 1984).

In summary, the present results strongly suggest that an activation of α_2-adrenoceptors in the brain is involved in the central gastric antisecretory effect of PGE_2, whereas they do not present any evidence for the participation of mechanisms involving central α_1- or β-adrenoceptors, D_2-dopamine receptors, 5-hydroxytryptamine, histamine or opioid receptors or adenosine.

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