Central nervous system effects of arachidonic acid, PGE$_2$, PGF$_{2\alpha}$, PGD$_2$ and PGI$_2$ on gastric secretion in the rat

Juhani Puurunen

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

1   The effects of arachidonic acid, prostaglandin E$_2$ (PGE$_2$), PGF$_{2\alpha}$, PGD$_2$ and PGI$_2$ on gastric secretion (acid, pepsin and volume) after intracerebroventricular administration were investigated in conscious, pylorus-ligated rats.

2   Arachidonic acid 30–1000 µg had no effect on gastric secretion.

3   PGE$_2$ 3 and 10 µg, reduced gastric secretion as measured 1 hour after injection, although the inhibition induced by 3 µg disappeared by 2 h.

4   PGF$_{2\alpha}$ 10 and 30 µg, inhibited gastric secretion as measured after 1 h, whereas no change was observed in the gastric contents collected 2 h after 10 µg of PGF$_{2\alpha}$. Intramuscular injection of 30 µg of PGF$_{2\alpha}$ had no effect on gastric secretion.

5   Intracerebroventricular administration of 1–30 µg of PGD$_2$ or PGI$_2$ had no effect on gastric secretion.

6   The results indicate that PGE$_2$ and PGF$_{2\alpha}$ have a potent central antisecretory action in conscious, pylorus-ligated rats, whereas arachidonic acid, PGD$_2$ and PGI$_2$ do not have any central effects on gastric secretion. It is suggested that PGE$_2$ and PGF$_{2\alpha}$ may be involved in the central nervous system control of gastric secretion.

Introduction

The participation of certain brain areas, especially the hypothalamus and related limbic structures, in the regulation of the cephalic phase of gastric secretion has been documented (Grijalva, Lindholm & Novin, 1980). More recently, growing interest has been focused on the identification of chemical transmitters acting at these sites. As a result, a number of endogenous brain compounds, including noradrenaline, acetylcholine, γ-aminobutyric acid (GABA) and certain neuropeptides in particular, have been reported to have central effects on gastric secretion in experimental animals (Taché, Vale, Rivier & Brown, 1981; Morley, Levine & Silvis, 1982). Whether or not these compounds play any physiological role in the central control of gastric secretion still remains to be determined.

Prostaglandins, which are synthesized from arachidonic acid in mammalian brain, have been implicated as modulators of central neurotransmission (Wolfe, 1982). When administered to experimental animals, prostaglandins have centrally-mediated effects on thermoregulation, the cardiovascular system, respiration, hypothalamic and pituitary hormone release and behaviour, as well as an an-

ticonvulsant action (Behrman, 1979; Wolfe & Coceani, 1979; Wolfe, 1982; Sirén, 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). However, an additional, central site of action, was indicated by our recent findings that PGE$_2$ inhibits gastric secretion in anaesthetized and conscious rats upon intracerebroventricular (i.c.v.) administration at doses of approximately one fiftieth of that which had to be given peripherally to obtain a similar response (Puurunen, 1983a; Puurunen, 1983b). Furthermore, i.c.v. administration of indomethacin, an inhibitor of prostaglandin biosynthesis, stimulates basal gastric secretion in anaesthetized and conscious rats and strongly enhances the stimulatory effect of insulin on gastric acid secretion in anaesthetized rats (Puurunen, 1983b; Puurunen, 1983c). These findings give rise to the suggestion that PGE$_2$, and perhaps also other metabolites of arachidonic acid formed by cyclo-oxygenase in the brain, may be involved in the central control of gastric secretion. In the light of these

findings, it seemed worthwhile to investigate the central effects of other prostaglandins found in the brain on gastric secretion. Arachidonic acid, PGD_2, $PGF_{2\alpha}$, PGE_2 and PGI_2, all administered i.c.v., were therefore tested in this respect in conscious, pylorus-ligated rats.

Methods

Animals

Male and female Sprague-Dawley rats weighing 200–240 g were used. The animals 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). They had free access to standard rat pellets (Hankkija Oy, Helsinki, Finland) and tap water. Although no significant differences in gastric secretion or secretory response to drugs were observed between the sexes, each experimental group consisted of an approximately equal number of male and female rats.

Intracerebroventricular administration

The rats were anaesthetized with chloral hydrate, 0.3 g kg^{-1} intraperitoneally combined with ether inhalation 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 bregma 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 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. The desired amount of the solution was allowed to flow by hydrostatic pressure. In order to minimize wastage of the

solution, PGI_2 was injected into the lateral ventricle with a Hamilton Microliter syringe. The injection volumes were 10–30 μl, the controls always receiving the corresponding vehicle.

Measurement of gastric secretion

Immediately after administration of the experimental compounds the abdomen was opened and the stomach rinsed with 20 ml of 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 any suckling of blood. Due to neutralization, any samples contaminated with an appreciable amount of blood were discarded. The rats regained the righting reflex 5–10 min after surgery. They were then killed with an overdose of ether 1 or 2 h after injection of the drugs and the stomach removed. The contents were centrifuged for 5 min at 3,000 g and the volume of the supernatant measured. 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).

Drugs

PGE_2 and PGD_2 (The Upjohn Company, Kalamazoo, U.S.A.) were dissolved in absolute ethanol (10 mg ml^{-1}) and stored at -20 °C. Dilutions were made daily in at artificial cerebrospinal fluid (artificial CSF (mM); NaCl 117, KCl 2.95, $CaCl_2$ 1.44, KH_2PO_4 0.01, $MgSO_4 7H_2O$ 1.12 and $NaHCO_3$ 23.6, pH adjusted to 7.3). $PGF_{2\alpha}$ (dinoprost, Prostin F 2 alpha, The Upjohn Company) was diluted freshly with the artificial CSF. Arachidonic acid (Sigma Chemical Co., St. Louis, USA) was dissolved in n-hexane (50 mg ml^{-1}) and stored at

Table 1 Effect of i.c.v. administration of arachidonic acid (AA) on gastric secretion in pylorus-ligated rats.

AA (μg)	No. of rats	Acid (μEq h^{-1})	Pepsin (μg h^{-1})	Volume (ml h^{-1})
0	9	137 ± 21	824 ± 99	1.6 ± 0.3
30	9	124 ± 20	836 ± 74	1.9 ± 0.3
100	12	125 ± 17	839 ± 68	1.6 ± 0.2
300	11	141 ± 32	966 ± 109	1.7 ± 0.4
1000	5	153 ± 41	1038 ± 138	1.5 ± 0.3

The animals were killed 1 h after injection of AA or 10–30 μl of the vehicle (1% Na_2CO_3). The results are means $\pm$ s.e.mean.
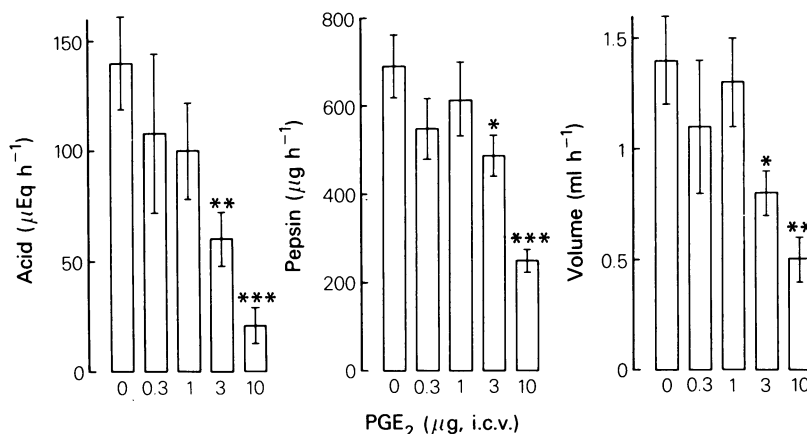
Figure 1   Effect of i.c.v. administration of prostaglandin E_2 (PGE_2) on gastric secretion in pylorus-ligated rats. PGE_2 or $10 \mu l$ of the vehicle (artificial CSF containing 10% (v/v) ethanol) was injected into the lateral cerebral ventricle and the gastric contents were collected 1 h after the injections. Each column represents the mean from 5–7 animals; s.e. mean indicated by vertical lines. *$P<0.05$, **$P<0.01$ and ***$P<0.001$ indicate the statistical significance as compared with the vehicle group (Student's t test).

$-20\,°C$. For i.c.v. injection, n-hexane was evaporated under nitrogen and the compound was dissolved in 1% Na_2CO_3 before administration. PGI_2 (The Upjohn Company) was dissolved in 0.05% NaOH

$(10\,mg\,ml^{-1})$ and stored at $0\,°C$ for not longer than 5 days, the dilutions being made daily with 0.05 M Tris buffer.

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

Arachidonic acid

Table 1 shows that $30–1000 \mu g$ of i.c.v.-administered arachidonic acid had no effect on the output of acid, pepsin and fluid as measured 1 h after injection.

Prostaglandin E_2

Dose-response relationships for the effect of an i.c.v. administration of PGE_2 on gastric secretion as measured 1 h after injection are shown in Figure 1. It was found that 3 and $10 \mu g$ caused a dose-dependent decrease in acid, pepsin and fluid output. All these parameters were once more similar to those in the control group by 2 h after the administration of $3 \mu g$ of PGE_2 (Figure 2).
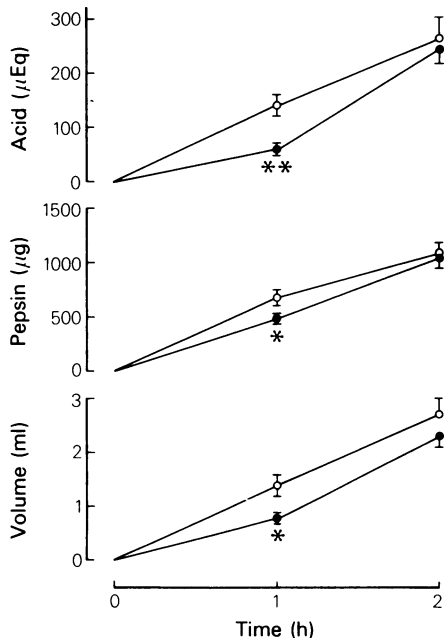

Figure 2   Temporal effect of i.c.v. administration of prostaglandin E_2 (PGE_2) on gastric secretion in pylorus-ligated rats. The animals received $3 \mu g$ of PGE_2 (●) or $10 \mu l$ of its vehicle (○) i.c.v. before pylorus ligation and were killed 1 or 2 h later. Each point is the mean from 6–7 animals; s.e.mean indicated by vertical lines. *$P<0.05$ and **$P<0.01$ vs. the vehicle group.

Prostaglandin $F_{2\alpha}$

Administration of 10 and $30 \mu g$ of $PGF_{2\alpha}$ (i.c.v.) resulted in a dose-dependent inhibition of gastric secretion as measured 1 h after injection and pylorus
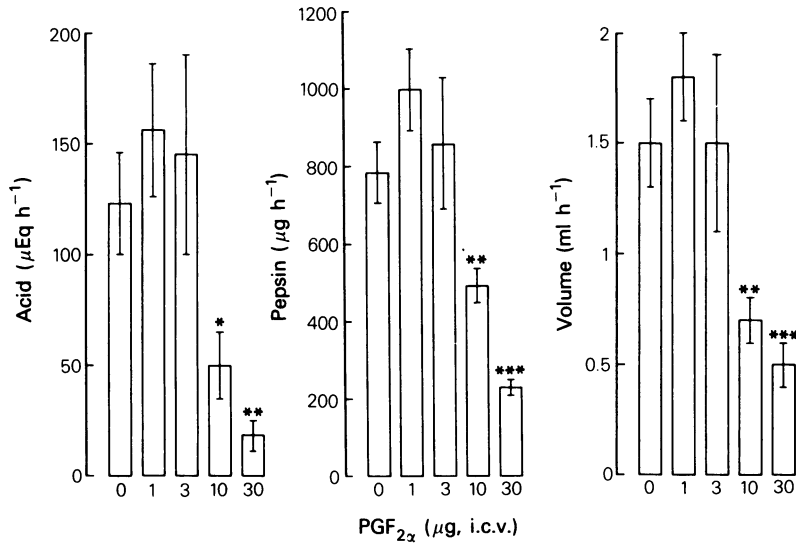
Figure 3 Gastric secretory response to various doses of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) administered i.c.v. to pylorus-ligated rats. The gastric contents were collected 1 h after the injection of $PGF_{2\alpha}$ or 10–30 µl of the vehicle (artificial CSF). Each column represents the mean from 6–8 animals; s.e.mean indicated by vertical lines. $*P<0.05$, $**P<0.01$ and $***P<0.001$ vs. the vehicle group
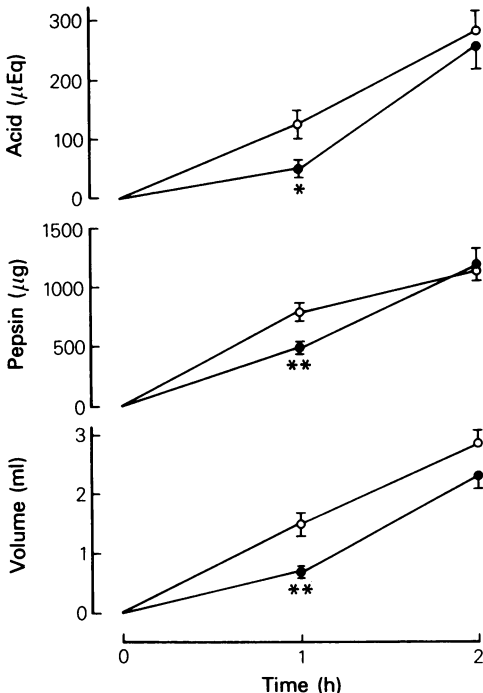

Figure 4 Time-course of the inhibition of gastric secretion induced by i.c.v. administration of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) in pylorus-ligated rats. $PGF_{2\alpha}$ 10 µg (●) or 10 µl of the vehicle (artificial CSF, ○) was given i.c.v. before pylorus ligation and the rats were killed 1 or 2 h later. Each point is the mean from 6–8 animals; s.e.mean indicated by vertical lines. $*P<0.05$ and $**P<0.01$ vs. the vehicle group.

ligation (Figure 3). The time-course of the gastric response to 10 µg of $PGF_{2\alpha}$ i.c.v. shown in Figure 4 demonstrates that the inhibition was no longer evident after 2 h. In contrast to i.c.v. administration, an intramuscular injection of 30 µg of $PGF_{2\alpha}$ had no effect on gastric secretion (Table 2).

Prostaglandin D_2 and I_2

When 1–30 µg of PGD_2 or PGI_2 was administered i.c.v. no change in gastric secretion was observed as measured 1 h after injection (Table 3 A and B).

Discussion

The basal *in vivo* concentrations of unesterified arachidonic acid and prostaglandins in the brain tissue are relatively low, approximately $10 \mu g\, g^{-1}$ and $10 \,ng\, g^{-1}$ wet weight respectively in the rat brain (Bosisio, Galli, Galli, Nicosia, Spagnuolo & Tosi, 1976; Marion & Wolfe, 1978). According to Abdel-Halim & Änggård (1979), total prostaglandin formation in the rat brain is highest in the limbic system and the cerebral cortex and lowest in the cerebellum. Cseh, Szabó, Láng & Palkowits (1978) found the highest levels of PGE and PGF-like activity in rat brain to be located in the median eminence and hypothalamus. The highest specific activity of prostaglandin D synthetase in rat brain has been reported to be the hypothalamus and thalamus (Shimizu, Mizuno, Amano & Hayaishi, 1971). An endogenous

Table 2   Effect of intramuscularly-injected prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) on gastric secretion in pylorus-ligated rats

	No. of rats	Acid ($\mu Eq\,h^{-1}$)	Pepsin ($\mu g\,h^{-1}$)	Volume ($ml\,h^{-1}$)
Controls	6	256 ± 41	1104 ± 107	2.5 ± 0.3
$PGF_{2\alpha}$ 30 μg	6	212 ± 23	1203 ± 93	2.3 ± 0.2

The animals were killed 1 h after the injection of $PGF_{2\alpha}$ or 0.1 ml of the vehicle (0.9% w/v NaCl solution). The results are means ± s.e.mean.

formation of the order $PGD_2 > PGF_{2\alpha} > PGE_2$ is found when rat hypothalamic or median eminence tissue in incubated *in vitro* (Wolfe, 1982). Furthermore, thromboxane B_2 (TxB_2) and 6-keto-$PGF_{1\alpha}$ is formed in the hypothalamus indicating synthesis of PGI_2 and the presence of the thromboxane pathway in this brain region (Ohtsu & Matsuzawa, 1980). Taken together, these reports indicate that PGD_2, $PGF_{2\alpha}$, PGE_2 and PGI_2 are formed in the brain areas which are implicated in the physiological regulation of gastric secretion, viz. the hypothalamus and the limbic system (Grijalva *et al.*, 1980).

PGE$_2$ was the most potent prostaglandin tested here in inhibiting gastric secretion when administered into the lateral cerebral ventricle. The ED_{50} ratio between subcutaneous and i.c.v. administration in pylorus-ligated rats is about 50 (Puurunen, 1983b) supporting the concept that upon i.c.v. administration PGE$_2$ acts, at least initially, within the central nervous system and not in the stomach after leakage into the periphery. Conversely, it is tempting to speculate that the well-known inhibitory effect of high parenteral doses of PGE$_2$ would be mediated via

a central nervous system action. The fact that PGE$_2$ similarly reduces acid output from isolated stomach preparations (Robert, 1981), however, indicates that this compound also has a peripheral site of action. The inhibitory effect of PGE$_2$ following i.c.v. administration was wholly reversible, as shown by the return of gastric secretion to the control level 2 h after the injection. Thus the effect was not due to irreversible tissue damage after the i.c.v. injection of PGE$_2$.

PGF$_{2\alpha}$ has been reported not to have any effect on histamine-stimulated gastric acid secretion in dogs following intravenous infusion (Robert, Nezamis & Phillips, 1967), while we have previously found that intravenous injection of high doses of PGF$_{2\alpha}$ stimulates basal gastric acid secretion in anaesthetized rats via a mechanism related to activation of the vagus nerve (Karppanen & Puurunen, 1976). The present results demonstrate that upon i.c.v. administration, PGF$_{2\alpha}$ was somewhat less potent than PGE$_2$ in inhibiting gastric secretion in conscious rats. That the inhibition was of central origin and not due to PGF$_{2\alpha}$ released into the periphery was indicated by the finding that an intramuscular injection of PGF$_{2\alpha}$ had

Table 3   Effect of i.c.v. administration of prostaglandin D_2 (PGD_2, A) and prostacyclin (PGI_2, B) on gastric secretion in pylorus-ligated rats.

Treatment	Dose (μg)	No. of rats	Acid ($\mu Eq\,h^{-1}$)	Pepsin ($\mu g\,h^{-1}$)	Volume ($ml\,h^{-1}$)
A					
Vehicle$_1$	—	8	140 ± 19	769 ± 36	1.7 ± 0.2
PGD_2	1	6	124 ± 30	730 ± 134	1.7 ± 0.3
PGD_2	3	6	165 ± 26	874 ± 110	1.6 ± 0.2
PGD_2	10	6	162 ± 41	843 ± 117	1.5 ± 0.2
PGD_2	30	9	113 ± 16	667 ± 63	1.2 ± 0.2
B					
Vehicle$_2$	—	10	106 ± 14	746 ± 89	1.5 ± 0.2
PGI_2	1	6	110 ± 42	709 ± 191	1.6 ± 0.4
PGI_2	3	6	137 ± 27	739 ± 114	2.1 ± 0.3
PGI_2	10	7	136 ± 38	664 ± 129	1.6 ± 0.4
PGI_2	30	10	73 ± 15	536 ± 66	1.1 ± 0.2

The animals were killed 1 h after the injection of the test compound or 10–30 μl or the corresponding vehicle. Vehicle$_1$: artificial CSF containing 10% (v/v) ethanol. Vehicle$_2$: 0.05 M Tris buffer, pH 9.3. The results are means ± s.e.mean.

no effect on gastric secretion. As in the case of PGE_2, the inhibitory effect of $PGF_{2\alpha}$ administered i.c.v. was wholly reversible as indicated by the normalization of the secretory parameters after 2 h.

Whittle, Boughton-Smith, Moncada & Vane (1978) report that intravenously-infused PGI_2 is somewhat more potent than PGE_2 in inhibiting pentagastrin-stimulated gastric acid secretion in anaesthetized rats. Contrary to this finding, even high doses of PGI_2 had no effect of gastric secretion in conscious rats as measured 1 h after injection into the lateral cerebral ventricle, suggesting that the gastric antisecretory action of PGI_2 is solely of peripheral origin. The metabolic capacity of brain tissue for catabolizing prostaglandins in considered to be low (Wolfe, 1982). PGI_2 is nevertheless very unstable at the physiological pH and temperature (Cho & Allen, 1978) so that the lack of any effect of an i.c.v. injection of PGI_2 on gastric secretion in the experimental model used here might be due to its rapid non-enzymatic breakdown to 6-keto-$PGF_{1\alpha}$, resulting in a short-term effect which is not observed when the gastric contents are collected 1 h after administration. PGE_2 and $PGF_{2\alpha}$ are chemically much more stable and probably remain therefore in the central nervous system in an active form for a longer period after i.c.v. administration before being eliminated by transport through the blood-brain barrier into the systemic circulation (Bito, Davison & Hollingsworth, 1976).

There are no reports available on the effects of PGD_2 on gastric secretion, but the present results show clearly that it does not affect gastric secretion in conscious rats upon i.c.v. administration even at high doses. This prostaglandin, which is the most common one in the rat brain (Abdel-Halim, Hamberg, Sjöquist & Änggård, 1977) similarly exerts only very weak cardiovascular and thermal effects after i.c.v. administration as compared with the action induced by PGE_2 and $PGF_{2\alpha}$ (Sirén, 1982). Hence PGD_2 may not have any important role in the regulation of these physiological functions.

Arachidonic acid, the precursor of prostaglandins, thromboxanes and leukotrienes, mimics many actions of its metabolic products when administered in sufficient amounts. These effects are inhibition of gastric acid secretion after intravenous injection (Conolly, Bieck, Payne, Adkins & Oates, 1977), cardiovascular effects following peripheral or i.c.v. administration (Cohen, Szatokalo & Hinsch, 1973; Sirén & Karppanen, 1981), direct vasodilation (Dusting, Moncada & Vane, 1978) and contraction of the stomach strip (Splawinski, Nies, Sweetman & Oates, 1973). These effects can be antagonized by inhibitors of cyclo-oxygenase, indicating that arachidonic acid exerts its action after metabolic activation by this enzyme. Contrary to these findings, arachidonic acid had no effect on gastric secretion in a wide range of doses when administered into the lateral cerebral ventricle of conscious rats. There are at least two reasons which may explain this lack of effect. Firstly, not enough arachidonic acid may have penetrated from the ventricular space into the brain structures in which inhibitory prostaglandins must exert their action and/or not enough inhibitory prostaglandins are formed from exogenous arachidonic acid at these sites. Secondly, the possibility cannot be ruled out that thromboxanes and leukotrienes formed from arachidonic acid administered in the brain have effects which will counterbalance the inhibitory effect of PGE_2 and $PGF_{2\alpha}$ on gastric secretion.

Although the present results clearly indicate that PGE_2 and $PGF_{2\alpha}$ inhibit gastric secretion upon i.c.v. administration, at least initially, by a central mechanism, they do not indicate the exact anatomical site(s) where they act, since rapid distribution in the cerebrospinal fluid probably takes place after injection into the ventricular space. This problem can be approached only by using microinjections of these compounds into discrete brain structures involved in the central control of gastric secretion. We have recently found that after i.c.v. administration, 1 or 3 μg of PGE_2 will not only inhibit centrally-mediated insulin stimulation, but also the effects of electrical vagal stimulation and acetylcholine on gastric acid secretion in anaesthetized rats (Puurunen, 1983a). Therefore, although PGE_2 acts initially in the brain to inhibit gastric secretion, the final site of action seems to be peripheral. Interestingly, the same is probably true for bombesin, the most active antisecretory neuropeptide after i.c.v. administration to conscious rats (Taché, Marki, Rivier, Vale & Brown, 1981). Although the exact neurohumoral pathways mediating the PGE_2 and $PGF_{2\alpha}$-induced impulses from the brain which inhibit gastric secretion still remain to be determined, recent findings indicate that hypophysectomy but not adrenalectomy or sympathectomy (extirpation of the ganglion coeliacum and mesentericus superius) strongly attenuates the effect of i.c.v.-injected PGE_2 suggesting the involvement of an altered pituitary activity (Puurunen, unpublished observations).

In summary, the present results demonstrate that PGE_2 and $PGF_{2\alpha}$ are capable of inhibiting gastric secretion in rats by a central mechanism, whereas arachidonic acid, PGD_2 and PGI_2 may not have any such central activity. The presence of the prostaglandin-synthesizing system in those brain areas which are thought to be of significance for gastric secretion, together with recent and previous findings, provides evidence for the involvement of

PGE$_2$ and PGF$_{2\alpha}$ as inhibitory modulators in the central nervous system regulation of gastric secretion.

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