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Recombinant interleukin-1β inhibits gastric acid secretion by activation of central sympatho-adrenomedullary outflow in rats

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Abstract

The inhibitory mechanism of gastric acid secretion induced by human recombinant interleukin-1β was investigated in bilaterally vagotomized, urethane-anesthetized rats. Intracerebroventricular administration of interleukin-1β (10, 50 and 100 ng/animal) dose dependently inhibited the gastric acid secretion induced by electrical stimulation of the vagus nerve at 3 Hz. Inhibition of gastric acid secretion induced by interleukin-1β (50 ng/animal) was abolished both by splanchnectomy and by phentolamine (5 mg/kg i.m.). Greater splanchnic nerves ramify into the adrenal branch and gastric sympathetic preganglionic branch. The interleukin-1β (50 ng/animal)-induced inhibition was also abolished by intracerebroventricular pretreatment with indomethacin (500 μg/animal), while pretreatment with the same dose of this reagent by the intraperitoneal route was without effect. These results suggest that centrally administered interleukin-1β induces a prostaglandin-mediated central excitation of the sympatho-adrenomedullary system, and the resultant activation of gastric α-adrenoceptors inhibits the vagally stimulated gastric acid secretion in rats.

Keywords: α-Adrenoceptor; Gastric acid secretion; Interleukin-1β; Indomethacin; Sympatho-adrenomedullary system

1. Introduction

Interleukin-1 is present as two distinct gene products, termed the α and β form. These two distinct forms share several features including binding to the same receptors and similar biological activities (Dinarello, 1991). Interleukin-1 is one of key mediators of immunological and pathological responses to stress, infection and antigenic challenge. Interleukin-1 is produced not only in the leukocytes, but also in the brain, especially in the microglia and astroglia (Fontana et al., 1982; Giulian et al., 1986). Recent immunohistochemical studies have demonstrated the existence of interleukin-1-like immunoreactivities in the hypothalamic neurons (Breder et al., 1988; Lechan et al., 1990). While there is controversy over the source of interleukin-1 in the central nervous system (Banks et al., 1989; Hashimoto et al., 1991; Nakamori et al., 1993), interleukin-1 has been considered to be an intrinsic neuromodulator in the brain and to affect various brain functions.

Application of interleukin-1 into the central nervous system produces a variety of effects, including induction of fever (Dascombe et al., 1989), alteration of slow wave sleep (Krueger et al., 1984), reduction of food intake (McCarty et al., 1985), stimulation of thermogenesis (Fontana et al., 1984), stimulation of the hypothalamic-pituitary-adrenocortical axis (Sapolsky et al., 1987), reduction of peripheral cellular immune responses (Brown et al., 1991) and elevation of plasma levels of catecholamines (Rivier et al., 1989; Hashimoto et al., 1993). Inhibition of gastric acid secretion induced by centrally administered interleukin-1, especially the β form, was also demonstrated in rats (Uehara et al., 1990; Ishikawa et al., 1990; Saperas et al., 1990). This inhibition was proposed to be mediated by central and/or peripheral prostaglandins, since intraperitoneal pretreatment of animals with indomethacin, a cyclooxygenase inhibitor, reduced the antisecretory effect of this cytokine (Ishikawa et al., 1990; Saperas et al., 1990). It was also reported that the medial preoptic area/anterior hypothalamus and par-

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aventricular hypothalamic nucleus are involved in the interleukin-1β-induced antisecretory effect in pylorus-ligated rats (Saperas et al., 1992b). These hypothalamic nuclei have been shown to project both to the dorsal vagal preganglionic neurons and to sympathetic preganglionic neurons (Swanson and Sawchenko, 1983). We have reported that the preoptic/anterior hypothalamic area and paraventricular hypothalamic nucleus are involved in the sympatho-adrenomedullary system-mediated antisecretory effect of centrally administered bombesin (Okuma et al., 1987a,b). Also, when α-calcitonin gene-related peptide is microinjected into these hypothalamic nuclei, central sympathetic outflow is activated (Hasegawa et al., 1993). Furthermore, we have reported that centrally administered prostaglandin E_2 inhibits acid secretion by activation of the sympatho-adrenomedullary system (Yokotani et al., 1988). In the present study, therefore, we examined possible roles of the sympatho-adrenomedullary system in interleukin-1β-mediated antisecretory effects using urethane-anesthetized rats.

2. Materials and methods

2.1. Subjects

Male Wistar rats weighing 350–400 g were deprived of food for 16 h but were allowed free access to tap water. Details of the experimental procedures were as described in our previous papers (Yokotani et al., 1986, 1988). Briefly, under urethane anesthesia (1.2 g/kg i.p.), the esophagus was ligated and the trachea was cannulated through a cervical incision. Bilateral vagus nerves were carefully separated from the carotid arteries and cut at the cervical portion. The peripheral end of the left side vagus nerve was placed on platinum ring electrodes and covered with cotton soaked in paraffin oil. The cervical incision was then sutured. The femoral vein was cannulated for infusion of saline (1.5 ml/h). The abdomen was opened by a midline incision, a round-tip polyethylene cannula (3.5 cm in length and 0.4 cm in diameter) was inserted into the stomach via an incision in the duodenum. The cannula was held in place by two ligatures around the duodenum, one at the rostral site and the other at the caudal site of the duodenal incision, and the abdominal incision was sutured. After these procedures, the animal was placed in a stereotaxic apparatus.

2.2. Measurement of gastric acid secretion

One hour was allowed to elapse before the start of each experiment for stabilization of the basal acid secretion. Gastric solution, 2 ml, prewarmed at 38° C was instilled and replaced at intervals of 15 min. The solution consisted of a 1/5 (v/v) mixture of glycine and mannitol adjusted to 300 mOsmol and pH 3.5 by the addition of 0.1 N HCl, according to Blair et al. (1975). After two 15-min collections in the basal state, gastric acid secretion was elicited by continuous electrical stimulation of the left vagus nerve using an electronic stimulator (Nihon-Kohden SEN-7103, Tokyo, Japan) and isolator (Nihon-Kohden SS-102J). The stimulation parameters were square-wave pulses of 0.5 ms duration, at 3 Hz, supramaximal intensity (1 mA). Gastric acid secretion was determined by titration with 0.01 N NaOH to pH 7.0 and expressed as μEq/15 min.

2.3. Details of specific experiments

For i.c.v. administration of interleukin-1β or its vehicle in all experiments, a stainless steel cannula (0.35 mm outer diameter) was inserted into the lateral cerebral ventricle at co-ordinates AP −0.8 mm from the bregma, L 1.5 mm from the midline, H 4.0 mm below the surface of the brain according to the rat brain atlas of Paxinos and Watson (1986). Vehicle (saline alone) or interleukin-1β (10, 50, 100 ng/animal) dissolved in sterile saline was slowly injected into the right lateral ventricle in a volume of 10 μl using a 50-μl Hamilton syringe 60 min after the start of the vagal stimulation.

In splanchnectomized animals, the bilateral greater splanchnic nerves which ramify into the adrenal branch and gastric sympathetic preganglionic nerve were cut just below the diaphragm.

Phentolamine (5 mg/kg) and propranolol (5 mg/kg) were dissolved in saline (5 mg/ml) and administered intramuscularly 30 min before the start of vagal stimulation. The dose of these blocking agents was based on our previous results (Yokotani et al., 1984, 1988). Indomethacin (500 μg/animal) dissolved in sterile saline was administered i.c.v. in a volume of 10 μl or i.p. in a volume of 500 μl, 30 min before the start of the vagal stimulation.

2.4. Treatment of data and statistics

Because the absolute values of acid secretion varied with individual animals, the effects of interleukin-1β on gastric acid secretion were expressed as percentages of the value obtained immediately before i.c.v. administration of this cytokine. The results were expressed as the means ± S.E.M. The statistical significance of differences was either computed with the unpaired Student's t-test (in Figs. 2–4) or the post-hoc test of Bonferroni/Dunn was used after two-way analysis of variance (ANOVA) (in Fig. 1), using StatView 4.0 (Abacus Concepts, USA). The accepted level of significance for all tests was $P < 0.05$.

2.5. Drug preparation

The following drugs were used: human recombinant interleukin-1β kindly provided by Dr. T. Hiyama (Otsuka Pharmaceutical Co., Japan); water-soluble indomethacin sodium trihydrate kindly provided by Merk and Co. (USA); phentolamine mesylate (Ciba-Geigy, Switzerland); *dl*-propranolol hydrochloride (Sigma, USA). All other reagents were of the highest grade available (Nacalai Tesque, Japan).

3. Results

3.1. Effect of interleukin-1β on the gastric acid secretion induced by electrical stimulation of the vagus nerve

Continuous electrical stimulation of the vagus nerve at 3 Hz evoked an increase in gastric acid secretion and this evoked level persisted for more than 120 min (Fig. 1). Acid secretion at 120 min after the i.c.v. administration of vehicle was 105.0 ± 7.4% of the preadministered values at 0 min ($n = 4$). Interleukin-1β (10, 50, 100 ng/animal i.c.v.) dose dependently reduced the vagally stimulated gastric acid secretion and these inhibitory effects lasted for over 120 min after its administration. Acid secretion at 120 min after the administration of interleukin-1β (10, 50, 100 ng/animal i.c.v.) was 41.8 ± 10.0%, 18.5 ± 5.0%, and 7.1 ± 1.0% of the preadministered values, respectively. On the other hand, intravenous administration of interleukin-1β (100 ng/animal) was without effect on the vagally stimulated gastric acid secretion (data not shown). The possibility that i.c.v. administered interleukin-1β inhibited acid secretion due to its leakage into the systemic circulation is therefore excluded.

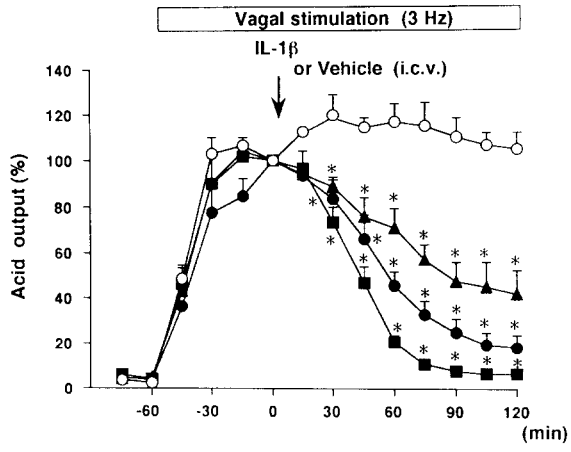

Fig. 1. Effect of interleukin-1β on the vagally stimulated gastric acid secretion. Sixty minutes after the start of vagal stimulation (3 Hz, 1 mA), vehicle or interleukin-1β (10, 50 and 100 ng/animal) was administered intracerebroventricularly. (○) vehicle (saline) 10 μl/animal ($n = 4$); (▲) interleukin-1β 10 ng/animal ($n = 4$); (●) interleukin-1β 50 ng/animal ($n = 4$); (■) interleukin-1β 100 ng/animal ($n = 4$). Each point represents a percentage of the preadministration value (0 min). * Significantly different ($P < 0.05$) from vehicle-treated control.

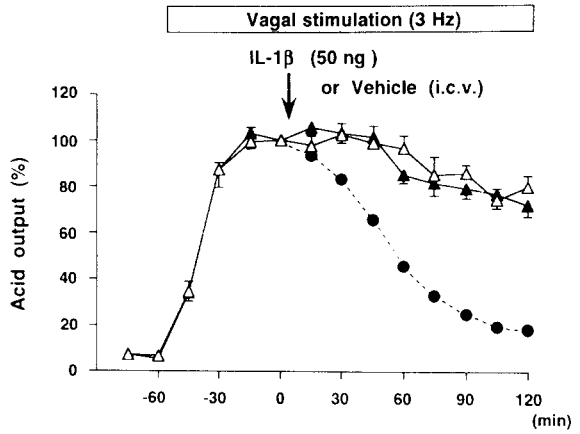

Fig. 2. Effect of splanchnectomy on the interleukin-1β (50 ng/animal, i.c.v.)-induced inhibition of the gastric acid secretion mediated by vagal stimulation (3 Hz, 1 mA). (△) vehicle (saline) 10 μl/animal ($n = 5$); (▲) interleukin-1β 50 ng/animal ($n = 4$); (●) interleukin-1β 50 ng/animal without splanchnectomy (cited from Fig. 1). Other conditions were the same as for Fig. 1.

The actual value of basal acid secretion was 4.3 ± 0.6 μEq/15 min ($n = 16$). The evoked acid secretion at 0 and 120 min after i.c.v. administration of vehicle and interleukin-1β was as follows: 85.5 ± 6.8 and 89.8 ± 7.8 μEq/15 min in the vehicle-treated control animals ($n = 4$), 102.1 ± 10.2 and 41.9 ± 13.2 μEq/15 min in the interleukin-1β (10 ng/animal)-treated animals ($n = 4$), 92.2 ± 8.5 and 18.1 ± 5.5 uEq/15 min in the interleukin-1β (50 ng/animal)-treated animals ($n = 4$), 90.6 ± 3.5 and 6.5 ± 1.0 μEq/15 min in the interleukin-1β (100 ng/animal)-treated animals ($n = 4$), respectively.

3.2. Effect of splanchnectomy on the interleukin-1β-induced central inhibition of gastric acid secretion

In the splanchnectomized rats, continuous electrical stimulation of the vagus nerve at 3 Hz rapidly increased the gastric acid secretion. This increase was maintained for 45 min after i.c.v. administration of vehicle, then a slight declining tendency of the level was observed (Fig. 2). Administration of interleukin-1β (50 ng/animal i.c.v.) also tended to decrease gastric acid secretion; however, the reduction of gastric acid secretion was not significantly different from that observed in animals treated with vehicle alone. Acid secretion 120 min after administration of interleukin-1β was 71.6 ± 5.1% of the preadministered value at 0 min, which was not significantly different from the value in vehicle-administered control (79.7 ± 4.6% of the value at 0 min). Interleukin-1β (50 ng/animal)-induced cen-

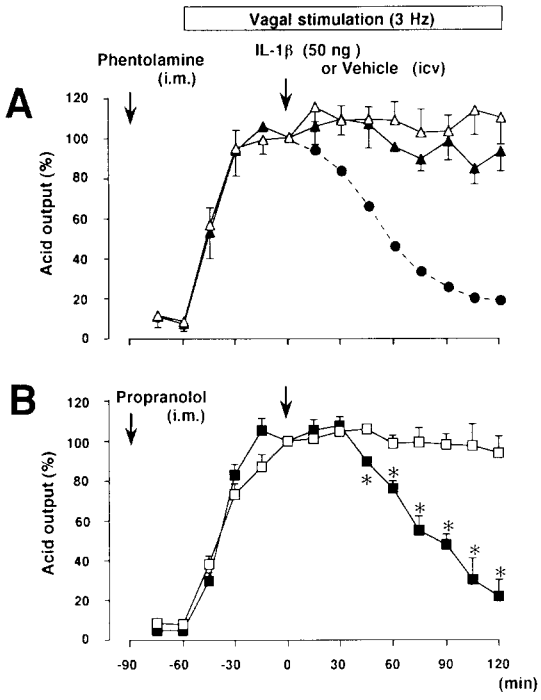

Fig. 3. Effects of phentolamine and propranolol on the interleukin-1β (50 ng/animal i.c.v.)-induced inhibition of gastric acid secretion mediated by vagal stimulation (3 Hz, 1 mA). (A) Phentolamine-pretreated group: (△) vehicle (saline) 10 μl/animal ($n = 5$); (▲) interleukin-1β 50 ng/animal ($n = 4$); (●) interleukin-1β 50 ng/animal without phentolamine (cited from Fig. 1). (B) Propranolol-pretreated group: (□) vehicle (saline) 10 μl/animal ($n = 4$); (■) interleukin-1β 50 ng/animal ($n = 4$). Phentolamine (5 mg/kg i.m.) or propranolol (5 mg/kg i.m.) was administered 30 min before the start of vagal stimulation. *Significantly different ($P < 0.05$) from vehicle-treated control. Other conditions were the same as for Fig. 1.

tral inhibition of gastric acid secretion was thus not observed in splanchnectomized rats.

The actual value of basal acid secretion was 6.5 ± 0.8 μEq/15 min ($n = 9$). The evoked acid secretion at 0 and 120 min after i.c.v. administration of vehicle and interleukin-1β was as follows: 91.1 ± 10.7 and 77.3 ± 13.2 μEq/15 min in the vehicle-treated control animals ($n = 5$), 107.7 ± 9.9 and 76.8 ± 8.9 μEq/15 min in the interleukin-1β (50 ng/animal)-treated animals ($n = 4$), respectively.

3.3. Effects of phentolamine and propranolol on the interleukin-1β-induced central inhibition of gastric acid secretion

The increase in gastric acid secretion induced by continuous electrical stimulation of the vagus nerve at 3 Hz was not modified by pretreatment with either phentolamine (5 mg/kg i.m.) or propranolol (5 mg/kg i.m.) (Fig. 3A and B). In phentolamine-pretreated animals, the interleukin-1β (50 ng/animal i.c.v.)-induced decrease in acid secretion was not observed (Fig. 3A), while propranolol was without effect on this interleukin-1β-induced inhibition (Fig. 3B).

The actual value of basal acid secretion in phentolamine-pretreated animals was 8.3 ± 1.2 μEq/15 min ($n = 9$). The evoked acid secretion in these animals at 0 and 120 min after i.c.v. administration of vehicle and interleukin-1β was as follows: 93.5 ± 8.9 and 100.5 ± 11.9 μEq/15 min (109.7 ± 13.0% of the preadministered values at 0 min) in the vehicle-treated control group ($n = 5$), 82.5 ± 10.9 and 72.5 ± 8.4 μEq/15 min (92.5 ± 9.5% of the values at 0 min) in the interleukin-1β (50 ng/animal)-treated group ($n = 4$), respectively. In propranolol-pretreated animals, the basal acid secretion was 6.6 ± 1.1 μEq/15 min ($n = 8$). The evoked acid secretion in these animals at 0 and 120 min after i.c.v. administration of vehicle and interleukin-1β was as follows: 106.6 ± 10.7 and 99.4 ± 13.1 μEq/15 min (94.1 ± 10.1% of the values at 0 min) in the vehicle-treated control group ($n = 4$), 101.2 ± 6.1 and 22.5 ± 9.3 μEq/15 min (21.8 ± 8.5% of the values at 0 min) in the interleukin-1β (50 ng/animal)-treated group ($n = 4$), respectively.

3.4. Effect of indomethacin on the interleukin-1β-induced central inhibition of gastric acid secretion

In indomethacin (500 μg/animal i.c.v. and i.p.)-pretreated animals, continuous electrical stimulation of the vagus nerve at 3 Hz evoked an increase in gastric acid secretion and the evoked levels persisted for more than 120 min (Fig. 4A and B). In the animals pretreated with indomethacin (500 μg/animal i.c.v.), interleukin-1β (50 ng/animal i.c.v.) had no effect on the evoked gastric acid secretion. Acid secretion 120 min after administration of interleukin-1β was 73.1 ± 17.1% ($n = 4$) of the preadministered value, which was not significantly different from the value in control animals that received vehicle alone (94.9 ± 8.8%, $n = 4$) (Fig. 4A). On the other hand, interleukin-1β (50 ng/animal i.c.v.) effectively attenuated the evoked acid secretion in the animals pretreated with indomethacin (500 μg/animal i.p.). The acid secretion 120 min after administration of interleukin-1β was 18.1 ± 6.1% ($n = 5$) of the preadministered value, which was significantly different from the value in control animals that received vehicle alone (78.5 ± 5.5%, $n = 4$) (Fig. 4B).

The actual value of basal acid secretion in indomethacin (500 μg/animal i.c.v.)-pretreated rats was 5.0 ± 1.3 μEq/15 min ($n = 8$). The evoked acid secretion in these animals at 0 and 120 min after i.c.v. administration of vehicle and interleukin-1β was as follows: 84.7 ± 12.4 and 78.2 ± 8.6 μEq/15 min in the vehicle-treated control group ($n = 4$), 73.9 ± 10.0 and 51.1 ± 9.0 μEq/15 min in the interleukin-1β (50 ng/animal)-treated group ($n = 4$), respectively. In animals intraperitoneally pretreated with indomethacin

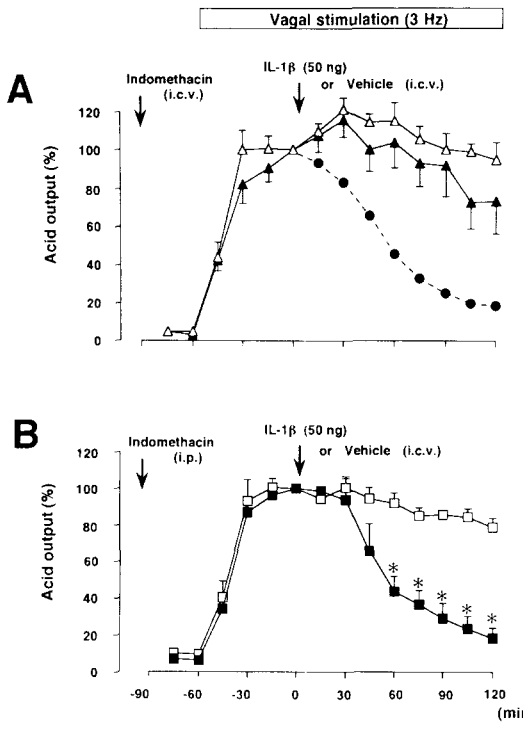

Fig. 4. Effect of indomethacin on the interleukin-1β (50 ng/animal)-induced inhibition of gastric acid secretion mediated by vagal stimulation (3 Hz, 1 mA). (A) Indomethacin was administered i.c.v.; (B) indomethacin was administered i.p. Pretreatment with indomethacin (500 μg/animal) was performed 30 min before the start of vagal stimulation. (A) (△) vehicle (saline) 10 μl/animal ($n = 4$); (▲) interleukin-1β 50 ng/animal ($n = 4$); (●) interleukin-1β 50 ng/animal without indomethacin (cited from Fig. 1): (B) (□) vehicle (saline) 10 μl/animal ($n = 4$); (■) interleukin-1β 50 ng/animal ($n = 5$). * Significantly different ($P < 0.05$) from vehicle-treated control. Other conditions were the same as for Fig. 1.

(500 μg/animal), the basal acid secretion was 6.4 ± 0.7 μEq/15 min ($n = 9$). The evoked acid secretion in these animals at 0 and 120 min after i.c.v. administration of vehicle and interleukin-1β was as follow: 87.1 ± 18.6 and 70.2 ± 18.4 μEq/15 min in the vehicle-treated control group ($n = 4$), 74.3 ± 4.9 and 14.8 ± 5.9 μEq/15 min in the interleukin-1β (50 ng/animal)-treated group ($n = 5$), respectively.

4. Discussion

Increasing evidence has demonstrated that centrally applied interleukin-1β inhibits gastric acid secretion (Ishikawa et al., 1990; Uehara et al., 1990; Saperas et al., 1990). Furthermore, centrally applied interleukin-1β elevates plasma levels of noradrenaline and adrenaline in rats (Rivier et al., 1989; Hashimoto et al., 1993). It is generally accepted that gastric acid secretion is inhibited by activation of the sympatho-adrenomedullary system (Jacobson, 1970; Reed and Sanders, 1971). More recently, we reported that activation of the sympatho-adrenomedullary system induces gastric α-adrenoceptor-mediated inhibition of acetylcholine release from the vagus nerve terminals and a resultant inhibition of gastric acid secretion occurs (Yokotani et al., 1984, 1993). Then we assumed that interleukin-1β centrally activates the sympatho-adrenomedullary system and inhibits gastric acid secretion. However, it was reported that the inhibition of acid secretion by interleukin-1β in conscious, pylorus-ligated rats was affected by neither adrenalectomy nor bretylium, and the authors suggested the possibility that interleukin-1β modulated central vagal outflow and decreased gastric acid secretion (Saperas et al., 1990). In the present study, therefore, we examined whether or not the interleukin-1β-induced central antisecretory effect is mediated by activation of the sympatho-adrenomedullary system, using an experimental model in which central vagal outflow had been completely abolished. In this model, the bilateral vagus nerves had been cut in the cervical portion and gastric acid secretion was elicited by electrical stimulation of the peripheral end of left cervical vagus nerves as reported in our previous papers (Yokotani et al., 1986, 1988; Okuma et al., 1987a,b). In these experiments, adrenalectomy or chemical sympathectomy alone had not completely blocked the central sympatho-adrenomedullary outflow. Activation of either gastric sympathetic nerve or adrenal medullary system is therefore sufficient to inhibit gastric acid secretion. Thus, we used both splanchnectomy and adrenoceptor blocking agents to block central sympatho-adrenomedullary outflow in the present study. Splanchnectomy (cutting the bilateral greater splanchnic nerves which ramify into the adrenal branch and gastric sympathetic preganglionic branch) blocks central activation of the gastric sympatho-adrenomedullary outflow. Adrenoceptor blocking agents also block the central sympatho-adrenomedullary outflow at the gastric adrenoceptors. In the present study, central inhibitory effects of interleukin-1β were abolished by both splanchnectomy and phentolamine (an α-adrenoceptor blocking agent). Propranolol (a β-adrenoceptor blocking agent) was without effect. It is therefore likely that interleukin-1β activates the central sympatho-adrenomedullary outflow, and inhibits vagally stimulated gastric acid secretion by activation of gastric α-adrenoceptors.

Peripherally administered interleukin-1β also inhibits gastric acid secretion in conscious, pylorus-ligated rats (Ishikawa et al., 1990; Robert et al., 1991; Saperas et al., 1992a). The peripheral inhibitory mechanisms of action of interleukin-1β were investigated by Wallace et al. using urethane-anesthetized rats (Wallace et al., 1991). They demonstrated that interleukin-1β (1–5 μg/kg i.v.) is a potent inhibitor of acid secretion stimulated by pentagastrin but not by histamine or bethanechol, and proposed that this cytokine-induced antise-

cretory action is mediated by inhibition of pentagastrin-stimulated histamine release. There are, however, discrepancies between the results obtained with a small dose of this cytokine (100 ng/animal): no effect and inhibition (Ishikawa et al., 1990; Saperas et al., 1992a). In the present study, intravenous administration of interleukin-1β (100 ng/animal) was without effect, as reported by Ishikawa et al. (1990). With the present experimental conditions, therefore, it is unlikely that interleukin-1β inhibited acid secretion by activation of peripheral inhibitory mechanisms.

It has been reported that the central inhibitory effects of interleukin-1β on gastric acid secretion are attenuated by intraperitoneal pretreatment with indomethacin (5–10 mg/kg) (Ishikawa et al., 1990; Saperas et al., 1990). Since systemic administration of indomethacin inhibits prostaglandin synthesis in the whole body, it was not clear whether the antisecretory effects of interleukin-1β were mediated by prostaglandins synthetized in the brain and/or in the peripheral organ system. Prostaglandin E_2 is released from the rat hypothalamus by interleukin-1β through indomethacin-sensitive mechanisms (Navarra et al., 1992) and centrally administered prostaglandin E_2 inhibits gastric acid secretion (Puurunen, 1983, 1984). Prostaglandin E_2 is also a well established peripheral inhibitor of acid secretion (Soll, 1978). It has been reported that indomethacin (500 μg/animal i.c.v.) inhibits ex vivo prostaglandin E_2 generation both in the brain and in the stomach (Saperas et al., 1991). In the present study, indomethacin (500 μg/animal i.c.v.) abolished the antisecretory effect of interleukin-1β, while the same dose of indomethacin given by the intraperitoneal route was without effect. This cytokine-induced antisecretory effect is therefore probably mediated by prostaglandins synthetized in the brain.

As for a possible inhibitory mechanism of gastric acid secretion by central prostaglandins, it has been reported that centrally administered prostaglandin E_2 (3–10 μg/animal) in conscious, pylorus-ligated rats inhibits gastric acid secretion through the release of vasopressin from the pituitary gland (Puurunen, 1983, 1984). In our previous experiments, however, centrally administered small doses of prostaglandin E_2 (0.01–0.5 μg/animal) also effectively inhibited the vagally stimulated gastric acid secretion under the same experimental conditions as in the present study (Yokotani et al., 1988). This prostaglandin E_2 (0.1 μg/animal)-mediated antisecretory effect was abolished by bilateral splanchnectomy, by adrenalectomy plus chemical sympathectomy with 6-hydroxydopamine, and also by phentolamine. Neither adrenalectomy nor chemical sympathectomy with 6-hydroxydopamine alone abolished this prostaglandin E_2-induced inhibition of vagally stimulated gastric acid secretion. 6-Hydroxydopamine almost completely depleted catecholamines from the gastric sympathetic nerves, while those in the adrenal medulla were not affected (Yokotani et al., 1988). In the present study, therefore, prostaglandins produced by interleukin-1β in the brain probably activate the sympatho-adrenomedullary outflow, and inhibit gastric acid secretion.

In conclusion, there exist two possible inhibitory mechanisms of gastric acid secretion by central interleukin-1β: one is promotion of central sympatho-adrenomedullary outflow as observed in the present study, another is inhibition of central vagal outflow as reported by other investigators (Saperas et al., 1990).

Acknowledgements

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