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Stimulatory effect of centrally injected capsaicin, an agonist of vanilloid receptors, on gastric acid secretion in rats

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Abstract

Capsaicin, the main pungent ingredient in chilli peppers, acts through specific vanilloid receptors on sensory neurons. The vanilloid receptors have been localized in the brain. We describe here a stimulatory effect of centrally injected capsaicin on gastric acid secretion in urethane-anesthetized rats. Injection of capsaicin (10–30 nmol per rat) into the lateral cerebroventricle markedly stimulated the secretion. Injection of capsazepine (30 nmol) or ruthenium red (30 nmol), antagonists for vanilloid receptors, into the lateral cerebroventricle inhibited the secretion induced by capsaicin, although these antagonists alone significantly stimulated the secretion. Injection of capsaicin into the fourth cerebroventricle also stimulated gastric acid secretion. The effects of centrally injected capsaicin into the lateral and fourth cerebroventricle were mediated via the vagus cholinergic nerve, because the effects were abolished by bilateral vagotomy at the cervical level. The present findings showed that central injection of capsaicin stimulated gastric acid secretion, via vanilloid receptors in the central nervous system (CNS), and through vagus nerve mechanisms in the perfused stomach of urethane-anesthetized rats.

Keywords: Gastric acid secretion; Capsaicin; Vanilloid receptor; Central injection; (Rat)

1. Introduction

Capsaicin, one of the flavoring ingredients in chilli peppers, excites subpopulation of somatic and visceral sensory afferents, and thus has been extensively used as a probe to elucidate the physiological function of these sensory neurons (for review see, Sterner and Szallasi, 1999; Szallasi and Blumberg, 1999). Activation of pain-sensing neurons by capsaicin produces sensations of burning pain or irritation, and the reactivity of capsaicin with the receptor responsible to mediate "pain" in the nervous system has been extensively studied (Sterner and Szallasi, 1999; Szallasi and Blumberg, 1999). It has been generally accepted that many of the capsaicin effects are mediated via vanilloid receptors. The distribution of vanilloid receptors (assessed using [^{3}H]resiniferatoxin binding) in the central nervous system (CNS) is confirmed to the dorsal horn and root of the spinal cord and discrete regions of the brain stem, namely in and around the nucleus of the solitary tract (Acs and Blumberg, 1994; Szallasi et al., 1995; Acs et al., 1996). Caterina et al. (1997) reported the cloning of the vanilloid receptor subtype 1, which binds capsaicin and other vanilloids. Sasamura et al. (1998) confirmed the existence of vanilloid receptor 1 expressing neurons in the rat hypothalamus by reverse transcription-polymerase chain reaction using primers based on the vanilloid receptor 1 sequence.

Vanilloid receptor 1 forms a nonselective cation channel, with high Ca^{2+} permeability and sensitivity to noxious heat and low pH (acids) (Tominaga et al., 1998). Because heat can gate the channel directly, heat could be viewed in one sense as an endogenous "ligand" of the vanilloid receptor 1. By contrast, decreased pH from the physiological pH potentiates both capsaicin and heat-induced currents and thus could be considered as an allosteric activator of the vanilloid receptor 1 (Szallasi and Blumberg, 1999). Recently, the endocannabinoid anandamide was shown to be expressed abundant in brain, and has been proposed as an endogenous agonist at the vanilloid receptor 1 (for review see, Szallasi and Di Marzo, 2000; Szolcsányi, 2000). However, anandamide is an endogenous ligand that exhibits an agonist effect at the GTP-binding protein-coupled cannabinoid receptor (Szallasi and Di Marzo, 2000; Szolcsányi, 2000). Capsaicin is well used as a pharmacological tool of activator of vanilloid receptor 1.

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Although there are numerous studies which describe the receptor and actions of capsaicin on primary afferent neurons as mentioned above, to date there is little information on the effect of capsaicin and the role of vanilloid receptors at supraspinal sites such as the hypothalamus. In the present study, we investigated the effect of capsaicin injected into the CNS on gastric acid secretion.

The functions and integrity of the stomach are regulated by both of the peripheral nervous system and the CNS. Stimulation of capsaicin-sensitive sensory nerves protected the rat gastric mucosa against injury produced by various ulcerogenic agents, and a various gastric functions such as mucosal blood flow are also regulated by capsaicin-sensitive neurons (Abdel-Salam et al., 1997; Matsuda et al., 1999; Calatayud et al., 2001). Several studies have indicated the involvement of capsaicin-sensitive neurons in the regulation of gastric acid secretion, however, contradictory findings have been reported. Treatment with systemic capsaicin (Dugani and Glavin, 1986; Alföldi et al., 1987) and application of capsaicin to the vagus nerve (Raybould and Taché, 1989; Sharkey et al., 1991) reduced the secretion in rats. By perivagal capsaicin pretreatment, however, the secretion was not changed (Yoneda and Raybould, 1990; Lloyed et al., 1993). Gastric acid secretions induced by gastric distension (Esplugues et al., 1990), by 2-deoxy-D-glucose (Evangelista et al., 1989) and by pepton (Ramos et al., 1992) were inhibited in the adult rats, which were treated when neonates with capsaicin and caused permanent degeneration of primary afferent neurons. In these reports, however, basal levels of acid secretion and histamine-stimulated acid secretion were not inhibited. In addition, the conflicting observations regarding the effect of capsaicin were also reported when capsaicin was administered into the stomach of animals (Abdel-Salam et al., 1997). The discrepancy in these previous findings is probably due to the different models and doses used and different regimens concerning capsaicin desensitization, etc. Although these studies show the regulation of gastric acid secretion by the peripheral nervous system, to our knowledge, there is no information on the acute effect of capsaicin injected into the CNS on the secretion.

In the present study, we investigated the effect of centrally injected capsaicin into the lateral and fourth cerebroventricle on gastric acid secretion in adult urethane-anesthetized rats. The present findings showed the involvement of capsaicin-sensitive neurons in the CNS on the positive regulation of gastric acid secretion through vagus nerve mechanisms in rats.

2. Materials and methods

2.1. Animals

Male Wistar rats (Takasugi Exp. Animals, Kusakabe, Japan) weighing 210–320 g were used. The animals were housed under controlled environmental conditions (temperature 24 ± 2 °C and light between 7:00 a.m. and 7:00 p.m.). The rats were fasted overnight before each experiment with free access to water. Animal experiments were performed in accordance with the Guiding Principles for the Care and Use of Laboratory Animals approved by the Japanese Pharmacological Society.

2.2. Drugs

Capsaicin was purchased from Wako (Osaka, Japan) and dissolved in a minimum of Tween 80 (Nakarai Tesque, Kyoto, Japan) and diluted with saline (the final concentration of Tween 80 was 1% (v/v)). The capsaicin solution was treated by sonication for 120 min at 40 °C (Branson-1200, Yamato, Tokyo, Japan) before use. Capsazepine, a competitive antagonist of vanilloid receptors in rat dorsal root ganglion neurons (Bevan et al., 1992; Szallasi et al., 1993, 1995), was purchased from RBI (Natic, MA, USA) and dissolved with saline containing 1% Tween 80, and 0.1% dimethyl sulfoxide. Ruthenium red, a non-competitive antagonist of vanilloid receptors (Amann and Maggi, 1991; Szallasi and Blumberg, 1999), was obtained from Sigma (St. Louis, MO, USA). The pH values of these drugs were pH 6.0–7.0. These drugs were administered to the rats in a volume of 5 or 10 μl over 30 s using a microliter syringe to the lateral and fourth cerebroventricle.

2.3. Cannulation for central injection and vagotomy

The cannulation for central injection and the vagotomy were performed as described previously (Ishihara et al., 2001). Briefly, rats were anesthetized with urethane (1.35 g/kg, i.p.), guide canula for microinjection of drugs was implanted into the lateral cerebroventricle with the following coordinates: 1.0 mm posterior to the bregma, 1.3 mm right lateral to the midsagittal suture, and 3.8 mm vertical to the surface of the skull with the incisor bar set 3.3 mm below the interaural line. For the injection into the fourth cerebroventricle, the implanting coordinates were as follows: 11.5 mm posterior to the bregma, 0.0 mm lateral and 7.5 mm vertical from the surface of the skull. The cannula was secured with dental cement. At the end of the experiments, Evans blue solution was injected to confirm that the solution had diffused into each cerebral cavity. To investigate the involvement of the vagus nerve in the mechanism of the effect of capsaicin, rats underwent bilateral vagotomy at the cervical level or sham operation after the implantation of the cannulae.

2.4. Measurement of gastric acid secretion

The rats were used for the measurement of gastric acid secretion 1 h after the implantation of the cannulae and the

vagotomy. This procedure is common in research concerning short-term neuronal regulation of gastric acid secretion (Watanabe et al., 1987; Yang et al., 1993; Garía-Zaragozá et al., 2000). Gastric acid secretion was determined by the gastric perfusion methods, as described previously by Watanabe et al. (1987, 2000) with minor modifications (Ishihara et al., 2001). The trachea was exposed, then cannulated and the esophagus was ligated at the cervical level. After laparotomy, the pylorus was ligated and a dual cannula was inserted into the gastric lumen from the forestomach. The stomach lumen was continuously perfused with saline (adjusted to pH 5.0 with 0.1 N HCl, at 37 °C) through the inlet tube of the dual cannula connected to the perfusion pump at the rate of 1 ml/min. After 30 min of pre-perfusion, the perfusate flowing from the outlet tube was collected as 10 min fractions with a fraction collector and titrated to pH 5.0 with 0.02 N NaOH using an autonomic titrator (AUT-201, Toa Electronics, Japan). Under the present study, titration to pH 5.0 was used to avoid the buffering action of gastric mucus (Watanabe et al., 2000; Ishihara et al., 2001). The acid output was expressed in terms of μEq HCl/10 min.

2.5. Statistical analysis

The values are expressed as means ± S.E.M. for four to seven rats. The statistical significance of differences between two groups was assessed using Student's *t*-test followed by the *F*-test. Multiple comparisons against a single control group were made by one-way analysis of variance (ANOVA) with Bonferroni Multiple Comparisons test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Effect of central injection of capsaicin into the lateral cerebroventricle on gastric acid secretion

First we investigated the effect of capsaicin injected into the lateral cerebroventricle on gastric acid secretion in urethane-anesthetized rats. Since the solubility of capsaicin in saline was low, we used saline containing Tween 80 (final concentration, 1%). The vehicle without capsaicin did not stimulate the secretion. Injection of capsaicin into the lateral cerebroventricle markedly increased gastric acid secretion (Fig. 1). The secretion began to increase about 20 min after the injection of capsaicin (20 and 30 nmol per rat). The secretion gradually increased until the peak level was reached at 40–50 min, and continued at least for 120 min. The secretion induced by 10 nmol of capsaicin began to increase slightly 30–40 min after the injection. The total acid output during the period of 0–60 min was significantly stimulated by 20 and 30 nmol of capsaicin; the

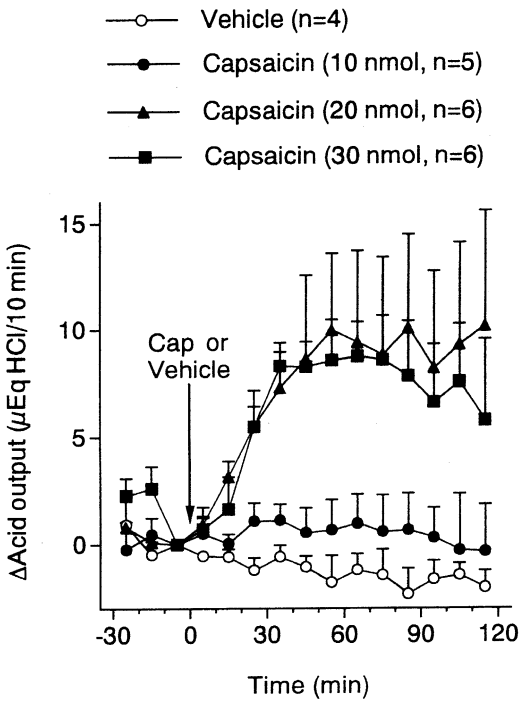

Fig. 1. Dose-dependent effect of capsaicin injected into the lateral cerebroventricle on gastric acid secretion in urethane-anesthetized rats. Vehicle (10 μl saline containing 1% Tween 80) or capsaicin (Cap, 10–30 nmol, 10 μl saline containing 1% Tween 80) was injected into the lateral cerebroventricle. Values represent the amount of gastric acid output for 10 min. The values are the mean ± S.E.M. for 4–6 rats.

value in the control rats was -5.7 ± 3.2 μEq HCl, and the values in the capsaicin (20 and 30 nmol)-treated rats were 35.5 ± 10.9 ($P < 0.05$) and 33.0 ± 3.0 μEq HCl ($P < 0.05$), respectively. The acid output induced by 30 nmol of capsaicin returned to the baseline at 3 h after the injection, and the second injection of the same dose of capsaicin into the lateral cerebroventricle also stimulated the secretion in a similar time pattern to that of the first injection. The total acid output during the period of 0–60 min after the second injection of capsaicin was 19.0 ± 9.7 μEq HCl ($n = 4$), which was smaller than that after the first injection. Intravenous injection of capsaicin (30 nmol per rat) did not stimulate gastric acid secretion (data not shown).

3.2. Inhibition of capsaicin-stimulated gastric acid secretion by vanilloid receptor antagonists, capsazepine and ruthenium red

We tested the capsaicin effect with regard to antagonists for vanilloid receptors. Injection of capsazepine (30 nmol per rat) into the lateral cerebroventricle by itself induced gastric acid secretion 20 min after the injection, and stimulated the secretion continuously (Fig. 2A). However, capsazepine significantly inhibited the secretion induced by 30 nmol of capsaicin during the period of 0–60 min (Fig. 2B).

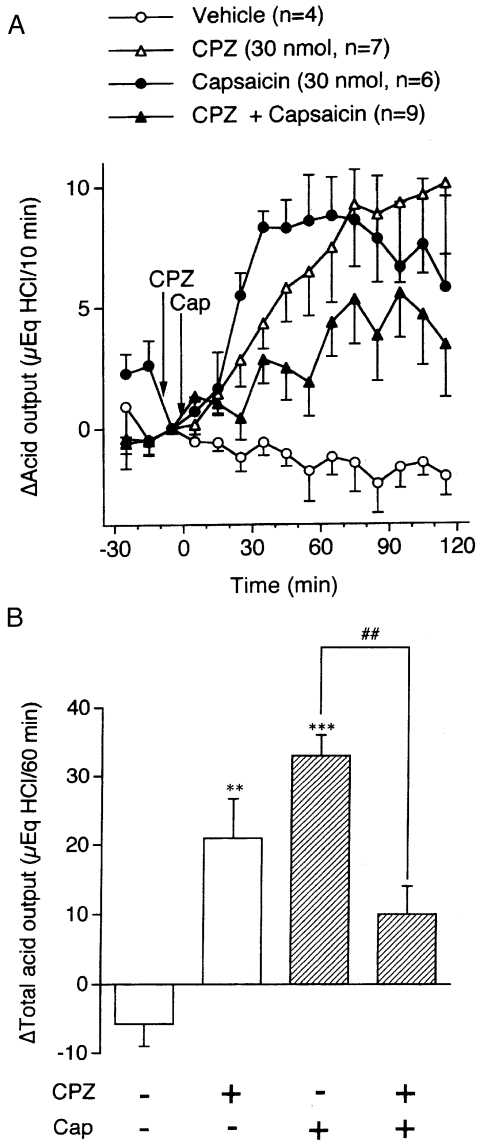

Fig. 2. Inhibitory effect of capsazepine injected into the lateral cerebroventricle on gastric acid secretion stimulated by capsaicin. Capsazepine (CPZ, 30 nmol, 5 μl) and vehicle (5 μl saline) were injected into the lateral cerebroventricle 10 min before the injection of capsaicin (Cap, 30 nmol, 10 μl). (Panel A) Values represent the amount of gastric acid output for 10 min. (Panel B) Values are the total gastric acid output for the initial 60 min. The values are the mean ± S.E.M. for 4–9 rats. $^{**}P < 0.01$, $^{***}P < 0.001$, statistically significant compared with the control (vehicle) group. $^{\#\#}P < 0.01$, statistically significant compared with the capsaicin-treated group.

Capsazepine at 10 nmol had no effects on basal and capsaicin-stimulated gastric acid secretion. Injection of ruthenium red (30 nmol) into the lateral cerebroventricle by itself induced the secretion about 60 min after the injection, and gradually stimulated the secretion (Fig. 3A). The total gastric acid output during the period of 0–60 min induced by 30 nmol of capsaicin was significantly inhibited by 30 nmol of ruthenium red (Fig. 3B). The acid output during the period of 60–120 min was also inhibited by ruthenium red ($P = 0.058$). Even in the total acid output during the period of 0–120 min, ruthenium red significantly inhibited the secretion induced by capsaicin; the total outputs in ruthenium red-treated, capsaicin-treated, and ruthenium red plus capsaicin-treated rats were 34.6 ± 16.8 ($n = 5$), 78.1 ± 16.5 ($n = 6$) and 6.6 ± 14.7 ($n = 7$, $P < 0.01$, compared with the capsaicin-treated groups) μEq HCl, respectively. Neither capsazepine nor ruthenium red at 30 nmol inhibited gastric acid secretion induced by injection of *N*-methyl-D-aspartate (20 nmol) into the lateral cerebroventricle (data not shown). These findings suggest that the effect of capsaicin injected into the lateral cerebroventricle on gastric acid secretion was mediated by the

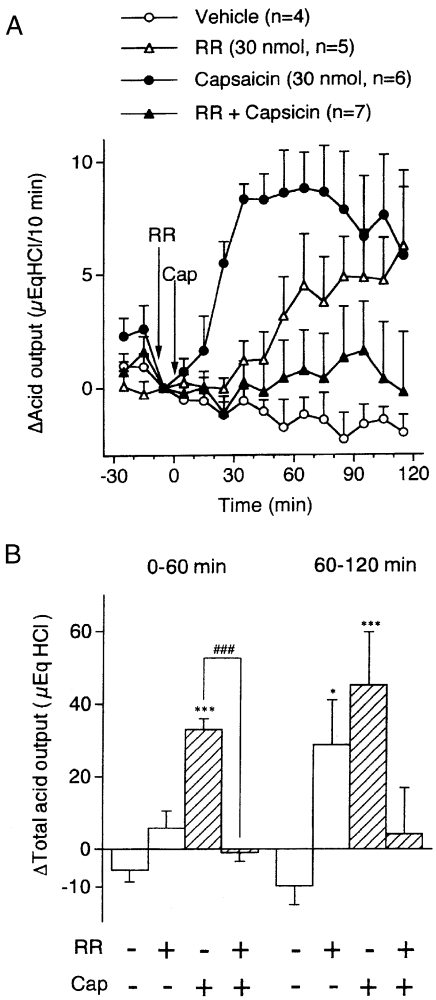

Fig. 3. Inhibitory effect of ruthenium red injected into the lateral cerebroventricle on gastric acid secretion stimulated by capsaicin. Ruthenium red (RR, 30 nmol, 5 μl) and vehicle (5 μl saline) were injected into the lateral cerebroventricle 10 min before the injection of capsaicin (Cap, 30 nmol, 10 μl). (Panel A) Values represent the amount of gastric acid output for 10 min. (Panel B) Values are the total gastric acid output during the periods of 0–60 min and 60–120 min, respectively. The values are the mean ± S.E.M. for 4–7 rats. $^{*}P < 0.05$, $^{***}P < 0.001$, statistically significant compared with the control (vehicle) group. $^{\#\#\#}P < 0.001$, statistically significant compared with the capsaicin-treated group.

capsazepine- and ruthenium red-sensitive vanilloid receptors in the CNS in rats, although the central injections of these antagonists alone stimulated the secretion by unknown mechanism(s).

3.3. Effect of central injection of capsaicin into the fourth cerebroventricle on gastric acid secretion

For further investigation of the effective site of capsaicin in the CNS, capsaicin was injected into the fourth cerebroventricle (Fig. 4). The injection of capsaicin (30 nmol per rat) markedly increased gastric acid secretion. Compared with the time course of gastric acid secretion induced by injection of capsaicin into the lateral cerebroventricle (Fig. 1), the secretion induced by capsaicin began to increase later, about 40 min after the injection, in rats injected into the fourth cerebroventricle. The secretion gradually increased until the peak level was reached at 60–70 min, and continued for at least 120 min. The total acid output during the period of 0–120 min induced by the fourth cerebroventricle injection of capsaicin (30 nmol) was similar as that by the injection into the lateral cerebroventricle; 78.1 ± 16.5 ($n = 6$) and 117.4 ± 28.9 ($n = 5$) μEq HCl in the lateral cerebroventricle- and the fourth cerebroventricle-injected groups, respectively.

3.4. Role of the vagus nerve in the gastric acid secretion stimulated by capsaicin

We investigated whether the vagus nerve was involved in the mechanism of the stimulatory effect of centrally injected capsaicin on gastric acid secretion. A group of rats underwent bilateral vagotomy at the cervical level. The

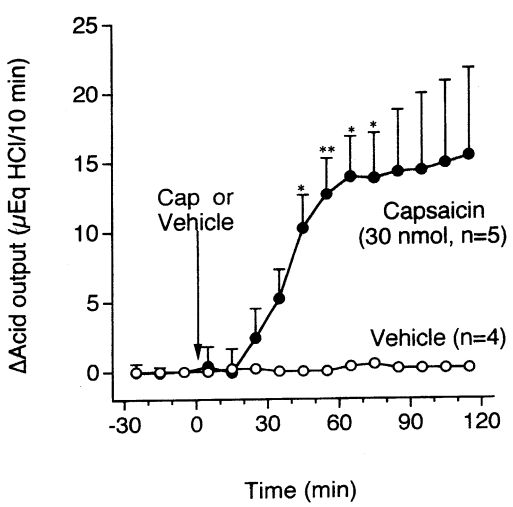

Fig. 4. Stimulatory effect of capsaicin injected into the fourth cerebroventricle on gastric acid secretion. Capsaicin (Cap, 30 nmol) or vehicle was injected into the fourth cerebroventricle. Values represent the amount of gastric acid output for 10 min. The values are the mean ± S.E.M. for 4–5 rats. $^{*}P < 0.05$, $^{**}P < 0.01$, statistically significant compared with the control (vehicle) group.

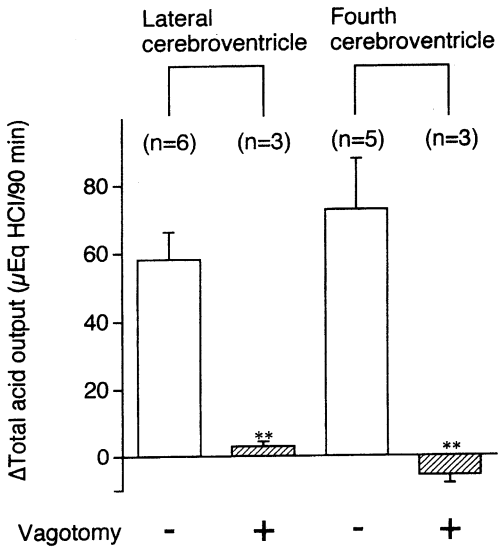

Fig. 5. Effect of vagotomy on gastric acid secretion stimulated by capsaicin injected into the lateral and fourth cerebroventricle. Bilateral vagotomy at the cervical level or sham operation was performed 60 min before the experiment. Capsaicin (30 nmol) was injected into the lateral or fourth cerebroventricle. The total gastric acid output during the period of 0–90 min is shown. The values are the mean ± S.E.M. for 3–6 rats. $^{**}P < 0.01$, statistically significant compared with the sham-operated group.

secretions stimulated by the lateral and fourth cerebroventricle injection of capsaicin (30 nmol) were almost completely inhibited in vagotomized rats, compared with that in sham-operated rats (Fig. 5). These findings suggest that the stimulatory effects of capsaicin in both brain regions were mediated via the vagus nerve. Interestingly, the effect of capsazepine (30 nmol) alone on the secretion decreased in vagotomized rats; the total acid output during the period of 0–60 min induced by the injection of capsazepine into the lateral cerebroventricle in vagotomized rats was −0.97 to 3.59 μEq HCl ($n = 4$), which was similar to the value in the control rats without capsazepine.

4. Discussion

4.1. Gastric acid secretion induced by activation of vanilloid receptors with capsaicin

In the present study, we showed that injection of capsaicin into the lateral cerebroventricle induced gastric acid secretion (10–30 nmol per rat) (Fig. 1). Secretion induced by the central injection of capsaicin appeared to be mediated by vanilloid receptors in the CNS, because pre-injection of capsazepine (30 nmol), a competitive antagonist of vanilloid receptors, significantly inhibited the effect of capsaicin (Fig. 2B). In addition, the secretion induced by capsaicin during the period of 0–60 min was almost completely inhibited by ruthenium red (30 nmol), a non-competitive antagonist (Fig. 3). Previously, we reported

that injection of *N*-methyl-D-aspartate (20 nmol) into the lateral cerebroventricle stimulated gastric acid secretion in rats (Tsuchiya et al., 2001). Since neither capsazepine nor ruthenium red inhibited the effect of *N*-methyl-D-aspartate, two reagents appeared to be relatively selective to the capsaicin-induced release. The injection of capsaicin into the fourth cerebroventricle also stimulated the secretion (Fig. 4). The effect of capsaicin was not due to neurotoxicity, because (1) the effect of capsaicin was observed in a low dose (30 nmol), (2) the effect decreased at about 3 h after the injection, and (3) the second injection of capsaicin (30 nmol) into the lateral cerebroventricle significantly stimulated the secretion. The effects of capsaicin injected into the CNS on gastric acid secretion in the present study satisfy three established criteria for pharmacological classification of vanilloid receptor; steep dose–effect relationship, desensitization with repeated administration, and antagonism by capsazepine and ruthenium red (Szallasi and Blumberg, 1996; Mazzone and Geraghty, 1999). The lower response induced by the second injection of capsaicin compared with the first response was probably due to the desensitization of vanilloid receptors, because it was reported that capsaicin-sensitive neurons are functionally desensitized easily depending on conditions (Szallasi and Blumberg, 1996) and that gastric acid secretion mediated by capsaicin-sensitive vagal neurons in rats was susceptible to the desensitization (Sharkey et al., 1991).

Injection of capsazepine (30 nmol) into the lateral cerebroventricle by itself markedly stimulated gastric acid secretion in the present experiments. The stimulatory effect of capsazepine on the secretion was inhibited in vagotomized rats. In addition, ruthenium red by itself stimulated the secretion during the period of 60–120 min after the injection. It is reported that capsazepine and ruthenium red stimulated Ca^{2+} entry into the C-fibres, causing release of tachykinins and contraction in the rabbit iris (Andersson and Greves, 1991; Wang and Håkanson, 1993). Wang and Håkanson (1993) proposed that capsazepine and ruthenium red acted as a partial agonist/antagonist for vanilloid receptors, because two reagents displayed tachyphylaxis upon repeated administration. Our findings may be derived from the agonistic effects of these two reagents to vanilloid receptors. In addition, the non-specific actions on Ca^{2+} channels and potassium channels of these agents, in addition to its antagonism of vanilloid receptors, were reported previously (Kuenzi and Dale, 1996; Docherty et al., 1997; Yamada et al., 1999; Cibulsky and Sather, 1999).

4.2. Capsaicin-sensitive neurons in the CNS stimulating gastric acid secretion via vagal-dependent mechanism

Capsaicin-sensitive neurons in the hypothalamus were suggested to mediate the well-known hypothermic action of capsaicin (Jancsó-Gábor et al., 1970). Several investigators showed that the distribution of vanilloid receptors (assessed using [^{3}H]resiniferatoxin binding) in the CNS (Acs and Blumberg, 1994; Szallasi et al., 1995; Acs et al., 1996). Recently, it was reported that mRNA for vanilloid receptor subtype 1-expressing neurons and 1-like immunoreactivity exist throughout the whole neuroaxis including cortical areas, several members of the limbic system (e.g., amygdala), hypothalamus, thalamic nuclei and the solitary tract nucleus (Sasamura et al., 1998; Mezey et al., 2000). The effects of capsaicin injected into the lateral and fourth cerebroventricle were almost completely abolished in vagotomized rats (Fig. 5). Intravenous injection of capsaicin (30 nmol) did not modify gastric acid secretion (data not shown). Thus, the stimulatory effect of centrally injected capsaicin on gastric acid secretion appeared to be mediated by activation of capsaicin-sensitive neurons in the CNS and then mediated by the vagus nerve, but not by direct activation of the peripheral nervous system.

Although the drugs administered by fourth cerebroventricle injection spread only around the brainstem, the drugs administered by the lateral cerebroventricle injection spread widely around the forebrain and the caudal regions such as the fourth cerebroventricle. Injection of capsaicin not only into the lateral cerebroventricle but also into the fourth cerebroventricle induced gastric acid secretion. It is probable that capsaicin injected into the lateral cerebroventricle spread into the fourth cerebroventricle and, thus, stimulated the capsaicin-sensitive neurons in the brainstem. However, the secretion induced by the injection of capsaicin into the lateral cerebroventricle started much faster that into the fourth cerebroventricle (Figs. 1 and 4). These findings suggest the existence of at least two sites of capsaicin-sensitive neurons; one is in the forebrain and the acid response is faster, and another is in the brainstem such as the solitary tract nucleus and the response is slower. Because application of capsaicin to the cervical vagi or the vagus nerve inhibited gastric acid secretion in rats (Raybould and Taché, 1989; Sharkey et al., 1991), the effect of capsaicin injected into the fourth cerebroventricle was not due to the direct activation of the dorsal motor nucleus of the vagus. As described below, it is probable that capsaicin-sensitive neurons both in the forebrain and in the brainstem interact with other neurons and/or the vagal motor neurons. The brain locations of capsaicin-sensitive neurons regulating gastric acid secretion are still to be studied.

4.3. Roles of capsaicin-sensitive neurons and possible interneurons activated by capsaicin-sensitive neurons in the CNS

Intracerebroventricular injections of capsaicin at 100–500 nmol elicited decreases in urine outflow volume in anesthetized rats (Tsushima and Mori, 1999). Microinjection of capsaicin (0.5–2 nmol) into the nucleus of the solitary tract reduced respiratory frequency in rats (Maz-

zone and Geraghty, 1999). In the present study, we showed the central injection of capsaicin (10–30 nmol) induced gastric acid secretion in rats. These previous and the present findings confirm the existence of capsaicin-sensitive neurons regulating physiological functions in the CNS.

Tsushima and Mori (1999) showed that capsaicin-induced antidiuresis was inhibited by the injection of a tachykinin NK-1 receptor antagonist into the hypothalamic supraoptic nucleus. Mazzone and Geraghty (1999) also showed that respiratory action of capsaicin injected into the nucleus of the solitary tract was mediated, at least partly, by the release of tachykinins from the central terminals of sensory neurons and subsequent stimulation of tachykinin NK-2 and/or NK-3 receptors. However, injections of substance P into the dorsal vagal complex (Yang and Taché, 1997) and agonists of tachykinin NK-2 receptor (Improta et al., 1997) and tachykinin NK-3 receptor (Improta and Broccardo, 1991) inhibited gastric acid secretion in rats. Stimulation of neurons with capsaicin stimulates the release of various neurotransmitters including dynorphins and somatostatin, etc. (Szallasi and Blumberg, 1996, 1999). Capsaicin induced glutamate release from the hypothalamus slices (Sasamura et al., 1998). These neurotransmitters were suggested to regulate gastric acid secretion in the CNS (Geoghegan and Pappas 1997). We previously reported that the central injection of glutamate or morphine regulated gastric acid secretion in rats (Ishihara et al., 2001; Tsuchiya et al., 2001). Further studies of the possible interneurons and/or intermediates on gastric acid secretion induced by activation of vanilloid receptors in the CNS are currently in progress in our laboratory. In addition, identification of endogenous ligands for capsaicin-sensitive receptors and/or vanilloid receptors, and the effects of anandamide and arachidonic acid derivatives in the CNS on gastric acid secretion should be determined in the future.

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