Convergence of Oropharyngolaryngeal, Baroreceptor and Chemoreceptor Afferents onto Insular Cortex Neurons in Rats

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Abstract

Forty-two neurons that responded to electrical stimulation of at least one of four nerves, the chorda tympani (CT), the lingual–tonsillar branch of the glossopharyngeal (LT–IXth) nerve, the pharyngeal branch of the glossopharyngeal (PH–IXth) nerve and the superior laryngeal (SL) nerve, were identified from the insular cortex by using glass microelectrodes in paralysed and anesthetized rats. Four, 42, 41 and 40 neurons responded to the CT, LT–IXth, PH–IXth and SL nerve stimulation respectively. Of these 42 neurons, most (37/42, 88.1%) responded to three nerves (the LT–IXth, PH–IXth and SL), two (4.8%) responded to two nerves and the remaining three (7.1%) responded to all four nerves. No neurons responded to one specific stimulus. The responsiveness of these 42 neurons to baroreceptor and chemoreceptor stimulation by an i.v. injection of three drugs was investigated. For baroreceptor stimulation, methoxamine hydrochloride (Mex) and sodium nitroprusside (SNP) were used; for chemoreceptor stimulation, sodium cyanide (NaCN) was used. Of the 42 neurons, 31 (73.8%) showed an excitatory or inhibitory response to baroreceptor and chemoreceptor stimulation with at least one of the three drugs, and the remaining 11 (26.2%) showed no response. Of these 31 baroreceptor and chemoreceptor-sensitive neurons, 19 (61.3%) responded to two or all three drugs, and the rest (12; 38.7%) responded to one. Most neurons recorded were distributed in the posterior insular cortex. These results indicate that the neurons in the posterior insular cortex receive convergent inputs from the oropharyngolaryngeal region, the baroreceptors and the chemoreceptors, suggesting that the posterior insular cortex may integrate various sensory information. **Chem. Senses 22: 399–406, 1997.**

Introduction

From the findings of many electrophysiological and anatomical studies, the insular cortex in rats is considered to be the cerebral cortical taste area (Yamamoto *et al.*, 1980, 1984; Kosar *et al.*, 1986; Ogawa *et al.*, 1990, 1992). However, some reports have suggested that the insular cortex has functions for the autonomic system (Saper, 1982; Shipley and Geinisman, 1984). Cechetto and Saper (1987) reported that the insular cortex can be divided into anterior and posterior portions in the anterior–posterior dimension, and that the former and latter are taste and visceral areas respectively. However, it is not clear whether there is an exact borderline between the two areas or if they overlap.

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Since it is known that gustatory information elicits various autonomic responses (Mattes, 1987; Shingai *et al.*, 1988; Hanamori and Ishiko, 1993) as well as taste sensation, there is a possibility that an interaction may exist between these two insular cortex areas.

Gustatory information generated from taste receptors in the oropharyngolaryngeal area is conveyed via five nerves: the chorda tympani (CT) innervates the anterior tongue, the greater superficial petrosal (GSP) nerve innervates the soft palate, the lingual–tonsillar branch of the glossopharyngeal (LT–IXth) nerve innervates the posterior tongue, the pharyngeal branch of the glossopharyngeal (PH–IXth) nerve innervates the pharynx and the superior laryngeal (SL) nerve innervates the larynx. We have recently shown that the neurons in the insular cortex respond to electrical stimulation of the CT, LT–IXth, PH–IXth and SL nerves, and that most of the neurons receive convergent inputs from these nerves (Hanamori *et al.*, 1994). Our results suggest that the insular cortex neurons receive convergent inputs from various kinds of sensory organs. Cechetto and Saper (1987) recorded the responses of the neurons in the insular cortex to baroreceptor and chemoreceptor stimulation. It would be interesting to determine if afferents from both the oropharyngolaryngeal region and the visceral sensory organs converge onto single neurons in the insular cortex.

In the present study, we first sampled the insular cortex neurons that responded to electrical stimulation of at least one of four nerves: the CT, PH–IXth, LT–IXth and SL. We then examined the responsiveness of these neurons to baroreceptor and chemoreceptor stimulation.

Materials and methods

Surgical procedures

Experiments were performed on 22 Sprague–Dawley male rats, weighing between 380 and 650 g. Animals were initially anesthetized with a mixture of urethane (800 mg/kg) and α-chloralose (70 mg). The trachea was cannulated for artificial ventilation. The left femoral artery and vein were cannulated for measurement of blood pressure (BP) and for administration of drugs respectively. The level of anesthesia was checked by whether the withdrawal reflex was provoked by pinching the tail. If required, supplemental doses of α-chloralose were administered i.v.

Four right taste nerves, i.e. the CT, LT–IXth, PH–IX and SL, were dissected from the surrounding connective tissue and transected, keeping the central connection intact. The central portion of each nerve was placed on a pair of platinum wire electrodes for electrical stimulation. For insertion of the glass microelectrodes, the head of the animal was fixed in a stereotaxic frame, and a square hole ~2 mm in diameter was made in the right skull approximately at the bregma and 5–6 mm lateral from the mid-line. During the recordings, the animal was paralysed by tubocurarine (3 mg/kg, i.v.) and artificially ventilated by a Harvard respiratory pump (Model-683, USA). This was employed for a stable unitary recording and to control respiration. Depth of anesthesia was assessed periodically by allowing recovery from paralysis and was maintained with supplemental doses of α-chloralose. The end-expired CO_2 was constantly monitored (NEC Sanei, Type-IH31, Japan) and maintained at 3.5–4.5%. Rectal temperature was maintained at 37–38°C by a thermostatically regulated heating pad (American Pharmaseal Company, Model-K20, USA).

Stimulation

The nerves were stimulated with a train of three rectangular pulses of 0.03 ms duration at 500 Hz. The stimulus strength used was 12 V, which is the maximal intensity for A-delta fibers in the nerves used (Hanamori *et al.*, 1996). Arterial baroreceptors were stimulated by i.v. administration of methoxamine hydrochloride (Mex, 20 μg/0.1 ml; increase in BP) or sodium nitroprusside (SNP, 10 μg/0.1 ml; decrease in BP). Arterial chemoreceptors were stimulated by i.v. administration of sodium cyanide (NaCN, 100 μg/0.1 ml). The drugs were injected doses of 0.05–0.1 ml per rat.

Recording

Extracellular unit responses of the neurons in the insular cortex were recorded with glass microelectrodes filled with pontamine sky blue in 0.5% sodium acetate. Neural activity was amplified (WPI, Model M-701, USA), displayed on an oscilloscope (Nihon Kohden, VC-10, Japan), led to an audio-monitor and stored on a data recorder (Teac, RD111-T, Japan). In the insular cortex neurons, single sweeps of impulses that were evoked following electrical stimulation of the nerves were recorded using a digital oscilloscope, and the data stored on a recorder (Nihon Kohden, JG-4122). Blood pressure in the femoral artery and heart rate (HR) obtained from the arterial pulse were amplified using a conventional amplifier and recorded on an eight-channel pen recorder (NEC Sanei, RH-8K).

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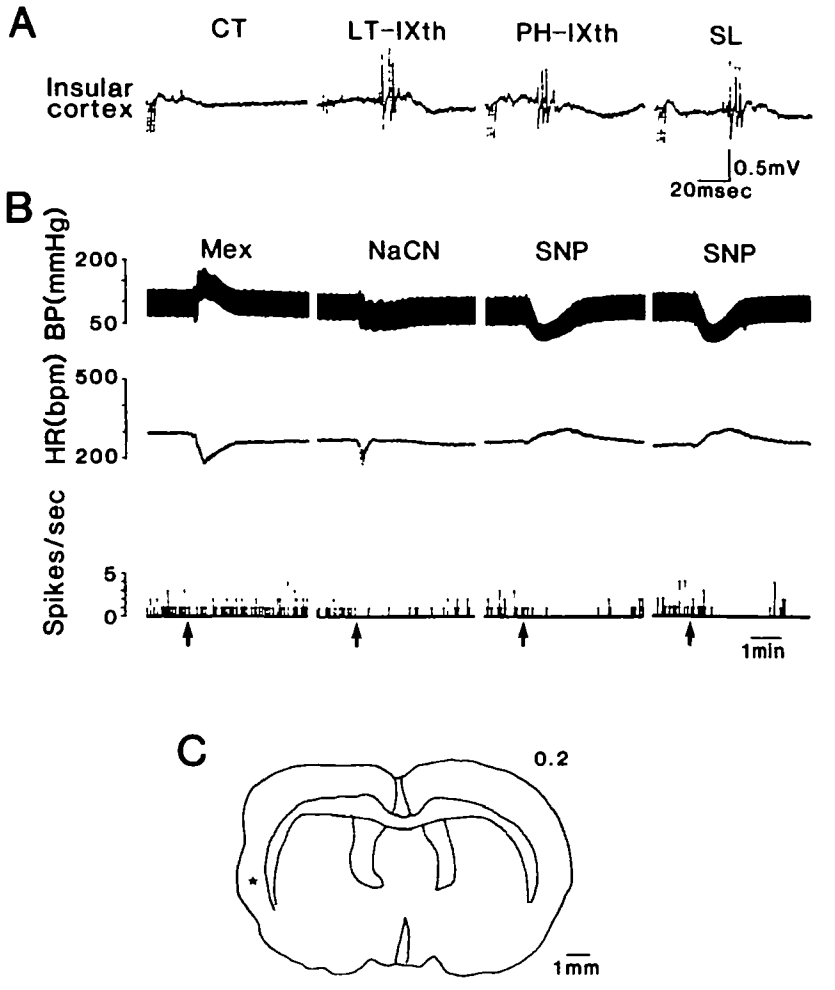

Figure 1 The responses of an insular cortex neuron to electrical stimulation of the CT, LT–IXth, PH–IXth and SL nerves **(A)** and to baroreceptor and chemoreceptor stimulation by i v injection of Mex, NaCN and SNP **(B)** In (A), the neuron responded, with three spikes, to electrical stimulation of LT–IXth, PH–IXth and SL nerves, but did not respond to CT stimulation Electrical stimuli were three pulses of 12 V for 0 03 ms duration at 500 Hz CT, chorda tympani, LT–IXth, lingual-tonsillar branch of the IXth nerve, PH–IXth, pharyngeal branch of the IXth nerve, SL, superior laryngeal nerve In (B), the neuronal activity (the number of spikes per second) of the same neuron as in (A) is shown simultaneously with the changes in BP and HR Arrows show the time of the i v. bolus injection of Mex (20 μg/0 1 ml), NaCN (100 μg/0 1 ml) and SNP (10 μg/0 1 ml) Mex, methoxamine hydrochloride, NaCN, sodium cyanide, SNP, sodium nitroprusside In (C), the position (*) of the same neuron as in (A) and (B) is shown by a transverse section of the brain in the anterior–posterior dimension The location of the neuron was 0 2 mm posterior to the AC, positioned in layer V

Data sampling and analysis

The electrodes were inserted vertically into the insular cortex between 5 and 6 mm lateral from the mid-line, between 2 mm anterior and 1 mm posterior to the bregma, and between 3.5 and 4 mm ventral from the dorsal surface of the cortex. Spontaneously active neurons in the insular cortex, which were encountered during electrode penetration, were tested for their responses to electrical stimulation of each of the four nerves. The neurons that responded to electrical stimulation of at least one of the four nerves were then investigated for their responses to baroreceptor and chemoreceptor stimulation. Action potentials that were evoked following electrical stimulation of the nerves could be easily identified, since the rate of the spontaneous discharges in the insular cortex neurons was relatively low (ranging from 0.1 to 4.6 Hz; mean = 1.3 Hz, n = 42) as shown previously by Yamamoto *et al* (1984). For the baroreceptor and chemoreceptor stimulation, the responses of the neurons were defined as excitatory if the number of impulses over a 30-s period after an i.v. injection of the drug increased >30% and inhibitory if the number decreased <30% of the rate before stimulation. The neurons whose activities after stimulation remained between 70 and 130% of the control were defined as no response. The values in the results were expressed as mean ± SEM. Multiple comparisons were made using one-way ANOVA.

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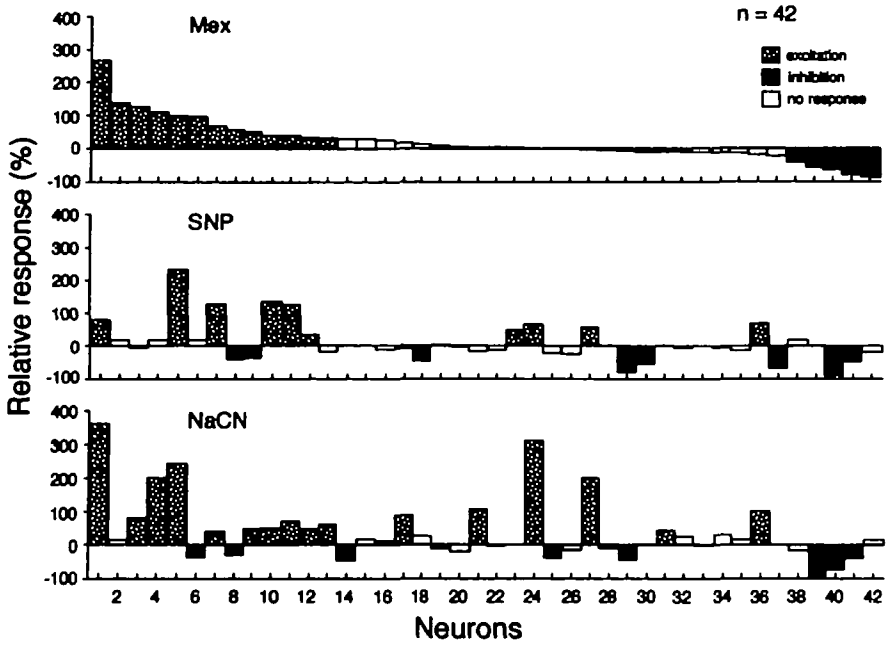

Figure 2 Response profiles of the 42 neurons to stimulation with Mex, SNP and NaCN The response magnitude is expressed as an increase or decrease (%) in the basal activity before stimulation Neurons in the abscissa are arranged according to the order of magnitude of responses to Mex

Histology

At the end of the experiments, the recording sites were marked by deposition of the dye when passing 5 mA of DC current through the tip of the electrode for 3–5 min. Then the brains were removed and fixed with 10% formalin. Sections of 50 μm were cut on a freezing microtome and stained with neutral red. Of the 42 neurons isolated, 37 (88.1%) were located in layer V, two were in layer IV and the remaining three were in layer VI. The location of the neurons was plotted on two-dimensional maps in which the anterior edge of the crossing of the anterior commissure (AC) and the rhinal fissure (RF) was adopted as standard zero point in the anterior–posterior and dorso-ventral axes respectively (Cechetto and Saper, 1987).

Results

Responses of the insular cortex neurons to electrical stimulation of the oropharyngolaryngeal nerves

Forty-two neurons in the insular cortex responded to electrical stimulation of at least one of the four oropharyngolaryngeal nerves. Usually one to three spikes were elicited by electrical stimulation of the nerves (Figure 1A). The mean latencies of the first spikes elicited were 42.0 ± 13.4 ms (n = 4) for the CT, 40.9 ± 2.5 ms (n = 42) for the LT–IXth, 42.7 ± 2.5 ms (n = 40) for the PH–IXth and 40.2 ± 2.5 ms (n = 41) for the SL nerve. There was no significant difference in the mean latencies among the four nerves [$F(3,122)$ = 0.175, P = 0.913]. Of the 42 neurons, all responded to the LT–IXth nerve stimulation, 41 responded to the SL, 40 responded to the PH–IXth and the remaining four responded to the CT. No specific neurons responded to only one stimulus. Most of the neurons (37/42) received convergent inputs from three nerves: LT–IXth, PH–IXth and SL (Figure 1A). Three neurons among the remainder received inputs from all four nerves, and another two neurons received convergent inputs from two nerves (one responded to CT and LT–IXth, and one to LT–IXth and SL).

Responses of the insular cortex neurons to baroreceptor and chemoreceptor stimulation

Of the 42 neurons, 31 (73.8%) showed an excitatory or inhibitory response to an i.v. injection of at least one of the three drugs (Mex, SNP and NaCN), and the remaining 11 (26.2%) showed no response. In Figure 1B, a neuron that had responded to electrical stimulation of the LT–IXth, PH–IXth and SL nerves (Figure 1A) showed an inhibitory response to stimulation of both NaCN and SNP, while it showed no response to Mex. The location of this neuron is

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shown in Figure 1C: 0.2 mm posterior to the AC, 1.3 mm dorsal to the RF, and in layer V. The spontaneous rate of this neuron was 0.5 Hz.

Response profiles for Mex, SNP and NaCN in the 42 neurons are shown in Figure 2. For Mex stimulation of the 42 neurons, 13 (40%) were excitatory, 5 (11.9%) were inhibitory and the remaining 24 (57.1%) were unresponsive. For SNP stimulation, 10 (23.8%) were excitatory, eight (19%) were inhibitory and 24 (57%) were unresponsive. For NaCN stimulation, 16 (38.1%) were excitatory, eight (19%) were inhibitory and 18 (42.9%) were unresponsive. Of the 31 baroreceptor and chemoreceptor-sensitive neurons, 12 (38.7%) responded to one stimulus (three to Mex, four to SNP and five to NaCN), nine (29.0%) responded to two stimuli (five to Mex and NaCN, and four to SNP and NaCN) and the remaining 10 (32.3%) responded to all three stimuli.

The similarities among the response profiles across 42 neurons were investigated (Figure 2). The correlation coefficients between Mex and SNP, between Mex and NaCN, and between SNP and NaCN were 0.43, 0.56 and 0.57 respectively.

Distribution of the 42 neurons in the insular cortex

The locations of the 42 neurons in the insular cortex and their responsiveness to stimulation of the taste nerves are shown in Figure 3. These 42 neurons were distributed between 2.5 mm anterior and 0.5 mm posterior to the AC in the anterior–posterior axis and between 0.3 mm and 3.5 mm dorsal to the RF in the dorso-ventral axis (Figure 3). The mean locations of the 42 insular cortex neurons were 0.7 ± 0.1 mm anterior to the AC and 1.7 ± 0.1 mm dorsal to the RF. Only four neurons responded to the CT stimulation. Three of these were located in a relatively anterior region. However, there was no statistical difference in the anterior–posterior distribution of the responsive neurons among the four nerves [$F(3,122) = 0.423$, $P = 0.737$]. Also, there was no statistical difference in the dorso-ventral distribution among the four nerves [$F(3,122) = 0.023$, $P = 0.995$].

The neurons responding to baroreceptor and chemoreceptor stimulation were also distributed diffusely in the insular cortex (Figure 4). In the anterior–posterior axis, the mean locations of the neurons responding to visceral sensory stimuli were –0.9 ± 0.2 mm ($n = 18$) for Mex, –0.5 ± 0.1 mm ($n = 18$) for SNP and –0.7 ± 0.1 mm ($n = 24$) for

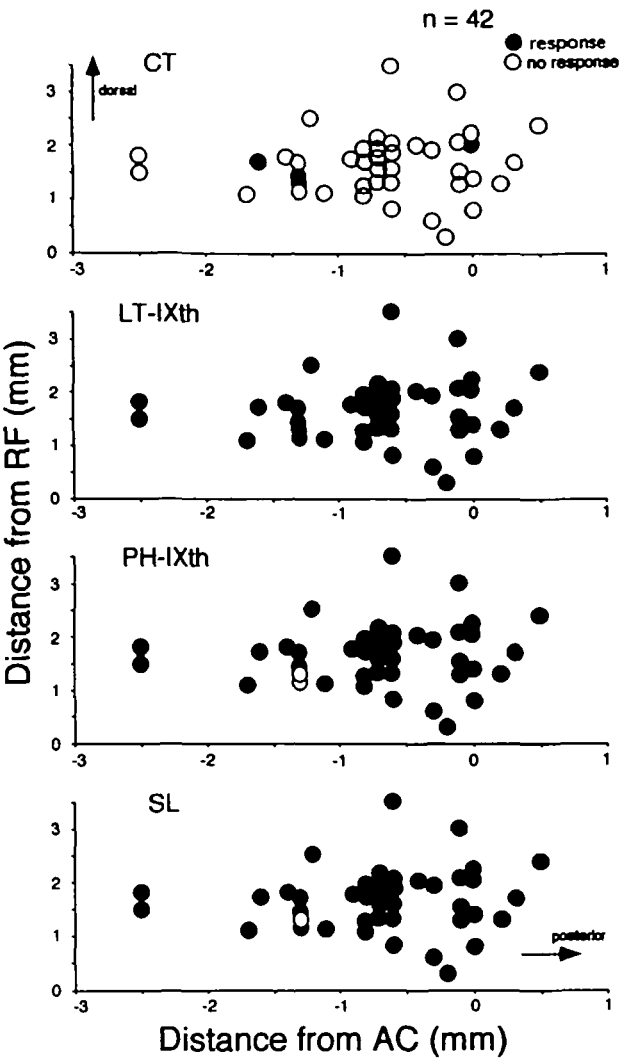

Figure 3 Distribution of the 42 neurons in the insular cortex and their responsiveness to electrical stimulation of the CT, LT–IXth, PH–IXth and SL nerves. The ordinate and abscissa show the distance from the rhinal fissure (RF) and the anterior edge of the crossing of the anterior commissure (AC) respectively.

NaCN. There was no statistical difference in the anterior–posterior distribution among the three drugs [$F(2,57) = 1.380$, $P = 0.260$]. The mean locations for the excitatory and inhibitory neurons responding to Mex were –0.9 ± 0.2 mm ($n = 13$) and –0.6 ± 0.3 mm ($n = 5$) respectively; those for the excitatory and inhibitory neurons responding to SNP were –0.8 ± 0.1 mm ($n = 10$) and –0.2 ± 0.1 mm ($n = 8$) respectively; and those for the excitatory and inhibitory neurons responding to NaCN were –0.7 ± 0.1 mm ($n = 16$) and –0.6 ± 0.3 mm ($n = 8$) respectively. In the SNP respondents, the excitatory neurons were located in a significantly more anterior region than the inhibitory neurons ($P < 0.005$, Student's t-test). For both Mex and

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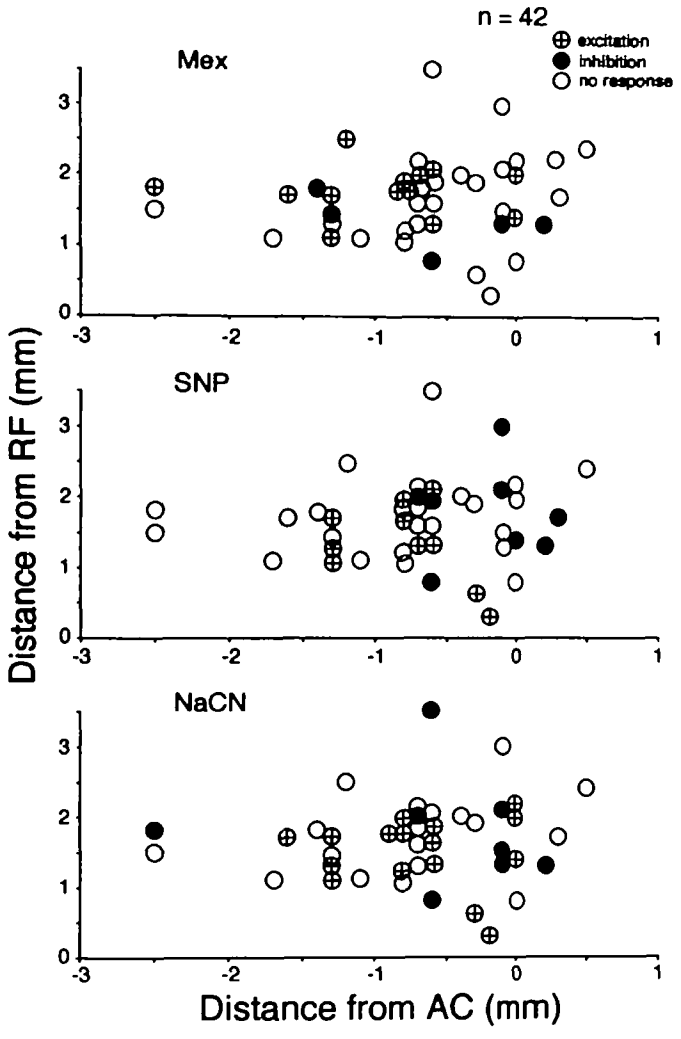

Figure 4 Distribution of the 42 neurons showing excitatory, inhibitory, or no response to i v application of Mex, SNP and NaCN The ordinate and abscissa show the distance from the RF and AC respectively In SNP, the excitatory neurons are distributed significantly more toward the anterior area than the inhibitory neurons ($P < 0$ 05, Student's t-test)

NaCN, however, there was no statistical difference in the anterior–posterior distribution between the excitatory and the inhibitory neurons ($P < 0.05$, Student's t-test). In the dorso-ventral axis, the mean location was 1.6 ± 0.1 mm ($n = 18$) for Mex, 1.5 ± 0.2 mm ($n = 18$) for SNP and 1.6 ± 0.1 mm for NaCN ($n = 24$). There was no significant difference among the three drugs in the dorso-ventral distribution [$F(2,57) = 0.17$, $P = 0.84$]. There was no significant difference in the dorso-ventral distribution between the excitatory and inhibitory neurons for both Mex and NaCN ($P > 0.05$, Student's t-test). However, the excitatory neurons (1.8 ± 0.1 mm) for Mex were located significantly more toward the dorsal position than the inhibitory neurons (1.3 ± 0.2 mm; $P < 0.05$, Student's t-test).

Discussion

Neurons in the anterior portion of the insular cortex respond to gustatory stimuli (Yamamoto *et al*, 1980, 1984; Kosar *et al.*, 1986; Ogawa *et al.*, 1990, 1992). According to Ogawa *et al.* (1990), the taste neurons seem to be distributed between 0.6 mm and 2.1 mm anterior to the AC in the anterior–posterior dimension. They adopted the bed nucleus of the anterior commissure (BNAC) as the standard point, which is located 0.6 mm posterior to the AC according to the atlas of the rat brain [Paxinos and Watson (1986); the presumed distance from the BNAC to the AC may not be correct for SD rats, since the atlas was made using the brain of Wistar rats]. In contrast, Cechetto and Saper (1987) recorded the neurons responding to baroreceptor and chemoreceptor stimulation in the area between 1.0 mm anterior and 0.5 mm posterior to the AC. In the present study, we recorded neuronal activity from the neurons in the region 2.5 mm anterior to 0.5 mm posterior to the AC. Although we attempted to record the neurons in the entire insular cortex, most neurons were distributed in the posterior insular cortex (mean location was 0.7 mm anterior to the AC, $n = 42$).

Cechetto and Saper (1987) recorded baroreceptor and chemoreceptor-sensitive neurons from the insular cortex; seven neurons were responsive to baroreceptor stimulation by an i.v. injection of phenylephrine hydrochloride (PE) and six to chemoreceptor stimulation by an i.v. injection of NaCN. In their results, most of the visceral-sensitive neurons responded specifically to either baroreceptor or chemoreceptor stimulation. Of 12 baroreceptor- and chemoreceptor-sensitive neurons, only one responded to both stimuli. Our results are somewhat different from those of Cechetto and Saper. We found 27 neurons that were responsive to baroreceptor (Mex) and/or chemoreceptor stimulation (NaCN). Of these 27 neurons, 15 (55.5%) responded to both baroreceptor and chemoreceptor stimulation, while the remaining 12 responded to one or the other stimulus. Therefore, more than half of the neurons obtained in the present study received convergent inputs from the baroreceptors and chemoreceptors. The differences may be due to several possible reasons. First, we sampled only the neurons that responded to electrical stimulation of the four nerves. Second, we used a high concentration dose of the NaCN (100 μg/0.1 ml) while Cechetto and Saper used a lower concentration (50 μg/0.1 ml). Further studies are needed to reach a conclusion about the degree of con-

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vergence in the insular cortex neurons from the baroreceptor and chemoreceptor afferents.

We previously found that the insular cortex neurons are responsive to electrical stimulation of the CT, LT–IXth, PH–IXth and SL nerves (Hanamori *et al.*, 1994), and the present study shows similar results. In the present study, the four oropharyngolaryngeal nerves were stimulated at the maximum intensity (Hanamori *et al.*, 1996). Thus, the responses of the insular cortex neurons are not only due to an activation of taste fibers but also other types of sensory fibers. In a previous study, we demonstrated that A-delta fibers (i.e. such as taste fibers and nociceptive fibers) in the LT–IXth, PH–IXth and SL nerves contribute to the cardiovascular responses elicited following repetitive electrical stimulation of these nerves (Hanamori *et al.*, 1996). From these results, it is supposed that afferents from the posterior tongue and pharyngolarynx play a role in autonomic regulation in the posterior insular cortex.

The neurons recorded in the present study were distributed mainly in the posterior region of the insular cortex where visceral information projects (Cechetto and Saper, 1987). Several researchers found that electrical stimulation of the posterior insular cortex elicits cardiovascular responses (Ruggiero *et al.*, 1987; Yasui *et al.*, 1991; Sun, 1992). These studies revealed that the posterior portion of the insular cortex can be further divided into the caudal and rostral areas, according to the cardiovascular responses following electrical stimulation of the insular cortex. Electrical stimulation of the caudal area of the posterior insular cortex induced a decrease in BP, while that of the rostral area of the insular cortex induced an increase in BP (Cechetto and Chen, 1990; Yasui *et al.*, 1991). Interestingly, in the present study, there was a difference in the responsiveness between rostral and caudal areas in the posterior insular cortex. That is, in SNP stimulation, the excitatory neurons were distributed more anteriorly in the posterior insular cortex, while the inhibitory neurons were distributed more posteriorly (Figure 4, SNP). Although we could not find a regional difference in sensitivity among the oropharyngolaryngeal nerves or drugs used in the present study, there is a possibility that more refined research can show a function-dependent localization in the posterior insular cortex.

In the present study, activity of most of the insular cortex neurons did not correlate to changes in BP (decrease or increase) as shown in Figure 2 (Mex, SNP). In addition, the similarity of the response profiles between Mex and SNP (r = 0.43) did not show a negative high value. Of the 26 neurons that responded to Mex and/or SNP, only 2 (7.7%) changed the discharges in the same direction as BP; an excitatory response when the BP was increased by an i.v. injection of Mex, and an inhibitory response when the BP was decreased by an i.v. injection of SNP. In eight neurons (8/26, 30.8%), changes in activity of the insular cortex neurons after Mex stimulation were in the same direction as those after SNP; most of the neurons (16/26, 61.5%) responded to either Mex or SNP. Similar results have been shown for the neural activity in the bed nucleus of the stria terminalis (Wilkinson and Pittman, 1995). In this study, the neural discharges were not always simply correlated with BP changes. Some neurons changed discharges only in one and the same direction in response to either direction of BP changes (see Figure 2). Our present study indicates that the neuronal activity in the insular cortex does not directly reflect the changes in baroreceptor activity.

In conclusion, most of the neurons distributed in the posterior insular cortex received convergent inputs from the oropharyngolaryngeal region, the baroreceptors and the chemoreceptors. It seems that the neurons in the posterior insular cortex have an important role in processing the various afferents in autonomic regulation. However, gustatory information, at least conveyed via the CT, seems to have little effect on the neuronal activity in the posterior insular cortex, since only a few neurons responded to the CT stimulation.

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