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Central Projections of Sensory Information Produced by Topical Application of Capsaicin to the Tongue in the Cat

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= ABSTRACT =

In order to elucidate whether capsaicin applied topically acts as a pain-producing subastance or as a tastant, neuronal activities of the chorda tympani nerve(CN), lingual nerve(LN), solitary tract nucleus (STN), and trigeminal nucleus(TGN) were recorded while thermal and taste stimuli, and capsaicin were being applied topically, and algesics intra-arterially to the tongue of cats anesthetized with α-chloralsoe. In addition, the STN neurons were examined after wheat germ agglutinin-horseradish peroxidase(WGA-HRP) was applied to the CN. The CN fibers responded to taste and thermal stimuli, algesics, and capsaicin. Responses to capsaicin were significantly correlated with those to taste and thermal stimuli. The LN fibers mainly responded to mechanical and thermal stimuli, algesics, and capsaicin. Responses to capsaicin were significantly correlated with those to algesics. The STN neurons responded to taste and thermal stiumli, algesics, and capsaicin. Responses to capsaicin were significantly correlated with those to taste and thermal stiumli in somewhat different fashion from those of the CN fibers. The TGN neurons mainly responded to mechanical stimuli, algesics, and capsaicin. Correlations between responses to capsaicin and any others were not significant. After WGA-HRP was applied to the CN, the STN neurons which receive input from the CN were identified largely in the medio-ventral portion to the solitary tract. These results suggest that capsaicin produce taste as well as pain sensation. Sensory information evoked by capsaicin can be conveyed to the STN, especially medio-ventral portion, via the CN as gustatory information on the one hand, and to the STN or TGN via the LN as noxious information on the other. In addiation, the noxious information may be conveyed to the STN via the CN.

Key Words: Capsaicin, Taste, Pain, Tongue.

INTRODUCTION

Capsaicin, the chemical compound which tastes hot while eating chili red peppers, has been known to show various biological actions. It produces numerous changes in the cardiovascular(Longhurst et al, 1980; Markara et al, 1967), respiratory(Coleridge & Coleridge, 1977; Markara et al, 1967), and digestive systems(Limlomwongse et al, 1979; Napanitaya, 1973). Furthermore, it destroys neural cells as a neural toxin(Jancso et al, 1977; Lawson & Nickels, 1980).

Capsaicin is also very irritant subastance on the skin and the mucous membrane. Capsaicin applied topically on the human skin or injected intradermally induces burning pain, hyperalgesia by lowering the threshold of pain for heat, and increases sensitivity to innocu-

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ous mechanical stiumlations(Becerra-Cabal et al, 1983; Simone et al, 1987). Electrophysiological studies indicate that capsaicin applied topically on the local portion of the body or injected intra-arterially activates the C-polymodal nociceptor and the warm receptor and sensitizes polymodal nociceptors for heat(Foster & Ramage, 1981; Szolcsanyi, 1977). When capsaicin is inhaled into the oral cavity of an animal, it evokes cough reflex which seems to be resulted from the activation of chemosensitive afferent C-fiber by the inhaled capsaicin(Forsberg & Karlsson, 1986; Jancso et al, 1977). Intrathecally injected capsaicin induces the response regarded as pain (Hunskaar et al, 1986) and the release of substance-P at the presynaptic terminals of the afferent sensory fibers in the spinal cord (Theriault et al, 1979). These studies indicate that capsaicin produces pain peripherally and induces hyperalgesia for heat which seem to be related to C-polymodal nocicptors.

In contrast to pain-producing and sensitizing effects, capsaicin is able to show desensitizing effects. When capsaicin is applied to the human skin or tongue repeatedly, it provokes rigorous irritation initially and then sensory nerve terminals gradually become insensitive to pain-producing chemical substances(Jancso, 1960, 1968; Jancso-Gabor & Szolcsanyi, 1969).

Although capsaicin seems to produce pain peripherally and to be related to the transmission of pain, it is not known at all that what is the substrate of the hot taste, the primary characteristic of capsaicin and the hot taste has not been classified into basic tastes. Thus, it is still unclear whether capsaicin acts as a pain-producing substance or as a tastant when applied topically on the tongue.

It is known that there are many nociceptors in the cat tongue from the fact that noxious heat stimulation of the tongue surface can cause significant discharge in single fibers of the lingual nerve(Naito et al, 1987a,b). Anatomically the information about pain is known to be transmitted to the trigeminal nucleus(TGN) in the central nervous system via the lingual nerve(LN), a branch of the trigeminal nerve, which innervates the tongue. The information about taste is transmitted to the solitary tract nucleus(STN) via the chorda tympani nerve(CN) which innervates the anterior two-thirds of the tongue. Therefore, if capsaicin produces pain on the tongue, the information of the pain would be transmitted to TGN. However if it acts as a tastant itself, the information of the taste would be transmitted to STN via CN. This study was performed to determine whether capsaicin acts as a pain-producing substance or as a tastant in the CN and LN peripherally and in the STN and TGN centrally through the electrophysiological technique. In addition, neuroanatomical study was conducted to confirm which portion of the STN receives the sensory information from the CN.

METHODS

Electrophysiological study

Animal preparation

Cats of 2.6~4.3 kg body wt were used as experimental animals. Animals were anesthetized with α-chloralose(60 mg/kg, i.m.). Trachea, cephalic vein, femoral artery, and arterial profunda of the tongue were cannulated for artificial ventialtion, intravenous injection, blood pressure monitor, and intra-arterial injection of pain-producing substances, respectively. The concentration of end-expiratory CO_2 was monitored on capnometer (Travers Medical Monitors, Model 2200) and maintained at 3.0~4.5 Vol%. Blood pressure was monitored from the femoral artery and maintained avove 90 mmHg. The body temperature was maintained at 37 ± 0.5°C with a heating blanket(Homeothermic Blanket Control Unit, Harvard apparatus Ltd.). An incision was made on the skin above mandible and the lingual and chorda tympani nerves were isolated. After operation, cats were mounted on the stereotaxic apparatus and immobilized with pancuronium bromide (Mioblock®).

Stimulation and recording procedure

Nerve recording: The incised skin was used to set up mineral oil pool in the exposed re-

gion by operation. In order to record from the CN or LN, the stimulating electrode was placed on the distal portion of the same nerve. Impulse discharges from nerve fibers were detected with platnium electrode, amplified with an AC differential amplifier (DAM-80, WPI), monitored on oscilloscope (TEK 5113), feeded into personal computer via interface(CED 1401) to draw post-stimulus time histograms(PSTHs). In addition, spikes were stored on video cassette recorder (VCR) via A/D VCR adaptor(PCM-2, Medical System) for further analysis.

Nucleus recording: Stimulating electrode was placed on the CN or LN for recording from the STN or TGN, respectively. To stimulate the CN, the LN was cut and to stiumlated the LN, the CN was cut with a microscissor. Occipital craniotomy was performed and the cerebellum was retracted forward to exposes the medulla beneath the cerebellum.

Action potentials of the STN and TGN neurons were recorded with glass micropipettes filled with 3M NaCl and 2% pontamine sky blue, amplified and analysed with the conventional amplification and analysis system.

Experiment procedure: After the activities of nerves or neurons were identified with electrical stimulation, mechanical stimulation with a glass rod, chemical stimulation with algesic substances injected into the arteria profunda of the tongue, thermal stimulation with various degrees of washing water, and taste stimulation were treated sequentially.

The algesic substances were KCl(3.3 mg/0.25 cc) and bradykinin (25 ug/0.25 cc). The taste solutions were: Sucrose(Suc; 0.5, 1.0 M), NaCl(0.5, 1.0 M), quinine-hydrochloride(Q-HCl; 0.05 M), HCl(0.1 N), and capsaicin(Cap; 0.1%). Each stimulation was about 5 ml of a test solation passed by gravity flow from syringe and was followed 1~2 min. later by washing water.

Histology: After completion of recording from a neuron, a cathodal current(5~20 uA, 20 min.) was passed through the recording electrode in order to deposit a dye mark. At the end of the experiment, the animal was deeply anesthetized with sodium pentobarbital and the brain was perfused with saline through the ascending aorta and fixed by 10% formalin. Serial frozen sections were cut frontally at 40 μm thick and stained with Cresyl violet. Subsequently, the dye marks were located by microscopic examination.

Histological study.

After the CN was exposed, the distal portion of the CN was cut, crushed, and soaked in a tube which was filled with 3% horseradish peroxidase conjugated with wheat germ agglutinin(WGA-HRP) dissolved in 0.1 M phosphate buffer(pH 7.4) and was enveloped with grease at each opening.

After a survival period of 48 hours, the cats were deeply anesthetized and perfused through ascending aorta with 200 ml of physiological saline and 100 ml of a mixture of 1% of paraformaldehyde and 1.5% glutaraldehyde in 0.1 M phosphate buffer(pH 7.4). The brain was then removed, saturated with a cold solution of 30% sucrose in the same solution, and serially cut into frontal sections of 40 um thickness on a freezing microtome (CRYOCUT, AO). For the histochemical demonstration of HRP, the sections were treated with tetramethylbenzidine(Mesulam, 1978). After the enzyme reaction was completed, sections were mounted onto gelatinized slides, and one series from each brain was rapidly counterstained with safranin. The distribution of labeled cells and nuclear borders was plotted in detail on each diagram with the aid of a camera lucida.

RESULTS

Electrophysiological study

Nerve recording: A total of 25 CN and 19 LN fibers were used in the analysis. Response characteristics of the CN and LN fibers are shown in Table 1. Most of the CN fibers (83.33%; 20 out of 24 fibers) responded to taste stimuli and many CN fibers(52.17%; 12 out of 23 fibers) responded to capsaicin(Fig. 1 A, B). The CN fibers also responded to mechanical(36.84%), thermal stimulation(45.45 %; 10 out of 22 fibers), and algesics injected

Table 1. Responses of chorda tympani and lingual nerves to mechanical, thermal, and chemical stimulations applied to the tongue

		Mech	Thermal		Taste				Cap	Alg
			40°C	4°C	NaCl	Suc	Q-HCl	HCl		
Chorda Tympani Nerve	Res	7	6	9	13	10	8	9	12	6
	No-Res	12	15	13	11	14	10	8	11	11
	Total	19	21	22	24	24	18	17	23	17
Lingual Nerve	Res	18	4	5	2	2	2	2	5	5
	No-Res	0	4	4	10	10	5	5	14	2
	Total	18	8	9	12	12	7	7	19	7

Each number denotes the number of nerve fibers. Mech: mechanical, Alg: algesics applied intra-arterially, Res: response, No-Res: no-response.

intra-arterially(35.29%). All the LN fibers which were tested responded to mechanical stimulation(Fig. 1 C). Large proportion of the LN fibers responded to capsaicin(26.32%), thermal stimulation(60%; 6 out of 10 fibers), and algesics(71.43%). A few LN fibers responded to taste stimuli(16.67%; 2 out of 12 fibers).

Although both the CN and LN fibers responded to capsaicin, correlation coefficients between responses to capsaicin and other criteria including responses to taste and thermal stimulation and to intra-arterial injection of algesics, conduction velocity produced by electrical stimulation, and spontaneous discharges, were calculated in terms of peak discharges in order to determine the characteristics of responses to capsaicin. Fig. 2 A shows the correlation coefficients between responses to capsaicin and various classes of neuronal activities and conduction velocity in the CN fibers. Responses to capsaicin were significantly correlated with spontaneous activity($r=.85$, $t(21)=7.39$, $p<.001$),those to thermal stimulation, 40°C($r=.76$, $t(17)=4.82$, $p<.001$), and taste stimulation including NaCl($r=.68$, $t(20)=4.15$ $p<.001$), sucrose($r=.64$ $t(20)=3.72$, $p<.01$), and Q-HCl($r=.87$, $t(16)=7.06$, $p<.001$). Correlation coefficient between responses to capsaicin and algesics was .36 which was not significant($t(15)=1.49$, $p>.10$). The correlation cefficients between responses to capsaicin and various classes of neuronal activities and conduction velocity in the LN fibers are shown in Fig. 2 B. Responses to capsaicin was significantly correlated with those to algesics injected into the tongue intra-arterially($r=.78$, $t(5)=2.79$, $p<.05$).

Nucleus recording: Fig. 3 shows the recording sites in both the STN and TGN. All of the neurons in the STN and TGN were identified to receive input from the CN and LN respectively by electrical stimulation of the nerves in advance. A total of 34 STN and 17 TGN neurons were used in the analysis. Response characteristics of the STN and TGN neurons are shown in Table 2. The STN neurons responded to not only taste(58.62%; 17 out of 29 neurons) and thermal stimulation(33.33%; 3 out of 9 neurons), and capsaicin(33.33%), but also mechanical stimulation(20%) and algesics(54.84%)(Fig. 4 A). The TGN neurons responded to algesics(52.94%) in similar extent to STN neurons, but the higher proportion of the TGN neurons responded to capsaicin(52.94%) and mechanical stimulation (52.94%). Fig. 4 B shows responses of a TGN neuron to capsaicine and an algesic. A few TGN neurons responded to thermal(18.18%; 2 out of 11 neurons) and taste stimulation (28.57%; 4 out of 14 neurons).

In order to see the characteristics of responses to capsaicin, correlation coeefficients between responses to capsaicin and other criteria in the STN and TGN neurons were calculated. The correlation coefficients in the STN neurons are shown in Fig. 5 A. Responses to capsaicin were significantly correlated with those to thermal stimuli, 40°C($r=.70$, $t(7)=2.59$, $p<.05$) and 4°C($r=.77$, $t(7)=3.19$, $p<$

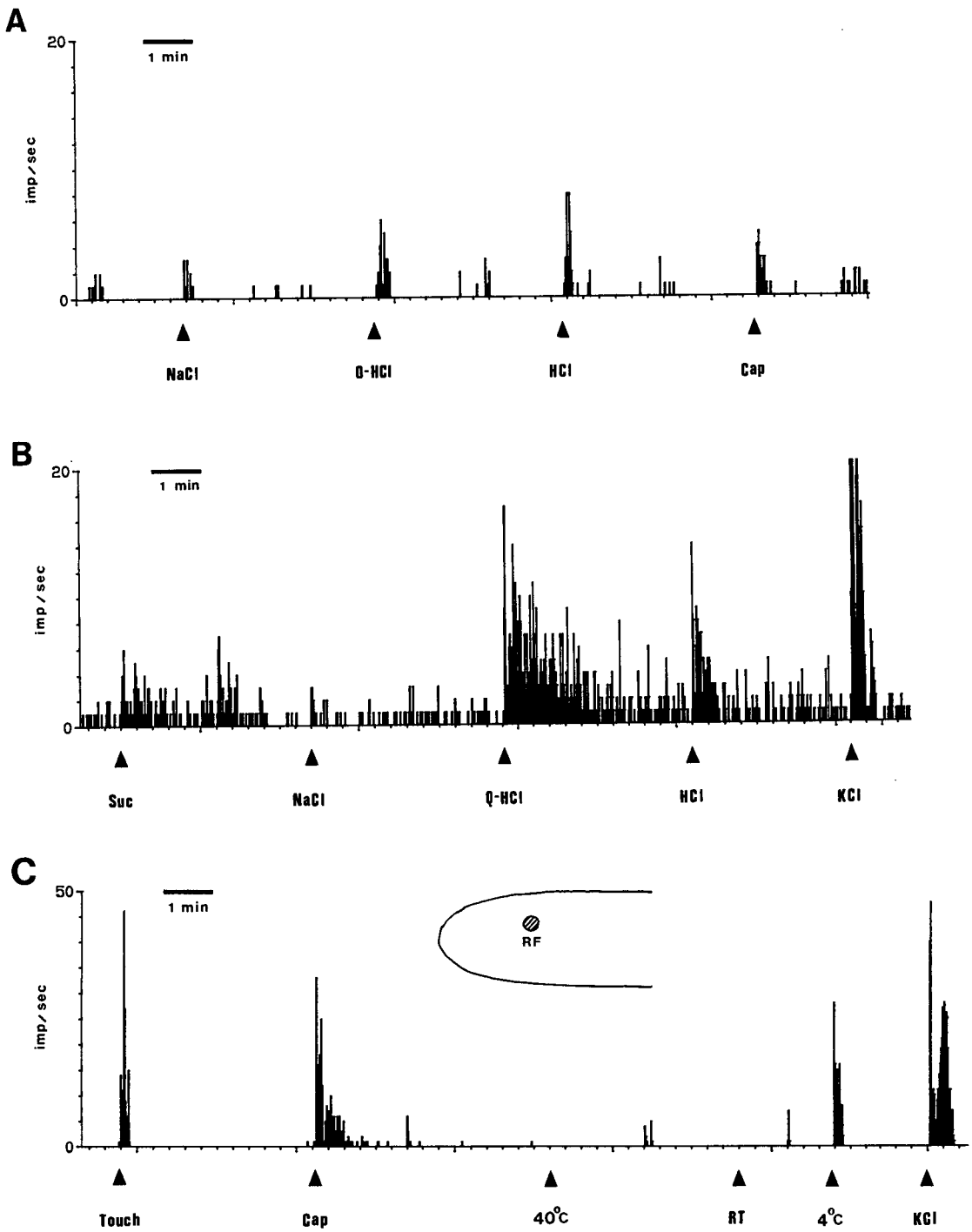

Fig. 1. Unit activities of the chorda tympani nerve(CN) and lingual nerve(LN) during stimulation of the togue. A and B: responses of 2 CN nerves to taste stimuli, capsaicin, and KCl, an algesic. C: responses of an LN to mechanical(Touch) and thermal stimuli, capsaicin, and KCl. Suc; sucrose, RT: room temperature. Hatched line reveals receptive field(RF) to mechanical stimulation.

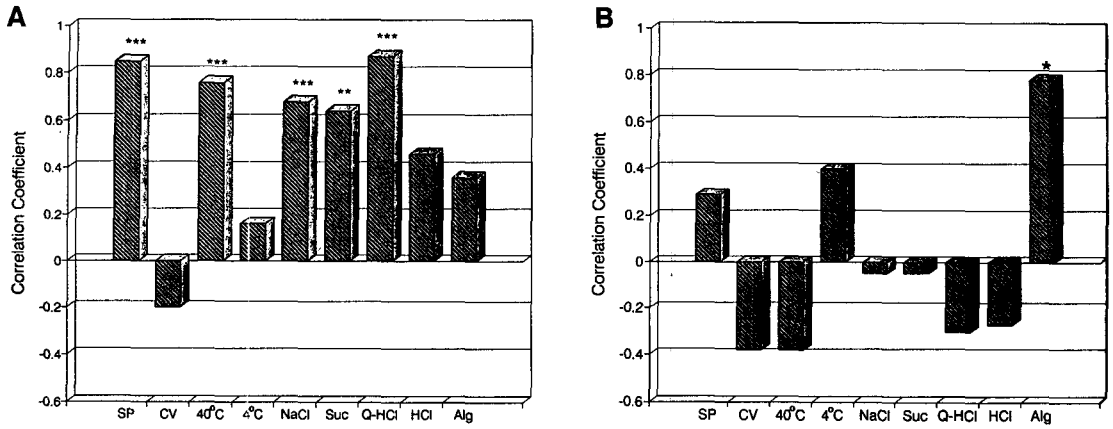

Fig. 2. Correlation coefficients between responses to capsaicin and other criteria in the chorda tympani(A) and lingual nerves(B). Correlation coefficients were calculated by Pearson's product moment method from the impulse counts of individual neurons in terms of peak discharges. SP: spontaneous discharges, CV: Conduction velocity, Alg: algesics applied intra-arterially.

* *significant at 0.05(Student t test)*

** *significant at 0.01(Student t test)*

*** *significant at 0.001(Student t test)*

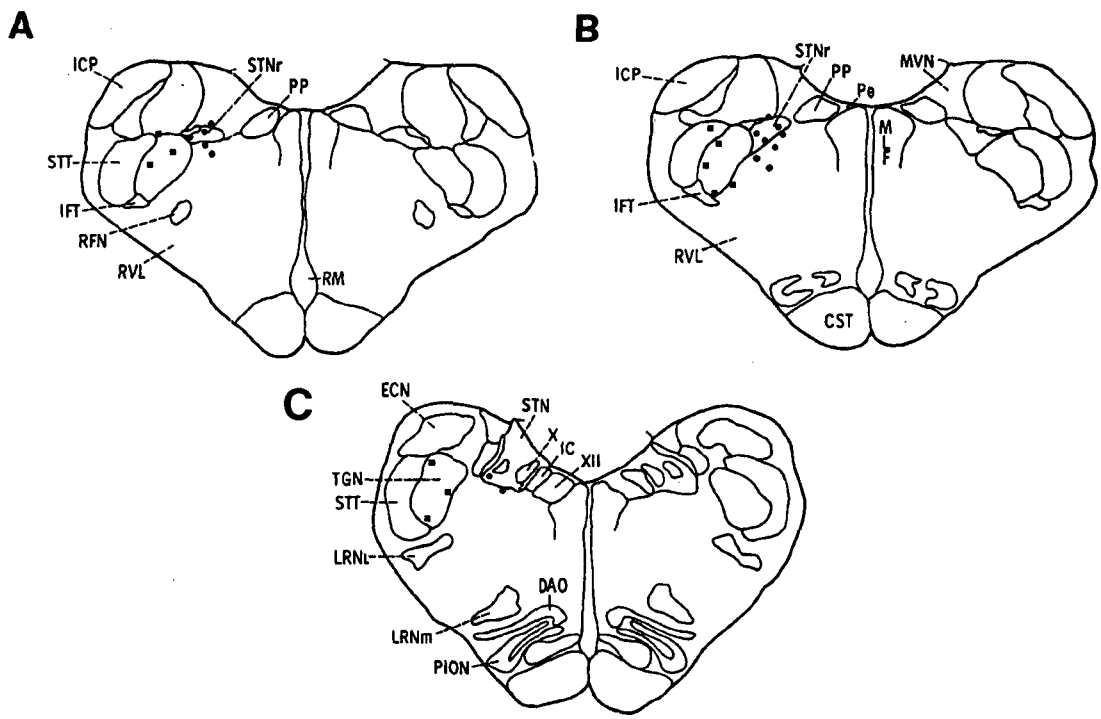

Fig. 3. Camera lucida drawings of recording sites in the solitary tract nucleus(STN) and trigeminal nucleus (TGN). Filled circles and squares indicate the sites in the STN and TGN, respectively. A: rostral, B: middle, C: caudal portions.

Table 2. Responses of the STN and TGN neurons to mechanical, thermal, and chemical stimulations applied to the tongue

		Mech	Thermal		Taste				Cap	Alg
			40°C	4°C	NaCl	Suc	Q-HCl	HCl		
Solitary Tract Nucleus	Res	3	1	2	8	6	6	7	9	17
	No-Res	12	8	7	20	23	21	20	18	14
	Total	15	9	9	28	29	27	27	27	31
Trigeminal Nucleus	Res	9	1	1	1	2	2	2	9	9
	No-Res	8	10	10	13	12	12	12	8	8
	Total	17	11	11	14	14	14	14	17	17

Each number denotes the number of neurons. Mech: mechanical, Alg: algesics applied intra-arterially, Res: response, No-Res: no-response.

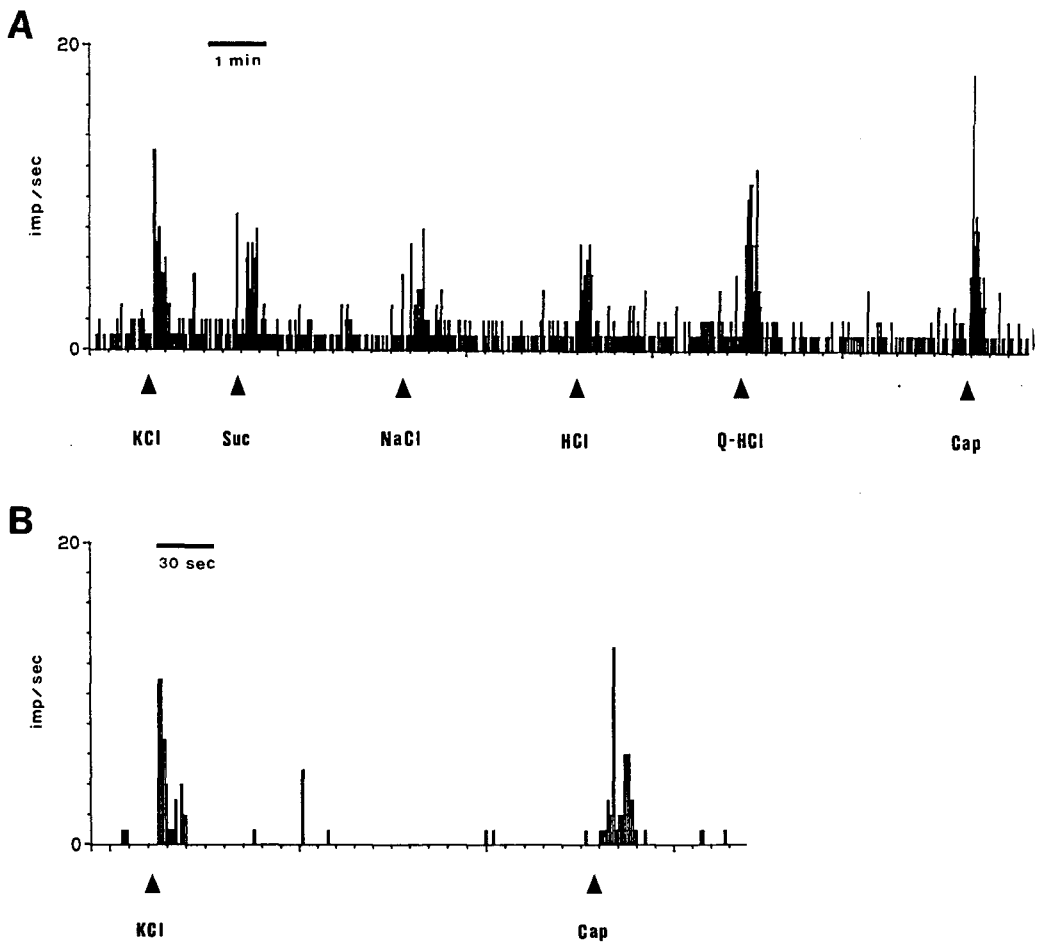

Fig. 4. Unit activities of the solitary tract nucleus(STN) and trigeminal nucleus(TGN) during stinulation of the tongue. A: responses of an STN neuron to taste stimuli, capsaicin, and KCl, an algesic. B: responses of a TGN neuron to capsaicin and KCl. Suc: sucrose, Q-HCl: quinine-HCl, Cap: capsaicin.

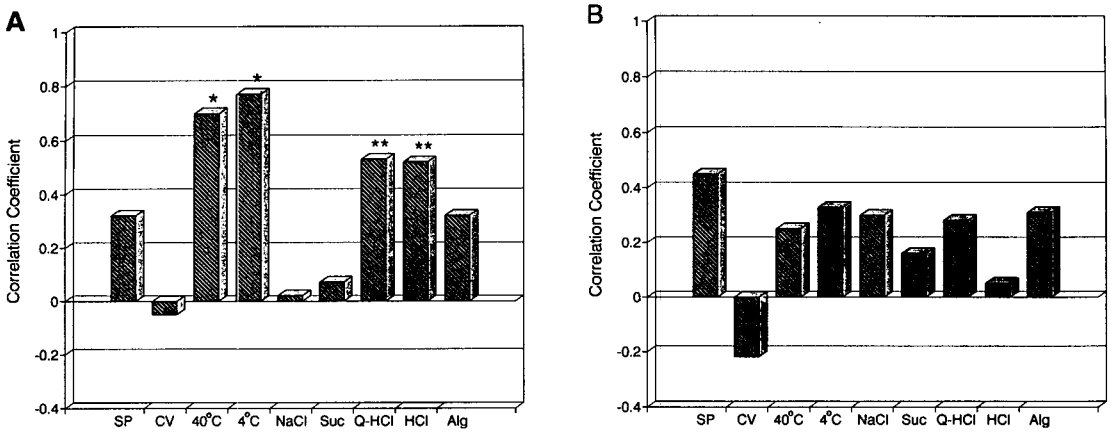

Fig. 5. Correlation coefficients between responses to capsaicin and other criteria in the solitary tract nucleus (A) and trigeminal nucleus(B). Correlation coefficients were calculated by Pearson's product moment method from the impulse counts of individual neurons in terms of peak discharges. SP: spontaneous discharges, CV: conduction velocity, Alg: algesics applied intra-arterially.

** significant at 0.05(Student t test)*

*** significant at 0.01(Student t test)*

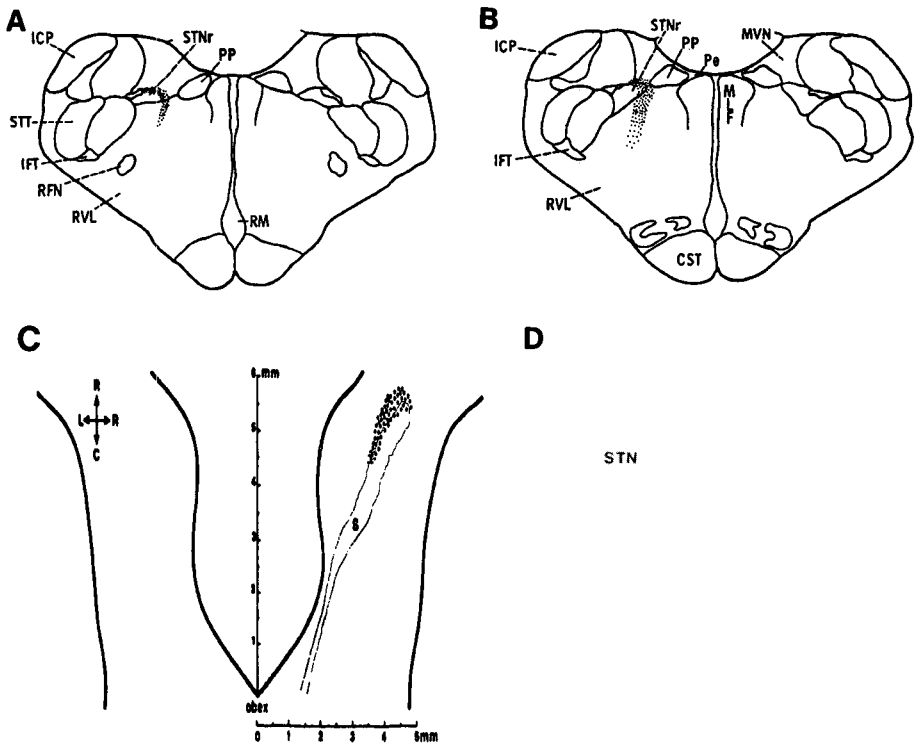

Fig. 6. Camera lucida drawings of WGA-HRP labeled neurons. A: rostral, B: caudal portions. C: horizontal diagram. D: photograph of labeled cell bodies(×250).

.05), and taste stimuli, Q-HCl($r=.53$, $t(25)=3.13$, $p<.01$) and HCl($r=.52$, $t(25)=3.04$, $p<.01$). Correlation coefficient between responses to capsaicin and algesics was .32 which was not signficant($t(22)=1.58$ $p>.10$) as was in the CN fibers. Fig. 5 B shows the correlation coefficients between responses to capsaicin and various classes of neuronal activities and conduction velocity in the TGN neurons. Responses to capsaicin were not significantly correlated with any other criteria(in all the cases, $p>.20$).

Histological study

The present histological study aims to reveal fiber connections of the CN with the STN. We tried to observe the cell bodies of post synaptic neurons in the STN rather than presynaptic terminals themselves of the CN, because presynaptic terminals are the same neurons as the CN and WGA-HRP is known to be transported trans-synaptically. The pattern of distribution of WGA-HRP-labeled central components was quite similar among all animals used in the present study. The resulting data are summarized in Fig. 6. In the STN of cats, labeled neuronal cell bodies were seen ipsilaterally. These labeled cell bodies were distributed in the rostral STN and adjacent areas, especially medullary reticular formation. In the caudal part(Fig. 6 B) rather than rostral part(Fig. 6 A) of labeled areas, the more labeled neuronal cell bodies were observed in the subjacent reticular regions. Labeling was extended 1.5~1.6 mm rostro-caudally(Fig. 6 C). Fig. 6 D shows a photograph of representative labeled cell bodies.

DISCUSSION

Capsaicin produces a burning sensation when applied to the apex(anterior) but not when applied to the radix(posterior) of the human tongue(Duner-Engstrom et al, 1986). In order to elucidate whether capsaicin acts as a pain-producing substance or as a tastant when it is applied topically on the tongue, our experiments were performed in the CN, LN, STN, and TGN, because the CN and LN innervate the anterior tongue and project to the STN and TGN, respectively.

In the present study, most of the CN fibers responded to various tastants and capsaicin. The responses to capsaicin were significantly correlated with those to tastants. This indicates that capsaicin could act as a tastant. Some CN fibers were also activated thermally but relatively few could be activated mechanically. These were consistent with the findings of Ogawa et al(1968) and Boudreau et al (1971). The responses to capsaicin were significantly correlated with those to warm stimulation but not those to cold stimulation. This may suggest that capsaicin seems to play a role in burning sensation resulting from topical application. The CN fibers also responded to algesics injected intra-arterially, although the correlation coefficient between responses to capsaicin and algesics was not significant. The LN fibers, on the other hand, are sensitive to primarily tactile aspects of stimuli, including thermal and nociceptive sensitivity (Biedenbach & Chan, 1971; Naito et al, 1987a,b). This is confirmed by the present data. Responses to capsaicin were significantly correlated with those to algesics. This suggest that capsaicin can produce pain sensation that can be transmitted via the LN. Very rarely the LN fibers responded to tastants. This seems to be explained by the evidence that only strong chemical stimuli will cause them to respond(Hellekant, 1965; Kawamura et al, 1968).

The STN neurons responded to taste, thermal and mechanical stimulation, capsaicin, and algesics. But there were certain changes. Responses to capsaicin were significantly correlated with those to warm stimulation and Q-HCl as with the CN. However, there was no significant correlation between responses to capsaicin and those to NaCl and sucrose but correlation coefficient between responses to capsaicin and those to cold stimulation and HCl became significant. Responses to algesics were still insignifcantly correlated with those to capsaicin. These indicate that the sensory information produced by capsaicin seems to be that of taste. Yet, the matter is somewhat complex because i) correlation between res-

ponses to capsaicin and those to thermal and taste stimulation changed in the STN, compared to those of the CN, and ii) correlation between capsaicin and algesics in the TGN disappeared, contrary to the LN.

Firstly, according to the anatomical study (Whitehead and Frank, 1983), the STN is not a simple relay station which transmits taste information up to the higher-order nuclei, but there are a lot of branches of the taste afferents and fiber connections within the STN, indicating the possibility of convergence of NaCl, HCl, and Quinine inputs on single STN neurons. More recent neurophysiological evidence shows that gustatory afferents innervating different areas of the oral cavity converge onto single neurons in the STN(Sweazey & Smith, 1987). These findings indicate that response patterns of the STN may be different from those of the CN. For example, the correlation coefficient between Q-HCl and HCl is. 84 in the CN but .67 in the STN in the present study. Frank et al.(1983) reported .83 of the correlation coefficinet between the pairs of the same stimuli in the CN of the rat. In the experiment with monkey, the correlation coefficient between the patterns of activity evoked by Q-HCl and HCl was .60 in the STN (Scott et al, 1986).

Secondly, despite their similar peripheral distribution to the anterior tongue, the CN and the LN project predominantly to separate areas in the medulla - the STN and the TGN complex, respectively. However, anatomical studies in various species, using the Nauta method and autoradiography, described a substantial trigeminal input to the solitary nucleus(Contreras et al, 1982; Torvik, 1956, in rat; Beckstead & Norgren, 1979, in monkey). Responses to electrical stimulation of the lingual branch of the trigeminal nerve in the rat have been localized electrophysiologically within a region of the STN which also responds to electrical stimulation of the chorda tympani(Blomquist & Antem, 1965). Similarly, neural responses in the STN of the rat could be elicited by thermal and tactile as well as gustatory stimulation of the anterior tongue(Halpern & Nelson, 1965). Single unit analyses in the rodent have identified neurons in the STN which respond to stimulation of both the chorda tympani by tastants and the trigeminal afferents from the nose and tongue by chemical and tactile stimuli, respectively (Erickson, 1958; Van Buskirk & Erickson, 1977a,b). As the LN was cut when the CN was stimulated and vice versa, there is no possibility that both nerves were excited electrically during the experiment. However, when we recorded neuronal activities in the TGN, it is possible that noxious information produced by capsaicin was transmitted to the STN via the LN. This may explain the disappearance of correlation between capsaicin and algesics in the TGN.

In the histolgical study, we observed medullary neurons to receive the input from the CN. They were located in the medial and ventral portions of the solitary tract. Many labeled neurons were found in the subjacent reticular formation. Nomura and Mizuno(1981) examined central distribution of the CN in the cat like the present study. They found that the CN afferents enter the solitary tract and run caudally as far as the levels slightly rostral to the obex. On descending in the solitary tract, the HRP-labeled CN afferents appeared to end in the STN; in the whole extent of the nucleus at the rostral levels, mainly in the ventrolateral and dorsomedial portions of the STN at the middle levels, and in the lateral portions of the STN at the levels of the area postrema. Besides the last portion, the location of labeled neurons is similar to the present study. However, we found the labeled cell bodies in more medial portions. As they used HRP rather than WGA-HRP, they could not find post-synaptic cell bodies. In the present, more medial and ventral neurons would be labeled with WGA-HRP by trans-neural transport. But the possibility that cell bodies of the CN efferents were labeled in part can not be excluded.

Taken together, capsaicin could produce taste as well as pain sensation. Sensory information evoked by capsaicin applied topically to the tongue can be conveyed to the STN, especially medio-ventral portion, via the CN as gustatory information on the one hand, and to the STN or TGN via the LN as noxious infor-

mation on the other. In addition, the noxious information may be conveyed to the STN via the CN. But the matter might be more complicate. In order to elucidate the nature of capsaicin, further studies in the each level of sensory processing system in the brain would be required.

Abbreviation

CST	Corticospinal tract	Pe	Periventricular gray
DAO	Dorsal accessory olive	PION	Principal lamellae of inferior olive
ECN	External cuneate nucleus		
IC	Nucleus intercalatus	PP	nucleus prepositus
ICP	Inferior cerebellar peduncle	RFN	Retrofacial nucleus
IFT	Infratrigeminal nucleus	RM	Raphe magnus
LRN_L	Lateral reticular nucleus, lateral limb	RVL	Rostral ventrolateral medulla
LRNm	Lateral reticular nucleus, medial limb	s	Solitary tract
MLF	Medial longitudinal fasciculus	TGN	Spinal trigeminal nucleus
MVN	Medial vestibular nucleus	STT	Spinal trigeminal tract
STN	Solitary tract nucleus	X	Dorsal motor nucleus of vagus
STNr	Solitary tract nucleus pars rostralis	XII	Hypoglossal nucleus

REFERENCES

Becerra-Cabal L, LaMotte RH, Ngeow JYF & Putterman GJ(1983) Chemically induced itch, pain and hyperalgesia by intraepidermal injection. *Soc Neurosci Abstr* **9,** 1063

Beckstead M & Norgren R(1979) An autoradiographic examination of the central distribution of the trigeminal, facial, glossopharyngeal, and vagal nerves in the monkey. *J comp Neurol* **184,** 455-472

Biedenbach MA & Chan KY(1971) Tongue mechanoreceptors: Comparison of afferent fibers in the lingual nerve and chorda tympani. *Brain Res* **35,** 584-588

Blomquist AJ & Antem A(1965) Localization of the terminals of the tongue afferents in the nucleus of the solitrary tract. *J Comp Neurol* **124,** 127-130

Boudreau JC, Badley BE, Bierer PR, Kruger S & Tsuchitani C(1971) Single unit recordings from the geniculate ganglion of the facial nerve of the cat. *Exp Brain Res* **13,** 461-488

Coleridge JC & Coleridge HM(1977) Afferent C-fibers and cardiorespiratory chemoreflexes. *Am Rev Respir Dis* **115,** 251-256

Contreras RJ, Beckstead RM & Norgren R(1982) The central projections of the trigeminal, facial, glossopharyngeal and vagus nerves: An autoradiographic study in the rat. *J Auton Nerv Sys* **6,** 303-322

Duner-Engstrom M, Fredholm BB, Larsson O, Lundberg JM & Saria A(1986) Autonomic mechanism underlying capsaicin induced oral sensations and salivation in man. *J Physiol* **373,** 87-96

Erickson RP(1958) Responsiveness of single second order neurons in the rat to tongue stimulation. Ph D. Dissertation, Brown University. Cited in Van Buskirk RL & Erickson RP (1977b) Odorant responses in taste neurons of the rat NTS. *Brain Res* **135,** 287-303

Forsberg K & Karlsson JA(1986) Cough induced by stimulation of capsaicin-sensitive sensory neurons in conscious guineapigs. *Acta Physiol* **128,** 319-320

Foster RW & Ramage AG(1981) The action of some chemical irritants on somatosensory receptors of the cat. *Neuropharmachology* **20,** 191-198

Frank ME, Contreras RJ & Hettinger TP(1983) Nerve fibers sensitive to ionic taste stimuli in

chorda tympani of the rat. *J Neurophysiol* **50,** 941-960

Halpern BP & Nelson LM(1965) Bulbar gustatory responses to anterior and to posterior tongue stimulation in the rat. *Am J Physiol* **209,** 105-110

Hellekant G(1965) The effect of ethyl alcohol on non-gustatory receptors of the tongue of the cat. *Acta Physiol Scand* **65,** 243-250

Hunskaar S, Post C, Fasmer OB & Arwestrom E (1986) Intrathecal injection of capsaicin can be used as a behavioral nociceptive test in mice. *Neuropharmacology* **25,** 1149-1153

Jancso N(1960) Role of the nerve terminals in the mechanism of inflammatory reactions. *Bull Millard Fillmore Hosp*(Buffalo, N.Y.) **7,** 53-77

Jancso N(1968) Desensitization with capsaicin and related acylamides as a tool for studying the function of pain receptors. In: *Pharmacology of pain.* Pergamon press, Oxford and New York p 33-55

Jancso G, Kiraly E & Jancso-Gabor A(1977) Pharmacologically induced selective degeneration of chemosensitive primary sensory neurons.*Nature(London)***270,** 741-743

Jancso-Gabor A & Szolcsanyi(1969) The mechanism of neurogenic inflammation. In: Bertelli A & Houck JC(ed) *Inflammation, biochemistry and drug interaction.* Excerpta Medica Foundation, Amsterdam, pp. 210-217

Kawamura Y, Okamoto J & Funakoshi M(1968) A role of oral afferents in aversion to taste solution. *Physiol Behav* **3,** 537-542

Lawson SN & Nickels SN(1980) The use of morphometric techniques to analyse the effect of neonatal capsaicin treatment of rat dorsal root ganglia and dorsal roots. *Proc Phys Soc Fed* 19P

Limlomwongse L, Chaitauchawong C & Tongyai S(1979) Effect of capsaicin on gastric acid secretion and mucosal blood flow in the rat. *J Nutr* **109,** 773-779

Longhurst JC, Achgton JH & Iwamoto GH(1980) Cardiovascular reflexes resulting from capsaicin stimulated gastric receptors in anesthetized dogs. *Circ Res* **46,** 780-785

Markara GB, Gyorgy L & Molnar J(1967) Circulatory and respiratory responses to capsaicin, 5-hydroxytryptamine and histamine in rats pretreated with capsaicin. *Arch Int Pharmacodyn* **170,** 39-44

Mesulam MM(1978) Tetramethyl benzidne for horseradish peroxidase neurohistochemistry. A noncarcinogenic blue reaction-product with superior sensitivity for visualizing neural afferents and efferents. *J Histochem Cytochem* **26,** 106-117

Naito K, Hanashima N, Kagaya K, Iwata K, Kamogawa H & Sumino R(1987a) Responses of the lingual nerve afferents to thermal, mech anical and chemical stimulation on the tongue. *J Physiol Soc Japan* **49,** 474

Naito K, Iwata K, Kagaya K, Kamogawa K, Mexawa S & Sumino R(1987b) Thin fiber receptors responding to mechanical, chemical and thermal stimulation in the cat tongue. *Pain suppl* **4,** 269

Napanitaya W(1973) Long-term effects of capsaicin on fat absorpation and the growth of the rat. *Growth* **37,** 269-275

Nomura S & Mizuno N(1981) Central distribution of afferent and efferent components of the chorda tympani in the cat as revealed by the horseradish Peroxidase method. *Brain Res* **214,** 229-237

Ogawa H, Sato M & Yamashita S(1968) Multiple sensitivity of chorda tympani fibers of the rat and hamster to gustatory and thermal stimuli. J *Physiol(London)* **199,** 223-240

Scott TR, Yaxley S, Sienkiewicz ZJ & Rolls ET (1986) Gustatory responses on the nucleus tractus solitrarius of the alert cynomogus monkey. *J Neurophysiol* **55,** 182-200

Simone DA, Ngelow JYF, Putterman GJ & LaMotte RH(1987) Hyperalgesia to heat after intradermal injection of capsaicin. *Brain Res* **418,** 201-203

Sweazey RD & Smith DV(1987) Convergence onto hamster medullary taste neurons. *Brain Res* **408,** 173-184

Szolcsanyi J(1977) A pharmachological approach to elucidation of the role of different nerve fibers and receptor endigns in mediation of pain. *J Physiol(Paris)* **73,** 251-259

Theriault E, Otsuka M & Jessel TM(1979) Capsaicin evoked release of substance P from primary sensory neurones. *Brain Res* **170,** 209-213

Torvik A(1956) Afferent connections to the sensory trigeminal nuclei, the nucleus of the solitary tract and adjacent structures. An experimental study in the rat. *J Comp Neurol* **106,** 51-132

Van Buskirk RL & Erickson RP(1977a) Responses in the rostral medulla to electrical

stimulation of an intranasal trigeminal nerve: Convergence of oral and nasal inputs. *Neurosci Lett* **5**, 321-326

Van Buskirk RL & Erickson RP(1977b) Odorant responses in taste neurons of the rat NTS. *Brain Res* **135**, 287-303

Whitehead MC & Frank ME(1983) Anatomy of the gustatory system in the hamster: Central projections of the chorda tympani and the lingual nerve. *J Comp Neurol* **220**, 378-395