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Parabrachial Unit Activities After the Acquisition of Conditioned Taste Aversion to a Non-preferred HCl Solution in Rats

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Abstract

In a behavioral experiment, rats reliably acquired a taste aversion to non-preferred 0.01 M HCl that had been previously paired with intraperitoneal injection of 0.15 M LiCl. These rats showed aversions to other acidic solutions such as malic acid and tartaric acid. In a neurophysiological experiment, the neuronal activities of the parabrachial nucleus (PBN) were recorded after the acquisition of conditioned taste aversion (CTA) to 0.01 M HCl in urethane-anesthetized rats. Neuronal responses to the conditioned stimulus (CS) did not change on the whole but decreased in the dorsal region to the brachium conjunctivum. The proportion of HCl-best to NaCl-best units was lower in the CTA group than in controls. The spontaneous firing rate was lower in the CTA group than in controls. Correlation coefficients between the HCl CS and normally preferred tastes (sucrose and NaCl) were more negative and those between HCl and quinine were more positive in the CTA group than in the controls. These results may be explained by the notion that gustatory responses of PBN neurons are concerned with alterations in taste hedonics after the acquisition of conditioned taste aversions.

Introduction

When consumption of a taste substance is followed by visceral malaise, animals avoid ingesting this substance on future occasions. This behavior is based on a biologically salient learning called a conditioned taste aversion (CTA), and plays an important part for the animal's survival (Bures *et al*., 1998). Several lines of evidence have shown that the pontine parabrachial nucleus (PBN), the second gustatory relay in rodents, is critically involved in the formation of CTA. Bilateral electrolytic (Di Lorenzo, 1988; Spector *et al.*, 1992; Reilly *et al.*, 1993; Sakai and Yamamoto, 1998) or ibotenic acid lesions (Scalera *et al*., 1995; Yamamoto *et al*., 1995; Grigson *et al*., 1997b, 1998) thoroughly disturbed the acquisition of CTA. Intracerebral injections of several chemicals (Ivanova and Bures, 1990; Bielavska and Krivanek, 1994; Sacchetti and Bielavska, 1998; Gallo *et al*., 1999) in the PBN impaired the formation of CTA. Although these results suggest that the integrity of the PBN is required for the acquisition of CTA, it is still unclear how taste information is processed in the PBN for the establishment of CTA. Previously, we reported that PBN neuronal responses are more salient to the conditioned stimulus (CS) in conditioned animals than in unconditioned control animals (Shimura *et al.*, 1997b). Several studies also reported a similar modification in the responsiveness to the CS in other gustatory areas (Aleksanyan *et al*., 1976; Buresova *et al*., 1979; Chang and Scott, 1984; Di Lorenzo, 1985; Yamamoto *et al*., 1989; Yasoshima *et al*., 1995; Yasoshima and Yamamoto, 1998). However, it should be noted that the CS used in those studies were normally preferred taste solutions such as saccharin or NaCl. It is believed that the taste quality seems to contribute to its adequacy as a cue for a learned taste aversion (Kalat and Rozin, 1970; Nowlis *et al*., 1980). In fact, it has been documented that the aversion is much stronger to a non-preferred CS than to a preferred CS (Etscorn, 1973; Massey and Calhoun, 1977). In contrast, it was reported that rats failed to acquire an aversion to non-preferred citric acid as the CS (Brackbill *et al*., 1971). These results indicate that the neural mechanisms underlying the CTA may be different between naturally preferred and non-preferred tastes. To examine the possibility, we examined the characteristics of CTA to a non-preferred sour taste using a behavioral experiment, then compared the firing patterns of PBN neurons in response to various taste stimuli in rats previously conditioned to non-preferred HCl with those of unconditioned control rats.

Experiment 1

Materials and methods

Twelve male Wistar rats (230–260 g) were used. They were divided into two groups and habituated to a schedule with

access to one bottle of fluid for 15 min in a test box for 5 days. On day 6, each rat in the experimental group (n = 6) was given 20-min access to 0.01 M HCl (CS) in the home cage and then injected with 0.15 M LiCl (2% of body wt, i.p.). The other rats (n = 6) were given 20-min access to distilled water in the home cage and then injected with saline (2% of body wt, i.p.). On day 7, all the rats were retrained to drink distilled water for 15 min in the test box. On days 8–10, 15 taste solutions and distilled water were randomly presented for 10 s to each rat in the test box and the number of licks to each solution was counted. We used 15 different taste stimuli, four of which were prototypes of the putative basic taste [0.5 M sucrose, sweet; 0.1 M NaCl, salty; 0.01 M HCl, sour (the CS); 0.01 M quinine hydrochloride (QHCl), bitter]. The remaining 10 were $NaNO_3$ (0.01 M), a mixture of 0.1 M monosodium glutamate and 0.01 M inosine 5′-monophosphate, HCl (0.003, 0.006, 0.03 and 0.06 M), malic acid (0.01 M), tartaric acid (0.01 M), KCl (0.1 M), $MgCl_2$ (0.03 M) and NH_4Cl (0.1 M).

Results

Figure 1 shows the mean lick numbers for 10 s to the 15 taste stimuli and distilled water in the experimental and control groups. Two-way analysis of variance (ANOVA) with repeated measures (Group × Stimulus) detected a significant main effect of Group [$F(1,10) = 12.13$, $P < 0.01$] and Stimulus [$F(15,150) = 21.49$, $P < 0.001$], and a Group × Stimulus interaction [$F(15,150) = 2.91$, $P < 0.001$]. Post-hoc comparisons using the Fisher's least significant difference test indicated that licks to 0.01, 0.03 and 0.06 M HCl, malic acid, and tartaric acid were lower in the experimental group than in the control group.

Discussion

These results clearly demonstrated that the rats in the experimental group acquired a strong aversion to the 0.01 M HCl CS. As the aversion generalized to 0.03 and 0.06 M HCl, malic acid and tartaric acid but not to the other solutions, the acquired aversion seems to be specific to acidic tastes. Although it was reported that non-preferred tastes were inadequate as a cue for a CTA (Brackbill *et al.*, 1971), the present results support previous reports that rats can acquire an aversion to normally non-preferred sour tastes (Fitzgerald and Burton, 1981; Smith and Theodore, 1984; Grigson *et al.*, 1997a). Therefore, in experiment 2 we examined firing characteristics of PBN neurons in rats who had previously acquired an aversion to 0.01 M HCl.

Experiment 2

Materials and methods

Forty-eight male Wistar rats (200–350 g) were used. They were divided into two groups and acclimated to a schedule with access to one bottle of fluid for 20 min in the morning (10:00) and 60 min in the afternoon (17:30). The 20 min

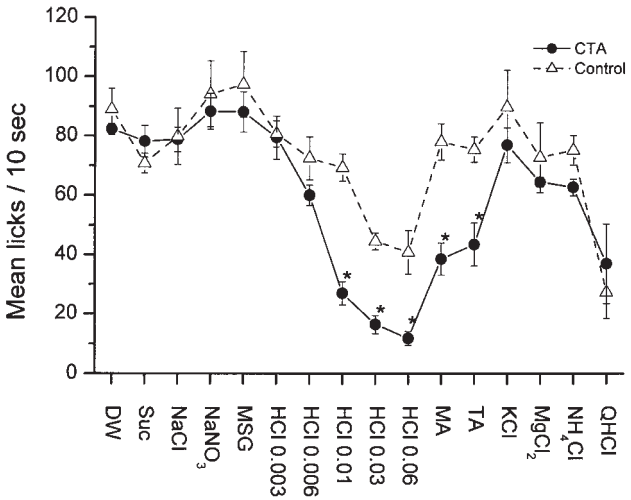

Figure 1 Mean lick numbers (±SE) during 10 s to 15 taste stimuli and distilled water in the CTA and control groups. DW, distilled water; Suc, sucrose; MSG, a mixture of monosodium glutamate and inosine 5′-monophosphate; MA, malic acid; TA, tartaric acid. *$P < 0.05$ from the corresponding solution of the control group.

morning period was the training and testing session during which all experimental manipulations were performed. The afternoon session was always a distilled water presentation and allowed for adequate hydration of the animals. After baseline responses to water during 20 min/day were established, the CTA group (n = 26) received three conditioning trials on alternate days; each rat was given 20-min access to 0.01 M HCl (CS) in the home cage and then injected with 0.15 M LiCl [2% of body wt, i.p.; unconditoned stimulus (US)] in each trial. The control animals (n = 22) were similarly treated except that they were given physiological saline instead of LiCl after the CS. At least 24 h after the last injection of LiCl or saline, each rat was anesthetized with urethane (1.3 g/kg body wt, i.p.). The body temperature was maintained at ~36.8°C using an infrared lamp. Neuronal activity was recorded from the PBN with a glass-insulated tungsten electrode (Z = 1.5–3 MΩ at 1 kHz). The electrode was oriented 20° from vertical (tip pointing rostrally) to avoid the transverse sinus. Neuronal activity was amplified with a conventional method, monitored with a computer system (CED 1401, Spike2; Cambridge Electronic Design, Cambridge, UK), and stored on a DAT recorder for offline analysis. After isolating unitary discharges in the PBN, taste stimuli were presented at room temperature (23–24°C) into the oral cavity of animals according to a method described elsewhere in detail (Shimura *et al.*, 1997b). Each stimulus trial consisted of a 10 s flow of distilled water, a 10 s taste stimulus and a 10 s rinse with distilled water. The flow rate was 0.5 ml/s for all the stimuli, including the rinse. If taste responses remained after the 10 s post-stimulus rinse with distilled water, we continued the water rinse until the neural activity returned to the pre-stimulus level. Ninety seconds were allowed to elapse

between the stimuli to avoid the effects of adaptation. The taste stimuli used were the same as those in experiment 1. All the stimuli were made with reagent grade chemicals and dissolved in distilled water.

All data analyses were based on the neuronal activity in 5 s samples. Spontaneous activity and responses to pre-stimulus water were calculated from multiple samples. The spontaneous rate was determined during the periods just before the pre-stimulus water rinse. Water and taste responses were calculated during the first 5 s period after the onset of stimulation with pre-stimulus water or a taste solution. An adjusted score (a net response rate) was employed for data analyses, which was obtained by subtracting the mean raw water responses from the raw taste responses. A response to taste stimulus was considered to be significant if the neuronal activity increased or decreased at least 2 SD from the mean of the spontaneous activity of the neuron. After the recording sessions, electrolytic lesions were made in the final recording sites (20 μA for 20 s, electrode positive). The rats were perfused intracardially with phosphate-buffered saline and 10% formalin. The location of each recording site was histologically examined.

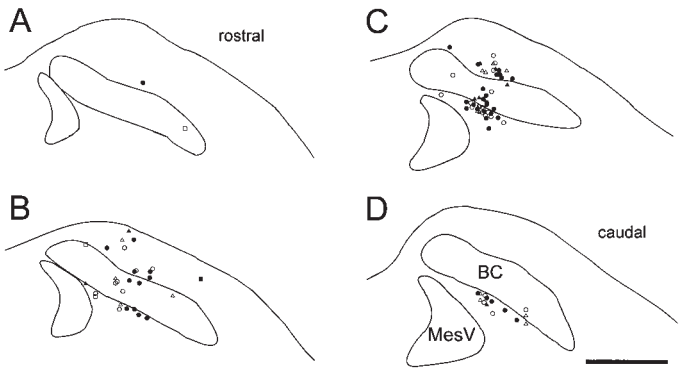

Figure 2 Anatomical reconstruction of recording sites. **(A–D)** Arranged rostral to caudal throughout the extent of the taste-responsive region of the parabrachial pons separated by ~200 μm. Filled symbols, the CTA group; open symbols, the control group; squares, sucrose-best units, circles, NaCl-best units; triangles, HCl-best units. BC, brachium conjunctivum; MesV, mesencephalic trigeminal nucleus. Scale bar in D = 0.5 mm.

Results

The CTA animals acquired a strong aversion to the CS (0.01 M HCl), because the intake of the CS significantly decreased across trials [$F(2,50) = 77.81$, $P < 0.05$].

Taste-responsive neurons in the CTA and control groups were found both above and below the brachium conjunctivum in the area that has been described previously as the pontine taste area (Norgren and Pfaffmann, 1975). As illustrated in Figure 2, there was no fundamental difference in the distribution of recording sites between the CTA and control groups. A total of 95 taste-responsive neurons were recorded from the PBN: 49 from the CTA and 46 from the control groups. All the neurons showed excitatory responses to at least one of the four basic tastes (sucrose, NaCl, HCl or QHCl). The mean spontaneous firing rate in the CTA group was 2.53 ± 0.29 (mean ± SE). It was significantly lower than that of the control group (4.27 ± 0.59) ($t = 2.69$, $P < 0.01$).

Figure 3 illustrates the response profiles of PBN taste neurons to the four standard taste stimuli of both groups. On the basis of their largest response to the four basic taste stimuli, we classified PBN neurons as follows: one sucrose-best (2%), 39 NaCl-best (80%) and nine HCl-best (18%) in the CTA group; three sucrose-best (6%), 28 NaCl-best (61%) and 15 HCl-best (33%) in the control group. Taste neurons are ordered by best-stimulus category and, within categories, by response magnitude. As shown in the figure, the proportion of HCl-best to NaCl-best neurons was significantly smaller in the CTA group than in the control group (one-tailed χ^2 test, $P < 0.05$). In addition, the proportion of HCl-best to NaCl-best units tended to be higher in the dorsal than in the ventral PBN in controls (83.3 versus 35.3%), but not in the CTA group (23.1 versus 16.7%). The

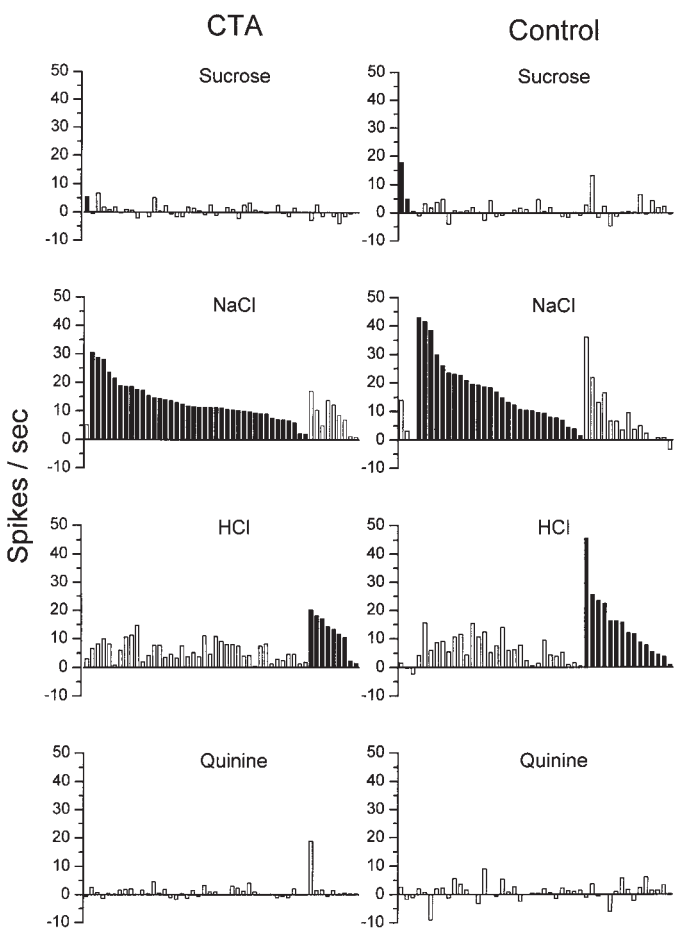

Figure 3 Response profiles of PBN taste neurons to the four standard taste stimuli. Taste neurons were grouped into best-stimulus categories and arranged within those categories in descending order of response magnitude to the best-stimulus.

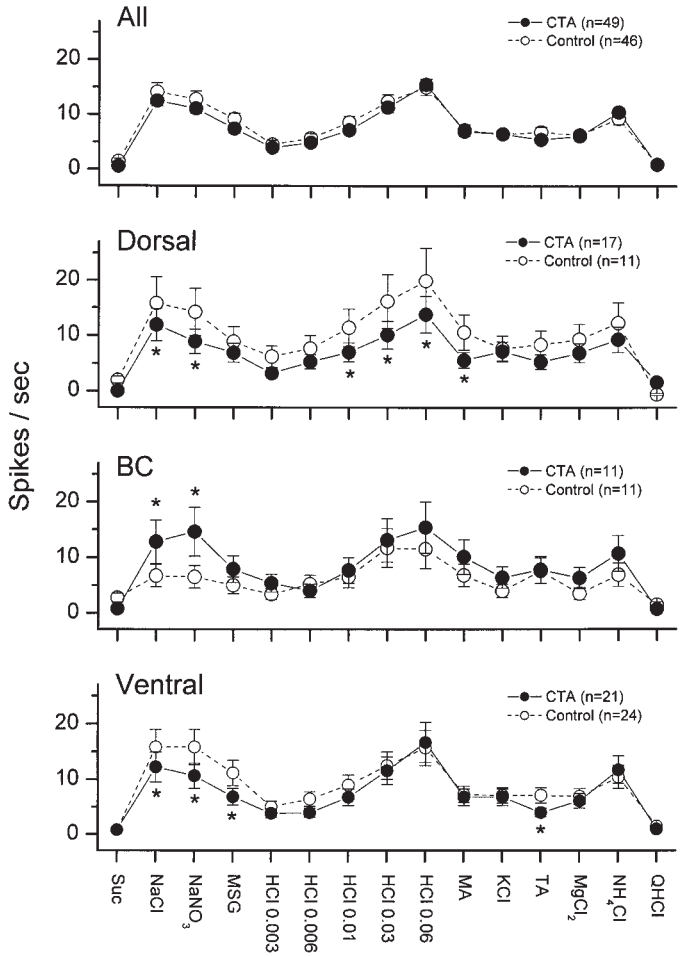

Figure 4 Mean response profiles (during 1 s, mean ± SE) to 15 taste stimuli of taste-responsive neurons in both groups. From top to bottom, the four parts of the figure show respectively overall units; units dorsal to the brachium conjunctivum; units within the brachium conjunctivum (BC); units ventral to the brachium conjunctivum. Suc, sucrose; MSG, the mixture of monosodium glutamate and inosine 5′-monophosphate; MA, malic acid; TA, tartaric acid. *$P < 0.05$ from the corresponding solution of the control group.

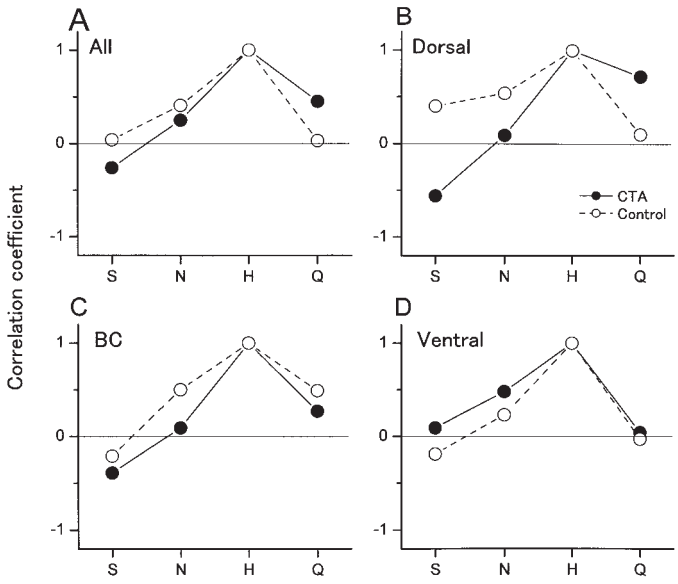

Figure 5 Pearson product-moment correlation coefficients between the 0.01 M HCl CS and other three basic tastes (sucrose, NaCl and QHCl). **(A)** Overall units; **(B)** units dorsal to the brachium conjunctivum; **(C)** units within the brachium conjunctivum (BC); **(D)** units ventral to the brachium conjunctivum. S, sucrose; N, NaCl; H, HCl; Q, QHCl.

number of HCl-best units was smaller in the CTA group than in controls regardless of the recording sites.

Figure 4A shows the mean responses of all PBN neurons to the 15 taste stimuli in both groups. Two-way analysis of variance (ANOVA) with repeated measures (Group × Stimulus) revealed a significant main effect of Stimulus [$F(14,1302) = 62.88$, $P < 0.001$]. However, a main effect of Group and a Group × Stimulus interaction were not significant [$F(1,93) = 1.276$, $F(14,1302) = 0.889$, respectively]. Figure 4B–D indicate the mean responses of PBN neurons to taste stimuli recorded from the area dorsal to, within, and ventral to the brachium conjunctivum, respectively. A three-way ANOVA with repeated measures (Group × Region × Stimulus) detected a main effect of Stimulus [$F(14,1246) = 56.22$, $P < 0.001$] and a Group × Region × Stimulus interaction [$F(28,1246) = 1.72$, $P < 0.05$]. Other main effects and interactions were not significant. Post-hoc analyses of these data using the Fisher's least significant difference test indicated that responses to 0.01, 0.03 and 0.06 M HCl and malic acid were higher in the control group than in the CTA group in the dorsal PBN. Responses to NaCl and $NaNO_3$ were higher in the control group than in the CTA group in the dorsal and ventral PBN, and lower in the control group than in the CTA group in the brachium conjunctivum (Ps < 0.05).

To investigate how similarly the neurons responded to the four basic taste stimuli, we calculated Pearson product–moment correlation coefficients between the 0.01 M HCl CS and other three basic tastes (sucrose, NaCl and QHCl). As shown in Figure 5, the correlation coefficients between the HCl CS and normally preferred tastes (sucrose and NaCl) were more positive in the control group than in the CTA group except for neurons recorded ventral to the brachium conjunctivum. In contrast, when calculated from all the neurons, the correlation coefficient between HCl and QHCl was higher in the CTA group than in controls (Figure 5A). The tendency was more prominent in neurons recorded dorsal to the brachium conjunctivum (Figure 5B).

Discussion

The PBN neuronal responses to the CS showed slight but noticeable changes after the acquisition of CTA to the normally non-preferred HCl CS. As the animals in the CTA group acquired a robust aversion to the CS, these alterations in PBN neuronal activities seem to be plastic as suggested in our previous study (Shimura *et al.*, 1997b). The present

results, however, were somewhat different from previous ones using a normally preferred taste as the CS. In the previous study, PBN neuronal responses to the CS increased after the acquisition of CTA to the NaCl CS compared with those in controls. In contrast, neuronal responses to the HCl CS in the present study did not change on the whole but decreased only in the dorsal PBN. In addition, the proportion of HCl-best to NaCl-best units was lower in the CTA group than in controls in the present study. There was no difference in the proportion of NaCl-best to HCl-best units between the CTA and control groups in the previous study. These comparative results, therefore, suggest that the PBN neuronal mechanisms underlying the CTA are different between preferred and non-preferred tastes as the CS. Alternatively, these minor alterations in the firing rates may indicate that some change in taste hedonics rather than taste quality is primarily responsible for the acquisition of CTA, because the PBN is thought to be concerned with processing of not only taste quality but also taste hedonics (Yamamoto *et al*., 1994a,b).

The spontaneous firing rate was also lower in the CTA group than in controls in the present study. On the other hand, it was not different between the CTA and control groups in the previous study. Our preliminary results indicated that the spontaneous firing rate was lower in rats given three injections of LiCl US without CS than in the control rats. Injections of LiCl US might generally suppress the PBN neuronal activity in the CTA group. However, as we used a net response rate (raw taste response – raw water response) as a taste response for data analyses, lowered spontaneous firing rates in the CTA group might be negligible for responses to each taste.

It was documented that HCl-best units were preferentially located in the dorsal PBN (Ogawa *et al*., 1984, 1987). In line with these observations, the proportion of HCl-best to NaCl-best units was higher in the dorsal than in the ventral PBN in controls in the present study. However, the number of HCl-best units was smaller in the CTA group than in controls regardless of the recording sites. The lowered proportion of HCl-best units in the CTA group might reflect an overall decrease in the response magnitude to HCl in this group. Thus, originally second-best to NaCl units presumably turned out to be NaCl-best in the CTA group after the acquisition of taste aversion.

Interstimulus correlation coefficients indicate that the taste similarities are lower between the HCl CS and normally preferred tastes (sucrose and NaCl), and higher between normally non-preferred QHCl in the CTA group than in controls. These results suggest that the hedonics of originally non-preferred HCl becomes worse after the acquisition of taste aversion to the HCl. Thus, the PBN appears to be concerned with alterations in taste hedonics induced by aversion learning. In line with this suggestion, c-*fos* immunoreactivity studies (Yamamoto *et al*., 1994a,b) have shown that the PBN is involved in the processing of taste hedonics as well as taste quality. As the recipient zone for originally preferred saccharin taste shifts from the dorsal lateral to external lateral subnucleus after the acquisition of CTA, it is plausible that the neurons in the lateral portion of the PBN are primarily responsible for the acquisition of CTA. Behavioral lesion studies (Sakai and Yamamoto, 1998; Reilly and Trifunovic, 2000) also support this notion. Therefore, we could have obtained clearer alterations in taste responses if the neurons from the lateral PBN were recorded.

The importance of the PBN in CTA and sodium appetite has been repeatedly documented (Spector *et al*., 1992; Reilly *et al*., 1993; Scalera *et al*., 1995; Yamamoto *et al*., 1995; Grigson *et al*., 1997b, 1998; Sakai and Yamamoto, 1998). We have shown that PBN neuronal responses to high concentrations of NaCl decrease in sodium-deprived rats (Shimura *et al*., 1997a), which may be favorable for ingestion of an otherwise unpalatable concentration of NaCl. It is thus accepted that PBN neuronal responses to NaCl increase when NaCl is aversive in CTA and decrease when NaCl is preferred in sodium appetite. Although not so robust as shown above for NaCl responses, we could detect the decrease in responsiveness of PBN neurons to the HCl CS in the present study. Alterations in the neuronal activity of PBN neurons may contribute for animals to discriminate, select and avoid the relevant stimulus selectively.

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