

Review article

## Neural substrates for conditioned taste aversion in the rat

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### Abstract

Conditioned taste aversions (CTAs) are well known to be robust and long-lasting instances of learning induced by a single CS (taste)–US (malaise) pairing. CTA can be taken as a general model to search for neural mechanisms of learning and memory. In spite of extensive research on CTAs using a variety of approaches during the last three decades, the neural mechanisms of taste aversion learning still remain unsolved. In this article we propose a model of neural substrates of CTAs on the basis of our recent studies incorporating previous findings by other workers. Our studies mainly included experiments using ibotenic acid injections into various parts of the rat brain as a lesion technique, and *c-fos* immunohistochemistry in naive and CTA trained rats. CTAs were established by pairing the ingestion of saccharin (CS) with an ip injection of LiCl (US). Behavioral studies have shown that the parabrachial nucleus (PBN), medial thalamus, and basolateral nucleus of the amygdala are essential for both acquisition and retention of CTAs. *C-fos* studies suggested that association between gustatory CS and visceral US takes place in the PBN. The gustatory cortex (GC) may modify the strength of this association depending on the nature of the CS, viz., novel or familiar. The amygdala is indispensable for the expressions of CTAs. Tastes with hedonic values are stored in the GC in a long-term manner.

**Key words:** Conditioned taste aversion; Ibotenic acid lesion; *C-fos* immunoreactivity; Parabrachial nucleus; Thalamus; Amygdala; Cortex; Learning; Memory

### 1. Conditioned taste aversion

Memories of events which are based on combinations of sensory signals can lead animals to select correct adaptive behaviors to the environmental changes. Typical examples are memories governing food ingestion. Organisms have to ingest food to maintain their lives. Some food components stimulate sensory organs, i.e., the exteroceptive olfactory and gustatory chemoreceptors. The food is swallowed and its nutrients are absorbed. When ingestion of specific food improves feeble body conditions or elicits a highly preferable feeling, organisms remember the taste and/or smell of that particular food and will develop a preference for it. However, on some occasions food may cause toxic effects. Animals can remember the chemical signals corresponding to a particular food that once elicited malaise after being ingested, and they will develop an aversion for it.

To facilitate elucidating the basic brain mechanisms of feeding-related learning, we have to employ a simple para-

digim leading to convincing behavioral results. A good example for such a paradigm is conditioned taste aversion (CTA) which has been described above briefly. More specifically, when ingestion of a substance is followed by malaise manifested by gastrointestinal distress and nausea, an association between the taste of the ingested substance and internal consequences of its ingestion is quickly established, maintained in a long-term manner, so that the animals reject ingestion of the substance at subsequent exposures. CTA is a rapidly established and robust phenomenon and has the following characteristics which are not found in other forms of classical conditioning [13,24]. 1) Strong CTAs to novel taste stimuli can be established after only one pairing of a conditioned stimulus (CS) that is followed by an unconditioned stimulus (US). 2) Successful CTAs can develop after delays of as long as several hours between exposure to the CS and delivery of the US. 3) The association between the CS and the US can proceed under deep pentobarbital anesthesia.

CTAs have been well documented [7,19,22,24,57,126] in terms of their behavioral mechanisms and phenomenological aspects since the pioneering studies by Garcia and

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his colleagues [54–56]. However, brain mechanisms of this kind of learning, especially neural substrates for acquisition and retention of CTAs, are still unclear.

In the present article, we would like to elaborate on the possible neural substrate for CTA learning on the basis of recent experimental results obtained in our laboratory together with previous findings from other laboratories.

## 2. CS–US interaction

Lithium chloride (LiCl) is one of the most commonly used USs in the CTA paradigm. According to Nachman and his colleagues [103,104], an intraperitoneal (ip) injection of isotonic (0.15 M) LiCl (2% of body weight) following a gustatory CS is very effective in establishing strong CTAs in the rat. Signs of sickness such as decreased activity, diarrhea, and urination appear within 5–10 min after injection of LiCl [38,102,104]. An electrophysiological study [162] showed that neurons in the viscerosensory insular cortex of the rat responded tonically to an i.p. injection of 0.15 M LiCl with the shortest latency being approximately 5 min. These findings suggest that LiCl exerts its effect on the peripheral gastrointestinal organs and central nervous system with the latency of 5–10 min.

Nijijima and Yamamoto [105] have recently shown in anesthetized rats that direct application of 0.15 M LiCl onto the visceral organs elicits gradually increasing and long-lasting discharges in afferent fibers of the vagal (parasympathetic) and splanchnic (sympathetic) nerves with an onset latency of 5–10 min. According to their results, the following findings are noted: (1) The splanchnic and vagal nerves respond to LiCl administered not only intraperitoneally but also intraduodenally. This finding explains the fact that drinking of LiCl as well as an i.p. injection of LiCl exerts its US effects [101]. (2) The magnitude of neural discharges is larger in the splanchnic nerve than in the vagal nerve both after intraduodenal and ip application of LiCl, suggesting a more important role of the splanchnic nerve than of the vagal nerve in transmitting LiCl-induced sensory information. These results are in agreement with the finding by Martin et al. [94] that bilateral subdiaphragmatic vagotomy in rats did not prevent subsequent acquisition of CTAs when toxicosis was induced with isotonic LiCl. (3) LiCl primarily activates C-fibers rather than B-fibers, suggesting that the information transmitted is related to nociceptive information. The activation of nociceptive fibers to LiCl application corresponds well with the recent *c-fos* immunohistochemical study showing that after i.p. injections of LiCl [163,166] or acetic acid [97], Fos-labeled neurons were found in the superficial dorsal horn, a projection site for viscerosensory information

in the thoracolumbar spinal cord [146]. This spinal viscerosensory information is known to project to the parabrachial nucleus [70], a nucleus receiving also gustatory information.

Several researchers [8,141,169] have shown that reliable CTAs can be established when the CS presentation coincides with the injection of LiCl (US), or even when the US precedes the CS by 5 to 10 min. In other words, when the US precedes the CS more than 10 min, no reliable CTAs can be formed. Comparison of such interstimulus interval effects on CTA acquisition together with the aforementioned latency of viscerosensory discharges explains why a successful formation of CTAs requires that gustatory neural information should reach the brain simultaneously with or before the entry of visceral sensory information.

In the reverse situation, CTAs can be acquired with long CS–US intervals extending up to several hours. One explanation for such a long delay is that the gustatory CS information is stored in the brain in form of a short-term memory, which will be associated with the subsequent US [20,130]. Alternatively, peripheral afferent discharges elicited by the CS may last long enough to be associated with the following US. This latter possibility may not be plausible on the basis of several experimental data showing that taste aversion learning is possible under conditions that should greatly minimize any aftertaste [131]. However, if CS–US delay is within 1 h, peripheral afferent discharges outlasting the application of the taste stimulus might also participate in CTA acquisition. The idea of such an aftertaste involvement comes from the recent finding by Matsuo et al. [95,96], who recorded the chorda tympani fibers during ingestive behavior of the rat, that the taste responses were slowly adaptive, and if the animals did not exhibit grooming, licking, or feeding behaviors after exposure to a taste stimulus, the fibers continued to discharge more than 30 min.

Neuroanatomical studies suggest that the possible sites for an interaction between gustatory and general visceral signals in the rat are the pontine parabrachial nucleus (PBN), amygdala, and gustatory cortex (GC). Therefore, the role of these areas in CTA formation will be discussed in the following sections.

## 3. PBN, site for taste–visceral interaction?

### 3.1. Neuroanatomy of the PBN: tract tracing study

The PBN is the second-order relay nucleus of the taste pathway in the rat [110]. Axons of neurons in the gustatory zone in the rostral part of the nucleus of the tractus solitarius (NTS) ascend ipsilaterally through the reticular formation to the PBN in the caudal pons [108]. The PBN

is also a principal target of neurons in the caudal general visceral zone of the NTS [32]. Anatomical studies [66,109,125] suggest that these two parts of the NTS project to different subnuclei in the PBN, i.e., the majority of neurons from the gustatory zone of NTS project to the medial subnuclei of PBN and from the visceral zone of NTS to the lateral subnuclei of PBN. Herman et al. [67] have shown that first-order hepatic and gustatory afferents project to separate regions of the NTS and do not converge upon the same neurons within this structure, but that both gustatory and hepatic divisions of the NTS send efferents to a confined region of the PBN at posterior levels besides the aforementioned separate recipient sites, suggesting convergence of hepatic-vagal and gustatory afferents. The PBN also receives projections from the area postrema [139,149] which is known to be responsive to various emetic stimuli including LiCl [1–3,147].

### 3.2. Functional neuroanatomy of the PBN: *c-fos* study

To elucidate the functional segregation more precisely within the PBN, we have tried to use *c-fos* protein as an anatomical marker for activated neurons [155,163,165–167]. *C-fos* is a proto-oncogene which is expressed in neurons following voltage-gated calcium entry into the cell [98]. Neurons showing *c-fos*-like immunoreactivity (*c-fos* neurons) were surveyed in the PBN after visceral stimulation with an i.p. injection of LiCl and oral stimulation with taste solutions of different qualities and different hedonic values.

Fig. 1 summarizes the results of our *c-fos* immunoreactivity study [165] as a schematic drawing showing functional localization at 4 rostrocaudal levels of the PBN. Cytoarchitectural subdivisions of the PBN are according to Fulwiler and Saper [50]. Abdominal visceral information projects to the rostral part of the external lateral subnucleus (els) (Fig. 1A). Caudally, taste information of quinine and HCl projects to the lateral border of the brachium in a 'capping' pattern including the els and external medial subnucleus (ems) (Fig. 1B). More caudally, hedonics of taste may be represented, i.e., the dorsal lateral subnucleus (dls) may be related to ingestive behavior or positive hedonics, and the els may be related to aversive feeling or negative hedonics (Fig. 1C). Most caudally, taste information of sweeteners and NaCl may project to the central lateral subnucleus (cls) and central medial subnucleus (cms), respectively (Fig. 1D). Generally speaking, the medial part of the PBN (PBNmed), which consists of dls, cls and cms, seems to be concerned with palatable tastes and hedonically positive value, while the lateral part (PBNlat), which consists of els and ems, is related to aversive tastes with hedonically negative value and gastrointestinal distress.

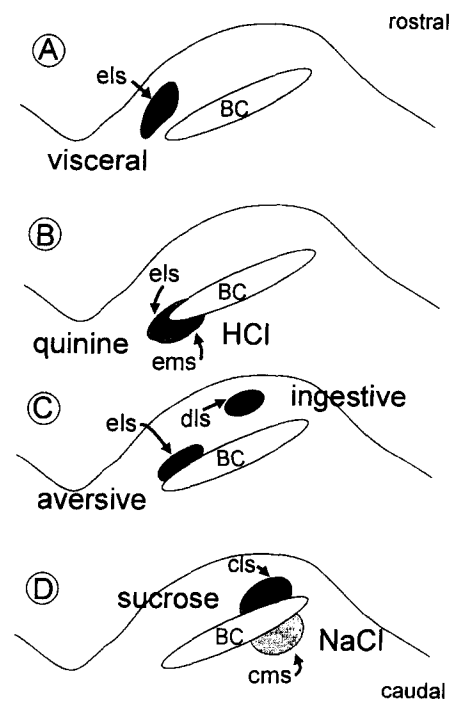


Fig. 1. Diagram depicting functional segregation in the parabrachial nucleus of the rat. Gastrointestinal signals project to the rostralateral part of the external lateral subnucleus (els in A), caudally taste information of quinine and HCl projects to the els and external medial subnucleus (ems) in a 'capping' pattern (B), more caudally hedonically negative (els) and positive (dorsal lateral subnucleus, dls) sites are located (C), and most caudally taste information of sucrose (and saccharin) and NaCl projects to the central lateral subnucleus (cls) and central medial subnucleus (cms), respectively (D). From Yamamoto et al [165].

As mentioned above, saccharin induced *c-fos* neurons in both dls and cls in naive rats. On the other hand, rats with CTAs to saccharin showed *c-fos* neurons predominantly in the els as well as in the cls of the PBN after forced ingestion of saccharin [154,155]. These results suggest that the recipient zone for saccharin taste shifts from the dls to els after acquisition of CTAs, although saccharin-induced *c-fos* neurons in the cls being similarly observed in the aversively conditioned rats just like in naive rats. In other words, the hedonic aspect of saccharin taste shifts from positive to negative with quality aspect unchanged after aversive conditioning to saccharin.

It is possible that activation of PBN neurons in the dls and els of the PBN is due to descending influences from higher brain centers rather than to ascending inputs. Namely, the shift of saccharin projections from the dls to the els after CTA acquisition can be mediated by higher brain sites. To elucidate this point, a *c-fos* immunohistochemical study [155] was performed in rats with combined large ibotenic acid lesions of the GC, VPMpc, and amygdala. Lesions of these areas are considered to eliminate almost all the ascending and descending taste information from and to the PBN. When an unconditioned lesioned rat drank (10.5 ml/h) the saccharin solution, *c-fos*

neurons appeared in the dls as in naive rats. Since the rats with the combined lesions could not acquire CTAs [154], they drank the saccharin solution even after its intake had been paired with an i.p. injection of LiCl. When such a conditioned lesioned rat ingested saccharin (9.0 ml/h), *c-fos* neurons were observed in the els, but not in the dls, of the PBN. It is of great interest that even though the conditioned lesioned rat drank saccharin as much as the naive rat did, *c-fos* expression was observed in the region corresponding to the hedonically negative value. These results suggest that (1) gustatory hedonic responses of PBN neurons can be expressed without involvement of the higher levels of the central nervous system, and (2) even if the hedonic shift has occurred at the PBN level after the CTA procedure, expression of aversive as well as of avoidance behavior requires the higher nervous centers. The latter statement is consonant with Grill and Norgren's finding [60] that chronically decerebrate rats neither rejected nor decreased ingestive reactions to a novel taste after that taste had been repeatedly paired with LiCl-injected illness.

### 3.3. Electrophysiology of PBN neurons

The aforementioned *c-fos* study suggests the existence of two types of taste-responsive neurons in the PBN: the 'taste-quality' neurons, which respond best in excitatory or inhibitory manner to one specific taste stimulus, and 'taste-hedonic' neurons, the responses of which reflect the palatability of a liquid. Such classification has been suggested by Yamamoto et al. [162] to exist for neurons in the cortical taste area of the rat but has not yet been examined in PBN neurons. Although a number of researchers have recorded and analyzed responses of PBN neurons to taste stimuli within cms, cls, and ventral lateral subnuclei in anesthetized [39,40,42,111,114] and conscious [106] rats, electrophysiological data on chemotopy of taste-responsive neurons in the PBN with regard to their functional roles are not enough. The chemotopy revealed by the *c-fos* studies is partly consistent with the electrophysiological results obtained by Ogawa et al. [114] who showed that NaCl-best neurons were located primarily in the cms and sucrose-best neurons were located in the cls. They did not find quinine-best neurons in the PBN.

Decerebration [39], infusions of procaine into the GC [40], or electrical stimulation of the GC [83] all influenced responsiveness of PBN neurons, suggesting the existence of corticofugal control of PBN neuronal activity. Preliminary studies [37,41] suggest that some PBN neurons of the rat show enhanced responses to a taste stimulus which has been paired with LiCl administration. Modulation of gustatory responses after CTAs were reported for neurons in the NTS [36], GC [26,162], hypothalamus [6,26], and

amygdala [26,164,170]. The neural mechanisms mediating such response modifications in CTA-trained rats will be a key to understanding the neural basis of CTAs.

Suemori et al. [145] have shown in the rat that PBN neurons located mainly in the els (according to Fig. 7 of their paper) respond to visceral stimulation such as distension of the stomach. Yuan and Barber [172] recorded unit responses in the lateral parabrachial nucleus of the cat to electrical stimulation of gastric vagal and greater splanchnic nerves and suggested that this nucleus receives and processes a substantial amount of general visceral afferent input. Herman and Rogers [68] recorded unit responses of the rat PBN to electrical stimulation of the vagal and taste nerves and found convergence of both inputs onto neurons within an interstitial zone in the caudal PBN. These representative electrophysiological studies showing projections of gustatory and general visceral signals to the PBN together with the recent *c-fos* immunohistochemical studies and behavioral lesion studies will provide a basis for a neural substrate of taste-visceral integration during the formation of CTAs.

### 3.4. Lesion effects on CTAs

Several investigators have reported that bilateral reversible [73] or irreversible [137,158] lesions of the whole PBN (PBNmed + PBNlat), which invade the taste and visceral recipient zones, severely impair the ability of rats to acquire CTAs. Ivanova and Bures [74] also showed that functional PBN lesions with tetrodotoxin made after a conditioning trial disrupted CTA consolidation.

Electrolytic lesions confined to the PBNmed, which receives taste information of gustatory CSs (0.1 M sucrose, 0.1 M NaCl, 0.3 M alanine, or 0.004 M saccharin), disrupt acquisition of CTAs to these CSs [38,48,124,143]. Flynn et al. [48] and Spector et al. [143] found this disruption by analyzing consummatory oral motor responses (taste reactivity) to the intraorally infused CS that had been paired with LiCl injection. Di Lorenzo [38], with the intake test, showed that medial PBN lesions disrupted CTAs to saccharin, but not to LiCl whose taste is similar to the taste of NaCl. According to our *c-fos* study, her 'medial' lesions (Fig. 1 in her paper) seem to invade the projection zone for sweeteners, but not the projection zone for NaCl. This might explain the different effects on CTAs depending on the kind of CSs, saccharin vs. LiCl. However, as suggested by her there is a possibility that rats with PBN lesions require considerably more CS-US continuity (or less CS-US delay) for the establishment of CTAs. In addition, her 'lateral' PBN lesions are not lateral enough to invade the els where general visceral and aversive taste inputs terminate.

More lateral lesions which included the PBNlat im-

paired CTAs induced by intragastric administration of LiCl [4] or electrical stimulation of the area postrema [5]. Another study by Bechara et al. [10] showed that cytotoxic lesions of the PBNlat disrupted CTAs induced by morphine but not by LiCl. In the latter paper, flavored solutions (CSs) were paired 10 times with LiCl (US). The rats with PBNlat lesions could learn aversions to the CSs on the basis of non-gustatory sensory cues after such a strong conditioning procedure. Therefore, the conclusion that lesions of the PBNlat do not disrupt CTAs induced by LiCl must be accepted with caution.

In our recent study [133] we destroyed the PBNmed and PBNlat separately to examine the role of these areas on acquisition and retention of CTAs to saccharin. It was found that the rats with PBNmed lesions did not show neophobia to saccharin (CS) and failed to establish CTAs to the CS paired with LiCl. This might have been caused by blockade of transmission of taste quality information. Rats with PBNlat lesions showed neophobia, but failed to establish CTAs. Further, we found that the retention of CTAs is impaired severely by the PBNmed lesions but only slightly by PBNlat lesions. These results suggest that taste quality information of saccharin transmitted through the PBNmed is important for both acquisition and retrieval of CTAs, but that the PBNlat, which may be concerned with processing of general visceral signals and taste-visceral association (see below), is crucial only for acquisition of CTAs.

### 3.5. CS-US association in the PBN

As described above, neuroanatomical, electrophysiological, and behavioral lesion studies all indicate that the PBN plays a crucial role in the formation of CTAs. We should like to present here a hypothesis about the integration of gustatory and visceral signals within the PBN. The idea, which has already been introduced elsewhere [154], derives from our *c-fos* immunohistochemical study in naive rats and brain lesioned rats with or without CTAs. The nomenclature of subnuclei in Fig. 3 of Yamamoto's paper [154] has been revised in the present article. When the rat ingests saccharin as the CS, saccharin derived neural information projects primarily to the cls for taste quality processing, to the dls for positive hedonics, and weakly to the caudal els for negative hedonics (Fig. 2A). We assume that gustatory signals of any taste stimulus project to the hedonically positive site, negative site, and quality transmission site with different projection densities depending on the particular taste stimulus. When the rat receives a LiCl injection as the US during ongoing activity of the CS, neural information of injected LiCl projects primarily to the rostral els for transmission of visceral sensation, to the caudal els for negative hedonics, and

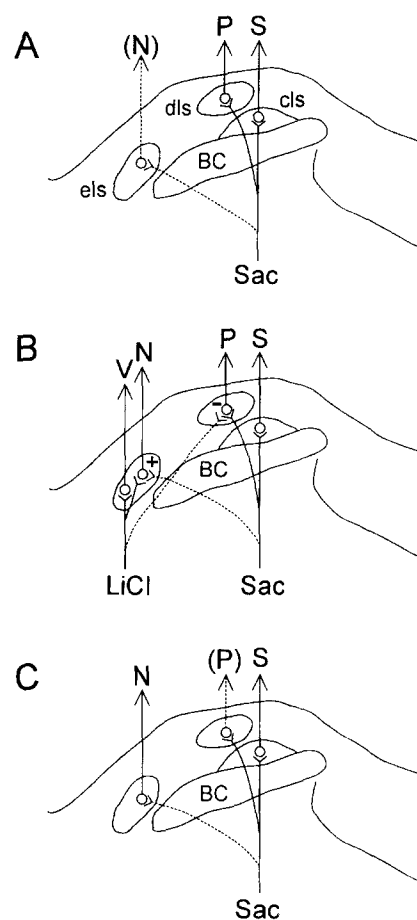


Fig. 2. Diagram depicting association of visceral and taste information in the parabrachial nucleus before (A), during (B), and after (C) CTA learning. Visceral and taste inputs are induced by an intraperitoneal injection of 0.15 M lithium chloride (LiCl) and 0.01 M sodium saccharin (Sac), respectively. S, sweetness; P, positive hedonics; N, negative hedonics; V, abdominal visceral sense; BC, brachium conjunctivum; cls, central lateral subnucleus; dls, dorsal lateral subnucleus; els, external lateral subnucleus; +, potentiation; -, suppression. See text for details.

weakly to the dls for positive hedonics (Fig. 2B). We assume that the US and CS inputs converge on neurons in the els and the US signal potentiates the CS transmission in a long-term manner, whereas neurons receiving the convergent inputs in the dls show depressed CS transmission by the US signal in a long-term manner. The possible existence of such neurons co-activated by both taste and general visceral stimuli has been suggested by Hermann and Rogers [68] in the interstitial zone of the posterior PBN, but neither in the els nor dls. More extensive studies are needed to explore the existence of co-activated neurons to both taste and visceral stimulations and their location within the PBN. After acquisition of CTAs (Fig. 2C), therefore, even if the CS information projects similarly, the neural activity in the hedonically negative site (els) increases and the activity in the hedonically positive site (dls) decreases, whereas the activity of quality transmission neurons in the cls is unchanged. Such changes in neural responses in the dls and els may be represented as

a shift of *c-fos* neurons from the dls to els as the result of formation of CTAs.

It is conceivable that saccharin information projects to the els because saccharin contains 'bitter', i.e., a kind of aversive, component [9] and a learned quinine aversion generalizes to saccharin [99]. Our model, therefore, is applicable to saccharin but not to sucrose which is also sweet but is supposed to have only a small aversive component. However, Moskowitz et al. [100] have shown that sweetness and the pleasantness of the sweetness of sucrose solutions and sweetened food are two different functions, i.e., sweetness increases with concentration, whereas pleasantness first increases and then decreases, suggesting a participation of unpleasantness in gustatory effects of sucrose. In fact, we have observed (unpublished) that *c-fos* expression elicited by sucrose stimulation also shifts from the dls to the els after the rat has learned aversion to sucrose. We assume that every taste more or less projects to the els and dls besides its quality projection site and that the model is applicable to every taste. The finding [18] that quinine is more easily associated with illness than saccharin may reflect the more abundant projections to the els for quinine than for saccharin.

Another claim might be that the taste quality of saccharin changes to 'bitter' or a quinine-like taste after aversion learning to saccharin [99] since saccharin contains a 'bitter' taste [9], *c-fos* neurons shift from the dls to els as the result of learned aversion to saccharin, and quinine also elicits *c-fos* neurons in the els. In accordance with this claim, Chang and Scott [36] showed that within the three-dimensional taste space, as determined by neural activity in the NTS, the saccharin CS after the acquisition of CTA was in close alignment with quinine. It should be noted here that the taste spaces represent similarities among stimuli in terms of taste hedonics as well as of taste quality. In the same paper [36], they found that the CS evoked a significant larger response from CTA-acquired rats than from control rats, and that the effect was limited to the subgroup of neurons sensitive to sweeteners. On the basis of these results, Scott and Giza [138] have suggested that among the gustatory processes performed in NTS it is primarily the hedonic appreciation of a taste, rather than its quality, that appears to be altered. In fact, behavioral studies [49,112] have shown that aversion learning to saccharin generalizes only to sweeteners, but not to other taste stimuli representing salty, sour, and bitter tastes, indicating that the taste quality of saccharin does not change from 'sweet' to 'bitter'.

The interaction of gustatory and general visceral signals has been addressed by Blake and Lin [15] and Cabanac [30,31] who have indicated that visceral information has the ability to bias or 'switch' the affective aspect of a gustatory stimulus, i.e., pleasure or displeasure, and the

consequent ingestive behavior, i.e., acceptance or rejection. We can assume that such a gustatory-visceral association primarily takes place at the lower brainstem level considering the facts that CTAs (more precisely, association of gustatory trace and malaise) can be acquired under deep anesthesia [21,29,123], under deep hypothermia [71] supposed to elicit functional decerebration, or under cortical spreading depression [27], and that neural responses to sensory stimulations can be recorded from the PBN (or PBN neurons are active) under deep anesthesia [40,68,111]. It should be kept in mind, however, that no CTAs can be acquired when the CS is applied under these conditions as shown by Bures and his colleagues [21,27,29,74].

There is a possibility that 'taste-quality' neurons in the PBN show increased responsivity [37,41] to the CS, because some taste-responsive neurons show increased responses to the CS in the NTS [36], GC [162], and amygdala [164,170] after acquisition of CTAs. Our model should of course be examined with different approaches especially including electrophysiological analyses. It should also explain in terms of the neuronal circuitry why a successful formation of CTAs requires that the CS precedes the US.

Thus, the neural substrate for associative taste aversion learning can be implemented by the convergence of CS and US inputs in the PBN. Important in this context is the observation by Garcia and Koelling [56] who have shown that taste stimuli can be easily associated with the internal consequences of X-irradiation or LiCl injections, but not with noxious electrical stimulation of the paws. After repeated pairings of taste-electrical shock, however, rats can discriminate a taste stimulus from water, tasty vs. tasteless [144], or they can avoid consuming sucrose without showing aversive reactions when tested with the taste reactivity test [122]. Nachman demonstrated that orosomatic stimuli such as a change in the temperature of distilled water [102] or as a change in the tactile stimulation of the tongue corresponding to lapping vs. licking or to licking from a spout with a large vs. small opening [7] could be sufficient CSs when followed by LiCl injections. These results are in agreement with the neuroanatomical and electrophysiological findings indicating that orosomatic inputs transmitted through the trigeminal nerve project to the PBN [34,113]. On the other hand, it is assumed that somatosensory inputs to the PBN from the body surface, in contrast to general visceral inputs, are at the most modest [12,34,65,70] and that PBN neurons receiving convergent inputs from the gustatory and somatosensory afferents are few in number. It is possible, therefore, that discrimination learning between a taste stimulus (tasty) and water (tasteless) [144] or electrical shock-motivated taste avoidance learning [122] in rats is per-

formed in other parts of the brain than the PBN. Furthermore, the existence of neurons responsive to olfactory stimuli alone or to both olfactory and gustatory stimuli in the PBN [42] may serve as a neural basis for taste-potentiated odor aversions [121,132].

Plastic changes to those as depicted in Fig. 2 might also occur in the NTS [69] or might not occur in the NTS since the projection zones for taste and gastrointestinal inputs are separated rostrocaudally [32,67,109]. A possible alteration of response patterns of NTS neurons [36,69] is considered to reflect descending effects from higher centers, because a temporal analysis of responses of the NTS neurons showed that the increased CS response after aversive conditioning started with a fairly long latency of 600 ms [36].

If one assumes that acquisition of CTAs can change the hedonic value of the CS without involvement of higher brain centers, decerebrate rats should be able to establish CTAs. However, Grill and Norgren [60] could not demonstrate CTAs in rats decerebrated at the precollicular level. This means successful CTA acquisition requires that quality information about the CS, gastrointestinal, and hedonic signals reaches the post-PBN gustatory circuitry, and that the pre-PBN circuitry alone is insufficient for CTA formation, i.e., the NTS and its local brainstem circuitry are capable of processing the taste signals on the basis of hedonic signals but cannot perform the integration of taste and visceral inputs [47,142,143].

Since PBN as well as NTS are centers of reflex gustatory responses, some behavioral features of CTAs may be implemented by the local PBN circuitry, i.e., although CTA formation requires participation of post-PBN structures, some behavioral manifestations of CTAs may be a result of a plastic change in the PBN as shown in Fig. 2. For example, Halpern and Tapper [64] showed that rats conditioned to avoid a CS (0.3 M NaCl) could discriminate the CS within a brief period (250 to 600 ms) after stimulus onset. Preabsorptive insulin secretion, which is known to be reflexively elicited by intraoral infusions of glucose in chronic decerebrate rats [59], disappears after aversive conditioning to glucose [14]. Such a quick reaction time and such dramatic changes of the CS-elicited reflexes after CTA formation may result from switching the activated neurons from positive hedonics to negative hedonics at the PBN level. Although it is not known how long does such a plastic change last after a taste-visceral association, we assume that its existence parallels the process of CTA extinction.

Bures and his colleagues [22–24,52,73,74], Norgren and his colleagues [48,124,137,143], and Yamamoto and his colleagues [133,154,155,158,165] all agree with the notion that the initial integration of gustatory and visceral signals takes place in the PBN, and that the behavioral expression

of acquisition and retention of CTAs require participation of the forebrain structures including the GC and amygdala. Bures et al. believe that the CTA engram is formed in the PBN after receiving descending gustatory information from the GC. Norgren et al. suggest that their PBN lesions do not impair taste processing or general visceral information, but interfere only with taste-visceral integration. They seem to believe that CTAs can be acquired even if taste quality is processed in one region and visceral information in another region. Yamamoto et al. propose that PBNmed lesions impair taste quality transmission and PBNlat lesions impair the function of the hedonically negative site where taste-visceral integration occurs.

Since the behavioral expression of CTA formation requires participation of forebrain structures rostral to the PBN, the functional relevance of the amygdala, thalamus, and cortex in the formation of CTAs will be discussed in the following sections.

#### 4. Amygdala, site for learning and memory?

##### 4.1. Behavioral lesion study

The amygdala is known to be involved in learning and memory [136]. Functional significance of individual amygdaloid nuclei has been assessed mainly by lesion-induced deficits in a variety of behavioral tasks [136]. The central nucleus of the amygdala (Ce), for example, plays an essential role in conditioning of both active and passive shock avoidance responses [128], and the lateral nucleus (La) is important in fear conditioning to auditory stimuli [89]. Several investigators [103,127,140] have indicated that the basolateral nucleus of the amygdala (BLA) plays a crucial role in acquisition and/or retention of CTAs.

Recently, however, other researchers [35,43,46] pointed out that the amygdala is less important than GC for the formation of CTAs. They suggest that the impairment of CTAs after lesions of the BLA is due to the destruction of the corticofugal fibers passing to the brainstem, but not to the destruction of the cell bodies in the BLA. Although it is true that corticofugal fibers affect taste responsiveness of neurons in the brainstem nuclei [39,40,83], and that they might carry information whether the CS is novel or familiar, experienced as safe or dangerous, we do not think that these descending influences are indispensable for formation of CTAs. Our behavioral studies [154,155,158], using cytotoxic ibotenic acid lesions before or after acquisition of CTAs, have shown that the BLA plays a major role both in acquisition and retention of CTAs. Impairment of CTA acquisition by amygdala lesions is more severe than that induced by GC lesions, but is less severe than that caused by PBN lesions. Combined lesions of

amygdala and GC completely disrupted CTA acquisition, indicating that these two structures are essential for CTA formation and that if one of them is eliminated, weak CTAs can be established with the other structure. On the other hand, retention of CTAs is almost completely disrupted by lesions of BLA [155].

#### 4.2. Inputs to amygdala

The above lesion studies suggest that the integrated gustatory and visceral signals formed in the PBN are probably sent to the amygdala. Neuroanatomical studies in the rat have shown that gustatory information from the PBN [107] and VPMpc [148] projects exclusively to the Ce, and from the insular cortex including GC [119,134,148,150,151], to the Ce, La, BLA, and other amygdaloid nuclei. General visceral inputs also project to the Ce from the NTS [125] and PBN [32,108,135]. An immunohistochemical study [163] showed that gustatory and visceral stimulation elicited *c-fos* expression in the Ce. Thus, the main projection site for brainstem gustatory and visceral inputs to the amygdala is the Ce. However, lesions of the Ce have essentially no or only minor disruptive effects on acquisition and weak effects on retention of CTAs [51,75,154,155,158]. It may be relevant to say that the gustatory and visceral information necessary for CTAs project directly to other nuclei than the Ce via thalamus or insular cortex. Concerning this issue, Ottersen [119] showed the following interesting comment on the basis of his tract-tracing study: "...the Ce was identified as the major intra-amygdaloid target of connections from sensory relay nuclei of the brainstem. Provided the perirhinal cortex, perhaps together with the entorhinal cortex, are the main sources of cortical sensory input to the rat amygdala, such input will predominantly reach the La and BLA. The lack of intrinsic projections from Le would, therefore, seem to preclude an integration between the relatively unprocessed sensory information thought to reach the amygdala from the brainstem and the more highly processed information supposedly relayed to the amygdala from the cortex".

As will be shown in the following sections, the fact that cortical lesions induce only minor effects on CTA suggests that amygdala receives gustatory and visceral information via the thalamus.

### 5. Thalamus, relay station from PBN to amygdala?

Earlier thalamic lesion studies in the rat employed different CTA paradigms, which makes it difficult to compare the results with each other. Loullis et al. [93] presented rats with 0.125% saccharin followed by a LiCl injection.

They found that animals with VPMpc electrolytic lesions showed a loss of neophobia and a marked attenuation of CTA formation. Lasiter [85] also showed that an electrolytic lesion of the VPMpc markedly attenuated CTA learning, i.e., normal rats acquired CTAs to LiCl following the first conditioning trial, but rats lacking VPMpc required approximately five conditioning trials to acquire similar LiCl aversions. Furthermore, he found that animals lacking both the olfactory bulbs and VPMpc could not acquire taste aversions to ingested LiCl, suggesting that olfactory cues associated with drinking solutions play a significant role in CTA when the gustatory thalamic nuclei are destroyed. On the other hand, Flynn et al. [48] reported that rats with VPMpc lesions could acquire taste aversions to alanine which had been paired with injections of LiCl. They measured the number of ingestive and aversive oral motor responses elicited by intraoral infusion of 1 ml of alanine instead of using an intake test. However, they did not exclude the possibility that response could be mediated by nongustatory cues, e.g., olfactory cues.

Our recent studies [154,155,158,168] have shown that cytotoxic lesions of the VPMpc markedly attenuated both acquisition and retention of CTAs, whereas lesions of the midline part of the VPM (or the area between both sides of the VPMpc) attenuated acquisition, but had no effects on retention of CTAs. Moreover, we have found that lesions of both VPMpc and the midline part of the thalamus caused a more severe disruption of CTAs than isolated lesions of either structures. Neuroanatomical findings [62] indicating that midline and intralaminar parts of the thalamus receive projections from PBNlat [61,135] and send axons to the BLA [63,120], support the assumption that general visceral and hedonically negative information is sent to the amygdaloid nuclei other than the Ce via the midline and intralaminar thalamic nuclei. However, further studies are needed to ascertain these possible routes.

### 6. Gustatory cortex, site for short-term or long-term memory?

#### 6.1. Effects of dysfunction of GC on CTAs

The GC is primarily located in the dysgranular insular cortex [33,115,152,162], and the viscerosensory cortex is in the granular insular cortex caudodorsal to the GC [33,72] in rats. Lesions of the insular cortex including the GC, and often also a part of the viscerosensory cortex, attenuated both acquisition [17,18,28,44,45,53,76–80,82,86–88,92] and retention [16,53,156,160,161] of CTAs.

The essential findings by Braun and his colleagues [16,17,77,92] can be summarized as follows: (1) rats with

GC lesions can learn to avoid ingesting a taste stimulus paired with illness, but this learning requires more CS–US pairings. (2) Rats with GC lesions tend to show greater generalization to unpaired taste stimuli, indicating less efficient learning as compared to normal rats. (3) Increasing the strength of the conditioned taste stimuli facilitates, though not completely, CTA learning in rats with GC lesions. (4) Retention of learned taste aversion to a taste stimulus is disrupted by GC lesions, but the rats can acquire CTAs to the same taste again.

Bures and his colleagues [23,24,52] have shown in a series of experiments using the cortical spreading depression (CSD) technique that no CTAs develop when the gustatory CS is presented under CSD, but strong CTAs develop when CSD is elicited after the CS and before the US (i.e. administration of LiCl). They believe that gustatory CS signals are initially processed in the GC, and that the gustatory trace is then transferred from the GC to the PBN to be associated with the US in this nucleus. Bermudez-Rattoni and his colleagues [44,45,91,171] also stressed the important role of the GC in formation of CTAs by showing that in rats in which CTA learning has been impaired by GC lesions this capability can be restored by transplantation of homotopic cortical tissue grafts. They also indicated the importance of cholinergic transmission in the formation of CTAs within the GC [44,91]. Rosenblum et al. [129] have suggested the importance of protein synthesis in the GC for formation of taste memories by showing that application of a protein synthesis inhibitor attenuates CTA formation and latent inhibition to saccharin in rats.

In contrast to these results, our recent behavioral experiments [154,155,158] with cytotoxic lesions showed that the GC is not indispensable for acquisition of CTAs, but that it is rather important for retention of CTAs. To examine the possibility that taste potentiated odor aversion [132] may account for our experimental results, we familiarized the rats previously with the odor of 0.01 M saccharin which served as the CS, or we used lower concentration (0.005 M) of saccharin, which was used by the aforementioned authors, to avoid possible odor effects. In spite of these precautions procedure results remained the same, i.e., no major disruptive effects on acquisition of CTAs were observed. Our results seem to be different from those of other researchers. The differences may largely result from procedural variables, i.e., 0.01 M saccharin vs. 0.005 M saccharin [18,53,171], 0.1 M sucrose [79,81], 0.146 M sucrose [77,92], 0.1 M NaCl [81], 0.153 M NaCl [77,92], 0.12 M LiCl [88], 0.25% HCl [92], 0.1 mM quinine hydrochloride [18,92], 5% alcohol [79], or a mixture of 0.075 M sucrose and 0.05 M NaCl [86] as the CS, 0.15 M LiCl (i.p. injection of 2% volume of the body weight) vs. cyclophosphamide [18,92], apo-

morphine hydrochloride [77], or ingestion of LiCl [44,88,91] as the US, single CS–US pairing vs. several pairings [77,81,88], ibotenic acid lesions vs. aspiration [77,79,81,92], electrolytic lesions [44,86,88,91,171], tetrodotoxin blockade [53], or cortical spreading depression [27], and single bottle test vs. multiple choice test [53] or taste reactivity responses [81]. Another point to be noted is the expression of the results such as ‘disruption’, ‘impairment’, or ‘attenuation’. To our judgment, most of the earlier data show that elimination of the GC impairs CTAs less completely than subcortical lesions. All earlier data are, however, consistent with the ours in the sense that the effects are best expressed as attenuation rather than disruption or impairment of CTA. We would like to quote the following sentences from the review paper by Braun et al. [17] saying that “Everyone was right. The neocortex is clearly involved, but not essential, in the establishment and retention of a taste aversion learning engram”.

## 6.2. Functional significance of GC

Our recent study (unpublished) has shown that lesions of the GC facilitate rats’ capability to acquire CTAs to a familiar CS, i.e., GC lesioned rats behave as if the familiar CS is a novel one. As shown in Fig. 3, rats preexposed for 30 days to saccharin showed no neophobia to this solution on the conditioning day and formed markedly weaker CTA (Fig. 3B) than normal control rats who experienced the CS for the first time on the conditioning day (Fig. 3A). Another group of rats was similarly preexposed to saccharin, then received bilateral lesions of the GC after 30 days of preexposure. As shown in Fig. 3C, these rats showed neophobic ingestion (decreased intake compared to saccharin intake level) on the conditioning day and acquired CTAs to this solution. These results suggest that GC is the site where long-term memory of taste is stored, and a judgment is made whether the taste is novel or familiar. Concerning retrieval of CTA, Buresova [25] used combinations of unilateral lesion of BLA with unilateral functional decortication by CSD in rats, and suggested an important interplay between GC and amygdala by showing a mechanism which involves projections of stored gustatory trace from the GC to the BLA or facilitation of memory readout from the GC under the influence of amygdala. Very interesting is the suggestion by Rosenblum et al. [129] that syntheses of certain proteins after gustatory learning are the molecular basis of learning and memory in the GC.

The GC has dense fiber connections with subcortical structures. Both amygdala [157] and PBN [40,83] receive corticofugal input from the GC. These cortical connections to taste-responsive neurons in the PBN and

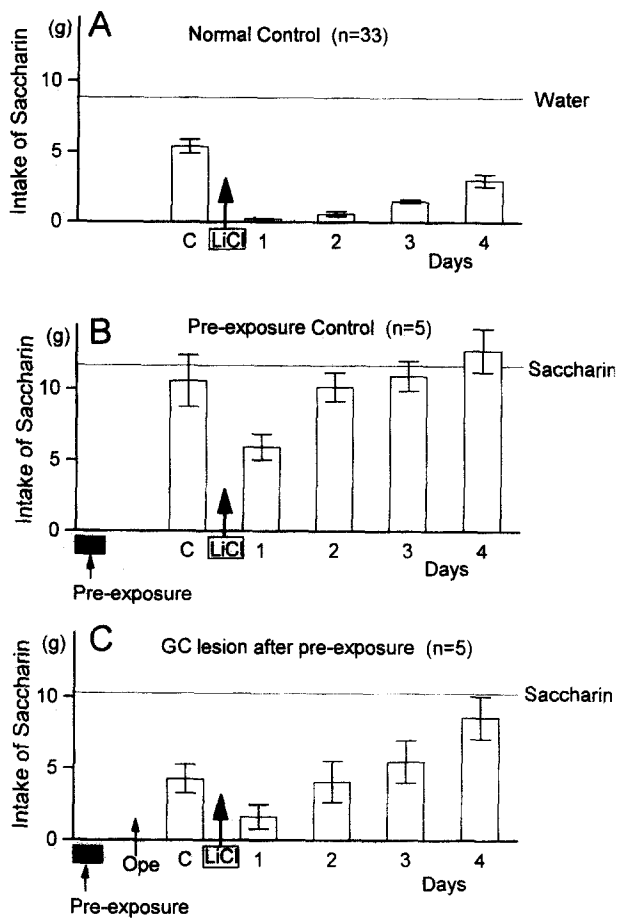


Fig. 3. Acquisition and retention of CTA learning in neurologically normal rats (A and B) and rats with bilateral ibotenic acid lesions of the gustatory cortex (C). Rats in each group were preexposed to 0.01 M sodium saccharin for a month (Pre-exposure). Each column shows the mean  $\pm$  S.D. saccharin intake for 20 min on the conditioning day (C) and on the subsequent 4 days. The horizontal lines in the graph show the mean  $\pm$  S.D. water or saccharin intake during 4 days before conditioning. Ope, lesions of the gustatory cortex (GC).

amygdala may convey the information on whether the ongoing taste stimulus is familiar or novel, acceptable or undesirable, safe or harmful. If the CS is familiar, cortical feedback suppresses association between the CS and the US, whereas if the CS is novel, association between the two stimuli is enhanced. Cortical damage precludes the ability to respond normally to the novelty of the CS, and this diminishes the subsequent aversion [76].

Kiefer and Orr [81] recently reported that rats with GC lesions avoided drinking sucrose and NaCl after repeated taste-illness pairings, but failed to display aversive reactivity to intraoral infusions of these tastes. These rats, however, showed normal aversive reactivity to strong quinine solution. The authors have concluded that rats lacking GC can learn taste avoidance (not to consume the tastants paired with illness), but cannot show taste aversion (disgust, distaste, or unpalatability after hedonic shift) to those tastes. Brain-lesioned rats as well as normal rats can display an aversive reactivity to unpalatable quinine

since taste reactions are established by the lower brain-stem centers including both NTS and PBN [60]. Hedonic value of sucrose and NaCl can be changed from ingestive to aversive in the PBN after having been paired with LiCl (see Fig. 2), but this hedonic shift may not be retained firmly without descending influences from the GC. Moreover, the GC may play an important role in storing aversive information about the CSs and in the expression of aversive reactivity to the CSs; the GC is known to be responsible for jaw-tongue movements [153,162], and calcitonin gene-related peptide found in the GC is related to aversive tastes [159]. Even if aversive reactions disappear after GC lesions, the CS can be avoided as far as intact amygdala receives hedonic and qualitative taste information from the PBN via the thalamus.

Finally, it must be pointed out that GC lesions interfere with taste memory and with association processes, but leave odor conditioning and the potentiation of odor by taste relatively unaffected. This suggests that the GC is not necessary for the acquisition or retention of odor aversions or taste-potentiated odor aversions [78,80,82]. The ventrolateral prefrontal cortex (VLPC), which is located rostral to the GN, probably contributes to the higher-order integration of olfactory stimuli, because several morphological studies have demonstrated olfactory afferents from the mediodorsal nucleus of the thalamus and from the piriform cortex to the VLPC [11,58,84,90]. Further, Onoda et al. [116-118] showed neural responses to odors in the VLPC. Lasiter et al. [87], however, could not confirm that the VLPC involvement in taste-potentiated odor aversion learning. They suggested that GC was involved in the odor aversion as well as in taste aversion learning. Further studies are needed to determine the cortical area critical for learning and memory of odors.

## 7. Summary: neural substrate for CTA

Our behavioral lesion studies [154,155,158,165] can be summarized as follows. When ibotenic acid lesions were made *before* acquisition of CTAs to saccharin by pairing its intake with an i.p. injection of LiCl, rats lacking PBN completely failed to establish CTAs. The second most effective lesion was in the medial thalamus including the VPMpc and the midline part, followed by the damage of the lateral subnuclei of the amygdala including the BLA. Lesions of the GC and hippocampus induced moderate effects, but lesions of the other subnuclei of the amygdala, entorhinal cortex, bed nucleus of the stria terminalis, substantia innominata, lateral hypothalamic area, ventromedial hypothalamus induced slight or no effects.

When ibotenic acid lesions were made *after* acquisition of CTAs, rats with PBN, VPMpc or BLA lesions showed

a dramatic disruption of retention of the taste aversion. Lesions of the GC or the hippocampus elicited a gradual disruption of retention, and a weak disruption of retention of the CTA was observed by lesions of the Ce. Essentially the same results were obtained when the ibotenic acid lesions were made *before* or *after* CTA procedures, i.e., the PBN, medial thalamus, and BLA are indispensable for acquisition and retention of a strong CTA.

On the basis of our results together with the findings by other workers, possible neural substrates for CTA formation are diagrammatically shown in Fig. 4. Association between taste and gastrointestinal information takes place in the PBN, but not in the NTS. Parabrachial neurons in the els, which is concerned with aversive hedonics, are assumed to receive collateral convergence from taste (saccharin) and gastrointestinal (LiCl) inputs (as indicated by dashed lines and dotted area in the figure). Since the saccharin responses in these els neurons are assumed to be enhanced by the visceral input in a long-term manner, the taste of saccharin is changed to be hedonically aversive, and this information is transmitted to the amygdala (BLA) via the thalamic midline and/or intralaminar nuclei (dashed lines and dotted area). Taste quality information of saccharin is also sent to the amygdala via the thalamus and/or GC. Thus, the integrative learning that “saccharin taste is aversive and should be avoided” is established in the amygdala. In this idea, therefore, LiCl information serves as an enhancer of saccharin responses in the els and depressor of these responses in the dls of the PBN. Cor-

tical influences upon the PBN can modify the strength of this taste–visceral association. The amygdala plays an essential role in behavioral expression of CTAs (*viz.*, avoidance of the CS). The experienced tastes with aversive hedonics are sent from the amygdala to the GC and will be stored there in a long-term manner. In turn, corticofugal feedback to the amygdala is important in retention of the CTA. Blockade of either transmission of saccharin taste (PBNmed lesions) or integration of taste–visceral signals (PBNlat lesions) will result in disruption of CTA formation. Finally, it must be stressed that the gustatory or general visceral information is generally conveyed via multiple routes so that lesions of a single brain site may demonstrate only subtle or incomplete effects due to compensation of the deficit by other routes and sites.

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### References

- [1] Adachi, A. and Kobashi, M., Chemosensitive neurons within the area postrema of the rat, *Neurosci. Lett.*, 55 (1985) 137–140.
- [2] Adachi, A. and Kobashi, M., Electrophysiological analysis of chemosensitive neurons within the area postrema of the rat, *Prog. Brain Res.*, 74 (1988) 77–83.
- [3] Adachi, A., Kobashi, M., Miyoshi, N. and Tsukamoto, G., Chemosensitive neurons in the area postrema of the rat and their possible functions, *Brain Res. Bull.*, 26 (1991) 137–140.
- [4] Aguero, A., Arnedo, M., Gallo, M. and Puerto, A., The functional relevance of the lateral parabrachial nucleus in lithium chloride-induced aversion learning, *Pharmacol. Biochem. Behav.*, 45 (1993) 973–978.
- [5] Aguero, A., Arnedo, M., Gallo, M. and Puerto, A., Lesions of the lateral parabrachial nuclei disrupt aversion learning induced by electrical stimulation of the area postrema, *Brain Res. Bull.*, 30 (1993) 585–592.
- [6] Aleksanyan, Z.A., Buresova, O. and Bures, J., Modification of unit responses to gustatory stimuli by conditioned taste aversion in rats, *Physiol. Behav.*, 17 (1976) 173–179.
- [7] Ashe, J.H. and Nachman, M., Neural mechanisms in taste aversion learning, *Prog. Psychobiol. Physiol. Psychol.*, 9 (1980) 233–262.
- [8] Barker, L.M. and Smith, J.C., A comparison of taste aversions induced by radiation and lithium chloride in CS–US and US–CS paradigms, *J. Comp. Physiol. Psychol.*, 87 (1974) 644–654.
- [9] Bartoshuk, L.M., Bitter taste of saccharin related to the genetic ability to taste the bitter substance 6-*n*-propylthiouracil, *Science*, 205 (1979) 934–935.
- [10] Bechara, A., Martin, G.M., Pridgar, A. and van der Kooy D., The parabrachial nucleus: a brain stem substrate critical for mediating the aversive motivational effects of morphine, *Behav. Neurosci.*, 107 (1993) 147–160.
- [11] Beckstead, R.M., Convergent thalamic and mesencephalic projections to the anterior medial cortex in the rat, *J. Comp. Neurol.*, 166 (1976) 403–416.

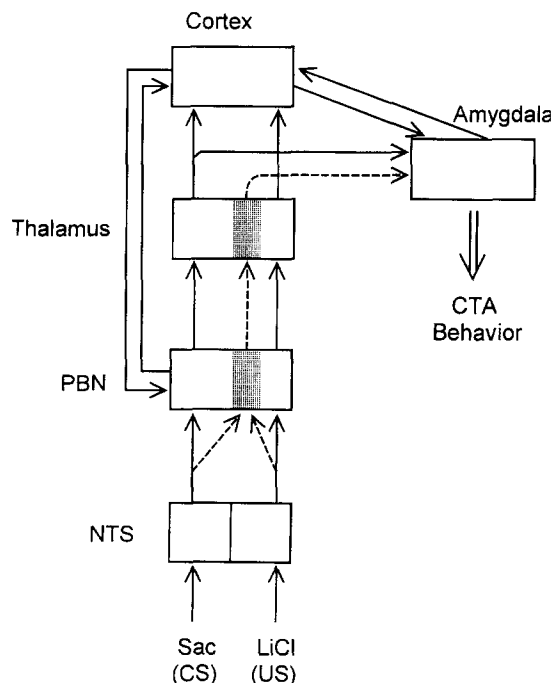


Fig. 4. Diagram depicting possible neural substrates for formation of conditioned taste aversion (CTA). NTS, nucleus of the tractus solitarius; PBN, parabrachial nucleus; Sac, saccharin. See text for details.

- [12] Bernard, J.F. and Besson, J.M., The spino(trigemino) ponto-amygdaloid pathway: electrophysiological evidence for an involvement in pain processes, *J. Neurophysiol.*, 63 (1990) 473-490.
- [13] Bernstein, I.L., Flavor aversion. In T.V. Getchell, R.L. Doty, L.M. Bartoshuk and J.B. Snow (Eds.) *Smell and Taste in Health and Disease*, Raven Press, New York, 1991, pp. 417-428.
- [14] Berridge, K., Grill, H.J. and Norgren, R., Relation of consummatory responses and preabsorptive insulin release to palatability and learned taste aversions, *J. Comp. Physiol. Psychol.*, 95 (1981) 363-382.
- [15] Blake, W.D. and Lin, K.K., Hepatic portal vein infusion of glucose and sodium solution and the control of drinking in the rat, *J. Physiol.*, 274 (1978) 129-139.
- [16] Braun, J.J., Kiefer, S.W. and Ouellet, J.V., Psychic ageusia in rats lacking gustatory neocortex, *Exp. Neurol.*, 72 (1981) 711-716.
- [17] Braun, J.J., Lasiter, P.S. and Kiefer, S.W., The gustatory neocortex of the rat, *Physiol. Psychol.*, 10 (1982) 13-45.
- [18] Braun, J.J., Slick, T.B. and Lorden, J.F., Involvement of gustatory neocortex in the learning of taste aversions, *Physiol. Behav.*, 9 (1972) 637-641.
- [19] Braveman, N.S. and Bronstein, P. (Ed.), Experimental assessments and clinical applications of conditioned food aversions, *Ann. NY Acad. Sci.*, 443 (1985) 1-441.
- [20] Bures, J. and Buresova, O., Neurophysiological analysis of conditioned taste aversion. In M.A.B. Brazier (Eds.) *Brain Mechanisms in Memory and Learning: From the Single Neuron to Man*, Raven Press, New York, 1979, pp. 127-138.
- [21] Bures, J. and Buresova, O., Conditioned taste aversion to injected flavor: differential effect of anesthesia on the formation of the gustatory trace and on its association with poisoning in rats, *Neurosci. Lett.*, 98 (1989) 305-309.
- [22] Bures, J. and Buresova, O., Reversible lesions allow reinterpretation of system level studies of brain mechanisms of behavior, *Concepts Neurosci.*, 1 (1990) 69-89.
- [23] Bures, J., Buresova, O. and Ivanova, S.F., Brain stem mechanisms of conditioned taste aversion learning in rats, *Arch. Int. Physiol. Biochim. Biophys.*, 99 (1991) A131-A134.
- [24] Bures, J., Buresova, O. and Krivanek J., *Brain and Behavior, Paradigms for Research in Neural Mechanisms*, Academia, Praha, 1988, 304 pp.
- [25] Buresova, O., Neocortico-amygdalar interaction in the conditioned taste aversion in rats, *Activ. Nerv. Sup. (Praha)*, 20 (1978) 224-230.
- [26] Buresova, O., Aleksanyan, Z.A. and Bures, J., Electrophysiological analysis of retrieval of conditioned taste aversion in rats. Unit activity changes in critical brain regions, *Physiol. Bohemoslov.*, 28 (1979) 525-536.
- [27] Buresova, O. and Bures, J., Cortical and subcortical components of the conditioned saccharin aversion, *Physiol. Behav.*, 11 (1973) 435-439.
- [28] Buresova, O. and Bures, J., Functional decortication in the CS-US interval decrease efficiency of taste aversion learning, *Behav. Biol.*, 12 (1974) 357-364.
- [29] Buresova, O. and Bures, J., The effect of anesthesia on acquisition and extinction of conditioned taste aversion, *Behav. Biol.*, 20 (1977) 41-50.
- [30] Cabanac, M., Physiological role of pleasure, *Science*, 173 (1979) 1103-1107.
- [31] Cabanac, M., Sensory pleasure, *Quart. Rev. Biol.*, 54 (1979) 1-29.
- [32] Cechetto, D.F., Central representation of visceral function, *Fed. Proc.*, 46 (1987) 17-23.
- [33] Cechetto, D.F. and Saper, C.B., Evidence for a viscerotopic sensory representation in the cortex and thalamus in the rat, *J. Comp. Neurol.*, 262 (1987) 27-45.
- [34] Cechetto, D.F., Standaert, D.G. and Saper, C.B., Spinal and trigeminal dorsal horn projections to the parabrachial nucleus in the rat, *J. Comp. Neurol.*, 240 (1985) 153-160.
- [35] Chambers, K.C., A neural model for conditioned taste aversions, *Annu. Rev. Neurosci.*, 13 (1990) 373-385.
- [36] Chang, F.-C.T. and Scott, T.R., Conditioned taste aversions modify neural responses in the rat nucleus tractus solitarius, *J. Neurosci.*, 4 (1984) 1850-1862.
- [37] Di Lorenzo, P.M., Responses to NaCl of parabrachial units that were conditioned with intravenous LiCl, *Chem. Senses*, 10 (1985) 438.
- [38] Di Lorenzo, P.M., Long-delay learning in rats with parabrachial pontine lesions, *Chem. Senses*, 13 (1988) 219-229.
- [39] Di Lorenzo, P.M., Taste responses in the parabrachial pons of decerebrate rats, *J. Neurophysiol.*, 59 (1988) 1871-1887.
- [40] Di Lorenzo, P.M., Corticofugal influence on taste responses in the parabrachial pons of the rat, *Brain Res.*, 530 (1990) 73-84.
- [41] Di Lorenzo, P.M. and Garcia, J., Taste responses of parabrachial units to NaCl and saccharin in rats that were pretrained to avoid saccharin, *Soc. Neurosci. Abstr.*, 9 (1983) 1023.
- [42] Di Lorenzo, P.M. and Garcia, J., Olfactory responses in the gustatory area of the parabrachial pons, *Brain Res. Bull.*, 15 (1985) 673-676.
- [43] Dunn, L.T. and Everitt, B.J., Double dissociations of the effects of amygdala and insular cortex lesions on conditioned taste aversion, passive avoidance, and neophobia in the rat using the excitotoxin ibotenic acid, *Behav. Neurosci.*, 102 (1988) 3-23.
- [44] Escobar, M.L., Jimenez, N., López-García, J.C., Tapia, R. and Bermudez-Rattoni, F., Nerve growth factor with insular cortical grafts induces recovery of learning and reestablishes graft choline acetyltransferase activity, *J. Neural Transplant. Plast.*, 4 (1993) 167-172.
- [45] Fernandez-Ruiz, J., Escobar, M.L., Pina, A.L., Díaz-Cintra, S., Cintra-McGlone, F.L. and Bermudez-Rattoni, F., Time-dependent recovery of taste aversion learning by fetal brain transplants in gustatory neocortex-lesioned rats, *Behav. Neural Biol.*, 55 (1991) 179-193.
- [46] Fitzgerald, R.E. and Burton, M.J., Neophobia and conditioned taste aversion deficits in the rat produced by undercutting temporal cortex, *Physiol. Behav.*, 30 (1983) 203-206.
- [47] Flynn, F.W., Grill, H.J., Schwartz, G.J. and Norgren, R., Central gustatory lesions: I. Preference and taste reactivity tests, *Behav. Neurosci.*, 105 (1991) 933-943.
- [48] Flynn, F.W., Grill, H.J., Schulkin, J. and Norgren, R., Central gustatory lesions: II. Effects on sodium appetite, taste aversion learning, and feeding behaviors, *Behav. Neurosci.*, 105 (1991) 944-954.
- [49] Frank, M.E. and Nowlis, G.H., Learned aversions and taste qualities in hamsters, *Chem. Senses*, 14 (1989) 379-394.
- [50] Fulwiler, C.E. and Saper, C.B., Subnuclear organization of the efferent connections of the parabrachial nucleus in the rat, *Brain Res. Rev.* 7 (1984) 229-259.
- [51] Galaverna, O.G., Seeley, R.J., Berridge, K.C., Grill, H.J., Epstein, A.N. and Schulkin, J., Lesions of the central nucleus of the amygdala I: effects on taste reactivity, taste aversion learning and sodium appetite, *Behav. Brain Res.*, 59 (1993) 11-17.
- [52] Gallo, M. and Bures, J., Acquisition of conditioned taste aversion in rats is mediated by ipsilateral interaction of cortical and mesencephalic mechanisms, *Neurosci. Lett.*, 133 (1991) 187-190.
- [53] Gallo, M., Roldan, G. and Bures, J., Differential involvement of gustatory insular cortex and amygdala in the acquisition and retrieval of conditioned taste aversion in rats, *Behav. Brain Res.*, 52 (1992) 91-97.
- [54] Garcia, J., Ervin, F.R. and Koelling, R.A., Learning with prolonged delay of reinforcement, *Psychon. Sci.*, 5 (1966) 121-122.
- [55] Garcia, J., Kimmeldorf, D.J. and Koelling, R.A., Conditioned aversion to saccharin resulting from exposure to gamma radiation, *Science*, 122 (1955) 157-158.
- [56] Garcia, J. and Koelling, R.A., Relation of cue to consequence in avoiding learning, *Psychon. Sci.*, 4 (1966) 123-124.
- [57] Gaston, K.E., Brain mechanisms of conditioned taste aversion

- learning: a review of the literature, *Physiol. Psychol.*, 6 (1978) 340–353.
- [58] Gerfen, C.R. and Clavier, R.M., Neural inputs to the prefrontal agranular insular cortex in the rat: horseradish peroxidase study, *Brain Res. Bull.*, 4 (1979) 347–353.
- [59] Grill, H.J. and Berridge, K.C., Chronic decerebrate rats demonstrate preabsorptive insulin secretion and hyperinsulinemia, *Soc. Neurosci. Abstr.*, 7 (1981) 29.
- [60] Grill, H.J. and Norgren, R., Chronically decerebrate rats demonstrate satiation but not bait shyness, *Science*, 201 (1978) 267–269.
- [61] Groenewegen, H.J., Organization of the afferent connections of the mediodorsal thalamic nucleus in the rat, related to the mediodorsal-prefrontal topography, *Neuroscience*, 24 (1988) 379–431.
- [62] Groenewegen, H.J. and Berendse, H.W., The specificity of the 'nonspecific' midline and intralaminar thalamic nuclei, *Trends Neurosci.*, 17 (1994) 52–57.
- [63] Groenewegen, H.J., Berendse, H.W., Wolters, J.G. and Lohman, A.H.M., The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala: evidence for a parallel organization, *Prog. Brain Res.*, 85 (1990) 95–118.
- [64] Halpern, B.P. and Tapper, D.N., Taste stimuli: quality coding time, *Science*, 171 (1971) 1256–1258.
- [65] Hayashi, H. and Tabata, T., Physiological properties of sensory trigeminal neurons projecting to mesencephalic parabrachial area in the cat, *J. Neurophysiol.*, 61 (1989) 1153–1160.
- [66] Herbert, H., Moga, M.M. and Saper, C.B., Connections of the parabrachial nucleus with the nucleus of the solitary tract and the medullary reticular formation in the rat, *J. Comp. Neurol.*, 293 (1990) 540–580.
- [67] Hermann, G.E., Kohlerman, N.J. and Rogers, R.C., Hepatic-vagal and gustatory afferent interactions in the brainstem of the rat, *J. Auton. Nerv. Syst.*, 9 (1983) 477–495.
- [68] Hermann, G.E., Rogers, R.C., Convergence of vagal and gustatory afferent input within the parabrachial nucleus of the rat, *J. Auton. Nerv. Syst.*, 13 (1985) 1–17.
- [69] Houpt, T.A., Philopena, J.M., Wessel, T.C., Hoh, T.H. and Smith, G.P., Quinine induces c-fos immunoreactivity in the rat nucleus of the solitary tract after conditioned taste aversion formation, *Soc. Neurosci. Abstr.*, 19 (1993) 583.
- [70] Hylden, J.L., Anton, F. and Nahin, R.L., Spinal lamina I projection neurons in the rat: collateral innervation of parabrachial area and thalamus, *Neuroscience*, 28 (1989) 27–37.
- [71] Ionescu, E. and Buresova, O., Effects of hypothermia on the acquisition of conditioned taste aversion in rats, *J. Comp. Physiol. Psychol.*, 91 (1977) 1297–1307.
- [72] Ito, S., Multiple projection of vagal non-myelinated afferents to the anterior insular cortex in rats, *Neurosci. Lett.*, 148 (1992) 151–154.
- [73] Ivanova, S.F. and Bures, J., Acquisition of conditioned taste aversion in rats is prevented by tetrodotoxin blockade of a small midbrain region centered around the parabrachial nucleus, *Physiol. Behav.*, 48 (1990) 543–549.
- [74] Ivanova, S.F. and Bures, J., Conditioned taste aversion is disrupted by prolonged retrograde effects of intracerebral injection of tetrodotoxin in rats, *Behav. Neurosci.*, 104 (1990) 948–954.
- [75] Kemble, E.D., Studelska, D.R. and Schmidt, M.K., Effects of central amygdaloid nucleus lesions on ingestion, taste reactivity, exploration and taste aversion, *Physiol. Behav.*, 22 (1979) 789–793.
- [76] Kiefer, S.W. and Braun, J.J., Absence of differential associative responses to novel and familiar taste stimuli in rats lacking gustatory neocortex, *J. Comp. Physiol. Psychol.*, 91 (1977) 498–507.
- [77] Kiefer, S.W. and Braun, J.J., Acquisition of taste avoidance habits in rats lacking gustatory neocortex, *Physiol. Psychol.*, 7 (1979) 245–250.
- [78] Kiefer, S.W., Leach, L.R. and Braun, J.J., Taste agnosia following gustatory neocortex ablation: dissociation from odor and generality across taste qualities, *Behav. Neurosci.*, 98 (1984) 590–608.
- [79] Kiefer, S.W., Metzler, C.W. and Lawrence, G.J., Neocortical involvement in the acquisition and retention of learned alcohol aversions in rats, *Alcohol*, 2 (1985) 597–601.
- [80] Kiefer, S.W., Morrow, N.S. and Metzler, C.W., Alcohol aversion generalization in rats: specific disruption of taste and odor cues with gustatory neocortex or olfactory bulb ablations, *Behav. Neurosci.*, 102 (1988) 733–739.
- [81] Kiefer, S.W. and Orr, M.R., Taste avoidance, but not aversion, learning in rats lacking gustatory cortex, *Behav. Neurosci.*, 106 (1992) 140–146.
- [82] Kiefer, S.W., Rusiniak, K.W. and Garcia, J., Flavor-illness aversions: gustatory neocortex ablations disrupt taste but not taste-potentiated odor cues, *J. Comp. Physiol. Psychol.*, 96 (1982) 540–548.
- [83] Kiyomitsu, Y., Yamamoto, T., Matsuo, R. and Kitamura, R., Centrifugal influence from the cortical gustatory area on neuronal activities of the parabrachial nucleus in rats, *J. Physiol. Soc. Jpn.*, 50 (1988) 515.
- [84] Krettek, J.E. and Price, J.L., The cortical projection of the mediodorsal nucleus and adjacent thalamic nuclei in the rat, *J. Comp. Neurol.*, 171 (1977) 157–192.
- [85] Lasiter, P.S., Thalamocortical relations in taste aversion learning: II. Involvement of the medial ventrobasal thalamic complex in taste aversion learning, *Behav. Neurosci.*, 99 (1985) 477–495.
- [86] Lasiter, P.S., Deems, D.A., Oetting, R.L. and Garcia, J., Taste discriminations in rats lacking anterior insular gustatory neocortex, *Physiol. Behav.*, 35 (1985) 277–285.
- [87] Lasiter, P.S., Deems, D.A. and Garcia, J., Involvement of the anterior insular gustatory neocortex in taste-potentiated odor aversion learning, *Physiol. Behav.*, 34 (1985) 71–77.
- [88] Lasiter, P.S. and Glanzman, D.L., Cortical substrates of taste aversion learning: dorsal prepiriform (insular) lesions disrupt taste aversion learning, *J. Comp. Physiol. Psychol.*, 96 (1982) 376–392.
- [89] LeDoux, J.E., Cicchetti, P., Xagoraris, A. and Romanski, M., The lateral amygdaloid nucleus: sensory interface of the amygdala in fear conditioning, *J. Neurosci.*, 10 (1990) 1062–1069.
- [90] Leonard, C.M., The prefrontal cortex of the rat. I. Cortical projection of the mediodorsal nucleus. II. Efferent connections, *Brain Res.*, 12 (1969) 321–343.
- [91] Lopez-Garcia, J.C., Fernandez-Ruiz, J.F., Bermudez-Rattoni, F. and Tapia, R., Correlation between acetylcholine release and recovery of conditioned taste aversion induced by fetal neocortex grafts, *Brain Res.*, 523 (1990) 105–110.
- [92] Lorden, J.F., Effects of lesions of the gustatory neocortex on taste aversion learning in the rat, *J. Comp. Physiol. Psychol.*, 90 (1976) 665–679.
- [93] Loullis, C.C., Wayner, M.J. and Jolicoeur, F.B., Thalamic taste nuclei lesions and taste aversion, *Physiol. Behav.*, 20 (1978) 653–655.
- [94] Martin, J.R., Cheng, F.Y. and Novin, D., Acquisition of learned taste aversion following bilateral subdiaphragmatic vagotomy in rats, *Physiol. Behav.*, 21 (1978) 13–17.
- [95] Matsuo, R. and Yamamoto, T., Taste nerve responses during licking behavior in rats: importance of saliva in responses to sweeteners, *Neurosci. Lett.*, 108 (1990) 121–126.
- [96] Matsuo, R., Yamamoto, T., Ikehara, A. and Nakamura, O., Effect of salivation on neural taste responses in freely moving rats: analyses of salivary secretion and taste responses of the chorda tympani nerve, *Brain Res.*, 649 (1994) 136–146.
- [97] Menetrey, D., Gannon, A., Levine, J.D. and Basbaum A.I., Expression of c-fos protein in interneurons and projection neurons of the rat spinal cord in response to noxious somatic, articular, and visceral stimulation, *J. Comp. Neurol.*, 285 (1989) 177–195.
- [98] Morgan, J.I. and Curran, T., Role of ion flux in the control of c-fos expression, *Nature*, 322 (1986) 552–555.
- [99] Morrison, G.R. and Jessup, A., A dual taste for saccharin in the

- rat II. Taste change following alloxan injection, *Chem. Senses Flavor*, 2 (1977) 395–400.
- [100] Moskowitz, H.R., Kluter, R.A., Westerling, J. and Jacobs, H.L., Sugar sweetness and pleasantness: evidence for different psychological laws, *Science*, 184 (1974) 583–585.
- [101] Nachman, M., Learned aversion to the taste of lithium chloride and generalization to other salts, *J. Comp. Physiol. Psychol.*, 56 (1963) 343–349.
- [102] Nachman, M., Learned taste and temperature aversions due to lithium chloride sickness after temporal delays, *J. Comp. Physiol. Psychol.*, 73 (1970) 22–30.
- [103] Nachman, M. and Ashe, J.H., Effects of basolateral amygdala lesions on neophobia, learned taste aversions, and sodium appetite in rats, *J. Comp. Physiol. Psychol.*, 87 (1974) 622–643.
- [104] Nachman, M. and Hartley, P.L., Role of illness in producing learned taste aversions in rats: a comparison of several rodenticides, *J. Comp. Physiol. Psychol.*, 89 (1975) 1010–1018.
- [105] Nijijima, A. and Yamamoto, T., The effects of lithium chloride on the activity of the afferent nerve fibers from the abdominal visceral organs in the rat, *Brain Res. Bull.*, in press
- [106] Nishijo, N. and Norgren, R., Responses from parabrachial gustatory neurons in behaving rats, *J. Neurophysiol.*, 63 (1990) 707–724.
- [107] Norgren, R., Taste pathways to hypothalamus and amygdala, *J. Comp. Neurol.*, 166 (1976) 17–30.
- [108] Norgren, R., Central neural mechanisms of taste. In I. Darian-Smith (Ed.), *Handbook of Physiology, Section 1, The Nervous System, Vol. III, Sensory Processes, Part 2*, Am. Physiol. Soc., Bethesda, 1984, pp. 1087–1128.
- [109] Norgren, R., Projections from the nucleus of the solitary tract in the rat, *Neuroscience*, 3 (1978) 207–218.
- [110] Norgren, R. and Leonard, C.M., Taste pathways in rat brainstem, *Science*, 173 (1971) 1136–1139.
- [111] Norgren, R. and Pfaffmann, C., The pontine taste area of the rat, *Brain Res.*, 91 (1975) 99–117.
- [112] Nowlis, G.H., Frank, M.E. and Pfaffmann, C., Specificity of acquired aversions to taste qualities in hamsters and rats, *J. Comp. Physiol. Psychol.*, 94 (1980) 932–942.
- [113] Ogawa, H., Hayama, T. and Ito, S., Convergence of input from tongue and palate to the parabrachial nucleus neurons of rats, *Neurosci. Lett.*, 28 (1982) 15–20.
- [114] Ogawa, H., Hayama, T. and Ito, S., Response properties of the parabrachio-thalamic taste and mechanoreceptive neurons in rats, *Exp. Brain Res.* 68 (1987) 449–457.
- [115] Ogawa, H., Ito, S., Murayama, N. and Hasegawa, K., Taste area in granular and dysgranular insular cortices in the rat identified by stimulation of the entire oral cavity, *Neurosci. Res.*, 9 (1990) 196–210.
- [116] Onoda, N. and Iino, M., Selective responses to odors of animal products in the neocortex neurons of rabbits, *Proc. Japan Acad.*, 56B (1980) 300–305.
- [117] Onoda, N., Imamura, K., Ariki, T. and Iino, M., Neocortical responses to odors in the dog, *Proc. Japan Acad.*, 57B (1981) 355–358.
- [118] Onoda, N., Imamura, K., Obata, E. and Iino, M., Response selectivity of neocortical neurons to specific odors in the rabbit, *J. Neurophysiol.*, 52 (1984) 638–652.
- [119] Ottersen, O.P., Connections of the amygdala of the rat. IV. Corticoamygdaloid and intraamygdaloid connections as studied with axonal transport of horseradish peroxidase, *J. Comp. Neurol.*, 205 (1982) 30–48.
- [120] Ottersen, O.P. and Ben-Ari, Y., Afferent connections to the amygdaloid complex of the rat and cat. I. Projections from the thalamus, *J. Comp. Neurol.*, 187 (1979) 401–424.
- [121] Palmerino, C.C., Rusiniak, K.W. and Garcia, J., Flavor-illness aversions: the peculiar roles of odor and taste in memory for poison, *Science*, 208 (1980) 753–755.
- [122] Pelchat, M.L., Grill, H.J., Rozin, P. and Jacobs, J., Quality of acquired responses to tastes by *Rattus norvegicus* depends on types of associated discomfort, *J. Comp. Physiol. Psychol.*, 97 (1983) 140–153.
- [123] Rabin, B.M. and Rabin, J.S., Acquisition of radiation- and lithium chloride-induced conditioned taste aversions in anesthetized rats, *Anim. Learn. Behav.*, 12 (1984) 439–441.
- [124] Reilly, S., Grigson, P.S. and Norgren, R., Parabrachial nucleus lesions and conditioned taste aversion: evidence supporting an associative deficit, *Behav. Neurosci.*, 107 (1993) 1005–1017.
- [125] Ricardo, J.A. and Koh, E.T., Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat, *Brain Res.*, 153 (1978) 1–26.
- [126] Riley, A.L. and Baril, L.L., Conditioned taste aversions: a bibliography, *Anim. Learn. Behav.*, 4 (1976) 1S–13S.
- [127] Rolls, B.J. and Rolls, E.T., Effects of lesions in the basolateral amygdala on fluid intake in the rat, *J. Comp. Physiol. Psychol.*, 83 (1973) 240–247.
- [128] Roozendaal, B., Koolhaas, J.M. and Bohus, B., The central amygdala is involved in conditioning but not in retention of active and passive shock avoidance in male rats, *Behav. Neural Biol.*, 59 (1993) 143–149.
- [129] Rosenblum, K., Meiri, N. and Dudai, J., Taste memory: the role of protein synthesis in gustatory cortex, *Behav. Neural Biol.*, 59 (1993) 49–56.
- [130] Rozin, P., Central or peripheral mediation of learning with long CS-US intervals in the feeding system, *J. Comp. Physiol. Psychol.*, 67 (1969) 421–429.
- [131] Rozin, P. and Kalat, J.W., Specific hungers and poison avoidance as adaptive specializations of learning, *Psychol. Rev.*, 78 (1971) 459–486.
- [132] Rusiniak, K.W., Hankins, W.G., Garcia, J. and Brett, L.P., Flavor-illness aversions: Potentiation of odor by taste in rats, *Behav. Neural Biol.*, 25 (1979) 1–17.
- [133] Sakai, N., Tanimizu, T., Sako, N., Shimura, T. and Yamamoto, T., Effects of lesions of the medial and lateral parabrachial nuclei on acquisition and retention of conditioned taste aversion. In K. Kurihara, N. Suzuki and H. Ogawa, (Eds.) *Olfaction and Taste XI*, Springer, Tokyo, 1994, pp. 495–496.
- [134] Saper, C.B., Convergence of autonomic and limbic connections in the insular cortex of the rat, *J. Comp. Neurol.*, 210 (1982) 163–173.
- [135] Saper, C.B. and Loewy, A.D., Efferent connections of the parabrachial nucleus in the rat, *Brain Res.*, 197 (1980) 291–317.
- [136] Sarter, M. and Markowitsch, H.J., Involvement of the amygdala in learning and memory: a critical review, with emphasis on anatomical relations, *Behav. Neurosci.*, 99 (1985) 342–380.
- [137] Scalera, G., Grigson, P.S., Shimura, T., Reilly, S. and Norgren, R., Excitotoxic parabrachial nucleus lesions disrupt conditioned taste aversion, conditioned odor aversion, and sodium appetite in rats, *Soc. Neurosci. Abstr.*, 18 (1982) 1039.
- [138] Scott T.R. and Giza, B.K., The effect of physiological condition on taste in rats and primates. In Y. Kawamura and M.R. Kare (Eds.), *Umami: A Basic Taste*, Marcel Dekker, New York, 1987, pp. 409–437.
- [139] Shapiro, R.E. and Miselis, R.R., The central neural connections of the area postrema of the rat, *J. Comp. Neurol.*, 234 (1985) 344–364.
- [140] Simbayi, L.C., Boakes, R.A. and Burton, M.J., Effects of basolateral amygdala lesions on taste aversions produced by lactose and lithium chloride in the rat, *Behav. Neurosci.*, 100 (1986) 455–465.
- [141] Spector, A.C., Breslin, P. and Grill, H.J., Taste reactivity as a dependent measure of the rapid formation of conditioned taste aversion: a tool for the neural analysis of taste-visceral associations, *Behav. Neurosci.*, 102 (1988) 942–952.
- [142] Spector, A.C., Grill, H.J. and Norgren, R., Concentration-dependent licking of sucrose and sodium chloride in rats with

- parabrachial gustatory lesions, *Physiol. Behav.*, 53 (1993) 277–283.
- [143] Spector, A.C., Norgren, R. and Grill, H.J., Parabrachial gustatory lesions impair taste aversion learning in rats, *Behav. Neurosci.*, 106 (1992) 147–161.
- [144] Spector, A.C., Schwartz, G.J. and Grill, H.J., Chemospecific deficits in taste detection after selective gustatory deafferentation in rats, *Am. J. Physiol.*, 258 (1990) R820–R826.
- [145] Suemori, K., Kobashi, M. and Adachi, A., Effects of gastric distension and electrical stimulation of dorsomedial medulla on neurons in parabrachial nucleus of rats, *J. Auton. Nerv. Syst.*, 48 (1994) 221–231.
- [146] Sugiura, Y., Terui, N. and Hosoya, Y., Difference in distribution of central terminals between visceral and somatic unmyelinated (C) primary afferent fibers, *J. Neurophysiol.*, 62 (1989) 834–840.
- [147] Tsukamoto, G. and Adachi, A., Neural responses of rat area postrema to stimuli producing nausea, *J. Auton. Nerv. Syst.*, 49 (1994) 55–60.
- [148] Turner, B.H. and Herkenham, M., Thalamoamygdaloid projections in the rat: a test of the amygdala's role in sensory processing, *J. Comp. Neurol.*, 313 (1991) 295–325.
- [149] van der Kooy, D. and Koda, L.Y., Organization of the projections of a circumventricular organ: the area postrema in the rat, *J. Comp. Neurol.*, 219 (1983) 328–338.
- [150] van der Kooy, D., Koda, L.Y., McGinty, J.F., Gerfen, C.R. and Bloom, F.E., The organization of projections from the cortex, amygdala, and hypothalamus to the nucleus of the solitary tract in rat, *J. Comp. Neurol.*, 224 (1984) 1–24.
- [151] Veening, J.G., Cortical afferents of the amygdaloid complex in the rat: an HRP study, *Neurosci. Lett.*, 8 (1978) 191–195.
- [152] Yamamoto, T., Taste responses of cortical neurons, *Prog. Neurobiol.*, 23 (1984) 273–315.
- [153] Yamamoto, T., Role of the cortical gustatory area in taste discrimination. In R.H. Cagan (Ed.), *Neural Mechanisms in Taste*, CRC Press, Boca Raton, FL, 1989, pp. 197–219.
- [154] Yamamoto, T., Neural mechanisms of taste aversion learning, *Neurosci. Res.*, 16 (1993) 181–185.
- [155] Yamamoto, T., A neural model for taste aversion learning. In K. Kurihara, N. Suzuki, and H. Ogawa (Eds.), *Olfaction and Taste XI*, Springer, Tokyo, 1994, pp. 471–474.
- [156] Yamamoto, T., Azuma, S. and Kawamura, Y., Significance of cortical-amygdalar-hypothalamic connections in retention of conditioned taste aversions in rats, *Exp. Neurol.*, 74 (1981) 758–768.
- [157] Yamamoto, T., Azuma, S. and Kawamura, Y., Functional relations between the cortical gustatory area and the amygdala: electrophysiological and behavioral studies in rats, *Exp. Brain Res.*, 56 (1984) 23–31.
- [158] Yamamoto, T. and Fujimoto, Y., Brain mechanisms of taste aversion learning in the rat, *Brain Res. Bull.*, 27 (1991) 403–406.
- [159] Yamamoto, T., Matsuo, R., Ichikawa, H., Wakisaka, S., Akai, M., Imai, Y., Yonehara, N. and Inoki, R., Aversive taste stimuli increase CGRP levels in the gustatory insular cortex of the rat, *Neurosci. Lett.*, 112 (1990) 167–172.
- [160] Yamamoto, T. and Kitamura, R., A search for the cortical gustatory area in the hamster, *Brain Res.*, 510 (1990) 309–320.
- [161] Yamamoto, T., Matsuo, R. and Kawamura, Y., Localization of cortical gustatory area in rats and its role in taste discrimination, *J. Neurophysiol.*, 44 (1980) 440–455.
- [162] Yamamoto, T., Matsuo, R., Kiyomitsu, Y. and Kitamura, R., Taste responses of cortical neurons in freely ingesting rats, *J. Neurophysiol.*, 61 (1989) 1244–1258.
- [163] Yamamoto, T., Shimura, T., Azuma, S., Bai, W.-Zh., Fujimoto, Y. and Wakisaka, S., Induction of *c-fos*-like protein in the central nervous system of the rat following internal malaise. In R. Inoki, Y. Shigenaga and M. Tohyama (Eds.), *Processing and Inhibition of Nociceptive Information*, Elsevier, Amsterdam, 1992, pp. 165–168.
- [164] Yamamoto, T., Shimura, T., Fujimoto, Y. and Bai, W.-Zh., Role of the amygdala in conditioned taste aversion learning in the rat, *Neurosci. Res.* 16 Suppl. (1991) S140.
- [165] Yamamoto, T., Shimura, T., Sakai, N. and Ozaki, N., Representation of hedonics and quality of taste stimuli in the parabrachial nucleus of the rat, *Physiol. Behav.*, in press.
- [166] Yamamoto, T., Shimura, T., Sako, N., Azuma, S., Bai, W.-Zh. and Wakisaka, S., *C-fos* expression in the rat brain after intraperitoneal injection of lithium chloride, *NeuroReport*, 3 (1992) 1049–1052.
- [167] Yamamoto, T., Shimura, T., Sako, N., Sakai, N., Tanimizu, T. and Wakisaka, S., *C-fos* expression in the parabrachial nucleus after ingestion of sodium chloride in the rat, *NeuroReport*, 4 (1993) 1223–1226.
- [168] Yamamoto, T., Shimura, T., Yasoshima, Y. and Sakai, N., Some critical factors involved in formation of conditioned taste aversion to sodium chloride in rats, *Chem. senses*, 19 (1994) 209–217.
- [169] Yamamoto, Y., Fujimoto, Y., Shimura, T., Sako, N., Yasoshima, Y., Sakai, N. and Matsuo, R., Conditioned taste aversion in rats with excitotoxic brain lesions, submitted.
- [170] Yasoshima, Y., Shimura, T. and Yamamoto, T., Modulation of amygdaloid unit responses to taste stimuli after taste aversion learning in conscious rats, *Jpn. J. Physiol.*, in press.
- [171] Yirmiya, R., Zhou, F.C., Holder, M.D., Deems, D.A. and Garcia, J., Partial recovery of gustatory function after neural tissue transplantation to the lesioned gustatory neocortex, *Brain Res. Bull.*, 20 (1988) 619–625.
- [172] Yuan, C.-S. and Barber, W.D., Parabrachial nucleus: Neuronal evoked responses to gastric vagal and greater splanchnic nerve stimulation, *Brain Res. Bull.*, 27 (1991) 797–803.