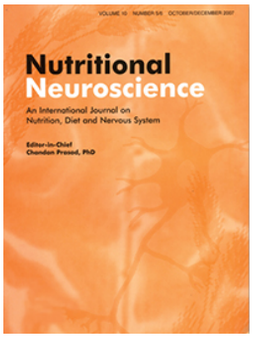

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Nutritional Neuroscience

An International Journal on Nutrition, Diet and Nervous System

ISSN: 1028-415X (Print) 1476-8305 (Online) Journal homepage: http://www.tandfonline.com/loi/ynns20

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To cite this article: Giuseppe Scalera (2002) Effects of Conditioned Food Aversions on Nutritional Behavior in Humans, Nutritional Neuroscience, 5:3, 159-188, DOI: 10.1080/10284150290013059

To link to this article: http://dx.doi.org/10.1080/10284150290013059

Nutritional Neuroscience, 2002 Vol. 5 (3), pp. 159–188

Taylor & Francis
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Review

Effects of Conditioned Food Aversions on Nutritional Behavior in Humans

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(Received 3 August 2001; Revised 15 October 2001; In final form 24 January 2002)

Conditioned food aversion (CFA) and taste aversion (CTA) are widely occurring phenomena mediating rejection of solids or liquids, the ingestion of which has induced the onset of post-ingestional malaise. It is a powerful and durable imprint learning that may influence food choice and intake in all animals, including humans. For ethical reasons, CTA has been extensively investigated in a wide variety of laboratory animal's species but only incidentally in humans. Nevertheless, convincing evidence has been provided that CFA and CTA learning are possible in a wide range of human subjects. The results in humans may have some limitations in accuracy since data are sparse, sometimes indirect, and poorly controlled. There is only limited information on the extent of CFA in the elderly since most studies have employed questionnaire and/or interview methods on young people (i.e. college students). The present review evaluates the literature derived both from laboratory animals and humans. In the first instance, the salient features of food and taste aversion learning and the neural mechanisms involved in this learning behavior will be examined. Then, the problems encountered when trying to assess the role of learned food and taste aversions in the nutritional status of healthy as well as sick young or elderly people will be considered. In particular, the importance of CFA on the nutritional status of cancer patients and treatment of alcoholism will be examined. It is concluded that the data are compelling enough to warrant further research and, some indications and recommendations are suggested.

Keywords: Alcoholism therapy; Appetite disorders; Cancer patients; Conditioned food and taste aversion; Neural mechanisms; Nutritional status

INTRODUCTION

The capability to learn an unpleasant experience associated with the potentially damaging ingestion of a food is powerful and durable, and it may influence everyday food choices in all animals, including humans. Conditioned learning of food aversion (CFA) and/or taste aversion (CTA) is a widely distributed phenomenon in the animal world and involves the rejection of solids or fluids whose ingestion had induced the onset of aversive post-ingestional consequences and/or malaise. CFA behavior evolved as an adaptive and protective response to the danger of ingesting toxins or avoidance of non-poisonous food that in some circumstances might become aversive or noxious. Taste or food aversion is something that many people experience at least once in their lives, even if sometimes they are not aware of it. There are some types of food that a person refuses to eat because he/she once became sick after eating it. This person may find the very thought of eating this food a bit nauseating, although others may enjoy the food. Moreover, sometimes an aversion may develop even if the individual is certain that the food is not the cause of the subsequent illness. Because CFA has been maintained across phylogeny, from insects to primate including humans, it may assume importance in survival. Research on CTA have seen interests shift from CTA as a phenomenon *per se* to its use as a method to investigate other phenomena. The net result has been a flourishing of research using CTA methodology to study the control of

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ISSN 1028-415X print/ISSN 1476-8305 online © 2002 Taylor & Francis Ltd
DOI: 10.1080/10284150290013059

predation among various wild animals, to study both normal and abnormal human feeding behavior, to study the pharmacological and toxicological action of chemicals and drugs, to modify and/or control behaviors such as alcoholism or abuse of illegal substances, and to study the central nervous, endocrine and immune system. Food aversive conditioning may provide an effective management tool to prevent animals from eating palatable poisonous plant (Ralphs and Provenza, 1999). Sufficient excess of even an essential nutrient can be toxic, and the satiated lack of interest in food can be viewed as a positive aversion to foods (Booth, 1985). Since satiety is not a permanent relative aversion or loss of palatability but a relative aversion temporarily induced by food, conditioned satiation has to be defined as a conditioned aversion distinguished by its dependence on the effects of ingested food (Booth, 1985). Even though some conditioned satiation may be true aversions, they are state-dependent and conditioned by the everyday consequences of the food stimuli in question. CFA is a gut protection mechanism in the service of homeostasis (Bermudez-Rattoni, *et al.*, 1988). To be effective, a protective mechanism must be as rapid as possible, and this is the case of CFA in all species of animals. Indeed, usually, one trial is enough to establish a new and relatively strong CFA. The temporal dynamics of visceral events result in most ingested toxin having delayed rather than immediate effects; thus, relatively long delayed learning may sometimes be needed to achieve a very strong food aversion (Nachman, 1970; Schafe *et al.*, 1995a–c). Multiple sampling of a noxious food might induce serious poisoning problems in the animal that would lead to severe morbidity and death. In some situations, animals do not eat because they have strong conditioned aversions to the only food available, and such aversions may add to the effects of illness and persist after illness has subsided. Because experiments typically do not test for learned aversions when their treatments reduce food intake, we do not yet have a clear picture of the overall contribution aversions make to anorexia symptoms studied in the laboratory. With regard to anorexia nervosa or depressive anorexia the case for learned food aversions is far more speculative (Bernstein and Borson, 1986). The case for learned food aversions as a contributing factor in clinical syndromes of appetite loss is less well established, but the evidence for involvement of aversion learning in cancer anorexia is strong. Converging data from different disciplines have provided compelling evidence that the immune system is integrated with other physiological processes and is subject to the influence of central nervous system (CNS). Moreover, it has been postulated that the immune system can be modulated and/or stimulated to produce apparently normal antibody responses by a simple behavioral conditioning procedures, such as CTA (Ader and Cohen, 1993; Ader *et al.*, 1995; Alvarez-Borda *et al.*, 1995).

This review will examine, in the first instance, the salient features of food and taste aversion learning and the neural mechanisms involved in this learning behavior. Then, the problems encountered when trying to assess the role of learned food and taste aversions in the nutritional status of healthy as well as sick young or elderly people will be considered. Furthermore, the importance of CFA on the nutritional status of cancer patients and on the treatment of alcoholism will be examined.

FOOD AND TASTE AVERSIONS: DEFINITION AND DESCRIPTION

CFA and CTA have been observed under natural conditions and demonstrated in the laboratory in

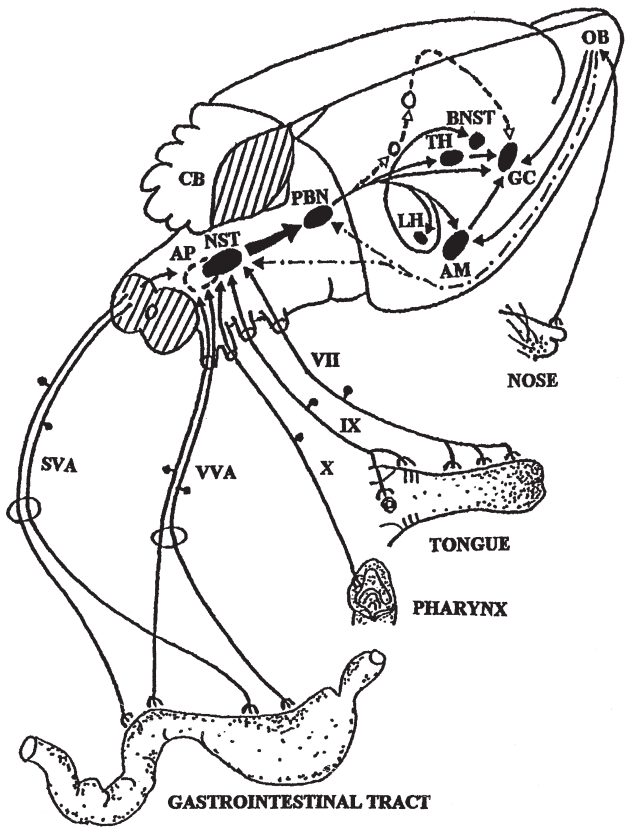

FIGURE 1 Schematic illustration outlining the principal gustatory, olfactory and visceral pathways in the rat. *Abbreviations*: AM, amygdala; AP, area postrema; BNST, bed nucleus stria terminalis; CB, cerebellum; GC, gustatory cortex; LH, lateral hypothalamus; NST, nucleus solitary tract; OB, olfactory bulb; PBN, parabrachial nucleus; TH, gustatory thalamus (nucleus ventroposteromedialis parvicellularis); VII, chorda tympani nerve; IX, glossopharyngeal nerve; X, vagus nerve; SVA, spinal visceral afferents; VVA, vagal visceral afferents. Solid lines represent ipsilateral projections; the dash-dot lines represent the hypothetical route; dashed routes represent the pathways to the controlateral side.

many species. In CFA learning paradigms, taste represents the principal part of the repertoire of elicited responses for conditioned stimulus (CS) sensory modality. Other important components include olfactory, thermal, tactile, and visceral stimuli, which may be integrated with taste stimuli in different areas of the central gustatory system (Fig. 1). CTA has been considered a form of CFA learning, and no substantial differences exist between them (Chambers, 1990). CFA may be applied as a generic term including CTA in mammals and visual or odor aversions in the other species. Even in mammals, it can also include potentiation of odor aversions by taste. Thus, in this review, both CTA and CFA will assume the same meaning, except where noted otherwise. The behavioral effects of associating the taste of food with visceral malaise are rapid and dramatic. Following this association, animals avoid consuming foods with a taste that they had once readily consumed. CTA is a form of associative learning and could represent a model system for studying neural mechanisms of learning and memory. CTA learning persistently changes the animal's behavior response to taste stimuli, and this radical change persists for days to months and requires restructuring of the underlying neural circuitry by alterations of synapses, changes in receptors, second messengers, and/or transmitters levels—all which require protein synthesis and hence gene expression (Yamamoto *et al.*, 1998; Houpt, 2000). Obviously, in this condition, the physical properties of food taste stimulus have not changed, but the neural coding of taste has been altered to yield an opposite response. Changes of unit neural activity after the acquisition of CTA are reported at different levels of gustatory pathway (Buresova *et al.*, 1979; Chang and Scott, 1984; Yamamoto *et al.*, 1989; Yasoshima *et al.*, 1995; Shimura *et al.*, 1997; Hadarits *et al.*, 2001). The enhanced (but see, Buresova *et al.*, 1979) neural response to the CS after acquisition of CTA suggests that "the increase responsiveness to the CS is useful for detecting low concentrations of the stimulus used as a CS to avoid its ingestion" (Yamamoto *et al.*, 1998). The modification of taste neural code may be due to the integration in the CNS of factors that derive from the peripheral and central gustatory, and afferent systems sensitive to emetic stimuli, and from hormones and neurotransmitters (Grill, 1985). In conceptualizing the physiological mechanisms responsible for production of conditioned taste aversion (CTA) one must consider how the CNS integrates taste and visceral stimuli and within which of its structures this integration takes place. Discussions have focused on how the taste of food stimulus and illness are integrated neurally to produce a new response to food. For example, when rats are poisoned after consuming a sweet preferred food, their prior behavioral responses to sucrose resemble those exhibited after consumption of a non-preferred taste. Thus, illness alters the response elicited by taste with this conditioning, the response elicited by the CS is altered because of its association with the unconditioned stimulus (US). Food aversion learning is a very robust phenomenon that can occur following a single learning trial, that is, after one pairing of CS and US, even when delays from 30 min to up to 24 h (or more) elapsed between consumption of the CS and exposure to the US (Revusky and Garcia, 1970). The robustness of food aversion learning is also underscored by the findings that rats will acquire aversions even when they are profoundly anesthetized or unconscious during or after the US administration (Roll and Smith, 1972; Bermudez-Rattoni, *et al.*, 1988; Shimura *et al.*, 1997). This result is extremely important since it shows that the CFA may affect food choices and hedonic responses to foods and beverages unconsciously (Bernstein, 1999a). During CTA acquisition, CS must be presented to intact, conscious subject, but the US can be applied under anesthesia, anoxia, hypothermia or other states of disturbed consciousness (Roll and Smith, 1972; Lasiter *et al.*, 1985a,b; Bermudez-Rattoni, *et al.*, 1988; Bures and Buresova, 1989; Bures *et al.*, 1991; Tassoni *et al.*, 1992; Shimura *et al.*, 1997; Misanin *et al.*, 1998; Metzger and Riccio, 1999). During retrieval, the animal must be conscious to be able to express eating or drinking behavior. The subject is not aware, however, of the situation which has lead to the CS-US association when the US was applied under unconscious status.

Since investigation of conditioning procedures in the late 1950s, some psychologists have suggested that the CFA is a variant of classical Pavlovian conditioning, while others suggested that it is not an example of classical conditioning because it violates some of the general principles that apply to classical conditioning (Chambers, 1990; Mazur, 1994; Bermudez-Rattoni, 1998). Very recently, it has been stated that "…CTAs conditioned and tested with the I/O (intraoral) method share similar features with other Pavlovian aversive classical conditioning paradigms" (Schafe *et al.*, 2000). Gallo *et al.* (1999a) stated that "Although variations in the behavioral procedure used to study taste aversion learning in the laboratory may involve other forms of learning, CTA is widely accepted as a form of classical conditioning (CC)…CTA shows peculiar features that do not appear together in other Pavlovian conditioning preparations. …However, all the complex learning effects that appear in Pavlovian conditioning are also found in CTA.". In conclusion, CTA may be considered a kind of Pavlovian conditioning with some unique properties: (a) Strong CTA is established after only one CS-US pairing; (b) CTA may be formed also when an interval of several hours is

allowed between exposure to CS and delivery of US; (c) Deep anesthesia does not prevent the CS–US association. Intracellular, molecular and genetic studies have recently been performed to elucidate the basic mechanisms of taste aversion learning. In recent models of learning and memory, short-term and long-term phases of memory have been distinguished (Bailey *et al.*, 1996). It has been shown that a rapid short-term memory for CTA learning exists; it is independent of protein synthesis and labile in the absence of a long-term memory formation (Houpt and Berlin, 1999; Fenu *et al.*, 2001). However, if a consolidation occurs, the memory may persists for a long period (long-term phase of memory) (Lamprecht *et al.*, 1997; Houpt, 2000). The formation of long-term CTA memory needs persistent structural changes in neural gustatory circuits and seems dependent on muscarinic and β-adrenergic receptors, mitogen-activated protein kinase (MAPK), and protein synthesis (Rosemblum, *et al.*, 1993; 1995; 1997; Lamprecht *et al.*, 1997; Yasoshima and Yamamoto, 1997; Berman and Duday, 2001). Whereas CTA is an association of the taste with a negative reinforcer (US), extinction is an association with the absence of the negative reinforcer. The action of extinguishing a CTA is probably not one of forgetting but, rather, is an active process where new associations are formed regarding the nature of the CS (McCaughey *et al.*, 1997). It seems that the long-term CTA memory extinction mechanism in the cortex overlaps that of learning a new association of a familiar taste, and it is subserved by the same brain circuits that process the acquisition and consolidation of CTA memory (Berman and Duday, 2001). Nevertheless, in rats, at least seven steps have been identified that must be accomplished for the successful acquisition of a CTA (Reilly *et al.*, 1993). Briefly, to develop a CFA, a rat must: (1) detect the CS; (2) process that information to guide its behavior; (3) detect the US; (4) integrate the information with prior internal or external cues; (5) form an association between the gustatory CS and visceral US; (6) remember that association over time; (7) express the learned association in behavior.

It is important to point out that CTA is distinguished from Unconditioned Taste Aversions (UTA) elicited by some unpleasant substances (i.e. quinine, methyl anthranilate, 5% iodized NaCl, etc.), which are used in conditioning experiments not as CS but as US. For example, after a single peck at a bead smeared with methyl anthranilate (bitter taste) chicks refrain from pecking at beads of similar shape and color (Lee-Teng and Sherman, 1966). This conditioning aversion of bitter taste cannot be called CTA because the CS is the visually perceived stimulus object and US the bitter taste so that the association proceeds between stimuli transmitted by exteroceptors. Furthermore, intravascular (Bradley and Mistretta, 1971; Bradley, 1973; Coil and Norgren, 1981; Miyagawa *et al.*, 1984) or intraperitoneal (Baum *et al.*, 1974; Deutsch, 1978; Miyagawa *et al.*, 1984) injections of a drug can increase the blood concentration of that substance (e.g. saccharin, copper-sulfate, etc.) to a level stimulating the taste buds in absence of consummatory activity.

The Conditioned Stimulus (CS)

To induce a CTA very rapidly the CS must be novel. Indeed, if an animal has had prior safe experience with a substance, conditioning is significantly slower and retarded (Revusky and Bedarf, 1967; Rozin and Kalat, 1971). Likewise, prior exposure to the CS will also retard the development of food aversion, and familiar foods are much less likely to become targets of learned food aversion than novel ones (Bernstein, 1991; 1999a). A taste stimulus that has been repeatedly presented to the animal in the absence of aversive consequences requires more pairing with poisoning to elicit CTA of comparable intensity; this phenomenon has been named "latent inhibition" (Albert and Ayers, 1989; De La Casa and Lubow, 1995; Bures, 1998). In the past, latent inhibition (LI) has been explained by interference with the processing of stimuli: LI results in a failure to acquire new association to such stimuli (Lubow, 1973; Bures, 1998). A more recent interpretation of LI asserts that it is due to retrieval failure. In other words, the association of the pre-exposed CS to the US proceeds normally but during retrieval, the earlier CS—no consequence association competes with the later CS—poisoning association (Bakner *et al.*, 1991; Kraemer *et al.*, 1991; Batsell and Best, 1992). In a series of studies, Schmajuk, *et al.* (2001) modeled the behavioral, pharmacological and neurophysiological aspects of LI. Their data suggest that LI might be controlled by a neural network that involves the entorhinal cortex, nucleus accumbens, and mesolimbic dopamine projection from the ventral tegmental area to the nucleus accumbens. Hippocampal involvement in LI is apparently contradictory; indeed the effects of lesions show either disruption, no effect, or potentiation in LI (Gallo *et al.*, 1999a,b; Grecksch *et al.*, 1999). The novel gustatory stimulus used in CTA experiments should elicit only a mild neophobia; CS intake is thus only slightly lower than the usual intake. The different sapidity of CS markedly influences the robustness of a CTA. Indeed, the stronger stimulus may overshadow the weaker one so that no sign of conditioning of the latter stimulus can be detected even by the most sensitive methods (Lindsay and Best, 1973; Best and Meachum, 1986). A "blocking" effect has been demonstrated in the CTA paradigm (Kamin, 1969; Gustavson *et al.*, 1992). Blocking is established when a new stimulus is mixed with a well-established CS,

but the new stimulus is not associated with the US. Thus, reliable predictability of the US by the CS reduces the associability with other cues that may serve as potential CS (Bures, 1998). The conditioning method of establishing a CTA (intraoral exposure to a taste CS; bottle presentation; etc.) is important for CTA acquisition (Schafe *et al.*, 2000). CTA can be acquired in the absence of any consummatory responses (Domjan and Wilson, 1972). In this case, CS only acts on the taste receptors of the oral cavity and does not enter the intestinal tract, thus eliminating a possible stimulation of visceral receptors by CS ingestion. CTA can be induced by systemically applied flavors (Bradley and Mistretta, 1971; Bradley, 1973; Coil and Norgren, 1981; Miyagawa *et al.*, 1984). Flavor is the complex information contained in the total spectrum of stimuli in a food, including taste and olfaction, as well as tactile sensation and temperature. Some substances inducing aversions when used as US can reach blood concentrations that are enough to elicit gustatory sensations that may serve at the same time as CS. This seems to be the case of alcohol, where parenteral application may induce CTA manifested by reduced alcohol intake (Cunningham, 1978; Miceli *et al.*, 1980).

The CS for CFA learning involves stimuli that are usually used for food identification. Of the many parameters normally implicated in the regulation of fluid and food ingestion, the chemical senses (taste and olfaction) are probably the most important. Taste and olfaction cooperate in the management of food selection and together represent a core of chemosensitivity that serves to nourish and protect the animal (Scott and Verhagen, 2000). Both gustatory and olfactory inputs are needed to form a representation of the flavors of foods and fluids (Rolls, 1993). Thus, in the real world, food aversions may actually develop against a flavor of a food instead of a pure taste or smell of a food. For many species taste is the primary stimulus to form a CFA, but odor can also serve as a weak cue (Palmerino *et al.*, 1980; Kiefer, 1985). An odor may become a potent cue for avoidance when it is conditioned in association with a taste. This phenomenon has been referred to as "taste potentiation of odor" (Bernstein, 1999a). Thus, under normal circumstance, odor may sometimes assume a relevant importance in aversion learning. For example, Brot *et al.* (1987) found that the presence of a particular odor along with a taste makes a food a very potent target of learned aversions. The "taste potentiation of odor" may assume great survival value because odor perceptions allow animals to actually avoid ingestion or sampling of a toxic or suspicious substance. It must be noted that even if the main CS pathways include the peripheral and central structures of gustatory and olfactory systems, some species use other senses (such as vision in domestic chicks, quail, guinea pigs) as primary stimulus in CFA learning (Lee-Teng and Sherman, 1966; Wilcoxon *et al.*, 1971; Braveman, 1974; Gaston, 1977).

The Unconditioned Stimulus (US)

Food and taste aversion literature show an enormous and varied list of drugs and other treatments that may be used as US in conditioning paradigms (Braun and McIntosh, 1973; Riley and Tuck, 1985; Gamzu *et al.*, 1985; Bell *et al.*, 1998; Bermudez-Rattoni, 1998; Nolte *et al.*, 1998; Gallo *et al.*, 1999a,b; Singer *et al.*, 1999; Stephan *et al.*, 1999; Shobi and Goel, 2001). The most effective drugs producing US are those inducing emetic activity and malaise; but many drugs that are not emetics can be effective (Goudie, 1979; Grant, 1987), as well as some drugs of abuse (Hunt and Amit, 1987; Grigson, 1997a). Food aversions can develop in the course of medical treatments that induce emesis or distress (Bernstein and Webster, 1980; Logue, 1985). Although nausea is a sufficient but not always necessary condition for the development of food aversions, it plays a potent role in CFA learning, when food becomes distasteful (Pelchat and Rozin, 1982; Pelchat *et al.*, 1983). Some authors believe that a shift in the hedonic value of taste constitutes a pure learned taste aversion (Bernstein, 1999a). There are drugs or agents considered toxic and that produce illness but which do not produce CFA (Riley and Tuck, 1985). There are differences in the effective dosage utilized and species-specific effects of the same drugs (Bermudez-Rattoni, 1998; Bermudez-Rattoni and Yamamoto, 1998). These differences are probably due to the different anatomical connections of the vomiting centers. Indeed, radiation-induced emesis in the cat can be abolished by high spinal cordotomy and vagotomy but not by lesions of the area postrema (AP). On the contrary, in dogs and monkeys AP-lesions abolish emesis induced by radiation or LiCl treatments (Fox *et al.*, 1990; King, 1990). Some years ago, Rozin (1967) showed that rats eating thiamin-deficient diets develop a strong aversion to those deficient diets. Rats continued to avoid the deficient diet even after they had recovered from the effects of deficiency. These data suggest that ingestion of an unbalanced diet for some time may develop a CFA as an adaptative role in nutrient selection. Recently, Galef (1991) questioned Rozin's hypothesis and stated that CFA is a rather poor mechanism for insuring proper nutrient selection. Still the controversy has not been resolved but, as recently suggested by Bernstein (1999a), Galef's position seems more persuasive.

The route by which information on the agents used as US is conveyed to the brain varies with the particular chemical or physical agents and the route of administration. For the most part, the ascending pathway for general visceral information runs parallel to that of gustatory system (Cechetto, 1987).

NEURAL MECHANISMS OF CONDITIONED FOOD AND TASTE AVERSIONS

An awareness of the anatomy of central gustatory, olfactory and visceral systems is a prerequisite to better understand the logic of experiments and the implications of their results to explain the mechanisms of CFA. However, a detailed description of these complicated systems is not necessary for the purpose of this review. Some excellent and detailed reviews of the vertebrate olfactory system (Halasz, 1990) and gustatory system in rodents (Norgren, 1984; 1995; Finger, 1987; Cechetto, 1987; Kruger and Mantyh, 1989), primates (Pritchard, 1991; Pritchard *et al.*, 2000) and humans (Norgren, 1990) have recently been published. Since the majority of experimental studies use laboratory rodents as subjects, here, the major components of the central gustatory system in the rat will be briefly described. An outline of the principal gustatory, olfactory and visceral pathways in the rat is shown in Fig. 1. Gustatory axons from the facial, glossopharyngeal and vagus nerves converge in an overlapping rostral to caudal manner to an area within the nucleus of the solitary tract (NST) (Travers and Norgren, 1995). Gustatory neurons are located in the anterior one third to one half of the NST (Norgren and Leonard, 1971; 1973). The sub-diaphragmatic vagus nerve conveys viscerosensory information from the gastrointestinal tract mainly to the caudal portion of the NST (Torvik, 1956; Hamilton and Norgren, 1984; Norgren and Smith, 1988). The lateral portion of the pontine parabrachial nucleus (PBN) receives visceral afferences from the caudal NST and projects to a number of structures including the parvicellularis pars of the ventroposteromedial nucleus of thalamus (VPMpc), the central nucleus of amygdala (AM), the lateral hypothalamus, and the insular cortex (IC) (Norgren, 1978; Saper and Loewy, 1980; Cechetto and Saper, 1987; Herbert *et al.*, 1990; Krukoff *et al.*, 1993; Krout and Loewy, 2000). The PBN is composed of 14 subnuclei, each with their own unique set of afferent and efferent projections. Information from the PBN reaches the cerebral cortex by direct and indirect pathways. From the PBN, the gustatory pathway takes at least two independent ways to the forebrain. The first route projects the PBN axons to the neurons of the parvicellular division of the ventroposteromedial nuclei of thalamus (VPMpc) (Norgren, 1974; Cechetto and Saper, 1987; Krout and Loewy, 2000). The thalamic neurons then project to the agranular IC (Kosar *et al.*, 1986). The second route, the ventral pathway, projects monosynaptically to the limbic structures including the central nucleus of the AM, the bed nucleus of the stria terminalis, the substantia innominata and the lateral hypothalamus (Norgren, 1974, 1976; Saper and Loewy, 1980; Fulwiler and Saper, 1984). A third path sends afferents directly to the gustatory cortex and some projections become controlateral (Yamamoto, 1989). In the monkey, gustatory axons from the NST apparently bypass the PBN all together and synapse directly in the thalamic gustatory nucleus (Beckstead *et al.*, 1980). The PBN in Old World monkeys receives massive axonal projections from the visceral afferent NST and projects heavily to the central nucleus of the AM and to the bed nucleus of stria terminalis, but it sends only a small number of fibers to the ventrobasal thalamus, which closely mimic the ventral forebrain projections of the rat (Pritchard *et al.*, 2000). Experimental manipulation and measurement of neural processes are very limited in humans, and the literature on the central gustatory system is scarce, incomplete, often contradictory (Norgren, 1990; Lenz *et al.*, 1997; Aglioti *et al.*, 2000; Onoda and Ikeda, 1999; Small *et al.*, 1997; 2001a; Cerf *et al.*, 1998; Pritchard *et al.*, 1999; Schmitt *et al.*, 2000). Until the advent of neuroimaging techniques (PET, fMRI, etc.) knowledge of the human gustatory representation derived entirely from studies of lesions in clinical populations (Lee *et al.*, 1998; Pritchard *et al.*, 1999; Onoda and Ikeda, 1999; Small *et al.*, 2001a). For these reasons, information on the central processing of gustatory afferent activity in human derives primarily from non-humans primates and relies on inference from Old-World monkeys and other vertebrate research (Norgren, 1990; Pritchard, 1991; Scott and Plata-Salaman, 1999; Pritchard *et al.*, 2000; Spector, 2000).

Since food aversions learning have a survival value in all species, it must be based on relatively primitive associative mechanisms perhaps involving neural integration occurring in lower brain areas such as brain stem (Bernstein, 1999a). Studies employing permanent and/or reversible lesions and stimulation methods have been used to elucidate the role of specific brain areas in CTA learning, beginning with the lower brain stem and moving upward through the thalamus and limbic system to the neocortex. The majority of experimental studies have been performed in rodents, thus, the area of the CNS involved in the CFA learning in rats will be described for the most part.

Area Postrema

The AP, a circumventricular organ located on the caudal floor of the fourth ventricle in the brain stem, which lacks a blood–brain barrier, detects chemicals in the blood (van der Kooy and Koda, 1983; Shapiro

and Miselis, 1985; Borison, 1989). It receives inputs from the vagus nerve (Contreras *et al.*, 1982; Kalia and Sullivan, 1982) and from neurons in the paraventricular and dorsomedial hypothalamus (Shapiro and Miselis, 1985) and projects to many structures of the brain stem, among which the NST and PBN (van der Kooy and Koda, 1983; Shapiro and Miselis, 1985). As there are reciprocal neural connections between the AP and NST (Morest, 1967), information on blood–borne toxins may be conveyed to the NST. Although the vagus nerve and the AP are important pathways for many different chemicals, they may not be the only means by which information is conveyed to the brain (Chambers, 1990). AP has been considered a site of chemoreceptors for detection of blood toxins that is implicated in neural and humoral integration of visceral sensation to trigger and integrate emetic reflexes (Borison and Wang, 1953). The finding that acute LiCl treatments in rats increase *c-Fos* expression in the AP (Olson *et al.*, 1993) supports the view that this structure is a direct chemosensory site for the neural feedback loops involved in toxin defense mechanisms (Ossenkopp and Eckel, 1994; Chambers and Bernstein, 1995; Ossenkopp and Eckel, 1995). In CTA paradigms, AP detects the US either directly as a toxic substance present in the blood or indirectly via visceral afferent nerves. Electrical stimulation (prolonged or intermittent) of the AP is sufficient to induce a CTA when paired with a novel gustatory stimulus, and it clearly mimics the pharmacological effects of LiCl (Gallo *et al.*, 1988). Numerous ablation experiments of AP have been reported to interfere with CTA learning when some drugs are used as US, but other treatments are ineffective (Berger *et al.*, 1973; Ritter *et al.*, 1980; Coil and Norgren, 1981; van der Kooy *et al.*, 1983; Rabin *et al.*, 1987). Kenney *et al.* (1994) showed that AP-ablation results in the development of an unconditioned stimulus capable of supporting food-aversion conditioning, which remains effective even one month after ablation. Kosten and Contreras (1989) have proposed that the disruption of CTA in AP-lesioned rats is the result of a decrease in the capability of rats to recognize the taste solution as novel (taste novelty hypothesis). However, reversible lesioning procedures of AP (cooling) do not support this hypothesis (Wang *et al.*, 1997). AP seems important only in the acquisition phase of CTA but not for long-term persistence and retrieval (Rabin *et al.*, 1983). The role of AP in the acquisition phase does not exclude the possibility of this area being necessary for taste-visceral integration.

Nucleus of the Solitary Tract

The NST receives primary taste afferents from the entire tongue (nerves VII and IX), soft palate (nerve VII), and larynx and pharynx (nerve X). These nerves terminate in a rostro to caudal sequence within the NST. Gustatory neurons lie in the rostral one third to one half of the NST, which projects to the medial part of the PBN, whereas the caudal NST (general visceral zone) projects to the lateral part of the PBN. In addition, NST receives descending input from several gustatory relays (i.e. gustatory cortex, AM, hypothalamus, PBN, etc.) (Norgren, 1995). In particular, *c-Fos* experiments have shown that projections from the AM to the intermediate NST (iNST), a region that receives both taste and visceral projections (Norgren, 1995) mediate the behavioral expression of CTA learning (Schafe *et al.*, 2000). The role of NST in CTA associative processes is not yet completely clear. Grigson *et al.* (1997a) reported that extensive electrolytic lesions of the gustatory NST did not disrupt the acquisition of a CTA since rats with NST lesions show a marked impairment of gustatory preference and aversion but can still use taste cues for learned aversions. They concluded that the NST is involved in basic sensory but not in associative processing of gustatory information. Their data identify a role for the NST in innate, basic taste function, rather than in associative gustatory processes (Grigson *et al.*, 1997a). However, *c-Fos* results indicate that activation of cells in the iNST is exclusively correlated with rejection of tastes that have been made aversive by conditioning and with a specific neural correlate of CTA expression but not with the stress of general aversiveness produced by CTA (Schafe *et al.*, 2000). Nevertheless, Houpt (2000) recently stated that "*c-Fos* induction in the iNST stands as the best neuronal correlate of CTA acquisition and expression."

Pontine Parabrachial Nuclei

Permanent electrolytic or neurotoxic lesions, or reversible lesions of the gustatory PBN disrupt acquisition of a CTA more effectively than lesions of other brain sites including NST, VPMpc, cortical gustatory area, lateral and ventromedial hypothalamus (Yamamoto *et al.*, 1995; Scalera *et al.*, 1995; Sclafani *et al.*, 2001). With the exception of the PBN, no other brain region has been demonstrated unambiguously to be necessary for CTA acquisition (Schafe *et al.*, 1995a–c). The results obtained using reversible or permanent lesions, irrespective of the aversive agents used (i.e. motion-sickness, LiCl, etc.), point to an associative role of the PBN in CTA (Ivanova and Bures, 1990a,b; Spector, 1995; Grigson *et al.*, 1998; Gallo *et al.*, 1999b; Reilly, 1999), and they support the proposed universal role of this area in CTA (Bielavska and Bures, 1994). The specific contributions of different PBN subnuclei and the nature of the associative changes that take place in the PBN are not yet totally clear. The results from

medial and lateral PBN lesions demonstrate the critical role of this nucleus in taste aversion learning; however, an intact PBN is a necessary but not sufficient condition for taste aversion learning (Reilly and Trifunovic, 2000). The PBN appears necessary for taste aversion acquisition but not expression (Grigson *et al.*, 1997b). The PBN may be involved in at least three of the CTA stages described earlier: CS detection, US detection, and the associative mechanism (for review, see Reilly *et al.*, 1993; Reilly, 1999). The associative function for the medial PBN has been supported by results obtained using reversible and/or permanent lesions (see Spector, 1995; Grigson *et al.*, 1998; Reilly, 1999). The effects of lateral PBN lesions on lithium-induced CTA are controversial (Sakai and Yamamoto, 1998; Reilly and Trifunovic, 2000; Mediavilla *et al.*, 2000), and it seems that distinct regions of the nucleus are implicated in different ingestive behaviors such as neophobia and anorexia induced by systemic injection of CCK (Reilly and Trifunovic, 2001). *c-Fos* experiments have clearly shown that the external lateral subnucleus of the PBN is a critical site receiving aversive information of different USs and is important for acquisition but not for retrieval of a CTA (Sakai and Yamamoto, 1997). An altered pattern of activity is required for CTA acquisition (Swank *et al.*, 1996), and *c-Fos* induction during CTA expression varies with the number of aversion conditioning trials and conditioning methods (Navarro *et al.*, 2000a,b; Spray *et al.*, 2000). Bures and Buresova (1990) believe that the CTA engram is formed in the PBN after this structure has received descending gustatory information from the gustatory IC. Thus NST appears to have a primary role in sensory processing, whereas the PBN, besides its sensory role, appears to have a major role in associative and regulatory tasks (Ivanova and Bures, 1990a,b; Spector *et al.*, 1992; Reilly *et al.*, 1993; Spector, 1995; Grigson *et al.*, 1998; Reilly, 1999; Gallo *et al.*, 1999b). Moreover, the data underscore a role for the pontine taste nucleus in associative, rather than in memory processes, and support the conclusion that CTA deficits following PBN lesions reflect interruption of the connections between the pontine nuclei and forebrain (Grigson *et al.*, 1997a).

Parvicellular Division of the Ventroposteromedial Nucleus of the Thalamus

The different CTA paradigms used in early thalamic lesion studies in rats makes it difficult to compare the outcomes. The first studies (Loullis *et al.*, 1978; Lasiter *et al.*, 1985b) showed that electrolytic lesions of VPM severely attenuated or abolished CTA. Animals lacking both the olfactory bulbs and VPMpc could not acquire CTA (Lasiter, 1985). However, more recent research has failed to replicate these deficits (Flynn *et al.*, 1991; Reilly and Pritchard, 1996; Scalera *et al.*, 1997). It has been shown that the integrity of VPMpc is not critical for acquisition of a CTA (Scalera *et al.*, 1997). Moreover, rats with bilateral neurotoxic lesions of the VPMpc learned their taste aversions in a single trial, thus making mediation solely by olfactory cues extremely unlike (Scalera *et al.*, 1997). Yamamoto *et al.* (1995) showed that excitotoxic lesions of VPMpc have little effect on the acquisition of CTA; but combined lesions of the gustatory thalamus and insular cortex (IC) almost completely disrupted the acquisition of CTAs. Recently, it has been shown that an intact VPMpc is critical for the suppressive effects of substances of abuse, but not for those of LiCl in a CTA paradigm (Grigson *et al.*, 2000). It has been shown that decerebrate rats are incapable of forming the association necessary for taste aversion learning (Grill and Norgren, 1978; Schafe *et al.*, 1995a–c), which suggests that integration of taste and visceral input within the brain stem of the rat is insufficient to support the acquisition or expression of taste aversions (Bernstein, 1999a). Taken together, the more recent results (Flynn *et al.*, 1991; Yamamoto *et al.*, 1995; Reilly and Pritchard, 1996; Scalera *et al.*, 1997; Grigson *et al.*, 2000) provide convincing evidence that "the gustatory thalamus has little functional significance in the acquisition of simple (i.e. first-order) taste aversion learning" (Reilly, 1998). There is, however, indication that the gustatory thalamus may contribute to more complex forms of aversion learning (i.e. taste attenuated odor aversion learning, autoshaping, anticipatory negative contrast, etc.) (Reilly, 1998). In humans, like in the monkey, the thalamic taste relay mediates multiple sensations in addition to taste (Lenz *et al.*, 1997).

Amygdala

The AM in mammals can be divided into two main nuclear groups: a phylogenetically older group composed of the medial, central and cortical nuclei; and a phylogenetically new group composed of lateral and basal nuclei. Both divisions have extensive interconnections with many other parts of the nervous system (hypothalamus, prepiriform and orbital frontal cortex, thalamus, all sensory modalities, limbic system, brain-stem area), and together with the IC, influence autonomic activity and receive visceral afferent inputs (for an exhaustive review, see Aggleton, 1992; Davis, 1994). The AM receives gustatory, visceral, and olfactory afferents (Norgren, 1974; Swanson and Petrovich, 1998); in the monkey, the PBN projects heavily to the central nucleus of the AM (Pritchard *et al.*, 2000). Moreover, it receives projections from brainstem nuclei involved in CTA (Karimnamazi and Travers, 1998), and returns projections to the PBN (Petrovich and Swanson, 1997; Lundy and Norgren, 2001) and NST

(Schafe *et al.*, 2000). Various kinds of studies (electrophysiological, neurochemical, behavioral, lesions, etc.) suggest an involvement of the AM in CTA behavior; but, these results are questionable and contradictory. Electrophysiological recording from AM neurons after induction of CTA in rats suggests that not all the amygdaloid nuclei are involved in the formation of CTA (Yasoshima *et al.*, 1995). *c-Fos* studies pointed out a role of AM in CTA learning (Lamprecht and Dudai, 1996; Yamamoto *et al.*, 1997). However, the data obtained in lesion studies are particularly conflicting and contradictory. Indeed, they show either no effect on CTA acquisition (Simbayi *et al.*, 1986; Touzani *et al.*, 1997; Bermudez-Rattoni and McGaugh, 1991), attenuation (Gallo *et al.*, 1992; Yamamoto *et al.*, 1995; Bermudez-Rattoni and Yamamoto, 1998; Aja *et al.*, 2000), or disruption (Yamamoto and Fujimoto, 1991; Roldan and Bures, 1994; Yamamoto *et al.*, 1994; 1995; Bielavska and Roldan, 1996; Schafe and Bernstein, 1996; Morris *et al.*, 1999; Rollins *et al.*, 2001). The different behavioral procedures used to induce CTA (i.e. intraoral cannula, bottle presentation, etc.) and the different types of lesions might explain these contradictions at least in part (Schafe *et al.*, 1998; Bernstein, 1999a; Gallo *et al.*, 1999a,b). Molecular neurobiology experiments have pointed out that the AM is involved in the formation of long-term CTA memories and that the parameters for this involvement may depend on the amygdalar glutaminergic neural transmission (Lamprecht *et al.*, 1997; Yasoshima and Yamamoto, 1997; Tucci *et al.*, 1998; Yasoshima *et al.*, 2000). The AM is also capable of modulating the ability of the gustatory IC to form taste memory (Escobar and Bermudez-Rattoni, 2000), and it is involved in the cholinergic modulation of the memory (Gutierrez *et al.*, 1999a–c). Impairment of taste-conditioned immunosuppression after AM lesions has also been reported (Ramirez-Amaya *et al.*, 1998; Ramirez-Amaya and Bermudez-Rattoni, 1999). In the primate, the AM and its associate circuitry appears to be relevant in conditioned food reinforcement (Parkinson *et al.*, 2001). In humans, PET and fMRI experiments showed that the AM, orbitofrontal and prefrontal cortex respond to both olfactory and gustatory unconditioned aversive stimuli (Pardo *et al.*, 1997; Zald *et al.*, 1998; Schneider *et al.*, 2000). These authors stated that aversive taste stimuli activate a network of interconnected limbic and para-limbic structures and that "the capacity of these regions to respond during exposure to aversive stimuli may underlie their role in avoidance learning and emotional conditioning" (Zald *et al.*, 1998).

Insular Cortex

In the rat, the IC approximately includes the area from the lateral frontal cortex to the perirhinal cortex and from the ventral edge of the somatomotory cortex to the piriform cortex (Saper, 1982; Zilles, 1985). The gustatory neocortex is located in the dysgranular IC and the viscerosensory cortex in the granular cortex caudodorsal to the gustatory neocortex (Yamamoto, 1984; Kosar *et al.*, 1986; Cechetto and Saper, 1987; Ogawa *et al.*, 1990; Ito, 1992). The gustatory cortical neurons may participate in chemosensory coding in response to different tastants at different times. Temporal analysis of these neurons also permits the separation of gustatory responses into their somatosensory and chemosensory components (Katz *et al.*, 2001). The IC neurons distributing between the taste and the visceral areas receive convergent inputs from visceral and gustatory organs and may have a role in taste aversion learning or in the regulation of visceral responses (van der Kooy *et al.*, 1984; Hanamori *et al.*, 1998). It has been suggested that the primary sensory inputs and the signals arising from the limbic system converge onto the IC, and this convergence may be important for mnemonic processes (Krushel and van der Kooy, 1988). Permanent or reversible lesion studies have shown that the IC is required for CTA acquisition and other taste-related tasks (Yamamoto *et al.*, 1981; Lasiter and Glanzman, 1985; Dunn and Everitt, 1988; Bermudez-Rattoni and McGaugh, 1991; Gallo *et al.*, 1992; Nerad *et al.*, 1996). However, the effect of IC lesions depends on the adopted behavioral paradigms (Kiefer *et al.*, 1985; Yamamoto, 1994) and on the size and location of the lesions (Nerad *et al.*, 1996). Lesions of the IC do not disrupt hedonic responses to taste, but they attenuate or impair taste aversion learning (Braun *et al.*, 1982); moreover, IC integrity is more important for CTA retrieval than for CTA acquisition (Yamamoto *et al.*, 1995; Ormsby *et al.*, 1998). Combined lesions of the IC and AM completely disrupt CTA acquisition suggesting that both structures are complementary, in the sense that IC may support CTA acquisition when the AM has been eliminated, and vice versa (Yamamoto *et al.*, 1995). It has been hypothesized that IC is also crucial for taste-potentiation of odor (Kiefer *et al.*, 1987). This hypothesis may be plausible since "gustatory and olfactory information may converge, at least in part, to the IC and that this convergence contributes to the sensations described by humans as flavors" (Bermudez-Rattoni and Yamamoto, 1998). Several studies show that the ipsilateral cortical feedback to the taste nuclei in the brainstem is critical for CTA acquisition (Allen *et al.*, 1991; Gallo and Bures, 1991; Di Lorenzo and Monroe, 1992; Schafe and Bernstein, 1998). IC seems to be involved in taste memory processes that could be relevant at different stage of CTA acquisition and expression. Indeed, IC could be involved in "keeping the memory of the CS during delay, in modulating the new taste memory established after the association in the PBN, in

memory consolidation processes, in memory retrieval, or even in storing the long-term CTA memory" (Gallo *et al.*, 1999a). The existence of short- and long-term excitability enhancement of neurons activity in the IC (short-term rostrally; long-term caudally) after CTA learning suggests that the IC is involved in short- and long-term CTA acquisition (Yasoshima and Yamamoto, 1998), even if the results of Rabin *et al.* (1983) do not support long-term storage by CTA memory. Long-term potentiation enhances CTA retention (Escobar and Bermudez-Rattoni, 2000). It has been reported that multiple neurotransmitters and neuromodulators are required for encoding taste memory in the IC (Berman *et al.*, 2000). For example, when a rat samples a novel taste, some molecular mechanisms are activated in the IC that probably encode the saliency on one hand, and trigger long-term memory of the new taste on the other hand (Naor and Duday, 1996; Rosemblum *et al.*, 1997; Schafe and Bernstein, 1998; Berman *et al.*, 2000; Miranda *et al.*, 2000). In the IC, the cholinergic system is involved in CTA formation, and it plays an obligatory role in encoding the representation of the CS (a novel taste) but not of the US; moreover, a relationship between the familiarity of a taste and cortical ACh release has been described (Shimura *et al.*, 1995; Naor and Duday, 1996; Gutierrez *et al.*, 1999a; Misanin *et al.*, 2000). ACh, compared to other neurotransmitters, is directly involved in the recovery processes of the acquisition of CTA induced by homotopic cortical transplant. Indeed, homotopic fetal neocortex transplant in IC lesioned rats induces recovery of a previously learned CTA (Ormsby *et al.*, 1998) or a new CTA acquisition since the transplant induces an increase of Ach levels in IC (Miranda *et al.*, 1997; Miranda and Bermudez-Rattoni, 1998). Furthermore, a novel taste activates the extracellular signal-regulated kinase 1-2 (ERK1-2) which seems necessary for encoding long-term but not short-term memory of the new taste (Berman *et al.*, 1998; 2000). In the IC, protein kinase C activation (Yasoshima and Yamamoto, 1997; 1998), protein tyrosine phosphorylation of NMDA receptors and/or NMDA receptors activation (Rosemblum *et al.*, 1995; 1997; Gallo *et al.*, 1988; Escobar *et al.*, 1998a,b; Gutierrez *et al.*, 1999c), c-AMP mediated gene transcription (Dudai, 1987; Lamprecht *et al.*, 1997), new protein synthesis (Rosemblum *et al.*, 1993; 1995; Serova *et al.*, 1996; Gallo *et al.*, 1998), are important for CTA learning. NMDA-induced lesions of the IC and AM, but not of the parietal cortex and hippocampus disrupt the acquisition of a CTA and conditioned immune response (Ramirez-Amaya *et al.*, 1996; 1998; Ramirez-Amaya and Bermudez-Rattoni, 1999).

Recently, Scott and Plata-Salaman (1999) showed that the alert macaque offers a reliable neural model for human representation of gustatory modality and intensity-response functions to the basic taste stimuli. Even if data obtained by brain imaging techniques are limited, the results suggest the presence of multiple gustatory areas within the insula/opercular cortical region of the human brain. Moreover, these results show that the dorsal and ventral insula, frontal and parietal operculum correspond to the three gustatory regions identified in non-human animal studies (Small *et al.*, 1999). Furthermore, it seems that the preferential processing of higher-order gustatory function is located in the right cerebral hemisphere (Small *et al.*, 1997). Small *et al.* (2001a) showed that the anterior temporal lobe is involved in taste perception in human subjects. They compared taste intensity estimations made by patients who had removal from either the left or the right anterior temporal lobe for the treatment of intractable epilepsy with a group of healthy subjects, and they found that the subjects in the right temporal group rated the bitter taste as more intense that did subjects in control groups. They concluded that the anteromedial temporal lobe (AMTL) in humans "is important for processing aversive taste, and suggests that inhibitory mechanisms may play an important role in such processing" (Small *et al.*, 2001b). Cerf *et al.* (1998), using the fMRI technique, found activation in the insula and perisylvian region in agreement with previous electrophysiological studies on monkeys and clinical reports in humans; they also found a lateralization of brain processing involved in taste perception (see Pritchard *et al.*, 1999; Aglioti *et al.*, 2000).

Other Areas

Some other areas of the brain [hypothalamus (Caulliez *et al.*, 1996; Tucci *et al.*, 1998), globus pallidus (Hernadi *et al.*, 1997), hippocampus (Gallo *et al.*, 1999a,b), entorhinal cortex (Yamamoto *et al.*, 1995), prefrontal cortex (Hernadi *et al.*, 2000), Zona Incerta (Sakai and Yamamoto, 1999), septum (Compton and Weed, 1992; Turgeon *et al.*, 2001), perirhinal cortex (Tassoni *et al.*, 2000), nucleus basalis magnocellularis (Gutierrez *et al.*, 1999b; Miranda and Bermudez-Rattoni, 1999; Gonzales *et al.*, 2000), nucleus accumbens (Fenu *et al.*, 2001)] have been suggested to be interested in CTA, but the results are at the moment inconsistent, ambiguous and incomplete.

CONDITIONED FOOD AVERSIONS IN HUMANS

The CTA has been extensively investigated in a wide variety of laboratory and wild animal species but only incidentally in humans. The toxic nature of the USs (chemicals, radiation, drugs, etc.) employed in taste aversion protocols in animals has prevented

controlled experiments in human subjects. Indeed, ethical problems preclude similar investigations in humans, even if chemical aversion therapy for alcoholism is employed with some success (Lemere and Voegtlin, 1950; Boland *et al.*, 1978). Nevertheless, interview studies have documented that many people experienced the development of aversions as a result of a food-illness pairing (Garb and Stunkard, 1974). Some reports on taste aversions in man provided convincing evidence that CTA learning is possible in a wide age range of human subjects (Garb and Stunkard, 1974; Bernstein and Webster, 1980; Logue, 1985), although the role it plays in human food selection remains quite unexplored. The accumulation of learned aversion can continue throughout the life span. When there is a coincidental association between consumption of a food and gastrointestinal discomfort (nausea, vomiting, stomachache, etc.), humans may develop a CTA (Logue, 1985). Nausea and vomiting are apparently not necessary part of the unconditioned stimulus complex in the acquisition of taste aversions in humans; but other symptoms, such as fatigue and/or numbness are effective (Bernstein and Webster, 1980). The cognitive development of humans, which enables them to understand that their discomfort is ascribable to causes unrelated to the foods eaten, does not override the conditioning (Bernstein and Webster, 1980). Taste aversions are frequently acquired by humans even though they are convinced that the food to which they formed the aversion did not make them sick (Logue, 1985). Thus, CTAs appear to "defy" cognition, and "strong aversions arise despite a person's awareness that the target food was not actually the cause of their illness" (Bernstein, 1999a). These findings suggest that in humans, as in rats, the CTA is probably based on relatively primitive associative mechanisms in the sub-cortical structures of the brain. Since food aversion learning is a powerful and primitive form of learning, one might ask what role this learning plays in the everyday food preferences of normal healthy people. Conditioned food aversions, consciously or unconsciously, may play a significant role in human food choices and hedonic responses to foods, even if this role is quite difficult to assess methodologically (Bernstein, 1999a). Some people who are chronically sick and/or experiencing unpleasant gastrointestinal distress may more easily develop a CTA against some foods and limit their acceptability and choices, thus sometimes inducing anorexia (Bernstein and Borson, 1986; MacIntosh *et al.*, 2000). Like many sub-human species, humans learn CTA after one or two pairings of CS and US. CTAs are more readily learned when the target food is novel rather than familiar; and learning is better when the CS precedes the US ("forward conditioning" in opposition to "backward conditioning", when the CS follows the US) (Garb and Stunkard, 1974; Bernstein, 1978; Cannon *et al.*, 1982; Midkiff and Bernstein, 1985; Logue, 1985). Pure backward conditioning is as difficult in humans as in animals, but backward and forward conditioning cannot be well separated in cases when vomiting and regurgitation return the stomach content into the mouth cavity so that overlap of the CS and US may change the typical trace conditioned response (CR) into a simultaneous CR. Difficult acquisition of CTA with backward conditioning may explain why some therapists have had difficulty to induce taste aversions to alcoholic beverage in a large percentage of their subjects (Wiens *et al.*, 1976; Logue, 1985; Amit *et al.*, 1991).

Usually, in healthy people with a broad range of food preference, food aversion learning plays a relatively minor role in establishing food and fluid intake, but in people disliking many kinds of food, with a fussy appetite or narrow preference ranges, it may assume a relevant aspect because they may experience frequent pairings of specific foods with symptoms of malaise. Such people may not be able to select alternative non-aversive food choices, and thus they may progressively reduce their food intake (Bernstein, 1991). Most vulnerable to this effect are children, who usually tend to avoid new flavors (Birch and Marlin, 1982; Birch, 1998); older adults, who often show social distress (poverty, solitude, etc.), problems with mastication, swallowing, and altered taste and olfaction sensitivity (MacIntosh *et al.*, 2000); and people who tend to consume a narrow range of foods for ethnical and/or religious beliefs. These considerations lead to the hypothesis that in humans learned food aversions might play an etiologic role in appetite and body weight loss. This hypothesis has been clearly shown in laboratory animals, where learned food aversions can lead to anorexia and body weight loss (Logue *et al.*, 1983). In humankind health, direct evidence implicating food aversions in anorexia nervosa is lacking even if, in a study with 19 anorexic/bulimic women, a total of 58% of these subjects reported taste aversions (Campbell and Coulter, 1976; Logue, 1985; Bernstein and Borson, 1986; Lesko, 1989; Ohzeki *et al.*, 1994; Van Binsbergen *et al.*, 1988; Vaz *et al.*, 1988).

Since ethical reasons prohibit experiments on taste and food aversions conditioning in humans, it has been necessary to rely on retrospective questionnaires and interviews of aversions occurring naturally over life. This methodology is questionable because the data collection (questionnaire and/or interviews) may be affected by the conditions under which the subjects are asked to report these aversions. Even if comparing results across studies is difficult unless the conditions of data collections are constant and the questionnaire standardized, surveys are currently the only method applicable to

humans. In a pioneering report, Garb and Stunkard (1974) surveyed 696 subjects of different ages and culture (from children to elders; from elementary students to University professor emeritus) using a self-report questionnaire or an oral questionnaire for preschool children. They found that 38% of subjects reported taste aversions at some times in their lives. But, Logue *et al.* (1981) in a study involving 517 college students, report that 65% of the subjects had taste aversions. This result was higher than that of Garb and Stunkard but similar to that of Midkiff and Bernstein (1984), who obtained positive results of taste aversions (57%) from a questionnaire distributed to 856 undergraduate students. The discrepancy between this data may depend on the age range of subjects surveyed. Indeed, subjects recruited in the studies by Logue *et al.* (1981) and by Midkiff and Bernstein (1985) were all college students with homogeneous age, whereas those in Garb and Stunkard (1974) had a higher age distribution.

Since most studies on taste and food aversions in human were obtained by surveying college students, only limited data are available on the incidence and extension of aversions in the elderly. These data might be of interest to explain and correct some of their negative alimentary habits. Even if empirical evidence is not yet available, it is possible to speculate that a set of several physiological, psychological, social, economical, medical, and physical factors might contribute to the vulnerability of the elderly toward development of food aversions that could compromise their nutritional status (Bernstein, 1999b; Rolls, 1999; MacIntosh *et al.*, 2000). Frequently, the elderly take multiple medications, which increases the risk of drug interactions that can cause anorexia and/or malnutrition (MacIntosh *et al.*, 2000). It is clear that some decrements in taste and olfactory perception occur normally in healthy people around 60 years old, and it may be more severe in sick elderly (Ship, 1999; Finkelstein and Schiffman, 1999; MacIntosh *et al.*, 2000). Age-associated changes in taste may influence food choice in elderly; for example, in healthy elderly the preference for salty foods decreases (Drewnowski, 1997). Studies of age-related changes in taste and smell generally suggest that there are more substantial declines in olfactory sensitivity and memory than in gustatory sensitivity (Stevens *et al.*, 1984; Schiffman, 1986; Cain and Murphy, 1987); nevertheless, aging impairs the ability to discriminate foods and odors (Schiffman and Pasternak, 1979; Schiffman, 1997; MacIntosh *et al.*, 2000). In the elderly, chemosensory deficits can alter food choices and intake and subsequently exacerbate medical conditions (Schiffman *et al.*, 1999) and impair nutritional status inducing CFA that may produce weight loss, anorexia and malnutrition (Rolls, 1999). Flavor enhancement of foods can improve food palatability and acceptance, reduce the possibility to form CFA, increase energy intake, salivary flow, and improve mood and quality of life in elderly (Schiffman, 1998; 2000). Interestingly, Garb and Stunkard (1974) found that higher rates of aversions were in the youngest age group (6–12 years; 30%), and the lowest rate (6%) in the oldest subjects (over 60 years old). Recently, Pelchat and LaChaussee (1994), reported that 77% of young referred food aversions and about 56% of elderly subjects surveyed reported a similar experience. Even if the rates between these two studies are significantly different, in both studies, the trend shows that a significantly smaller percentage of old people reported having learned food aversions than young people. Why elders acquire less number of food aversions is not yet clear (Rolls, 1999). A speculative hypothesis might be that the old people prefer to eat every day the well-known foods. The decline in sensory-specific satiety could further contribute to the consumption of a less varied, more monotonous diet in the elderly inducing micro- and macro-nutrient deficiencies that may compromise both their nutritional status and immune function (MacIntosh *et al.*, 2000). Studies in old rats have been reported no decline in the strength of food aversion conditioning (Guanowsky *et al.*, 1983), and in cattle aversions are retained better in mature that in young animals (Ralphs and Provenza, 1999). Misanin and coworkers widely studied CTA learning in weanling (20–25 days), young-adult (90–105 days), and old (over 635 days) rats. They found that taste-illness associations (CTA) in old rats are stronger than in young-adult rats (Guanowsky *et al.*, 1983). Cs-pre-exposure attenuates CTA only in old rats, whereas it eliminates CTA in young-adult rats and leads to a latent inhibition of CTA in weanling rats (Misanin *et al.*, 1983). The simultaneous presence of a familiar odor during CTA acquisition potentiates CTA learning in young-adult but not in weanling and senescent rats (Peterson *et al.*, 1985; Hinderliter and Misanin, 1988). The possibility of stronger aversions in aged rats due to a higher sensitivity to the US has been advanced (Misanin and Hinderliter, 1994). Indeed, manipulation of the intensity of the US (LiCl concentrations) explains the superior CTA performance of old-aged rats (Misanin *et al.*, 1985; Misanin and Hinderliter, 1994). The response to manipulation of the CS may also be influenced by the age of rats (Martin and Timmins, 1980). Indeed, it seems that old-aged rats forget the specifics of the CS sooner than young-adult rats and show greater stimulus generalization (Misanin and Hinderliter, 1994). Some intermediate effects between the combined remote and proximal US pre-exposure in old-age rats points to an attenuation of CTA (Valliere *et al.*, 1988; Misanin *et al.*, 1997; 2000). The role of context familiarity and delay in CTA learning may differ with age; indeed, it

is important in CTA learning for young-adults but not for old-aged rats (Hinderliter and Misanin, 1993). Thus these data do not confirm the trend demonstrated in humans. The discrepancy between trends in old humans and old animals may depend on the accuracy and sensitivity of the methods used. Indeed, human interview and questionnaire methods are less accurate and sensitive than experiments performed on laboratory animals.

Theoretically, under natural conditions, any given food or beverage may become aversive when it precedes illness, but the probability is not constant, and aversions are acquired to some foods much more easily than to others. Humans, like lower animals, naturally acquire taste aversions more easily to foods that are less familiar, neutral or less preferred (Etscorn, 1973; Garb and Stunkard, 1974; Kalat, 1974). Although unfamiliarity with a food may increase the possibility of forming an aversion to that food, a total lack of experience with a food may completely remove any chance of forming an aversion to that food. The "opportunity effect" (Logue, 1985) may be another cue responsible for aversions forming more often to certain foods and/or beverage than to others. A typical example of the *opportunity effect* is shown by aversion to alcohol in young people. Indeed, one-fourth of the aversions acquired by college students and hospitalized alcoholics was against alcoholic beverages (Logue *et al.*, 1981; 1983; Midkiff and Bernstein, 1985). Alcohol aversions show a sharp peak of incidence around the age of 17, since prior to that age children do not have access to alcohol, but when school-age children experiment with alcohol, it is very likely that they acquire aversions because they usually overdrink.

An interesting matter is the study of factors influencing the tendency of various foods to develop aversive behaviors. A general survey shows that many factors may induce taste aversions. Logue (1985) reported that not all the differential tendencies of various foods to become aversive are consistent with an explanation based on differences in prior preference and familiarity of those foods. For example, tendency to form aversions towards hot-dogs is higher than that for hamburgers. This may be due to the relatively worse reputation of hot-dog ingredients. A "social facilitation" (Ralphs and Provenza, 1999) may be responsible for this prejudice. In this case, social and/or cultural opinions and irrational prejudice concerning hot-dogs may be based on a personal experience, whereas the formation of taste aversion to a food is probably not (Logue, 1979; 1985). Usually, a meal is inclusive of some foods, and thus it is not always easy to identify which caused the aversion. When a subject has consumed several foods including one reputed to cause illness and then become sick, there is a greater tendency to acquire an aversion to the food with the bad reputation. For example, shellfish have the reputation of frequently causing illness, and they represent 62% of the total aversion to fish (Logue, 1985). Thus, if people become sick after a meal that includes shellfishes, they in the major part of cases will refer the sickness to the shellfish.

The principal characteristics of a CS that increase the associability with illness are taste and smell intensity and texture (flavor), novelty, food preference, and compositions. Aversions are more likely to be formed to less preferred and less familiar foods, although aversions to some foods that are also highly preferred are acquired (Logue *et al.*, 1981). Indigestion (dyspepsia) accompanied by pain or discomfort in the lower chest or abdomen, nausea and vomiting may follow the ingestion of a large amount of preferred foods. In this case, people may erroneously refer aversions to the quality instead of the quantity of foods eaten. In any case, "it is impossible to say definitively whether certain foods ranked highly in terms of number of aversions reported to them because they actually make people ill more often than do other foods, or whether illness is just attributed to them more often and so aversions form to them more often, or a mixture of these two factors" (Logue, 1985). Another interesting aspect of food aversions is whether some types of foods are more likely to be targets of aversions than others on account of their nutrients content. The categories of foods that may be considered major protein sources (eggs, milk, cheese, red meats, poultry, fish) constitute about 42% of all food conditioned aversions (Midkiff and Bernstein, 1985; Mooney and Walbourn, 2001). Categories of foods that infrequently form targets for aversions are sweet (sugar, candies, cakes, pies, etc.) or non-sweet carbohydrates (bread, crackers, flour products, rice, potatoes, etc.) (Logue, 1985; Midkiff and Bernstein, 1985). Experiments in rats self-selecting diets from separate protein and carbohydrate sources consistently developed aversions to proteins but not to carbohydrates (Bernstein *et al.*, 1984). Thus the survey findings in humans that protein sources are more salient targets for aversion learning than other nutrients, are also supported by results obtained in rats. However, it is unclear whether the aversion to protein sources is based on flavor properties intrinsic to the protein, or on their post-ingestive consequences. Dairy products are a case a part since controversial data are present in the literature. Logue *et al.* (1981), found that dairy products ranked high in preference and high in the number of reported aversions. They explained aversions by the fact that dairy products can sometimes cause unpleasant abdominal discomfort and reactions (diarrhea, abdominal pain, stomachache, borborygmus, bloating, etc.) in persons who lack lactase, the enzymes which digests the milk sugars (lactose). On the

contrary, Midkiff and Bernstein (1985) found that diary products form only 5% of all aversions and hus they are significantly underrepresented as targets for aversions. The controversy may be due to the selection of dairy products included in the questionnaire surveyed by the subjects. For example, Midikiff and Bernstein (1985), excluded dairy desserts but stated that milk and butter constitute the overwhelming majority (78%) of such items on diet lists, and these familiar items are unlikely targets for aversions.

A learned taste aversion to a particular CS will generalize to other tastes that are similar to the CS. Studies examining generalization of CTAs have been used to examine the qualitative characteristics of taste perception and thresholds in animals. Generalization is also present in humans that generalize their aversions to foods that taste qualitatively similar (Logue *et al.*, 1981). For example, these authors found that an aversion to fried chicken generalizes to other fried foods; an aversion to chocolate cookies generalizes to other foods containing chocolate; an aversion to alcohol may generalize to most strong-smelling and strong-tasting liquors. However, some people do not generalize their aversions. For example, hospitalized alcoholics and college students who are "heavy-drinkers" do not generalize their aversions to alcohol. This behavior is probably not related to the quality of the alcoholic beverage ingested but rather to excessive drinking, which frequently causes gastrointestinal discomfort and pain. Thus, alcoholics treated using a taste aversion paradigm will sometimes simply switch to drink another alcoholic beverage that has not been paired with illness (Quinn and Henbest, 1967; Mellor and White, 1978).

People avoid different foods and have different reasons for doing so. Taste is not always responsible for food aversions or rejections (Mooney and Walbourn, 2001), even if it has been reported that taste is the most important influence on food choice, followed by the cost of foods (Glanz *et al.*, 1998). Specific socio-cultural issues such as sex, weight, health, unnatural content of food, and ethic considerations may influence decisions to reject certain foods were examined in a total of 113 college students of both sexes (Mooney and Walbourn, 2001). Body weight problems were the most prevalent reasons for consciously avoiding a certain food. The most frequently rejected food was meat, followed by vegetables. Rationales for these rejections include ethics of raising/killing animals, health concerns, disgust and influence of peers friends (Santos and Booth, 1996; Mooney and Walbourn, 2001).

FOOD AVERSIONS IN CANCER PATIENTS

Among many other problems, more than 50% of cancer patients frequently complain of impaired taste and smell function during the course of disease and treatments, which may be associated with decreased food intake and body weight loss (DeWys and Walters, 1975; DeWys, 1979; Shils, 1979; Kern and Norton, 1988; Fearon and Carter, 1988). Malnutrition commonly occurs in cancer patients and adversely affects their quality of life and survival (Holmes, 1993). It is caused by a variety of factors, including decreased food intake, adverse effects from anticancer treatment, and wasteful metabolic processes. Dietary factors may be associated with modification of the risks of breast cancer recurrence and death after diagnosis (Saxe *et al.*, 1999), and an analysis of food avoidance may provide information as to the dietary guidelines and adequate nutrient consumption among these patients (McEligot *et al.*, 2000). Today, the cachexia–anorexia syndrome is a common, and devastating symptom encountered by cancer patients; moreover, patients with these problems lose their "locus of control" and become dependent on others (MacDonald, 2000). The causes of cancer anorexia and cachexia remain poorly understood, but both may come from the disease itself, from other symptoms associated with the illness, and from side effects associated with treatments (MacIntosh *et al.*, 2000; MacDonald, 2000; Plata-Salaman, 2000). It has been shown that cancer anorexia is influenced by sex-related hormones, and probably an interaction exists between cytokines and estradiol (Varma *et al.*, 2001). The release of cytokines, interleukins, and tumor necrosis factors in cancer patients seems to produce anorectic effects (Plata-Salaman, 1998; Langhans and Hrupka, 1999; MacIntosh *et al.*, 2000). Cytokine immunotherapy also induces the production of a large array of endogenous cytokines which may act synergically to cause anorexia, taste aversion and other neuropsychiatric manifestations (Plata-Salaman, 2000). The onset of anorexia in tumor-bearing rats (TB) is correlated with both an increase in serotonin and decrease in dopamine brain concentration (Muscaritoli *et al.*, 1996; Varma *et al.*, 1999; Meguid *et al.*, 2000b). Often, the use of chemotherapy as well as acute small or large bowel irradiation leads to taste aversion and consequently to decrease of food intake. It has also been shown that taste aversion in rats can be conditioned with radiation exposure when a sweet solution (saccharine) is injected intravascularly instead of the usual oral ingestion (Bradley and Mistretta, 1971). Thus, chemotherapeutic drugs injected intravascularly in cancer patients might also produce taste aversion, apparently without modification of taste sensation. In fact, systemically applied drugs (e.g. cyclohexamide, cyclophosphamide) are often used as US in most CTA experiments in animals (Revusky and Martin, 1988; Elkins *et al.*, 1992), but this does not mean that they modify taste sensations and/or taste

preferences (Di Bella *et al.*, 1981). Treatment of anorexia and its ravaging effects in patients affected by cancer is a serious problem for patients and physicians. Artificial nutrition might allow a patient to complete a treatment course of chemotherapy or radiation therapy (Bozzetti, 1997). The two main routes of providing nutritional support are enteral and parenteral (Cohen and Lefor, 2001). Enteral feeding (EN) and parenteral nutrition (PN), are both effective ways to deliver nutrients directly into the gastrointestinal tract or into the blood stream when patients are unable to ingest food. The role of EN as an adjuvant to anticancer therapy has not been fully evaluated, but numerous studies have assessed the role of PN as adjuvant therapy. A clear benefit from their routine use has been demonstrated only in very limited specific situations. As an adjuvant to chemotherapy or radiotherapy, total PN has not been particularly successful with cancer patients, and the usefulness of this method have not been very encouraging (Hill and Daly, 1995; Shike, 1996; MacIntosh *et al.*, 2000; Nitenberg and Raynard, 2000; Cohen and Lefor, 2001). Even if experimental data in humans are not available, both EN and PN feeding might theoretically develop a CFA that worsens the patient's quality of life. Thus, further studies are needed to determine the efficacy of such novel approaches in specific populations of cancer patients and should also address the question of the overall cost-benefit ratio and the effect of EN or PN support on length and quality of life (Nitenberg and Raynard, 2000; Cohen and Lefor, 2001). Patients may develop aversions toward foods or beverages when they are associated with some aspects of the malaise accompanying cancer or its treatments (Smith *et al.*, 1984; Bernstein, 1985; Mattes *et al.*, 1992). Moreover, several lines of evidence have implicated CFAs in the syndrome of cancer anorexia and cachexia (Bernstein, 1986). The incidences of CFA in cancer chemotherapy and radiation therapy regimens were 56% and 62%, respectively (Mattes *et al.*, 1992). It is interesting to note that these percentages do not differ significantly from that in healthy people (Garb and Stunkard, 1974; Logue *et al.*, 1981; Midkiff and Bernstein, 1985).

In light of the evidence that, in some cases, the nutritional status of a patient may influence the treatment efficacy (Donaldson *et al.*, 1981; Nitenberg and Raynard, 2000), it is important to clarify the influence of food aversions on ingestive behavior and nutritional status. Moreover, food aversions may adversely influence the quality of life of a patient because highly preferred and commonly consumed foods often become aversion targets. In this regard, it is important to note that aversions are usually directed to specific foods consumed before cancer chemotherapy and/or radiation therapy (Bernstein, 1978; Bernstein and Webster, 1980; Smith *et al.*, 1984). Frequently consumed and highly preferred items such as chocolate, coffee, and meats (especially red meats) are particularly prone to cause aversive problems (Mattes *et al.*, 1992). It was found that such foods frequently became the targets of learned aversions. For example, the consumption of an ice-cream before chemotherapy may reduce the aversions that would develop to foods in the normal diet (Broberg and Bernstein, 1987). This "interference effect" in food aversion acquisition is consistent with results from studies in rats (Bernstein *et al.*, 1980), and, prompted by these findings, Broberg and Bernstein (1987) studied the possibility that exposure to novel tastes may be an effective approach for preventing the formation of learned aversions to familiar and more nutritious foods. Consumption of strongly flavored candies before chemotherapy (Broberg and Bernstein, 1987) or specific fruit juice before radiotherapy (Smith *et al.*, 1985) appear to be a simple and effective way to reduce the impact of chemotherapy or radiotherapy on preference for normal diets. The basis for this effectiveness is presumed to be the development of aversions to the "scapegoat" which then block or interfere with the development of aversions to other food or tastes (Broberg and Bernstein, 1987). The scapegoat technique is effective in the hospital clinic or ward, and it may be safely employed to reduce conditioned aversions to home-prepared meals that, due to their familiarity, are weaker targets for aversions (Nakajima *et al.*, 1999). Thus, consumption of a strongly flavored food before chemotherapy may be an effective and simple intervention for preventing or blocking the impact of chemotherapy on the formation of learned aversions. An anticipatory nausea and vomiting can be a distressing side effect of cancer chemotherapy. It is also important to note that chemotherapy in patients which have experienced drug-induced nausea and/or vomiting in the presence of a certain set of contextual cues (such as sight, sound, smell) report that these cues themselves become capable of evoking nausea and/or vomiting (Andrykowski and Redd, 1987; Meachum and Bernstein, 1992). A parallel of the clinical state of context of conditioned nausea has also been reported in controlled experiments in rats (Rodriguez *et al.*, 2000). The complex of environmental stimuli, denoted as the "situation" could affect the conditioning process and cannot be ignored (Wyrwicka and Chase, 2001). Thus, contextual-conditioning may be also used as a scapegoat. Previous attempts to prevent the development of aversions have included diet abstinence before treatments. However, as also based on animal studies (Bernstein *et al.*, 1980), it is not recommended that a patient totally fasts before chemotherapy. Additionally, total fasting for the periods of time required to protect foods from aversions is not feasible especially for patients

receiving daily treatments. Indeed, it is evident that aversion conditioning may occur with very long delays (up to 24 h before and after treatment) between the CS (consumption of food) and the US (illness) (Garb and Stunkard, 1974; Logue, 1979; Logue *et al.*, 1981; Mattes *et al.*, 1987). A useful recommendation is that patients eat a moderately small meal at least 4 h before cancer therapy, and that they avoid categories of foods considered major protein sources (red meats, poultry, fish, eggs, milk, cheese products, and some dairy products), since proteins are more salient targets for food aversions than are carbohydrates (Bernstein *et al.*, 1984; Midkiff and Bernstein, 1985). In addition, they should intentionally ingest a novel strongly flavored but not nutritionally important food shortly before treatment ("scapegoat strategy"). Patients should be informed that chemotherapeutic drugs and/or irradiation might create food aversions; this knowledge may decrease the possibility to form new adverse conditionings (Beidler and Smith, 1991). Finally, the "social facilitation" technique (Ralphs and Provenza, 1999) should be of aid to prevent or attenuate the formation of new food aversions conditioning. It has been shown that the social influences on diet choice may be transmitted in rats and cattle (Ralphs and Provenza, 1999; Galef, 1996; Kuan and Colwill, 1997; Galef *et al.*, 1999) and that social learning of flavor aversion is a less generalizable than social learning of flavor preferences (Galef and Whiskin, 2000). Another interesting question is that food aversions generating anorexia in cancer patients can be intrinsic with the disease and may arise as a consequence of the cancer itself. Indeed, laboratory studies using transplantable tumors in rats and mice have shown that tumor growth can be associated with the development of strong aversions to the diet available during tumor growth, and these aversions appear to play an important role in the development of tumor-induced anorexia (Bernstein and Fenner, 1983; Bernstein, 1996; McCarthy *et al.*, 1997), but the same results have not yet been demonstrated in human cancer patients (Bernstein and Sigmundi, 1980; Bernstein, 1985; Thompson *et al.*, 1993). Chemosensory intensification of foods may be helpful in treating anorexia in cancer patients, and aside from other aspects of tumor response, improvements in nutrition may prolong the patient's life (Gogos and Kalfarentzos, 1995; MacIntosh *et al.*, 2000). Recently, Schiffman, (2000) reported that the breast cancer patients preferred flavor-enhanced to not-enhanced foods, and patients did not report aversions to flavor-enhanced foods. Moreover, in these patients odor enhancement of foods triggered pleasant memories. This observation is important because odors are processed in the limbic system of the brain where memories and emotions are processed (Schiffman, 1997). Moreover, the limbic system subserves olfaction and the immune system; thus, olfactory stimulation could positively influence immunological function directly via these connections (Felten *et al.*, 1991), and ameliorate mood and reaction to illness in cancer patients. Schiffman and Miletic (1999) found that repeated taste and smell stimulation in healthy and sick elderly and young people improves the salivary flow and the elevation of salivary IgA. These improvements may have clinical potential for treatment of immune deficiencies and dry mouth which frequently occur in cancer patients.

CONDITIONED TASTE AVERSIONS AND TREATMENT OF ALCOHOLISM

Moderate consumption of alcohol may provide protection against some pathologies (Fuchs *et al.*, 1995), may influence the perception of food flavors (Mattes and DiMeglio, 2001), and may stimulate food intake (Hetherington *et al.*, 2001). Alcoholism is the adverse consequence of alcohol abuse. Alcoholism is both a chronic metabolic disease that causes physical dependence on alcohol and a disorder of behavior, which is associated with psychological, psychiatric, and social problems (Walker *et al.*, 1996; Hunter *et al.*, 2000; Murray *et al.*, 2000). Alcoholism is a multifaceted pathology that involves both structural and behavioral disorders, and a broad range of biological and psycho-social components contribute to the development of this disease. Thus, a variety of alcoholism subtypes (typologies) may be diagnosticated, and treatment must be differentiated in accordance with the preeminent component of the disease (Penick *et al.*, 1999). This would enable treatments to be targeted towards those types of alcoholic patients who may benefit most. In the United States and Europe alcohol abuse is the fourth leading cause of death (Liskow *et al.*, 2000; Powell *et al.*, 1998), and alcoholics are among the highest cost users of medical care. This high economic and social cost has been correlated with the severity of alcohol-related problems, especially among alcoholics with co-morbid substances abuse and psychiatric disorders. Alcohol is considered a neurotoxin and the brain is a major target of the actions of heavy alcohol consumption (see Hunt and Nixon, 1993 for a monography; Lemere *et al.*, 1976; Bachtell *et al.*, 1999), but it affects every organ and tissue of the body either directly or indirectly (Parson, 1986; Charness, 1993). Like other self-administered drugs, alcohol may produce CTA (Sherman *et al.*, 1988). Alcohol intake may produce CTA depending on the amount consumed by two mechanisms: at lower amounts the mechanism seems to be chiefly central (Sklar and Amit, 1977), but at higher doses a peripheral emetic mechanism has been suggested that seems mediated

by an accumulation of acetaldehyde in the blood (Aragon *et al.*, 1991). Recently, it has been shown that rats and alcoholic humans may posses a genetic predisposition to alcoholism (Elkins, 1986; Risinger and Cunningham, 1998) and that neurotransmitter systems in the meso-cortico-lymbic pathway mediate some of alcohol's rewarding effects associated with its abuse liability. Differences in voluntary ethanol consumption seem to be associated with differences in the sensitivity to aversive effects of ethanol (Quintanilla *et al.*, 2001). Moreover, early-onset alcoholism differs from late-onset alcoholism by its association with greater serotoninergic abnormality and antisocial behaviors (Johnson *et al.*, 2000b). A review of the literature concerning the actions of alcohol on neurotransmitter systems and neuropharmacological challenge within the transmitter systems during the juvenile through adolescent period indicates that unique neurochemical and behavioral changes occur during the post-natal and adolescence period that mediate the response to alcohol (Witt, 1994). An involvement of central serotonergic neurons of the dorsal raphe nucleus seems play a modulatory role in the development of CTA induced by moderate alcohol intake (Piasecki *et al.*, 2001). Reduced alcohol intake noted in alcoholic patients treated with specific blockers of neuronal serotonin uptake (citalopram, fluoxetine, zimelidine) has been explained by decreased appetitive behavior and by a CTA learning to alcohol promoted by increased brain serotonin activity (Gorelick, 1989). Between many clinical features of alcoholism, craving and the "obsessional thinking about drinking" are the most important. Craving is very strong desire for alcohol that is always present in the mind of alcoholics. This state of mind is referred to the abnormal activation of some not yet well-defined or quantified subcortical area of the brain (Carter *et al.*, 1997). On the contrary, the obsessional thinking refers to a mental state of continuous internal conflict between "drink, or not drink alcohol" that seems lie in the cerebrocortical structures (Kranzler and Anton, 1994; Carter *et al.*, 1997). Alcoholism therapy has as its first goal the achievement and maintenance of abstinence and the prevention of relapse. This therapy has a multifaceted aspect: sociological, psychological and pharmacological, which can produce additive effects in the control of addiction to alcohol and maintenance of alcohol abstinence (Walker *et al.*, 1996). In particular, psychological and social approaches may enhance cerebrocortical inhibitory control mechanisms, and pharmacological approaches may decrease the drive of craving, acting on the mechanism of subcortical areas of the brain (Kranzler and Anton, 1994; Carter *et al.*, 1997; Addolorata *et al.*, 2000). For example, it may be useful in the treatment outcome studies of sociopathic alcoholics to distinguish between those who are also depressed and those who are not depressed. A recent study found that compared to alcoholics with antisocial personality disorder (ASPD) but no affective disorders, alcoholics with ASPD who also had an affective disorder had a more positive outcome when treated with antidepressant (Penick *et al.*, 1996).

A wide range of behavioral treatment methods, which almost all induce aversion, have been employed to treat alcoholic patients (Nathan and Niaura, 1985; Smith and Frawley, 1990; 1993; Elkins, 1991; Howard *et al.*, 1991; Walker *et al.*, 1996). The chemical aversion conditioning therapy is the "cornerstone" of some packages of treatment modalities utilized at some Hospitals in the USA and Europe. Available evidence supports the efficacy of these packages and of chemical aversion therapy with respect to production of conditioned aversion to alcohol and treatment outcome (Dunn *et al.*, 1971; Howard and Jenson, 1990a,b; Smith and Frawley, 1990; 1993; Smith *et al.*, 1991; 1997; Walker *et al.*, 1996). Two modalities used for a long time with success and failure, have been electrical shock aversion and chemical aversion therapies. The results obtained by electrical shock aversion were disappointing, and in the late 1970s, Wilson (1978) stated that "The evidence on the efficacy of electric aversion conditioning is overwhelmingly negative. Its use as a treatment modality with alcoholics should be discontinued." At the Shadel Hospital in Seattle, WA, Voegtlin (1940) and Lemere and Voegtlin (1950) reported the useful and flattering method of chemical aversion to treat alcoholism, since alcoholics may easily develop and maintain an association between alcohol and nausea (Wilson and Davison, 1969; Nathan, 1985). This point of view has been reinforced by the data of Garb and Stunkard (1974), Logue *et al.* (1981) and Midkiff and Bernstein (1985), who found that college students acquire taste aversions to alcoholic beverages which induced nausea and vomiting. In general (but with some variations), the protocol to induce CTA against alcohol consists of the administration of an emetine–pilocarpine–ephedrine mixture that produces nausea within a few minutes. Immediately after the injection and before the first signs of nausea, the patient might select his/her favorite alcoholic beverages to smell, taste and drink. Additional drinks are provided as nausea, vomiting, sweating, increased respiration and heart rate, and other side-effects of the three drugs mixture are experienced (Lemere and Voegtlin, 1950). Other drugs have been also employed (Disulfiram, Cyanamyde, LiCl, etc.), but their uses have been discouraging because of their heavy side-effects. The treatment programs, along with the chemical aversive conditioning that is the fulcrum of the programs, include psychotherapy, family therapy, social rehabilitation, access to local

Alcoholics Anonymous groups, etc. (Nathan, 1985; Smith and Frawley, 1990; 1993; Smith *et al.*, 1991; 1997). "Booster" reconditioning sessions are offered routinely. The stronger are the aversions, the longer the patients abstain (Cannon *et al.*, 1988). Many variables (age, sex, educational level, occupational status, type of work, marital status, history of alcoholism, etc.) are important in the type of treatment and its success. Younger, unemployed, unmarried, and less-well educated patients are more resistant to the aversive package treatments (Neubuerger *et al.*, 1981; 1982). Interoceptive (i.e. depression, anxiety, etc.) and environmental stimuli may become conditioned stimuli (CSs) and can be effective in reducing responsivity to alcohol intake (Staiger *et al.*, 1999). An important question is to establish the percentage of success that may be attributable to chemical aversion conditioning therapy and which to the other components of the treatment program. An indirect answer to this question may be obtained from data showing that patients treated without chemical conditioned aversion have a higher rate of relapse and shorter periods of abstinence (Nathan, 1985; Smith and Frawley, 1990; 1993; Smith *et al.*, 1991; 1997). For example, in a multimodal treatment program at some Schick Addiction Treatment Hospitals, patients treated with aversion therapy for alcohol had higher alcohol abstinence rates after 6 and 12 months from treatment (Smith *et al.*, 1991, 1997). A minimum of 13 and a maximum of 25 months (mean 20.5 months) had elapsed since treatment. On average, 65% of patients were totally abstinent for 1 year after treatment, and about 60% were abstinent at follow-up a mean of 14.7 months later (Smith and Frawley, 1990, 1993). Thiele *et al.* (1996) have shown that taste aversion to alcohol becomes stronger with greater delays between training and testing. In other words, an "incubation effect" may be responsible for the aversions at delayed testing intervals (Marcant *et al.*, 1985). Such results may have direct implications for improving CTA therapy as a treatment for alcoholic patients. Indeed, consuming alcohol soon after treatment may limit the effectiveness of CTA therapy and patients may be more vulnerable to relapse within the first few months after therapy, i.e. before aversions had reached their maximum strength (Thiele *et al.*, 1996). Patients may display strong aversions if they completely abstain from alcohol immediately after conditioning. Thus, patients must be strongly encouraged to avoid all kind of alcohol shortly after therapy (Thiele *et al.*, 1996). Another important aspect of treatment of alcoholism is that patients must be highly motivated to change their drinking habits since chemical conditioning aversive treatment, *per se*, is extremely unpleasant and may cause heavy discomfort. Moreover, since conditioning is a cognitive process, it works well if the patient is knowledgeable consenting and collaborative during the chemical conditioning aversive treatments (Wilson, 1987).

Selective medications may be effective in the treatment of alcoholism, and some drugs have been shown to be effective, alone or in combination. For example, naltrexone reduces the rewarding effects of alcohol (Koob, 1992; Hemby *et al.*, 1997; Cramer *et al.*, 1998) and acomprosate diminishes negative or conditioned alcohol craving post-drinking cessation (Spanagel and Zieglgansberger, 1997). The combination of naltrexone and acomprosate (Johnson and Ait-Daoud, 2000) or naltrexone and isradipine (Cramer *et al.*, 1998) will make it easier to abstain and to prevent a relapse as well as to treat alcoholics with a biological (genetic) predisposition (King *et al.*, 1997; Johnson *et al.*, 2000a). Recent advances in neurobiology have developed some new medications to treat alcoholism by modifying the activity of specific chemical neurotransmitters in the brain and by pharmacological blockade of central voltage-operated calcium channels. For example, pharmacological blockade of central dihydropyridine (DHP) sensitive voltage-operated calcium channels (VOCCs) leads to a reduction of ethanol intake ("antialcohol effects"). Antialcohol effects of nimodipine, a DHP-calcium channel antagonist, have been demonstrated in non-genetic and genetic models of alcoholism in rats but not yet verified in alcoholic patients (De Vry *et al.*, 1999). Clinical trials with isradipine or amlodipine (Gardell *et al.*, 1999) which are DHP-calcium channel antagonists showing similar efficacy as nimodipine in animal models of alcoholism (De Beun *et al.*, 1996a,c; Cramer *et al.*, 1998; Smith and Little, 2000), confirmed that this compound is effective in reducing craving for, and consumption of, alcohol in alcoholic patients (DeMet *et al.*, 1997). Dopaminergic processes are important for the development of ethanol-induced CTA, and D1 and D2 dopaminergic receptors influence the motivational effects of ethanol (Risinger *et al.*, 1999). Interestingly, pimozide, a blocker of dopamine D2 receptors, also blocks calcium channels and probably its action in the reduction of ethanol-CTA may depend on this second mechanism (Risinger *et al.*, 1999). It is important to point out that nimodipine, isradipine, and other DHP-antagonists induce a significant effect on CTA learning; thus, the antialcohol effects of these substances may be due to their ability to induce aversive effects in a CTA paradigm (De Beun *et al.*, 1996b,c; Pizzi and Cook, 1996; Gardell *et al.*, 1998; Risinger *et al.*, 1999; Smith and Little, 2000), but this hypothesis needs further and more in depth evaluation. Moreover, development of future clinical studies should resolve issues related to medications combinations, psycho-social and behavioral treatments of alcoholics.

CONCLUSIONS AND PERSPECTIVES

The preceding discussion points out the enormous amount of experimental attention given to CFA in laboratory animals and the paucity of studies on human ingestive behavior, due to the ethical problems limiting these kinds of experiments. Moreover, there has been relatively little interaction between investigators examining food and/or taste aversion conditioning and investigators interested in the regulation of ingestive behavior and body weight homeostasis. An interesting problem that might be resolved by the interaction between both kinds of investigators is the controversy on the hypothesis that ingestion of an imbalanced diet may develop a CFA as an adaptive role in nutrient selection or that CFA represents a rather poor mechanism for insuring proper nutrients selection. In humans, aversion conditioning has been attempted to reduce the excessive body weight, but the results have not been promising. This failure may be due to the procedures used to condition human satiation that are insufficient; moreover, evidence of satiation conditioning has not been provided. However, by inducing better conditionability, weight reduction strategies might be more effective if they were structured to exploit nutritional conditioning mechanisms, whatever social, pharmaceutical, or cognitive supports are also recruited. Nevertheless, the conditioning effects of ingestion are merely one set of negative feedback stimuli in a much more complex system from which the overweight issue arises (Booth, 1985). A factor of discrepancy in the cited studies in humans may be a different formulation of questionnaires and interviews that might compromise the sensitivity and the accuracy of assessment. The methodology used in these works is questionable because the questionnaires and/or interviews may be affected by the conditions under which the subjects are asked to report their aversions (hospitals, home, compilations of questionnaires, medical problems, etc.), by the demographic characteristics of the subjects (age, sex, work, social state, ethnic, religion, etc.), by characteristics of the aversions, by recall of taste aversions, and by the willingness to report taste aversion. Sometimes, subjects will not remember a taste aversion because this may be coincident with other mood problems that the subjects will forget. Very young (less than two years of age) and very old subjects may have difficulty recalling or reporting aversions (Bernstein and Borson, 1986) or compiling questionnaires. An important point to be resolved is the standardization of methodology and of data collection and elaboration to be used by all investigators studying taste and food aversions conditioning in humans. It is important that a Committee of experts develops a "Food Aversion Questionnaire" and other effective screening tools that all researchers involved in CFA studies in humans can use so that the results obtained in different laboratories in all parts of the World can be compared. Furthermore, the intensity and longevity of these learned aversions as related to appetite problems need to be more fully explored. A careful, empirical evaluation of increasing vulnerability to food conditioning with age is needed, using new tools for assessing aversion development, tools that are sensitive to implicit memories. Such work could then determine whether, as indicated by some questionnaire and interview studies (Garb and Stunkard, 1974; Pelchat and LaChaussee, 1994) whether the elderly are at a lower risk of developing aversions or if their food choices are subtly affected by accumulating food aversions of which they are not consciously aware (Bernstein, 1999a). Toward this end, it is interesting to remember that rats acquire aversions even when they are profoundly anesthetized or unconscious (Roll and Smith, 1972; Bermudez-Rattoni *et al.*, 1988). If this result applies to humans, it will be very difficult to assess methodologically the role of subconscious CTA in food selection. Careful examination of dietary patterns in patients with anorexia symptoms could begin with an evaluation of the hypothesis that aversion learning is involved in the etiology or maintenance of clinically important anorexia (Bernstein and Borson, 1986). There is reason to suspect a role for taste aversion learning in several clinical situations in which anorexia and weight loss significantly impair the patient's quality of life (Bernstein and Borson, 1986). It is evident that cancer patients readily acquire food aversions as a consequence of chemotherapy and radiotherapy treatments and that aversions play an important role in cancer anorexia and cachexia. Since serotonin (5HT) is involved in normal feeding behavior (Leibowitz *et al.*, 1988; Leibowitz and Alexander, 1998; Meguid *et al.*, 2000a), its role in cancer anorexia-cachexia syndrome has been evaluated in rats and humans (Gietzen *et al.*, 1991; Edelman *et al.*, 1999; Meguid *et al.*, 2000a). The blockade of $5HT_3$ receptors improved the ability of cancer patients to enjoy food but failed to prevent body weight loss and to improve nutritional status (Edelman *et al.*, 1999). Usually, $5HT_3$ receptor antagonists are used as antiemetics for cancer chemotherapy, and there is frequent amelioration of cancer- or chemotherapy-relate anorexia (Fraschini *et al.*, 1991). Animal data support a serotonergic pathway for CTA formation (Gietzen *et al.*, 1998). Thus, the saturation of $5HT_3$ receptors may increase the acceptability of foods reducing the eventual CTAs acquired by chemotherapy and/or tumor growth *per se*. In cancer anorexia, a significant decrease in food intake, which depend on the meal number (MN) and meal size (MS) occurs primarily via a decrease in MN and subsequent decrease in MS

(Meguid *et al.*, 2000b). Both MS and MN are correlated, but controlled independently by the lateral (LH) and ventromedial (VMH) hypothalamus by changes in dopamine and serotonin levels, respectively. Changes in LH dopamine influences MS, whereas in the VMH decreasing dopamine and increasing serotonin levels sinfluences MN (Varma *et al.*, 1999). A derangement of the hypothalamic dopamine–serotonin system secondary to the effects of cancer on the brain, might be responsible for the onset of anorexia. In TB-rats, a significant increase in serotonin and a decrease in dopamine levels in the VMH has been reported at the onset of anorexia (Varma *et al.*, 1999). A potential strategy for reducing the onset of cancer anorexia, and thus improving the nutritional status of patients, might be the use of combination of effective pharmacologic agents able to "reset" the hypothalamic serotoninergic and dopaminergic system deranged by cancer-side effects. But, at moment, this remains an important therapeutic hypothesis. Scapegoat strategies have significant protective effects and may prevent or decrease aversions towards foods containing important nutrients. However, further studies are needed to better clarify the mechanisms of this important behavior. It has been shown that social influences on diet choice may be transmitted in animals. In humans, a "social facilitation" affecting food intake has not yet been evaluated, even if, in theory, it might be of importance in cancer patients (mainly children) to extinguish the aversions developed by therapy and to prevent the formation of new food aversions conditioning. For example, healthy people and patients should eat the same food all together and take note that food is not responsible for malaise and/or disgust developed. This demonstration might attenuate aversions in patients and persuade them to eat a hypothetical aversive food containing important nutritionals. Health advisors trained to conduct nutritional program education sessions among cancer patients might also improve the alimentary behavior of these patients (Navarro *et al.*, 2000a,b).

CTA therapy in alcoholics can be effective in the context of a carefully orchestrated treatment program accompanied by adjunctive counseling and attention to social support systems and followed by booster sessions. Consequently, it seems important to consider ways to reduce costs and increase the availability of a treatment approach with demonstrated utility (Nathan, 1985). The literature on chemical aversion therapy is remarkably lacking in controlled clinical research, and the validity of the outcome measures employed in many of the published uncontrolled reports are questionable (Wilson, 1987). Although some well-known alcohol treatment Centers continue to use CTA therapy as part of their treatment package, the use of this specific treatment modality cannot be said to have received widespread acceptance (Bernstein, 1991). The lack of controlled clinical trials has contributed to the controversy surrounding the efficacy of CTA therapy in alcoholism. For example, psychometric properties of the Essential-Reactive Alcoholism Questionnaire, the instrument generally used to assess the essential-reactive dimensions, rarely have been examined (Walker *et al.*, 1996). Research is needed to assess the prognostic utility of the essential-reactive typology of alcoholism and the degree to which the distinction may facilitate patient-treatment matching (Walker *et al.*, 1996). Although short-term testing supports the idea that CTA learning produces aversions to the taste of alcohol in alcoholics (Boland *et al.*, 1978), the long-term effects of such CTA therapy in promoting abstinence have not been clearly established because, sometimes it is very difficult to control patients after discharge from the hospital setting. Health services research on alcohol-dependent populations needs to consider the importance of psychiatric co-morbidity and the age of onset of alcohol dependence (Murray *et al.*, 2000). The contribution of early alcohol exposure to excessive drinking and abnormal cognitive and social functioning during subsequent stages of development needs more research. Some trends for future research have already been identified in the use of some new pharmacological agents able to improve the treatment of alcoholism. For example, the effectiveness of substances used as calcium antagonists, enhancers of brain serotonin, or inhibitors of neurotransmitters must be better evaluated. Larger scale studies that test these medications, both alone and/or together, among various alcoholic subtypes are needed to establish and extend some promising findings (Johnson *et al.*, 2000a). Additional research is needed to determine how new medications interact with different psychosocial factors and chemical aversive treatments for various types of alcoholism. This remains a formidable challenge for clinical trials research (Johnson and Ait-Daoud, 2000). Finally, given the evidence that aversions to a specific alcoholic beverage may affect beverage selection but not overall consumption, these issues require more detailed evaluation.

Acknowledgements

This review is dedicated to my unique, wonderful son Marcello Agostino, for the precious hours taken away from him during my experimental work abroad and during the writing of this review.

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