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Taste Aversion Learning: A Contemporary Perspective

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ABSTRACT

Food aversion learning has attracted widespread interest because it is a highly adaptive, powerful type of learning with both practical and theoretical ramifications. It has features that make it unusual and robust when compared with other learning paradigms. It has relevance to human problems in that it is likely to contribute to food choice and appetite problems in certain clinical situations. And the robustness of this learning makes it a promising model for neurobiologists interested in understanding neural mechanisms of plasticity. This review provides a broad overview of these aspects of taste aversion learning and points to areas where questions remain and additional research is needed. *Nutrition* 1999;15:229–234. ©Elsevier Science Inc. 1999

Key words: food aversion learning, food choice, appetite problems, neural mechanisms of plasticity

INTRODUCTION

The propensity to acquire strong learned taste aversions as a result of unpleasant experiences with foods represents a potent defense mechanism against poisoning.[1–3] An enormous range of animal species, from the garden slug, *limax*, to primates including humans, demonstrate this learning.[4–6] That this learning has been conserved across the phylogenetic spectrum attests to its survival importance. Thus, *learned* food aversions combine with *innate* food aversions (unlearned responses to tastes such as sour and bitter that warn of toxins or spoilage) to guard the internal milieu from potentially damaging ingesta. The ability to learn to avoid foods based on unpleasant experiences with them allows for personal history, as well as evolutionary history, to influence food choice.

Although food aversion learning may have evolved as an adaptive response to the danger of ingested toxins, it can also lead to the avoidance of foods that are not poisonous and are, in fact, quite nutritious.[7–9] Although the evidence for food aversion learning as a powerful and durable form of conditioning is incontrovertible, the role this learning plays in everyday food selection in humans or animals is relatively unclear. This review examines salient features of taste aversion learning and some of its unusual characteristics. Recent advances in the definition of neural mechanisms involved in this learning are briefly reviewed. Problems encountered when trying to assess the role of learned food aversions in the nutritional status of healthy people as well as those with serious illnesses are considered.

DEFINITION AND DESCRIPTION

Food aversion learning is a form of conditioning in which animals or humans come to avoid consumption of a food (conditioned stimulus [CS]) that has been paired previously with a treatment that produces transient illness (unconditioned stimulus [US]).[1–3] It has been argued that taste aversion conditioning contains elements of both instrumental (avoidance) learning and classical (Pavlovian) conditioning.[10] The degree to which the learning paradigm conforms to a classical or an instrumental model may differ depending on subtle procedural details such as how the taste CS is delivered.

Food aversion learning is extremely robust; strong aversions to a novel food can be acquired in a single learning trial, that is, after one pairing of CS and US.[3] Even more unusual is the fact that significant aversions develop to the CS despite long delays between exposure to the CS (food) and US (symptoms).[2] Viewed from the vantage point of more traditional learning paradigms in which CS-US delays of more than a few seconds significantly retard the development of conditioned responses, the strong food aversion learning that occurs after delays of many minutes or even hours is remarkable. This difference is dramatically evident in a very shallow slope of the gradient expressing strength of conditioning as a function of CS-US delays between 30 min and several

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hours.[11] Most other learning paradigms require close temporal contiguity between CS and US, with an optimal range being between 500 ms and 2 s, and this common feature of most learning paradigms has been used to build models of the type of cellular signaling processes that might underlie plasticity.[12] This raises the challenging question of how neural systems underlying taste aversion learning bridge CS-US intervals of minutes and hours.[13] The degree to which similar or unique mechanisms of neural plasticity are recruited or modified for this task, or both, remains to be determined.

The robustness of food aversion learning is also underscored by the findings of Roll and Smith[14] that rats will acquire aversions even when they are completely anesthetized during and after the time when the US is administered. These findings, replicated more recently by Bermudez-Rattoni and colleagues,[15] imply that these associations can be formed when a subject is unconscious. This observation, combined with the fact that simple invertebrates are capable of acquiring these conditioned responses,[4,16] gave rise to the impression that the neural circuitry required for this learning was fairly primitive. Although this may be true in the case of slugs and pond snails, it is not necessarily the case for mammals such as the rat, as the discussion of neural mechanisms will illustrate.

THE CONDITIONED STIMULUS

Novelty

Although the preceding discussion makes a case for the uniqueness and robustness of food aversion learning, it is also clear that many of the parameters that modulate the strength of conditioning in other learning paradigms have similar effects on conditioned taste aversions. A particularly good example is CS novelty. Aversions arise extremely rapidly if a CS food or taste is novel, but if an organism has had prior, safe exposure to the food, conditioning is significantly retarded.[17,18] Thus, familiar foods are much less likely to become the targets of learned food aversions than are novel ones. This is analogous to the phenomenon of latent inhibition in classical conditioning where CS pre-exposure slows the progress of conditioning.[19]

Taste Versus Odor

The sensory modalities commonly implicated in regulation of ingestion in mammals are the chemical senses, that is the gustatory and olfactory systems. In common parlance, we think of the *flavors* of foods and fluids, which involves a blend of both taste and odor cues. So, in the real world, food aversions may actually be flavor aversions, aversions to both the taste and odor of a food. In the laboratory, the contribution of these two modalities can be assessed independently. In the rat it has been found that odor cues, presented without tastes, are much less effective than taste cues as CSs in aversion conditioning.[20] Curiously, however, if an odor is conditioned in compound with a taste, a phenomenon referred to as *taste potentiation of odor* is observed. That is, once conditioning is established, when the odor is tested by itself, it is clear that it has become a highly potent cue for avoidance. Under most normal circumstances, then, odors may be important cues in aversion conditioning. For example, we found that the presence of an odor, along with a taste, makes a food or fluid a very potent target of learned aversions.[21] Furthermore, it should be noted that reliance on odor cues allows animals to actually avoid ingestion of a toxic or suspicious substance, whereas reliance on taste cues requires some sampling and its associated risk.

Nutrient Composition

Some years ago, we found that cancer patients receiving chemotherapy were at risk for developing aversions to foods in their diet that were eaten before their drug treatments. In those studies, and in a survey of college students, aversions seemed more likely to be directed at foods that were protein sources (eggs, cheese, meat) than carbohydrates.[22] Possible reasons for the salience of proteins as targets for food aversions were: 1) proteins are known to spoil more readily than carbohydrates and humans may, therefore, have a cognitive predisposition to "blame" their unpleasant symptoms on proteins; 2) the gastric clearance and digestion of proteins is slower than that of carbohydrates, so that proteins may be associated with more severe symptoms; and 3) some flavor attribute of proteins may make them more associable with unpleasant symptoms.

These possibilities were explored further using an animal model. In one study, rats selected from separate protein and carbohydrate macronutrient sources (with fat content held constant) during a sequence of toxic drug treatments—we found that they readily formed significant aversions to the protein but not to the carbohydrate. We replicated this using a variety of protein and carbohydrate sources.[23] These observations, in both humans and rats, suggested a degree of generality to the salience of proteins as targets for aversions, but they did not indicate what features of proteins are responsible. Two possibilities were assessed; that the postingestive effects of proteins are responsible or that some flavor characteristics of proteins are the basis of their salience. Using a sham-feeding preparation, we determined that the salience of proteins is based on flavor properties and not postingestional events.[21] At this time, we believe that the presence of a strong odor, as well as a taste, may be important in making a food a potent target for aversion conditioning. Thus, proteins, as well as other foods with strong odors, such as chocolate and coffee, may frequently become the targets for aversions because of these flavor properties.

THE UNCONDITIONED STIMULUS

The US in food aversion conditioning has prototypically been a drug, such as LiCl, with known emetic activity. As a consequence, it has sometimes been assumed that if a treatment is capable of acting as an US in a taste aversion-conditioning test, it probably causes nausea, or at least it is probably aversive. This is almost certainly not the case. Instead, we find that the food aversion literature is characterized by an enormous and varied list of drugs and other treatments that can effectively serve as US in conditioning.[24] A careful examination of the list fails to reveal any particular feature(s) that these treatments have in common.[25] Although emetic drugs are highly effective as US, many drugs that are not emetic can be effective.[26,27] Even more puzzling, some effective drugs do not appear to be particularly aversive; in fact, some are drugs that humans and animals will self-administer.[28] So the claim that taste aversion conditioning can serve as a behavioral assay of aversiveness or toxicity requires careful scrutiny.

Although there is clearly evidence that nausea is not necessary for the development of food aversions, there is an indication that nausea may play a unique and particularly potent role in this learning. Evidence both from humans and rats[29,30] suggests that the prototypical learned food aversion, where the food becomes genuinely distasteful, generally is associated with the symptom of nausea. A study with human subjects demonstrates this point well. Pelchat and Rozin[30] surveyed human subjects who suffered from food allergies. When allergic symptoms included nausea, subjects reported not only that they avoided the food, but that they actually disliked the taste. In contrast, when the allergic response included symptoms such as mouth sores or hives, subjects avoided the food but reported no change in the food's hedonic rating. In other words, these subjects avoided eating the food because it would cause unpleasant symptoms, not because they actually found it distasteful. Thus, Pelchat and Rozin[30] argue that nausea is not only sufficient for the establishment of a taste aversion but is actually

necessary for the development of hedonic shifts or distaste toward foods. It is this shift in the hedonic or incentive value of a taste that, some believe, constitutes a genuine learned taste aversion.

FUNCTIONAL SIGNIFICANCE OF CONDITIONED TASTE AVERSIONS

Toxin Avoidance

As already noted, taste aversion learning, combined with an innate dislike for tastes that signal toxins or spoilage, provide animals with a means of avoiding ingesting or reingesting toxic foods. It is clear that many of the characteristics of food aversion learning, which make it so unusual in the roster of learning paradigms, are modifications that are necessary for its effectiveness in this role. Take one trial learning. To be effective, a learning mechanism for avoiding poisoning would have to be rapid. A need for multiple conditioning trials would necessitate the ingestion of more and more of a possibly lethal toxin and this would lead to morbidity or mortality. Likewise, tolerance of lengthy delays between CS and US seems to have been shaped by the adaptive needs of the system. Because the temporal dynamics of visceral events result in most ingested toxins having delayed, not immediate, effects, long-delay learning was needed.

In fact, effective behavioral strategies of rodents for avoiding poisoning were recognized by exterminators long before the discovery of taste aversion learning by Garcia et al.[2] Indeed, it is probably serendipitous for Garcia et al.'s discovery that rats are such common subjects in the experimental laboratory. Two characteristics of this species make taste aversion learning a particularly important behavioral strategy for them. One is that Norway rats are omnivores, which means that in their natural environment they are opportunistic foragers, taking advantage of nutrient sources as they become available. They must be willing to try new foods. But they try them first in very small amounts (*neophobia*) and if the food proves toxic they learn to avoid it, sometimes for life. The other characteristic is that rats are a non-emetic species, which means they cannot vomit. Foods that are swallowed cannot be ejected so the avoidance of toxic edibles is particularly important for the rat. Although emetic species also show the ability to learn taste aversions, I suspect that the rat has a particularly well-developed ability as far as this learning is concerned.

Nutrient Selection

Although a strong case can be made for taste aversion learning as an effective mechanism for avoiding the ingestion of toxins, the role of this learning in nutrient selection is less clear. In work that is now several decades old, Rozin[18] demonstrated that nutrient deficiency provided a highly effective US for the development of learned food aversions. In those studies, rats maintained on diets deficient in nutrients or vitamins developed a strong aversion to those deficient diets. Using thiamin-deficient diets, they found that rats developed a strong aversion to the deficient diet when they were maintained on it long enough to become ill as a result of thiamin deficiency. The thiamin-deficient rats displayed an immediate preference for any new food offered to them, and continued to avoid the deficient diet, even after they had recovered from the effects of the deficiency. These findings support the idea that food aversion learning has an adaptive role in nutrient selection through the development of aversions to nutritionally inadequate nutrient sources.

Galef,[31] however, argues against this position. He states that although taste aversion learning may be a good mechanism for poison avoidance, it is a rather poor mechanism for insuring proper nutrient selection. First, taste aversion learning would not be an effective mechanism for the avoidance of nutritional deficiencies. Since the learning relies on the development of illness or malaise as the US, it would only be triggered after animals are in a state of outright nutrient deficiencies. Second, Galef argues that strategies for avoidance of poisoning (e.g., shun novel foods) are quite the opposite of strategies for curing or avoiding nutrient deficiencies (e.g., seek novel foods). I find this position quite persuasive. Perhaps it is only in cases where animals choose a single, very poor nutrient source over a prolonged period that food aversion learning mechanisms come into play in directing the animal to vigorously seek alternative food sources.

CLINICAL RELEVANCE AND APPLICATIONS

Food Aversions in Humans

Food aversion learning in humans has been examined principally through the use of survey methods. Garb and Stunkard[5] surveyed nearly 700 subjects and found that 38% reported having had at least one food aversion at some time in their lives, whereas subsequent studies, also with large numbers of subjects and similar methodology, report somewhat higher rates (50–65%; see refs. 6 and 22). Differences may be related to age of the subject sample; Garb and Stunkard's subjects included a very wide age range from childhood to old age, whereas others have focused on subjects of college age. In samples drawn from college students, aversions to specific alcoholic beverages are frequent, representing 14% of aversions in one study[22] and 25% of those reported in another.[6] The high rate of alcohol aversions in this population has been attributed to the fact that students often begin to consume significant amounts of alcohol in their college years, and overconsumption produces symptoms that are known to be quite effective in the conditioning of taste aversions.

Characteristics of food aversions reported by humans are generally similar to those observed in laboratory studies of rats. Acquisition often occurs in a single trial, often with long delays interposed between tasting the food and experiencing illness. Aversions were more likely to develop to less familiar as well as less preferred foods. Extinction was reported to be more effective at reducing aversions than forgetting. Thus, survey data support the idea that food aversion conditioning occurs in humans as well as other animals and that the characteristics of this learning are similar across species. Given that this learning appears to be both powerful and primitive, it is important to consider what role this learning plays in human food choice.

The extent to which food aversions, learned as a consequence of the association of specific foods with gastrointestinal symptoms, play a significant role in human food choice turns out to be difficult to assess. Some investigators who have evaluated this issue have concluded that the role of aversion conditioning is minor. They base their conclusion on the following reasoning. Many studies have shown that a majority of people surveyed report having experienced the development of a food aversion at some time in their life. However, when one considers the number of people reporting existing food aversions and the number of foods they actually have aversions to, this number is small relative to the large number of foods people seem to dislike. This seems to leave a vast number of "food aversions" unaccounted for in terms of their cause.[32]

There is another line of reasoning that leads to a different conclusion. It could be argued that there are reasons why verbal reports of learned food aversions underestimate the actual number of such aversions. Memory researchers distinguish between implicit and explicit memories.[33] *Explicit* memories are those you are aware of consciously, whereas *implicit* memories are those you have but are not consciously aware of. Because classical conditioning is more likely to generate implicit than explicit memories, most food aversion learning experiences in humans may form implicit, not explicit, memories. Research indicates that implicit

memory formation is less susceptible to anesthesia,[34] which might explain the resistance of food aversion learning to anesthesia.[14,15] Thus, if all but the most severe learned food aversions form implicit and not explicit memories, subjects' recall of taste aversion experiences may not be the most sensitive way to assess aversion conditioning. If this is true, then conditioned food aversions may affect food choices and hedonic responses to foods unconsciously and such conditioning may play a significant role in human food choice, but this role would be quite difficult to assess methodologically.

Also some people who are chronically ill, prone to motion sickness, or otherwise vulnerable to experiencing unpleasant gastrointestinal symptoms may be at a much higher risk of developing these aversions and having them limit their acceptable food choices.[35]

Food Aversion Learning and Cancer Anorexia

Loss of appetite and weight are problems frequently encountered by cancer patients.[36,37] Appetite loss may stem directly from the disease or result from side effects associated with cancer treatments. The mechanisms responsible for these symptoms remain poorly understood and the management of cancer anorexia and cachexia remains a serious problem. Several lines of evidence have implicated food aversion learning as a contributing factor in cancer anorexia. The similarity between the aversive side effects of certain cancer treatments, including chemotherapy and radiation, and the US in taste aversion studies prompted the investigation of whether learned food aversions develop in patients receiving gastrointestinally toxic chemotherapy regimens.[7] Controlled clinical studies indicated that learned food aversions develop in patients receiving gastrointestinal toxic chemotherapy, and that these aversions were directed at specific foods consumed before these treatments. Recent work further characterizes the nature of this conditioning and points to nausea as a critical variable in the development of food aversions.[38,39] These findings led to the assessment of a method for reducing the incidence of chemotherapy-induced learned food aversions in pediatric cancer patients.[40] Candy (coconut or rootbeer Lifesavers, Nabisco brands, East Hanover, NJ) was used as a scapegoat, given between the consumption of a meal and the delivery of chemotherapy, to determine whether this would interfere with the development of aversions to items in the meal. The scapegoat was found to have a significant protective effect; children were twice as likely to eat some portion of their test meal at assessment if they had received the scapegoat at conditioning than when there had been no intervention. This suggests that consumption of strongly flavored candies before chemotherapy is a simple, effective way to reduce the impact of chemotherapy on preference for nutritional foods in the diet. Interference effects also have been observed to be effective in adult patients.[41]

A profound role for food aversion learning in cancer anorexia has been suggested by studies indicating that food aversions can arise as a consequence of the disease itself. Rats implanted with some experimental tumors are known to develop significant depressions in food intake and body weight several weeks after tumor implant. When such animals were exposed to a distinctive target diet during a period of active tumor growth they were found to develop very strong aversions to that diet, and the aversions were clearly specific to the diet available during tumor growth.[8] In addition, although the tumor-bearing rats were quite anorexic when only the target diet was present, the availability of an alternate diet led to an immediate elevation of food intake. Thus, tumor-bearing animals can develop a pronounced aversion to a target diet available while a tumor is growing and dislike for the available diet appears to contribute to depressions in their food intake. Learned food aversions appear to contribute to tumor anorexia because prevention of the aversions reduces severity of the anorexia.[42]

Although food aversions attributable specifically to the growth of tumors have yet to be demonstrated in cancer patients, there is evidence that symptoms that are likely to promote food aversion conditioning are prevalent in patients with certain kinds of cancer. Symptoms of abdominal fullness, nausea, and vomiting have been found to be quite common in cancer patients,[43] with more than half of patients queried reporting such symptoms. Patients experiencing weight loss are significantly more likely to report such symptoms than those without weight loss. Reports that cancer patients also report odor and food aversions as well as early satiety[44,45] are consistent with a role for aversion learning in cancer anorexia.

NEURAL MEDIATION OF FOOD AVERSION LEARNING

Food aversion learning has been demonstrated in a remarkably broad range of animal species ranging from invertebrates[4,16] to primates, including humans.[5,7] When humans develop aversions as a result of the coincidental association between consumption of a food and chemotherapy or symptoms of the stomach flu, the aversions appear to defy cognition. That is, strong aversions arise despite a person's awareness that the target food was not actually the cause of their illness. These findings suggest that food aversion learning is based on relatively primitive associative mechanisms perhaps involving neural integration occurring in "lower" brain areas such as the brain stem.

Taste and visceral information do converge in the brain stem, within the nucleus of the solitary tract (NTS). Gustatory neurons from the facial, glossopharyngeal, and vagus nerves terminate in the rostral portion of the NTS. The NTS would therefore appear to be a critical part of the pathway mediating taste aversion learning. It is somewhat paradoxical, then, that Grigson and her colleagues[46] recently reported that rats with extensive lesions of the rostral (gustatory) zone of the NTS demonstrated normal taste aversion learning. Because reception of gustatory information would appear to be necessary for taste aversion learning, one is tempted to assume that those lesions, though extensive, did not completely eliminate incoming gustatory signals and that a degraded signal is sufficient for the learning. The role of even more extensive lesions of NTS, including regions involved in receiving visceral signals, has not been examined, in part because the importance of this region in cardiovascular and other vital functions makes lesion studies problematic.

Also located in the brain stem is the area postrema, site of chemoreceptors for detection of circulating toxins and for integration of emetic reflexes. The role of this region in taste aversion learning has been assessed using conventional lesion methodologies. Ablation of the area postrema has been reported to interfere with taste aversion learning when certain drugs are used as the US (LiCl; iv copper sulfate; see refs. 47–49). However, area postrema lesions do not attenuate aversions induced by other treatments (apomorphine, amphetamine; see refs. 49, 50). These observations indicate that the area postrema plays a key role in detection of some USs, but not others, and therefore it is not a *necessary* structure for the integration of taste (CS) and visceral (US) information.

In contrast with the rather limited role indicated for NTS, the next site in the ascending gustatory and visceral relay, the pontine parabrachial nucleus (PBN), appears to be crucial for taste aversion acquisition. Rats with lesions of the PBN are unable to acquire a conditioned taste aversion.[51] This deficit appears to be quite specific. It does not appear to be due to an inability to taste the CS or experience the US but rather to an inability to associate the two stimuli at the time of conditioning. Also, if conditioning occurs before lesioning, PBN lesions do not disrupt CTA expres-

sion.[52] Thus, the PBN appears necessary for taste aversion acquisition but not expression.

Although taste and visceral information converge within the brainstem and pons, these regions do not appear to be sufficient for the integration needed for taste aversion learning. The chronic decerebrate rat has been shown to be incapable of forming the associations necessary for taste aversion learning,[53,54] which suggests that integration of taste and visceral inputs within the brainstem of the rat is insufficient to support taste aversions acquisition or expression. A variety of studies indicate that certain forebrain structures within the ascending gustatory projection are involved in taste aversion learning.[10,55] Two regions of particular interest are the amygdala and gustatory (insular) cortex.

Studies examining the effects of amygdala lesions on taste aversion learning have been particularly inconsistent. Some laboratories report that lesions of the amygdala significantly interfere with taste aversion learning,[56,57] whereas others find little or no effect.[58] In fact, a case has been made that when amygdala lesions do interfere with taste aversion learning, the effect is principally due to damage to fibers passing from the insular cortex through the amygdala.[59] Our laboratory recently obtained clear effects of lesions of the amygdala on taste aversion learning.[60] Lesions completely eliminated evidence of conditioning, an observation that contrasts with that of several previous studies[55,57] that have found attenuation, but not elimination, of this learning after amygdala lesions. Subsequent work in our laboratory has demonstrated that the effects of amygdala lesions on taste aversion learning depend very much on details of the conditioning protocol.[61] Briefly, our methods involve presentation of the taste CS through an intraoral cannula without any response required of the animals, and we believe this conforms closely to a classical conditioning procedure. Under these conditions the amygdala is necessary for learning. With more conventional taste CS presentation, involving animals drinking the solution from a bottle, the involvement of the amygdala appears less critical. These findings suggest that taste aversion learning may actually represent two types of learning, a classical version and an instrumental version, and the neural circuitry underlying these two types of learning may differ significantly. Like the amygdala, the insular cortex (IC) has strong reciprocal connections with NTS and PBN [62,63] and lesion studies have been quite consistent in demonstrating attenuation of taste aversion learning after destruction of this area.[58, 59,64,65] More recent studies have shown that transient impairment of cholinergic function or blockade of *N*-methyl-D-aspartate receptors in the rat IC disrupts taste aversion learning,[66] and that protein tyrosine phosphorylation is altered in IC following training.[67] Collectively, results strongly suggest an important role for this region in taste memory and taste aversion learning.

Thus, lesion studies and more advanced methodologies as well as neuroanatomical approaches have begun to define the pathways involved in processing taste and visceral signals. Those pathways involved in forming the durable associations between taste and visceral signals are the basis of a conditioned taste aversion. The cellular mechanisms that underlie these associations have yet to be identified, and this leaves open the interesting question of whether taste aversion learning and other types of conditioning employ the same cellular and molecular changes to accomplish neuronal plasticity.

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