Review Article

Conditioned taste aversions

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Abstract
When one becomes ill after consuming a meal, there is a propensity to target a particular taste as the cause of the illness. The qualities of the taste most likely targeted include more novel, less preferred, and higher protein content. This association between a particular taste and illness is a form of learning that is termed conditioned taste aversion (CTA). A consequence of the learned association is that the taste will become aversive. When experiencing the taste again, individuals will show aversive reactions such as expressions of loathing, will experience mimicked illness sensations such as nausea, and subsequently, will avoid further exposure to the taste. The ability to acquire CTA occurs across species and across ages within a species. In the rat animal model, however, age differences exist in the capability of acquiring CTAs when increasingly longer intervals are imposed between consumption of a novel sweet solution and onset of illness. Pups have a decreased ability compared to young adults while aged rats have an increased ability. Evidence suggests that the failure of pups to acquire CTA at longer intervals is due to an immature retrieval mechanism and the facilitated ability of aged rats is due to a compromised clock mechanism that tracks the passage of time. Learned taste-illness association serves the critical function of informing individuals of the toxic nature of certain foods, thus preventing further illness and potentially death. Additionally, it contributes to the hypophagia observed during cancer chemotherapy and may contribute to the hypophagia found while suffering from bacterial infection, chronic medical conditions such as cancer, and restrictive food intake disorders such as anorexia nervosa.

KEYWORDS
Age differences; Aversion reactions; Avoidance; Hypophagia; Illness sensations

Description of conditioned taste aversion

For omnivores such as humans, there is a wide range of substances that potentially can serve as food. Some of these substances provide nutrients and calories necessary for survival, but others are harmful and potentially lethal. There are particular characteristics associated with both beneficial and harmful substances that serve as identifiers for omnivores to avoid consuming substances that might not be beneficial for their health.
and become signals for the consequences of ingestion. In humans, a number of sensory systems are engaged when processing foods, including visual, gustatory, and olfactory systems. For most mammals, however, taste is the primary cue that identifies the post-ingestion consequences of the food.

Mammals enter postnatal life with existing predispositions to exhibit a preference for and an aversion to certain tastes. That is, they exhibit positive ingestion or negative rejection reactions to certain tastes without having had prior experience with the tastes. Premature and full-term neonatal humans and neonatal rats show ingestion orofacial responses to sweet tastes and rejection orofacial responses to bitter tastes. Ingestion predispositions also have been found for the tastes of salt, starch, and fat. Post hoc explanations for these predispositions point to the calorific and nutritive value of foods with the preferred tastes and the toxic characteristics of many foods that taste bitter.

Although the positive or negative value of these predispositions generally are stable, they can change. Some changes are tied to the internal state of the individual such that preferred tastes can become temporarily less positive and aversive tastes can become temporarily less negative. The change in internal state can be either a shift away from homeostasis or a shift back to a homeostatic state. For example, rats deprived of sodium increase their preferences for solutions that contain this substance, even when the solution contains concentrations that are normally aversive. When homeostatic levels of sodium are restored, their aversion to the hypertonic solutions returns. On the other hand, reactions to calorie-rich sweet solutions change from positive to negative as humans and rats go from food depletion to food repletion. When a depleted state returns, reactions to calorie-rich sweet solutions become positive again. These temporary shifts in hedonic value are referred to as allesthesia.

Other changes in the valence of predispositions are based on postnatal experience and are relatively permanent. The valence can be strengthened, changed from negative to positive, or changed from positive to negative. For example, preferences for sweet tastes are strengthened simply through repeated exposure. Rats increase their consumption after repeated exposure to sweet sucrose or saccharin solutions. Because saccharin does not have caloric or nutritive value, positive post-ingestion consequences are not critical for the strengthening of preference for sweet tastes. On the other hand, preferences for sweet tastes change to aversions if illness follows the consumption of the sweet taste. The illness can be a consequence of consumption of a food that contains a toxic substance or it can be coincidentally associated with consumption of a nontoxic food such as happens during a bout of flu. Humans and other animals have a strong propensity to blame illness on "something I ate." The subsequent reversal in the preference for a taste (commonly referred to as the conditioned stimulus or CS) that has been associated with illness (commonly referred to as the unconditioned stimulus or US) is called conditioned taste aversion (CTA). It constitutes a learned association between the sensory properties of the taste and the sensory properties of illness and can occur when the onset of illness occurs minutes and even hours after consumption.

In the rodent laboratory, CTA typically is induced by intraperitoneal injections of a lithium chloride (LiCl) solution after consumption of a highly palatable novel solution such as sucrose or saccharin-flavored water. LiCl evokes nausea and vomiting in humans and a gaping response in nonemetic rats that appears to be an incipient vomiting response. The consequences of acquisition of a CTA are threefold. When experiencing that sweet solution again, individuals will: (1) exhibit rejection reactions to this solution; (2) experience and show mimicked illness reactions, that is, reactions that mimic some of the behavioral and physiological reactions that occur during true illness; and (3) reduce or cease consumption of this solution (Fig. 1).

Descriptions of reactions to foods when consumption had been followed by poisoning suggest that rejection reactions are species specific. In rats, rejection responses resemble those exhibited after consumption of a bitter taste such as quinine. These responses include somatic responses (e.g., paw treading and chin rubbing), spillage of the food associated with illness from eating containers, and burying of drinking spouts containing the solution associated with illness. Coyotes respond by urinating on and rolling over the food. Humans report that the avoided food is distasteful and simply thinking of learned food aversions elicits facial expressions of loathing.

Exposure to illness-inducing agents evoke a wide variety of behavioral and physiological responses. In rats, LiCl elicits hypothermia, decreased heart rate, and the behavior lying-on-belly. After a novel taste has been paired with LiCl, re-exposure to the taste will mimic these same responses. Responses to illness also include sensations derived from the detection of negative changes in the body. One sensation that commonly is reported during illness in humans is nausea. Simply hearing or thinking about a conditioned taste elicits nausea.

Reductions in consumption of a conditioned taste generally are assessed in two ways. The amount consumed before pairing the taste with LiCl is compared to the amount consumed after pairing. Comparisons also are made between the amount consumed by animals that received pairing of the taste with LiCl and the amount consumed by control animals that received pairing of the taste with normal saline.

When studied in the laboratory, animals typically are given access to only one food/drink before administering an illness-inducing agent. However, under free feeding conditions for humans and many other species, most meals include a number of different food items. Thus, identifying the culprit can be problematic. There are certain types of foods that are more likely to be targets in humans. Frequent targets are major protein sources (red meats, poultry, fish, and eggs) while infrequent targets include sweet (cakes and pies) and non sweet carbohydrates (bread, crackers, rice, and potatoes). In addition, blame is directed towards foods that are less preferred and less familiar.
Fig. 1  A simplified schematic showing neural connections during (A) and after acquisition (B) of a conditioned taste aversion. During acquisition, an association is made between the taste of a food that has been consumed and subsequent illness. This association is stored and any encounter with this taste after acquisition will evoke rejection, such as spitting out the food, mimicked illness responses and sensations such as nausea, and subsequently, avoidance, by ceasing further exposure to the taste.
The strength of acquisition of CTA is reflected in the degree to which consumption of the conditioned taste is reduced and by the intensity of the display of rejection and mimicked illness responses. The strength increases as each of the following increase: the intensity of the illness (e.g., the dose of LiCl or other illness-inducing agents), the amount of the taste consumed before experiencing illness, and the number of times consumption of the taste is followed by illness. In contrast, as the length of the interval between consumption of the taste and onset of illness increases, the strength of CTA decreases. Although some humans have reported aversions persisting since childhood or more than 50 years, animal studies reveal that even strong CTAs can be extinguished and palatability restored if the food is experienced repeatedly without subsequent illness.

Conditioned taste aversion across the life span

Acquisition of CTA has been demonstrated in 1 day old pups and across every major stage of rat life, including preweanling, weanling, peri-adolescence, adulthood, and old age. The ability to acquire CTA also has been found in late stage fetal life. In one study, mothers were given a pairing of garlic flavored water and LiCl when their fetuses were 18–19 days old. Forty-two days later, which was after birth when the pups were peri-adolescents, they drank less garlic flavored water than control pups whose mothers had been given a pairing of garlic flavored water with normal saline. In another study, 20-day-old fetuses were given a pairing of apple juice (infused into amniotic fluid near their nose-mouth area) and LiCl (injected intraperitoneally while the uterine horn was exposed). Sixteen days after birth, the pups spent less time suckling apple-coated nipples than control pups.

The capability of acquiring a CTA throughout life does not mean there are no age differences. A considerable amount of research has been conducted to determine whether there are age differences in the facility with which CTAs are acquired and retained by rats. There is a reasonable expectation that compromised facility would be evident in preweanlings-weanlings because of immature development of neural systems mediating CTA acquisition and memory processes and in aged because of deterioration of those same systems. Some of the existing data for both young and old rats suggest that changes in facility are due to compromised function of ancillary mechanisms rather than primary pathways critical for acquisition and retention of CTA.

CTAs expressed by weanlings are similar in strength to that of adults when short intervals are imposed between exposure to the taste solution and administration of the illness-inducing agent. However, as this interval is lengthened, they express progressively weaker CTAs than young adults until an interval length is reached in which adults continue to express CTA while young pups fail to express an avoidance. However, it is not necessarily the case that failure to express avoidance means that a CTA was not acquired or the memory retained. Preweanlings fail to express CTA when a 1-hr taste-illness interval is imposed, but if an ACTH fragment is administered prior to re-exposure to the taste, they exhibit CTA. These data suggest that failure to express CTA at this interval is a retrieval problem not an acquisition or memory retention problem.

Unlike preweanlings and weanlings, aged rats exhibit CTAs at longer taste-illness intervals than young adults. The relationship between age and the taste-illness interval is such that as the age of the animal increases, there is an increasing ability to acquire CTAs at longer intervals (Table 1). These findings suggest that aged rats acquire CTAs more easily than young adult rats. However, Mislin and his colleagues have proposed that aging may slow down a metabolic pacemaker and therefore speed up time within the time frame of the animal. According to this model, 6 h might be perceived as 1.5 h by a 2-year-old rat and thus, like a young adult rat, it acquires a CTA. Studies in which metabolic rate was manipulated have provided behavioral and perceptual evidence supporting this hypothesis. In humans, estimation of time is shorter when metabolic rate is decreased by lowering body temperature and it is longer when metabolic rate is increased by raising body temperature via diathermy. The results of studies examining the relationship between metabolic rate and the length of the taste-illness interval at which CTAs can be acquired are consistent with the human data. When metabolic rate is decreased in rats by reducing body temperature, CTAs can be acquired with longer taste-illness intervals. The relationship is such that as decreases in temperature progress, CTAs can be acquired with increasingly longer intervals. Conversely, when metabolic rate is increased by tail-pincher stress, the length of the effective taste-illness interval is shortened. Taken together, these data suggest that the apparent increased facility of aged rats in acquiring CTA is due to alteration in a timing mechanism rather than changes in neural pathways critical for acquisition and retention of CTA.

Illness hypophagia and conditioned taste aversion

Animals exhibit a constellation of physiological and behavioral changes during the acute phase response to infections caused by microorganisms such as bacteria and viruses. These include fever, activation of the hypothalamic pituitary axis (HPA), reduction in motor activity, general

| Table 1 | Age differences in the ability of rats to express conditioned taste aversion with increasing intervals between consumption and illness. |
|---|---|
| Taste-illness interval | Age of animal |
| | Days | Days | Year | Year | Year | Year |
| 0 h | CTA | CTA | CTA | CTA | CTA | CTA |
| 0.75 h | No CTA | CTA | CTA | CTA | CTA | CTA |
| 1.5 h | No CTA | CTA | CTA | CTA | CTA | CTA |
| 3.0 h | No CTA | No CTA | No CTA | CTA | CTA | CTA |
| 6.0 h | No CTA | No CTA | No CTA | No CTA | CTA | CTA |

Abbreviations: CTA, conditioned taste aversion; hrs, hours. Based on combining results obtained from references 41 and 48.
environmental responsiveness and social exploration, increases in sleepiness and slow-wave sleep, and hypophagia. These responses are thought to be part of a homeostatic strategy that has evolved to facilitate survival.

Examination of the survival rates of mice on different feeding regimens has demonstrated the importance of hypophagia in facilitating survival. Depriving mice of food 2–3 days before bacterial infection increases survival rates, while force-feeding mice during bacterial infection reduces survival time and increases mortality. Hypophagia also is triggered in other situations in which the body is compromised, e.g., while in the chronic disease state cancer and during exposure to toxins such as LICI and the cytotoxins used to treat cancer.61–63

Evidence supports the involvement of the cytokines in the hypophagia that occurs during bacterial infection and while suffering from cancer. The cytokines interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and high mobility group-1 (HMG-1) protein are released by lipopolysaccharides (LPS) from gram-negative bacteria cell walls, and each of these cytokines reduces food intake in rodents. Advanced-stage cancer patients with hypophagia have high serum levels of IL-1 and TNF-α and treatment with megestrol acetate, which downregulates the synthesis and release of cytokines, increases appetite.

Toxins trigger hypophagia via a different mechanism than found during bacterial infection and cancer. While being treated with the cytokotoxin methotrexate, rats reduced their food intake and subsequent examination of c-FLI revealed expression in vasopressin neurons located in the hypothalamic supraoptic and paraventricular nuclei. In contrast, there was no evidence of IL-1 activation. Exposure to LiCl in rats triggers increases in systemic blood levels of vasopressin and vasopressin-neuron activity and it induces c-FLI expression in vasopressin neurons in the supraoptic and paraventricular nuclei. Increasing the vasopressin levels of rats has been shown to reduce their food intake and subsequently treating them with a vasopressin receptor antagonist reverses their hypophagia. Taken together, these data suggest that toxins elicit hypophagia via a vasopressin mechanism.

Given the propensity to target food as the culprit when ill, it seems likely that CTAs contribute to the hypophagia triggered by infections, cancer, and toxin exposure. Three types of evidence support this hypothesis. First, CTA is induced by pairing a novel diet or solution with LPS, IL-1, HMG-1, implantation of experimental sarcoma, and chronic infusion of LiCl. Second, it has been demonstrated that aversions to specific foods consumed before treatment are learned in patients receiving gastrointestinal toxic chemotherapy. Third, when a distinctive flavored food (such as coconut or root beer Lifesavers) is used as a target food by giving it to children and adults after consumption of a meal but before administration of chemotherapy, this “scapegoat” interferes with the development of aversions to items in the meal. Thus, the impact of chemotherapy on consumption and preferences for normal meal items is reduced.

When bacterial infections and cancer are destroyed and toxins are cleared from the body, the stimuli that triggered hypophagia are no longer present and normal levels of eating return. However, any CTAs acquired during the compromised states will remain unless the individual experiences exposures to the targeted food without illness.

Anorexia nervosa and CTA

Anorexia nervosa is an eating disorder characterized primarily by persistent behaviors or attitudes that interfere with expected weight gain and maintenance. The essential features are persistent energy intake restriction, fear of gaining weight, and disturbance of self-perceived weight and shape. A number of different psychological and psychosocial therapies have been employed to treat this disorder. In general, these treatments are plagued by limited successes, relapses, and high dropout rates. Follow-up studies twenty years after treatment show that as much as 71 percent of patients had not fully recovered and 15 percent had died of suicide or complications of the disorder. Rates of suicide have been reported as 12 per 100,000 per year. There also has been little success with the use of chemical interventions. Analyses of psychotropic medication use have revealed that although a high number of individuals with anorexia nervosa use these medications, there is no conclusive evidence supporting their efficacy. This disorder remains a mysterious illness with unknown etiology.

It has been suggested that estrogen could be an originating cause of anorexia nervosa in some pubertal girls experiencing their first cyclical surges of estrogen. Specifically, it is suggested that contaminants present during fetal development sensitize the brain to the satiating and aversive properties of estrogen, and consequently, the increased production of estrogen at puberty sets off an exaggerated hypophagic response and a malaise that triggers the development of CTAs. Together these precipitate substantial weight loss. There is compelling evidence to support this hypothesis.

First, there is a greater prevalence of anorexia nervosa in women than in men. Clinical populations show a 10:1 female-to-male ratio. Second, evidence unequivocally establishes estradiol as a hypophagic hormone. Physiological levels of estradiol have been associated with systemic variations in the amount of food consumed across the reproductive cycle of a number of different mammalian species, including rats and humans. These variations are inversely associated with circulating levels of estradiol such that during the follicular phase, when endogenous estradiol levels are highest, eating is at its lowest, while the opposite is true of the luteal phase, when levels of the hormone are lowest. Estradiol specifically acts as a satiety hormone in that it reduces food intake by decreasing the size of meals rather than the number of meals. Early satiety has been reported in patients with anorexia nervosa.

Third, estradiol also acts as an illness-inducing agent. Rats acquire a CTA when consumption of a novel sweet solution is followed by administration of supraphysiological levels of estradiol. When female rats are administered diethylstilbestrol (DES, a synthetic non-steroidal estrogen) during fetal/neonatal development, they acquire CTA as adults with lower doses of estradiol than females not given
DES. This indicates that the DES-treated females have a heightened sensitivity to the conditioning properties of estradiol and suggests that the brains of these female rats were altered by the DES during fetal/neonatal development.\(^{100}\) In patients with anorexia nervosa, episodes of vomiting are associated with estrogenic vaginal smears and estrogen therapy worsens the vomiting episodes.\(^{101}\) This suggests that some individuals with anorexia nervosa have a heightened sensitivity to the illness-inducing properties of estrogen.

Fourth, there is an association between DES and anorexia nervosa in humans.\(^{100}\) DES was used in medicine and agriculture, beginning in 1947 and 1950, respectively, and continuing through 1971 when the FDA encouraged the discontinuation of its use because of its association with vaginal and cervical cancer.\(^{102–105}\) This usage corresponds with the increase in the incidence of anorexia nervosa in 14–20 year old females, but not other age groups, in the US and Switzerland beginning about 1965 and continuing through 1976.\(^{106,107}\) In addition, women exposed to DES when fetuses are 5 times more likely to show inexplicable weight loss and to be diagnosed with an eating disorder such as anorexia nervosa or bulimia nervosa, compared to women who were not exposed to the drug.\(^{100,107}\) Although one cannot draw a causal relationship, these two observations allow the possibility that the increased incidence of anorexia nervosa is the result of DES induced alteration of the developing fetal brain.

Finally, a case study of a 15-year-old girl who was placed on birth control pills containing ethinyl estradiol has revealed the effectiveness of the illness-inducing properties of estradiol in producing anorexia nervosa and the contribution of CTA to its production.\(^{93}\) While on the pills, she suffered incidences of nausea and repeated vomiting. Over the course of months, the range of foods that she would eat became limited, her body weight decreased from being overweight (26% more than expected for her age and height) to underweight (more than 27% below her expected weight), and she eventually met the criteria at that time for anorexia nervosa. She indicated that some of the rejected foods had become unpalatable and identified food for anorexia nervosa. She suffered incidences of nausea and repeated vomiting. Over the course of months, the range of foods that she would eat became limited, her body weight decreased from being overweight (26% more than expected for her age and height) to underweight (more than 27% below her expected weight), and she eventually met the criteria at that time for anorexia nervosa. She indicated that some of the rejected foods had become unpalatable and identified food as the source of her illness. This shift in palatability of foods from positive to negative also has been reported in other patients with anorexia nervosa.\(^{109}\) After she was taken off the birth control pills, the vomiting subsided, and one month later, she participated in a CTA experiment. One time she was administered an ethinyl estradiol tablet after consumption of peppermint-flavored water and another time she was administered a sucrose tablet after consumption of orange-flavored water. She experienced nausea and vomiting after the ethinyl estradiol tablet but not after the sucrose tablet. When later offered the peppermint-flavored water, she suppressed consumption but did not suppress consumption when offered the orange-flavored water. This finding substantiates the ability of ethinyl estradiol to promote acquisition of CTA.

There is enough support for an estrogen-based hypothesis to warrant serious consideration and further study, especially in light of the fact that anorexia nervosa remains an intractable and serious eating disorder. These data, as well as the ease with which estradiol induces hypophagia and CTA, suggest that rats would make a viable animal model for further study of the relationship between estrogen and this eating disorder. An estrogen hypothesis does not preclude the involvement of other factors. Certainly, personal, social and cultural factors are powerful forces that could help maintain and exacerbate the anorexia that estrogen triggered and promote fear of gaining weight and disturbance of body image.

**Conclusion**

Conditioned taste aversion is a learned association between the taste of a particular food and illness such that the food is considered to be the cause of the illness. As a result of the learned association, there is a hedonic shift from positive to negative in the preference for the food. This hedonic shift is enduring and will continue to remain until the food is experienced repeatedly without ensuing illness. CTA serves the critical function of informing individuals of toxic foods. The importance of this learned association to survival is exemplified by its presence throughout the lifespan. Furthermore, evidence suggests that the propensity to associate food with illness is so strong, it contributes to the hypophagia during medical conditions such as bacterial infection, cancer, and anorexia nervosa and treatments such as cancer chemotherapy. For bacterial infection, this contribution is beneficial because hypophagia facilitates survival, while for cancer chemotherapy, the contribution is deemed detrimental. Knowledge of how to increase or decrease the impact of CTA could aid in the success of treatment and recovery from medical conditions that feature hypophagia. The learning of taste-illness association engages a number of different neural systems, including feeding, illness, stress, and hedonic systems. The study of this learned behavior also could provide insight into how the different systems function and interact with one another to promote our well-being.

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