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Development of food aversions during illness

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Food aversions, particularly those which are acquired as a result of unpleasant experiences with foods, represent a potent defence mechanism against poisoning. Humans, as well as a broad range of animal species, appear strongly predisposed to associate certain symptoms of discomfort with foods they have eaten and to subsequently dislike and avoid those foods. Although food aversion learning serves a clearly adaptive function in certain circumstances, there appear to be other situations, such as chronic illness, in which food aversions arise and have deleterious effects on nutritional status and general health. The present article will review the basic research literature on food aversion learning and then go on to a discussion of evidence that chronic illness can be associated with the development of food aversions, and that such aversions can affect food intake and body weight. Although many of these studies were done in rats, evidence for comparable processes in humans will be included when available.

FOOD AVERSION LEARNING

A potent learning mechanism

When animals eat a particular food before receiving a drug or radiation treatment that induces gastrointestinal discomfort, they subsequently avoid that food (Garcia *et al.* 1966; Garcia & Koelling, 1966). This response, termed a learned food aversion, apparently occurs because symptoms induced by the toxic treatment become associated with the food, producing a marked reduction in preference for that food. A number of features of this very robust type of learning provoked controversy when initial reports appeared in the literature.

One of the features of food aversion learning that struck many learning theorists as anomalous was the observation that strong aversions to novel taste cues could be acquired in a single learning trial, that is after one pairing of conditioned stimulus (CS; the taste) and unconditioned stimulus (UCS; the toxic treatment) (Garcia *et al.* 1974). Even more unusual was the fact that significant aversions develop to the CS in spite of long delays between exposure to the CS (taste) and UCS (symptoms) (Garcia *et al.*

1966). In more traditional learning paradigms CS–UCS intervals of more than a few seconds significantly retard the development of conditioned responses. Thus, the strong food aversion learning which occurs after CS–UCS delays of many minutes or even hours is viewed as remarkable. Another characteristic of food aversion learning, sometimes referred to as 'selective associations', is that visceral illness, as induced by toxins, appears much more readily associated with tastes than with visual or auditory cues.

Food aversion learning has been documented in a broad range of species, ranging from invertebrates such as the garden slug *Limax* (Sahley *et al.* 1981) to primates, including humans (Garb & Stunkard, 1974; Bernstein, 1978). The incidence of learned food aversions in humans has been examined by a number of investigators using survey methods. In a survey of subjects by Garb & Stunkard (1974) 38% of subjects, ranging in age from 6 years to more than 60 years, reported having had at least one food aversion at some time in their lives. These aversions were typically directed at the taste of the food and were based on the association of the food with gastrointestinal upset. Surveys restricted to subjects of college age (Logue *et al.* 1981; Midkiff & Bernstein, 1985) report a higher incidence of aversions (65 and 57% respectively). The reason for this is not known, although college students' initial experiences with alcohol intoxication may play a role by providing gastrointestinal symptoms that promote this learning.

Several controlled studies of food aversion learning in humans have also been reported. In one study from my own laboratory we examined whether pediatric cancer patients receiving drugs which were associated with nausea and vomiting would acquire aversions to a novel ice cream consumed before their drug treatments (Bernstein, 1978). We found that children who consumed the ice cream before receiving GI-toxic chemotherapy were much less willing to eat that ice cream again some weeks later than were children in control groups who had either been exposed to the ice cream or the drug treatments but not both. Thus, children will avoid eating a food which previously has been associated with GI-toxic chemotherapy. Furthermore, this learning is not limited to children, as similar results have been obtained with adult patients (Bernstein & Webster, 1980).

Over all, the available evidence indicates that humans are predisposed to acquire aversions to foods which are eaten before episodes of illness or nausea. Furthermore, when people develop aversions as a result of the coincidental association between consumption of a food and chemotherapy or symptoms of the stomach flu, their food aversions seem to defy cognition. That is, strong aversions arise despite the clear awareness that the target food is not actually the cause of their discomfort. These observations have led some to suggest that food aversion learning is based on relatively primitive associative mechanisms (Garcia *et al.* 1974). This is reinforced by the remarkable finding that rats will acquire aversions even when they are completely anaesthetized during and after the time when a toxic drug is delivered (Roll & Smith, 1972; Bermudez-Rattoni *et al.* 1988).

Nature of the unconditioned stimulus

Characterization of treatments which are effective in inducing food aversion learning is important in considering the clinical conditions under which such aversions are likely to arise. Initial animal studies employed drugs such as apomorphine and LiCl, or irradiation as unconditioned stimuli. These treatments were known to activate emetic mechanisms

and it appeared that food aversion learning was a response to symptoms of internal malaise, especially nausea. Since that time, however, there have been hundreds of studies employing dozens of different pharmacological agents and it is clear that many agents which are capable of producing learned food aversions do not produce aversive emetic symptoms (Gamzu et al. 1985). It is generally agreed, then, that nausea is not a necessary condition for the development of learned food aversions.

However, a convincing case has been made that nausea does, in fact, play a special role in food aversion learning. Studies clearly indicate that nausea is a particularly effective UCS and appears to produce aversions which differ in important respects from those produced by other types of symptoms (Pelchat & Rozin, 1982; Pelchat et al. 1983). For example, Pelchat & Rozin (1982) surveyed people with food allergies who avoid eating the foods to which they are allergic. When the allergic response includes symptoms of nausea, subjects actually reported disliking the taste of the offending food. In contrast, when the allergic response involved symptoms like hives or mouth sores, hedonic ratings of the foods by subjects were unaffected. Thus, although they do not eat the food, they wish they could. These types of results are the basis of the proposal, by Pelchat and her colleagues (Pelchat & Rozin, 1982; Pelchat et al. 1983), that nausea not only is a sufficient condition for the development of learned food aversions but also is necessary for the hedonic shift or the development of an actual distaste toward target foods.

Nature of the conditioned stimulus

Also of clinical relevance is the characterization of the types of foods which become the targets of aversions. Perhaps the single most important characteristic of a food, in terms of its vulnerability to aversion, is its novelty. It is well established that learned aversions develop rapidly when a target food is novel whereas aversions to familiar foods ocur far less readily (Revusky & Bedarf, 1967; Kalat & Rozin, 1973).

Foods provide a variety of sensory cues including their taste, odour and texture. Interestingly, when presented alone, tastes appear much more effective than odours as cues in aversion formation. In one study, for example, rats were exposed to an almond odour alone (presented on filter paper located behind the drinking spout of a water bottle) and then injected with LiCl. Aversions to the odour were not evident after a single conditioning trial. By comparison, very strong aversions were evident in a group conditioned with saccharin-flavoured water (Palmerino et al. 1980).

Another attribute of foods which could affect their likelihood of becoming the targets of aversions is their nutrient composition. Our initial evaluation of chemotherapy-induced aversions in patients suggested that they were more likely to be directed at foods which were protein sources (eggs, cheese, meat) than to carbohydrates. To examine the generality of this finding and extend it we surveyed a large group of college students regarding their food aversion experiences (Midkiff & Bernstein, 1985). The target foods for these aversions were classified into general food categories. A prominent category for human aversions proved to be foods which were protein sources, with aversions arising significantly more often than would be expected by chance.

Additional evidence for the salience of proteins as targets for learned aversions comes from rat studies. Rats allowed to self-select from separate protein and carbohydrate macronutrient sources during a sequence of toxic drug injections formed significant

aversions to the protein but not the carbohydrate (Bernstein *et al.* 1984). When we explored the question of whether the salience of proteins was based on flavour or postingestional properties we were able to eliminate postingestional events as necessary for this effect (Brot *et al.* 1987). At this time we believe that the presence of a strong odour, 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 odours, such as chocolate and coffee, may frequently become the targets for aversions because of these flavour properties (Mattes *et al.* 1987).

CHRONIC ILLNESS AND LEARNED FOOD AVERSIONS

Virtually all the studies I have discussed so far involve acute episodes of illness like the flu, allergies or drugs which generate transient symptoms followed by recovery. There is abundant evidence that such episodes can lead to the development of learned food aversions. The idea that chronic illness can provide a basis for food aversion learning is conceptually and procedurally much more difficult to evaluate. In a chronic condition, particularly one with gradual onset, there may be ill-defined but unpleasant symptoms which somehow come to be associated with the available diet, causing the diet to become distasteful. One problem with this formulation is the apparent lack of any temporal pairing between the food and the symptoms of illness. A second problem arises when one attempts to relate this learning to the clinical situation. Since humans eat a variety of foods over the course of the weeks or months that an illness develops, one needs to address the question of which foods would be expected to become the targets of aversions and how overall food intake would be influenced? We have good evidence, from an animal model, that food aversion learning does occur in response to chronic illness and that it contributes significantly to decline in food intake. This evidence will be reviewed briefly later (p. 135). With regard to the extension of this model to the clinical situation, I will discuss available evidence and speculate further.

Food aversion learning and disease

To examine whether symptoms of prolonged discomfort can become associated with the available food and lead to anorexia, as well as learned food aversions, we developed the following rat model (Bernstein & Goehler, 1983). To simulate a condition of chronic illness we utilized implantable infusion pumps which delivered LiCl continuously over an 8 d period at the rate of 1 μl/h. The target food was the specific diet available continuously throughout this period. In one group the target food was novel, presented for the first time just before implantation of the pumps and, hence, a prime target for the development of aversions (Revusky & Bedarf, 1967). In another group the food was laboratory chow, a diet which, because of its familiarity, is resistant to the development of aversions. Differences in food intake and diet preference were evident when the novel and familiar diet groups were compared with each other. Chronic LiCl infusions caused marked reductions in food intake in animals eating a novel diet but had relatively little effect on those eating familiar chow. Furthermore, significant aversions were evident to the novel but not the familiar diet. These findings suggest that learned aversions can arise during the course of a chronic illness and that such aversions can lead to declines in food intake. Studies described in the next section add support for this hypothesis.

Tumour anorexia and learned food aversions

There is a lengthy history of investigations into the causes of tumour anorexia, the loss of appetite and weight which accompany the growth of certain tumours. These symptoms, which are manifested in cancer patients as well as animals implanted with experimental tumours, are important contributors to the morbidity and mortality of this disease. Although there are clearly multiple mechanisms involved in the generation of anorexia symptoms, we hypothesized that food aversion learning could play a role in the aetiology of this syndrome (Bernstein & Sigmundi, 1980).

To examine this hypothesis we used an animal model, rats implanted with tumours which are associated with significant depressions in food intake and body weight. To determine whether learned aversions arise during the period of tumour growth, tumour-bearing and control animals were exposed to a novel target diet for 10 d. At the end of this period food intake of tumour-bearing animals had declined to levels significantly below those of controls. At this time diet preference was assessed; the results were strikingly clear. Tumour-bearing animals, but not controls, displayed a profound distaste for the diet they had been eating while the tumour was growing. Furthermore, when an alternate diet was available during the preference test, food intake of the tumour-bearing animals nearly doubled. These findings indicate that the tumour-bearing animals had developed a pronounced aversion to the target diet by the day of the preference test and that dislike for the available diet had depressed their food intake. Our results also indicate that the introduction of a new food, after anorexia has developed, can lead to immediate increases in food intake.

Additional work has explored the relative contribution of learned aversions to the overall tumour anorexia syndrome (Bernstein *et al.* 1985). As in the case of chronic LiCl infusions, diet novelty proved to be an important influence on symptom severity. Tumour-bearing animals consuming a novel diet during their illness displayed more severe anorexia and weight loss than those on familiar laboratory chow, and significant aversions to the novel but not familiar food were evident during preference testing. Diet variety was also found to have significant effects on the severity of anorexia. It was predicted that frequent changes in the diet would attenuate the effects of food aversions on tumour anorexia because as foods became aversive they would promptly be replaced by new ones. The effect of diet variety was examined by introducing a different food every 3 d. Frequent changes in the diet available to tumour-bearing rats led to significantly greater food intake than the presentation of a single (initially highly palatable) food for the entire period. Apparently, when learned food aversions were prevented, or aversive foods were replaced by new ones, the impact of these aversions on food intake of tumour-bearing animals was minimized.

Are learned food aversions clinically relevant?

At this point we need to consider whether learning mechanisms defined in experimental settings are implicated in the genesis of clinically significant appetite loss. We know from our own studies in patients receiving chemotherapy (Bernstein, 1978; Bernstein & Webster, 1980), as well as the work of others (Mattes *et al.* 1987; Andrykowski & Otis, 1990), that humans readily form food aversions. Not only can foods eaten before chemotherapy become distasteful to patients, a recent study indicates that exposure to a beverage which was previously paired with chemotherapy can actually trigger symptoms of

nausea (Bovbjerg *et al.* 1992). Thus, learning can promote very potent psychological and physiological responses to foods and beverages, responses which would be likely to affect food choices and appetite. Nonetheless, it is also important to recognize the enormous difference between the clinical situation and our animal model in terms of access to food and food choice. It would appear that the development of aversions to a food or a number of foods could simply lead people to choose something else to eat. How could learned aversions to specific foods generate anorexia or the reduction of food intake, in general? One feature of learned aversions that may be important to consider is the tendency to generalize. Aversions acquired to one food or taste will often lead to avoidance of foods that share similar taste properties (Logue, 1985). In spite of generalization, healthy people with diverse diets may be buffered against the effects of learned food aversions. However, certain disease states may promote food aversion learning and severe or prolonged symptoms may broaden the impact of such aversions on food intake (Bernstein & Borson, 1986). For example, with some disorders, ingestion of food produces discomfort. In others, chronic malaise may become linked with foods because it is so pervasive. Food aversions form rapidly; it is easy to imagine that illness of long duration could promote aversion to a broad range of foods and thereby lead to a general reduction in food intake. Most at risk would be people who are finicky and have a narrow range of preferences. Such people may not be willing or able to make alternate food choices and, instead, could progressively reduce their food intake. Whether food aversion learning is of clinical relevance in the aetiology of anorexia during illness remains an empirical question. At this point it seems premature to exclude this possibility simply because of differences in human feeding opportunities.

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