Physiological and Psychological Mechanisms of Cancer Anorexia

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Abstract

Recent research addressing possible causes of the decline in spontaneous food intake which accompanies tumor growth and antitumor therapies is reviewed. Investigations of whether disruptions in brain mechanisms involved in feeding are responsible for cancer anorexia are briefly summarized. Studies evaluating the contributions of learned food aversions to the anorexia induced by tumors and antitumor therapy are discussed in some detail. Evidence is presented, from both the clinic and the laboratory, that learned food aversions occur as a result of the association of foods with the discomfort induced by chemotherapy and/or tumor growth. The possible role these aversions play in the etiology of cancer anorexia is discussed, and studies aimed at developing methods for preventing them are described.

Cancer anorexia refers to the decline in food intake which accompanies neoplastic diseases, both in the clinical setting and in experimental animal models (15, 31, 43). The appetite and weight loss frequently seen in cancer patients may be caused by the disease itself and also by the unpleasant side effects of a number of therapies used in its treatment (17, 23, 33).

The major cause of host weight loss has been attributed by some investigators to primary metabolic effects of tumor growth, such as excessive or inefficient energy utilization (9, 21, 41). However, it has been argued that organisms will compensate for a variety of treatments which increase their energy requirements (i.e., exposure to the cold, forced exercise, and pregnancy) by increasing their food intake (31). However, the tumor-bearing organism fails to increase food intake (and more frequently decreases its food intake) in the face of increased energy requirements imposed by tumor growth. Morrison has therefore emphasized that the ultimate cause of weight loss and host wasting in the tumor-bearing organism is the failure of spontaneous food intake to keep pace with nutrient requirements. The focus of this paper will therefore be on recent research addressing possible causes of these changes in spontaneous food intake which accompany tumor growth and antitumor therapies. Emphasis will be placed on very recent work, since several extensive reviews of this area have appeared in the past few years (13, 16, 31, 39).

Mechanisms Regulating Feeding

In an effort to understand the mechanisms responsible for cancer anorexia, investigators have turned first to those systems known to be involved in food intake regulation in normal humans and animals. These include central brain mechanisms, such as the hypothalamus and specific neurotransmitters, as well as learning mechanisms, and these approaches will be discussed individually below.

Hypothalamic Mechanisms. Over the last 2 decades, the hypothalamus and related structures have been the focus of attention for investigators examining the brain regions critical to the control of feeding behavior. Dramatic effects of lesion and stimulation studies have pointed to the ventromedial and lateral areas of the hypothalamus as "inhibitory" and "excitatory" regions involved in initiation and cessation of feeding. For example, lesions in the ventromedial nucleus of the hypothalamus produce the well-known syndrome of hyperphagia and obesity, while lesions in the lateral area produce anorexia (28). Early efforts to assess the involvement of hypothalamic regions in tumor anorexia included examination of the effects of ventromedial or lateral lesions of the hypothalamus on the food intake of tumor-bearing animals (2, 25). These lesions did not prevent or attenuate the appearance of tumor-induced anorexia, and the apparent independent effects of lesion and tumor manipulations on food intake strongly suggested that they are unlikely to involve the same control mechanisms. Furthermore, the characteristics of the feeding behavior of tumor-bearing animals, including increased feeding responses to exogenous insulin and increased feeding efficiency (30, 32), are in marked contrast to those seen in animals anorexic as a consequence of lesions in the lateral hypothalamus. In addition, more recent results have suggested that the view that the control of feeding can be explained by activity in "excitatory" and "inhibitory" centers located in the hypothalamus is greatly oversimplified (22, 28).

Neurotransmitters and Feeding. Paralleling the anatomical complexity of food intake regulation is the recent implication of a variety of neurotransmitters in the control of food intake (28). Recent work has suggested major roles for noradrenergic (26), dopaminergic (42), serotonergic (1, 10), and to a lesser extent endorphinergic (29) systems in the modulation of food intake. The actual role of these transmitters in normal food intake regulation is as yet poorly understood. It is, therefore, not surprising that any aberrations in these systems which may be responsible for pathologies in food intake regulation (such as obesity and cancer anorexia) have not been identified, although these issues are currently under active investigation. For example, Krause et al. (24), investigating possible alterations in serotonin metabolism in rats with Walker 256 tumors, found elevations in tryptophan and the serotonin metabolite, 5-hydroxyindoleacetic acid, in the brains of tumor-bearing animals. Since treatments which decrease brain tryptophan and/or serotonin have been reported to cause increases in food intake (12, 38), Krause et al. have hypothesized that increases in serotonin turnover may be responsible for the anorexia seen in Walker 256 tumor-bearing animals. An alternate hypothesis involving endorphin systems has been proposed by Lowy and Yim (27) to explain the anorexia in Walker 256 tumor-bearing rats. They found a similarity between the feeding profiles of
tumor-bearing and dexamethasone-treated rats and suggested that endorphin depletion may play a role in cancer anorexia-cachexia. At this time, assessment of the degree to which either serotonin or endorphin mechanisms contribute to tumor anorexia awaits further research.

Learned Food Aversions and Feeding. A common feature of most explanations of tumor anorexia has been the suggestion that some physiological effect of tumor growth acts directly to suppress appetite. An alternate approach to this problem has recently been suggested, namely, the idea that the unpleasant symptoms associated with tumor growth and antitumor therapy may provide the basis for the development of learned aversions to the available food and that appetite suppression in cancer patients may be an indirect effect of the disease or the therapy (3, 4).

Learned food aversions are aversions to specific foods or tastes which develop as a result of the association of those foods with unpleasant internal symptoms (i.e., nausea and vomiting). In initial studies, Garcia et al. (20) reported that, when animals eat a particular food before receiving a drug or radiation treatment which induces GI² discomfort, they will subsequently avoid that food. This is presumably because the symptoms of the treatment are associated with the food itself. Furthermore, they avoid that specific food long after all symptoms of discomfort have subsided. This phenomenon of learned or conditioned taste aversions has been viewed as a variant of classical conditioning with animals learning to associate a conditioned stimulus (the taste) with an unconditioned stimulus (the illness) (11). This learning is evidenced by reduction of a previously acceptable and preferred food by the animal after the food has been paired with these aversive treatments. One of the important and unusual features of food aversion learning is that it is possible to introduce a delay of many hr between the tasting of the food (conditioned stimulus) and subsequent discomfort (unconditioned stimulus) and still produce an aversion to the taste (19). Another important feature is that this learning occurs very rapidly. In many taste aversion experiments, significant aversions are acquired in a single trial, i.e., following one pairing of food consumption and discomfort. Novelty of the food is also important, since studies have shown that aversions are most likely to develop to the most novel food consumed around the time discomfort is experienced (34). Repeated pairings of food and illness, on the other hand, can cause even the most familiar items to become aversive (18).

In the following sections, research will be described which suggests that learned food aversions can occur as a result of chemotherapy in cancer patients and that intervention procedures, tested in laboratory animals, may be effective in preventing aversions. Following that, evidence will be presented that growth of an anorexigenic tumor alone can produce learned aversions to the specific diet consumed during tumor growth and may account for anorexia in the absence of drug treatments.

The possible implications of this evidence for a role of drug- and tumor-induced food aversions in the etiology of anorexia in patients with cancer will also be discussed.

Learned Food Aversions Can Result from Chemotherapy. Learned food aversions have been extensively documented in a wide variety of animal species (20, 35). On the basis of these results, we have examined children receiving chemotherapy for the treatment of neoplastic diseases to determine whether they acquire aversions to foods consumed prior to drug treatments (3, 7). These studies were of particular interest inasmuch as learned food aversions had previously not been demonstrated in humans. Patients receiving drugs associated with a moderate to severe degree of nausea and/or vomiting (e.g., cyclophosphamide, doxorubicin, and 1-β-D-arabinofuranosyl-cytosine) were randomly assigned to an experimental or control group. Patients assigned to the experimental group were offered a serving of an unusually flavored ice cream (Mapletoff) shortly before their scheduled treatment. Those in the control group were not given ice cream but were occupied for a comparable amount of time with a toy. An additional control group consisted of clinic patients who were either receiving vincristine (a drug not associated with GI discomfort) or no drug treatment. They were offered the same ice cream as the experimental group. Patients were tested for the development of aversions approximately 1 to 4 weeks later by being offered a choice between eating that ice cream or playing with a game. Patients in the control groups were found to be 3 times as likely to choose the ice cream as patients in the experimental group (p < 0.01). Thus, children will avoid eating a food which has previously been associated with GI toxic chemotherapy. These aversions were not caused by the GI toxic drugs alone, since patients that had received GI toxic treatments but were not exposed to the flavored ice cream were not averse to eating the ice cream. That the ice cream was not distasteful is indicated by the acceptance of it by patients who had tasted it previously at a time when they were not receiving GI toxic therapy.

These findings were confirmed when similar experimental and control group patients were tested for their flavor preference by being offered a choice between 2 ice creams, Mapletoff (the flavored paired with GI toxic therapy in the experimental group) and Hawaiian Delight (a novel, orange-pineapple ice cream). Subjects were asked to taste both ice cream flavors, indicate which they preferred, and eat as much of each as they wished. Flavor preference and amount consumed were recorded. In the experimental group, preference for Mapletoff ice cream, whether based on amount consumed or statement of preference, was significantly lower than preference for Mapletoff in the control groups. Again, these results indicate that the consumption of a distincitively flavored ice cream before GI toxic chemotherapy is associated with a significantly lower preference for that particular flavor during subsequent testing. Similar results have also been obtained in adult patients (8).

These studies were extended to determine whether patients receiving chemotherapy form aversions to familiar and/or preferred foods in their usual diets. To accomplish this, pediatric patients (or their parents) who also participated in the ice cream study completed diet inventory forms by listing (a) favorite foods, (b) foods they are reluctant to eat, (c) 2 typical breakfast, lunch, and dinner menus, and (d) any specific foods they have eaten in the past 4 to 5 hr. For patients who were about to receive a GI toxic chemotherapy treatment (experimental group), the specific items consumed 4 to 5 hr prior to therapy were considered potential candidates for the formation of an aversion. One week later or more at a subsequent clinic visit, patients filled out another inventory that was much like the first. Thus far, 2 inventory forms of food preferences for 52
patients have been compared to see if there were systematic changes in the way patients rate the specific food they ate just before their therapy. An aversion was scored when a specific food eaten before GI toxic drug treatments was no longer preferred, actively disliked, or no longer listed in usual menus. The number of patients showing at least one aversion was then determined. The control group consisted of patients receiving vincristine or no drug. The results (Table 1) revealed that more than half the patients receiving chemotherapy associated with GI discomfort showed aversions. This was compared to 26% of patients in the control group who experienced no nausea and vomiting. The difference between these 2 proportions is significant (p < 0.01). Excluding specific aversions, inventories from patients receiving GI toxic chemotherapy did not undergo more changes from Session 1 to Session 2 than did those from controls. Therefore, the aversions appear to be fairly specific to foods eaten before GI toxic therapy. Thus, learned food aversions may occur not only to a food presented by the experimenter just before drug administration but also to foods in the usual diet of the patient which happen to be eaten up to several hr before treatment.

The studies described above were confined to chemotherapy treatments given in a single clinic visit. However, patients actually receive many such treatments. If one-half or even one-fourth of them are associated with the formation of aversions, we may be looking at a significant etiological factor in the frequent reports of capricious and frustrating changes in food preferences experienced by these patients (14). It is also possible that these learned food aversions are of significance in the development of anorexia and weight loss in patients with cancer. Importantly, if a learning mechanism does account for at least part of the observed appetite loss, intervention approaches which alter the stimulus association may prove successful in alleviating these symptoms.

In related studies, Smith and Blumsack (40) examined taste aversions induced by radiotherapy. They have reported that the administration of antihistamines to rats prior to treatment will block radiation-induced, but not drug-induced, taste aversions. Smith has suggested that if similar learned food aversions arise in patients undergoing radiotherapy, antihistamine pretreatment may prove an effective means of blocking these aversions.

**Experimental Approaches to Prevent Learned Food Aversions.** In order to more thoroughly define conditions leading to learned food aversions and to evaluate intervention procedures for preventing their occurrence, studies have been initiated using an experimental animal model. In the initial studies, a conditioned taste aversion paradigm was used and a single injection of chemotherapeutic drugs (e.g., cyclophosphamide and Adriamycin), in dosages comparable to those used clinically, produced aversions to a saccharin solution in rats (6). Next, a paradigm which would more closely model conditions in the clinic was developed. This learned food aversion model involved exposing nondeprived rats to a sequence of cyclophosphamide injections (20 mg/kg) and evaluating whether they developed aversions to the food (a complete rat diet, AIN3 meal), which was continuously available during drug treatments. Aversions to the AIN meal were assessed in a 24-hr preference test with AIN and a novel diet available. Results of studies with this model express AIN preference as the ratio of AIN consumption to total food consumption. Reduced intake of AIN relative to the choice diet is reflected in low ratios. Significant reductions in preference for AIN diet (drug-treated group versus 0.9% NaCl solution-treated controls: preference ratio of 0.16 versus 0.58) indicated that a series of chemotherapy injections can produce a reliable aversion to the food which was continuously available during these treatments.

This food aversion model was used to test a variety of intervention methods for reducing or eliminating learned food aversions. The basic study was repeated with the inclusion of additional groups exposed to an intervention manipulation and a sequence of drug treatments (5). The success of these intervention methods was evaluated by determining the degree to which they blocked or reduced aversions to the AIN diet.

Approaches which have been studied included (a) withholding all food for 6 hr before and after each treatment, (b) introducing a novel flavor in the water around the time of each treatment, and (c) replacing the standard AIN diet with a novel food on treatment days. Food deprivation and novel liquid interference stimuli did not reduce the magnitude of aversions to the AIN diet. The only method which significantly reduced the magnitude of the drug-induced food aversions was the introduction of a novel diet on treatment days. These studies are continuing in an effort to identify the parameters determining the effectiveness of intervention approaches so that successful approaches may be modified and implemented in the clinic.

**Tumor Growth Itself May Cause Learned Food Aversions.** The preceding clinical and laboratory studies have pointed to the role of learned food aversions in contributing to the appetite loss experienced by patients receiving treatments with severe and unpleasant side effects (i.e., chemotherapy and radiotherapy). Although anorexia induced by antitumor therapy is an important problem, tumor growth alone can produce severe anorexia. Learned food aversions might be of more general significance if learned aversions develop in response to the tumor itself. Thus, some tumor-induced appetite loss, like drug-induced appetite loss, could be based indirectly on learned aversions with chronic symptoms secondary to tumor growth, rather than the acute effects of drug injection, acting as the unconditioned stimulus.

This hypothesis was investigated in rats bearing transplantable tumors, which produce anorexia and weight loss (4). A polyoma virus-induced sarcoma (PW-739) was s.c. implanted in a group of experimental animals. Tumor-bearing and control animals were given continuous access to AIN diet for 10 days in the mid to late stages of tumor growth. Aversions were assessed in a preference test, such as those in the previously described food aversion studies.

During the 10-day diet exposure period, intake of AIN diet by tumor-bearing rats declined to levels considerably lower

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**Table 1**

<table>
<thead>
<tr>
<th>Aversions to foods in the diet</th>
<th>No. of patients with aversions*</th>
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<tr>
<td>Patients receiving GI toxic chemotherapy</td>
<td>20/30 (67)</td>
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<tr>
<td>Patients receiving vincristine or no drug</td>
<td>6/22 (26)</td>
</tr>
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* Numbers in parentheses, percentage. First patient group differs from second patient group, p <0.01.

3 AIN-78. Semipurified diet, ICN, Nutritional Biochemicals, Cleveland, Ohio.
than those of controls (Table 2). Mean AIN preferences scores were 0.11 in the tumor group and 0.48 in the control group; they indicate that tumor-bearing animals appear to have developed a significant and pronounced aversion to the AIN diet \((p \leq 0.01; t\ test)\), which had been available during recent tumor growth. In addition, striking elevations of 24-hr food consumption were seen in tumor-bearing animals but not in controls when an alternate diet was available. Food intake of tumor-bearing animals (Table 2) showed an 85% increase over pretest intake levels. Thus, tumor-bearing animals which had been consuming considerably less AIN diet than the controls ate as much as controls when a novel diet was introduced.

These results suggest that tumor-bearing animals associate their tumor-induced discomfort with their diet and that these aversions contribute to tumor-induced anorexia. However, it was possible that the AIN aversion manifested by tumor-bearing animals was not due to a learned association but was a direct effect of tumor growth on taste preferences or responsiveness. DeWys (14) has reported that tumor growth alters taste responsiveness of cancer patients as well as laboratory animals. Therefore, a cross-over design using 2 different preexposure diets was used in a subsequent study in order to determine whether AIN aversions were due to general tumor effects or learned associations. Five weeks after tumor implant, groups of tumor-bearing and control animals were assigned to one of 2 diets (AIN or NIH-07); they received continuous access to one of these diets for 21 days. On the 22nd day, they received a preference test with a choice between these 2 diets for 24 hr. Preference for the preexposed food was calculated by dividing consumption of the preexposed food by total food consumption. Tumor-bearing animals in both diet groups showed a significantly lower preference for the preexposed food (or the food paired with tumor growth) than did controls (Chart 1). These results support the idea that aversions are specific to the diet to which the animals were exposed during tumor growth and represent a learned association. This is emphasized by examining AIN preference of tumor-bearing animals. Preference was quite different depending on preexposure experience, i.e., 0.17 for AIN diet if animals were preexposed to AIN and 0.88 for AIN diet if they were preexposed to NIH-07. Obviously, tumor growth alone is not sufficient for the development of an aversion to AIN diet.

These studies indicated that learned food aversions occur in animals that are anorexic as a consequence of tumor growth, and they further demonstrated that it was possible to increase food intake of these animals by presenting a new diet. These results suggest that learned food aversions play a causal role in the development of tumor anorexia.

The suggestion that learned food aversions can contribute to anorexia has been made by Rozin et al. (36, 37) studying vitamin-deficient rats. Rats deficient in thiamin demonstrate an aversion to their thiamin-deficient diet by spillage and a strong preference for any new diet offered them. Rozin concluded that the anorexia characteristic of many vitamin deficiencies reflects, at least in part, a learned aversion to the deficient diet, since anorexia disappears when a new diet is offered. In this regard, PW-739 tumor-bearing animals are similar to animals suffering from certain nutrient deficiencies. In spite of the fact that the diets used in these studies were considered nutritionally adequate for normal animals, deficiencies may have arisen in host organisms as a consequence of excessive or preferential utilization of essential nutrients by the tumor. This possibility is currently being investigated in our laboratory.

In summary, our laboratory and clinical studies have indicated that learned food aversions arise as a result of both therapy treatments and tumor growth itself. Food aversions learning has evolved in rats and many other species, enabling them to learn to select needed nutrients and to avoid toxins (20, 37). This mechanism is clearly adaptive in that it allows organisms to associate the delayed internal effects of toxins and imbalanced nutrients with the taste of consumed foods and to adjust their intake accordingly. However, this mechanism may be triggered under inappropriate circumstances, as in patients receiving cancer treatment or tumor-bearing animals, in which the discomfort and illness induced by drugs or tumor are associated with specific foods. It therefore seems probable that this mechanism plays a role in the anorexia produced by certain tumors and in the aversions and appetite loss seen with certain antitumor therapies. An understanding of the factors controlling the acquisition of these aversions may enable us to assess the degree to which they contribute to cancer anorexia and to successfully develop methods for preventing them.

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References


Discussion

Dr. Morrison: I think it is a pity that we have this term anorexia built into the language of this problem. I am realistic enough to know there's no hope of changing the use of the term, but I hope that we might start thinking on what we get ourselves into when we use this term, because we immediately answer ourselves when we talk about anorexia; we say it's a problem of appetite. It is not necessarily a problem of appetite, and especially at the animal level all we know is that it's a problem of reduced food intake; we do not know if there is anorexia; we do not know if there's a problem with appetite; we know that there is a reduced food intake; or, to be more precise, sometimes we know this. We don't always even see a reduced food intake. What we see, of course, is depression, depletion of host tissues. If there is depletion of host tissue, we know that there must be a relative shortfall of food intake over cost, so that really we can have an increased food intake and still have a relative depression of food intake. In all normal physiological situations, increased food intake follows increased energy cost; there's a time lag, but intake eventually follows any change in cost. The problem in cachectic situations is that this doesn't happen, and so what we are looking at is depression. From that, we can infer that there must be a shortfall of food intake. This does not mean that we have to find an actual fall in food intake, and this makes for considerable complications of interpretation of animal data. One possible cause of the relative decline in food intake can be that the decline is appropriate, that it's a defense mechanism, that it's advantageous to the animal. A defense mechanism, to be a defense mechanism, has to work, and on balance the relative shortfall of food intake has to work. If it is a defense mechanism, it is a miserably ineffective one, and you would imagine that in the 4 billion years of evolution, or whatever it is, a better one would have become available. Another possibility is that there is impairment of specific feeding control mechanisms, and a third possibility is that there is impairment of nonspecific factors influencing eating. There are some necessary conditions for feeding which are not really control mechanisms. For example, a necessary condition for feeding is that there be arousal. We have to be awake if we are going to eat; therefore, the ability to be awake is a necessary condition for feeding. Another necessary condition for feeding is the ability to undertake motor activity because feeding is a motor activity and depends on the ease of access to food, and the ease of mastication and digestion of the particular kind of food. The energy cost, the motor energy cost of feeding, can be quite substantial, especially for animals, up to as much as 25% of the total spontaneous activity of the rat. Energetically, it's quite a costly procedure. If the animal loses its capacity to engage in motor activity, then feeding will stop or it will be reduced. Of the 4 rat host-tumor combinations that we've examined, which includes the Walker 256 in Sprague-Dawley rats, mammary
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