

The Role of Food in the Pathogenesis of Migraine Headache[†]

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Recent textbooks of neurology and internal medicine cite food, or pharmacologic agents in foods, as provokers of migraine (1,2). Nevertheless, this area remains controversial. Many authorities recognize foods containing pharmacologic agents, such as tyramine, as possible provokers of migraine. However, the importance of foods lacking these properties is less clear. During the 1980s, there was renewed interest in food-induced migraine. Studies have attempted to address the incidence of food-induced migraine and have recently begun to study potential mechanisms. This paper will review the general features of migraine, including prevalence, differential diagnosis, and known provokers, and then focus on the link between food and migraine.

Introduction

The Ad Hoc Committee on the Classification of Headache (3) defined migraine as "Recurrent attacks of headaches widely varying in intensity, frequency, and duration. The attacks are commonly associated with anorexia, and sometimes, with nausea and vomiting; in some are preceded by, or associated with, conspicuous sensory, motor, or mood disturbances; and are often familial." Migraine may be further subdivided into "classic" migraine, in which headache symptoms are preceded by a disturbance in neurologic function or prodrome, and "common" migraine, in which such warning signs are absent (1). The classic form accounts for <20% of attacks, with most patients suffering with common migraine (4). In addition, the

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Table 1
Differential Diagnosis of Migraine

Seizure	Cluster headache
Aneurysm \ angioma	Pheochromocytoma
Temporal arteritis	Carcinoid syndrome
Mastocytosis	
Pituitary, parapituitary, or occipital tumor	

term "complicated" migraine is used to describe migraine headaches in which focal neurological defects may persist throughout the headache period and even leave permanent residual (2).

Migraine is a common disorder. Prevalence estimates range from 3–5% to 20–30% of the general population (1,2,5). Waters and O'Connor, in three separate epidemiological surveys, found prevalences of 23–29% in women and 15–20% in men (5).

Symptoms of migraine may begin at any age; however, up to 50% of subjects will suffer their first attack before the age of 20 (6). The frequency and severity of migraine symptoms tend to decrease as patients reach the age of 50–60 (7). The disease is more common in women, and a positive family history of migraine is present in 60–70% of subjects (6,8).

The diagnosis of migraine is usually straightforward, based on a thorough history and physical examination. However, other disease processes may mimic the presentation of migraine (Table 1). Seizures occur slightly more frequently in subjects with migraine than in the general population. In a rare individual, headache may be a presenting symptom of seizure (7,8). In questionable cases, the electroencephalogram is a useful diagnostic tool.

Aneurysms and angioma may be associated with recurrent headaches. However, these headaches are invariably located on the same side of the head, whereas migraine will, at least on occasion, be on alternate sides. In addition, with these lesions, focal neurological signs may be present (7,9). Pituitary, parapituitary, and occipital lobe tumors may mimic migraine in some patients; however, papilledema and focal neurological findings help differentiate these possibilities (9). Temporal arteritis can present with unilateral, throbbing headache. The superficial temporal artery may be tender, firm, or nodular, and the erythrocyte sedimentation rate is markedly elevated (10). Temporal artery biopsy is diagnostic for temporal arteritis (7,11).

Cluster headaches can usually be differentiated from migraine by the clinical history. Cluster headaches are short-lived attacks of acute, severe head pain. The clusters of headaches may last for sev-

Table 2
Precipitating Factors of Migraine

Stress	Alcohol
Light stimulation	Emotional disturbances
Fasting	Fatigue
Lack of sleep	Too much sleep
Menstrual periods	Food
Medications	Pharmacologic
Oral contraceptives	Tyramine
Reserpine	Phenylethylamine
Nitroglycerine	Histamine
Ergotamine withdrawal	Monosodium glutamate
Caffeine withdrawal	Sodium nitrite/nitrate
	Nonpharmacologic

eral weeks and then disappear for months to years at a time (6,9). Pheochromocytoma, carcinoid syndrome, and mastocytosis may have associated headache that could possibly be mistaken for migraine.

Although the pathogenesis of migraine is unclear, multiple precipitating factors have been proposed (7,11,12) (Table 2). The precise mechanism by which these stimuli provoke migraine is unknown. The vascular nature of the headache precipitated by pharmacologic agents, e.g., tyramine, supports the hypothesis of dilatation of intracranial and/or extracranial arteries or erratic modulation of vasomotor tone as a potential mechanism (12). Stress, bright light, emotional disturbance, fasting, lack of sleep, or even too much sleep (Sunday morning headache), may exacerbate migraine.

Estrogens and/or progesterones appear to be significant triggers of migraine in some women. Approximately 50% of women with migraine suffer primarily premenstrual or menstrual attacks (7). In addition, 10–15% of women who begin oral contraceptives develop migraine attacks, and 40–50% of women with migraine who begin these preparations report worsening of their headache symptoms (13,14). Somerville demonstrated the onset of migraine headache with decreasing estrogen and/or progesterone levels and postulated that the fluctuating levels of these hormones exert some effect on the cranial vasculature (15,16).

Over the last 50 years, a number of medical papers linked the ingestion of certain foods to the onset of migraine. In the 1980s, the double-blind, placebo-controlled model for evaluation of food hypersensitivity was applied to food and migraine, and encouraging results sparked new interest in this arena. However, papers from

the 1920s and 1930s reported the utility of elimination diets (17–20) and the importance of reintroducing the food to the diet to confirm the results (18–20). Admittedly, most lacked adequate controls and none were blinded studies, but the clinical observations of these early investigators set the stage for work that is continuing today.

Historical Perspective

In 1921, T. R. Brown proposed that migraine was a consequence of (1) excessive intake of carbohydrates, (2) excessive intake of protein, (3) an intestinal toxemia or bacteremia, or (4) a metabolic error (17). Dr. Brown employed elimination diets and noted that “by modifying the diet cure may be obtained in a few cases, and a very considerable amelioration of symptoms in many cases.” He observed that many patients who improved with diet manipulation had not previously considered food as a potential trigger of their headaches. In addition, a dose–response phenomenon was observed with certain foods, i.e., whereas small quantities produced no symptoms, larger amounts resulted in migraine. Brown noted that the food skin test was of little value; however, McClure and Huntsinger, in a later study, reported that four of five subjects with positive food skin tests improved when these items were removed from the diet (18).

Warren T. Vaughan published “Allergic Migraine” in 1927 (19). This was perhaps the most important paper of the era regarding food and migraine. Dr. Vaughan evaluated 33 migraine subjects with elimination diets based on the results of food skin testing. Using this approach, 12 of 33 (36%) improved, 4 had temporary relief, 10 were no better, and 7 were lost to follow-up. Importantly, this paper describes the recurrence of migraine with reintroduction of suspected foods in 5 subjects. Vaughan was the first to demonstrate that patients sensitive to foods could be partially or wholly relieved of migraine by specific avoidance and that an attack of migraine could be produced by the ingestion of a specific food. The skin testing performed in this study was of the intradermal type. Vaughan felt the immediate skin test results were of little value, but that skin reactions present at 6–24 h were likely to be clinically relevant.

In 1930, Eyermann studied 63 patients with headache using the food skin test to design an elimination diet (20). Of these, 44 patients improved and experienced recurrence of headache when the suspected foods were returned to the diet. To decrease the possibility of coincidence, these challenges were repeated on multiple occasions. The onset of headache was noted to occur within 3 h in most subjects; however, on some occasions, symptoms did not occur until 6 h following ingestion.

Other studies have demonstrated a positive response to elimination diets. DeGowin reported a 78% response rate to elimination diets based on intradermal skin testing to foods (21). Unger and Unger introduced the "feeding test" in 1952 (22). These authors used an elimination diet for 2 wk, during which one major food was excluded. Following the elimination period, patients were challenged in the office with the excluded food. If a headache was induced, the food was avoided. If no symptoms were provoked, the food was returned to the diet and a different food eliminated for 2 wk. Using this technique, the authors reported that 35 of 55 subjects (64%) achieved complete relief. Finally, Glaser reported similar responses to elimination diets in children (23).

In summary, these early studies demonstrate a role for food in the pathogenesis of migraine. The prick food skin test did not demonstrate consistent efficacy in targeting clinically relevant foods. The elimination diet was most helpful in identifying subjects with possible food-related migraine, but the reintroduction of suspect foods was essential in confirming the association.

Recent Investigations

In 1979, E. C. G. Grant reported work with 60 migraine patients (24). Each subject was placed on a strict elimination diet consisting of pears, lamb, and spring water for 5 d. Most patients were headache free by the fifth day when they began to test individual foods by reintroducing them to the diet and monitoring pulse rate and other symptoms every 20 min for 90 min. Any food producing a reaction was eliminated. Subjects tested between 1 and 3 foods per day with this method and found a range of 1–30 (mean = 10) foods producing reactions per patient.

When these foods were eliminated, all patients improved and 51 of the 60 became headache free. Although this paper generated interest, it suffers flaws in methodology. The pulse change is not a sensitive measure of adverse reactions to foods, but, more important, no blinded challenges were done to confirm the results. Therefore, a strong placebo effect may account for some of these positive responses.

Monro et al. described findings with 47 subjects who were studied prospectively with rotation and elimination diets over a 2-yr period (25). Thirty-three completed the diets, and migraine-provoking foods were identified in 23 (70%). Most subjects who could identify and eliminate provoking foods gained complete relief, usually within 2 wk. Following the diet portion of the study, Radioallergo-sorbent Test (RAST) to a battery of foods showed a good correlation

to those foods thought to provoke migraine. To study this more closely, 26 subjects were studied prospectively. Based on the RAST results, an elimination diet was designed. Twenty-three of 26 responded to this dietary manipulation. Although these results were intriguing, they were not confirmed with double-blind challenge techniques.

The first studies to utilize double-blind, placebo-controlled techniques in evaluating food and migraine were published in 1983. Vaughan et al. reported results in 43 adult patients (26,27), and Egger et al. studied 99 children with migraine (28). Vaughan et al. evaluated 43 subjects with neurologist-confirmed migraine. Each subject was tested with a battery of 83 prick food skin tests. All patients then avoided skin-test-positive foods plus milk, eggs, corn, and wheat. After 1 mo on the diet, those who demonstrated a 2/3 reduction in migraine frequency underwent a series of single-blind challenges with suspected foods. Positive single-blind challenges were repeated in the clinic using double-blind, placebo-controlled techniques. Challenges consisted of opaque capsules containing 8 g of freeze-dried food or an identical number of capsules containing placebo.

Thirteen subjects (31%) reported a 2/3 reduction in headache frequency while on the diet, and 8 of 13 had positive single-blind challenges (61%). All 8 patients completed double-blind challenges, and 6 were positive with food alone. No placebo challenge was positive. In summary, this study demonstrated food-induced migraine in 6 of 43 unselected patients using strict double-blind, placebo-controlled food challenges.

Egger et al. published the largest series on children with migraine (28). These investigators studied 99 patients who suffered at least one migraine headache per week and had demonstrated this frequency of headaches for at least 6 mo before entering the study. Those with middle ear disease, sinusitis, refractive errors, dental disease, hypertension, or increased intracranial pressure were excluded. Following the initial evaluation, each patient began an oligoantigenic diet consisting of one meat (lamb or chicken), one carbohydrate (rice or potato), one fruit (banana or apple), one vegetable (brassica), water, and vitamin supplements. The diet was maintained for 3–4 wk. If headaches resolved or diminished to only one episode during the last 2 wk of the diet trial, foods were reintroduced to the diet. Foods were returned to the diet one food per week in normal helping-size portions.

Eighty-eight completed the diet trial and 78 recovered completely, 4 improved greatly, and 6 showed no improvement. When suspect foods were returned to the diet, 74 of 82 relapsed. Forty

Table 3
Migraine Elimination Diet

Foods allowed:		
Tapioca	Beets	Water
White potato	Artichoke	Prunes
Rice	Squash	Peaches
Sweet potato	Asparagus	Pears
Lamb	Cane or beet sugar	Pineapple
Beef	Salt	Apricots
Chicken	Gelatin, plain	Cranberry
Lettuce	Maple syrup	
Spinach	White vinegar	
Carrots	Vanilla extract	
Crisco or any vegetable shortening not containing dried milk solids (check label)		

patients agreed to double-blind, placebo-controlled challenges. Twenty-six had headache with active food alone, 2 with placebo, 4 with both active and placebo, and 8 subjects did not have headache symptoms with either ($p < 0.01$, $\times 2$). The onset of migraine occurred at a median of 2 d after the food was returned to the diet (range <1 h to >7 d). Seventeen subjects had symptoms with only one food, but several reported multiple food triggers, ranging up to 24 separate foods. Skin testing to a panel of 33 food antigens showed no difference in response to diet between patients with positive skin tests and those with negative skin tests. In addition, though some migraine-provoking foods were also skin-test-positive foods, the correlation was weak. If only skin-test-positive foods had been eliminated, only 3 subjects would have recovered.

Vaughan et al. recently completed a study of 104 adult subjects with migraine (29). To exclude as few patients as possible, minimal entry criteria were used: the diagnosis of migraine must be confirmed by a board-certified neurologist and the patients must have a minimum of three headaches per month. Subjects meeting these criteria maintained their regular diets for 1 mo and recorded all foods ingested, all migraines, and all medications required. After this period, subjects returned to the clinic and were prick-skin tested to a battery of 82 foods. For an additional 1-mo period, patients adhered to a diet eliminating all skin-test-positive foods, all food suspected of provoking migraine from the first month's trial, and wheat, corn, milk, and eggs (Table 3).

Those with a 50% or greater reduction in headache frequency on the diet reintroduced foods singly in an open fashion. Each food was ingested three times daily for three consecutive days. If no head-

Table 4
Foods Producing Migraine with Double-Blind Challenge

Wheat (6) ^a	Coffee (2)
Egg (3)	Milk (1)
Corn (2)	Black eye peas (1)
Cheese (2)	

^aNumber of patients with positive double-blind challenge to this food.

ache was precipitated, the food was returned to diet. If a migraine occurred, the food was avoided and the patients were asked to participate in double-blind, placebo-controlled challenges.

Forty of 104 reported a 50% or greater reduction in headache frequency (38%) on the elimination diet. Thirty-six underwent open food challenges, and 27 identified at least one food that would reproducibly precipitate a headache. The number of foods found to provoke migraine ranged from one to four foods per patient. In 9 subjects no provoking food could be identified. Double-blind, placebo-controlled challenges were performed with 24 patients. Seventeen had a migraine only with active food challenge, 3 had migraine on placebo days, and 4 did not have a headache with either food or placebo ($p < 0.01$, $\times 2$). Foods provoking migraine during double-blind challenges are listed in Table 4. In agreement with Egger et al., the food skin test was of little value. Some foods provoking migraine were also positive by skin test, but the correlation was again weak. The skin test neither consistently identified migraine-provoking foods nor identified subjects more likely to respond to dietary manipulation.

Not all studies of food and migraine have resulted in positive results. Atkins, Ball, and Bock have reported their experience with 36 children with migraine (30). Sixteen children felt that a specific food would precipitate migraine. However, when double-blind challenges were performed using these foods, no migraine headaches were observed.

The additional 20 children presented a problem in that the frequency of migraine was low. Only 5 of the 20 children had two or more headaches per week. These 5 children were placed on a 1- to 2-wk elimination diet, and 2 (40%) became headache free. However, when the regular diet was resumed, there was no recurrence of migraine.

The previous section reviewed several papers that, in most part, establish a role for food as a precipitant of migraine. The identification of subjects with reproducible food-induced migraine has presented the opportunity to study the mechanism of this phenomenon. Although work in this arena is only beginning and involves small numbers of patients, several interesting findings have emerged.

Mansfield et al. (27) studied three subjects with food-induced migraine. These individuals were administered active food challenge or placebo in double-blind, placebo-controlled fashion. In addition, baseline and serial samples of blood were obtained to measure plasma histamine levels. In all three patients, migraine was precipitated with active food challenge, and in no subject did placebo produce symptoms. In each patient, plasma histamine concentrations increased before or in concert with the onset of migraine. No changes in plasma histamine levels were seen with any placebo challenge.

Steinberg et al. (31) reported a detailed evaluation of one subject with multiple food triggers for migraine. The authors describe a 19-yr-old female with migraine regularly occurring 4–6 h after the ingestion of specific foods. Double-blind, placebo challenges were positive to suspect foods, while four placebo challenges were negative.

Repeat double-blind, placebo challenges were performed with serial blood sampling for mediator measurements. After challenge with beef, plasma histamine levels increased threefold. In addition, prostaglandin F_{2a} (PGF_{2a}) levels were elevated. Another challenge with beef was performed with serial measurements of mediators, but in addition, measures of cerebral blood flow by Doppler ultrasonography and xenon computerized tomography were performed. Cerebral blood flow was shown to increase and coincided with rises in mediators and the onset of migraine. This is the first tangible evidence of cerebral vascular changes occurring temporally to the ingestion of a known migraine-provoking food.

Finally, Olson et al. (32) studied five subjects with reproducible food-induced migraine. Double-blind, placebo-controlled challenges were performed with serial measurements of plasma histamine and prostaglandin D₂ (PGD₂) at baseline, 30 and 60 min, and hourly for a total of 6 h. All subjects had a 3- to 38-fold increase in plasma histamine and a rise in PGD₂ levels with active food challenges. These initial increases in mediator levels either preceded or occurred concomitantly with the onset of migraine. At 4–6 h after ingestion of the active food, histamine levels had returned to baseline, but a second rise in PGD₂ levels were noted in all subjects. Of interest, all subjects in this study were skin-test-negative by prick and intradermal testing to the active food used for challenge.

Pharmacologic Agents in Food

Some investigators hold that food-induced headache is the result of chemical agents in foods. Tyramine is most commonly incriminated; however, phenylethylamine, nitrites, alcohol, monosodium glutamate, histamine, and aspartame have also been

reported to cause symptoms. This section will briefly review pharmacologically induced headache.

Tyramine

A vasoactive amine, tyramine may provoke vascular headache (33). Foods rich in tyramine include aged cheeses, fermented sausages, sour cream, wines, pickled herring, and pods of broad beans (34,35). Although tyramine is often touted as an important provoker of migraine, controlled studies yield conflicting results.

Hanington, using placebo-controlled challenges with 100 mg tyramine, reproduced migraine symptoms in four of four subjects with a history of food-induced migraine (36).

Smith et al. used multiple double-blind challenges in 45 patients with food-induced migraine (37). Of 94 tyramine challenges (125 mg), 75 (80%) precipitated migraine. Placebo led to migraine in only 5 of 60 challenges (8%).

Several studies, however, have not demonstrated an important role for tyramine (34,38,39). Moffett et al., in a double-blind, placebo-controlled trial, studied 10 patients with migraine alone, 7 with migraine and epilepsy, and 8 who felt tyramine-containing foods would precipitate an attack of migraine (38). Patients ingested 125 mg tyramine or placebo and recorded symptoms for 48 h. None of the subjects with migraine alone reported headache with tyramine. Tyramine precipitated a headache in one subject with migraine and epilepsy, but in those who believed tyramine to be a provoker of their headaches, symptoms were as common with placebo as tyramine. Ziegler and Stewart studied 80 patients with migraine using 200 mg tyramine in a double-blind, placebo-controlled trial (39). Active and placebo challenges were negative in 49, 12 had migraine with both, 11 had headache with placebo alone, and only 8 had migraine with tyramine alone.

Based on the above data, it appears that tyramine may provoke headache in some patients, but its role as a major provoker of migraine may be overstated.

Phenylethylamine

Phenylethylamine, another vasoactive amine, is found in certain cheeses, red wines, and chocolates (40). Sandler et al. studied 36 subjects who felt that chocolate provoked migraine (41). They were challenged in a single-blind fashion with either 3 mg of phenylethylamine or placebo in capsules. Eighteen reported migraine with phenylethylamine, and 6 had symptoms of migraine with placebo. However, Moffett et al. studied 25 patients with a history of chocolate- or cocoa-induced migraine with double-blind, placebo-controlled

challenges (42). Eight reported headache only after chocolate, 5 with placebo only, 1 with both, and 11 with neither ($p = \text{NS}$).

Nitrites

Foods with the highest concentrations of nitrites include hot dogs, bacon, ham, lunch meats, smoked fish, and some imported cheeses (43). Headaches following the ingestion of frankfurters or other cured meats have been reported (12,44) and are pulsatile approx 50% of the time (43).

Ethyl Alcohol

Migraine patients often mention alcohol as a provoker of headaches, with symptoms typically beginning 30–45 min after ingestion (12). Certain red wines may contain tyramine and/or phenylethylamine (45). Well-controlled studies addressing the provoker in alcoholic beverages are lacking.

Monosodium Glutamate (MSG)

Up to 30 of people who eat Chinese food have some adverse reaction, presumably to MSG (46). The most commonly reported symptoms are headache and tightness around the face that typically begins approx 20 min after ingestion (12). Quantities of MSG required to precipitate symptoms in susceptible individuals range from 1.5 to 12 g.

Histamine

Endogenous histamine is found in certain foods. Tuna, mackerel, and mahi-mahi are commonly implicated (33). Other foods have been reported to release histamine and cause headache. These include wine, egg whites, strawberries, shellfish, tomatoes, oranges and other citric fruits, and alcohol (33).

Aspartame

Aspartame as a provoker of migraine has been described in a single case report (47). However, when 40 subjects with a history of aspartame-induced headache were studied in a double-blind, placebo-controlled fashion, no difference in headache frequency was observed with aspartame or placebo (48).

Comment

The available data clearly support a strong role for food in the pathogenesis of migraine. If one considers only those studies using double-blind, placebo-controlled methods, approx 15–20% of adults

(29) and 30% of children (28) have at least one food that is a trigger for migraine. It has been our experience that few adult patients with migraine become headache free with dietary manipulation. Only 6 of 104 subjects (5.8%) in our most recent study became completely free of migraine (29). However, greater than one-third of the patients reduced the frequency of headaches by 50% or more with only minimal dietary manipulation, i.e., eliminating a maximum of four foods from the diet.

There is no reliable method to identify subjects more likely to respond to dietary intervention. Skin testing by the prick technique has not consistently identified either clinically relevant foods or subjects likely to respond to elimination diets. Although the delayed response to intradermal testing with foods was thought to be useful in older studies (19), these results have not been confirmed by double-blind, placebo-controlled trials. In addition, intradermal skin testing with foods can be associated with severe adverse effects, including death, and therefore cannot be recommended (49). The results of RAST testing for foods has also been disappointing. *Monro et al.* found RAST to be helpful (25); however, other investigators have found RAST to be of no value in the evaluation of migraine patients (50,51).

In view of these results, one is left with only the elimination diet to screen for food-induced migraine. Strict elimination diets, such as that used by *Grant* (24), are unlikely to be tolerated by most patients and may include the risk of being nutritionally unsound if used for extended periods. The wheat-, corn-, milk-, and egg-free diet used by *Vaughan et al.* eliminated clinically relevant foods in most subjects and was generally well tolerated (Table 3) (29). Patients demonstrating marked improvement on the diet should return foods to the diet singly and consume them daily for three consecutive days. Foods not precipitating headache can be returned to the diet. Positive challenges should be repeated to confirm sensitivity before recommending avoidance. We reserve skin testing for patients failing the elimination diet who wish further evaluation and those with such severe disease as to warrant this low-yield procedure. Double-blind challenges may be needed in subjects with multiple positive open challenges to avoid nutritionally unacceptable elimination diets.

In summary, a significant number of migraine patients have food as a trigger. In view of the ease and safety of dietary manipulation, this option should be offered to all patients who continue to suffer with migraine headaches.

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