REVIEW

Flushing Reactions: Consequences and Mechanisms

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The mechanisms of flushing reactions are pharmacologically and physiologically heterogeneous. Flushing may result from agents acting directly on the vascular smooth muscle or may be mediated by vasomotor nerves. Vasomotor nerves may lead to flushing as a result of events at both peripheral and central sites. In susceptible persons, frequent, intense flushing leads to a cluster of physical signs (rosacea). Flushing provoked by alcohol has been associated with ethnic sensitivity, a possible predisposition to alcoholism, various disulfiramlike agents, one type of diabetes mellitus, and the carcinoid syndrome and other types of neoplasia. Flushing reactions also occur during the menopause, after glutamate ingestion, and in response to oral thermal challenges.

FLUSHING is a transient reddening of the face and frequently other areas, including the neck, upper chest, and epigastric area. Many of our current concepts of flushing have undergone little change over the past century. Darwin (1) borrowed much of the conceptional framework of flushing reactions from an earlier study by Burgess (2). The wealth of personal observations and collected anecdotes compiled by Darwin provided considerable support for these persisting concepts of flushing reactions. However, terminology of questionable value has survived from these early works—for example, facial vasodilatation can be regarded as a blush or flush depending on the specific underlying emotion. This preoccupation with the emotional basis of flushing has done little to enhance our understanding of flushing reactions. However, information obtained over the past 5 years has provided a better understanding of the mechanisms of pharmacologically and physiologically heterogeneous flushing reactions.

Anatomic Basis

The Burnstock-Iwayama model of autonomic innervation of vascular smooth muscle emphasizes the dual control of vascular smooth muscle by nerves and circulating agents, especially catecholamines (3, 4). Thus, as flushing is a phenomenon of transient vasodilatation, flushing mechanisms may be broadly classified into those resulting from direct smooth muscle effects and those flushing reactions mediated by nerves. The cutaneous blood vessels are more numerous in the face than in other cutaneous regions (5, 6), and the cutaneous blood flow in the face is greater also (7). These facts may account for the limited region of flushing when the provocative stimulus is systemic in nature. There is no evidence that the cutaneous blood vessels of the face react in a manner that is qualitatively different from cutaneous vessels in other regions of the body.

The vasomotor innervation of cutaneous vessels consists of two types of fibers, vasodilator and vasoconstrictor. In most areas of the body studied, one mechanism predominates and the vasomotor control of the region can be characterized as either vasoconstrictor or vasodilator. When vasodilatation is achieved by inhibiting the activity of nerves that constrict the blood vessels, the control is vasoconstrictor. When vasodilatation is achieved by increased activity in nerves that dilate the blood vessels, the control is vasodilator. In the ear, cheek, chest, and forehead, areas in which flushing may be most intense, the control is vasodilator. Vasodilatation normally seen in these flushing areas is not due to release of vasoconstrictor tone, but rather to an active vasodilator mechanism, mediated through fibers running with cutaneous nerves (8, 9). In addition to the classical, sympathetic innervation of the cutaneous vessels of the face, there is a second system composed of vasodilator fibers that originate in the brain stem and leave the brain stem directly with the trigeminal nerve (10).

In addition to the neurons that innervate the vascular smooth muscle, other, central neurons may be important in provoking and modifying the flushing reaction. The role of these central sites will be discussed along with specific types of flushing reactions.

Consequences of Flushing Reactions

Rosacea is a cosmetic disorder of the face, characterized by telangiectasia, papules, pustules, and eventually connective tissue hypertrophy, including rhinophyma. Current theories of the pathogenesis of rosacea emphasize that flushing is important in the genesis of rosacea stigmata (11). This notion is supported by a variety of observations. There is an increased frequency of flushing in patients with rosacea (12). There is a correlation between severity of ocular rosacea and tendency to strong flushing (13). Patients with severe flushing due to carcinoid develop all of the various rosacea stigmata, including ocular rosacea, facial telangiectasia, and severe connective tissue hypertrophy (13-17). Mild rosacea is commoner in women and usually appears after age 35 when the frequency of "hot flashes" and flushing increases (16, 18-20). Flushing is invariably the earliest component of rosacea to be apparent (18-20). Rosacea responds to massage therapy, supporting the theory that flushing leads to edema, which then leads to the other stigmata (11, 12, 20, 21). Rosacea stigmata are typically in those areas of the face overlying relatively inactive musculature where the edema caused by the flushing tends to persist

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(11, 22). Rhinophyma may be explained by the observation that chronic cutaneous edema is frequently followed by connective tissue hypertrophy and fibrosis (23). The frequent occurrence of overt facial edema in the course of rosacea has been documented (19). Rosacea is exacerbated during vasodilator therapy accompanied by flushing (24). "Extrafacial rosacea" may occur in extrafacial areas of flushing (25). Finally, there is an extensive clinical literature (26) that has broadly incriminated flushing in the genesis and exacerbations of rosacea.

Although the commonest changes associated with flushing reactions are cutaneous, episodes of vasodilation manifested as flushing reactions can have severe consequences. Profound systemic hypotension during severe flushing in systemic mastocytosis has progressed to refractory shock and death (27).

That flushing reactions and their consequences were largely regarded as only of cosmetic concern may explain the limited scientific investigation of flushing. The general disregard in the past by investigators for the large red nose of the alcoholic and the red cheeks, or rubeosis, of the diabetic is noteworthy. The current interest in mechanisms of flushing is largely the result of speculations that certain flushing reactions may identify populations at risk for alcoholism and non-insulin-dependent diabetes mellitus.

Alcohol-Induced Flushing

Generally, alcohol is thought to act indirectly through the vasomotor nerve supply to effect vasodilatation (28-31). In one study, however, alcohol was associated with cutaneous vasodilatation in sympathectomized limbs (32). Because these studies were carried out on cutaneous blood vessels in limbs, and as the face has a dual innervation of the cutaneous blood vessels, the mechanism of alcohol-induced flushing must be regarded as unknown.

Several possibilities may account for the alcohol-induced flush. Ethnic differences in responses or number of mast cells, enterochromaffin cells, and others are possible. Alcohol, by provoking flushes, may uncover subclinical disease, for example, carcinoid, medullary carcinoma of the thyroid, or mastocytosis. Most of the work to date, however, has focused on possible differences in alcohol metabolism and acetaldehyde levels.

Three clues would be compatible with such a biochemical mechanism for alcohol-induced flushing. First, many Mongoloids flush strongly after drinking amounts of alcohol that have no detectable effect on Caucasians (33, 34). As the difference between these racial groups is present at birth, genetic factors and not dietary or cultural factors are likely (33). A similar alcohol sensitivity found in American-born Japanese and Chinese and in one tribe of North American Indians may reflect such a genetic factor in Mongoloid populations (35). Second, genetically controlled factors seem to be much more important than environmental factors in differences in rates of ethanol metabolism (36). Third, 85% of Japanese have an atypical liver alcohol dehydrogenase with increased activity. The frequency of alcohol dehydrogenase polymorphism is identical to the reported frequency of alcohol sensitivity in the Japanese population (37).

The results of these metabolic studies seem almost as varied as the possibilities: Mongoloid populations metabolized alcohol at a significantly lower rate than Caucasians (38); Mongoloid populations metabolized ethanol more rapidly than Caucasians (39); Mongoloid populations metabolized ethanol at the same rate as Caucasians (40); and, although Mongoloids had greater blood acetaldehyde levels than Caucasians after ingesting alcohol, no relation was found between the acetaldehyde level and the severity of flushing (41).

An additional problem for this possible biochemical mechanism was the widely accepted notion that the velocity of this first reaction in the metabolism of ethanol is slower than the subsequent ones and is, therefore, rate-limiting. The rate of ethanol elimination was regarded as constant regardless of its tissue concentration, because liver alcohol dehydrogenase is saturated at low concentrations of ethanol (42). Thus, blood levels of acetaldehyde should not vary regardless of the concentration of ethanol. It is not surprising that acetaldehyde was largely overlooked as a possible mediator of flushing or the predisposition to alcoholism.

In 1975, Korsten and colleagues (43) reported that blood acetaldehyde levels were much higher at elevated than at low concentrations of ethanol, and that this difference is greater in alcoholics than in nonalcoholic subjects. They suggested that, at high ethanol blood levels, an ethanol oxidizing system other than alcohol dehydrogenase contributes to ethanol elimination, and further, that the higher acetaldehyde levels in alcoholism may result from both greater activity of this system and from mitochondrial damage. In another study (44), blood acetaldehyde concentrations were found to be significantly elevated in young men with alcoholic parents or siblings compared with matched controls with no familial alcoholism.

Acetaldehyde levels may be important not only in identifying subjects at risk for alcoholism, but also in explaining the enhanced sensitivity to alcohol in Mongoloid patients, manifested as flushing. Harada and coworkers (45) have suggested that the initial intoxication after alcohol intake in Japanese might be due to the delayed oxidation of acetaldehyde rather than to its increased production by a typical or an atypical alcohol dehydrogenase. A majority of autopsy liver specimens from Japanese persons had an unusual phenotype of acetaldehyde dehydrogenase that had an abnormally low affinity for acetaldehyde (45). In 1980, Jenkins and Peters (46) reported a lower hepatic acetaldehyde dehydrogenase activity in noncirrhotic alcoholics than in control subjects. That the basis for the biological sensitivity to alcohol relates to the ability of the body to handle acetaldehyde suggests a possible pharmacologic relationship with the disulfiram-alcohol reaction (47).

As pointed out by Zeiner (47), the disulfiram-alcohol reaction and the alcohol-induced reaction in Mongoloid populations have several characteristics in common: facial flushing; decreases in blood pressure; and increases in

heart rate, cardiac output, and rate and depth of respiration. Thus, it may be that the biological sensitivity to ethanol found in some racial groups may be related to acetaldehyde concentrations. However, the disulfiram-ethanol reaction may be more complex than the simple accumulation of acetaldehyde in the blood.

Disulfiram-Ethanol Reaction

Various mechanisms have been proposed to explain the unpleasant symptoms, including flushing, in persons drinking alcoholic beverages after ingesting disulfiram (48). In addition to the accumulation of acetaldehyde as the primary cause of the reaction, accumulation of free alcohol in the body and the production of a toxic quaternary ammonium compound from the disulfiram and ethanol has been postulated. Another suggestion is a hypothetical synergistic toxic action of disulfiram and accumulated free alcohol. The liberation of and decreased degradation of serotonin have also been suggested. As aliphatic aldehydes release histamine (49, 50), mast cell degranulation may also contribute to the flushing reaction. Another theory is that an inhibition of the glucuronic-acid-conjugating system leads to a decreased conjugation of endogenous compounds and that these compounds are the source of the toxicity. Finally, dopamine β-hydroxylase, the rate-limiting enzyme in catecholamine synthesis, is inhibited by disulfiram.

Sauter and colleagues (51) found that the intensity of the disulfiram-ethanol reaction depends on the concentration of acetaldehyde in the blood, a disulfiram-induced predisposition reflected by alkalosis, and a particular predisposition reflected by dopamine β-hydroxylase activity. The nature of the variability of blood acetaldehyde levels, the disulfiram-induced predisposition, and the serum dopamine β-hydroxylase activity is not understood. Although acetaldehyde may cause the release of norepinephrine (52) and lead to vasoconstriction, this should occur only transiently, as disulfiram is an inhibitor of dopamine β-hydroxylase. With the inhibition of dopamine β-hydroxylase, and the decreased content of norepinephrine, acetaldehyde causes a vasodilatation (53). Low dopamine β-hydroxylase levels appear to predict susceptibility to adverse reactions to disulfiram (54). Thus, the combined inhibition of dopamine β-hydroxylase and aldehyde dehydrogenase by disulfiram increases the effects and the levels of acetaldehyde.

A disulfiram-alcohol-like reaction occurs when alcohol is taken after other drugs such as calcium carbamide, phentolamine, griseofulvin, metronidazole, antidiabetic drugs (55), and β-lactam antibiotics (cephalosporins) (56-60); various industrial agents (61, 62); and mushrooms (63). The reaction to alcohol after treatment with chlorpropamide recently has been intensively studied as a possible marker for one type of diabetes mellitus (64).

Chlorpropamide-Alcohol Flushing

Although the effects of alcohol in diabetics receiving chlorpropamide therapy are quite similar to the disulfiram-ethanol reaction, important qualitative differences have been reported. There appears to be no excess accumulation of acetaldehyde after chlorpropamide treatment and alcohol ingestion (64), and no specific in-vitro interaction between the sulfonylureas and aldehyde dehydrogenase (65).

Pyke and coworkers (66-69) concluded that chlorpropamide-alcohol flushing is a dominantly inherited trait; is associated with non-insulin-dependent diabetes (51%) but not with insulin-dependent diabetes (only 10%); and that non-insulin-dependent diabetics who are positive for chlorpropamide-alcohol flushing are less likely to develop retinopathy and macroangiopathy. Because the pure opiate antagonist naloxone blocks chlorpropamide-alcohol flushing, and chlorpropamide-alcohol flushing is mimicked by an enkephalin analogue with opiate-like activity, they suggested that the flushing results from an increased sensitivity to endogenous opiates (70).

Because enkephalin and other opioids affect carbohydrate metabolism and insulin release, Pyke and colleagues (70-71) suggested that these endogenous opiates act as neurotransmitters causing non-insulin-dependent diabetes by a sympathetically mediated effect on the liver and pancreas. It has been suggested that endogenous opiates stimulate the second phase of insulin secretion in non-insulin-dependent diabetics positive for chlorpropamide-alcohol flushing, leading to insulin resistance via secondary down-regulation of insulin receptors or accelerated β-cell failure (72). Jefferys and colleagues (73) concluded that the site of enkephalin activity in chlorpropamide-alcohol flushing is central rather than peripheral. Additionally, the same group found that this flushing reaction could be blocked by aspirin, and they proposed a prostaglandin-dependent step, probably central (74). Others have suggested that the prostaglandin-dependent step operates peripherally (75). Because indomethacin blocks chlorpropamide-alcohol flushing in non-insulin-dependent diabetics who were free from vascular complications but not in those patients with vascular complications, a role for prostaglandins in the cause of both retinopathy and macroangiopathy associated with diabetes has been suggested (76). In this chlorpropamide-alcohol flushing theory, both genetic and physiologic elements of diabetes mellitus are interwoven.

Discordant reports have appeared. Köbberling and associates (77) argue that studies by Pyke and colleagues on flushing induced by an enkephalin analogue did not justify the conclusion that endogenous opioids play a role in mediating chlorpropamide-alcohol flushing. They pointed out that the difference between the chlorpropamide-alcohol flushing-positive and flushing-negative groups is solely due to the difference in baseline malar temperature. Other workers (78) found that the incidence of chlorpropamide-alcohol flushing in patients with non-insulin-dependent diabetes mellitus was only 20%, unlike the 51% reported (66), and was actually less among those patients with a positive family history. Also, Radder and colleagues (79) found no distinct threshold for the rise in malar skin temperature for chlorpropamide-alcohol flushing in non-insulin-dependent diabetics. This experience was found in other studies (78, 80, 81). Finally, Köbberling and colleagues (82), in the largest study

to date, concluded that chlorpropamide-alcohol flushing is not specific for non-insulin-dependent diabetes.

Although Köbberling and associates claim that "no plausible explanation can be provided for the differences between the results by Leslie and Pyke and their study," at least some of the apparent discrepancies may be attributed to methodologic problems (83). Results from studies using a more accurate method indicate that the baseline facial temperature is less in subjects with chlorpropamide-alcohol flushing and non-insulin-dependent diabetes than in normal subjects; and the lower baseline facial temperature alone may account for the reported differences in the findings of the chlorpropamide-alcohol flushing test. Also, using more accurate methods, elevated levels of acetaldehyde and chlorpropamide have been found recently in chlorpropamide-alcohol flushing-positive patients after chlorpropamide therapy and alcohol ingestion (84, 85). Finally a role has been suggested for endogenous opioids, not only in the mechanism of chlorpropamide-alcohol flushing and the pathogenesis of diabetes mellitus, but also in alcohol-induced flushing and the pathogenesis of alcoholism (86-92).

Flushing and the Endorphinergic System

Naloxone not only blocks the flushing provoked by alcohol after chlorpropamide, but also blocks the flushing reactions of menopause (93, 94). An enkephalin analogue, DAMME (Sandoz Pharmaceuticals, Hanover, New Jersey; IND FK 33824) given intravenously to normal subjects was accompanied by a flushing reaction that occurred within 15 minutes and lasted up to 2 hours (95). Not only does morphine cause flushing, but the cutaneous vasodilatation is blocked by naloxone (96). In addition, a child with a hyperendorphin syndrome was observed to have neurologic attacks that included flushing (97). Further, three patients with ectopic production of methionine enkephalin and β-endorphin had exceptionally high concentrations in the tissue of their carcinoid tumors (98).

Carcinoid Flushing

Alcohol is a well-known stimulus of flushing in the carcinoid syndrome. The inhibition of alcohol-induced flushing by α-adrenergic blockade suggests that alcohol might release a catecholamine that acts on the tumor cells. Catecholamine-induced and alcohol-induced flushing are both accompanied by a rise in the bradykinin concentration in arterial blood. The time sequence of alcohol-induced flushing coupled with these observations suggests that alcohol releases a catecholamine that acts on the tumor cells releasing kallikrein, which leads to the rise in bradykinin (99). Although elevated kinin levels have been found during flushing in patients with carcinoid tumors (100), this finding is by no means universal (101). Also, although bradykinin is a potent vasodilator in humans (102), these effects may be mediated by prostaglandins (103). Because nonsteroidal anti-inflammatory agents have not been effective in ameliorating flushing in the carcinoid syndrome, a prostaglandin-mediated kinin effect seems unlikely.

Ethanol also provokes the release of gastrin (104). Interestingly, the synthetic analogue of gastrin, pentagastrin, provokes flushing reactions in the carcinoid syndrome of gastric origin, which may be inhibited by the naturally occurring antagonist of gastrin, somatostatin. In addition, beef meal, a known stimulus for gastrin release, also provokes a gastric carcinoid flush that similarly is blocked by somatostatin. Thus, it has been suggested that gastrin may provoke the release of a vasodilating mediator from the tumor in some types of carcinoid flushes, namely, those of gastric or foregut origin (105, 106).

Many of the activities of gastrin are somehow coupled with or mediated by histamine (107, 108). In one patient with gastric carcinoid syndrome in whom pentagastrin was a potent inducer of flushing, this reaction was completely blocked with combined H1 and H2 receptor antagonists (109). Because elevated levels of histamine excretion are only found in patients with gastric carcinoids, antihistamines should be ineffective in patients with intestinal carcinoids and normal histamine excretion. Further evidence of pharmacologic heterogeneity is the unique type of vivid, patchy red flushing that occurs with carcinoid of gastric origin (110).

Additional evidence that catecholamines may provoke the release of a vasodilating mediator from the tumor causing the carcinoid flush has been reported (111). Clonidine administration leads to decreased plasma catecholamine levels and a blockade of flushing associated with endogenous adrenergic discharge. The decrease in endogenous catecholamines may explain how the block is achieved with clonidine; exogenous epinephrine caused an enhanced flushing reaction in a patient with carcinoid syndrome after clonidine pretreatment (possibly due to up-regulation of adrenergic receptors). That a pharmacologic agent may block one form of flushing and potentiate another suggests two concepts. First, pharmacologic agents may be used as tools to characterize the mechanisms of heterogeneous flushing reactions. Second, one should not assume that an agent that successfully blocks one type of flushing reaction will be successful in blocking another. Even within the carcinoid syndrome, which may appear clinically homogeneous, biochemical and pharmacologic heterogeneity is present (112), especially between carcinoids of gastric origin and the commoner midgut carcinoid (110). Biochemical diagnosis is the key to rational pharmacologic therapy, not only in the carcinoid syndromes, but in all types of flushing reactions (WILKIN JK. In preparation; 113).

Flushing and Neoplasia

Flushing reactions, including an enhanced sensitivity to alcohol, may be the first indication of neoplastic disease, including carcinoid (114). In some neoplastic disorders characterized by excessive histamine release, such as basophilic chronic granulocytic leukemia (115) and systemic mastocytosis (116), the mediator of the flushing reaction appears obvious. However, in systemic mastocytosis flushing is only partially ameliorated with combined blockade of H1 and H2 histamine receptors. Increased

production of prostaglandin D2, presumably by mast cells, has been found in patients with systemic mastocytosis (27). Aspirin, an inhibitor of prostaglandin synthesis, with a combination of H1 and H2 histamine antagonists almost completely prevented attacks of flushing in one patient (27).

Although the mediator of flushing associated with pancreatic tumors has been elusive in the past (117), recent evidence suggests a role for vasoactive intestinal polypeptide (118). Interestingly, some patients with pancreatic tumors and flushing reactions have normal vasoactive intestinal polypeptide levels and increased prostaglandin production (119). Thus, vasoactive intestinal polypeptide cannot be firmly established as the mediator of flushing and a potential role for prostaglandins must be considered. Flushing associated with medullary carcinoma of the thyroid may result from the excess of calcitonin in plasma (120). Calcitonin may cause flushing by stimulating prostaglandin synthesis (121). Prostaglandin synthetase inhibitors reduce flushing in normal subjects during calcitonin infusion and in patients with medullary carcinoma of the thyroid (121, 122). In addition, a carcinoid-like syndrome, including flushing attacks, caused by a prostaglandin-secreting renal cell carcinoma was successfully treated with aspirin (123). At least 17 different human tumors, both nonendocrine and endocrine, including carcinoid tumors, produce substantial amounts of prostaglandins (124, 125).

Supporting the concept that prostaglandins may mediate some types of neoplasia-associated flushing is the observation that prostaglandin E2, prostaglandin F2α, prostaglandin I2 (prostacyclin), and prostaglandin E1 lead to flushing reactions (126-128). Further, there is evidence that prostaglandins may mediate the flush induced by nicotinic acid (129-132). Prostaglandins may affect vascular tone by a direct action on the vascular smooth muscle and, also, by influencing vascular reactivity to adrenergic stimuli and several vasoactive substances (103, 133).

Fermented-Alcohol-Induced Flushing

Finally, some criticism must be leveled against most studies of alcohol-induced flushing, which use a fermented alcoholic beverage such as sherry or beer as the testing agent. A variety of potentially vasoactive pharmacologic agents is found in alcoholic beverages and includes tyramine (134) and histamine (135). Thus, the blocking of alcohol-induced flushing with a combination of H1 and H2 histamine antagonists (136) could be due to a blockade of the histamine present in the fermented alcoholic beverage (in this case sherry); to a blockade of endogenous histamine release as a result of a particular sensitivity to alcohol; or to the pharmacokinetic consequences of decreased blood flow to the liver and upper gastrointestinal tract (137).

Menopausal Flushing

Two major changes occurring at the menopause are decreased estrogen production by the ovaries, and the consequent increase in circulating gonadotropins. Hence, the two previously widely held theories on the cause of menopausal flushing were the theory of excess gonadotropins and the theory of estrogen deficiency.

However, flushing cannot be caused by estrogen deficiency alone (138-140). First, not every estrogen-deficient postmenopausal woman has hot flashes. Second, the onset of flushing does not always coincide chronologically with the onset of estrogen deficiency. Finally, flushing is absent in other persons with low estrogen levels, including women before puberty and patients with gonadal dysgenesis. On the other hand, patients with low estrogen syndromes who have estrogen therapy for several months and then have therapy withdrawn may have the classic vasomotor symptoms of the menopause. Also, flushing may occur during antiestrogen treatment in premenopausal women. In these cases, as in the menopause, estrogen replacement invariably reverses the vasomotor symptoms.

Similarly, flushing is not caused by elevated gonadotropin levels (138-140). First, flushing does not occur in other states of excessive gonadotropins, including gonadal dysgenesis and Kleinfelter's syndrome. Second, flushing in menopause may be relieved by estrogen dosages too low to inhibit gonadotropin synthesis. Third, danazol markedly lowers serum gonadotropin levels but hot flashes remain unchanged (141). Finally, a significant inverse relation between flushing and urinary gonadotropin excretion was shown in at least one study (142).

Whatever the mechanism of menopausal flushing, it is clear that hormone therapy is quite effective in stopping hot flashes. In a double-blind, crossover study of estrogen replacement versus placebo, conjugated equine estrogens blocked the menopausal flushing (143). Other estrogen preparations successful in relieving the flushing are estriol (144) and 17β-estradiol (145). Medroxyprogesterone acetate, a progestational agent, prevents menopausal flushing when given intramuscularly (140) or orally (146). Thus, any proposed mechanism for menopausal flushing should also explain the effectiveness of estrogen therapy.

Interestingly, estrogens appear to exert a modulatory effect on central nervous system catecholaminergic systems (the dopamine and norepinephrine pathways). Specifically, the activity of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis (147), and the turnover rate of norepinephrine in the hypothalamus are found to increase after ovariectomy (148, 149). In this manner, estrogen withdrawal appears to induce an increase in the ratio of norepinephrine to dopamine in the brain; this increase is reversed with the administration of estrogen (147-149). Since central catecholamines seem to be important in the modulation of mood, vasomotor responses, and hypothalamic function, these effects of ovariectomy and estrogen replacement may provide a clue to the mechanism of menopausal flushing. Further, clonidine, a central α-adrenergic agonist, is quite effective in suppressing menopausal flushing (150-153).

Additional evidence found during the past 5 years supports the central catecholaminergic system as the site of dysfunction in menopausal flushing. First, catechola-

mines have been linked to hypothalamic release of gonadotropin-releasing hormone (154, 155) and temperature regulation (156, 157). Second, characteristics of menopausal hot flashes suggest a disorder of the thermoregulatory mechanism (158), possibly originating from an excitatory central state established by the discharge of a neurohumor in the thermal centers of the brain. Further, the onset of the hot flush is associated with a sudden and transient increase in sympathetic activity, including an increased heart rate (159).

Recently, a neuroendocrine link has been established for menopausal flushing and pulsatile luteinizing hormone secretion (160, 161). In these studies menopausal flushing episodes were associated with the pulsatile pituitary release of luteinizing hormone. Since pulsatile luteinizing hormone release results from episodic secretion of luteinizing-hormone-releasing factor by the hypothalamus, these findings suggest a common hypothalamic mechanism (160). Not only does the central catecholaminergic system regulate the release of luteinizing-hormone-releasing factor, but also these same neurons are in close proximity to the thermoregulatory centers in the preoptic anterior hypothalamus (162-166). As noted above, catecholamines play a role in both central thermal regulatory function (167) and the release of luteinizing-hormone-releasing factor (168). It is unlikely that luteinizing hormone directly provokes the menopausal flush, as hot flushes may occur after removal of the pituitary (169). The possibility does exist, however, that increased brain luteinizing-hormone-releasing factor levels could provoke thermoregulatory changes in menopausal women (170).

In addition, the catecholaminergic-system-dysfunction theory of menopausal flushing may also explain hot flashes and sweats in the male climacteric (171). The view that estrogen is the most specific treatment for the hot flash (172) should be reevaluated and the search for nonhormonal pharmacologic agents continued more vigorously.

Glutamate-Induced Flushing

Monosodium glutamate ingestion in large doses causes transient increases in an acetylcholine-like substance, which is responsible for the symptoms of the "Chinese restaurant syndrome" (173). Atropine suppresses the flush, while prostigmine enhances the flushing reaction. Because some individuals may be more sensitive to the adverse reactions to glutamate, it has been suggested that the reaction, including the flushing, may result from an inborn error of metabolism that otherwise would go unnoticed (174). Thus, as with alcohol, the flushing reactions provoked by glutamate may reflect an inherited sensitivity.

Substance-P-Induced Flushing

Because substance P acts directly on vascular smooth muscle causing vasodilatation, it may serve as a mediator of flushing reactions. Also, because substance P occurs naturally in enterochromaffin cells (175, 176) and carcinoid tumors (177), it may have a role in carcinoid flushing. Other endogeneous agents that cause vasodilatation may similarly be regarded as potential mediators of flushing reactions (178, 179).

Thermal-Induced Flushing

The ingestion of hot beverages and resultant increased heat in the oral cavity may cause flushing by a countercurrent heat exchange mechanism (26). The increased heat in the tissues surrounding the oral cavity increases the temperature of the blood draining this region, thereby raising the temperature of the blood in the internal jugular vein. A countercurrent heat exchange provided by the parallel, contiguous arrangement of the internal jugular vein and common carotid artery would lead to an increase in temperature of the blood flowing via the internal carotid artery to the base of the brain. Here resides the body's thermostat in the anterior hypothalamus. The anterior hypothalamus reacts to very slight increases in temperature of its arterial blood supply leading to various heat-dissipating mechanisms, such as flushing. Thus, contrary to most textbook accounts, the active agent in hot coffee causing flushing is heat, not caffeine (26).

Conclusion

The importance of flushing reactions goes beyond their cosmetic consequences. Characterization of the pharmacologically and physiologically heterogeneous mechanisms of flushing may provide biologic markers for prealcoholism, one type of diabetes mellitus, and certain types of neoplasia. Current investigations of various flushing reactions should enhance our understanding of these important pathologic processes.

ACKNOWLEDGMENTS: The author thanks Thomas Andreoli, M.D., and Walter Kirkendall, M.D., for their critical reading of the manuscript.
Grant support: Dermatology Foundation research grant

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