A Case of Episodic Flushing and Organic Psychosis: Reversal by Opiate Antagonists

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A woman had episodic attacks of flushing associated with severe skin, bone, and abdominal pain, accompanied by mood alterations and anxiety, and followed by an organic psychosis. These symptoms and signs could be induced by small doses of clonidine, L-5-hydroxytryptophan, pentagastrin, insulin, epinephrine, compound 48/80, methacholine, morphine, histamine, or d-tubocurarine. Skin testing showed abnormally sensitive mast cells and an exaggerated axon flare. Cimetidine initially prevented the attacks but became less effective after 18 months. Thyrotropin-releasing hormone stopped the skin pain whereas neurotensin reproduced the burning sensation in the skin without inducing the attack. Both the flush and the organic psychosis were reversed entirely by naloxone or naltrexone, and the hallucinosis could be reversed by vasodilators.

THE EFFECTS OF naloxone or its long-acting analog, naltrexone, on mental illness are still subjects of controversy and active research (1-3). Clinical data have shown that naloxone induces temporary suppression of the signs and symptoms of subacute nectrotizing encephalomyelopathy (4) and reversal of the neurologic deficits of patients with cerebral ischemia (5). We report the case of a woman with periodic spontaneous attacks of generalized flushing and skin, bone, and right upper quadrant abdominal pain, accompanied by mood changes, and followed by an organic psychosis. This cutaneous, vasomotor, gastrointestinal, and psychiatric syndrome can be reversed with extremely low doses of intravenous naloxone or oral naltrexone and the organic psychosis can also be suppressed by vasodilators.

Case Report

A 29-year-old white woman was admitted to the Clinical Center at the National Institutes of Health in April 1977 for evaluation of vasomotor episodes of unknown cause. At age 25, early in 1973, the patient began to have painful flushing episodes. These attacks were preceded by thirst, intense cold, violent shivering, skin pallor, piloerection, and "jittery" sensations. The flushing began generally in the face and rapidly extended to the rest of the body. Initially, the flushing attacks lasted only 1 to 15 minutes, but in a matter of weeks the attacks become longer, lasting more than 1 hour. A papular eruption, more evident on the face, accompanied the flushing. Generalized hyperalgesia, a burning sensation in the skin, right upper quadrant abdominal pain, and diarrhea occurred during the episodes. Definite mood changes were associated with the flushing attack: restlessness, anxiety, a sensation of impending doom, and paranoid delusions. The patient complained of an altered perception of colors and distorted spatial perception.

Periodic flushes were not induced by alcohol, physical activity, diet, or emotions. The patient had always had dermographism and flushed brightly when exercising, but these instances of vasodilation were different from her intense periodic flushes; with the former there was itching and no alterations of mood, and with the latter intense cutaneous pain.

Later that year, the patient began to have grand mal seizures that were frequently preceded by extreme thirst and could be brought on by photic stimulation. Six months later she was hospitalized with status epilepticus. Phenytoin and primidone therapy were effective in suppressing the seizures. However, 1 year later her periodic flushing was more severe and frequent, lasting from 12 to 24 hours. By April 1977, 4 years after the onset of her seizures, she had weekly episodes of flushing.

A 4-cm tender mass was found in the left ovary, and confirmed by computerized tomography and ultrasound. The mass, and a marginally elevated level of urinary 5-hydroxyindole acetic acid, 10.4 to 12.9 mg/d (normal, up to 9.0 mg/d), suggested an ovarian carcinoid. An exploratory laparatomy showed a corpus luteum cyst in the left ovary. There was no other tumor or pathologic finding. Results of a new series of biochemical studies for pheochromocytoma, carcinoid, and mastocytosis, which included plasma epinephrine, norepinephrine, histamine, bradykinin, and kallikrein, and urinary kallikrein, histamine, and 5-hydroxyindole acetic acid levels, were negative. No differences in these substances were found between the normal periods and the flushing episodes. Biopsy specimens of skin and bone marrow were normal, and mast cells were not increased in number. A ^{99m}Tc bone scan showed patchy uptake in the left sacroiliac joint and slightly prominent uptake in the spinous process of the second cervical vertebra. These areas, however, were normal as shown by conventional radiography.

H1-antihistamines were tried without success. Indomethacin did not alleviate the periodic flushes but significantly increased the bone pain. In March 1979, the patient was started on cimetidine, 1200 mg/d, and the weekly flushes disappeared. In the summer of 1979, the patient developed a peptic ulcer, confirmed by radiologic examination, and had watery diarrhea. The cimetidine dose was increased to 1800 mg/d and antacids were prescribed. By January 1980, the symptoms were gone, the ulcer had healed, and the cimetidine dose was decreased to 1200 mg/d. This incident raised the possibility of Zollinger-Ellison syndrome. Cimetidine was stopped and basal gastric secretion was found to be normal. Thirty-six hours after discontinuation of the drug, however, the patient had a severe flush, the first attack in 7 months. Results of new biochemical and radiologic examinations were negative.

A selective celiac angiogram was done to exclude the presence of a polypeptide-producing tumor of the pancreas or duodenum. The angiogram showed a hypervascular lesion, 1 cm in diameter, in the head of the pancreas. To rule out an insulinoma, the patient fasted for 72 hours. Insulin levels were always less than 4 μU/mL. During the third day of the fast, at the nadir of her blood glucose response (40 mg/dL), she developed a flush. Results of a tolbutamide tolerance test were also negative. To exclude the possibility of a calcitonin-producing tumor, serum levels of the hormone were measured and found to be normal after either intravenous calcium or pentagastrin. However, 5 minutes after the pentagastrin infusion the patient had a flush. To explore further the cause of her flushing, the patient was given 5 μg of epinephrine intravenously because this intervention is known to cause flushes in some patients with carcinoid syndrome. Epinephrine produced a flush in this patient.

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In October 1980, the patient had generalized pruritus without a rash. Later, red maculopapular lesions developed on her torso, buttocks, legs and the back of her hands. The pruritus was incapacitating and made worse by hot showers. A higher dose of cimetidine was tried (1800 mg/d) but was ineffective, as were chlorpheniramine and cyproheptadine. More importantly, flushes reappeared and their frequency increased to two or three per week, and each episode lasted for nearly 24 hours, leaving her completely exhausted. Biopsy results of one skin lesion showed a lymphocytic vasculitis consistent with the diagnosis of dermatitis herpetiformis, and another lesion showed nonspecific vesicopapular dermatitis. Mast cells were not increased and no neuronal-specific-enolase positive cells were found. Skin histamine content was in the normal range and no significant differences were found between normal (6.2 μg/g) skin and lesions (10.4 μg/g). The concentration of histamine in her urine was essentially normal before and during flushes in April 1980. However, after December 1980, the levels of urine histamine were markedly increased during flushes (40 to 145 ng/mg of creatinine per mL of urine; normal values are 0 to 30 ng/mg).

Extreme pruritus continued. Disodium cromoglycate, used to control itching and abdominal pain in patients with systemic mastocytosis (6), was started (100 mg/d, via spinhaler). After 3 months of therapy, the itching disappeared but the flushes and the abdominal pain continued unaffected. The therapeutic success of disodium cromoglycate again suggested the participation of mast cells in the disease process. A series of skin tests was done to determine the sensitivity of her mast cells to various secretory stimuli, as well as her sensitivity to histamine. The following agents known to release histamine from mast cells were used: morphine, compound 48/80 (Sigma Chemical Co, St. Louis, Missouri), d-tubocurarine, methacholine, and epinephrine; all produced an exaggerated axon reflex (Table 1). Very low doses of histamine also induced significant flares that became a typical flush. Lidocaine used for nerve block inhibited the axon reflex but did not prevent the appearance of the flush after an intradermal injection of histamine.

The mood changes, right upper quadrant abdominal pain, and the flushing and itching resembled the effects of opiates in naive people (7). The administration of naloxone, 0.4 mg intravenously, during a spontaneous attack resulted in the complete resolution of the flush and the suppression of the associated mood changes. Less than 1 minute after the injection of the drug, the patient became euphoric and slightly manic. Her skin still itched and burned but she no longer cared. She had orgasmic sensations. The skin, abdominal, and bone pain, and the flush and the itching abated within 15 minutes. The euphoric state lasted for about 30 minutes until the fear, abdominal pain, and the sensation of impending doom returned suddenly. A second dose of naloxone again brought a complete reversal of the symptoms and another euphoric episode. Thirty minutes later the mood changes returned without a flush. The waves of anxiety subsided spontaneously in the next hour and no more naloxone was needed.

During the next flush, naloxone, 20 μg, induced complete and immediate relief for 10 to 15 minutes. The dose was repeated as soon as alterations in her mood reappeared. In this way, the episode resolved without bursts of euphoria. Intradermal injection of naloxone, 0.4 mg, did not modify the flushes or the changes in mood, and did not affect the flush and pain where the drug was given. Acute administration of oral naltrexone, 50 to 200 mg, produced relief from all her symptoms in 20 to 30 minutes.

Clonidine, used to relieve the withdrawal syndrome in narcotic addicts (8), has been reported to induce the release of endogenous opioids (9, 10). Either clonidine, 100 μg orally, or morphine sulphate, 2 mg intravenously, provoked a flush, completely reversed by intravenous naloxone, 0.4 mg.

Because the patient's flushes and seizures could be due to an epileptogenic focus in the temporal lobe of her brain, several electroencephalograms including one with nasopharyngeal leads during an attack, were done. The electroencephalograms were always within normal limits and no focus could be detected. Computed tomographic scans of her brain, with and without contrast material, also appeared normal. The patient stopped the antiseizure medication in December 1980, and has had no further seizures.

Table 1. Skin Test Responses

Drug	Wheal	Flare
	mm	
Saline	0	30
Histamine		
1 ng	0	15
10 ng	0	150
100 ng	9	Whole arm
100 ng + lidocaine 1%	8	0
Compound 48/80		
1 ng	0	30 + satellite flares
10 ng	0	30
100 ng	4	25
250 ng	10	30
Methacholine		
1 μg	0	25
10 μg	0	30
50 μg	5	25
100 μg	5	25
d-Tubocurarine		
681 pg	0	30
Epinephrine		
183 pg	0	30
Neurotensin		
100 ng	0	Whole arm
Morphine		
0.6 μg	3	Whole arm
2.0 μg	...	Whole arm
6.0 μg	10	Whole arm

In March 1981, the frequency of attacks increased to three to four per week, but were now followed by a complex psychiatric syndrome that started from 2 to 6 hours after the onset of the flush and lasted for 2 to 12 hours. The syndrome was characterized by vivid visual illusions and hallucinations, paranoia, and panic. The patient was always alert, oriented, and able to communicate intelligently. These symptoms were preceded by a craving for sweets, and distorted geometric and chromatic perceptions. The patient lapsed into a complete paranoid state, with delusions and florid hallucinations, during which she was never confused but always terrified. The experience was so threatening that her reaction was to escape. Walls fell in on her, otherwise familiar objects acquired a sinister character. Stethoscopes turned into animals, figures on the bed clothes became aggressive spiders, distant lights of the city were thought to be lanterns carried by people looking for her, a bulldozer digging up the pavement was a monster eating the street, and a blimp became a menancing fish. There were little people in the ceiling lights, iguanas and prehistoric monsters in the room; the right upper quadrant pain was due to a big cat eating her liver. The patient had a complex sense of persecution: house detectives were following her, she was the victim of complicated, systematic political plots incorporating real elements of the daily political scene. In the midst of these horrors, she was able to maintain normal conversation, until she was completely overtaken by panic. Sometimes, but not always, she knew that what she saw was not real, but she could not help feeling terrorized. Both intravenous naloxone, 0.4 mg, and oral naltrexone, 200 mg, were effective in suppressing the hallucinosis when given in a single blinded fashion. Repeated psychiatric evaluations have shown that the patient was always normal during the intervals between attacks.

In its new form, the disease was remarkably similar to the syndromes induced by lysergide (LSD) (11) and mescaline (12), two drugs known to produce their effects through central serotonergic neurons (13). To explore the role of serotonin in the process, we gave the patient the serotonin precursor, L-5-hydroxytryptophan, which induces only a temporary sleepiness in

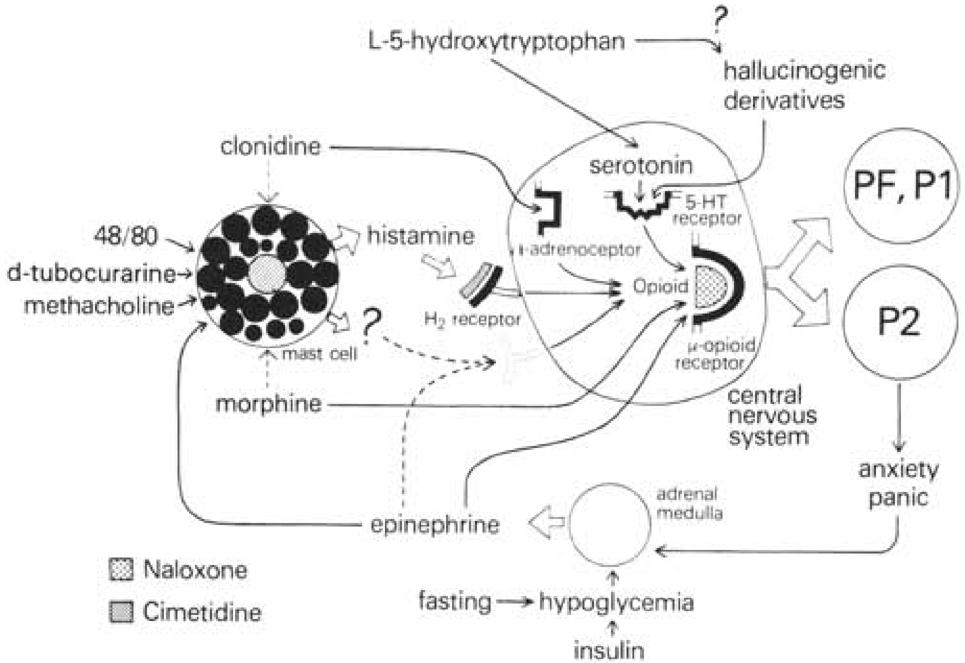

Figure 1. A preliminary model of the processes involved in the generation of the periodic flushing and the subsequent hallucinosis. Solid lines represent facts; broken lines represent hypothetical interactions and structures. PF = periodic flushing; PI = mood alterations during the flush; P2 = post-flush hallucinosis.

normal subjects (14). The drug (500 mg) was administered orally 4 hours after lunch, and 45 minutes later the patient developed a psychiatric syndrome indistinguishable from her spontaneous psychiatric syndrome. While hallucinating, she had a flush, and both the flush and the hallucinosis were reversed by 0.4 mg of naloxone. Plasma epinephrine and norepinephrine levels during the psychiatric symptoms were extremely high, 3608 pg/mL and 25 237 pg/mL, respectively, although basal values were in the normal range.

The hallucinogenic activity of phencyclidine, LSD, and mescaline has been correlated with their spasmogenic potency on isolated cerebral blood vessels (15). Therefore, we decided to explore the possibility that the psychiatric symptoms could be due to vasospasm. Either nitroglycerin, 0.4 mg sublingually, or nitroprusside, 0.1 mg/mL intravenously, in a slow drip, controlled the psychiatric symptoms. Stopping either vasodilator was associated with the immediate return of the psychosis. Attempts to achieve continuous vasodilation with prazosin, 1 mg/d orally, failed because the drug induced severe orthostatic hypotension, weakness, and severe headaches.

Because the hallucinosis had begun when antiepileptic drugs were stopped, the patient was again given primidone, 500 mg/d, for 1 month. The pattern of the attacks was unaffected. To exclude the role of cimetidine in the generation of the organic psychosis (16), the patient was not given the drug for 7 days; as a result daily attacks of flushes occurred, followed by psychiatric symptoms. The reinstitution of cimetidine reduced the frequency of attacks to its previous level. Attacks tended to occur predominantly in the morning, with the highest frequency around noon, suggesting the participation of either insulin or hypoglycemia in the induction of the spontaneous attacks. Fasting had already been shown to precipitate a flush. A standard insulin tolerance test (0.1 U/kg) induced a typical flush that was reversed with naloxone.

Thyrotropin-releasing hormone is known to reverse some of the behavioral (17), cardiovascular (18), and neuroendocrine (19) effects of beta-endorphin and morphine. The recent demonstration that thyrotropin-releasing hormone, like naloxone (20-22), improves cardiovascular function in hemorrhagic and endotoxic shock (18), and the neurologic outcome of experimentally induced spinal trauma (23), prompted us to explore its effects on our patient. The administration of thyrotropin-releasing hormone, 50 μg intravenously, during a spontaneous flush resulted in nausea, exacerbation of the right upper quadrant abdominal pain, and an urge to urinate. The flush was unaffected, but the burning pain in the skin disappeared. Later psychiatric symptoms were unaffected by more thyrotropin-releasing hormone but naloxone again relieved the hallucinosis.

This experiment suggested a role for neurotensin in her disease, because thyrotropin-releasing hormone blocks many of the behavorial and pharmacologic effects of neurotensin (24-26), which is itself a mast-cell secretory activator (27, 28). The intradermal injection of 100 ng of neurotensin elicited a flare that covered the entire forearm and a severe burning cutaneous pain the patient felt was identical to that during a flush. This same amount of neurotensin produced neither a flare nor pain in a normal subject. The neurotensin-induced flare, however, did not precipitate a flush.

Discussion

This patient may be the index case of a new disease that links a functional mast cell abnormality and some mast cell products to a neurologic syndrome with vasomotor, dermatologic, gastrointestinal, and psychiatric manifestations. Some of the signs and symptoms were characteristic of carcinoid disease, some were compatible with mast cell disease, and others suggested dermatitis herpetiformis. It was impossible, however, to confirm any of these diagnoses; urinary excretion of 5-hydroxy-indoleacetic acid was never unequivocally abnormal, and no tumor could be shown after exploratory laparatomy. Urine and plasma levels of histamine were normal for years, and only during the last months was an increased level of urinary histamine detected during flushes. No anatomic evidence of mast cell abnormality could be found in repeated biopsy specimens of skin and bone marrow. The patient's histologic evidence and clinical course indicated that this was not a case of dermatitis herpetiformis. But even more fascinating was the evolution of the clinical picture to incorporate, as an aftermath of the flushing attack, a series of psychiatric symptoms, an organic psychosis—that is, hallucinosis separated by completely lucid intervals (Figure 1).

The fact that the patient's complete syndrome (flushes plus psychiatric symptoms) could be suppressed by naloxone and naltrexone suggests that an endogenous opiate is involved in the pathogenesis of both phases of the disease. The intradermal injection of naloxone neither reversed the clinical picture nor locally reversed the flush. This result differentiates this case from other naloxone-suppressible flushing syndromes (29, 30). Thus, peripheral vasodilation is not produced by a circulating opioid with μ-type receptor specificity, and we are led to infer that the opiate antagonists act centrally in the suppression of the clinical manifestations of the disease. Naloxone not only abolished the flush and the skin pain, but changed the sensation of doom and depression during the flush to euphoria, reminiscent of the young woman suffering from a bipolar affective psychosis described by Emrich and associates (31), in whom the injection of naloxone induced an enhancement of mania. Clearly naloxone and naltrexone may have other actions independent of those as an opiate-antagonist. However, both morphine and clonidine, a drug with opiate-releasing properties, can induce typical attacks that are blocked by naloxone or naltrexone. This fact strongly suggests that the mechanism involves opiate receptors.

Although the endogenous stimulus for the flushes is unknown, we found numerous ways to provoke them (Table 2). Epinephrine and morphine induced the worst attacks that the patient has ever had. Clonidine also provokes the syndrome, but although this drug releases beta-endorphin immunoreactive material from the rat brain and may do the same in humans, it also releases histamine from the rat mast cell (32). Given the extraordinary sensitivity of our patient's mast cells (Table 1), we cannot exclude this latter mechanism in the induction of the syndrome.

Flushing, itching, and thirst strongly suggest mast cell involvement and histamine release. Mast cell numbers were either normal or reduced as shown by the results of all skin biopsies. This fact could be due to their massive degranulation and the difficulty in recognizing degranulated mast cells by light microscopy (33). More perplexing, however, is the normal histamine content of the skin and the absence of meaningful differences between the histamine content of normal skin and of skin lesions. Similarly, plasma and whole blood histamine were never elevated during a flush. The search for diffuse infiltration of the skin with non-mast-cell amine-precursor uptake and decarboxylation elements, in which neuronal-specific enolase was used as a marker (34, 35), was also unsuccessful.

Several findings suggest that histamine and mast cells play a role in the disease. An increase of urinary histamine was detected during flushes experienced in the last two admissions to the clinical center. Peptic ulcer disease was controlled by increased doses of cimetidine. Thirst is a prodromal symptom of both her grand mal seizures and the flush. The injection of histamine (36, 37) or histamine releasing agents (38) either peripherally or into the hypothalamus (39) of rats elicits a powerful dipsogenic effect. The H2-antihistamine, cimetidine, successfully prevented spontaneous flushes for 18 months. The reduction of the dose or its complete withdrawal induced attacks, confirming cimetidine's therapeutic effectiveness. The intradermal injection of histamine, 100 ng, induced a flush and the subsequent organic psychosis. The only drug that relieved the incapacitating pruritus was the mast cell secretion inhibitor, disodium cromoglycate. The fact that the intradermal injection of compound 48/80, a specific mast-cell secretory activator, induced axon flares and precipitated a complete flushing attack at doses (10 to 100 ng) that are ineffective in normal skin, shows that the patient's mast cells are extraordinarily sensitive to exocytotic stimuli and that mast cell products are involved in triggering the syndrome.

Table 2. Drugs and Procedures that Induce Flushing Attacks and Hallucinosis, Suppressed by Naloxone and Naltrexone

Epinephrine, 5 μg intravenously*; and 183 pg intradermally*†
Clonidine, 100 μg orally*†
L-5-hydroxytryptophan, 500 mg orally†
Insulin, 0.1 U/kg (regular), intravenously†
Morphine, 2 mg intravenously*
d-Tubocurarine, 681 pg intradermally†
Pentagastrin, 0.5 μg/kg intravenously*
Histamine, 100 ng intradermally†
Compound 48/80, 100 ng intradermally†
Methacholine, 50 μg intradermally†
Fasting for 48 hours*
Withdrawal of cimetidine*†
Reduction of cimetidine from 1200 to 600 mg/d*

* Tested before the appearance of the hallucinatory stage.
† Tested when the disease incorporated the organic psychosis.

Even if not increased in number, the mast cells of this patient are functionally abnormal—exquisitively sensitive to a number of substances (Table 1). Furthermore, she has an exaggerated axon reflex; concentrations of histamine, compound 48/80, methacholine, and neurotensin that did not induce wheals elicited significant flares. Skin tests also indicated that the flush is caused by a humoral substance, because the vasodilation included areas of the skin that were previously anesthesized with lidocaine and failed to show an axon flare on an injection of histamine.

The patient has marked dermographism, spontaneous flushing of the face and neck, and she flushes violently after exercise or hot showers. This flushing is not synonymous with her periodic flushes because the former lacks the skin, bone, and abdominal pain, and the characteristic mood changes. Not everything that induces an axon flare elicits a periodic flush: compound 48/80 and methacholine did, but neurotensin did not. The flares induced by histamine, compound 48/80, and methacholine were painless, and the skin only hurt when there was a complete flush. The intradermal injection of neurotensin, however, reproduced the burning, radiating, "between layers" type of pain of the periodic flush. Thyrotropin-releasing hormone, an antagonist of many of the pharmacologic actions of neurotensin, eliminated the skin pain without modifying the other manifestations of the periodic flush. These are the necessary conditions for implicating endogenous neurotensin in the syndrome. However, we have not yet done the definite experiment, suppressing neurotensin-induced pain by thyrotropin-releasing hormone.

The administration of L-5-hydroxytryptophan resulted in hallucinosis, suppressible by naloxone, and followed by a flush. We do not know if the psychotomimetic action of the serotonin precursor is due to its conversion to the amine in the central nervous system or to the generation of a tryptophan derivative with hallucinogenic properties (40). Naloxone also antagonizes LSD effects in cats (3). The inversion of the temporal pattern (psychiatric symptoms followed by the flush) could have been due to massive release of epinephrine during the hallucinosis (which was especially terrifying) and the subsequent activation of the mechanisms which provoke the flush.

Both the periodic flush and the psychiatric symptoms were suppressed by naloxone and naltrexone, but vasodilators only abolished the psychosis. This finding shows that even if the whole disease is dependent on an opioid link, only the psychosis is due to vasospasm. The reversal of ischemic brain syndromes by the administration of naloxone gives further evidence for a role of endogenous opioids in the regulation of the brain circulation (41).

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