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PHARMACOLOGY OF MIGRAINE

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Migraine may be tentatively regarded as a hereditary, paroxysmal, vasoregulative instability, and is characterized by episodes during which there is often a phase of intracerebral arterial constriction and/or a phase of extracerebral arterial dilatation. The two phases often occur sequentially, but also commonly appear concurrently. Although substantial data have been generated describing the vascular alterations that characterize migraine attacks, the mechanisms by which these phenomena occur remain enigmatic. The recent demonstration that the capacity for vasomotor regulation resides within the central nervous system (CNS) itself via serotonergic neural circuits (1) is consistent with other lines of evidence that support the hypothesis that the modulation of synaptic serotonin—centrally as well as peripherally—is an important pathogenetic mechanism of the disorder (2).

The two general hypotheses regarding etiology are that migraine is the manifestation of (*a*) a CNS disorder of vasomotor regulation and (*b*) a systemic metabolic disorder. The lack of an animal model of migraine has precluded much testing of the former hypothesis, so that much of the accumulated data bear on possible circulating biochemical factors. Of the biological alterations that attend migrainous attacks (Table 1) it is uncertain at present whether any of these are but epiphenomena; the release of platelet serotonin as head pain commences appears to be the most specific of these since it is probably not the result of anxiety, pain, or cerebral ischemia (8). Psychologic factors are certainly important in the precipitation of migrainous headaches, but they are almost certainly a trigger mechanism with the

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Table 1 Biologic alterations occurring during migraine headache attacks

Finding	Reference
Intra- and extracranial vasodilatation	3
Cerebral vasomotor dysautoregulation	3–5
Opening of cephalic arteriovenous shunts	6
Release of platelet serotonin	7, 8
Increased concentration of plasma free fatty acids	9
Platelet activation	10, 11
Decreased concentration of plasma norepinephrine	12
Decreased platelet monoamine oxidase activity	13, 14
Increased CSF concentrations of γ-aminobutyrate, lactate, 3′,5′-cyclic adenosine monophosphate	15, 16

same import as exposure to glare, hunger, high altitudes, and the ingestion of certain foodstuffs.

The drugs that have proved effective in aborting individual attacks as well as in preventing them have been used for empirical reasons or for actions that subsequently have been shown to be unrelated to the benefits observed clinically (Table 2). These agents traditionally have been classified according to their actions in other conditions for which an effect outside the CNS has usually been implicated. Included in this group are the extracranial vasoconstrictors (ergotamine, dihydroergotamine, and caffeine), the serotonin antogonists (methysergide and cyproheptadine), a β-adrenergic blocker (propranolol), a tricyclic antidepressant (amitriptyline), a monoamine oxidase inhibitor (phenelzine), and a vasodilator (papaverine). However, there is evidence (see below) that the beneficial effect of propranolol is mediated

Table 2 Drugs effective in the prevention of migraine

Drug	Percentage of patients: Headache-free	Percentage of patients: >50% improved	Number of patients	Reference[a]
Methysergide	22	35	325	17, 18
Cyproheptadine	15	31	100	19, 20
Ergotamine-phenobarbital-belladonna	10	28	198	17, 21
Amitriptyline	57[b]	15	110	22–24
Propranolol	3	31	40	25–27
Papaverine	32	26	19	28
Phenelzine	28	52	25	29
Placebo	2	18	50	18

[a] Data presented are drawn from first citation.
[b] 80% improved.

by an action other than, or in addition to, peripheral β-receptor antagonism, and similarly that the actions of amitriptyline and papaverine in migraine are probably not as antidepressant and vasodilator. It has not been generally appreciated that these drugs through somewhat different mechanisms depress the firing rate of serotonergic neurons within the brainstem. Since migraine may be a disorder of the CNS, the role of these agents in altering the neurotransmitter function of serotonin is examined further in this review.

ERGOTAMINE

Modern orientations toward migraine probably began 100 years ago with the publication of the first major treatise on the subject (30). Liveing believed that the analogy of migraine to epilepsy was obvious, and that the clinically apparent circulatory phenomena that occurred during the attacks were secondary to CNS discharges, or "nerve storms." These views were shared by the eminent neurologists of this era (31). Attention shifted to a primary vascular mechanism of migraine in 1925, when ergotamine was shown to be remarkably successful in terminating headache attacks (32). Although it was originally believed to be effective because of its sympathetic blocking action, Graham & Wolff (33) in 1938 presented evidence that ergotamine constricted branches of the external carotid artery that were dilated during a migrainous episode. They administered ergotamine intravenously to patients after their focal neurologic symptoms had subsided and headache had just begun. Pulsation of the temporal or occipital arteries was recorded by tambours placed over the vessels. In 16 out of 20 patients, the injection of ergotamine was followed by a decrease in arterial pulsations that bore a close relationship to the decline in the intensity of headache; if the pulse amplitude declined slowly, headache diminished slowly. Precipitous declines in pulse amplitude were paralleled by the prompt cessation of headache. However, in four patients a correlation was not evident. These findings, together with other evidence suggesting that dampening of arterial pulsations by pharmacologic or physical means often ameliorated migraine headaches, led to general acceptance of the conclusion that the beneficial effects of ergotamine were mediated by constriction of the extracranial arterial bed. Subsequent experiments have established that powerful and selective constriction of the external carotid artery and its branches is produced by ergotamine (34, 35). Only slight α-adrenergic blockade occurs at the doses used clinically, and there is evidence that vasoconstriction is mediated by a direct effect on arterial serotonin receptors (36, 37).

The effect of ergotamine on arterial tone depends on the preexisting resistance of the vascular bed; when the vascular resistance is low, ergota-

mine acts as a constrictor, but when the resistance is increased it may produce vasodilation (38). This action may explain how ergotamine may prevent either phase of a migrainous attack (39). Regional cerebral blood flow studies performed during both the focal neurologic and headache phases of migraine attacks after the administration of ergotamine have shown no constrictor effects on the internal carotid circulation (4, 40). Sakai & Meyer (3) have shown that hyperemia in the basilar artery distribution was markedly reduced by therapeutically effective doses of ergotamine, suggesting the possibility that pain-sensitive arteries at the base of the brain may contribute to the pain of headache attacks. An additional effect of ergotamine is the closure of cephalic arteriovenous shunts that open during migrainous attacks (6). Whether this action is related to the therapeutic effects of the drug is uncertain.

Extracranial arterial constriction is probably important to the benefits conferred by ergotamine in aborting headache attacks; however, this may not be the primary site of the drug's effect. Ergotamine has significant effects on serotonin turnover in brain (41), and several ergot alkaloids have been found to depress the firing rate of central serotonergic neurons (42). Since there is evidence that central serotonergic circuits participate in circulatory regulation (1, 43–45), it is possible that the primary site of action of ergotamine is central rather than peripheral. Pichler et al (46) made the following observations in 13 subjects who were given ergotamine: Blood pressure elevation during the cold pressor response was not prevented; carotid sinus reflex activity was unaltered; reflex bradycardia occurred during infusions of norepinephrine; and cranial vasoconstriction was as evident in two subjects who had undergone cervical sympathectomy as in the other 11 subjects. This evidence was interpreted as rendering unlikely a primary central action of ergotamine. However, it has recently become clear that there is little or no involvement of the autonomic nervous system in the centrally modified circulatory response to serotonin (47); hence the preservation of reflex responses after ergotamine administration and the failure of sympathectomy to inhibit cranial vasoconstriction neither confirm nor deny a central locus of action for ergotamine.

PUTATIVE MECHANISMS OF THE MIGRAINE DRUGS

The highly diverse or lack of effects of the antimigrainous drugs on arterial wall receptors renders unlikely direct vasoconstriction or vasodilatation as their modes of action. Whereas their peripheral actions may contribute to their beneficial effects in migraine, all (Table 1) are known to cross the blood-brain barrier, so their central actions are also potentially important. Their dual actions centrally and peripherally are not mutually exclusive.

Brain Serotonin

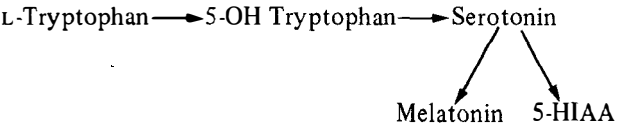
Brain serotonin is contained within specific neural circuits and generally functions as an inhibitory neurotransmitter (42, 48). Serotonin-containing neuronal cell bodies are principally those located in the brainstem raphe; axons of the rostral cell groups project to a large portion of the cerebrum (49), whereas the more caudal cell groups project to the medulla and spinal cord. Neuronal receptors of serotonergic nerve terminals are affected by serotonin in a fashion that mimics the stimulation of the brainstem raphe system; drugs that simulate the effects of serotonin on postsynaptic receptors also simulate the response to electrical stimulation of the raphe system or to serotonin applied microiontophoretically to the raphe neurons (42).

The serotonin antagonist drugs, so classified on the basis of actions on peripheral receptor systems, do not generally block the inhibitory effects of serotonin within the CNS (50, 51). Moreover, methysergide and cyproheptadine mimic the actions of serotonin centrally by depressing the firing rate of the raphe neurons; hence serotonin agonism is a more apt description of the central effects of these agents.

There appears to be a relationship between the firing rate of serotonergic neurons and the metabolic turnover of serotonin. For example, electrical stimulation of the raphe nuclei increases the synthesis and turnover of serotonin postsynaptically in the cerebrum. In general, an elevation of the synaptic neurotransmitter concentration depresses the firing rate and synthetic activity of the presynaptic neuron, suggesting the possibility that serotonin receptors are a link in a feedback loop that regulates the rate of firing of raphe neurons (52). Stimulation of the receptor by a neurotransmitter agonist also results in a depression of the raphe neuron firing rate. Conversely, blockade of the receptor results in an increase in the firing rate and release of transmitter by the presynaptic neuron (53). These observations are consistent with the reciprocal relationship between synaptic serotonin levels or availability and serotonergic neuronal activity. Thus, amitriptyline, a drug that blocks serotonin reuptake more than other tricyclic drugs (54), probably produces sustained higher intrasynaptic concentrations of serotonin and has been shown to produce a reduced firing rate of the raphe neurons (55). Similarly, phenelzine, a monoamine oxidase (MAO) inhibitor, blocks the primary route of brain serotonin catabolism, also probably resulting in elevations of intrasynaptic serotonin and a measured depression in the firing rate of raphe neurons (52).

There is some evidence, although not compelling at present, that the effects of serotonin at its receptor sites are mediated by cyclic AMP (56). Both caffeine (57) and papaverine (58, 59) inhibit phosphodiesterase, the catalyst of cyclic AMP degradation. There is evidence that phosphodiesterase inhibition in cyclic AMP-mediated postsynaptic potentials results in a

potentiation of the effects of the neurotransmitter in activating the postsynaptic receptor (56). Caffeine substantially increases brainstem serotonin levels (60) and decreases brain serotonin turnover (61); the effects of papaverine on serotonin turnover have not been studied. The effects of papaverine and caffeine on the firing rate of the raphe neurons have not been examined either, so these putative central effects are speculative.



The above schema outlines the metabolism of serotonin within the CNS. L-Tryptophan, derived from dietary sources, crosses the blood-brain barrier by an active energy-dependent process; the rate of synthesis of brain serotonin increases almost immediately after the administration of L-tryptophan (62). This linkage of the rate of serotonin synthesis in brain to the availability of its precursor is explicable by the observation that tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis, is not saturated by the levels of tryptophan normally present in brain; therefore the concentration of brain tryptophan plays a determinant role in the rate of serotonin synthesis. The highest activities of brain tryptophan hydroxylase are found within the midbrain raphe system (63), so serotonin synthesized from L-tryptophan is relatively selectively located within serotonergic neurons. Consistent with these observations, the rate of firing of the raphe neurons is markedly depressed by injections of L-tryptophan (52). In a preliminary controlled study in which eight patients with migraine were given 2 g of L-tryptophan daily, four of the eight experienced less frequent and less severe headaches (64).

Molecular oxygen is required for the hydroxylation of tryptophan; the inhalation of 100% oxygen by rats substantially increases brain serotonin synthesis and hypoxia has the opposite effect (65). The expansion of the metabolic pool of serotonin may explain the action of oxygen in migraine (66) but neuronal firing rates after oxygen administration have not been measured.

There probably is an interaction between central adrenergic and serotonergic neural circuits; one line of evidence includes a correlation between the capacity of certain drugs to depress the raphe neuron firing rate and central adrenergic blocking efficacy (67). Propranolol weakly depresses the raphe neuron firing rate when administered systemically, but not when applied iontophoretically (68). Thus, the action of propranolol may be indirect, affecting a central adrenergic system that influences the serotonergic neuronal circuit. The localization of the adrenergic system is not known at present.

Propranolol appears to be a potent inhibitor of the uptake of serotonin by human platelets, both in vivo and in vitro (69, 70). The platelet may be applicable as a model for the presynaptic nerve terminal owing to similarities in the manner in which both tissues transport, store, and metabolize serotonin (71); the effect of propranolol on platelet serotonin uptake may reflect a similar central action although no evidence supports this possibility. Similarly, that epinephrine-induced release of serotonin from duodenal enterochromaffin cells is blocked specifically by propranolol (72) may be relevant to the action of propranolol in migraine. If the enterochromaffin cell is assumed to be a model for the synapse, the inhibition of sporadic releases of serotonin from the synaptic cleft, a putative mechanism of migraine, may be a mode of action of propranolol.

Pathophysiology of Migraine

The evidence presented above suggests that a depression of the firing rate of the raphe neurons may be the common mode of action of the drugs effective in migraine. By serotonin agonism, by extending the biologic half-life of serotonin in the synaptic cleft (through blockade of its reuptake or metabolic degradation or an increase in its synthesis), or by activation of cyclic AMP (Figure 1), a unitary expression for the action of these drugs can be formulated, which is corroborated, for the most part, by direct measurement of serotonergic neuronal firing rates.

Migraine may therefore represent a defect in the modulation of transmitter release, resulting in sporadically low synaptic serotonin levels and secondarily increased neuronal firing rates. Many of the phenomena of migraine may be rationalized by this hypothesis. For example, the administration of reserpine to migrainous subjects that results in the reproduction of migrainous attacks in the majority (73) is as close as we have come thus far to an experimental model of migraine in man. The mechanism of reserpine is probably related to a release of serotonin from neurons and nerve terminals, resulting in a depletion of brain serotonin to negligible levels (74). Reduction of synaptic serotonin in patients whose synaptic levels are already low, or whose compensatory mechanisms for response to changes in serotonin release are defective, might be expected to result in a greater increase in neuronal firing rates than in control subjects. It is also understandable that nonmigrainous subjects may experience mild headaches after reserpine administration. Moreover, the previous administration of methysergide has been shown to prevent reserpine-induced headaches in migrainous subjects as well as in control subjects (75), without preventing the release of serotonin from its stores. The mechanism of action of methysergide appears to be as a serotonin agonist affecting receptor sites directly; hence the biologic consequences of inadequate synaptic serotonin may be reversed by its action.

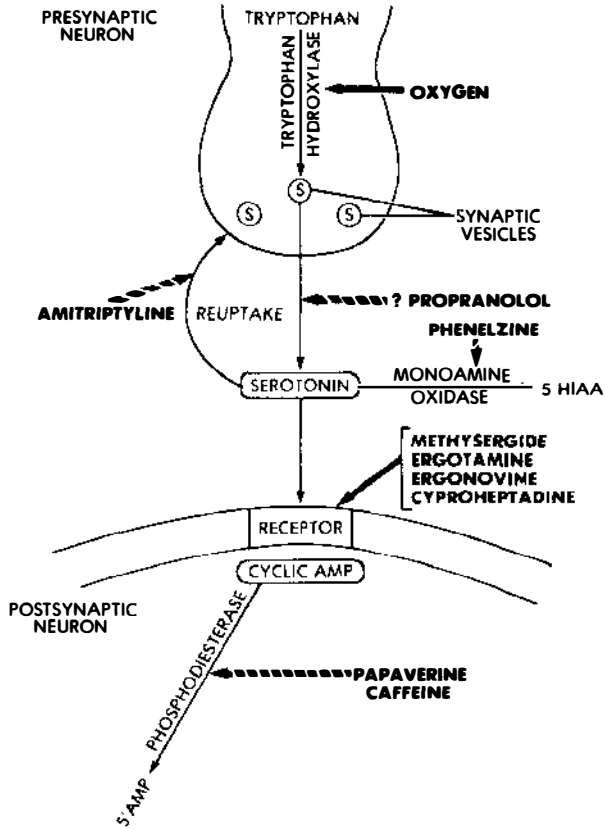


Figure 1 Putative actions of drugs effective in migraine at brainstem serotonergic synapse. The solid arrows indicate stimulative or agonist actions and the interrupted arrows indicate inhibitory properties. [From ref. (2). Reproduced by permission of W. B. Saunders, Philadelphia.]

The implication of serotonergic raphe cells in pain suppression (76), sleep regulation (77), endocrine regulation (78), and stress (79) parallels the protean clinical manifestations of migraine, conferring plausibility to the hypothesis.

Effects of Migraine Drugs on the Cranial Vasculature

METHYSERGIDE The first clinical trial of methysergide (1-methyl-D-lysergic acid butanolamide) in migraine (80) was carried out because of speculation at the time that serotonin was involved in the mechanism of migraine, and the observation that methysergide blocked the edema pro-

voked by serotonin in the rat's paw with more potency than 16 other lysergic acid derivatives (81).

Methysergide blocks the vasoconstrictor effect of serotonin, more so in the internal than in the external carotid circulation; the drug itself has only a mild and transient vasoconstrictor effect and it also potentiates the constrictor effects of norepinephrine (82, 83). The direct constrictor effect of methysergide is probably unrelated to its norepinephrine-potentiating effect (84). Methysergide also antagonizes the dilator effects of serotonin on cranial arteries noncompetitively (85); it has no effect on the vasodilator responses to histamine, bradykinin, or prostaglandin E_1.

CYPROHEPTADINE The demonstration that serotonin, in addition to histamine, may be released in certain allergic reactions gave rise to studies of the serotonin-blocking actions of various antihistaminic agents. Cyproheptadine was found to be the most active peripheral serotonin antagonist of all the antihistaminics studied (86). It bears some resemblance to the phenothiazine antihistaminics and also to the ergot alkaloids in possessing an N-substituted heterocyclic ring.

The vasoactivity of cyproheptadine is quantitatively less than that of methysergide. It only weakly antagonizes the vasoconstrictor effects of serotonin (87). The effects of norepinephrine are not potentiated by cyproheptadine. Its platelet antiaggregating properties may be relevant to its therapeutic effect in migraine (88).

PROPRANOLOL The original observation that propranolol was effective in migraine was made fortuitously (89). Blockade of peripheral vasodilator β-receptors, preventing the vasodilatation that underlies the headache phase of a migraine attack, was put forth as a possible mode of action of the drug. Although β-receptors have been identified in both the intracerebral and extracerebral vasculature (90), it is unlikely that β-blockade is important to propranolol's action in migraine. A number of β-blockers, in addition to propranolol, have been studied for their possible benefits in migraine—including prindolol, alprenolol, oxprenolol, and acebutolol (2). In none of these latter studies were the results significantly better than with placebo. A careful examination of potency, β-receptor selectivity, agonist activity, and membrane-stabilizing action fails to reveal any β-blocking action characteristic to explain propranolol's superiority. Furthermore, *d*-propranolol appears to be almost as effective as the levo optical isomer of the drug in migraine (91) even though the *d*-isomer is almost devoid of β-blocking activity (92, 93).

Propranolol produces no significant alterations of either cerebral blood flow or cerebral metabolism (94, 95). The dilator effect that a low concentra-

tion of serotonin produces in cerebral arteries and arterioles is blocked by propranolol (85, 96).

AMITRIPTYLINE Two lines of reasoning led to trials of amitriptyline in the treatment of migraine. First, the demonstration that carbamazepine, an analogue of imipramine, was effective in the suppression of trigeminal neuralgia, led to informal empirical trials of imipramine and other tricyclic drugs in a variety of painful states. Second, because patients who sustain chronic headaches often become depressed (97), it was believed that headache could be an expression of depression that might be alleviated by antidepressant drug therapy. However, the beneficial effect of amitriptyline in migraine probably occurs independently of its antidepressant actions (22, 23) and drugs with equivalent antidepressant actions, such as imipramine, have been relatively ineffectual in the treatment of migraine (17).

Other than the potentiation of the pressor effects of norepinephrine (98) there are no known effects of amitriptyline on cerebral arteries that might explain its actions in the treatment of migraine.

PHENELZINE The single study of phenelzine therapy in migraine was carried out on the premise that the platelet release of serotonin that accompanies migrainous attacks might result in arterial dilatation via the removal of a vasoconstrictor influence (serotonin) from the circulation. The catabolism of serotonin would be retarded by an inhibitor of MAO, resulting in an elevation of tissue and plasma levels, thus preventing sporadic vasodilatation. However, in their study, Anthony & Lance (29) found that whereas platelet serotonin levels rose during phenelzine treatment, there was no correlation between the magnitude of the elevations and the clinical response. One patient with only a modest increase in platelet serotonin had become headache-free, and another with the greatest elevation of the group studied was unimproved.

Some support for Anthony & Lance's hypothesis may be derived from the observation that treatment of baboons with tranylcypromine, a potent MAO inhibitor, markedly enhanced the intracerebral vasoconstriction produced by intraarterial serotonin (99).

PAPAVERINE Poser (100) successfully treated a group of migrainous patients with papaverine on the basis that the intracerebral vasoconstrictive phase of a migrainous attack may be an obligatory part of the mechanism and its prevention with a vasodilator drug therefore may prevent headache attacks. It has become clear that oral papaverine produces modest increments in cerebral blood flow by a reduction in cerebrovascular resistance. Poser's hypothesis is supported by the observation that the higher the cerebrovascular resistance the greater is the increase in cerebral blood flow produced by papaverine (101).

PROSTAGLANDINS

That prostaglandins may be implicated in migraine was suggested by the observation that intravenous prostaglandin E_1 (PGE_1) in nonmigrainous subjects consistently resulted in a vascular headache that bore migrainous features (102). In laboratory animals pulmonary arterial infusions of serotonin release prostaglandins into the pulmonary vein (103); this response can be blocked by methysergide or ergotamine (104, 105). Serotonin is one of few compounds that release PGE into the ventricular fluid when perfused into the cerebral ventricles (106).

In most vascular beds, prostaglandin Es are potent vasodilators and intraarterial infusions of PGE_1 result in a loss of cerebral vasomotor autoregulation (107, 108). In some peripheral arterial beds, prostaglandins have been implicated in the regulation of arterial tone (109); cranial arteries have only begun to be studied in this regard (110). Some of the vasomotor effects of systemically administered PGE_1 are mediated by a central serotonergic mechanism (111).

No alterations in arterial or venous PGE_1 levels have been found during migrainous attacks (112, 113). Fenamates, inhibitors of prostaglandin synthesis, have been shown to be remarkably effective in aborting individual migraine attacks but are ineffectual in preventing then when used regularly (114, 115). Trials with other prostaglandin synthesis inhibitors, including indomethacin (116), naproxen (117), and ketoprofen (118) have produced results not substantially better than with placebo. Whether the mode of action of the fenamates or aspirin in aborting migraine attacks is through prostaglandin inhibition or by some other mechanism is uncertain.

The prostaglandins are an interesting group of compounds, and much more needs to be known about them to assess their potential role in migraine (119). Since serotonin is a prostaglandin-releasing factor, hypotheses implicating either of these agents are not mutually exclusive.

CONCLUSIONS

Much of the phenomenology of migrainous attacks as well as the pharmacology of the drugs effective in migraine is imperfectly explained by solely considering circulatory alterations. Several lines of evidence suggest that migraine may be a disorder arising from within the CNS; the most persuasive of these is that the common mode of action of the antimigrainous drugs is probably the suppression of the firing rate of brainstem serotonergic neurons. By serotonin agonism, by prolonging the half-life of serotonin in the synaptic cleft—through blockade of its reuptake or metabolic degradation or an increase in its synthesis, or by activation of cyclic AMP—a unitary expression for the action of these drugs can be formulated, which

is corroborated, for the most part, by direct measurement of serotonergic neuronal firing rates. The cardinal abnormality of migraine may be that the modulation of serotonin release is defective, leading to sporadically low synaptic serotonin levels and secondarily increased raphe-neuronal firing rates. The dramatic circulatory alterations that accompany migrainous attacks can be inferred from evidence imputing the participation of the brainstem serotonergic circuit in the central regulation of the cerebral circulation. Serotonin dysmodulation may also occur at the synapses of the myenteric plexus of the intestinal walls, explaining the alterations of gastrointestinal motility that often accompany migrainous attacks.

The implication of the serotonergic raphe cells in pain suppression, sleep regulation, hormone-releasing factors, and stress parallels the protean clinical manifestations and precipitants of migraine attacks, lending plausibility to the hypothesis. Furthermore, the hypothesis lends itself to an animal model of migraine, so that it may be tested in a controlled laboratory setting.

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