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Pathogenesis of the Migraine Attack

Egilius L. H. Spierings, MD, PhD

Department of Neurology, Brigham and Women's Hospital, Harvard Medical School Boston, Massachusetts

Abstract:

Background: There is *clinical* experimental evidence that extracranial arterial vasodilation, extracranial neurogenic inflammation, and decreased inhibition of central pain transmission are involved in the pathogenesis of the migraine headache. The migraine aura is likely caused by a neurophysiologic phenomenon akin to Leão's cortical spreading depression, a wave of short-lasting neuronal excitation that travels over the cerebral cortex, followed by prolonged depression of cortical neuronal activity.

Method: A concept of the pathogenesis of the migraine attack is presented, in which the relation of the mechanism of the migraine aura and that of the migraine headache is considered parallel rather than sequential in nature.

Conclusions: The process driving the pathogenesis of the migraine attack and susceptible to the migraine trigger factors may be located in the brain stem.

Key Words: arterial vasodilation, cortical spreading depression, migraine attack, migraine aura, migraine headache, neurogenic inflammation, parallel concept, pathogenesis, sequential concept

> To approach the treatment of migraine in a rational way it is helpful to have a concept of the mechanisms involved in its production.
>
> John R. Graham, MD, MACP
> Treatment of Migraine, 1955

Migraine is a chronic condition of recurring headaches of moderate or severe intensity that affects 6% of men and 18% of women, 12 years and older.[1] The headaches are generally so intense that they interfere with the ability to function; sometimes they are incapacitating and require bed rest. The headaches last for at least part of a day but can continue for days, especially when occurring perimenstrually. In so-called migraine with aura, they are preceded by transient focal neurologic symptoms, generally referred to as aura symptoms.

In this article, the pathogenesis of the migraine headache as well as that of the migraine aura will be discussed. There is *clinical* experimental evidence for the involvement of at least three mechanisms in the pathogenesis of the migraine headache. These mechanisms are extracranial arterial vasodilation, extracranial neurogenic inflammation, and decreased inhibition of central pain transmission. The notion that the peripheral changes related to the pathogenesis of the migraine headache occur in the dura mater, as opposed to the extracranial tissues, is based on animal experimental evidence only. The migraine aura is likely caused by a neurophysiologic phenomenon akin to Leão's cortical spreading depression, a wave of short-lasting neuronal excitation followed by prolonged depression of cortical neuronal activity. The traditional, sequential concept of the pathogenesis of the migraine attack will be reviewed and an alternative concept will be presented, which considers the relation of the mechanism of the migraine aura and that of the migraine headache as parallel rather than sequential in nature.

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Address correspondence and reprint requests to Egilius L. H. Spierings, MD, PhD, 25 Walnut Street, Suite 102, Wellesley Hills, MA 02481–2106.

MIGRAINE HEADACHE

Arterial vasodilation

In the 1930s, Graham and Wolff[2] were the first to study the mechanism of extracranial arterial vasodilation

in the pathogenesis of the migraine headache. They observed that pressure exerted on the extracranial arteries temporarily decreased the intensity of the pain. In addition, they found that administration of ergotamine resulted in a decrease in intensity of the headache, parallel to a decrease in pulsation amplitude of the extracranial arteries. Schumacher and Wolff[3] observed that increasing the pressure of the cerebrospinal fluid by intrathecal injection of saline, thereby decreasing the pulsation amplitude of the intracranial arteries, did *not* decrease the intensity of the pain. This suggests that the intracranial arteries, cerebral or extracerebral, that is, dural or meningeal, do not significantly contribute to the pain of the migraine headache.

The artery that seems to be predominantly involved in the mechanism of migrainous vasodilation is the frontal branch of the superficial temporal artery, giving rise to the pain in the temple that is so characteristic of migraine. In 1953, Tunis and Wolff[4] reported on the systolic pulse-wave amplitude of the frontal branch of the superficial temporal artery in migraineurs during and between headaches and in nonheadache controls. They found the amplitude, taken as a measure of artery caliber, to be significantly increased in between headaches in comparison with controls, with a further increase during headache (Fig. 1).

More recent clinical experimental evidence for the involvement of the temporal artery in the pathogenesis of the migraine headache is shown in Figure 2.[5] It shows that, during the migraine headache, the artery is dilated on the side of the pain. The dilation is relative because generalized vasoconstriction occurs owing to activation of the sympathetic nervous system, secondary to the pain of the migraine headache. The generalized vasoconstriction causes the paleness of the face and coldness of the hands and feet, as is often observed during migraine headache. Heyck[6] has suggested opening of arteriovenous anastomoses as an alternative explanation for the dilated arteries and paleness of the face. The fact that patients with migraine have dilated temporal arteries also between headaches was recently confirmed as well, as shown in Figure 3.[7]

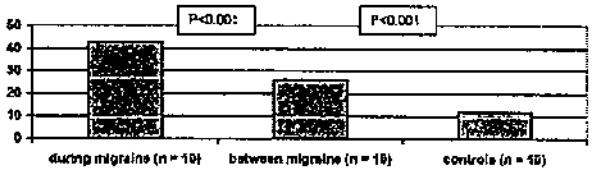

FIGURE 1. Systolic pulse-wave amplitude of the frontal branch of the superficial temporal artery, in millimeters, during and between migraine headaches and in nonheadache controls. Data obtained from Tunis and Wolff.[4]

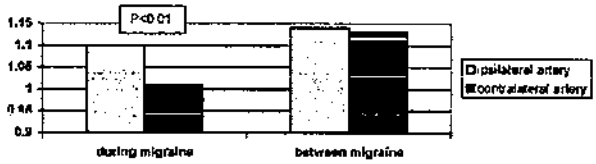

FIGURE 2. Luminal diameter of the superficial temporal artery, in millimeters, during and between migraine, ipsilateral and contralateral to the headache (n = 25). Data obtained from Iversen et al.[5]

Neurogenic inflammation

Neurogenic inflammation is an inflammation of peripheral tissue, caused by the release of chemicals from the primary sensory nerve fibers involved in nociception. It finds its origin in the neurohumoral features of afferent nerve fibers, which were revealed in studies of the axon reflex flare (Lewis) and antidromic vasodilation (Bayliss).[8] The chemicals, which include substance P, calcitonin gene-related peptide, and neurokinin A, are released from the nerve fibers when they are activated. In migraine, the activation of the nerve fibers is thought to result from the dilation of the extracranial arteries. The nerve fibers coil around the arteries and are stretched, thereby depolarized and activated, when the blood vessels dilate. The phenomenon was implicated in migraine to explain the decrease in pain threshold found locally at the site of the pain[9] (Fig. 4) and because it was understood that vasodilation alone could not account for the intensity of the migraine headache.[10]

In the 1950s, Chapman and Wolff[11] were the first to study neurogenic inflammation as a mechanism involved in the pathogenesis of the migraine headache. They observed that subcutaneous perfusates of sites of migraine headache possessed inflammatory activity, proportional to the intensity of the pain (Fig. 5). In addition, they found that administration of ergotamine resulted in a decrease in inflammatory activity, parallel to a decrease in intensity of the pain. More recently, Goadsby et al[12] showed that, during migraine headache, the level of calcitonin gene-related peptide in blood drawn from the external jugular vein is increased, in comparison with blood drawn from the antecubital vein (Fig. 6). Calcitonin gene-related peptide, a potent vasodilator, is one of

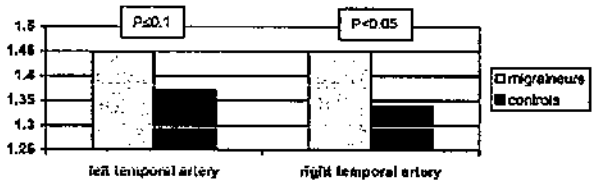

FIGURE 3. Luminal diameter of the superficial temporal artery, in millimeters, in migraineurs between headaches (n = 50), in comparison with non-headache controls (n = 50). Data obtained from De Hoon.[7]

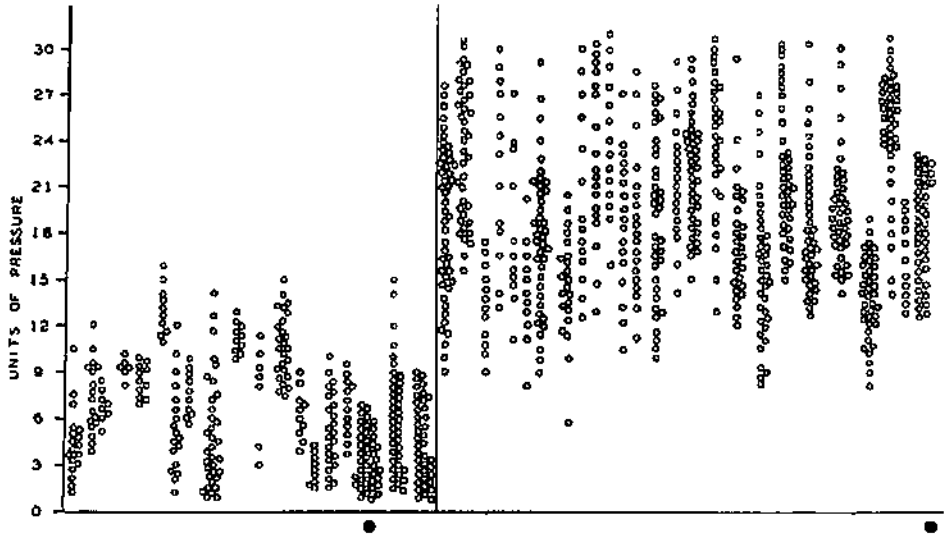

FIGURE 4. Deep pain threshold measured in the area of pain during (left) and between migraine headaches (right; n = 10). Reproduced from Wolff et al.[9]

the chemicals involved in neurogenic inflammation; the external jugular vein drains blood from the extracranial tissues.

The decrease in pain threshold at the site of the pain during migraine headache was recently confirmed as cutaneous allodynia.[13] Allodynia refers to pain resulting from non-noxious stimulation of normal (looking) tissue and was found present in the ipsilateral periorbital area during migraine headache in 79% of the 42 patients studied.

Central pain transmission

Apart from neurogenic inflammation, there is probably also a central mechanism involved in the decrease in pain threshold at the site of the migraine headache. Evidence for this was provided by a study[14] of the enkephalin level, determined in the cerebrospinal fluid during migraine headache. Enkephalin is an endogenous opioid that inhibits the transmission of pain signals in the central nervous system. It was found to be decreased during migraine headache in comparison with between headaches and with nonheadache controls (Fig. 7).

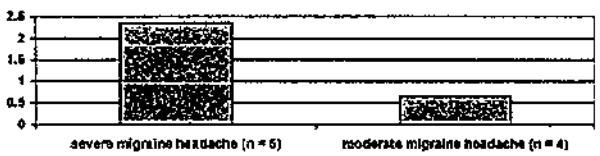

FIGURE 5. Inflammatory activity of subcutaneous perfusates of sites of migraine headache, in bradykinin units, in relation to the intensity of the pain. Data obtained from Chapman et al.[11]

MIGRAINE AURA

Cerebral vasoconstriction

In the 1940s and 50s, Schumacher, Marcussen, and Wolff[2,15] were the first to study experimentally the pathogenesis of the migraine aura. They observed that inhalation of a cerebral vasodilator, such as amyl nitrite or carbon dioxide, during the migraine aura resulted in a transient regression of the symptoms (Fig. 8). Hence, they concluded that the migraine aura is caused by transient cerebral vasoconstriction.

Spreading depression

In 1958 Milner[17] reported on the similarities in features and progression between the scintillating scotoma and cortical spreading depression, a neurophysiologic phenomenon described by Leão in 1944. Cortical spreading depression is a wave of inhibition of neuronal activity that travels over the cerebral cortex at a slow rate. It is preceded by a short-lasting phase of intense neuronal activity and, therefore, is better referred to as "spreading

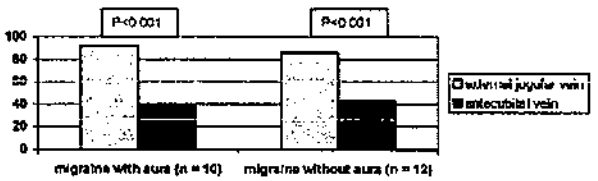

FIGURE 6. Level of calcitonin gene-related peptide in blood drawn from the external jugular vein, in pmol/L, during migraine headache in comparison to blood drawn from the antecubital vein. Data obtained from Goadsby et al.[12]

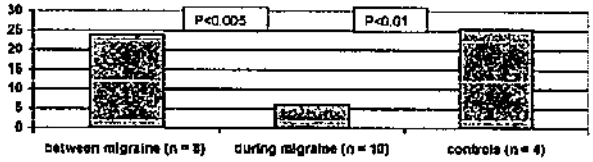

FIGURE 7. Enkephalin level of the cerebrospinal fluid, in pmol equivalents of met-enkephalin/mL, during and between migraine headaches and in nonheadache controls. Data obtained from Anselmi et al.[14]

excitation." Scintillating scotoma is a typical presentation of the migraine aura. It usually begins near the center of vision as a twinkling star, which develops into a circle of bright and sometimes colorful, flickering zigzag lines. The circle subsequently opens up on the inside to form a semicircle or horseshoe, which further expands into the periphery of one visual field or the other. On the inside of the visual disturbance, a band of dimness follows in the wake of the crescent of flickering zigzag lines. The disturbance of vision ultimately disappears as it fades away in, or moves outside of, the periphery of the visual field in which it developed.

Cerebral blood flow

In the 1970s, relatively accurate measurement of cerebral blood flow (CBF) became possible with the development of the Xenon-clearance technique. Olesen et al[18] summarized the results of blood flow studies applying this technique in 63 patients with attacks of migraine with aura triggered by angiography. They concluded that the aura symptoms come on *after* a decrease in blood flow occurs in the posterior region of the opposite hemisphere. The headache comes on *while* blood flow is still decreased but is followed by a gradual increase in blood flow to an abnormally high level (Fig. 9). The increase in CBF that follows the decrease was initially attributed to reactive hyperemia. The decrease did *not* reach ischemic levels, however, as is required to cause reactive hyperemia, and, therefore, was referred to as oligemia.[19] The oligemia was shown to spread over the cerebral cortex at a slow rate, similar to Leão's spreading excitation–depression.

The development of functional magnetic resonance imaging made it possible to study the changes in CBF during spontaneous migraine attacks. The resolution of this method is also much better than that of the Xenon-clearance technique and, in addition, the brain can be studied in different cuts. Sanchez del Rio et al[20] found that, during migraine aura, CBF is decreased by 27% in the contralateral occipital cortex and this decrease persists for up to 2½ hours into the headache. Whether CBF subsequently increases, as suggested by the Xenon-clearance studies, is not clear: an increase of 20% over multiple attacks was observed in one of three patients studied. In the patients with migraine without aura, no changes in CBF were seen 1 to 11 hours after the onset of headache, as compared with between headaches.

A study using high-field functional magnetic resonance imaging looked at the blood oxygenation-level dependent signal during visual migraine aura.[21] The signal was elicited by visual stimulation through a flickering

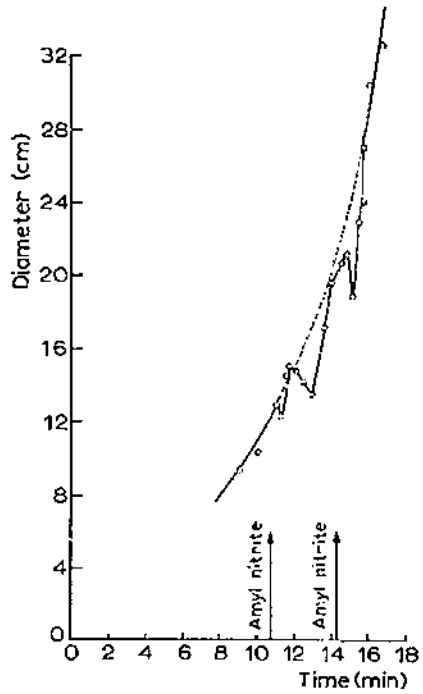

FIGURE 8. Effect of the cerebral vasodilator, amyl nitrite, on the progression of the scintillating scotoma. Reproduced from Hare.[16]

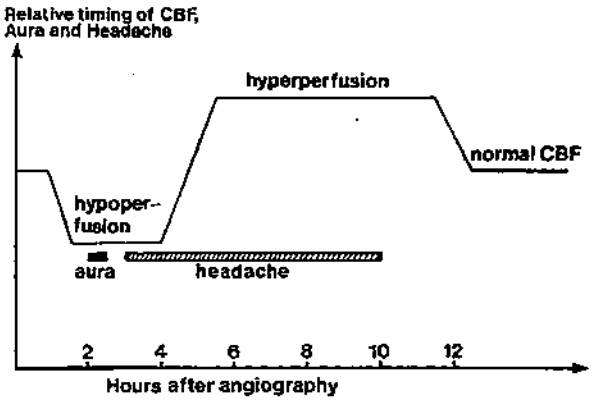

FIGURE 9. Changes in cerebral blood flow in relation to the occurrence of the aura and the headache in migraine with aura. Reproduced from Olesen et al.[18]

checkerboard and reflects the balance between oxygen delivery and oxygen consumption. Five attacks of migraine with aura were studied in three subjects, two attacks of which were triggered in one subject by strenuous exercise. In particular in the triggered attacks, a sequence of events was recorded consisting of a marked increase in the mean level of the signal, rapidly followed by its almost complete abolition despite continuing checkerboard stimulation (Fig. 10). The observed changes in the signal suggest a particular sequence of events, with brief excitation being followed by prolonged (active) depression of cortical neuronal activity. The changes started in the primary visual cortex or striate area and extended anteriorly over the occipital lobe at a rate of 3.5 mm/min, which is similar to the rate of progression of Leão's spreading excitation–depression.

Summary

On the basis of the clinical presentation of the migraine aura, the mechanism involved is more likely to be spreading excitation–depression than transient cerebral vasoconstriction. This notion is supported by the studies previously reviewed as well as by a study[22] using brain spectroscopy, which showed an alteration in energy metabolism during migraine with aura but without changes in pH. Cerebral vasoconstriction is the mechanism most likely involved in migrainous infarction, which can complicate migraine headache whether or not it is preceded or accompanied by aura.[23]

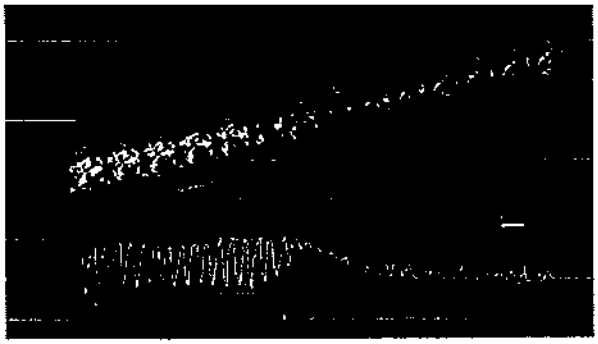

FIGURE 10. Above, high-field magnetic resonance images of an "inflated" right cerebral hemisphere taken over a time course of 20 minutes, including 12 minutes after the onset of exercise-induced migraine aura paracentrally in the left visual field (arrow). The circle projected on some of the images indicates the primary visual cortex or striate area. The activity shown in color is the so-called blood oxygenation–level dependent signal, elicited by visual stimulation through a flickering checkerboard and reflects the balance between oxygen delivery and oxygen consumption. At the onset of the migraine aura, the signal is suppressed starting in the striate area and gradually extending anteriorly at a rate of 3.5 mm/min. Below, a graphic display over the same time period of the amplitude of the blood oxygenation–level dependent signal. At the onset of the aura, the mean level of the amplitude increases markedly, which suggests heightened cortical neuronal activity. The increase in mean level is rapidly followed by almost complete abolition of the signal, indicating suppression of cortical neuronal activity despite continuing checkerboard stimulation. Courtesy of Margarita Sanchez del Rio, MD, Madrid, Spain; recorded at the Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

MIGRAINE ATTACK

Traditional, sequential concept

In approximately one third of patients, the migraine headache is preceded by an aura.[24] Otherwise, it involves migraine without aura, where the headache occurs without an aura but is otherwise the same. In the traditional view, the pathogenesis of the migraine aura and that of the headache are considered causally related. That is, the aura is considered to be the *cause* of the headache. The aura is related to cerebral vasoconstriction, which causes localized hypoxia of the brain and is followed by reactive vasodilation. The vasodilation occurs in the cerebral circulation but is *supposedly* associated with dilation of extracranial arteries. The extracranial arterial vasodilation initiates the mechanism of neurogenic inflammation, and the interplay of the two causes the pain of the migraine headache (Fig. 11).

In migraine without aura, as the traditional view maintains, the cerebral vasoconstriction and hypoxia occur as well but in a clinically silent area of the cerebral cortex. There is little evidence for this assumption, however, and there is also no evidence that cerebral vasodilation is associated with dilation of extracranial arteries. The two assumptions were made to causally connect the migraine aura with the headache and to bring the two forms of migraine, migraine with and without aura, together in one pathogenetic concept. On the basis of the results of the CBF studies, however, it can at least be stated that the aura and headache are *not* causally related through cerebral vasodilation because the cerebral vasodilation, if it happens at all, does not occur until *after* the onset of the headache.

Alternative, parallel concept

Except for the aura, the clinical presentations of migraine with and without aura are so similar that a common pathogenesis is plausible. Also, the two forms of migraine often occur in the same individual, with some headaches preceded, and some not, by an aura. The fact that the aura often occurs before the onset of the headache does not necessarily mean that it is the *cause* of the headache. It is relatively simplistic reasoning to assume that because one event follows the other, there is a causal relation between them.

The particular time-relation between the occurrence of the aura and that of the headache can also be explained

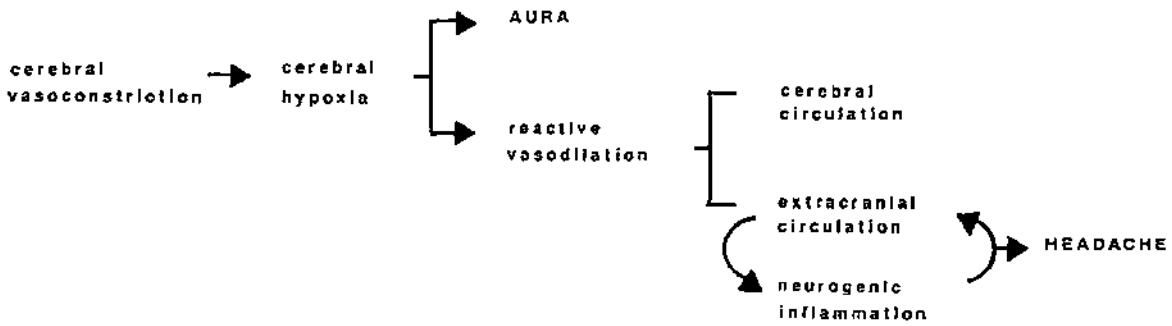

FIGURE 11. Traditional view on the pathogenesis of the migraine attack, in which the aura and headache are considered sequential and causally related.

in other ways. For example, with a disturbance in physiology, the reactivity of the cerebral cortex is much greater than that of the extracranial tissues in giving rise to symptoms. In the alternative concept, the relation of the mechanism of the migraine aura and that of the migraine headache is considered to be parallel rather than sequential in nature (Fig. 12). The two mechanisms are joined together by the migraine process, the driving force behind the migraine attack, which, often in unison, is activated by the migraine triggers. There is evidence from a psychophysiologic study that the visual cortex of patients with migraine *with* aura lacks inhibitory activity, as compared with patients with migraine without aura and nonheadache controls.[26] This lack of inhibitory activity could translate into hyperexcitability or a lower threshold for initiation of the phenomenon of spreading excitation–depression by the migraine process. It is possible that this hyperexcitability, in turn, relates to a genetically determined calcium channelopathy in the central nervous system.[27]

The parallel concept, better than the sequential one, explains the isolated occurrence of the migraine aura (migraine aura without headache) and the isolated occurrence of the migraine headache (migraine without aura). The concept also includes the associated autonomic and sensory symptoms of the migraine headache, explained as secondary to the headache through stimulation of the sympathetic nervous system and ascending reticular activating system, respectively.

MIGRAINE GENERATOR

A study using positron emission tomography showed CBF to be increased during the migraine headache in the cingulate as well as visual and auditory cortices.[28] The activation of the cingulate cortex, part of the limbic system, is directly related to the pain of the migraine headache and the emotional response to it. The activation of the visual and auditory associate cortices has been related tentatively to the photophobia and phonophobia commonly associated with migraine headache. In addition to these changes in cortical CBF, an increase in blood flow was observed in the contralateral brain stem at the level of the mesencephalon (Fig. 13). This change in blood flow, reflecting increased neuronal activity, was thought to be particular to migraine because it did not occur with capsaicin-induced head pain.[29] Weiller et al[28] also found that, while administration of sumatriptan resulted in relief of the migraine symptoms and disappearance of the cortical activation, the localized increase in mesencephalic blood flow persisted. The investigators, therefore, suggested that the observed activation in the brain stem contralateral to the pain was the first visualization of a postulated migraine generator. From this generator, the aforementioned migraine process could be initiated, activated by the migraine trigger factors.

Unfortunately, the finding of localized brain stem activation during the migraine headache has not been replicated yet, which would be the first step in establishing

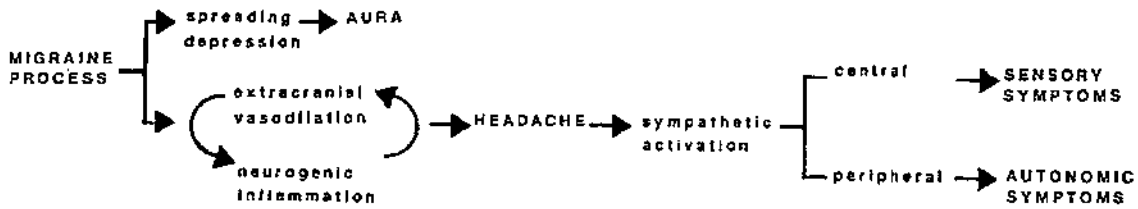

FIGURE 12. Alternative view on the pathogenesis of the migraine attack, in which the aura and headache are considered parallel phenomena and the associated symptoms looked on as secondary to the headache. Adapted from Spierings.[25]

its significance. Also, the brain stem area involved is thought to play an important role in central pain control rather than in the generation of pain. Paulson et al[30] also showed that painful thermal stimulation (50°C) of the arm increased blood flow in the same mesencephalic area, contralateral to the side of stimulation (Fig. 14). Furthermore, it is not known how activation of this area could cause the cerebrocortical and extracranial changes related to the migraine aura and headache, respectively. Equally obscure are the mechanisms and pathways through which this brain stem area could be activated by the diversity of trigger factors involved in migraine.

CONCLUSIONS

There is *clinical* experimental evidence that extracranial arterial vasodilation, extracranial neurogenic inflammation, and decreased inhibition of central pain transmission are involved in the pathogenesis of the migraine headache. The migraine aura is likely caused by a neurophysiologic phenomenon akin to Leão's cortical spreading depression, a wave of short-lasting neuronal excitation that travels over the cerebral cortex, followed by prolonged depression of cortical neuronal activity. A concept of the pathogenesis of the migraine attack is presented, in which the relation of the mechanism of the migraine aura and that of the migraine headache is considered parallel rather than sequential in nature. The process driving the pathogenesis of the migraine attack and susceptible to the migraine trigger factors may be located in the brain stem.

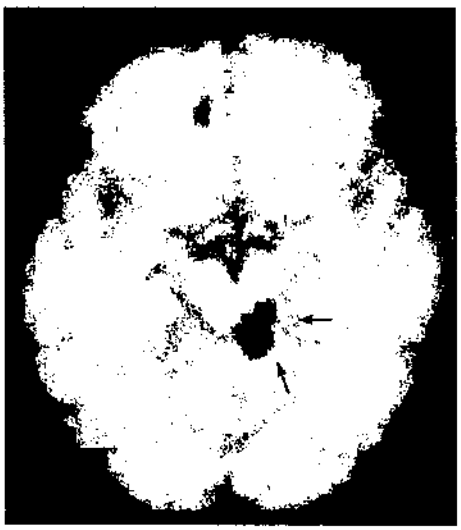

FIGURE 13. Increased blood flow in an area of mesencephalon contralateral to the pain in patients with unilateral migraine headache (n = 9), as observed with positron emission tomography (arrows). Reproduced from Weiller et al.[28]

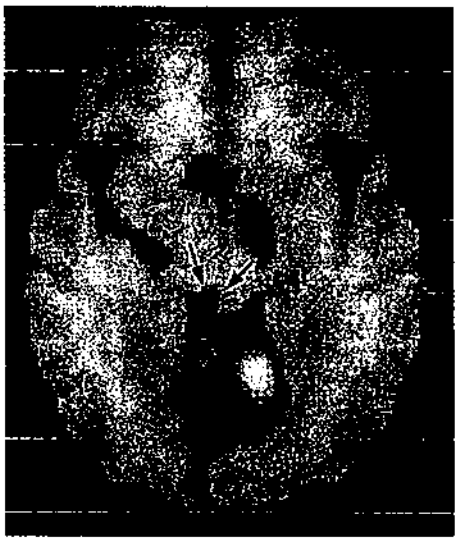

FIGURE 14. Increased blood flow in the contralateral mesencephalon in the area of the periaqueductal gray, as observed with positron emission tomography during painful thermal stimulation (50°C) of the arm (n = 10) (arrows). Reproduced from Paulson et al.[30]

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