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Chapter VII

The Role of the External Carotid Vasculature in Migraine

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Abstract

The pathogenesis of migraine pain has not yet been adequately explained and remains the subject of vigorous debate. Early studies by Harold Wolff and his associates on the extracranial terminal branches of the external carotid artery provided compelling evidence of their involvement in the evolution of migraine pain. They postulated that migraine pain emanates from dilated extracranial arteries. Since 1958, however, when Milner proposed that the visual aura of migraine may be caused by the "spreading depression" of Leão, migraine research has focused almost exclusively on the central neurovascular changes, to the exclusion of Wolff's postulates. Current theories implicate changes in the trigeminovascular system, which is defined as comprising the trigeminal subnucleus caudalis, the trigeminal nerve, and the intracranial arteries, particularly the middle meningeal artery. Although the middle meningeal artery is intracranial, it is one of the terminal branches of the external carotid artery. In this chapter experimental, clinical, and pharmacological evidence linking the extracranial terminal branches of the external carotid artery to migraine pain is presented.

Introduction

Some of the earliest records describe binding of the head as a method of treating headache. A Sumerian prescription from about 4000 BC suggests that the head be bound with the woven hair of a kid [1]. The Ebers papyrus dating back to about 1200 BC, discovered in a tomb at Thebes, offers the following advice: "bind a crocodile made of clay … to the head using a strap of fine linen" [2].

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The first written record of the involvement of the extracranial vasculature in headache is attributed to Abu Qasim al-Zahrawi (936-1013), the renowned Moorish physician (known in the West as Abulcasis or Abucalsis), who treated headache by surgical ligation of the superficial temporal artery [3]. A hundred years later, the prominent medieval Jewish physician, Moses Maimonides (1135–1204), stated that headaches in general can be alleviated by mild pressure to the head [4].

Ambroise Paré (1510-1590), regarded by many as the father of modern surgery, divided his own superficial temporal artery to relieve his migraine headaches [5].

In the 17th century Thomas Willis, widely regarded as one of the founders of modern neurology, suggested that the source of pain in some headaches was distended blood vessels, providing the basis for the vascular theory of migraine.

The early work, beginning in the 1930s, of Harold Wolff and his co-workers led to the postulate that the pain of migraine originated in the distended extracerebral arteries [6,7]. They showed that changes in the intensity of migraine headache were closely related to changes in the amplitude of pulsations in the occipital and superficial temporal branches of the external carotid arteries. Factors that decreased the amplitude of pulsations decreased the intensity of headache and vice versa. In some subjects, the headache was temporarily abolished by pressure on the temporal and/or occipital arteries. On the other hand, distention of the temporal artery by increasing experimentally the intramurine hydrostatic pressure resulted in pain. They established that ergotamine tartrate, while diminishing the intensity of migraine headache, simultaneously reduced the amplitude of pulsations of the temporal and occipital arteries by approximately 50%. When the intensity of the pain diminished rapidly the amplitude of pulsations likewise diminished rapidly. When the intensity of the headache diminished slowly, the pulsations decreased slowly. They concluded that the head pain of the migraine attack is produced by the distention of extracranial arteries, and that the termination of the headache by ergotamine tartrate is due to its capacity to constrict extracranial arteries and thus reduce the amplitude of pulsations. Wolff and Tunis showed that prior to the onset of headache, vasoconstriction and increased resistance to blood flow occurs. As the pain develops, there is progressive vascular dilation, hyperaemia, and diminished resistance to blood flow in the relevant vascular bed. They concluded that the extracranial arteries are a major source of pain in migraine [8,9]. They also observed tenderness of the dilated arteries, which suggested that some migraine pain may emanate from the arterial walls [10,11].

Wolff's observations provided a rationale for the use of drugs that relieve migraine pain by reversing vasodilation in the extracranial vascular system, in particular, ergotamine tartrate. [12-14].

Doubts were cast on this theory, though, because migraine was not always relieved by reversing the vasodilation. Recent advances, however, in the understanding of cutaneous allodynia, a sensory abnormality mediated by sensitization of central trigeminovascular neurons in the spinal trigeminal nucleus, may provide a logical explanation as to why vasoconstrictors do not relieve the pain in some patients. The majority of migraineurs seeking secondary or tertiary medical care develop cutaneous allodynia during the course of migraine. Once allodynia has set in, even administration of specifically engineered vasoconstrictors such as the triptans is ineffective [15,16]. Were researchers in Wolff's time aware of the phenomena of central and peripheral sensitization and cutaneous allodynia, the emphasis in migraine research may well have been different.

Instead, a sequence of events occurred which were to focus migraine research since that time almost exclusively on central neurovascular changes. In 1941 Lashley, himself a migraine sufferer, plotted the progress of his own visual aura. He noticed that his scotoma started as a small area, which enlarged progressively, moving toward the periphery of the visual field, and then disappeared. Anatomically, the steady enlargement of the scotoma could not be explained by progressive vasoconstriction of the arterial system, and he postulated that the visual aura was caused by a wave that moved across the surface of the cerebral cortex ant a rate of 2-3mm per minute, like ripples spreading in concentric rings from an initial stimulus [17].

Three years later, Leão described the phenomenon of “spreading depression”. The application of weak faradic or mechanical stimulation to the exposed cerebral cortex in the rabbit elicited a characteristic response which he termed spreading depression. Shortly after the stimulus was applied, spontaneous electrical activity decreased markedly at the stimulated region. This depression then slowly spread in all directions, successively affecting adjacent areas. Recovery required 5-10 minutes in each region. The spontaneous activity at the stimulated region was often well recovered by the time the depression is just starting in distant parts. It appears though, that Leão was more interested in the role of spreading depression in epilepsy, and did not make the connection with migraine aura, as migraine aura was not mentioned in his paper [18].

It was not until 14 years later that Milner suggested that “In view of the correspondence between these observations (of Lashley and Leão) there would seem to be a distinct possibility that migraine scotomas are manifestations of spreading depression triggered off in susceptible individuals. Other symptoms of migraine (tingling in the extremities, nausea, etc.) may be due to spread of depression in other areas of the cortex” [19]. Since the publication of Milner’s article, Leão’s paper was more and more frequently cited, and the postulate that spreading depression may be the initiating factor in migraine began to gain ground, even though most migraineurs never experience an aura of any kind. The neurogenic hypothesis became popular and the pendulum swung away from Wolff’s theories and the extracranial vasculature.

Current understanding of migraine pathophysiology implicates changes in the trigeminovascular system, which is defined as comprising the trigeminal subnucleus caudalis, the trigeminal nerve, and the intracranial arteries [20]. Despite considerable evidence, however, a complete picture of migraine pathophysiology is still in its relative infancy. Whether brainstem dysfunction plays a role as primary generator or as secondary contributor is yet to be determined. [21]

There is an important distinction to be made though, between the primary processes involved in the pathogenesis of migraine, and the possible site or sites of origin of the pain experienced during a migraine attack. In this chapter, compelling clinical, experimental, and pharmacological evidence is presented to suggest that in some patients, part or all of the pain of migraine originates in the terminal branches of the external carotid artery.

Clinical Findings

Digital Arterial Compression

Migraine pain can often be relieved by digital compression of the extracranial branches of the external carotid artery [7,9,22-24,26,35-37]. Hare, in 1905, observed that the pain of headache diminishes in intensity locally when the particular artery supplying the affected region is compressed. Compression of the occipital, superficial temporal or angular arteries relieved the headache over the distribution of the relevant vessel [22]. These findings were later confirmed by Graham and Wolff, who found that "pressure on the temporal artery relieved the pain in the anterior half of the head, and pressure on the occipital artery relieved pain in the posterior half." In four subjects in their series of sixteen, the migraine headache could be abolished completely by mechanical obliteration of the temporal and occipital arteries, suggesting that, at least in some subjects, the major portion of the pain arises from the superficial branches of the external carotid artery [7].

In a study of 63 migraineurs, digital compression of extracranial branches of the ipsilateral external carotid artery during migraine headache reduced or eliminated the pain in 23 (36%). The pain was relieved almost completely (75-100% pain reduction) in 11 patients, and partially in another 12 (50% pain reduction). Drummond and Lance made the incorrect assumption, however, that the pain is extracranial only in cases where occlusion of the ipsilateral superficial temporal artery eliminates the pain [30]. In the remaining 40 patients, who did not obtain relief from compression of the temporal artery, half derived partial or complete relief from compression of the common carotid artery, which led them to conclude incorrectly that in this group, the pain was definitely intracranial in origin. The researchers had omitted to examine the other terminal branches of the external carotid, which may also be the source of pain. [26-29,31-35]

Anatomically, each half of the scalp is supplied by the following arteries: superficial temporal, dividing into frontal and parietal branches, occipital, posterior auricular, angular, supra-orbital, and supra-trochlear. Between these arteries are homolateral as well as heterolateral anastomoses, the latter crossing the midline, and therefore able to supply the opposite half of the scalp. Homolateral and heterolateral intertemporal anastomoses are by far the most numerous, followed by homolateral occipito-occipital [36]. Because of these extensive anastomoses, occlusion of only one superficial temporal artery may not sufficiently reduce blood flow to the painful area to allow resolution of the pain.

A simple bedside test has been described, using the Valsalva maneuver and digital temporal-artery compression, to differentiate between intracranial and extracranial pain in cases of vascular headache. With headache due to vascular dilation, the pain improves during the initial stages maneuver, only to worsen again within 2 to 5 seconds thereafter, gradually settling down to its normal level in 15 to 30 seconds. This occurs with both intracranial and extracranial vascular pain, due to the lowering of the blood pressure resulting from the decreased venous return caused when the Valsalva maneuver is carried out. Once it has been established by this method that the pain is indeed of vascular origin, the test is repeated while the examiner applies digital pressure to obstruct the superficial temporal arteries. In those subjects where the pain does not recur when the Valsalva maneuver is carried out while both the superficial temporal arteries are occluded, it may be concluded that the pain originates in the superficial temporal arteries. In approximately 95% of patients with vascular pain, it can be shown using this technique that the pain originates in the extracranial and not the intracranial vessels [37].

Head Band

Blau and Dexter attempted to prove that the pain of migraine headache was exclusively of intracranial origin, but they actually found that by digital compression of the superficial temporal arteries, and by compression of all the superficial terminal branches of the external carotid by means of an inflated sphygmomanometer cuff, 43% of their subjects experienced pain relief [38].

This finding was confirmed by Vijayan, who used an elastic band secured around the head with Velcro and firm rubber discs inserted under the band to apply local pressure over the area of maximum pain in 23 patients with migraine headache. The band was used in a total of 69 headaches, 3 headaches in each patient. Pain relief was monitored for 30 minutes at 10 minute intervals. Sixty headaches (87%) were relieved. Nine headaches (13%) were not improved. Sixty-seven percent of those who improved (40 headaches) had relief of over 80%, twenty-five percent (15 headaches) improved between 50-60% and eight percent (5 headaches) had less than 50% improvement. Pain severity steadily increased when the band was released. Vijayan concluded that temporary relief of pain from mechanical compression of the scalp supports the hypothesis that at least part of the pain in migraine headache originates from dilated blood vessels in the scalp [32].

At The Headache Clinic in Johannesburg, South Africa, an inflatable cuff is routinely used to diagnose whether the pain originates in the extracranial arteries. It is particularly valuable in those cases where it is not possible to digitally compress all the involved vessels simultaneously. As previously reported, the best results are obtained when the cuff is inflated to 10 mm Hg below the systolic blood pressure with the patient seated. In a sample of 35 patients, 71% had pain relief, in 6% the pain was worse, and in 23% there was no change. When the pressure was increased to 10 mm Hg above the systolic blood pressure, however, only 47% experienced pain reduction, whereas in 18% the pain was worse, and 35% experienced no change [29].

The difference may be due to the increased pressure exerted on potentially tender scalp tissues, including skin, blood vessels, and muscles. Local pain threshold is decreased during migraine headache [10], and the development of cutaneous allodynia [39] may also complicate the diagnosis in some cases.

Prolonged Compression

A total of 94 patients were studied during a migraine attack. The pain was moderate in 58 cases, and severe in 36. Digital compression of the superficial temporal and/or the occipital arteries for a prolonged (at least 3 minutes) period was carried out, to establish whether migraine attacks could be aborted. Overall, 65% of patients obtained relevant or complete and enduring pain relief. In those subjects with moderate pain, the percentage increased to 90%. Sham artery compression never resulted in pain reduction. The authors concluded that prolonged compression of the occipital and/or superficial temporal arteries is efficacious in reducing or eliminating migraine pain [31].

Temporal Artery Massage

Lipton reported that migraine headaches could be prevented in patients suffering from migraine with aura. His technique consists of vigorous bilateral compression and massage of the frontal branches of the superficial temporal artery, using the second and third fingers. To be effective, the massage has to be started at the first sign of the visual aura, and must be continued until the aura has completely subsided. It is important that the massage be performed continuously and not be interrupted during the aura. The technique was successful in blocking 34 of 42 attacks (81%) in 15 patients [35].

Experimental Evidence

Pulsation Amplitude of the Temporal Artery

Migraineurs often describe the nature of their pain as pulsating. This and the often visible distension of the temporal vessels were the first indications that the extracranial vessels may be involved in migraine pain. Graham and Wolff demonstrated a positive correlation between the amplitude of pulsation of the branches of the external carotid artery and the intensity of the migraine headache [7]. Further studies showed that during a migraine attack, the mean pulse-amplitude of the frontal branch of the superficial temporal artery was twice that of normal controls [11].

Heyck [40] was unable to repeat Graham and Wolff's experiments and in the light of this Blau concluded that "there is no relationship between the temporal artery pulsation and the presence or absence of headache" [41]. Heyck's failure to confirm Graham and Wolff's findings may well have been due to the considerable technical difficulty in obtaining reproducible pulse recordings from scalp vessels. Nevertheless, although they did not confirm the previous findings, neither did their study offer evidence that Graham and Wolff were wrong.

Brazil and Friedman [42] were, however able to confirm the earlier findings of Graham and Wolff, and of Wolff and Tunis. They recorded the amplitude of pulsation of temporal, occipital, and supra-orbital arteries in 76 patients with migraine headache. Each patient was then administered 1cc. of dihydroergotamine intravenously, and of these 69 (91%) showed pulse wave changes of diminished amplitude and simultaneously experienced diminution of the headache that had been present. Based on these observations, they were able to confirm that there are indeed changes in the extracranial arteries during migraine attacks in a significant number of patients.

It was also shown that the temporal pulse diminished in amplitude by 12% to 84% in migraineurs as they stood up from lying down, while only minor changes (9% to 13%) took place in normal subjects [43]. Following exercise, the temporal artery on the affected side in migraineurs dilates more than on the headache-free side [44].

Luminal Diameter of the Superficial Temporal Artery

In the studies cited in the previous section pulse amplitude and not luminal size was measured. This increase in pulse amplitude could possibly be the result of intramural oedema of the arterial wall, and not necessarily be due to dilation of the lumen. Oedema of the adventitia of the superficial temporal artery has indeed been described in biopsies taken during migraine attacks [45].

Later studies confirmed, however, that the luminal diameter at least of the frontal branch of the temporal artery does indeed increase during migraine attacks. When measured with high resolution ultrasound, the luminal diameter of the frontal branch of the superficial temporal artery was found to be significantly larger during headaches on the symptomatic side than on the non-symptomatic side [34].

The extent to which the observed increase in pulse amplitude of the superficial scalp vessels is predominantly caused by oedema or by increased luminal diameter or both remains undecided. What is clear, however, is that there are observable and measurable changes in these vessels during migraine attacks.

Temoral Artery Regulation with Biofeedback

One of the methods of biofeedback that has been shown to be effective in reducing both the frequency and the intensity of migraine is self-regulation of vasomotion of the superficial temporal artery. A one-year follow-up on 16 chronic migraine patients treated with vasoconstriction biofeedback of the temporal arteries showed decreased frequency, duration and intensity of headaches, as well as amount of medication from baseline to the one-year follow-up [46]. These results were confirmed by later studies, which showed that clinically meaningful headache reductions could be achieved and maintained at follow-up. Interestingly, results showed that constriction and dilation biofeedback were equally effective in controlling migraines and produced greater benefits than untreated controls [47-49]. Although the results of temporal artery self-regulation are good, equally good results are achieved with thermal biofeedback. As thermal biofeedback is easier to teach and more practical for patients, temporal artery self-regulation is no longer widely used [50].

Increasing Intracranial Pressure

Based on the assumption that intracranial arteries, by virtue of their location within the skull, can be compressed by the extramural support provided by increasing intracerebral pressure, Schumacher and Wolff devised a method of rapidly increasing cerebrospinal fluid pressure by connecting the subarachnoid space with a high column of sterile physiological saline. This would result in diminution of their amplitude of pulsation, thus diminishing headache. [8]. The column could be raised or lowered to increase or decrease cerebrospinal fluid pressure. In headache due to dilation of cranial arteries, pain reduction when cerebrospinal fluid pressure is increased, indicates the intracranial arteries to be the origin of the pain. On the other hand, no reduction in pain intensity indicates the pain to originate extra-cranially. They studied two groups of patients: one with migraine headache and the other with histamine-induced headache.

As a background to the experiments on migraine, a control group of patients with histamine induced headache was used. It had been previously established that intracerebral arteries, particularly the internal carotid, vertebral, and basilar arteries, and the proximal portions of their branches, are the primary sites of origin of pain in histamine headache. In the eleven patients with histamine-induced headache, the pain was relieved within 15 to 90 seconds of raising the intracranial pressure. In seven of these, there was a constant relationship between increasing or decreasing the cerebrospinal fluid pressure and the intensity of the headache. The subjects always experienced a recurrence of the pain following a rapid reduction of the pressure. The headache was relieved when the intracranial pressure was increased by an average of 350 mm H_2O.

In six out of seven subjects with migraine headache, however, no change in pain intensity occurred, even when the cerebrospinal fluid pressure was increased to as high as 700 to 1000 mm H_2O for up to 30 minutes. In one subject, there was reduction in headache intensity, but the authors suggested that this was possibly due to a spontaneous resolution of the headache. Other patients had previously experienced spontaneous resolution of their pain while waiting for the experiment to be carried out, but it is possible that in this subject the pain was indeed intracranial. They concluded that: 1) The pain of histamine-induced headache originates from the intracranial vessels; 2) The pain of migraine headache originates in the extracranial vessels.

Inflatable Head Cuff

Blau and Dexter, in an attempt to prove the intracranial origin of migraine pain, used a specially designed sphygmomanometer cuff, fitted around the head and inflated to 10 mm Hg above the patient's systolic blood pressure for 20 seconds, to occlude the extracranial arteries in 49 patients with migraine headache [38]. Contrary to their expectations however, they found that in 28 (57%) of the 49 patients tested, there was an extracranial element to the pain.

Preliminary results of a similar study carried out at The Headache Clinic in Johannesburg indicate that the best results are obtained, when the cuff is inflated to 10 mm Hg below the systolic blood pressure with the patient seated. In a sample of 35 patients, 71% had pain relief, in 6% the pain was worse, and in 23% there was no change. When the pressure was increased to 10 mm Hg above the systolic blood pressure, however, only 47% experienced pain reduction, whereas in 18% the pain was worse, and 35% experienced no change. The difference may be due to the increased pressure exerted on potentially tender scalp tissue, including blood vessels and muscles. Also, local pain threshold is decreased during migraine headache [10], causing cutaneous allodynia [51].

There is no certainty though, that in patients who still have pain when the cuff is applied, the pain is indeed from an intracranial source. The inflatable cuff only compresses the extracranial arteries and not, for example, the internal maxillary artery, also a branch of the external carotid artery, and its branch, the middle meningeal artery. It remains a possibility that some of the patients without relief from the inflatable cuff are experiencing pain from these deeper branches of the external carotid artery, or may have pain related to non-vascular mechanisms, such as cutaneous allodynia.

Intracranial Vascular Tests

Blau and Dexter used three "intracranial" tests to determine whether the pain of the migraine headache was intracranial in origin. The tests were: 1) Breath holding in mid-inspiration for 30 seconds; 2) Head jolt – subjects rotated the head three times rapidly from side to side through 180^0; and 3) Coughing – patients were asked to give three vigorous coughs. In 49 of the 50 subjects that took part in the study, one or more of the above tests exacerbated the pain. They concluded that these 49 patients had pain of intracranial origin [38]. However, their assumption that the tests only affected the intracranial and not the extracranial vasculature is not logical. They clearly did not take into account the fact that performing any of these maneuvers would have the same effect on all the cranial blood vessels, extracranial as well as intracranial, as was demonstrated by Louis [37]

Functional Neuroimaging

Intracranial Blood Flow

The changes in intracranial haemodynamics during migraine with aura, demonstrated with functional imaging techniques such as ^{133}Xenon inhalation, ^{133}Xenon intra-arterial injection, single photon emission computed tomography (SPECT), and positron emission tomography (PET) are an initial brief hyperperfusion [52-54], followed by hypoperfusion (corresponding approximately with the aura) [52,54,55-61], and then a prolonged period of cerebral hyperperfusion [53,55,59]

If the headache were related to dilation of cerebral arteries, then it could be reasonably expected that the pain would coincide with the final phase of hyperperfusion. This is not always true. Often the headache actually coincides with the oligaemic phase [52-54], and may also subside long before the hyperaemic phase is over [62]

In migraine without aura, there is either no change in CBF during attacks, [53,58,61,63], or it is reduced, depending on the method used. All studies using PET show reduced blood flow [64,65] which may persist for up to 24 hours after the onset of the headache [66].

Extracranial Blood Flow

A positive correlation between the amplitude of pulsation of the branches of the external carotid artery and the intensity of the migraine headache was first demonstrated by Graham and Wolff [7]. The mean pulse-amplitude of the frontal branch of the superficial temporal artery was twice that of normal controls [11]. It was also shown that the temporal pulse diminished in amplitude by 12% to 84% in migraineurs as they stood up from lying down, while only minor changes (9% to 13%) took place in normal subjects [43]. Following exercise, the temporal artery on the affected side in migraineurs dilated more than on the headache-free side [67]. The luminal diameter of the frontal branch of the superficial temporal artery, measured with high resolution ultrasound, is significantly larger on the symptomatic side than on the non-symptomatic side, during but not between headaches [34].

The frontotemporal area is supplied by the frontal branch of the superficial temporal artery. In studies on migraineurs that were carried out using the tissue clearance method of the

isotope Na^{24} to measure frontotemporal blood flow, asymptomatic patients exhibited blood flows similar to those of normal control subjects, but during the headache phase, there was increased blood flow. Scalp blood flows were increased on both sides of the head in an attack of unilateral migraine compared to those of the same subjects when asymptomatic; but the increase was greater on the side of the headache than on the contralateral side [68].

Sakai and Meyer, using the ^{133}Xe-inhalation method to measure extracranial blood flow, found it to be increased during migraine headache, subsiding rapidly just as the headache subsides [62,69].

Trigeminal Ganglion Stimulation

The innervation of the cranial vessels by the trigeminal nerve, the trigeminovascular system, has been the subject of study in view of its possible role in the mediation of some aspects of migraine [70].

The trigeminal ganglion of anesthetized paralysed artificially ventilated Macaca nemestrina monkeys was electrically stimulated with frequencies varying from 0.2 to 200 Hz. This stimulation led to a frequency-dependent decrease in external carotid resistance but no significant change in internal carotid resistance was recorded [71]. Neither the dilator nor constrictor responses were affected by sectioning of the vagus nerve or sympathetic trunk in the neck. The simultaneous occurrence of intracranial vasoconstriction and extracranial vasodilatation bears a remarkable resemblance to the vascular changes of migraine [72].

In humans, when the trigeminal ganglion is activated by thermocoagulation during the treatment of trigeminal neuralgia, blood samples taken from the external jugular vein show elevation of plasma levels of calcitonin gene-related peptide (CGRP) [73]. Since stimulation of the trigeminal ganglion in humans leads to facial pain and flushing and associated release of powerful neuropeptide vasodilator substances, their local release into the extracerebral circulation of humans was determined in patients who had either common or classic migraine. Plasma levels of neuropeptide Y, vasoactive intestinal polypeptide, substance P, and calcitonin gene-related peptide were determined using sensitive radioimmunoassays for each peptide. A substantial elevation of the calcitonin gene-related peptide level in the external jugular blood was seen in both classic and common migraine. The increase seen in classic migraine was greater than that seen with common migraine. The other peptides measured were unaltered [70].

Pharmacological Evidence

Ergotamine

In 1925, a Swiss chemist by the name of Rothlin isolated ergotamine, which became the preferred medication for migraine [74]. Subsequently, the ergotamine preparations have been used in migraine abortive therapy for several decades. These drugs are classified as vasoconstrictors that specifically counteract the dilation of some arteries and arterioles, including branches of the external carotid artery [75-78]. Dihydroergotamine (DHE) is a

potent constrictor of the extracerebral arteries in humans, [79], but it has no demonstrable effect on cerebral blood flow (CBF). [80]

The efficacy of ergotamine in terminating migraine headache [12-14] provided the opportunity to study changes in the pulsation amplitude of the superficial temporal and occipital arteries before and after successful treatment. Graham and Wolff, using intravenous ergotamine, found that the "amplitude of pulsations declined with the diminishing intensity of the headache. When the amplitude of pulsations decreased slowly, headache likewise diminished slowly. When the amplitude dropped precipitously, the headache was ended promptly" [7]. They concluded that "the head pain of the migraine attack is produced by the distension of the cranial arteries and that termination of the headache by ergotamine tartrate is due to the capacity of this agent to constrict these cranial arteries and thus reduce the amplitude of their pulsations". These conclusions were confirmed in later studies on the extracranial arteries using dihydroergotamine [42].

Although ergotamine and dihydroergotamine cause vasoconstriction of the extracranial arteries, they do not affect cerebral blood flow [58,76,81,82], even when effective in abolishing migraine headache [77,83]. On the contrary, when the migraine pain is relieved with ergotamine tartrate, there is an associated reduction in scalp blood flow [55].

The conclusion that the therapeutic effect of ergotamine depends on its ability to produce extracranial vasoconstriction led to experimentation with other vasoconstrictors. Administration of ergonovine, caffeine, benzedrine, ephedrine, and pitressin all resulted in reduction of migraine headache, commensurate with a reduction in the pulsation amplitude of the superficial temporal artery, but only when the pulsation amplitude was diminished to a degree comparable with that produced by ergotamine tartrate, i.e., 40-50%. If the reduction of pulsation amplitude was only 20-25%, the intensity of the headache was not lessened. [84]

BIBN4096BS

The pain of migraine is believed to be associated with activation of the trigemino-vascular system and dilation of cranial blood vessels [85-87] Calcitonin gene-related peptide (CGRP) is a neuropeptide found in the perivascular nerve terminals surrounding arteries [88], and is one of the most potent endogenous vasodilators known [89]. Infusion of CGRP can trigger a migraine attack [90], and during a migraine attack, CGRP levels are increased. As CGRP has been implicated in the pathogenesis of migraine headache, [91,92] inhibition of CGRP-induced vasodilation could be expected to attenuate migraine symptoms [93]

In an international, multicentre, double blind, randomized clinical trial of the CGRP receptor antagonist BIBN4096BS, involving 126 patients, BIBN4096BS was effective in treating attacks of migraine, and was significantly superior to placebo (P=0.001) [94].

Large temporal and occipital arteries are surrounded by an extensive meshwork of nerve fibres containing CGRP [95], and BIBN4096BS significantly inhibits CGRP-induced headache and temporal artery vasodilatation, but it does not significantly affect the concomitant CGRP-induced middle cerebral artery vasodilation [96]. The middle meningeal artery has only a sparse supply of CGRP-containing nerve fibres [97], and is consequently also unlikely to be the site of action of BIBN4096BS.

It seems logical to conclude, therefore, that the origin of the pain in migraine is more likely to be from extracranial vessels such as the superficial temporal and occipital arteries, than the middle meningeal or middle cerebral arteries.

Conclusion

Although the pathogenesis of migraine remains poorly understood, current theories suggest a primary, possibly genetically influenced, central nervous system dysfunction to be involved [98]. There is activation of the trigeminovascular system, which is comprised of the intracranial vessels, the trigeminal nerve, and the trigeminal nucleus [99], in particular the trigeminal subnucleus caudalis [100]. The trigeminovascular system, by definition, does not include the superficial extracranial branches of the external carotid artery. In spite of possessing the most modern state of the art technology, scientists have been unable to correlate changes in the intracranial arterial systems with the development of the pain in migraine. Conversely, changes in the extracranial vasculature during migraine have been measured repeatedly and correlate with pain levels. If a phenomenon can be measured it is a fact; if it can't be measured, then it remains an opinion.

There is an important distinction to be made though, between the primary processes involved in the pathogenesis of migraine, and the possible site or sites of origin of the pain experienced during a migraine attack. In this chapter, compelling clinical, experimental, and pharmacological evidence has been presented to support the view that in some patients, part or all of the pain of migraine originates in the terminal branches of the external carotid artery.

Given the weight of evidence presented above, it would seem inconceivable that many headache experts still doggedly maintain that the extracranial vessels are not involved in migraine pain. The widely held view that the vascular pain in migraine emanates from the intracranial arteries to the exclusion of the extracranial vessels has never been substantiated by scientific investigation. This view has been so attractively presented, so often repeated, and so peopled with prestigious champions that its basic error has eventually come to be perceived as truth.

Despite the availability of many partly successful therapies, most migraineurs remain outside the medical system, suffering significant disability attributable to their disease. There is a large reservoir of patients who could benefit by proper diagnosis and management of headache, but until the headache community accepts that the extracranial arteries are a major source of pain in migraine, efforts to develop more effective treatment modalities can at best be only partly successful.

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