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Journal of Neural Transmission
Basic Neurosciences, Genetics and Immunology, Movement disorders, Dementias, Biological Psychiatry, Biological Child and Adolescent Psychiatry

ISSN 0300-9564
Volume 118
Number 4

J Neural Transm (2011)
118:525-530
DOI 10.1007/
s00702-010-0517-1

Springer

J Neural Transm (2011) 118:525–530
DOI 10.1007/s00702-010-0517-1

MOVEMENT DISORDER - CONY PRO/CON DEBATE

The extracranial vascular theory of migraine: an artificial controversy

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Received: 14 July 2010 / Accepted: 19 October 2010 / Published online: 5 January 2011

Abstract Over the years there has been a considerable amount of controversy over whether the vascular component of migraine pain arises from the intracranial or the extracranial vessels, or both. Some have even questioned whether vasodilatation actually plays a significant role in migraine pain, and have described it as an unimportant epiphenomenon. The controversy is an artificial one though, which has been generated as a consequence of misrepresentation of the facts in the headache literature. In this review, some of the more blatant distortions in the literature are exposed.

Keywords Migraine · Extracranial · Intracranial · Arterial · Vasodilatation

Introduction

In recent years, researchers have been able to elucidate some of the changes that occur in the cascade of events that leads to migraine attacks. The understanding of changes such as central sensitization (McMahon et al. 1993; Cumberbatch et al. 1999; Woolf and Salter 2000; Goadsby and Bartsch 2008), peripheral sensitization (Selby and Lance 1960; Hoheisel and Mense 1989; Dubner 1991, 1992; Strassman et al. 1996; Burstein et al. 1998), cutaneous allodynia (Wolff et al. 1953; Tunis and Wolff 1954; Gracely et al. 1992; Cumberbatch et al. 1999; Burstein et al. 2000), and the influence of genetic factors (Russell and Olesen 1995; Russell et al. 1996), has brought us nearer to unravelling the pathophysiology of migraine, but researchers have been hampered because a major element has been forgotten, ignored, and even actively suppressed.

Harold Wolff and his co-workers were the first to subject the phenomenon of vasodilatation to rigorous scientific testing. Wolff's vascular theory of migraine consisted of two elements: (1) that intracranial vasospasm causes cortical spreading depression (CSD), and (2) that extracranial vasodilatation causes migraine pain. The first part of Wolff's vascular theory was discredited by Olesen and the Copenhagen group, who found that the pattern of spread of CSD did not conform to the anatomical boundaries of the major cerebral blood vessels (Olesen et al. 1981), so vasospasm could not account for CSD. This research by Olesen did not, however, contradict the second part of Wolff's theory—that migraine pain could be caused by extracranial vasodilatation. It is only the second part of Wolff's theory that is discussed here.

It is apparent that there has been a concerted attempt to suppress the established facts—a prime example of this is an article by Professor Peter Goadsby that was recently published in *Brain*, entitled 'The vascular theory of migraine—a great story wrecked by the facts' (Goadsby 2009a, b). There are a number of instances in this highly misleading article where Goadsby has incorrectly cited references in an attempt to repudiate Wolff's work—references which not only have no relevance to Wolff's theory, but also in some instances actually confirm that Wolff was correct. Not only does Goadsby fail to provide evidence to support his claim that 'dilation is not a part of the migraine process' (Goadsby 2009a, b), but also some of the references that he uses to support his viewpoint in fact prove the exact opposite! This article exposes the logical inconsistencies and incorrect conclusions reached by Goadsby, and questions how references that prove that

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something is 'white' can be cited in the medical literature in an attempt to prove that it is 'black'. It is a bizarre state of affairs indeed, and demands an explanation.

There should in fact be no controversy regarding the role of vasodilatation in migraine—opinions and hypotheses may well be controversial, but observable and measurable scientific facts cannot be controversial. There is a plethora of irrefutable evidence to show that not only does vasodilatation plays a role in migraine pain, but also that this dilatation is extracranial and not intracranial. This evidence has been extensively documented elsewhere (Shevel 2011). Unfortunately for countless migraine sufferers around the world this information has been largely forgotten, and, as is shown below, actively suppressed.

The making of an artificial controversy

To illustrate the extent of the misinformation in the literature regarding the second part of Wolff's theory, reference will be made to Goadsby (2009a, b) article 'The vascular theory of migraine—a great story wrecked by the facts', published in *Brain* (Goadsby 2009a, b). Although in this article Goadsby claimed that the vascular theory has been wrecked, he failed to distinguish between the intracranial and the extracranial vasculature. Not a single shred of the evidence presented by him to support his claim has any bearing at all on Wolff's measurements concerning extracranial vascular pain as a vital component of the migraine process. In spite of this total lack of evidence, Goadsby clearly and specifically included Wolff's theory of extracranial vascular pain as having being 'wrecked'.

Graham and Wolff (1938) proved that ergotamine-induced changes in the terminal branches of the external carotid artery were closely correlated to both the severity and timing of the pain in migraine, findings that were later confirmed by Brazil and Friedman (1955) using dihydroergotamine, and again by Sakai and Meyer (1978).

In his article though, Goadsby cited research carried out by Olesen and the 'Copenhagen Group' in an attempt to refute Graham and Wolff's findings. He wrote 'vascular changes are unrelated to the phase of the attack, indeed blood flow could be reduced or normal during the pain phase' (Goadsby 2009a, b). The Copenhagen Group indeed found that changes in intracranial regional blood flow (rCBF) were unrelated to the severity and timing of migraine pain (Olesen et al. 1990)—but this study of the Copenhagen Group had no relevance to Wolff's extracranial vasodilatation research data. Graham and Wolff studied the superficial temporal and occipital terminal branches of the external carotid arteries (Fig. 1), while Olesen's group studied rCBF (Fig. 2)—two different and totally unrelated anatomical structures!

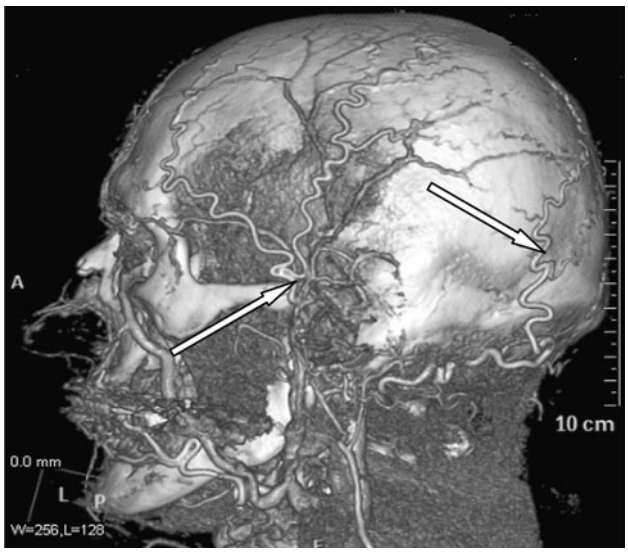

Fig. 1 CT angiogram showing the superficial temporal and occipital arteries which form the basis of Wolff's theory of extracranial vascular pain

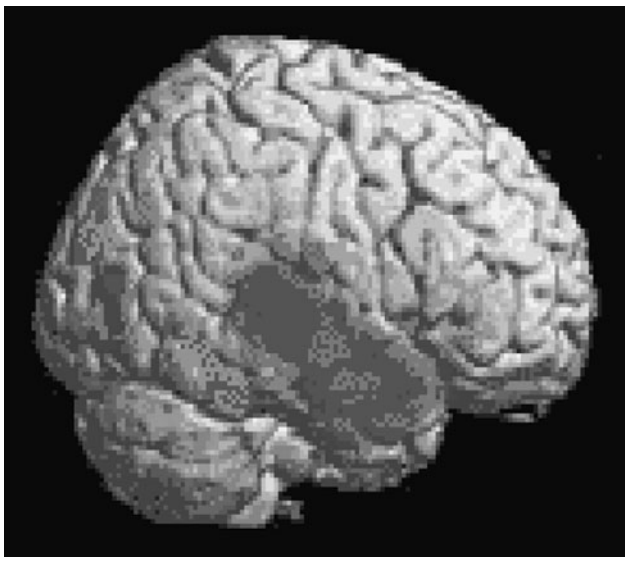

Fig. 2 Olesen studied the rCBF

This use of totally unrelated research conducted on different parts of the body to discredit Wolff's data is by no means an isolated incident—Goadsby has repeatedly used this reference of Olesen's to undermine Wolff's work on the extracranial vasculature (Goadsby 2006, 2009a, b; Goadsby et al. 2009). The use of the Copenhagen Group's observations on intracranial blood flow in an attempt to discredit Graham and Wolff's observations on the extracranial vasculature is at best gross negligence and at worst deliberately and fraudulently misleading.

The second misrepresentation in Goadsby's article concerns the findings of Schoonman et al. who were able

for the first time to directly and accurately measure the diameters of most of the major intracranial and some of the extracranial vessels, both during migraine and interictally, and on left and right sides during unilateral migraine. Their study showed that none of the vessels measured dilated during migraine (Schoonman et al. 2008). Goadsby subsequently claimed that Schoonman et al.'s research showed that migraine occurs without any change in, inter alia, the extracranial vessels. However, Schoonman et al. measured the diameter and blood flow of the intracranial vessels, including the internal carotid, middle cerebral, basilar, and posterior cerebral arteries, and extracranially the middle meningeal and the last 1 cm of the main trunk of the external carotid artery proximal to its splitting into its terminal branches (Fig. 3). They concluded 'In contrast to widespread belief, migraine attacks are not associated with vasodilatation of the cerebral or meningeal blood vessels.' Schoonman et al. made no mention of the terminal branches of the external carotid artery (Fig. 1), on which Wolff's research was conducted, as these vessels were not included in Schoonman's study.

To use Schoonman's study as justification for claiming that the terminal branches of the extracranial vessels are not involved in migraine is an absurdity based in fiction. The only thing that Schoonman disproved is the theory that Goadsby previously enthusiastically embraced for the better part of a decade—that the intracranial vasculature, as part of the trigeminovascular system, is involved in migraine pain. The section of the external carotid artery that Schoonman measured was never implicated in migraine by Wolff nor by anyone else—Wolff's research concerned that the part of the external carotid tree that Schoonman did not measure (Fig. 1). This surely warrants a retraction by Goadsby—allowing such a statement to stand will perpetuate this perversion of science with potentially disastrous consequences for millions of migraine sufferers.

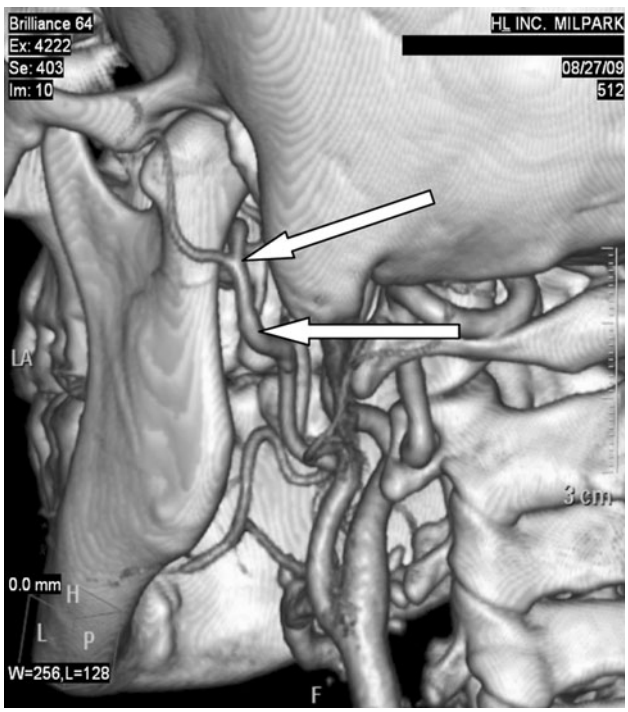

Fig. 3 The 1 cm section of the external carotid that Schoonman et al. (2008) measured, proximal to its bifurcation into its maxillary and superficial temporal terminal branches

The third serious misrepresentation concerns Goadsby's ludicrous claim, that BIBN4096BS is 'without vascular effects'. It has indeed been shown that BIBN4096BS is not an active vasoconstrictor of normal arteries (Petersen et al. 2005a), but that is completely different from being without vascular effects in the context of migraine. Goadsby has carried out extensive research on both CGRP and BIBN4096BS (Goadsby and Edvinsson 1994; Olesen et al. 2004; Storer et al. 2004; Goadsby 2005), and cannot claim to be ignorant of the vasoactive properties of BIBN4096BS on abnormally dilated migrainous blood vessels.

To substantiate his claim that BIBN4096BS is 'without vascular effects', Goadsby cited Petersen et al. (2005b). Petersen's article clearly states though, that BIBN4096BS is 'very effective in preventing CGRP-induced vasodilatation'. How can the scientific world and the medical community allow the use of a study that proves that BIBN4096BS is vasoactive in migraine, to be used to reference the exact opposite in a prominent peer reviewed journal like *Brain*?

CGRP is a potent vasodilator (Brain et al. 1985; McCulloch et al. 1986) and is elevated in migraine (Goadsby and Edvinsson 1994; Goadsby 2005). BIBN4096BS is a potent CGRP antagonist developed specifically to reverse the vasodilatation caused by the increased CGRP levels during migraine (Doods 2001). It is quite correct that because BIBN4096BS does not constrict normal vessels it may be safer than the triptans, but to claim that it is 'without vascular effects' in the context of migraine is a blatant contradiction of the scientific facts.

This is not an isolated occurrence. Goadsby has misrepresented Petersen's results on at least three occasions in 2009 alone (Goadsby 2009a, b; Goadsby et al. 2009). This begs the question—was this misrepresentation purely a mistake on Goadsby's part, or it was deliberate? If it was a mistake, then Goadsby should retract this unsubstantiated and misleading claim—if it was deliberate, then it is incumbent upon him to explain.

The reader's attention is further directed to the fact that BIBN4096BS completely inhibits CGRP-induced dilatation of the terminal branches of the extracranial vasculature, and more specifically, of the superficial temporal artery. This is

neither theory nor unsubstantiated speculation—it is proven scientific fact (Verheggen et al. 2002; Petersen et al. 2005b).

In the fourth serious misrepresentation in the same article Goadsby stated 'Triptans … have been known for some time to have effects on neuronal transmission in the brain' (Goadsby 2009a, b). What Goadsby neglected to mention is that in the study that he quoted in support of this statement, the administration of sumatriptan did not alter trigeminal evoked activity at all unless the permeability of the blood–brain barrier (BBB) had first been chemically damaged with mannitol (Kaube et al. 1993). Nor does he mention that the subjects in this reference were anaesthetized cats. As a co-author of the cited reference Goadsby could hardly have been unaware that it concluded "The data suggest that in normal circumstances (i.e., with an undamaged BBB) sumatriptan does not have sufficient access to trigeminal neurons to alter their function"—in other words, sumatriptan does not have an effect on neuronal transmission in humans with migraine.

That the human BBB remains intact during migraine has been confirmed in a comprehensive review published in *Cephalalgia*. The authors concluded that 'there exists no clear proof of breakdown or leakage of the BBB during migraine attacks' (Edvinsson and Tfelt-Hansen 2008). Goadsby was no doubt aware of this article, as he was Editor-in-Chief of the Cephalalgia at the time it was published.

That sumatriptan affects neuronal transmissions in the brains of anesthetized cats with chemically damaged BBB's is hardly relevant when discussing its mechanism of action in human migraineurs with intact BBBs, through which it do not pass. Goadsby's reference, if presented without omissions and misrepresentations, instead of supporting his unproven hypothesis that the triptans act centrally, actually proves exactly the opposite—that the triptans cannot and do not act by affecting neuronal transmission in the brain. Once again, the data that Goadsby quoted in support of his preferred theory clearly proved the exact opposite—only this time the study referred to was co-authored by Goadsby himself.

What has, however, been shown with respect to the triptans, is that they potently constrict human temporal arteries (Jansen et al. 1992)—in humans with migraine that is. What is even more astounding, given Goadsby's repeated and strident opposition to Wolff's extracranial vascular theory is that Goadsby has himself proven that the relief of migraine pain with triptans coincides with the reduction of CGRP levels in the extracranial blood (Goadsby and Edvinsson 1993).

The factual distortions outlined above are from a single two-page article—and these are only the more blatant distortions in the article. The effects of this misinformation are especially damaging given that the author is such a respected high-profile figure amongst migraine researchers and clinicians—people tend unquestioningly to accept the word of their influential peers. The understanding of migraine pathogenesis has been set back by years as a result, and it is vital that the scientific community devise measures to prevent this from happening again. Naturally no system is fool-proof, so it is equally important to have the courage to take the appropriate steps to reverse the inestimable damage that can be caused when science is distorted.

Discussion

Despite the existence of a great deal of verifiable experimental evidence to support Wolff's view that extracranial vasodilatation is a source of pain in migraine (Shevel 2011), many headache specialists are either unaware of the true facts or for some other reason just refuse to accept the evidence (Blau and Dexter 1981; Goadsby 2009a, b; Tfelt-Hansen and Le 2009; Brennan and Charles 2010). The publication of misleading information, such as that detailed above, has no doubt contributed to this sorry state of affairs. Regrettably, when such misleading information is published in reputable journals, especially by acknowledged 'experts' in the field, the possibility is that it becomes cited by others, and subsequently becomes entrenched in the current body of knowledge and eventually becomes accepted as 'fact'. Is this perhaps why the Education Committee of the American Headache Society has decreed that all mention of Wolff's vascular theory of migraine be omitted from the curriculum for American Medical students (Young et al. 2007)? One can understand their decision to omit the first, disproven part of Wolff's theory concerning CSD, but to actively discourage the teaching of the second part, despite all the evidence, flies in the face of logic. They have in effect thrown out the proven, factual baby with the disproven and discredited bathwater. It is also rather sad to note that all reference to Wolff's theory of extracranial vasodilatation has been expunged from recent editions of 'Wolff's Headache and Other Head Pain' (Wolff 2001). Is this, one wonders, also a consequence of the repeated disinformation?

Goadsby's previously preferred theory—that the intracranial vasculature (the vascular component of the trigeminovascular system) is involved in migraine—has indeed been wrecked by the facts, but these same facts do not apply to Wolff's theory and the extracranial terminal branches of the external carotid artery, which are without any shadow of doubt involved in the complex cascade of events that terminates in a migraine attack (Graham and Wolff 1938; Pickering 1939; Sutherland and Wolff 1940; Schumacher and Wolff 1941; Tunis and Wolff 1952; Tunis

and Wolff 1953; Wolff et al. 1953; Tunis and Wolff 1954; Brazil and Friedman 1955; Wennerholm 1961; Elkind et al. 1964; Hachinski et al. 1978; Sakai and Meyer 1978; Sakai and Meyer 1979; Blau and Dexter 1981; Drummond and Lance 1981; Louis 1981; Mikkelsen et al. 1981; Drummond and Lance 1983; Lipton 1986; Andersen et al. 1987; Goadsby et al. 1988, 1990; Iversen et al. 1990; Lisspers and Ost 1990; Jansen et al. 1992; Goadsby and Edvinsson 1993; Vijayan 1993; Edvinsson and Goadsby 1994; Farmer 1995; Olesen et al. 1995; Verheggen et al. 2002; Stepien et al. 2003; Shevel and Spierings 2004; Juhasz et al. 2005; Petersen et al. 2005b; Durham 2006; Shevel 2007a, b; Olesen et al. 2009).

Summary

It is difficult to see how the subject of extracranial arterial involvement in migraine pain remains mired in controversy. There is compelling evidence that shows that the terminal branches of the external carotid artery are most certainly involved in migraine pain. In addition to this evidence, the fact that the most widely used migraine rescue drugs have one thing in common—while reducing migraine pain they simultaneously constrict the dilated extracranial arteries—is confirmation that arterial dilatation is important in migraine. This is not only true of the drugs commonly used at present, i.e., the ergots and the triptans, but also of the gepants, the most promising new anti-migraine drugs being developed. It is equally significant that to date, all migraine-provoking agents have had vasodilating properties. As it has been shown that intracranial vasodilatation is not involved in migraine, the only arteries that can be affected are extracranial. Indeed, it is not Wolff's vascular theory of migraine that has been 'wrecked by the facts'—no amount of obfuscation, omission, misrepresentation, or distortion can obscure the facts. The extracranial vascular theory of migraine as espoused by Wolff is alive and well. Alas, what appears to have been wrecked instead is the unbiased and objective quest for scientific truth and accuracy.

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