Review

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The autonomic nervous system and the regulation of arterial tone in migraine

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Abstract

Abnormal regulation of the large cranial arteries seems to play a significant role in the mechanisms of migraine pain. Thus, vasodilatation of extra- and intracranial conductance arteries has been described both during spontaneous migraine attacks and during experimentally provoked vascular headaches. The regulation of the diameter of these arteries is complex and involves autonomic, trigeminovascular, endothelial and humoral mechanisms. Studies concerned with the function of the autonomic nervous system in migraine suggest that a mild parasympathetic dysfunction may be present. Cerebral arteries in migraineurs are hypersensitive to nitric oxide, which may induce migraine attacks. As the enzyme responsible for nitric oxide synthesis is present in parasympathetic nerve endings around cerebral arteries, this supports a role for the parasympathetic nervous system in migraine. In addition, vasoactive transmitters released from perivascular trigeminal nerve endings may be implicated. Several of these aspects are closely linked to the presumed mechanisms of action of modern migraine therapeutics.

Keywords: migraine; sympathetic; parasympathetic; nitric oxide

Introduction

Migraine affects approximately 16% of the adult population.[1] There are two main types of migraine: migraine with aura and migraine without aura.[2] In migraine with aura, the aura consists of 'marching' neurological symptoms which typically affect vision, speech, the sensory and/or motor systems, either alone or in combination. Apart from these aura symptoms, the attacks are the same as in migraine without aura and the pain phase is likely to involve the same mechanisms in both forms.[3] The characteristic spreading regional blood flow changes (rCBF) observed during the aura are probably secondary to the neurophysiological phenomenon called cortical spreading depression (a depolarization of neurons and glial cells that spreads slowly across the cortical surface).[4,5] Thus, the primary mechanism of the migraine aura is likely to be neural rather than vascular. The site of nociception in migraine is almost certainly the perivascular space around large cranial arteries, where nociceptors are activated. Dilatation of extra- and intracranial conductance arteries has been demonstrated both during spontaneous migraine attacks and during experimentally provoked vascular headaches and represents one potential mechanism of nociception.[6–11] Because of the vascular nature of migraine pain it is relevant to examine the role of the autonomic nervous system in its pathogenesis. This review pays particular attention to studies of autonomic function in migraine, but the trigeminal system and mechanisms of modern migraine therapy are also discussed.

Innervation of cranial arteries

The cranial arteries are surrounded by a network of perivascular nerves of sympathetic, parasympathetic and trigeminal origin (Figure 1).[12] The sympathetic nervous system arises in hypothalamic neurons passing to the intermediolateral cell column of the spinal cord and synapsing before proceeding out to the superior cervical ganglion. Here they again synapse and give rise to fibres which follow the internal and external carotid arteries and their branches and innervate the vessels. The parasympathetic system arises from cell bodies in the superior salivatory nucleus passing out with fibres of the facial and glossopharyngeal nerve and synapsing in the sphenopalatine and otic ganglia before reaching the vessels. The classical transmitters in these systems are noradrenaline and acetylcholine, respectively. During the last 25 years it has been demonstrated that some perivascular nerves contain other so-called non-adrener-

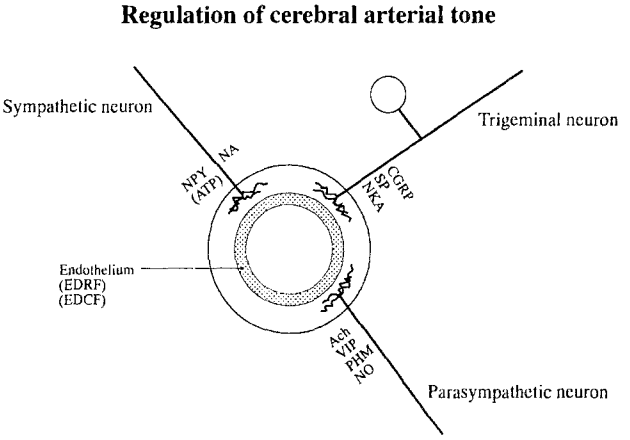

Figure 1. Dilatation of large cranial arteries is a suspected mechanism of migraine pain. Therefore, dysregulation of these arteries seems to play a significant role in migraine. This regulation involves perivascular nerve fibres as well as endothelium-derived factors. NPY, neuropeptide Y; NA, noradrenaline; ATP, adenosine triphosphate; CGRP, calcitonin-gene-related peptide; NKA, neurokinin ; Ach, acetylcholine; VIP, vasoactive intestinal peptide; PHM, peptide histidine methionine; NO, nitric oxide; EDRF, endothelium-derived relaxing factor, EDCF, endothelium-derived contracting factor

gic non-cholinergic (NANC) transmitters or modulator substances. Thus, neuropeptide Y (NPY) and possibly adenosine triphosphate (ATP) and 5-hydroxytryptamine (5-HT) act as transmitters in what may be classified anatomically as sympathetic neurons.[13,14] In the parasympathetic system, vasoactive intestinal peptide (VIP), peptide histidine methionine (PHM) and nitric oxide (NO) are transmitters or modulators[12,15] (Figure 1). Neurotransmitters released from autonomic nerve endings have presynaptic or postsynaptic modulatory actions in addition to the direct mediation of postsynaptic events. It is, for example, well known that noradrenaline and acetylcholine act on receptors located on autonomic nerve terminals to modify release of transmitters. In addition, transmission from autonomic neurons can be modulated by substances which are synthesized in nearby tissue or circulate in blood, e.g. adrenaline and 5-HT.[16,17]

The sensory innervation of cranial vessels belongs to the trigeminal system. Bipolar cell bodies located in the trigeminal ganglion are connected to the trigeminal nucleus caudalis in the brain stem and its extension down to the C_2 level. Neuropeptides released by antidromic activation of the trigeminal nerve [calcitonin-gene-related peptide (CGRP), substance P and neurokinin A] induce vasodilatation (Figure 1).[18]

Involvement of the autonomic nervous system in migraine

The possible involvement of the autonomic nervous system in migraine mechanisms has long been a subject of considerable interest. Based on cardiovascular tests,[19] vasomotor reactions to temperature changes and responses to pharmacological tests as well as changes in biochemical parameters, hypo- and hyperfunctioning of both the sympathetic and parasympathetic nervous systems have been suggested (Tables 1–4).

Cardiovascular reflexes

A number of studies have focused on sympathetically mediated cardiovascular reflexes such as the orthostatic test, the cold pressor test and the isometric work test. An extensive series of studies has been published by Havanka-Kanniainen *et al.*[20–22] They found no evidence of disturbances in young migraineurs outside of attack (11–22 years old) compared with a control group. Significant abnormalities suggesting sympathetic hypofunction were, however, found interictally in older migraineurs (aged 23–50 years). No difference was found between these responses in migraineurs suffering from migraine with and without aura. Decreased blood pressure response to an isometric work test was found to be more pronounced during, compared with outside of, attack. Based on decreased R–R variation during normal and deep breathing and a decreased Valsalva ratio in migraineurs, the same authors concluded that parasympathetic hypofunction was present in migraine. Gotoh *et al.* compared responses to a Valsalva manoeuvre, an orthostatic test and Achner's test (reflex bradycardia induced by pressure on the eyeballs) interictally in migraine patients suffering from migraine, either with or without aura, to age-matched healthy controls. In addition noradrenaline bolus injection and eye installation tests were evaluated. Sympathetic hypofunction with denervation

Table 1. Studies of cardiovascular reflexes in migraine

Reference	Age[a]	During or outside of attack	Conclusions
Gotoh *et al.* (1984)[23]	29 (±13)	Outside	Sympathetic hypofunction, parasympathetic hyperfunction
Drummond (1985)[25]	21 (17–31)	Outside	Sympathetic hyperfunction
Havanka-Kanniainen *et al.* (1986)[20]	35 (23–50)	Outside	Sympathetic hypofunction, parasympathetic hypofunction
Havanka-Kanniainen *et al.* (1986)[22]	17 (11–22)	Outside	Normal sympathetic function
Havanka-Kanniainen (1986)[21]	42 (26–56)	During	Sympathetic hypofunction
Cortelli *et al.* (1986)[26]	39 (22–53)	Outside	Sympathetic hypofunction
Cortelli *et al.* (1987)[27]	NA (21–44)	Outside	Normal sympathetic function
Mikamo *et al.* (1989)[28]	41 (±16)	Outside	Sympathetic hypofunction
Boccuni *et al.* (1989)[29]	35 (±14)	Outside	Sympathetic hypofunction
Cortelli *et al.* (1991)[30]	34 (17–49)	Outside	Normal sympathetic and parasympathetic function
Pogacnik *et al.* (1993)[31]	37 (21–50)	Outside	Sympathetic hypofunction
Thomsen *et al.* (1995)[24]	42 (19–66)	Outside	Normal sympathetic function, parasympathetic hypofunction
		During	Normal sympathetic function

[a] Mean age of the patients studied is given with either ±SD or range depending on the expression in the original material.
NA, not available.

Table 2. Studies of vasomotor reactivity in migraine

Vasomotor reactivity studied	During or outside	Conclusions of attack
Peripheral		
Downey and Frewin (1967)[34]	Outside	Deficient vasoconstriction
French *et al.* (1967)[36]	Outside	Normal responses
Hockaday *et al.* (1967)[35]	Outside	Normal responses
Appenzeller (1978)[32]	Outside	Deficient vasodilatation
Passchier *et al.* (1984)[33]	Outside	Deficient vasodilatation
Jensen (1987)[37]	During	Slightly decreased reactivity in temporal region on the headache side to a tilt test
Retinal		
Gomi *et al.* (1989)[47]	Outside	Sympathetic hypofunction
Cerebrovascular (TCD)		
Reinecke *et al.* (1989)[48]	Outside	Abnormal MCA velocity reativity to a Valsalva manoeuvre
Thomsen *et al.* (1995)[24]	During	Normal MCA velocity reactivity during increased sympathetic drive
	Outside	Normal MCA velocity reactivity during iincreased sympathetic drive

TCD, Transcranial Doppler; MCA, middle cerebral artery.

Table 3. Other functional tests of the autonomic nervous system in migraine

Test	During or outside of attack	Conclusions
Pupillometry		
Fanciullacci (1979)[49]	Outside	Sympathetic hypofunction
Herman (1983)[51]	During	Sympathetic hypofunction
Balottin *et al.* (1983)[50]	Outside	Normal sympathetic function
Gotoh *et al.* (1984)[23]	Outside	Sympathetic hypofunction
Rubin *et al.* (1985)[52]	Outside	Sympathetic hypofunction
Micielli *et al.* (1989)[53]	Outside	Sympathetic hyperfunction or parasympathetic hypofunction
Drummond (1990)[54]	Outside	Sympathetic dysfunction
Venotest		
Del Bianco *et al.* (1982)[55]	During	Noradrenaline receptor supersensitivity
Sweating function		
Gomi *et al.* (1989)[47]	Outside	Sympathetic hypofunction
Tyramine test		
Ghose *et al.* (1977)[56]	Outside	Increased sensitivity
Muscle nerve sympathetic activity		
Fagius (1985)[57]	During	Normal activity

hypersensitivity and parasympathetic hyperfunction was suggested.[23] In contrast to the suggested sympathetic hypofunction, other studies using similar cardiovascular tests have shown either sympathetic hyperfunction or normal sympathetic function (Table 1). Furthermore, normal parasympathetic function has also been described based on cardiovascular tests (Table 1). In our own experience migraine is not associated with disturbed cardiovascular tests reflecting sympathetic function, whereas a mild parasympathetic hypofunction does seem to be present.[24]

Arterial and arteriolar vasomotor reactivity

Reduced vasodilatation in the forehead and hands of migraineurs after heating has been reported.[32] In another study an increase of digital blood volume during heating was only absent in male migraineurs.[33] In contrast, a peripherally applied cold stimulus failed to induce decreased hand blood flow in migraineurs.[34] Finally, normal peripheral vasomotor reactivity in migraineurs has also been described (Table 2).[35, 36]

Local autonomic control regarding the cranial arterial bed is obviously more relevant than studies of systemic vascular reactivity but is more difficult to investigate. Using transcranial Doppler to study blood velocity in the middle cerebral artery (MCA), recent studies showed decreased velocity on the painful side during unilateral migraine attacks indicating abnormal dilatation.[8, 11] Dilatation of the superficial temporal artery has also been demonstrated on the headache side during attack.[7] This dilatation was found to be relative to a generalized vasoconstriction indicating systemic sympathetic activation.[7] Using tests of cardiovascular sympathetic function, no differences in MCA blood velocity responses were shown between migraineurs, studied during and outside of attack, and healthy controls.[24] This suggests normal MCA reactivity during increased sympathetic drive. In the tempo-

Table 4. Biochemical studies of autonomic function in migraine

Agent	During or outside of attack	Conclusions
Adrenaline/noradrenaline		
Hsu *et al.* (1977)[65]	During	Increase in venous noradrenaline
Fog Møller *et al.* (1978)[66]	During	Normal venous adrenaline Decrease in noradrenaline
Mathew *et al.* (1980)[67]	Outside	Increase in venous adrenaline and noradrenaline
Anthony (1981)[68]	During	Decrease in venous adrenaline
Gotoh *et al.* (1984)[23]	Outside	Decrease in arterial noradrenaline
Schoenen *et al.* (1985)[69]	Outside	Normal venous adrenaline, increase in noradrenaline
D'Andrea *et al.* (1989)[70]	Outside	(Platelets) sympathetic hypofunction
cGMP,cAMP		
Anthony (1981)[68]	During	Increase plasma cAMP
Okada *et al.* (1984)[64]	Outside	α- and cholinergic-receptor supersensitivity
Winther and Hedman (1985)[71]	Outside	Increased plasma cAMP
Dopamine-ß-hydroxylase		
Gotoh *et al.* (1976)[72]	Outside	Increased in venous blood
Anthony (1981)[68]	During	Increased in venous blood
Vanillyl-mandelic acid		
Curran *et al.* (1965)[73]	During	Increased in urine
Curzon *et al.* (1966)[74]	During	Normal in urine
Sicuteri (1967)[75]	During	Increased in urine
Neuropeptide Y		
Goadsby *et al.* (1990)[62]	During	Normal in external jugular blood
Friberg *et al.* (1994)[63]	During	Normal in internal jugular blood
Vasoactive intestinal peptide		
Goadsby *et al.* (1990)[62]	During	Normal in external jugular blood
Friberg *et al.* (1994)[63]	During	Normal in internal jugular blood

ral region, extracranial blood flow responses to an orthostatic test have been studied during and outside of migraine attacks. This study revealed no statistical difference between responses during and outside of attack, but a slightly decreased response on the headache side compared with the non-headache side during attack.[37]

Cerebral blood flow responses to functional tests such as speech, reading, listening and arm work have been studied during attacks of migraine with aura provoked by angiography. These activation procedures were not accompanied by the usual increase in regional cerebral blood flow (rCBF) in low-flow areas, whereas a normal, focal rCBF increase was observed in the non-affected parts of the brain.[38,39] It is most likely, but not definitely established, that autoregulation is normal during attacks of both forms of migraine.[38,40] Several studies have focused on cerebrovascular reactivity to alterations in P_aCO_2. During attacks of migraine with aura, P_aCO_2 reactivity seems to be impaired or abolished, whereas P_aCO_2 reactivity seems to be normal during attacks of migraine without aura.[38,40–44] Interictally, an exaggerated P_aCO_2 reactivity during hyperventilation has recently been reported but only in migraine with aura.[44] The interictal response to CO_2 inhalation may, however, be exaggerated in both forms of migraine,[45,46] and more studies are needed to establish whether interictal differences in cerebrovascular reactivity exist between migraine with and without aura.

Pupillometry

Autonomic function may be studied by pupillometry. Such results generally suggest sympathetic hypofunction and/or parasympathetic hypofunction in migraine (Table 3). Thus, interictally the mydriatic response to tyramine, phenylephrine, guanethidine and adrenaline was enhanced in adult migraineurs but not in children.[23,49,50] Furthermore pupillometric data has suggested α-receptor supersensitivity of the iris.[49]

Central sympathetic function

Involvement of the locus coeruleus in migraine has been suggested but never shown.[58] It has been suggested that the contingent negative variation (CNV) – a slow cerebral potential elicited by a reaction task with a warning and an imperative stimulus – can be modulated by catecholamine afferents to the frontal cortex.[59] If this is so, studies of CNV in migraine may indicate a central sympathetic involvement.[60] However, at present this possibility remains hypothetical.

Biochemical studies

Plasma levels and urinary excretion of catecholamines and their metabolites have been studied often but with contradicting results (Table 4).[61,65–68] NPY and

VIP in blood from the external and internal jugular vein were normal during migraine attacks.[62,63] Parasympathetic denervation supersensitivity in migraine has been suggested based on an exaggerated response to cholinergic agents. Thus, a larger rise in the second messenger cyclic guanosine monophosphate (cGMP), after methacholine provocation, has been described in peripheral venous blood.[64] Indirect evidence points towards a role for the vasoactive amine 5-HT in migraine.[76–78] In humans, 5-HT is found in the brain, the pineal gland, the blood, platelets and blood vessels, including the circle of Willis. There is a close interaction between the central 5-HT system and the central noradrenergic system[79] but it is not known if this interaction plays a role in migraine. During attacks of migraine without aura, the platelet content of 5-HT is decreased but not during attacks of migraine with aura. 5-HT in platelet-free plasma on the other hand, shows similar changes in both forms of migraine. Thus, interictally migraineurs have lower 5-HT and higher 5-hydroxyindoleacetic acid (5-HIAA, the main metabolite of 5-HT) compared with controls.[80] During attacks the plasma level increases significantly compared with outside of attack, whereas 5-HIAA levels fall.[80,81] This could imply a release of 5-HT from platelets during attack and/or an increased metabolic turnover of 5-HT outside of attack.[82] The relevance of these findings to the function of the autonomic nervous system in migraine is not known.

Conclusion on autonomic function in migraine

Clear dysfunction of the sympathetic nervous system remains to be shown. If sympathetic dysfunction is involved most studies suggest hypofunction. There have been several studies which have applied different methodological approaches, and the involvement is not yet clear. Also, the response of cranial arteries is normal during increased sympathetic activity, so it seems unlikely that sympathetic dysfunction plays any major role. Mild parasympathetic hypofunction with denervation supersensitivity may be present in migraine. The origin of such disturbances is unknown and it has yet to be demonstrated whether large cranial artery parasympathetic responses are abnormal and which transmitters or modulators may be involved. In this context it is interesting that cerebral arteries in migraineurs are hypersensitive to NO[10] as the enzyme responsible for NO synthesis is located in parasympathetic nerve endings around cerebral arteries.[15]

Nitric oxide

NO is not only a transmitter in parasympathetic perivascular nerves. It is also the main endothelium-derived relaxing factor (EDRF) (Figure 2).[83–86] NO is liberated from the endothelium upon stimulation of several receptors and also by shear stress phenomena.[87] Endothelial receptor stimulation may occur from the luminal

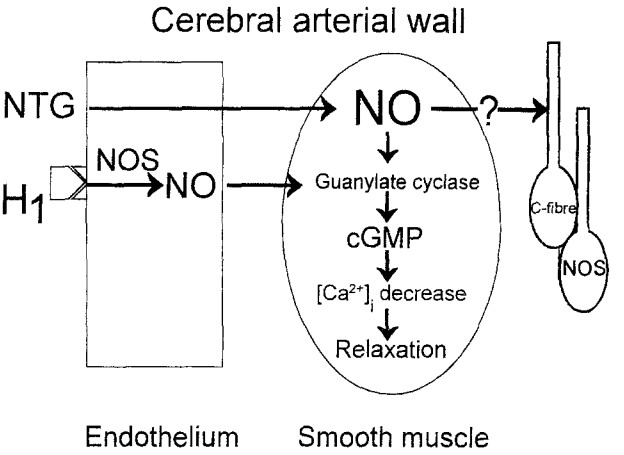

Figure 2. Nitric oxide (NO) is synthesized (via NOS) and released from endothelium upon receptor stimulation (here illustrated by the histamine H_1 receptor). NO is also released from perivascular nerve endings. NO diffuses to adjacent smooth muscle and activates guanylate cyclase causing increased cGMP eventually leading to relaxation. Glyceryl trinitrate (NGT) is a NO donor which induces migraine in susceptible individuals and activates the same pathway as receptor-mediated released NO suggesting that migraine is triggered by NO-related mechanisms. Blockade of this cascade may explain the mechanism of action of migraine prophylactic drugs

side and perhaps also from the abluminal side. Thus, relevant transmitters may be released from perivascular nerve endings in the adventitia, diffuse to the endothelium and stimulate the release of NO.[87] NO is a gas which easily crosses membranes. It thus enters smooth muscle cells and causes relaxation via activation of soluble guanylate cyclase hence causing accumulation of cGMP.[88] Glyceryl trinitrate (NGT) is a NO donor[89–91] and hypersensitivity to NO has indirectly been shown in migraineurs by means of intravenous infusion of NGT.[10,92,93] Interestingly, increased sensitivity has been shown both for induction of pain and for dilatation of the middle cerebral artery. A decreased platelet aggregability to collagen in migraine supports the suggestion that migraineurs have altered NO sensitivity.[94] Thus, platelet aggregability to collagen is increased and the level of cGMP decreased when platelets are incubated with the inhibitor of NO synthesis, *N*-monomethyl-L-arginine (L-NMMA).[94] It has been suggested that NO is a common final pathway for most (if not all) triggers of migraine pain.[95] Whether the described hypersensitivity to NO relates to endothelium-derived NO or to NO in perivascular nerves (or in the brain for that matter) remains to be clarified.

Trigeminovascular mechanisms

Antidromic activity in perivascular nerve endings of trigeminal origin releases neurotransmitters which in turn induce vasodilatation and plasma extravasation as part of a so-called neurogenic inflammation. Series of experimental studies in rats have shown alterations in vascular permeability and ultrastructural changes in the dura mater associated with stimulation of the trigeminal ganglion.[18] Trigeminal ganglion stimulation has been shown to be associated with a release of CGRP

and substance P in the rat and in man.[96] The possible significance of these findings in migraine relates to the finding of increased levels of CGRP in blood from the external jugular vein during migraine attacks.[62]

Therapeutic implications

Mechanisms of action of acute migraine therapy

Traditionally the mechanism of action of acute migraine therapy (except generally acting analgesics) has been ascribed to constriction of pathologically dilated cranial arteries. Thus, intravenous administration of the effective antimigraine drug ergotamine was long ago shown to reduce temporal artery pulsations in parallel with a decrease in headache intensity.[97] It has recently been suggested that the primary action of ergotamine is inhibition of the antidromic release of trigeminal neuropeptides as part of a neurogenic inflammation.[98] Ergotamine interacts with receptors for 5-HT, dopamine and noradrenaline.[99] Thus, elucidation of a specific receptor involvement requires more specific pharmacological tools. The most specific and highly effective acute migraine treatment so far available is the 5-HT_{1D} receptor agonist sumatriptan.[78] Several mechanisms of action of sumatriptan have been proposed. A direct pain-modulating effect in the central nervous system is unlikely as sumatriptan is soluble in water and crosses the blood–brain barrier very slowly.[100] One possibility is that constriction of dilated large intracranial arteries provides the causative mechanism.[8,101] However, as with ergotamine, another possible mechanism of action is blockade of the release of sensory neuropeptides as part of a neurogenic inflammation.[102,103] As these neuropeptides also induce vasodilatation, the observed vasoconstrictive effect may be a secondary phenomenon. The answer to what may be the primary mechanism of action is likely to be provided in the near future. Thus, even more specific 5-$HT_{1D\alpha}$ receptor agonists are under development. These compounds block neurogenic inflammation by prejunctional mechanisms on sensory nerves and have no vasoconstrictive effect.[104] The same is so for substance P antagonists.[105] Thus, if neurogenic inflammation is the primary event in migraine pain these drugs will be effective.

Interaction with the NO cascade provides a possible mechanism of action of prophylactic migraine therapy

The mechanism of action of drugs with an established prophylactic effect in migraine has long been an enigma. These drugs include ß-adrenergic drugs without partial agonist activity (i.e. propranolol, metoprolol, atenol, nadolol and timolol), antiserotonergic drugs (i.e. methysergide, pizotifen) and calcium antagonists (i.e. flunarizine and verapamil).[106] Many observations suggest that all these drugs do interact with the NO-triggered cascade of reactions.[95] Thus, calcium antagonists block voltage-dependent Ca^{2+} channels, thereby reducing the concentration of free cytosolic calcium. As the synthesis of NO in the endothelium is Ca^{2+}-dependent and is increased by a rise in intracellular Ca^{2+},[88] calcium antagonists might exert their prophylactic effect in migraine via decreased activity of nitric oxide synthase (NOS). Methysergide and pizotifen are 5-HT_2 antagonists which do not discriminate between the 5-HT_{2b} and the 5-HT_{2c} receptor. It has recently been suggested that their effect is via 5-HT_{2C} receptor antagonism.[107] 5-HT_{2c} (formerly called 5HT_{1c}) receptor stimulation liberates NO.[108] Thus, amine antagonists may well exert their action by reducing NO production. Propranolol blocks isoprenaline-induced relaxation of rat thoracic aorta in an endothelium-dependent fashion. The response is also blocked by the NOS inhibitor L-NOARG (NG-nitro-L-arginine).[109] Similar observations have been made in rabbit aorta.[110] The prophylactic effect of β-adrenergic blockers in migraine may thus result from blockade of β-adrenoceptor-induced NO production. Propranolol also antagonizes the 5-HT_{2C} receptor on the endothelium.[111] This is another mechanism whereby it may reduce endothelial NO production. In contrast to propranolol, pindolol, which is ineffective in migraine, lacks affinity to the 5-HT_{2C} receptor.[109] The central role of NO in migraine pain may not only explain the mechanisms of action of several well established treatments, but is also likely to offer future therapeutic possibilities. Thus, drugs which directly counteract the NO-activated cascade (NOS inhibitors, NO scavengers, guanylate cyclase inhibitors etc.) may be effective in migraine prophylaxis. The more specific these drugs become (e.g. only affecting endothelial NOS or NOS in perivascular nerves in and around cerebral arteries and not arterioles) the more effective they are likely to be, and the less side effects they are likely to induce. Furthermore such highly specific NO-antagonizing drugs are likely to become valuable tools in the elucidation of which NO-containing structures and NO-mediated physiological effects are involved in migraine mechanisms. Thus, further understanding of the molecular mechanisms of migraine seems near.

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