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Review

Is the 5-HT_7 receptor involved in the pathogenesis and prophylactic treatment of migraine?

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Abstract

The mechanisms underlying the pathogenesis of migraine and their possible association with serotonin (5-hydroxytryptamine; 5-HT) have not yet been elucidated. One of the major obstacles in achieving this goal is the lack of information on the mechanisms by which the monoamine could possibly trigger and/or modulate the basic pathophysiological features of the condition, that is, cranial vasodilatation and neurogenic inflammation. This information should provide a useful theoretical framework to insight the nature of the postulated fundamental triggering mechanism in the brain that ultimately results in head pain. Novel avenues for research and drug development may be envisaged upon the recent observations showing that 5-HT is actually able to produce vasodilatation of intra- and extra-cranial blood vessels through a mechanism pharmacologically resembling the 5-HT_7 receptor type, and that the messenger RNA (mRNA) encoding for this receptor is highly expressed in cranial vessels. Other lines of evidence have suggested that the 5-HT_7 receptor may play an excitatory role in neuronal systems and that it may be involved in hyperalgesic pain and neurogenic inflammation. On the basis of these observations, it is proposed that the 5-HT_7 receptor may well represent a link between the abnormal phenomena of 5-HT processing and neurotransmission that are observed in migraine patients, and the vascular and neurogenic alterations that account for migraine headache. This view is supported by the fact that most of the migraine prophylactic 5-HT receptor antagonists display relatively high affinity for the 5-HT_7 receptor, which significantly correlates with their pharmaceutically active oral doses.

Keywords: 5-HT_7 receptor; Migraine pathogenesis; Prophylactic drug; 5-HT (5-hydroxytryptamine, serotonin)

1. Introduction

After more than 50 years of investigation, an enormous amount of evidence has accumulated to suggest that serotonin (5-hydroxytryptamine; 5-HT) is implicated in the pathophysiology of migraine (Fozard, 1982, 1992; Humphrey, 1991; Kimball et al., 1960; Sicuteri et al., 1961; Silberstein, 1992; Sjaastad, 1975). Although all this evidence remains circumstantial, as an etiological link between 5-HT and migraine has not been definitively proven thus far, the reported changes in the overall 5-HT metabolism (Curran et al., 1965; Fozard, 1982; Sicuteri et al., 1961), the growing evidence for abnormal processing in central 5-HT-mediated events during and between migraine attacks (Proietti-Cecchini et al., 1997; Wang et al., 1996), along with the fact that effective acute and prophylactic antimigraine drugs target specific 5-HT receptors (Fozard, 1992; Fozard and Gray, 1989; Fozard and Kalkman, 1994; Humphrey, 1991; Pauwels and John, 1999; Saxena and Ferrari, 1989), have all contributed to reinforce the view that the monoamine may play a pivotal role in the pathogenesis of this disorder.

New lines of research have provided support to the hypothesis that migraine may result from a fundamental disturbance in central 5-HT neurotransmission involving abnormally low levels of 5-HT between attacks (Wang et al., 1996). Since solid epidemiological and pharmacological observations have associated the generation of migraine with an increased availability of 5-HT (see below), the concept that migraine attacks may result from a massive release of 5-HT in the brain has been set forth (Fozard, 1995; Fozard and Kalkman, 1994; Humphrey, 1991). At present, however, this idea has been difficult to conciliate with the primary pathophysiological mechanisms that are believed to underlie migraine headache, that is, craniovascular vasodilatation (Saxena and Ferrari, 1989; Humphrey and Feniuk, 1991; Humphrey, 1991) and dural neurogenic inflammation (Mos-

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kowitz, 1992). This is basically due to the lack of evidence for a mechanistic link between 5-HT and these latter events. Since new findings have shown that 5-HT may actually produce vasodilatation in the cranial vasculature (Ishine et al., 2000; Terrón, 1998a; Terrón and Falcón Neri, 1999; Villalón et al., 1997) and play an excitatory role in neuronal systems via the 5-HT_7 receptor (Cardenas et al., 1999), which may include hyperalgesia and facilitation of neurogenic inflammation (Fasmer et al., 1986; Pierce et al., 1996a; Taiwo et al., 1992), the gap in the relation of 5-HT with migraine pathogenesis may start to close.

The aim of the present article is to review and discuss the above evidence in the light of the potential implication of the 5-HT_7 receptor in the pathogenesis of migraine and its preventative treatment.

2. 5-HT levels and the central serotonergic system in migraine

The issue of the changes in 5-HT levels and their association with migraine pathophysiology has long been a matter of debate. At present, solid evidence has been provided to exclude the possibility that peripheral sources of 5-HT are responsible for the initiation of migraine attacks. Thus, intravenous administration of 5-HT to migraineurs did not trigger or worsened headache (Kimball et al., 1960), and migraine is not a symptom of the carcinoid disease in which whole blood and free plasma 5-HT concentrations are up to 20-fold higher than normal (Salmon et al., 1982). In fact, the increase in urinary excretion of 5-hydroxyindolacetic acid (5-HIAA) during migraine is much higher than that which would be expected if the sole source of the metabolite were the 5-HT released from platelets (see Fozard, 1982 for a detailed review). The conclusion is that the source of 5-HT is within the central nervous system (CNS) and that its association with anatomical elements relevant to migraine, such as brain microvessels and cranial large conduit arteries, represents a plausible locus for migraine headache to evolve. In keeping with this idea, 5-HIAA levels were found to be elevated about 40% in the cerebrospinal fluid of migraine patients (Kovács et al., 1989), which would point to enhanced turnover of 5-HT in the CNS.

That the central 5-HT system may be involved in the neurochemical alterations of migraine is further suggested by epidemiological studies showing that the syndrome has parallels with depression and anxiety. Since both diseases are known to be associated with a low serotonergic neurotransmission, it has been considered that migraine may be a low 5-HT alteration as well (Gordon et al., 1991). In support of this concept, recent physiological studies indicated that the amplitude of the auditory evoked potentials was inversely related to central serotonergic neurotransmission (Heger and Juckel, 1993). Interestingly, a marked increase in amplitude was observed between attacks in migraine patients, which is consistent with a low 5-HT transmission and abnormal cortical processing of sensory information (Wang et al., 1996). If migraine is indeed related to a decreased serotonergic neurotransmission, the question that can be asked in connection with a possible etiological mechanism is whether or not such abnormally low 5-HT transmission is the trigger of migraine per se. Accumulating evidence has now suggested that a chronic decreased availability of 5-HT certainly predisposes to the condition, but that the sudden release of the monoamine is what may actually trigger the attack (see Hamel and Saxena, 2000 for review). This view originally arose from the findings that reserpine, which consistently causes profound release of 5-HT from platelets, nerves and other sites (Zaimis, 1964), elicits migraine-like headaches in migraineurs (Anthony et al., 1967; Curzon et al., 1969). In accordance with this observation, a number of drugs whose common action is to increase the free levels of 5-HT were reported to promote headache, i.e. antidepressant 5-HT uptake blockers (see Humphrey, 1991 for review). Remarkably, it seems that headache appears only during the initial phase of treatment, which leads to transient increased amounts of 5-HT, and that depletion of 5-HT stores with chronic treatment confers some resistance to migraine (Genefke et al., 1975; Syvälahti et al., 1979). Consequently, even in the face of abnormally sensitized 5-HT receptors due to long-term decreased availability of 5-HT, its very low levels in intracellular stores would preclude the possibility that the monoamine was released in massive amounts by those conditions that trigger/promote migraine attacks. Alternatively, it may be conceived that chronic antidepressant treatment has a regulatory effect, i.e. downregulation, on the expression of certain 5-HT receptors implicated in migraine. In keeping with this notion, a decrease in migraine frequency and intensity with ultimate cessation over a 3-year period was reported in a patient with classic migraine concomitantly with the development of a 5-HT-producing carcinoid tumor. Interestingly, recurrence of migraine attacks was noticed upon surgery and relative reduction in plasma 5-HT and 5-HIAA levels (Hopf et al., 1992). On this basis, it may be speculated that normalization of 5-HT levels, which would lead to re-setting or down-regulation of hypersensitized 5-HT receptors, had a protective role against migraine attacks.

In further support of the view that migraine may originate in the brain, an increasing number of investigators believe that attacks may be initiated in the prodromal phase by a functional disturbance at the neuron level of the hypothalamus (Blau, 1984; Bruyn, 1980; Lance, 1993; Silberstein, 1992). Thus, it has been proposed that periodic central disturbances of hypothalamic activity or labile threshold may account for the periodicity of migraine attacks and that such alteration could also provide a mechanism by which emotional disturbances arising from the limbic system infringe upon the hypothalamic function (Rao and Pearce, 1971). Since disturbances of biorhythmic physiologic variables, such as hormone function, sleep and feeding, i.e. migraine-related factors, are frequently found in migraineurs (Bille, 1962; Lance, 1993; Nappi, 1994; Sahota and Dexter, 1990;

Wilkinson, 1986), the suprachiasmatic nucleus has been proposed as the site from which the hypothalamic affection may propagate to the occipital cortex and brain stem structures, e.g. midbrain raphe nuclei (Zurak, 1997). Actually, it is known that the serotonergic activity has circadian and circannual rhythmicity and that is, like other biorhythms, under a suprachiasmatic nucleus pacemaking control (Carlsson et al., 1980; Leibowitz, 1993). Likewise, available evidence indicates that serotonergic pathways, i.e. the ascending forebrain serotonergic tract, emanating from the midbrain raphe nuclei terminate in different brain areas including the suprachiasmatic nucleus (Hofman and Swaab, 1993; Hofman et al., 1996; Jacobs and Azmitia, 1992; Moore and Card, 1993), and that electrical stimulation of the dorsal raphe nucleus induces release of 5-HT in the suprachiasmatic nucleus and phase-resetting of the circadian activity rhythm (Glass et al., 2000). Given the existence of this anatomical communication between the suprachiasmatic nucleus and the midbrain raphe nuclei, it is seems therefore possible to conceive that a disturbance in the former may have an impact on the latter thus causing altered patterns of 5-HT neurotransmission. It might not be coincidental, in this regard, that a strong brain stem activation in association with acute spontaneous migraine attacks was noticed in patients with migraine without aura (Weiller et al., 1995; see below).

In the light of the concept that migraine is most likely associated with a chronically reduced serotonergic neurotransmission in the brain, with a sudden and massive release of 5-HT being responsible for its initiation (see Humphrey, 1991; Hamel and Saxena, 2000), it is important to consider the possible sources of 5-HT in the brain and the potential consequences of sudden high levels of this monoamine in anatomical sites relevant to the condition.

3. Craniovascular serotonergic innervation as a possible source of 5-HT in migraine

Several immunocytochemical studies have unequivocally demonstrated that small and large intra-cranial vessels are innervated by perivascular 5-HT containing nerve fibers that penetrate deeply within the vessel wall (Griffith et al., 1982; Griffith and Burnstock, 1983; Chang et al., 1987). The sources of these neurons are most likely the cell bodies of the median and dorsal raphe nuclei (Moskowitz et al., 1979; Reinhard et al., 1979; Edvinsson et al., 1983; Scatton et al., 1985) and the sympathetic nerves that originate primarily in the superior cervical ganglion (Alafaci et al., 1986; Cowen et al., 1987; Chang et al., 1988, 1989). It has been pointed out that such innervation by the raphe and sympathetic nervous systems may provide a direct link of the cranial vasculature with neuronal elements integrally involved in the reaction of the individual to stress and other major environmental precipitating factors of migraine (Fozard, 1995; Symposium, 1984). It follows that release of abnormally high amounts of 5-HT from perivascular serotonergic and 5-HT-containing sympathetic nerves during a migraine attack would target certain populations of 5-HT receptors located in the cerebrovascular smooth muscle with some though limited access to the endothelial compartment. This idea may actually be supported by a seminal positron emission tomography study demonstrating strong brain stem activation in association with acute spontaneous migraine attacks in patients with migraine without aura (Weiller et al., 1995). Interestingly, the foci of maximum increase of regional cerebral blood flow coincided with the anatomical location of the dorsal raphe nucleus and the locus coeruleus, i.e. the major regulatory nuclei of central serotonergic and noradrenergic activity, respectively. While subcutaneous sumatriptan decreased blood flow in the cortical areas of the hemispheres to values not different from those recorded during the headache-free interval, and relieved from headache, photophobia, phonophobia and other related autonomic symptoms, the activation in the brain stem persisted (Weiller et al., 1995). Thus, dysfunction in the regulation of the dorsal raphe nucleus and the locus coeruleus, which are involved in anti-nociception and extra- and intra-cerebral vascular control, may be the basis for the postulated irregular activity of the serotonergic and noradrenergic systems resulting in suddenly augmented neurotransmitter discharges to the cranial vasculature.

Since intra-cranial vascular structures, including large conduit arteries, e.g. middle cerebral artery, and small vessels in the meninges also receive innervation from trigeminal afferents (see Moskowitz, 1987 for review), a possible modulatory interaction of perivascular serotonergic fibers with such nociceptive neurons could be expected (see below).

4. 5-$HT_{2B/2C}$ and 5-HT_7 receptors as possible targets of 5-HT in migraine

If, as discussed above, neuronal 5-HT is involved in the vascular and neurogenic alterations of migraine, the potential receptor targets of 5-HT should have the ability to trigger and/or modulate those conditions either directly or indirectly. Evidence for the presence and function of specific 5-HT receptors in cerebrovascular smooth muscle and the trigeminovascular system with the above potential properties has been provided for the 5-$HT_{2B/2C}$ and 5-HT_7 receptors. Indeed, 5-$HT_{1B/1D}$ and 5-HT_{1F} receptor-mediated vascular and trigeminovascular responses are not considered pathological but the major mechanisms underlying the acute antimigraine therapeutic effect of sumatriptan and other 5-$HT_{1B/1D}$ receptor agonists, including the new generation of brain-penetrating triptans (see Pauwels and John, 1999 for review).

4.1. The 5-$HT_{2B/2C}$ receptors

The implication of 5-$HT_{2B/2C}$ receptors in migraine pathogenesis has been linked primarily with the production of nitric oxide (NO). Thus, the finding that NO donors induce migraine-like headaches in some patients led to Olesen et al.

(1994) to postulate that NO may play a key role in migraine and there is preliminary evidence indicating that NO synthase inhibitors had a beneficial effect in migraineurs (Lassen et al., 1997, 1998). Even though this concept is attractive because it links NO with sensory nerve activation and vascular vasodilatation, both well documented effects of this molecule (Olesen et al., 1994), pieces of information are still missing regarding the possible source of NO. Since 5-HT reportedly produces endothelium-dependent relaxation in peripheral vessels via activation of the 5-$HT_{2B/2C}$ receptors, and this response is in some cases dependent on NO release (Glusa and Richter, 1993; Sumner, 1991), it was speculated that 5-HT would also cause release of NO in cerebral blood vessels with subsequent activation of sensory neurons and vasodilatation (Fozard, 1995; Fozard and Kalkman, 1994). This mechanism has been proposed (Fozard, 1995; Fozard and Kalkman, 1994) to account for the ability of 1-(3-chlorophenyl)-piperazine (*m*-CPP), a non-selective 5-HT receptor agonist with moderately higher affinity at the 5-HT_{2B} receptor (Fozard and Gray, 1989), to trigger migraine-like attacks in susceptible patients (Brewerton et al., 1988). Consequently, the concept was invoked to explain the ability of some 5-HT_2 receptor antagonists to prevent migraine attacks, the orally active doses of which were found to significantly correlate with their affinity at the 5-$HT_{2B/2C}$ receptors (Schmuck et al., 1996; Kalkman, 1994; see below). It is important to highlight, notwithstanding, that agonist-induced stimulation of 5-HT_2 receptors hardly relaxed the pig cerebral artery, i.e. ~ 15% of the spasmogen-induced contraction (Schmuck et al., 1996), and that α-methyl-5-HT, a very potent and full agonist at the endothelial 5-$HT_{2B/2C}$ receptor in peripheral vessels (Glusa and Richter, 1993), was devoid of any relaxant activity in endothelium-intact pre-contracted cerebral arteries (Terrón, 1998a; Terrón and Falcón-Neri, 1999). These findings therefore argue against the 5-HT-NO connection and may also raise questions about the putative role of endothelial NO release as the primary step of the cascade of events leading to migraine headache (Fozard, 1995; Fozard and Kalkman, 1994). Actually, the ability of *m*-CPP to time-dependently elevate c-Fos expression in the rat trigeminal nucleus caudalis was recently reported to be unrelated to 5-HT_{2B} receptor activation or NO release since both the selective 5-HT_{2B} receptor agonist, 1-[5-(2-thienylmethoxy)-1*H*-3-indoyl]propan-2-amine hydrochloride (BW723C86), and the NO donor, glyceryl trinitrate, failed to increase c-Fos immunoreactivity in this structure (Martin and Martin, 2001). Furthermore, contrary to the view that the pro-migraine effects of *m*-CPP may result from activation of cerebrovascular endothelial 5-$HT_{2B/2C}$ receptors (Fozard, 1995; Fozard and Kalkman, 1994), it has been demonstrated that the drug barely displays efficacy (Schmuck et al., 1996), or even behaves as an antagonist (Schmuck et al., 1996; Thomas et al., 1996) at the human 5-HT_{2B} receptor. Within the same context, the classical antimigraine drugs, ergotamine and dihydroergotamine, were reported to behave as agonists at the endothelial 5-$HT_{2B/2C}$ receptor (Glusa and Roos, 1996). This property would provide both drugs with the ability to elicit migraine attacks in susceptible individuals, which is not the case (see Lipton, 1997).

4.2. The 5-HT_7 receptor

Several lines of pharmacological evidence have recently set up the bases to consider the 5-HT_7 receptor as another possible target of 5-HT with pathophysiological implications in migraine. Thus, reverse transcriptase polymerase chain reaction (RT-PCR) experiments showed high expression of 5-HT_7 transcripts in pig cerebral vessels (Ullmer et al., 1995; Ishine et al., 2000) and several human meningeal tissues, including the internal carotid and middle meningeal artery (Schmuck et al., 1996). Significantly, recent in vitro studies showed that 5-HT is in fact capable of producing endothelium-independent relaxant responses in canine (Terrón, 1998a; Terrón and Falcón-Neri, 1999) and pig (Ishine et al., 2000) cerebral vessels with a pharmacology closely resembling that of the 5-HT_7 receptor. Accordingly, the relaxant response to 5-HT in cerebral vessels was mimicked by 5-carboxamidotryptamine (5-CT) and 5-methoxytryptamine, but not by sumatriptan or α-methyl-5-HT. Furthermore, 5-HT- and 5-CT-induced relaxation was antagonized by clozapine, mesulergine, methiothepin, spiperone and *cis*-*n*-(2-hydroxycyclopentyl)-6-methyl-1-(1-methylethyl)ergoline-8-carboxamide (LY215840) with estimated affinity values that correlated significantly with their binding affinity at 5-HT_7 receptors, while the relaxant response to 5-CT was inhibited by a protein kinase A inhibitor (Ishine et al., 2000; Terrón and Falcón-Neri, 1999). In agreement with these data, earlier studies had shown an inhibitory effect of 5-HT on the spontaneous rhythmic contraction of porcine pial veins. Consistent with a role of the 5-HT_7 receptor, the 5-HT-induced effect was mimicked by 5-CT, antagonized by mesulergine, enhanced by a cyclic AMP phosphodiesterase inhibitor, diminished by a protein kinase A inhibitor, and accompanied by an increase in cyclic AMP, but not cyclic GMP synthesis (Lee et al., 1994; Ueno et al., 1995). It should be recalled, in this regard, that both native (Trevethick et al., 1986; Sumner et al., 1989) and cloned (Bard et al., 1993; Lovenberg et al., 1993; Plassat et al., 1993; Ruat et al., 1993; Shen et al., 1993) 5-HT_7 receptors are positively coupled to the adenylate cyclase system. Importantly, in contrast to the negligible relaxation mediated by the 5-HT_{2B} receptor in the pig cerebral artery (Schmuck et al., 1996), 5-HT_7 receptor-mediated relaxation in dog and pig cerebral vessels was strong as, in some cases, it abolished spasmogen-induced contraction (Ishine et al., 2000; Terrón and Falcón-Neri, 1999).

Similarly, in vivo studies have demonstrated an ability of 5-HT to produce potent vasodilator responses in the external carotid circulation of vagosympathectomized dogs pretreated with *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl) [1, 1, biphenyl]-4-carboxamide (GR127935) via a receptor pharmacologi-

cally resembling the 5-HT_7 type (Villalón et al., 1997). These functional studies paralleled those showing spiperone- and methiothepin-sensitive vasodilator responses to intra-left atrial 5-CT administration in the common carotid vascular bed of intact anesthetized dogs (Cambridge et al., 1995).

Thus, it can be seen from the above observations that the 5-HT_7 receptor-mediated vasodilator mechanism operates in vascular structures that have been implicated in migraine, such as the middle cerebral and the external carotid arteries (Graham and Wolff, 1938; Friberg, 1991; Friberg et al., 1991; Nichols et al., 1990; Olesen et al., 1994; Saxena, 1972; Saxena and De Vlaam-Schluter, 1974; Tunis and Wolff, 1952, 1953; Wolff, 1963). Since a correlation was found between headache and vasodilatation of these large vessels (Friberg et al., 1991; Nichols et al., 1990; Olesen et al., 1994; Wolff, 1963), the potential pathophysiological and therapeutic relevance of the 5-HT_7 receptor at this level can be envisaged. In view of the failure of several studies to show a correlation between migraine headache and changes in regional cerebral blood flow (see Friberg, 1991 for review), it seems then reasonable to hypothesize, on the basis of the observations described above, that the 5-HT_7 receptor may elicit vasodilatation in large conduit vessels during a migraine attack, which is consistent with Wolff's original proposal (Wolff, 1963; see also Graham and Wolff, 1938), and that the absence of changes in regional cerebral blood flow reflect the response does not take place in small caliber vessels, e.g. meningeal resistance vessels. In any case, additional studies will be required to test this hypothesis and to determine whether a similar mechanism operate in the human cranial vasculature, where expression of the 5-HT_7 receptor messenger RNA (mRNA) has already been detected by RT-PCR (Schmuck et al., 1996).

Several pieces of information have now become available, on the other hand, to suggest that the 5-HT_7 receptor may be involved in pain, hyperalgesia and neurogenic inflammation by mediating excitatory responses in neuronal systems (Cardenas et al., 1999; Fasmer et al., 1986; Pierce et al., 1996a; Taiwo et al., 1992). Thus, high expression levels of 5-HT_7 transcripts were detected centrally in areas implicated in sensory and pain processing, including the medial geniculate nucleus, superior and inferior colliculi, central gray and spinal trigeminal nuclei (To et al., 1995). In the periphery, the 5-HT_7 receptor mRNA was found strongly expressed in sensory neuronal groups, such as the dorsal root ganglia, superior cervical ganglia and lumbar sympathetic ganglia (Pierce et al., 1996b, 1997). Significantly, the 5-HT_7 receptor was recently reported to increase the hyperpolarization-activated cation current (I_H) in specific populations of rat dorsal root ganglion cells (Cardenas et al., 1999). This finding led to the suggestion that 5-HT may modulate excitability, neurotransmitter release and firing patterns in certain subpopulations of sensory neurons via (5-HT_7 receptor-mediated) changes in I_H (Cardenas et al., 1999).

Interestingly, a role for the 5-HT_7 receptor in peripheral neurogenic inflammation has been proposed as a high concentration of sumatriptan, which displays low to moderate affinity for the 5-HT_7 receptor (Bard et al., 1993; Ruat et al., 1993; Shen et al., 1993; To et al., 1995), significantly potentiated capsaicin-induced plasma extravasation in the rat knee joint (Pierce et al., 1996a). As mentioned above, the 5-HT_7 receptor mRNA was detected in the rat lumbar dorsal root ganglia, i.e. a tissue innervating the knee joint (Pierce et al., 1996a,b), and the 5-HT_7 receptor protein was shown to increase I_H in this tissue (Cardenas et al., 1999). That a similar excitatory mechanism may have strong clinical implications in migraine is suggested by the fact that 5-HT_7 receptor transcripts were found consistently expressed in human trigeminal ganglia (Terrón et al., 2001), and that 20–30% of patients treated with sumatriptan experience lack of migraine relief and excessive injection site pain (The Subcutaneous Sumatriptan International Study Group, 1991).

Although no functional evidence has been provided for a role of the 5-HT_7 receptor in hyperalgesia and neurogenic inflammation in humans, the above observations are in keeping with the hypothesis that a 5-HT_7 receptor-mediated excitatory mechanism may operate in the trigeminovascular system during a migraine attack. As pointed out above, such a modulatory role of 5-HT seems feasible given the anatomical proximity of the serotonergic and trigeminal innervations within the vascular wall of large and small intracranial cerebral vessels.

5. Correlation analysis between active doses of prophylactic 5-HT receptor antagonists and their affinity at 5-HT_7, 5-HT_{2B} and 5-HT_{2C} receptors

Since most of the migraine prophylactic drugs, including amitriptyline, chlorpromazine, cyproheptadine, dihydroergotamine, lisuride, methysergide and mianserin, display relatively high affinity at the 5-HT_7 receptor (Table 1; see Terrón, 1998b,c for review), the obvious implication from the observations referred to above is that vascular and neuronal 5-HT_7 receptors might be important targets of these drugs (Terrón, 1998b,c). This hypothesis does indeed gain weight when considering that the average orally active doses of the above drugs significantly correlate ($r = 0.949$; $P < 0.001$) with their reported 5-HT_7 receptor affinity (Fig. 1). It should be recalled that a significant correlation is also obtained when considering affinity values at the 5-HT_{2B} ($r = 0.716$; $P < 0.05$) receptor (Fig. 1; see also Kalkman, 1994; Schmuck et al., 1996), which raises the possibility that this receptor may also be involved in migraine pathogenesis.

Although no data on the effect of ritanserin as migraine prophylactic have been reported thus far, the drug has proven effective to reduce the pain total index and analgesic consumption in patients with chronic tension-type headache and patients with coexisting migraine and tension-type headache (Nappi et al., 1990). For this reason, ritanserin was included in the correlation analysis (Fig. 1). Another consideration that

Table 1
Orally active doses of several 5-HT receptor drugs with proven migraine prophylactic activity and their affinity for 5-HT receptors thought to be involved in migraine pathogenesis

	Dose (μmol/day)	Average log dose	Affinity (pK_i/pK_B/pA_2)		
			5-HT_7	5-HT_{2B}	5-HT_{2C}
Amitriptyline	31.9–191.2	1.980	7.03[a]	7.87	7.14
Chlorpromazine	112.6–422.2	2.339	7.15[a]	7.33	7.03
Cyproheptadine	37.1–74.1	1.720	6.91	8.44	7.47
Dihydroergotamine	7.4–14.7	1.018	8.04	7.97	7.48[b]
Lisuride	0.055–0.165	−1.000	9.15	–	8.0
Methysergide	4.3–12.8	0.870	7.6	11.24	8.94
Mianserin	99.7–199.5	2.149	6.82	7.59	8.29
Pizotifen	10.5–21	1.172	–	8.49	7.82
Ritanserin	20.9	1.320	7.35	8.76	8.7

Data for daily oral doses of migraine prophylactics in mg/day, and transformed here to μmol/day, were taken from Del Bene et al. (1983), Franchi and Mallucci (1983), Gomersall and Stuart (1973), Herrmann et al. (1977), Lance et al. (1970), Monro et al. (1985), Nappi et al. (1990), Saper (1978), Scott (1992) and Somerville and Herrmann (1978). Data for human 5-HT_7 receptors are from Bard et al. (1993), Bourson et al. (1997), Cushing et al., (1996) and Prins et al. (1999). Data for human 5-HT_{2B} and 5-HT_{2C} receptors are from Bourson et al. (1997), Schmuck et al. (1996) and Wainscott et al. (1996).

[a] Rat 5-HT_7 receptor (Ruat et al., 1993; Shen et al., 1993).

[b] Rat 5-HT_{2C} receptor (Hoyer, 1988).

should be taken into account for the analysis is the fact that methysergide is a pro-drug with methylergometrine being an active metabolite (see Tfelt-Hansen and Saxena, 2000 for review). Like methysergide (Table 1), methylergometrine also displays considerable affinity at 5-HT_{2B} ($pK_i = 9.31$) and 5-HT_{2C} ($pK_i = 7.91$) receptors (Rothman et al., 2000), though its affinity at the 5-HT_7 receptor is not known. It is to be recalled, however, that although methylergometrine is able to abort migraine attacks (see Mylecharane, 1991), most likely because of its higher affinity and efficacy than methysergide at contractile 5-$HT_{1B/1D}$ receptors (MacLennan and Martin, 1990), the drug has not been clinically proven as preventative treatment even if it admittedly may account, at least in part, for the migraine prophylactic efficacy of the parent compound, methysergide (Tfelt-Hansen and Saxena, 2000). In any case, the correlation values for both 5-HT_{2B} and 5-HT_{2C} receptors are not greatly affected if affinity values for methysergide are replaced by those corresponding to methylergometrine ($r = 0.716$ and 0.805, $P < 0.05$, for 5-HT_{2B} receptors with methysergide and methylergometrine binding data, respectively; and $r = 0.337$ and 0.319, $P > 0.05$, for 5-HT_{2C} receptors with methysergide and methylergometrine binding data, respectively).

Finally, it is worth highlighting that whereas lisuride gives much weight to the 5-HT_7 correlation, the drug is not present in the 5-HT_{2B} receptor correlation. Admittedly, a more reliable comparison between the correlations for both receptors will be possible when affinity values for lisuride at 5-HT_{2B} receptors become available.

6. Hypothesis on the involvement of the 5-HT_7 receptor in migraine pathogenesis

The hypothesis on the role of the 5-HT_7 receptor in migraine is illustrated in Fig. 2. It is suggested that migraine may result from suddenly increased levels of 5-HT released from perivascular serotonergic fibers and perhaps also from 5-HT-containing noradrenergic fibers that innervate the cranial vasculature. This massive discharge would arise from an increased activation of the dorsal raphe nucleus and locus coeruleus resulting as a consequence of a hypothalamic dysfunction probably situated in the suprachiasmatic nucleus. It

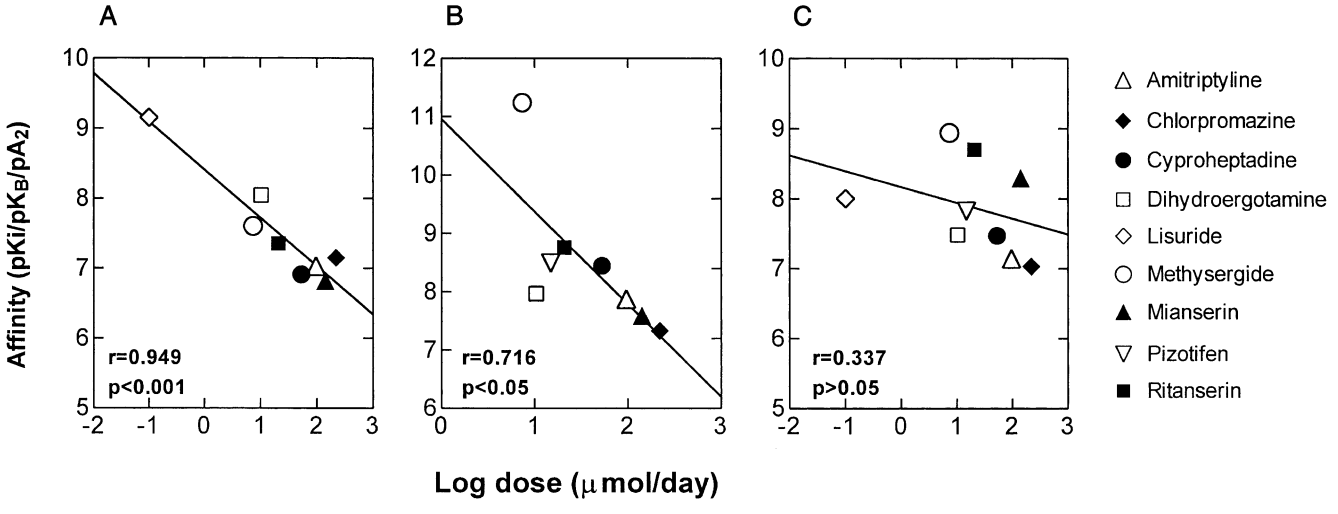

Fig. 1. Correlation between the average orally active doses of several 5-HT receptor drugs with proven migraine prophylactic activity with their reported affinity (pK_i/pK_B/pA_2 values) at 5-HT_7 (a), 5-HT_{2B} (b) and 5-HT_{2C} (c) receptors. In most cases, available affinity values corresponding to human receptors were included (see Table 1). Average doses were used to calculate the correlations. Significant correlations were obtained for 5-HT_7 ($r = 0.949$; $P < 0.001$) and 5-HT_{2B} ($r = 0.716$; $P < 0.05$) but not for 5-HT_{2C} ($r = 0.337$; $P > 0.05$) receptors.

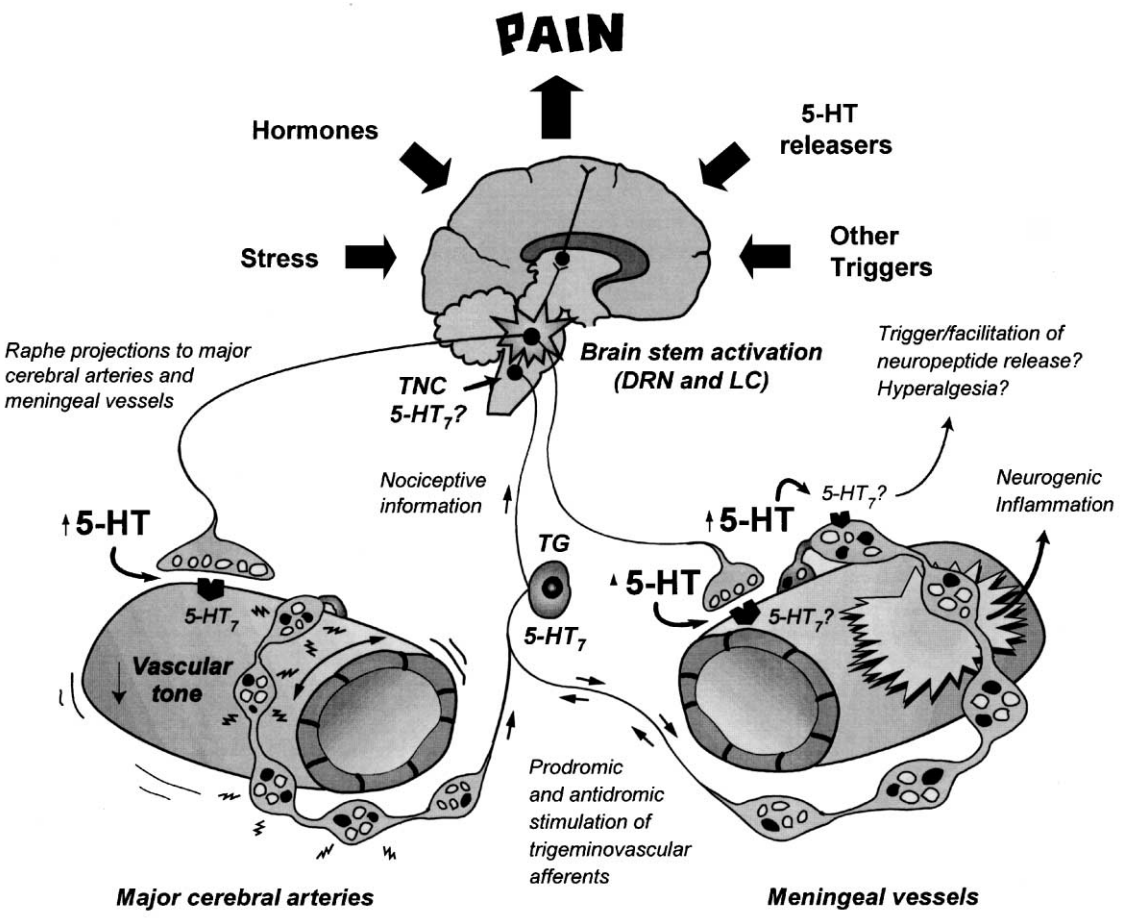

Fig. 2. Schematic representation of the hypothetic mechanisms involving the 5-HT_7 receptor in migraine pathogenesis. It is proposed that a massive release of 5-HT from serotonergic and 5-HT-containing noradrenergic fibers resulting from dorsal raphe nucleus (DRN) and locus coeruleus (LC) activation, respectively, would lead to stimulation of 5-HT_7 receptors located in large conduit vessels, e.g. middle cerebral artery, to produce abnormal vasodilatation. This process, involving increased transmural pressure, would cause mechanical distension and activation of trigeminal nerve terminals that innervate the vascular wall. A subsequent axo-axonal reflex would bring about antidromic stimulation of sensory nerve endings at the level of dural vessels in the meninges with the resulting release of pro-inflammatory peptides (e.g. substance P and CGRP). This pathological scheme is coherent with the absence of important and consistent changes in regional cerebral blood flow during migraine attacks. The proposed mechanism does not exclude the possibility that neuronally released 5-HT could also interact with trigeminovascular afferents to trigger and/or facilitate neuropeptide release at the level of meningeal vessels. TG, trigeminal ganglion. TNC, trigeminal nucleus caudalis.

follows that the increased amounts of 5-HT would target specific 5-HT receptors similar to the 5-HT_7 type located in the smooth muscle cells of large conduit vessels to cause vasodilatation. This view is consistent with results from regional cerebral blood flow studies suggesting that the blood flow changes that occur in migraine are restricted to large conduit vessels, e.g. middle cerebral artery (Friberg et al., 1991). Large vessel wall distension would then lead to activation of trigeminal sensory nerves (Moskowitz, 1984; Nichols et al., 1990). In accordance with what Humphrey and Feniuk (1991) have pointed out, activation of trigeminal fibers innervating meningeal arteries would be initiated antidromically via axo-axonal reflexes. We suggest these reflexes be generated by the earlier activation of trigeminal sensory nerves at the level of large intracranial vessels. Since the pain in migraine may arise from meningeal arteries, the resulting release of pro-inflammatory peptides, i.e. substance P and calcitonin gene-related peptide (CGRP), would be expected to occur primarily in these vessels. It could further be conceived that 5-HT_7 receptors located in the trigeminal fibers that neighbor cerebrovascular serotonergic terminals in meningeal vessels may also produce hyperalgesia and triggering/facilitation of neuropeptide release at this level (Fig. 2).

On the basis of the putative pathophysiological scenario described above, the therapeutic efficacy of migraine prophylactic 5-HT receptor antagonists could be explained by blockade of 5-HT_7 receptors mediating craniovascular vasodilatation and activation of perivascular trigeminal nerve endings. Thus, a prerequisite for these drugs to work would be that they were given *before* the migraine attack is initiated and the above pathological events established, i.e. before 5-

HT is released to activate 5-HT_7 receptors. This can explain why prophylactic 5-HT receptor antagonists offer no benefit in the acute treatment of migraine. Instead, a pharmacological approach (e.g. sumatriptan) leading to cranial vasoconstriction, i.e. via activation of 5-HT_{1B} receptors, and inhibition of neuropeptide release from trigeminovascular afferents, i.e. via activation of 5-HT_{1D} or 5-HT_{1F} receptors, will acutely work to relief migraine headache (see Hamel and Saxena, 2000). Indeed, exception made of methysergide, which reportedly causes cranial vasoconstriction by virtue of its partial agonist activity at 5-HT_{1B} receptors, and it also inhibits neuropeptide release from perivascular sensory nerve endings, the other prophylactic compounds are devoid of important cranial vasoconstrictor properties (see Tfelt-Hansen and Saxena, 2000 for review) and their effects on trigeminovascular nerve fibers are unknown.

7. Conclusion

The potential implication of the 5-HT_7 receptor in cerebrovascular vasodilatation, hiperalgesia and neurogenic inflammation might pave the way for new research efforts towards the understanding of migraine pathophysiological mechanisms and drug development. The putative involvement of this receptor in the vascular and neurogenic alterations of migraine is consistent with the concept that the condition may result from a massive release of 5-HT after abnormal activation of the brain stem that is secondary to a hypothalamic dysfunction (Fozard, 1995; Fozard and Kalkman, 1994), and that the disease arises primarily from a neurovascular interaction (May and Goadsby, 1999). Admittedly, despite the fact that the correlation analysis suggests the 5-HT_7 receptor be a target of migraine prophylactic compounds, interpretation of their antimigraine effects in terms of blockade at this site is at present speculative, just like in the case of 5-$HT_{2B/2C}$ receptors. Clinical trials with selective 5-HT_7 receptor antagonists will be awaited with interest so the potential involvement of the 5-HT_7 receptor in migraine pathogenesis and preventative treatment is elucidated.

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