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REVIEW ARTICLE

Serotonin and migraine: a reconsideration of the central theory

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Abstract The 5-hydroxytryptamine (5-HT) has been implicated in migraine pathophysiology for the past 50 years. A low central 5-HT disposition associated with an increase in 5-HT release during attack is the most convincing change of 5-HT metabolism implicated in migraine. Peripheral studies on plasma/platelet have not generally shown low 5-HT levels. Studies on 5-HT reactivity showed hypersensitivity, also expressed as reduced tachyphylaxis (habituation), which successively was evidenced as the most characteristic marker of an altered sensory neurotransmission. Even the gender and seasonal variations of 5-HT parameters seem to agree with a low 5-HT turnover with receptoral hypersensitivity. The interpretation of the effects of some serotonergic drugs and recent neuroimaging studies give major evidence for this cascade of events. Although the exact mechanism that links abnormal 5-HT neurotransmission to the manifestation of head pain has yet to be fully understood, a deficit on 5-HT descending pain inhibitory system is still probably today the most implicated in migraine pathophysiology. This short review focuses and discusses the alteration of peripheral and central 5-HT parameters in migraine patients.

Keywords Migraine · 5-Hydroxytryptamine · Gender differences · Seasons · 5-HT release · Habituation

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Introduction

Thirteen years ago, concluding a revision on studies concerning the alterations of peripheral (platelets, vessels) serotonergic parameters in migraine patients I stated, "Why conduct any more research in the periphery?" [1]. In fact, further studies in plasma/platelet do not yield substantial new findings, while other vascular studies were not performed.

Since the first evidence from the Florence researchers of an altered metabolism of 5-hydroxytryptamine (5-HT), that is an increased urinary excretion of the 5-HT metabolite 5-hydroxyndoleacetic acid (5-HIAA) [2], the aim of studies on 5-HT was to show if migraine subjects have others modifications of 5-HT parameters. The original hypothesis of a deficiency of central 5-HT neurotransmission (empty neuron) as a biological marker of migraine subjects, with consequent 5-HT receptoral hypersensitivity [3, 4] is today discussed. In this light, the concept of 5-HT vulnerability, defined as increased sensitivity to natural or experimental alterations of the serotonergic system, proposed for depression [5] can be valid also for migraine.

Other than peripheral studies (platelets/vessels), the action of drugs affecting 5-HT central neurotransmission, that is, 5-HT selective reuptake inhibitors (SRRI), 5-HT releasers, 5-HT precursors, 5-HT receptor agonists, in migraine subjects was evaluated [6]. More recently, studies on possible genetic basis for altered 5-HT neurotransmission and neuroimaging studies on 5-HT metabolism were performed [7, 8].

The aim of this review is to critically evaluate studies concerning variations of 5-HT parameters, to try to define some data in order to avoid that further research is based on incorrect statements, which are frequently deduced from

animal studies and therefore not completely transferable to humans.

Any research on possible alterations of central 5-HT neurotransmission (but also of other neurotransmitters) in migraine subjects must consider a few, but definite clinical remarks, which are evident to any headache specialist, as the clear prevalence in females and familiarity. Among the possible trigger factors, peri-menstrual period, the post-stress weekend headache, the time immediately after an intense emotion/alarm/fear, alcoholic drinks, are those clearly associated with pain.

Peripheral studies

Platelets as a model of central 5-HT neurons, and then as the mirror of possible alterations of 5-HT neurotransmission in the brain, concerning the content, receptors and reuptake/transporter (SERT), were suggested and debated in the literature. Plasma 5-HT and 5-HIAA are also misleading since most plasma 5-HT is derived from the gut and less than 10% of 5-HIAA comes from the brain. Although no correlation was reported between midbrain and platelet SERT, recent single photon emission tomography (SPECT) evidence shows gender differences; that is SERT in midbrain are positively correlated with 5-HT uptake and negatively with 5-HT concentration of platelets, but only in females [9]. An hypothetical alteration of brain 5-HT neurotransmission in migraine patients, probably genetically determined, was repeatedly searched in the periphery (platelets, vessels, etc.), and sex and seasons were underlined as critical variables in the interpretation of diagnostic group differences [1, 10].

Platelets

Generally, it was stated that migraine patients have low platelet 5-HT, a sign of hyposerotonergic status of migraine. However, the vast majority of data show normal platelet and plasma 5-HT concentrations in migraine without aura both between attack and during pain in comparison with control subjects [11–25] (Table 1). Even the number of platelet 5-HT transporters (indirect indices of 5-HT reuptake) was normal in migraine and in chronic tension headache [26]. The release of 5-HT from platelet reported in some studies was probably non-specific and was considered not casually related to migraine attack [10, 27]. The finding of higher 5-HT platelet content in migraine with aura [18] was not confirmed [15, 21, 23]. Even in tension headache, platelet and plasma 5-HT are not decreased in headache-free period in comparison to control subjects [12–15, 19, 21, 28–34] (Table 2). Therefore, we can state that a hyposerotonergic status is not present in migraine and tension headache patients in the periphery. The observed reduced platelet 5-HT in chronic migraine with or without medication overuse [20, 35, 36] are not found in chronic tension headache [34].

Table 1 Comparative studies of platelet/plasma 5-HT levels between patients with migraine without aura in attack (*In*) and in attack-free period (*Out*) and control subjects

References	Platelets		Plasma	
	Out	In	Out	In
Waldenlinden [11]	<			
Shukla [12]	=			
Takeshima [13]			>	
Anthony [14]	=	=		
Ferrari [15]	=	<	<	=
Nakano [16]	=			
D'Andrea [17]	=			
D'Andrea [18]	=		=	
Kitano [19]			=	
Srikiatkhachorn [20]	=			
Stronks [21]	=		=	
Evers [22]	<	<	=	=
Jerney [23]	=	=		
Juhasz [24]	<			
Drummond [25]	=			

Table 2 Comparative studies of platelet/plasma 5-HT levels between tension headache in attack (*In*) and in attack-free period (*Out*) with control subjects

References	Platelets		Plasma	
	Out	In	Out	In
Rolf [28]		<		
Shukla [12]	=			
Takeshima [13]			>	
Anthony [14]		<		
Ferrari [15]		=		=
Shimomura [29]		<		
Leira [30]		>		
Kitano [19]				<
Jensen [31]			=	>
D'Andrea [32]	>		>	
Mazzotta [33]	>			
Bendtsen [34]		=		=
Stronks [21]	=		=	

Vascular 5-HT reactivity

The larger amount of studies on 5-HT vascular reactivity in migraine patients were performed in hand vein and

previously reviewed [1]. From these studies three important findings deserve discussion: in fact they can be related to a possible 5-HT hypersensitivity provoked by hyposerotonergic state.

Gender differences

The evaluation of 5-HT reactivity in hand vein in a large sample shows that migraine subjects are more sensitive to controls. Moreover, female migraineurs are more sensitive than male migraineurs (Fig. 1). Higher 5-HT sensitivity in females was also found in other human vascular districts such as mammary and radial arteries [38, 39]. Interestingly, a heritable sexual dimorphism was described for whole blood 5-HT levels with higher level in women compared with men [40].

Important gender differences exist also in human brain 5-HT neurotransmission [41, 42], different to those with animal studies [43]. Studies of cerebrospinal fluid (CSF) concentrations of 5-HIAA, indirect indices of 5-HT synthesis and, by implication, of the transmitter for release into the synaptic cleft have yielded inconsistent results (see [42]). However, 5-HIAA reflects other processes in addition to 5-HT synthesis.

Validated positron emission tomography (PET) studies showed that men synthesize 5-HT significantly faster than women, and also with left-to-right differences [42, 44] even if an inverse finding was reported in a small study [45]. These gender differences are found in cortical regions but not in sub-cortical structures, including brainstem, where most 5-HT cell bodies are found [42]. Acute tryptophan depletion (ATP) causes a larger decrease in the rate of 5-HT synthesis in women [44]. It was affirmed that human males and females seem to have similar stores of brain 5-HT, but if there were increased utilization of 5-HT during stressful situations, a lower rate of synthesis in the females may not be as efficient in maintaining adequate stores of the neurotransmitter and then in such situations the 5-HT level would decline more in females [44]. Healthy women were reported to have higher 5-HT transporter availability in the diencephalon and brainstem compared to men. Since the 5-HT transporter functions to regulate 5-HT neurotransmission, these findings tend to suggest that baseline 5-HT functions may be higher in women versus men. Women have also higher number of 5-HT_{1A} receptors but not of 5-HT_{2A}: the latter are, however, increased by estrogens (see [41]). The greater (upregulation) 5-HT_{1A} bindings may be consequence of lower activity (synthesis) of serotonergic system (see [42]). Estrogens and estrogens + progesterone (that is the reproduction of the hormonal cycle of females) act on the gene and protein expression in dorsal raphe nucleus of non-human primates in a manner that suggests that 5-HT neurotransmission should increase: reduction of 5-HT_{1A}, decrease 5-HT reuptake transporter (SERT), increase of tryptophan hydroxylase, MAO-A inhibition. The direct evidence of steroid-induced 5-HT release was sought with microdialysis [46].

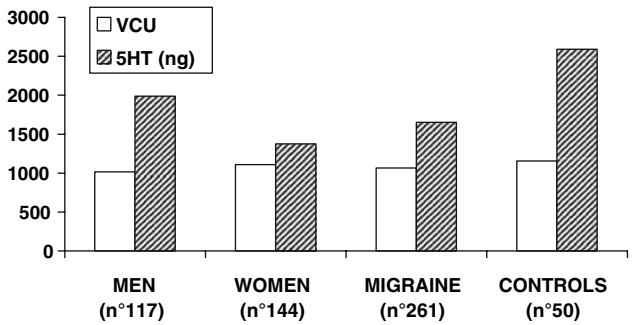

Fig. 1 5-HT reactivity in the hand vein expressed in venoconstriction units (VCU). Significant differences were found in the 5-HT doses eliciting roughly the same amount of contraction: migraine patients (examined in headache-free period) are more sensible (lower 5-HT dose) than controls ($P < 0.001$), migraine women are more sensible than migraine men ($P < 0.001$). Data from Panconesi et al. [37]

Seasonal variation

The evaluation of seasonal changes in the vascular 5-HT hand vein reactivity clearly shows a lesser 5-HT sensitivity in the summer (Fig. 2). Many clinical studies, conducted in Italy and Austria, show that migraine frequency is lower in the summer in comparison to winter or autumn [47–52] (Table 3). Other studies do not concord [49, 50]. However, in one of these [50], when a bias was corrected, the seasonal differences disappeared, and even if real the seasonal effect is weaker. Also the reported higher attacks of migraine with aura (but not without aura) in the light season compared to the dark season in the arctic area became insignificant when insomnia-related attacks were removed [53]. In spite of this, in this latter study the peak frequency of migraine without aura was in December and the lowest frequency in June.

There are many evidences of increased content/turnover of 5-HT associated to decreased 5-HT receptor sensitivity

Table 3 Frequency of migraine attack by seasons

References	Winter	Spring	Summer	Autumn
Marrelli [47]	++++	+++	+	++
Cugini [48]	++++		+	
Robbins [49]	+	++++	++	+++
Fox [50]	+	++	++++	+++
Rieder [51]			+	++++
Soriani [52]	++++		+	++++

in the brain, and also of plasma and platelet 5-HT content in the summer [1, 54].

The amount of 5-HT and its metabolites in the CSF are, at best, an imprecise indicator of brain serotonergic neuronal activity (synthesis). The measure of the differences between concentrations of neurotransmitters in the arteries and the internal jugular vein permit us to estimate the amounts produced in the brain. With this technique it was shown that in man, 5-HT turnover was lowest in winter and highest in summer, and was correlated to the bright sunlight of the day [55]. This finding was selective because extracerebral 5-HT turnover and also brain turnover of norepinephrine and dopamine did not show any seasonal variation. Another interesting preliminary finding is the reduced brain SERT availability in the winter compared to the summer [56].

Habituation

About 25 years ago, it was proved that migraine patients usually do not show tachyphylaxis (habituation) to the vasoconstrictive activity of 5-HT, different to control subjects [57].

Later on, the lack of habituation was thought to be the principal interictal abnormality in sensory processing in migraineurs, hypothesized due to hypofunction of 5-HT pathway to the thalamus and cortex [58–62]. Normalization of habituation during the attack was found [22, 63, 64] with a parallel decrease of platelet 5-HT [22]. According to Evers [22] the lack of significant association between the amount of habituation and platelet or plasma 5-HT suggested that the habituation phenomenon cannot be attributed to 5-HT neurotransmission; however, central 5-HT modification cannot be excluded.

Although the phenomenon of reduced habituation in migraineurs has been investigated mainly in the central nervous system, there are examples even in the peripheral system [65–67].

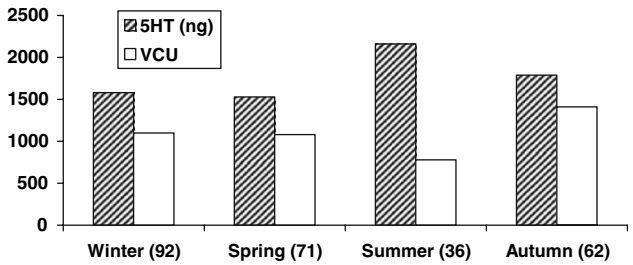

Fig. 2 Seasonal variations of 5-HT hand vein contraction, expressed in venoconstriction units (VCU), in a group of 261 migraine patients. In the summer higher 5-HT doses provoke a lesser amount of venoconstriction. From Panconesi et al. [37], modified

Central studies

Studies on the peripheral serotonergic system of migraineurs were often inconsistent, partly because of negative results, partly because of confounding factors, and their significance remains a matter of debate [1, 10]. Attempts toward an assessment of functional status of brain serotonergic system in migraineurs in vivo have been, until recently, possible only by the interpretation of mechanisms of action of some serotonergic drugs followed by measurement of their effects. There are few doubts that some 5-HT agonists can provoke a headache; what is in discussion is their mechanism [6]. Three major classes of 5-HT agonists exist: 5-HT releasing agents, 5-HT reuptake inhibitors (SSRI), 5-HT receptor agonists. Recently, methods for depletion of brain 5-HT and also neuroimaging studies to assess brain 5-HT level in vivo were applied to migraine.

5-HT releasing agents

Reserpine and fenfluramine

A single dose of reserpine will consistently induce headaches, closely resembling migraine, when administered intravenously, intramuscularly, or subcutaneously; but not or rarely in healthy controls [68]. Also fenfluramine provokes headache in more than 50% of migraine patients, with a mean latency of 4.5 h, which was suggested to be due to 5-HT depletion, but not or less frequently in control subjects [65, 69]. However, the hypothesized 5-HT neuronal depletion as a mechanism of induced-headache apparently contrasts with some reports showing that chronic treatment with these two drugs, which probably provokes more depletion than acute treatment, and with the prototype of the depleting drugs p-chlorophenylalanine (PCPA), can have therapeutic effect on some migraine patients [69–71]. Fenfluramine challenge test administered to healthy subject (no migraine sufferers), provoked side effects in 90% of cases during the day, but more than half the following day: headache/migraine account of 43% of cases [72].

m-Chlorophenylpiperazine (mCPP)

The 5-HT_{2C} receptor agonist mCPP is the most extensively used probe to show an altered serotonergic neurotransmission in migraine.

Brewerton et al. [73] reported that mCPP provoked severe headaches with migraine features 6-12 h after a single oral dose (0.5 mg/kg) in about 50% of female subjects. The incidence of headache was significantly greater in subjects with a personal or family history of migraine. Headache response following mCPP is greater

in female patients with bulimia nervosa than control, irrespective of a personal or family history of migraine [74]. Another study tested on a few subjects, predominantly men, reported that mCPP (0.25 mg/kg) induced headache in 50% of subjects, but without differences between migraine patients and controls, with a mean time onset of 5.3 h [75]. The induction of migraine-like headache in some subjects without personal history of migraine was also reported during pharmacokinetics studies, 5–10 h after oral administration [76]. However, that mCPP provokes more migraine (according to International Headache Society classification) than placebo and more likely in migraine patients than in controls was more recently confirmed [77].

The headache rating and duration was correlated with plasma peak concentration of mCPP occurring several hours earlier, and with the area under the curve (AUC), without differences between migraine and controls [73–75, 77], but no relation with plasma level was also reported [76]. Large inter-individual differences in mCPP pharmacokinetic parameters were shown [76, 78]. Interestingly, the AUC after oral administration varied more than 40-fold, was threefold higher than intravenous administration, reached their peak after more than 3 h, and could still be measured after 8 h, and no differences were seen between male and females [76].

The fact that there were no differences in the cortisol response to mCPP between migraine patients and controls had led to the suggestion that 5-HT_{2C} receptors are normal in migraine [75, 79]. Prolactin response was shown to be both normal [75] and increased [79]. The peak of these neuroendocrine responses was at 90–150 min, and both correlation [75, 79], and non-correlation [78] with mCPP plasma concentrations were reported. Also some subjective side effects, other than headache, occur within 3 h [78]. The fact that hormonal response precedes the headache suggests that mCPP interaction with 5-HT receptors in the brain occurs initially in the cascade of events that ultimately results in headache [75], or that headache is not due to direct 5-HT receptor stimulation. Moreover, whether 5-HT receptor sensitivity is decreased or increased probably depends on the anatomical location of the pathway mediating the target response, and differential involvement of 5-HT receptor subtype. In fact, mCPP in addition to its 5-HT receptoral agonist activity is similar to fenfluramine, a potent 5-HT releaser [80]. This property should be taken into account for the similar time latency in the headache provocation shown by these two drugs.

However, for its adverse side effects and its variability of pharmacokinetic and of clinical and hormonal effects, m-CCP was suggested to be an inadequate drug to carry out challenge tests to test receptor sensitivity in vivo [78].

Other 5-HT releasing drugs

The 3,4-methylenedioxymethamphetamine (MDMA/ecstasy) is an illicit drug that stimulates the release of 5-HT from neurons [80]. Although systematic studies have not been performed to show headache provocation, a comprehensive review of studies on the acute subjective effects of MDMA shows that not only headache, but also nausea and vomiting, is one of the more frequently reported somatic effects [81].

Selective serotonin reuptake inhibitors (SSRI)

Two good reviews show that SSRI have no therapeutic activity in migraine and tension headache [82, 83]. Moreover, the preventive effect of amitriptiline seems not due to 5-HT reuptake inhibition [84]. On the other hand, the headache is not a main side effect of SSRI reported in the headache treatment studies [6, 82]. Consequently 5-HT reuptake inhibition, differently by 5-HT release or 5-HT receptor agonism, seems not to be important in the pathogenesis of headache. What is the reason?

The SSRI and 5-HT releasers both elevate extracellular concentration of transmitter via transporter-dependent mechanism, but with important differences (see [80]): (1) SSRI tends to produce small increases in extracellular neurotransmitter whereas releasers tend to produce robust increases as shown by in vivo microdialysis (2) Fenfluramine, norfenfluramine, mCPP and MDMA are potent 5-HT releasers via carried-mediated exchange mechanism involving SERT sites in the brain, (3) Fenfluramine and mCPP also have direct agonist actions at 5-HT receptors. Fenfluramine, especially their metabolite norfenfluramine, are potent 5-HT_{2C} and 5-HT_{2B} receptor agonists, while mCPP is a very potent agonist in human 5-HT_{2C} receptors and also at 5-HT_{1A} [85]. One approach for discriminating presynaptic (i.e., 5-HT release) versus postsynaptic (i.e., 5-HT receptor agonism) activities is pretreatment with SSRI which antagonize SERT and then the presynaptic effect of 5-HT releasers. Using this paradigm it was shown that anorectic action of fenfluramine is mediated at least in part by postsynaptic action. In this light, it would be of interest to see if mCPP is capable of provoking headache during SSRI treatment.

Another interesting finding was that high-doses of mCPP do not deplete 5-HT in the brain, and therapeutic doses of fenfluramine seem not to provoke depletion and then neurotoxicity [80].

5-HT depletion

Historically, methods to functionally deplete serotonin have been problematic and inapplicable to humans. Rapid

tryptophan depletion (RTD) is a method that markedly diminishes plasma tryptophan and brain 5-HT synthesis and availability [44, 86], although there is evidence that it does not alter the efflux/release from neurons [87]. RTD as a method for studying 5-HT depletion is particularly suitable for subpopulations that show a vulnerability to 5-HT dysregulation. That is, those groups that show a reduced availability of central 5-HT are especially sensitive to RTD [87, 88]. It was shown that RTD does not trigger full-blown migraine attack, even if it intensifies migrainous symptoms [25, 89].

Neuroimaging studies

Recently, neuroimaging studies demonstrated a significant increase of mesopontine brainstem (but not in the thalamus, the rostral relay station for nociceptive signals) SERT availability in headache-free migraine patients, a site which neuroimaging studies pointed to be specific for migraine pathophysiology. However, it remains to be elucidated as to whether it is causally related to migraine pathophysiology, or whether it reflects a chronic pain condition, that is, if it is the cause, or the consequence of migraine chronification [90]. Imaging methods to assess brain 5-HT level in vivo are lacking; however, a PET study on a small group of female migraine patients reported a global, non-region-specific increase in the brain 5-HT synthesis capacity than female controls [91].

Different from this study, it was shown recently that in migraine patients the 5-HT synthetic rate was slightly reduced with a sudden increase early in the attack, especially in the dorsal brainstem, to levels of control subjects: sumatriptan promptly reduced the 5-HT synthesis to lower values than those measured interictally, independently from changes in pain intensity. No side effects appeared at any stage. No differences were found between controls and migraine subjects during the attack or interictally, even in the last case, a slightly non significant reduction was found [92]. The same study group shows that female migraine patients exhibit lower 5-HT synthesis than female controls [93]. As reported above, the reduced habituation of cortical auditory and visually evoked potential in migraineurs interictally is considered the most characterizing marker of migraine patients, hypothesized due to a reduced preactivation level of sensory cortices due to low 5-HT neurostransmission [58–62]. These PET findings support this interpretation, that is 5-HT availability is decreased in the raphe-cortical serotonergic pathway. Also the normalization of habituation deficit just before and during the attack is in agreement with the increase of brain 5-HT synthetic rate, and especially in the dorsal brainstem during attack.

However, from the numerous studies focused on genetic alteration of 5-HT gene in migraine, there is no clear evidence for 5-HT transporter polymorphisms associated with migraine without aura [7, 8].

Conclusions

Numerous studies on platelet/plasma levels of 5-HT, as a mirror of synapse of central 5-HT neurons, have led, in the greater number of cases, to findings not showing a hyposerotonergic status in migraine and tension headache [1]. However, since most plasma/platelet 5-HT derive from the gut, it is unlikely an index of brain 5-HT levels if there is no particular genetic polymorphism of 5-HT metabolism (concerning the reuptake, biosynthesis, receptors, etc.) characterizing migraine subjects, so far not evidenced [7, 8].

Some interesting aspects emerge from studies on 5-HT vascular reactivity in migraine subjects: (1) an higher sensibility, especially in women, in comparison to controls (2) a reduced tachyphylaxis (habituation) successively evidenced as the more characteristic abnormality of cortical evoked potentials and ascribed to low 5-HT neurotransmission, (3) a lesser 5-HT vascular reactivity in the summer, when some studies show a lower incidence of migraine. These peripheral findings could be in agreement with a possible central hyposerotonergic status with consequent postsynaptic receptoral supersensitivity, more evident in women, and less in the summer.

The evidence of a possible alteration of brain 5-HT neurotransmission was possible through the evaluation of the effects of 5-HT agonists and of late with neuroimaging studies. It was rather evident that 5-HT releasers provoke headache both in migraine and controls, even if migraine patients are generally more vulnerable [6]. The possible mechanisms of these drugs are mainly two in number: (1) a neuronal and thereafter extraneuronal 5-HT depletion, consequent to 5-HT massive neuronal release and synaptic metabolization, of 5-HT descending pain inhibitory neurons of the brainstem, as previously suggested [65], (2) a direct (or indirect through 5-HT release) action on postsynaptic receptors. The first mechanism clash with animal evidences showing that mCPP and fenfluramine do not deplete brain 5-HT [80], and that RTD which diminished brain 5-HT synthesis does not provoke migraine attack [25, 89]. The last mechanism could explain the induction of migraine attack only through pain facilitating descending neurons which impact on trigeminal dorsal horn nociceptive neurons. In fact, both descending inhibitory and facilitatory effects of 5-HT on nociceptive transmission system from the brainstem are described [94, 95]. On the other hand, there is no direct anatomical connection between 5-HT raphe neurons and meningeal blood vessels. These neurons innervate cortical microvessels [96], which,

however, are lacking of sensory innervation [97]. Neuroimaging studies show that sumatriptan given during migraine attack reduces 5-HT synthetic brain activity, independently from pain relief, suggesting both a central action of triptans, and that this mechanism is not involved in therapeutic activity [92].

Some well-known trigger factors have been shown to provoke 5-HT release. Acute alcohol intake increases 5-HT release in the animal brain and in the platelets, and also a biphasic effect, that is an initial facilitation of 5-HT activity followed by a decrease several hours later, was reported [98, 99]. Estrogens increase 5-HT neurotransmission and release (see [42]). Biochemical studies have clearly shown that 5-HT is a stress-responsive system with increase in 5-HT turnover during both acute and longer term stress [5, 100]. The observation that migraine appearing in the perimenstrual period, in the relaxation period after prolonged stress (weekend headache), after acute stress (intense emotion/fear), or several hours after alcohol intake, can share a previous period characterized by increased 5-HT neurotransmission/release, which mime the action of 5-HT releaser drugs, is particularly intriguing.

Sicuteri's 5-HT central theory stated that migraine pain originates from an alteration, apparently functional in nature, of the neuraxial pain transmission. Pain arises without any stimulation of nociceptors, but result from an automatism of the nociceptive system, due to a failure of anti-nociceptive 5-HT system [3]. According to a subsequent theory called "functional deafferentation" [101], it was argued that migraine is a sub-cortical system failure of sensory modulatory networks that resulted in an enhanced delivery to the conscious level of normal neuronal signals such that they are perceived as abnormal [102]. Imaging studies pointed that brainstem being specific for migraine pathophysiology [90] and that migraine is a disorder associated of low central 5-HT disposition associated with an increase in 5-HT release during attack [7, 92].

On the other hand, some observations are not in accordance with a peripheral genesis of migraine pain (neurogenic inflammation):

1) Intracranial dura is innervated by neurons that exhibit properties characteristic of nociceptors in other tissues, and sumatriptan has no inhibitory effect on the discharge of dural nociceptors, either in the basal condition or after sensitization with inflammatory mediators. Also calcitonin gene-related peptides (CGRP) have no effect on the discharge of dural nociceptors [97]. Instead sumatriptan itself produced a transient discharge of these neurons which might underlie the initial worsening of headache [97, 103] that has been reported after sumatriptan administration and ergot derivatives [6]. In fact not only subcutaneous sumatriptan, but also small intravenous doses of sumatriptan (500 μg), or of ergotamine (50 μg), increase or provoke transitory, but sometimes long-lasting, headache [104–106]. Interestingly, ergotamine (50 μg), given to two migraine patients with mild headache provoked after 2–3 min, concomitantly with the start of hand vein contraction, a strong increase of headache and nausea which was still present after 30 min and subsided after intramuscular diclofenac, despite the persistence of a pronounced venoconstriction (104). This initial worsening of headache was suggested to be due to transitory high blood, and perhaps cerebral, drug levels [6, 106].
2) The 5-HT_{1D} receptors are equally distributed in cranial afferents of the trigeminal system and in dorsal root ganglion afferents, and then triptans should regulate not only headache-associated pain, but also nociceptive response in extracranial tissues; but this is not the case [107].
3) Many 5-HT agonists, which potently inhibit neurogenic inflammation were ineffective in migraine treatment [108].

Therefore, the original theory of migraine as a deficit of central serotonergic antinociceptive system [3] is today perhaps the more explicit, as maintained by other researchers [7, 102].

Conflict of interest None.

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