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5-HT_7 Receptors Are Involved in Neurogenic Dural Vasodilatation in an Experimental Model of Migraine

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Abstract Neurogenic dural vasodilation has been demonstrated to play an important role in migraine. 5-HT_7 receptors have been found on trigeminal nerve endings and middle meningeal arteries and demonstrated involved in the dilatation of meningeal arteries. The aim of the present study was to demonstrate whether 5-HT_7 receptors are involved in neurogenic dural vasodilation in migraine. The neurogenic dural vasodilation model of migraine was used in this study. Unilateral electrical stimulation of dura mater was performed in anesthetized male Sprague–Dawley rats. Animals were pretreated with selective 5-HT_7 receptor agonist AS19, 5-HT_7 receptor antagonist SB269970, 5-$HT_{1B/1D}$ receptor agonist sumatriptan, or vehicles. Blood flow of the middle meningeal artery (MMA) was measured by a laser Doppler flowmetry. AS19 significantly increased the basal and stimulated blood flows of the middle meningeal artery following electrical stimulation of dura mater, and its effect was dose dependent at the early stage. SB269970 and sumatriptan significantly reduced the basal and stimulated blood flows of middle meningeal artery. The present study demonstrates for the first time that 5-HT_7 receptors are involved in neurogenic dural vasodilation evoked by electrical stimulation of dura mater and maybe of relevance in the pathophysiology and treatment of migraine.

Keywords Serotonin 5-HT_7 receptor · Neurogenic dural vasodilation · Migraine · Middle meningeal artery

Abbreviations

ANOVA	Analysis of variance
AS19	(2S)-(+)-5-(1, 3, 5- Trimethylpyrazol-4-yl)-2-(dimethylamino) tetralin
BI	Baseline
CGRP	Calcitonin gene-related peptide
DMSO	Dimethyl sulfoxide
LSD	Fisher's least significance difference
NS	Normal saline
MMA	Middle meningeal artery
SB269970	(2*R*)-1-[(3-Hydroxyphenyl) sulfonyl]-2-[2-(4-methyl-1-piperidinyl) ethyl] pyrrolidine hydrochloride
TRPV1	Transient receptor potential vanilloid 1

Introduction

Migraine is one of the most disabling chronic disorders, affecting approximately 10 to 15 % of the general population (Lipton and Bigal 2008). However, the pathophysiology of migraine is not yet fully understood. Over the years, the role of 5-HT, 5-$HT_{1B/1D}$ receptors, calcitonin gene-related peptide (CGRP), and CGRP receptors in migraine has been elucidated. 5-$HT_{1B/1D}$ receptor agonists (known as triptans) and CGRP-receptor antagonists (known as gepants) are presently specific drugs for treatment of acute migraine attacks. However, triptans are not effective in more than 1/3 of migraineurs, and less than 50 % of migraineurs achieve complete pain

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freedom (Ferrari et al. 2001). Similarly, only 27 % of migraine patients achieved pain freedom and 55 % achieved pain relief with telcagepant (Ho et al. 2008). These indicate other factors may be involved in the pathophysiology of migraine.

Neurogenic dural vasodilation has been demonstrated to play an important role in migraine. 5-HT_7 receptors have been found on trigeminal nerve endings and middle meningeal arteries (Terrón et al. 2001; Terrón and Martínez-García 2007) and have been demonstrated involved in the dilatation of meningeal arteries (Terrón and Martínez-García 2007). Here, we attempted to determine whether 5-HT_7 receptors are involved in neurogenic dural vasodilation evoked by activation of trigeminovascular system in animal model of migraine.

In order to study the role of 5-HT_7 receptors in neurogenic dural vasodilation, we used the neurogenic dural vasodilation model of migraine (Kurosawa et al. 1995), in which electrical stimulation of dura mater causes reproducible vasodilation. This is a useful and stable model system to dissect the pharmacology of the trigeminovascular system (Akerman et al. 2001). The middle meningeal artery (MMA), which is the largest artery supplying the dura mater and is pain producing in humans, has been implicated in the pathophysiology of neurogenic dural vasodilation during migraine attacks. For measurement of neurogenic dural vasodilation, blood flow in the middle meningeal artery was recorded following electrical stimulation of dura mater with laser Doppler probes.

Materials and Methods

Drug Administration

The drugs used in the present study were (2*R*)-1-[(3-hydroxyphenyl) sulfonyl]-2-[2-(4-methyl-1-piperidinyl) ethyl] pyrrolidine hydrochloride (SB269970) (Tocris, Ellisville, MO), (2*S*)-(+)-5-(1, 3, 5-trimethylpyrazol-4-yl)-2-(dimethylamino) tetralin (AS19) (Tocris, Ellisville, MO), and sumatriptan succinate (Sigma, St. Louis, USA). SB269970 and AS19 are selective 5-HT_7 receptor antagonist and agonist, respectively, and sumatriptan succinate is a selective 5-$HT_{1B/1D}$ receptor agonist. AS19 was dissolved in 1 % dimethyl sulfoxide (DMSO), and others were dissolved in 0.9 % normal saline (NS). All drugs and vehicles were administered in a volume of 2 ml/kg. SB269970 (5 and 10 mg/kg), AS19 (5 and 10 mg/kg), sumatriptan succinate (300 μg/kg), or vehicles (NS or 1 % DMSO) were slowly i.v. injected over 30 s.

Experimental Animals and Surgery

Experiments were performed on young adult male Sprague–Dawley rats weighing 180 to 220 g (Medical Laboratory Animal Center, Guangdong, China). Rats were housed in groups of three or four and were maintained on a 12-h light/dark cycle with free access to food and water. All experiments were conducted according to the National Institutes of Health (NIH) guidelines on laboratory animal use and care (Publication No. 80–23) and were approved by the Institutional Animal Care and Use Committee of Sun Yat-sen University. All efforts were made to minimize the number of animals used and their suffering. The animals were anesthetized with 10 % chloral hydrate (3.5 ml/kg, intraperitoneally) and then the right femoral vein and artery were cannulated for intravenous (i.v.) administration of drugs and continuous monitoring of the blood pressure, respectively. Body temperature was maintained at 37.0±0.5 °C using a heating blanket and a feedback temperature controller.

Electrical Stimulation of Dura Mater and Dural Blood Flow Recording

Electrical stimulation of dura mater was performed as previously described (Tröltzsch et al. 2007). Briefly, anesthetized rats were placed in a stereotaxic frame (Narishige, Tokyo, Japan) with the head held in a fixed position by ear bars. The eyes were covered with a protecting ointment. An incision was made along the midline of the scalp, and the right parietal region of the skull was exposed. Using a dental drill and liquid cooling with drops of saline, a cranial window of about 4×7 mm^2 (for recording) was drilled into the parietal bone to expose the dura mater about the middle meningeal artery. The dura mater in the recording window was protected from drying with pieces of cotton soaked with isotonic saline arranged around the recording probe. A second slit-like window of about 2×6 mm^2 was drilled apically along the superior sagittal sinus for electrical stimulation. In this stimulation window, a pair of parallel wire electrodes (diameter 0.2 mm, length 5 mm, separation distance 1 mm) were placed on the dura mater and covered with paraffin oil.

Electrical stimulation of dura mater was started not earlier than 1 h after trepanning the skull to ensure that the basal blood flow was stable. Dural blood flow was measured by a laser Doppler flowmetry. The needle probe of a Doppler flowmeter was positioned over branches of the middle meningeal artery at a distance of about 2 mm to the stimulation electrodes. The dura was stimulated at intervals of 10 min for periods of 30 s with rectangular pulses of 0.5-ms duration; 15–20 V at 5 Hz. Stimulus strength and frequency were optimized at the beginning of each experiment to elicit substantial and stable but not maximal increases in local blood flow without changes of the blood pressure. Systemic arterial blood pressure was recorded simultaneously with the flow.

Each drug test was preceded by three control stimulations at intervals of 10 min. About 15 min later, drugs or vehicles were administered. Stimulations were then repeated at 10, 20, 30, 40, 50, and 60 min after drug administration.

Data Collection and Analysis

Blood flow and vital parameter data were stored and processed with the DRTsoft program (Moore Instruments) as described previously (Tröltzsch et al. 2007). Changes in blood flow caused by electrical stimulation were calculated as mean flow within a period of 60 s from the onset of stimulation (spanning over the 30-s stimulation period and the ensuing 30 s). The three control values of stimulated flow (before drug administration) were averaged in each experiment, and all subsequent stimulated flow values were normalized to this mean. Basal flow values (mean flow within 60-s periods before stimulation) were also normalized to the control measurements. Data were statistically compared using the one-way analysis of variance (ANOVA) followed by Fisher's least significance difference (LSD) multiple-comparison post hoc test. Measurement data were presented as the mean±SD. A P value <0.05 was considered statistically significant. Statistical analyses were performed with the Statistical Package for Social Sciences for Windows, version 11.5 (SPSS, Inc, Chicago, IL, USA).

Results

Effects of Electrical Stimulation of Dura Mater on Blood Flow of MMA

Electrical stimulation of dura mater induced increases in blood flow that started after a latency of 2–5 s, increased to a maximum within 30–60 s, and returned to the base line within 1 min when the stimulus was switched off. These responses were reproducible and stable under repetitive stimulation at intervals of 10 min for more than 1 h. Figure 1 shows an example of a representative blood flow response to electrical stimulation.

Control Groups

As SB269970 and sumatriptan were dissolved in 0.9 % NS, and AS19 was dissolved in 1 % DMSO, and NS and DMSO were used as vehicles. The average values of basal and stimulated blood flows were 99.19±1.25 % and 99.25±1.59 % of control level, respectively after application of DMSO, and 102.48± 1.63 % and 101.16±1.72 % of control level for NS group.

Effects of 5-HT_7 Receptor Agonist AS19 on Blood Flow Response of MMA Evoked by Electrical Stimulation of Dura Mater

Following three control stimulation periods, AS19 was injected i.v., after which a further six stimulation periods at intervals of 10 min followed. The basal and stimulated blood flows increased significantly compared with vehicle (DMSO) at the time point of 10, 20, 30, 40, and 50 min after drug administration (P<0.05) (Fig. 2). On average of all six stimulation periods, the mean basal and stimulated blood flows were 111.23±4.97 and 113.11±3.77 % of control level, respectively, for 5 mg/kg AS19 (n=5), and 115.82±8.56 and 120.77± 4.21 %, respectively, for 10 mg/kg AS19 (n=5). On average of all six stimulations, the dose of 10 mg/kg caused higher stimulated blood flow than 5 mg/kg did (P<0.05). Besides, the higher dose of 10 mg/kg showed stronger effects both on basal and stimulated blood flows at the first two stimulation periods compared to the dose of 5 mg/kg (P<0.05) (Fig. 2), indicating its effect was dose dependent at the early stage.

Effects of 5-HT_7 Receptor Antagonist SB269970 on Blood Flow Response of MMA Evoked by Electrical Stimulation of Dura Mater

Following three control stimulation periods, SB269970 was injected i.v., after which a further six stimulation periods at intervals of 10 min followed. The basal and stimulated blood flows decreased significantly compared with vehicle (NS) at six stimulation periods after drug administration (P<0.05) (Fig. 3). On average of all six stimulation periods, the mean basal and stimulated blood flows were 90.31±1.23 and 87.69 ±2.03 % of control level, respectively, for 5 mg/kg SB269970 (n=5), and 86.92±2.5 and 84.92±4.16, respectively, for 10 mg/kg SB269970 (n=5). On average of all six stimulations, no significant difference was observed between the two doses of SB269970 (Fig. 4).

Effects of 5-$HT_{1B/1D}$ Receptor Agonist Sumatriptan on Blood Flow Response of MMA Evoked by Electrical Stimulation of Dura Mater

Similar to SB269970, the basal and stimulated blood flows decreased significantly compared with vehicle (NS) at six stimulation periods after sumatriptan administration (P<0.05) (Fig. 3). On average, the mean basal flow and stimulated flow were 88.2±2.53 and 82.01±3.16 % of control level respectively after sumatriptan administration. Sumatriptan had significantly stronger effects on basal flow at 50 min and stimulated flow at 10 min compared to 5 mg/kg SB269970 (P<0.05) (Fig. 3). No significant difference was observed at other time points between SB269970 and sumatriptan. On average of all six stimulations, sumatriptan caused lower stimulated blood flow than 5 mg/kg SB269970 did (P<0.05) (Fig. 4).

Discussion

Our present study reported for the first time that selective 5-HT_7 receptor agonist AS19 significantly increased the basal and stimulated blood flows of MMA following electrical

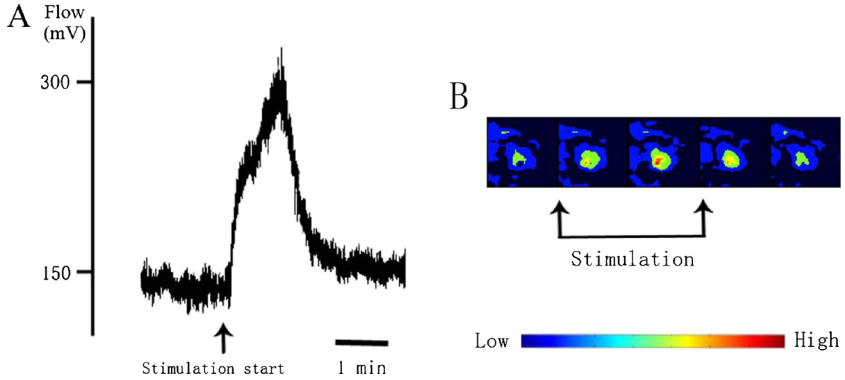

Fig. 1 A sample record of meningeal blood flow response to electrical stimulation of dura mater (15 V, 5 Hz, 0.5 ms, 30 s). **a** Original recording of the time course of the change in meningeal blood flow following electrical stimulation. A rapid increase in meningeal blood flow was observed with a latency of 2 s at the onset of electrical stimulation, and the blood flow increased to a maximum within 45 s and returned to the base line within 1 min. **b** Laser Doppler perfusion images of blood flow in the middle meningeal artery detected at the same time. A color scale illustrates blood flow variations from minimal (*dark blue*) to maximum (*red*) values

stimulation of dura mater in an experimental model of migraine, while selective 5-HT$_7$ receptor antagonist SB269970 significantly reduced the basal and stimulated blood flows of MMA. These suggest the involvement of 5-HT$_7$ receptors in

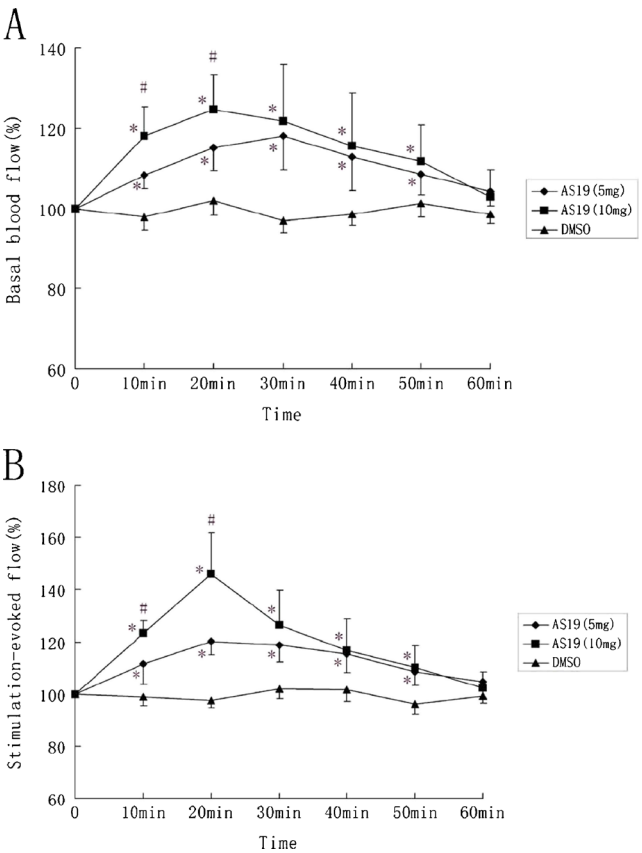

Fig. 2 Effects of 5-HT$_7$ receptor agonist on basal and stimulated blood flows evoked by electrical stimulation of dura mater. Flow increases (normalized to the mean of control responses) and their variation after application of AS19 and vehicle (DMSO). Both basal flow (**a**) and stimulated flow (**b**) were significantly increased in 50 min after administration of AS19. The higher dose of 10 mg/kg showed stronger effects both on basal and stimulated flow at the first two stimulations compared to the dose of 5 mg/kg. **a**, **b** *Asterisks* indicate $P<0.05$ vs. DMSO;*number signs* indicate $P<0.05$ vs. AS19 (5 mg/kg); $n=5$ (ANOVA followed by LSD post hoc test)

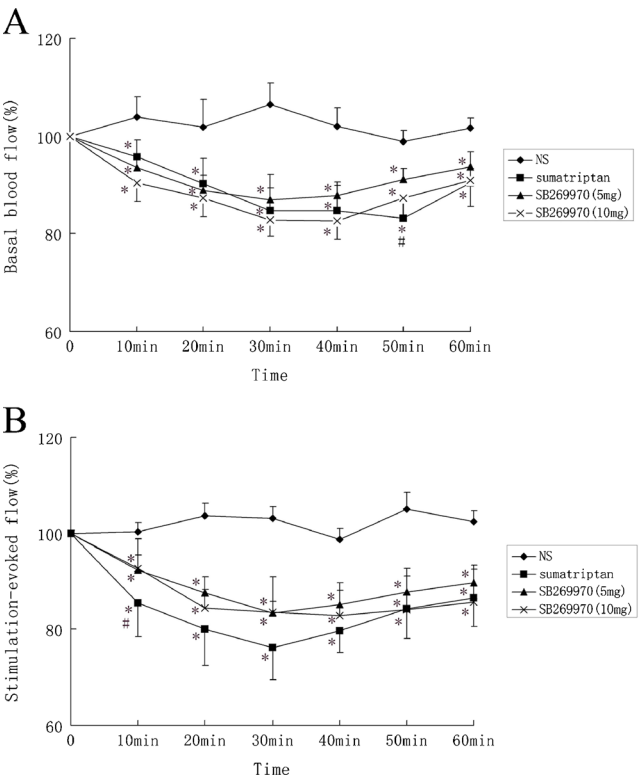

Fig. 3 Effects of 5-HT$_7$ receptor antagonist and sumatriptan on basal and stimulated blood flows evoked by electrical stimulation of dura mater. Flow decreases (normalized to the mean of the control responses) and their variation after application of SB269970, sumatriptan, and vehicle (normal saline). Basal flow (**a**) and stimulated flow (**b**) were significantly reduced at six stimulation periods after administration of SB269970 or sumatriptan. No significant difference was observed between the two doses of SB269970. Sumatriptan had significantly stronger effects on basal flow at 50 min and stimulated flow at 10 min compared to SB269970 (5 mg/kg). **a**, **b** *asterisks* indicate $P<0.05$ vs. NS; *number signs* indicate $P<0.05$ vs. SB269970 (5 mg/kg); $n=5$ (ANOVA followed by LSD post hoc test)

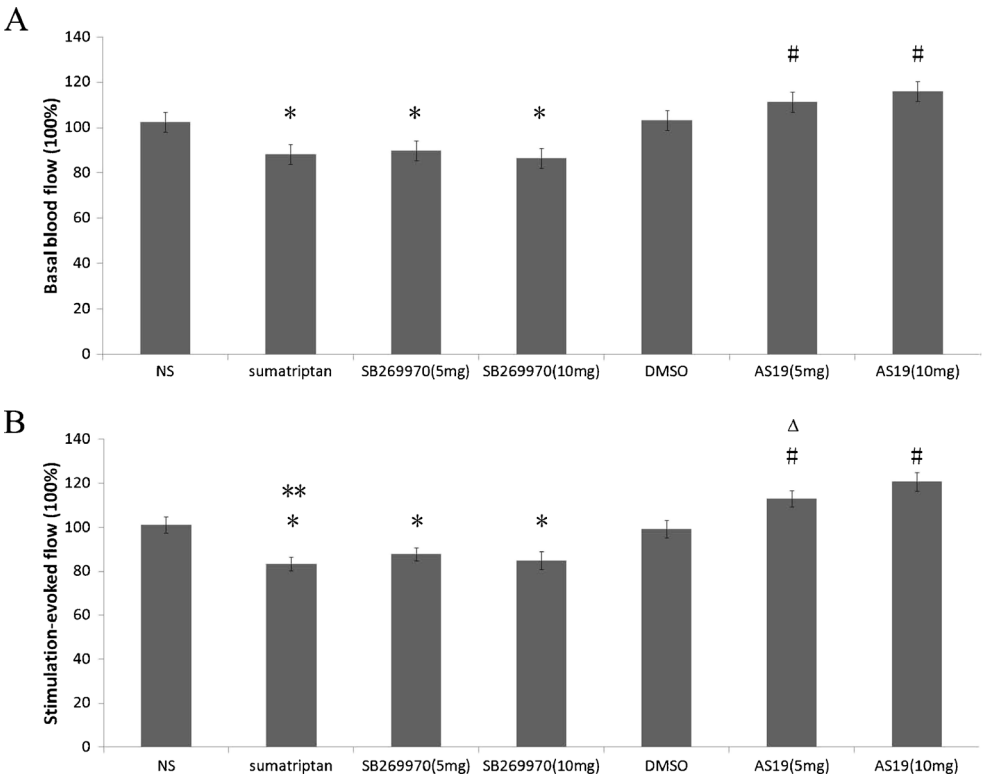

Fig. 4 Effects of sumatriptan, 5-HT_7 receptor agonist, and antagonist on mean values for basal and stimulated blood flows at six time points. On average of all six stimulations, sumatriptan caused lower stimulated blood flow than SB269970 (5 mg/kg) did, and AS19 (10 mg/kg) caused higher stimulated blood flow than AS19 (5 mg/kg) did. **a** *asterisks* indicate $P<0.005$ vs. NS; *number signs* indicate $P<0.005$ vs. DMSO; $n=5$. **b** *asterisks* indicate $P<0.005$ vs. NS; *number signs* indicate $P<0.005$ vs. DMSO; *two asterisks* indicate $P<0.05$ vs. SB269970 (5 mg/kg); *Increment symbol* indicates $P<0.05$ vs. AS19 (10 mg/kg); $n=5$ (ANOVA followed by LSD post hoc test)

neurogenic dural vasodilation evoked by activation of the trigeminovascular system in migraine.

Important functional roles for 5-HT_7 receptors have been established in thermoregulation, circadian rhythm, learning and memory, hippocampal signaling, sleep (Hedlund and Sutcliffe 2004), and neuronal morphology (Kobe et al. 2012). 5-HT_7 receptors have been found to be located in the pathway of trigeminovascular system, including the meninges, meningeal arteries, trigeminal ganglion, spinal trigeminal nucleus, dorsal raphe nucleus, periaqueductal gray, thalamus, and cortex (Terrón et al. 2001; Terrón and Martínez-García 2007; Martín-Cora and Pazos 2004; Schmuck et al. 1996). Increasing evidence suggests that 5-HT_7 receptors are possibly involved in depression, anxiety, and epilepsy (Graf et al. 2004; Hedlund et al. 2005; Pericić and Svob Strac 2007; Wesołowska et al. 2006), all of which have been demonstrated to be comorbidities of migraine. It has been well known that antidepressants and anticonvulsants are effective for migraine prophylaxis. Several studies found that blockade of 5-HT_7 receptors induced antidepressant-like and antiseizure effects (Hedlund et al. 2005; Bourson et al. 1997). Thus, it might be possible that 5-HT_7 receptors are treatment targets in migraine. Furthermore, other lines of evidence have shown that 5-HT_7 receptors are involved in neuroinflammatory processes, central sensitization, and pain control (Mahé et al. 2005; Brenchat et al. 2009; Yanarates et al. 2010), all of which are important in the migraine process. Finally, our previous study showed that selective blockade of 5-HT_7 receptors was capable of inhibiting CGRP release evoked by electrical stimulation of trigeminal ganglion in an animal model of migraine (Wang et al. 2010). These findings support the suggestion that 5-HT_7 receptors may play a role in the pathophysiology of migraine.

Neurogenic dural vasodilation has been demonstrated to play an important role in migraine, and it is one important manifestation of activation of the trigeminovascular system. However, the mechanism of neurogenic dural vasodilation is not well understood. So far, there are several receptors found to be involved in neurogenic dural vasodilation. 5-$HT_{1B/1D}$ receptors are among the most important and intensively studied receptors in mechanisms of migraine. Triptans, 5-$HT_{1B/1D}$ receptor agonists, work to relieve migraine attacks through the mechanisms of attenuating neurogenic dural vasodilation both by direct constriction of dilated cranial blood vessels via activation of 5-HT_{1B} receptors (De Vries et al. 1998, 1999) and presynaptic inhibition of CGRP release from peripheral and central trigeminal sensory nerves via 5-$HT_{1B/1D}$ receptors (Goadsby et al. 2002; Tepper et al. 2002; Williamson et al. 2001a). Besides, several studies have demonstrated that neurogenic dural vasodilation is mediated predominantly by CGRP released from trigeminal sensory fibers via activation of CGRP receptors located on dural blood vessels (Storer et al. 2004; Hargreaves 2007). Finally, iGluR5 kainate receptors, opioid receptors, and transient receptor potential vanilloid 1 (TRPV1) have found to be involved in neurogenic dural vasodilation (Andreou et al. 2009; Williamson et al. 2001b; Nicoletti et al. 2008).

In the present study, blockade of 5-HT_7 receptors with SB269970 significantly reduced the blood flow of MMA following electrical stimulation of dura mater, which suggests that 5-HT_7 receptors play a role in neurogenic dural vasodilation. Our previous study showed that selective inhibition of 5-HT_7 receptors inhibited CGRP release evoked by electrical stimulation of trigeminal ganglion (Wang et al. 2010). We hypothesize that the mechanism through which SB269970 inhibits neurogenic dural vasodilation is probably by an inhibition of the release of CGRP via blockade of 5-HT_7 receptors located on the terminals of trigeminal sensory nerves. Besides, 5-HT_7 receptors have been found to locate on the middle meningeal arteries (Terrón et al. 2001; Terrón and Martínez-García 2007). Therefore, it is also possible that SB269970 inhibits neurogenic dural vasodilation via blockade of 5-HT_7 receptors located on the meningeal arteries. We hypothesize that 5-HT_7 receptors could affect neurogenic dural vasodilation through two main mechanisms: by regulation of neurotransmitter release and vascular activity. Further studies are needed to confirm this.

The effects of 5-HT_7 receptors agonist AS19 showed a dose-dependent effect at two of the six stimulation periods, while the antagonist SB269970 did not show any difference. One explanation may be due to that the dose of 5 mg/kg SB269970 is large enough to produce a maximal response and there is little change in effect as the concentration increases. Another possibility may be that 5-HT_7 receptors have different affinities for agonists AS19 and antagonists SB269970.

Similar to previous study (Williamson et al. 1997), our study found that 5-$HT_{1B/1D}$ receptor agonist sumatriptan inhibited neurogenic dural vasodilation evoked by electrical stimulation of dura mater. Both the 5-HT_7 receptor and 5-$HT_{1B/1D}$ receptor are members of the family of 5-HT receptors. 5-$HT_{1B/1D}$ receptors are coupled through Gi/o proteins to inhibit cAMP production, while 5-HT_7 receptors are coupled to Gs proteins and activation of 5-HT_7 receptors stimulates cAMP production (Hoyer et al. 2002). In our study, both activation of 5-$HT_{1B/1D}$ receptors with sumatriptan and blockade of 5-HT_7 receptors with SB269970 inhibited neurogenic dural vasodilation evoked by electrical stimulation of dura mater, which indicates that activation of 5-$HT_{1B/1D}$ and 5-HT_7 receptors modulates opposite effects. Thus, it may be hypothesized that 5-HT_7 receptors may act to counterbalance 5-$HT_{1B/1D}$ receptors in mediating neurogenic dural vasodilation, and the balance between 5-$HT_{1B/1D}$ and 5-HT_7 receptors may be important in migraine pathophysiology. As mentioned above, CGRP receptors, iGluR5 kainate receptors, opioid receptors, and TRPV1 have found to be involved in neurogenic dural vasodilation. It may be hypothesized that neurogenic dural vasodilation is probably regulated by complicated presynaptic and postsynaptic mechanisms, in which is comodulated by several receptors located on the trigeminal nerve endings and meningeal arteries, including CGRP receptors, 5-$HT_{1B/1D}$ receptors, iGluR5 kainate receptors, opioid receptors, TRPV1, and 5-HT_7 receptors. Further studies are needed to demonstrate this.

Conclusions

In summary, the present study demonstrates for the first time that blockade of 5-HT_7 receptors reduced the basal and stimulated blood flows of MMA following electrical stimulation of dura mater. 5-HT_7 receptors may be involved in neurogenic dural vasodilation during migraine attacks and selective 5-HT_7 receptor antagonists may be a potential treatment for migraine headache.

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Conflict of Interest There is no conflict of interest to disclose.

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