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Mast Cell Degranulation Mediates Compound 48/80-Induced Meningeal Vasodilatation Underlying Migraine Pain

Mast Hücre Degranülasyonu Compound 48/80 ile Tetiklenmiş Migren Ağrısının Altında Yatan Meningeal Vazodilatasyona Aracılık Ediyor

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ABSTRACT

Objective: The cranial dura mater contains plenty of mast cells and is principally supplied by the middle meningeal artery which has a key role in the generation of headaches. Neurogenic inflammation caused by perivascular nerve activation and dural vasodilation is held responsible for migraine pain. Dural mast cells contribute neurogenic inflammation and migraine via vasoactive and proinflammatory mediators in their secretory granules. In the present study, it was aimed to investigate vasoactive effect of mast cell degranulating agent compound 48/80 induced dural mast cell degranulation on the middle meningeal artery and its anterior and posterior branches.

Methods: Isolated skulls obtained from male Wistar rats were divided into 2 halves. The skull cavities with intact the dura mater were applied synthetic interstitial fluid for control group or mast cell degranulating agent compound 48/80 (10 µg/ml) in synthetic interstitial fluid for treated group at 37 °C for 15 min. Diameters of middle meningeal artery and its anterior and posterior branches were measured and mast cells were counted from whole-mount preparations of meningeal dura mater.

Results: While compound 48/80 induced massive degranulation of dural mast cells ($P<0.01$), it did not change the number of mast cells in the dura mater. Moreover, compound 48/80 increased diameter of middle meningeal artery ($P<0.01$) and its anterior ($P<0.05$) and posterior ($P<0.01$) branches, respectively compared to synthetic interstitial fluid treatment.

Conclusion: Dural mast cell degranulation causes dilatation of middle meningeal artery which is involved in the pathophysiology of migraine, therefore testing of mast cell stabilizing agents in vivo models of migraine pain may promise hope for the next big things in the treatment of migraine headaches.

Keywords: Migraine, meningeal artery, dural mast cell, neurogenic inflammation.

ÖZ

Amaç: Kraniyal dura mater çok sayıda mast hücresi barındırmaktadır ve başlıca baş ağrılarının oluşumunda önemli bir role sahip olan middle meningeal arter tarafından beslenmektedir. Migren baş ağrısı oluşumunda, perivasküler sinir aktivasyonu ve dural vazodilatasyonun yol açtığı nörojenik enflamasyon sorumlu tutulmaktadır. Dural mast hücreleri sekretuar granüllerinde bulunan vazoaktif ve proinflamatuar mediyatörler aracılığıyla nörojenik enflamasyon ve migrene katkıda bulunmaktadır. Sunulan çalışmada bir mast hücre degranülatörü olan compound-48/80 ile oluşturulan dural mast hücre degranülasyonunun middle meningeal arter ve bunun anterior ve posterior dalları üzerine vazoaktif etkisinin araştırılması amaçlanmıştır.

Yöntemler: Wistar erkek sıçanlardan elde edilen izole kranyumlar iki yarıya bölündü. Dura materi sağlam hemi-kranyumların boşluğuna kontrol grubu için 37 oC' de yapay interstisyel sıvı ve çalışma grubu için bir mast hücre degranüle edici madde olan compound-48/80 (10 µg/ml) 15 dakika uygulandı. Middle meningeal arter ve bunun anterior ve posterior dallarının çapları ölçüldü ve meningeal dura mater preparasyonlarından mast hücreleri sayıldı.

Bulgular: Compound-48/80 dural mast hücrelerinin kitlesel degranülasyonunu tetiklerken ($P<0.01$), dura materdeki mast hücre sayısını değiştirmedi. Ayrıca compound-48/80, yapay interstisyel sıvı uygulaması ile karşılaştırıldığında, sırasıyla middle meningeal arter ($P<0.01$) ve bunun anterior ($P<0.05$) ve posterior ($P<0.01$) dallarının çaplarını artırdı.

Sonuç: Dural mast hücre degranülasyonu migren patofizyolojisi ile ilişkili olan middle meningeal arter dilatasyonuna neden olmaktadır böylece, mast hücre stabilizatörlerinin in vivo migren modellerinde test edilmesi migren baş ağrılarının tedavisinde bir sonraki adım için umut vaadedici olabilir.

Anahtar Kelimeler: Migren, meningeal arter, dural mast hücresi, nörejenik inflamasyon.

1. INTRODUCTION

Migraine is a multifactorial neurovascular disease affecting approximately 15 % of the general population. Although many studies have been performed to investigate the pathophysiology of migraine, the pathophysiology is not yet exactly understood. According to the vasodilatory theory

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of migraine, meningeal and cerebral arteries are dilated during the headache phase of migraine (1). It has been reported that neurogenic dural vasodilation plays a key role in migraine (2). The clinical use of vasoconstrictor drugs such as sumatriptan have also supported vasodilatory theory of migraine, by alleviating migraine pain.

The middle meningeal artery (MMA) is the largest of the three arteries supplying the dura mater, the others being the anterior and the posterior meningeal arteries. MMA has been associated with neurogenic dural vasodilation and generation of pain during migraine attacks (2). Trigeminal sensory fibers innervating the dura mater run perivascularly along middle meningeal artery and its branches (3) therefore changes in the diameter of meningeal arteries can be readily sensed by these trigeminal sensory nerve terminals.

Activation of meningeal trigeminal sensory fibers has been suggested to be a primary mechanism in the origin of migraine headache (4,5). Cranial dura mater which is held responsible for the generation of headaches is intensely innervated by trigeminal nerve fibers and contains a large number of mast cells (3,6). Mast cells are located close proximity to blood vessels and nerves in the dura mater and contain a wide variety of neuroactive and vasoactive mediators such as adenosine triphosphate (ATP), adenosine, substance-P (SP), calcitonin gene related peptide (CGRP), vasoactive intestinal peptide (VIP), histamine, serotonin (5-HT), nitric oxide (NO) and even proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) in their granules (7). It has been suggested that dural mast cells contribute considerably to the neurogenic dural inflammation underlying migraine attack via these mediators (8).

Inflammation of the dura mater occurs when it exposes mediators such as SP, CGRP and neurokinin A (NKA) released from trigeminal sensory nerve terminals during vasodilation of meningeal blood vessels (9). This sterile neurogenic inflammation of the dura mater leads to more sensitization of trigeminal sensory neurons innervating meninges.

When dural mast cells are activated they can release various mediators which have activating effect meningeal trigeminal nociceptors. Then activated meningeal nociceptors release CGRP and SP that in turn activate mast cells in the dura mater. Therefore, vasoactive mediators and cytokines such as adenosine, histamine, CGRP, NO, TNF-α and VIP released from activated mast cells increase vascular permeability of dura mater (10). This phenomenon has been suggested to participate in the vasodilatory phase of migraine headache (10). Dimitriadou and colleagues have shown that temporal artery of the painful side of cluster headache patients involved degranulated mast cells in the biopsy samples (11). Therefore mast cell stabilizing agents may inhibit vascular permeability of dura mater and neurogenic dural inflammation by preventing release of the mediators such as histamine, CGRP and SP from mast cells in meninges and be efficacious for the treatment of migraine.

In the present study, we showed that compound 48/80 induced dural mast cell degranulation leads to vasodilation of middle meningeal artery and its anterior and posterior branches. It is known that middle meningeal artery and middle cerebral artery are dilated during migraine attack, but in the present study, we show histologically for the first time that dural mast cell degranulation causes dilatation of meningeal arteries. We suggest that mast cell degranulation plays a key role in vasodilation and vascular permeability associated with activation of trigeminal sensory nerve fibers in the dura mater where is the origin of migraine pain.

2. METHODS

2.1. Experimental Animals

Experiments were carried out on twelve adult male Wistar rats weighing 130 to 170 g. This study was approved by the Animal Experiments Local Ethics Committee of our University (license number: 2013-42). All experiments were performed following the guideline for the care and use of experimental animals in the University with an approval from the local animal experiment research ethics committee of the University. The rats were housed in their cages with a 12 hour light/dark cycle at 22 ± 2 ^{o}C and fed ad libitum with a standard rodent diet and water.

2.2. Preparation and experimental procedures

Rats were randomly divided into a control group and a treated group (n=6). Then were killed by cervical dislocation under ketamine anesthesia (60 mg/kg, i.p.), and the isolated hemi skulls were prepared from the rat heads as described previously (4). Briefly, the head was separated from the body, and skin and muscles of the head were cleaned, then skull was divided into halves by a cut along the sagittal suture using a thin scissors. Both hemispheres of the brain were removed without damaging the trigeminal ganglion and the meningeal dura mater. The skull cavities were washed with synthetic interstitial fluid (SIF) containing (in mM): 120 NaCl, 5 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 11 glucose, 1 $NaHPO_4$, 24 $NaHCO_3$, continuously gassed with carbogen (95% O_2 and 5% CO_2), equilibrating the solution at pH 7.4 at room temperature. Then the hemi skulls were put to chamber of isolated organ bath and control hemi skulls was incubated with SIF at 37 ^{o}C for 15 min, on the other hand the hemi skulls in the treated group was applied compound 48/80 (10 µg/ml, Sigma-Aldrich, Schnelldorf, Germany) in the SIF at 37 ^{o}C for 15 min (8). After the incubation, the hemi skulls were immersed in 4% paraformaldehyde solution and kept for overnight.

2.3. Whole-mount preparations of meningeal dura mater

Dura mater was kindly removed from the hemi skull and placed onto a glass slide with poly-lysine via a whisker. The whole-mount preparations were left to dry in the open air at room temperature. The dura maters were stained with toluidine blue (pH: 2.5) to observe mast cells. Mast cells in the dura mater were firstly classified as either intact or degranulated then counted separately with a light microscope by a blinded observer (Olympus CX21) with 10X magnification in the bilateral five objective areas containing the main branches of the middle meningeal artery in each dura mater. The percent of degranulated mast cells for each rat was calculated as follows:

[(number of degranulated mast cells)/ (number of total mast cells)] X 100 %. Images of mast cells, middle meningeal artery and its anterior and posterior branches were taken with a camera (Nikon DS-Fi1, Japan) attached to the microscope (Nikon Eclipse 80i, Japan). Then diameters of middle meningeal artery and its anterior and posterior branches were measured from images using an imaging software (NIS-Elements D 3.2).

2.4. Statistical analysis

The values obtained from experimental groups are expressed as the mean ± SEM. The difference between the experimental groups in terms of mast cells and diameters of middle meningeal artery and its anterior and posterior branches was tested with the paired t-test using SPSS for Windows (version 17.0, SPSS Inc., Chicago, IL, USA). P<0.05 was considered to be statistically significant.

3. RESULTS

3.1. Middle meningeal artery and its branches

We found that the diameter of middle meningeal artery in the dura mater of Wistar rats was increased from 42.0 ± 2.6 µm to 54.1 ± 1.4 µm by SIF containing 10 µg/ml compound 48/80 compared to only SIF treatment (P<0.01, Fig. 1 and Fig. 3B) Likewise, SIF containing 10 µg/ml compound 48/80 caused significantly an increase in the diameter of both anterior and posterior branches of middle meningeal artery from 38.0 ± 4.2 µm to 49.5 ± 5.1 µm (P<0.05, Fig. 1 and Fig. 3B) and from 32.2 ± 1.6 µm to 44.1 ± 1.8 µm (P<0.01, Fig. 1 and Fig. 3B), respectively compared to only SIF treatment (Fig. 1 and Fig. 3A).

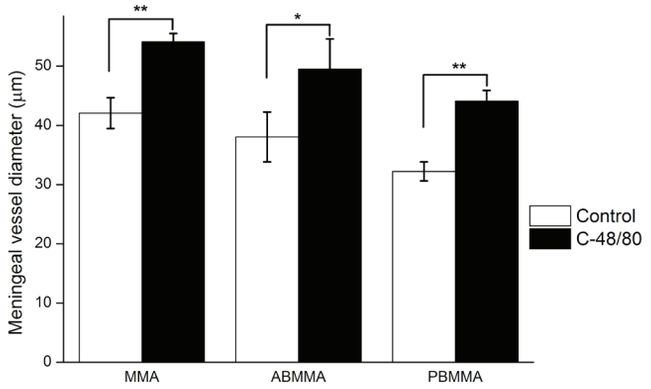

Figure 1. Vasodilator effect of mast cell degranulation on the meningeal arteries.
Compound 48/80 induced dural mast cell degranulation increased the diameter of middle meningeal artery and its anterior and posterior branches compared to control group (synthetic interstitial fluid treatment), respectively. MMA: middle meningeal artery, ABMMA: anterior branch of middle meningeal artery, PBMMA: posterior branch of middle meningeal artery, C-48/80: compound 48/80, *P<0.05; **P<0.01.

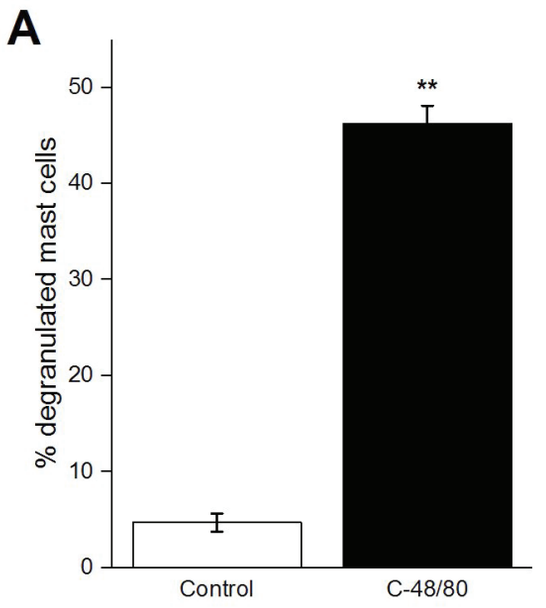

Figure 2A. Compound 48/80 increased the percent of degranulated mast cells (**P<0.01).

3.2. Mast cells in the meningeal dura mater

To induce degranulation of mast cells in the dura mater, we applied to the dura mater compound 48/80 which is known as a mast cell degranulating agent an IgE-independent manner[24]. While SIF containing 10 µg/ml compound 48/80 increased significantly the percent of degranulated mast cells from 4.6 ± 0.95 % to 46.2 ± 1.9 % (P<0.01, Fig. 2A), it did not lead to a significant change in the number of total mast cells (from 541 ± 2.7 to 530 ± 3.6; P>0.05) compared to only SIF treatment in the dura mater (Fig. 2B).

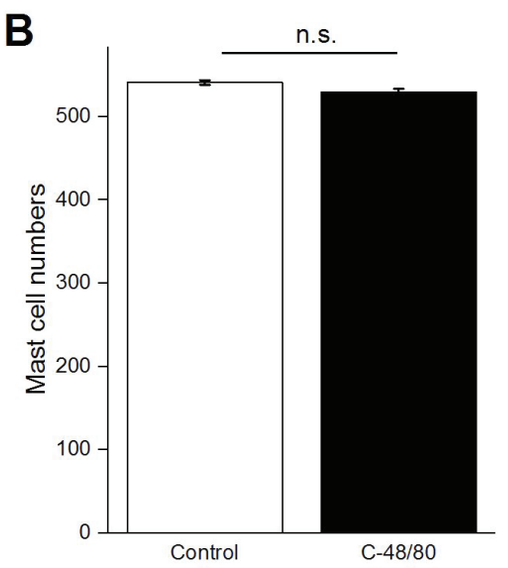

Figure 2B. Compound 48/80 did not change the number of total mast cells compared to control group (synthetic interstitial fluid treatment) in the dura mater.

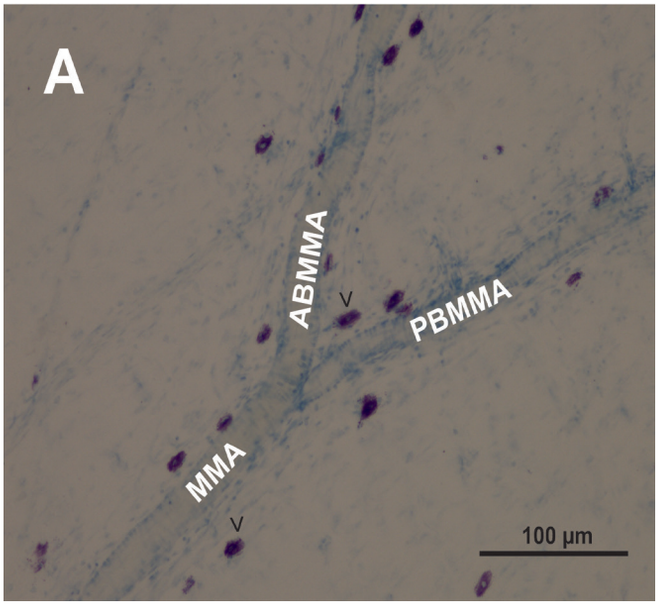

Figure 3A. Middle meningeal artery and its anterior and posterior branches and mast cells in the dura mater in control group, X10 magnification, MMA: middle meningeal artery, ABMMA: anterior branch of middle meningeal artery, PBMMA: posterior branch of middle meningeal artery.

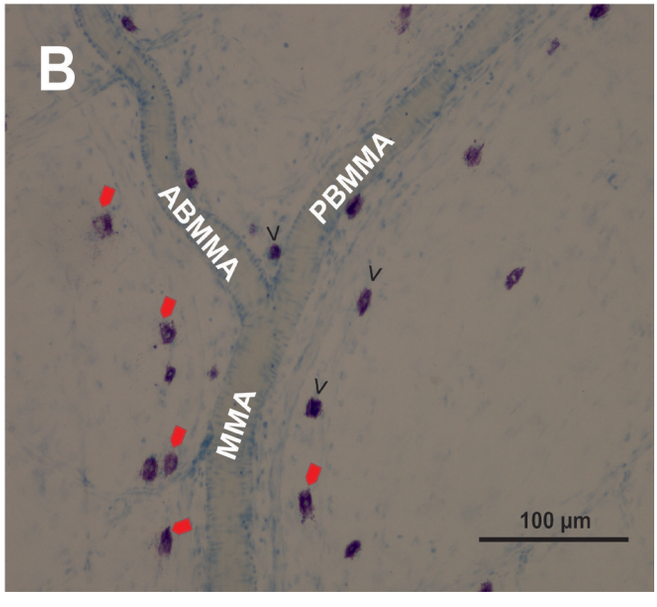

Figure 3B. Dilated middle meningeal artery and its anterior and posterior branches caused by mast cell degranulation in compound 48/80 treatment group, X10 magnification. Open arrowheads show intact mast cells and red solid arrowheads show degranulated mast cells (staining, toluidine blue). Please note, mast cells in the dura mater are located close to the middle meningeal artery and its branches. MMA: middle meningeal artery, ABMMA: anterior branch of middle meningeal artery, PBMMA: posterior branch of middle meningeal artery.

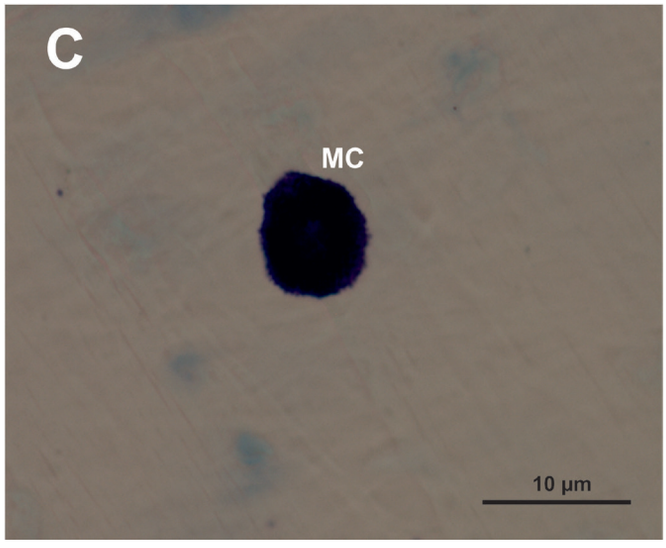

Figure 3C. A typical intact mast cell in control group, X100 magnification, MC: intact mast cell.

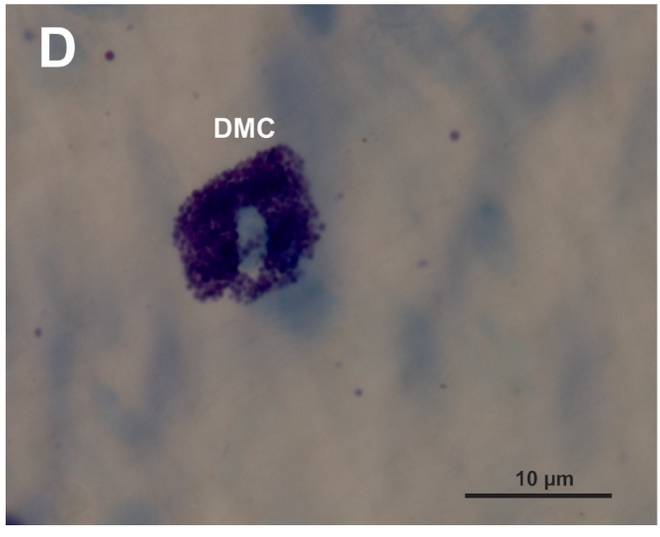

Figure 3D. A degranulated mast cell in compound 48/80 treatment group, X100 magnification. DMC: degranulated mast cell.

4. DISCUSSION

By investigating the effects of compound 48/80 induced dural mast cell degranulation on the meningeal vasodilation and mast cell numbers in the ex vivo rat meningeal preparations, we showed that compound 48/80 induced massive degranulation of mast cells in the dura mater and dural mast cell degranulation caused vasodilation of middle meningeal artery and its anterior and posterior branches by increasing the diameters of them, respectively.

In the present study, middle meningeal artery and its branches were chosen due to the relevance for the generation of headaches (1,6), therefore the change in diameter of middle meningeal artery and its branches in response to mast cell degranulation in the dura mater

has demonstrated that mast cells in the dura mater play a key role in the pathophysiology of migraine.

Vascular theory of migraine was suggested firstly by Wolff (12) and this theory was supported by the use of drugs such as sumatriptan which is a selective cephalic vasoconstrictor drug belonging to the triptan class. According to this theory, when intra and extra cerebral vessels are distended, sensory nociceptive fibers in the walls of these vessels produce a mechanical depolarization initiating headache. Not only sensory nociceptive fibers in the walls of intra and extra cerebral vessels but also trigeminal perivascular sensory nerves innervating cerebral blood vessels play a key role in the generation and conduction of headache pain signals (13). A lot of studies reported that direct stimulation of arteries in the dura mater in humans lead to migraine pain like sensations (14). In a clinical study, Asghar et al. measured arterial circumference of the MMA and the middle cerebral artery (MCA) during migraine attack, and after treatment with sumatriptan by using a high-resolution 3T magnetic resonance angiography technique in the patients with migraine without aura (15). They found that both MCA and MMA were dilated during migraine attack and sumatriptan administration provide a relief from migraine pain, moreover sumatriptan led to contraction of MMA but did not change dilatation of MCA (15). Therefore cerebral blood vessels, in particular MMA, seem to play a key role in the pathophysiology of migraine. In parallel with this results, our current findings are important to understand which players contribute dilatation of MMA and its branches.

In addition to vascular theory of migraine, recently neurogenic inflammation has been also implicated in the pathophysiology of migraine. Dalessio first suggested to be a relationship between neurogenic inflammation and migraine (16) but afterwards Moskowitz also proposed that migraine pain is involved in NI and dural vasodilatation (17). Therefore currently, migraine scientists have widely accepted that dura mater and neurogenic inflammation in pathophysiology of migraine is important. Vascular and neurogenic inflammation theories of migraine are close associated with each other and can not be thought independently. Because neurogenic inflammation process, in addition to neuronal activation and sensitization, involves also dilatation of cerebral arteries such as MMA. Sensory nerve fibers innervating intra and extra cerebral blood vessels contain vasodilator neuropeptides including SP, NKA and CGRP (9). When the sensory nerve fibers are stimulated by mechanical or chemical stimuli, SP, NKA and CGRP are released from these fibers terminals and in turn these neuropeptides cause vasodilatation, increased vascular permeability, and plasma protein extravasation in the dura mater. It was reported that plasma levels of some mast cell mediators including histamine, triptase, TNF-α and interleukin-1 (IL-1) were increased during migraine attack (18). First of all, testing of mast cell stabilizing agents in rodent models of migraine pain may promise hope for the next big things in the treatment of migraine headaches.

Dura mater is the most pain sensitive structure and contains abundant mast cells which are located close proximity to blood vessels in the dura mater (6, 19). SP and CGRP released from dural afferent terminals following mechanical or chemical stimuli lead to the release of histamine from adjacent mast cells in the dura mater by inducing degranulation of the mast cells (20). In turn, histamine causes both dilatation of meningeal blood vessels and the release of SP and CGRP from trigeminal sensory nerve terminals innervating meninges again. Thus, there is a bidirectional link between mast cells and sensory nerve fibers in dural vasodilatation and dural neurogenic inflammation processes underlying migraine pain. All three of these mediators including histamine, SP and CGRP are potent vasodilators and at the same time, they may further activate trigeminal sensory nerve terminals, because in a previous experimental study was demonstrated co-localization of the histamine H3 receptor (H3R) with CGRP on the Aδ nerve fibers (21). Moreover, several in vivo studies reported that histamine H1 and H2 receptors are involved in generation of thermal and mechanical hyperalgesia (22) and H3 and H4 receptors are related in mediating nociception (23,24). In an experimental study, it was showed that compound 48/80, SP and CGRP induced the release of histamine from mast cells in the dura mater, respectively (25). Therefore, in current study, dilatation of MMA and its branches may be caused by histamine released from degranulated mast cells in the dura mater, but to verify this, there is a need for further studies.

It is known that mast cell stabilizers from synthesized compounds or natural products are commonly used clinically to prevent allergic reactions. Most known and prescribed mast cell stabilizing drugs including ketotifen and sodium cromoglycate inhibit histamine and prostaglandin release from the sensitized mast cells by preventing their degranulation. Unlike allergic and inflammatory disorders, there have been very few studies reported on the effectiveness of mast cell stabilizers in the treatment of headaches. It was reported that ketotifen exhibited therapeutic effect in some patients with Horton's headache (26). Therefore, more investigations are needed to determine whether mast cell stabilizers may be effective for the treatment of migraine.

The concept of a bidirectional interaction between mast cells and the nerves has been promoted by the presence of various neuropeptide receptors such as SP, CGRP, histamine, VIP, pituitary adenylate cyclase-activating polypeptide (PACAP) on the surface of mast cells (27). Thus, dural mast cells are related in microvasculature control and regulation of local trigeminal nerve activity in the dura mater (25,28). Dural mast cells induce meningeal vasodilatation via not only release of histamine from mast cells but also axon reflex resulted in release of CGRP and SP from activated C-fibers in the dura mater. Taken together these processes, it can be seen that neurogenic dural vasodilation plays an important role in pathophysiology of migraine. However, the mechanism of neurogenic dural vasodilation is not dependent on only one factor, and there are various contributors such as mast cells, cerebral blood vessels, meninges, meningeal nerves and mast cell mediators (29). For instance, in an experimental study, it was shown that while AS19, selective 5-HT7 receptor agonist, increased blood flows of the middle meningeal artery following electrical stimulation of dura mater, 5-HT1B/1D receptor agonist sumatriptan decreased it (2). Normally, 5-HT is known as a vasoconstrictor agent but that study revealed its new vasodilator function via 5-HT7 receptor.

In the present study, this vasodilation of middle meningeal artery and its anterior and posterior branches may be caused by vasodilator molecules released from mast cells such as histamine, NO, VIP, CGRP, and vascular endothelial growth factor.

5. CONCLUSION

Our results suggested that dural mast cells contribute to the pathophysiology of migraine via one or more vasodilator mediators released from them during the degranulation process. However, there is a need for further studies to determine mast cell mediator/s that may be responsible for the vasodilatation effect of dural mast cell degranulation.

Limitations of the study

In addition to ex vivo experiments with topical administration of compound 48/80 in the present study, the selective receptor antagonists particular to mediators including adenosine, histamine, CGRP, SP and VIP released from activated mast cells should be tried together with compound 48/80 in the ex vivo meningeal preparations to reveal which mast cell mediator/s cause dilatation of these meningeal arteries. Moreover, in vivo investigations with compound 48/80 and mast cell stabilizing agents including ketotifen and sodium cromoglycate should be carried out by constituting animal models of migraine pain.

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