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Research Submission

Mast Cells Activate the Renin Angiotensin System and Contribute to Migraine: A Hypothesis

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Migraine is a chronic disease with episodic attacks, which, when frequent or severe, can be associated with poor quality of life, increased health resource utilization, lost productivity, and significant disability. Preventive therapy can therefore have a significant beneficial clinical and economic impact. However, many migraineurs are treated suboptimally. There is increasing evidence that activation and degranulation of meningeal mast cells result in meningeal irritation, vascular dilation, and stimulation of nearby nociceptive nerve endings of the trigeminal nerve, thus potentially contributing to the pathogenesis of migraine headache. The renin angiotensin system and its peptides are well represented in the mammalian central nervous system and can also promote neurogenic inflammation. Interestingly, mast cells are capable of releasing renin and increasing local production of Angiotensin II. We therefore hypothesize that mast cells contribute to migraine headache through activation of the renin angiotensin system. This hypothesis may help explain the association between migraine and cardiovascular disease as well as observations that medications that modulate the renin angiotensin system can reduce migraine-related morbidity in patients with frequently recurring migraine attacks.

Key words: **migraine, headache prevention, angiotensin blockade, angiotensin receptor blocker, angiotensin converting enyme, chymase, mast cell, neurogenic inflammation**

Abbreviations: **RAS renin-angiotensin system, ACE angiotensin converting enzyme, ACEIs ACE inhibitors, ARB angiotensin receptor blocker, NF-kappaB nuclear factor-kappaB, iNOS inducible nitric oxide synthase, CRH corticotrophin releasing hormone, Ang II angiotensin II, CGRP calcitonin gene-related peptide, R receptor**

(*Headache* **;**:**-**)

The renin-angiotensin system (RAS) plays a critical role in maintaining cardiovascular and fluid homeostasis through autocrine and paracrine activity. However, excessive upregulation of the RAS is capable of promoting endothelial dysfunction,[1] inflammation,[2] arrhythmogenesis,[3] and a prothrombotic environment.[4] The RAS has been shown to be activated in a variety of cardiovascular conditions with important therapeutic implications in hypertension, atherosclerotic vascular disease (including aortic aneurysms), left ventricular dysfunction, and atrial fibrillation.

The use of angiotensin converting enzyme inhibitors (ACEIs) in headache prevention in patients with essential hypertension was first proposed by the pioneer Italian headache researcher Sicuteri in 1981.[5] More recently, the angiotensin converting enzyme (ACE) inhibitor lisinopril 20 mg/day[6] and the angiotensin receptor blocker (ARB) candesartan 16 mg/day[7] have demonstrated some effectiveness in the

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prevention of migraine in randomized, double-blind, crossover trials with 55 and 60 patients, respectively. Indices reflecting number, severity, and duration of migraine headaches were reduced during the active treatment period with both medications compared to the placebo period. Importantly, in these 2 studies, there was no correlation between the effect on migraine attacks and degree of blood pressure reduction.

In a retrospective study of the impact of ACEIs on the consumption of specific acute care migraine medications in 95 patients initiating either ergotamine or a triptan, the frequency and severity of migraine attacks was significantly reduced during the use of ACE inhibitors as compared to diuretic treatment.[8] Other observational studies providing indirect evidence of benefit of angiotensin blockade in migraine prevention have been extensively reviewed by Tronvik et al.[9] Thus there is growing enthusiasm regarding the potential offered by manipulating the RAS in patients with migraine. In this report we review the central role of mast cells and the RAS in the pathophysiology of migraine and cardiovascular disease as well as observations that support the plausibility that mast-cell-related RAS activation could be an important target in migraine prevention.

ROLE OF RAS IN MAST CELLS ACTIVATION, INFLAMMATION, NOCICEPTION, AND MIGRAINE

Role of Mast Cells in Migraine.—There is increasing evidence that mast cells are involved in a variety of nonallergic inflammatory diseases, especially those worsened by stress.[10] That migraine was "a clinical syndrome of self-limited neurogenic inflammation" was first proposed by Don Dalessio in 1976,[11] who was in the last group of residents at New York hospital under Dr. Harold Wolff. Recent years have witnessed significant advances in our understanding of the pathophysiology and biochemical pathways in migraine. A variety of endogenous and exogenous triggers are thought to induce hormone-dependent and neuropeptide-mediated activation and degranulation of meningeal mast cells resulting in meningeal irritation, vascular dilation, and stimulation of nearby nociceptive nerve endings of the trigeminal nerve.[12-14] Mediators of these responses include histamine, serotonin, cytokines, nitric oxide, and other leukotrienes, all capable of being produced and secreted by meningeal mast cells.[13]

Nuclear factor-kappaB (NF-kappaB) is a family of cytoplasmic transcription factors actively sequestered in the cytoplasm by association with the inhibitory proteins I-kappaB. After activation, NF-kappaB dissociates from its inhibitor and translocates into the nucleus, where it induces expression of proinflammatory cytokine and inducible nitric oxide synthase (iNOS) mRNA, among many others. Interestingly many of these cytokines are themselves activators of NF-kappaB, resulting in a perpetual cycle of inflammation[15] common to many inflammatory diseases. Enhanced NF-kappaB activity also appears to be a mediator of the inflammatory response associated with migraine attacks. In an animal model of migraine, intravenous infusion of the nitric oxide donor nitroglycerin was associated with a significant increase in NF-kappaB activity. Monocytes obtained from jugular veins of 7 migraine patients without aura during attacks demonstrated an increase in levels of NF-kappaB, decrease in levels of its inhibitor I-kappaB, and 2 hours later increased iNOS activity.[16]

RAS and Neurogenic Inflammation.—The RAS and its peptides are well represented in the mammalian central nervous system. In addition to being involved in a variety of physiological effects, the RAS may play an important role in neuromodulation and may be involved in neurological disorders such as Alzheimer's or Parkinson's disease.[17] Most functions of the RAS are mediated by Ang II upon binding to type 1 receptors, which in the brain have been shown to occur in 2 highly homologous isoforms.[18] The physiologic role of type 2 receptors is not clear but may be involved in nociception[19] and inflammation by inducing mast cell degranulation.[20]

How might Ang II promote neurogenic inflammation? Angiotensin II activates NF-kappaB transcription factors,[2,21] through both type 1 and type 2 receptors[22] (Figure). ACEIs and ARBs prevent NF-kappaB activation and secondary inflammation.[22,23]

Ang II can, in a dose-dependent manner, also stimulate endothelin-1 secretion,[24] which itself has been possibly linked to the pathophysiology of migraine.[25] Ang II infusion also increases oxidative stress by

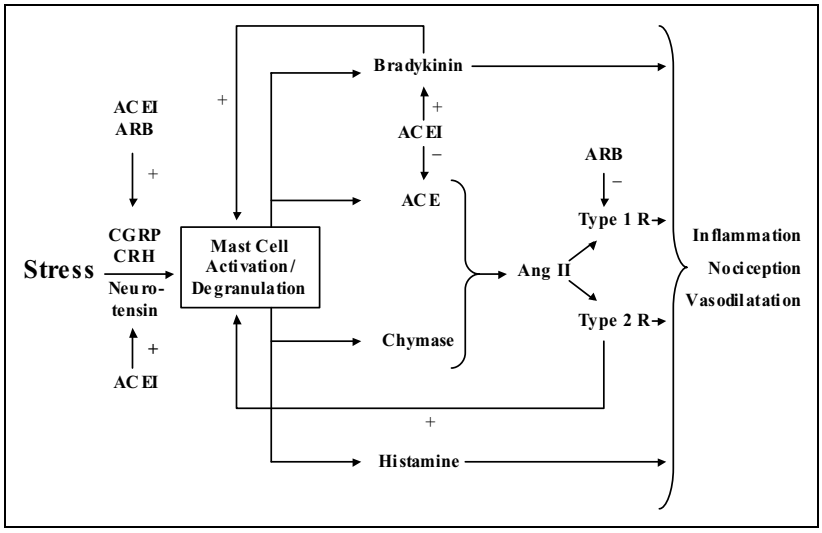

Figure.—ACEIs reduce Ang II production, but also inhibit the degradation of bradykinin and neurotensin. ARBs selectively block type I receptor (R) but leave type II R unopposed. Both ACEIs and ARBs maintain levels of CGRP and CRH. "+" indicates promotion; "−" indicates inhibition.

promoting superoxide production in the central nervous system.[26] Oxidative stress has been associated with migraine while antioxidants have demonstrated antimigraine capability in migraineurs.[27]

Finally, by binding to type 2 receptors, Ang II can enhance chemically induced mast cell degranulation and promote meningeal irritation.

ACE Gene Polymorphism and Plasma ACE Activity Are Linked to Migraine Frequency.—The advent of genomic techniques, including mapping of single-nucleotide polymorphisms, has contributed to our understanding of disease susceptibility and progression. ACE gene deletion polymorphisms has been shown to be associated with increased plasma ACE activity and increased frequency of migraine attacks in patients with[28] and without aura.[29] A similar association has been described in patients with a variety of cardiovascular diseases.[30] In the study by Schrader et al,[6] a reduction of at least 50% in days with migraine were seen in only 30% of patients during the lisinopril treatment period compared with the placebo period. Whether ACE phenotype can help predict response to Ang II blockade in patients with migraine is unknown. In hypertensive patients, ACE phenotype failed to predict response to ACE inhibitor therapy.[31]

Mast Cells Are an Important Source of Angiotensin II (Ang II).—In addition to releasing histamine, there is evidence that mast cells may contribute to clinically important activation of the local RAS.[3,32] Although the primary source of renin in the circulation is the kidney, Mackins et al[3] have recently demonstrated that in response to ischemia, mast cells in isolated guinea pig hearts are capable of releasing renin and increasing local production of Ang II. Renin release was blocked by mast cell stabilization and Ang II production was blocked by a selective renin inhibitor.

In addition to ACE, another Ang II forming serine proteinase (chymase) has been identified in human hearts. Human cardiac chymase levels are highest in ventricles especially in the secretory granules of mast cells, unlike ACE levels, which are highest in the atria.[33,34] Both ACE-dependent and chymase-dependent Ang II formation appear to occur in pathologic states affecting hearts or blood vessels. However, levels of chymase activities tend to be higher than those of ACE activities.[35] In fact, chymase appears to be the most specific and efficient Ang II-forming enzyme accounting for more than 80% of Ang II-formation in human or animal heart extract in the presence or absence of heart failure.[36]

MIGRAINE AND CARDIOVASCULAR DISEASE

Migraine and Cardiovascular Disease Are Related.—In the large prospective cohort Women's Health Study of US women age 45 and older without

clinical cardiovascular disease on entry with a 10-year follow-up, nearly 18% had active migraine.[37] Active migraine with aura was associated with a 2-fold increased risk of myocardial infarction, ischemic stroke, and death from coronary heart disease while active migraine without aura was not associated with increased risk of any cardiovascular event. Whether such observations are also true in men and younger women remains to be established.

In another retrospective study of nearly 80,000 patients enrolled in Kaiser Permanente, a strong relationship was found between migraine and chest pain. In addition, a 2-fold increase in the risk of subsequent myocardial infarction was observed in women with migraine.[38]

Stress Induces Mast-Cell Activation and Degranulation in Both Brain and Heart.—Physical, emotional, or other stressors may be contributing triggers to acute coronary syndromes and sudden cardiac arrest as well migraine attacks. One potential common mechanism by which stress can precipitate 1 or more of these clinical syndromes relates to stress-induced mast-cell degranulation and release of a variety of vasoactive and proinflammatory molecules. In a study using a model of nontraumatic restrain stress, Pang et al[39] showed that acute psychological stress can lead to corticotrophin releasing hormone (CRH)-dependent and neurotensin-mediated cardiac mast cell degranulation (Figure). Similar experiments by Theoharides et al[40] demonstrated that stress also induced CRH and neurotensin-mediated activation and degranulation of dural mast cells localized close to trigeminal nerve endings.

Ang-II as a Hypothetical Link Between Migraine and Cardiovascular Risks.—Based on the above, mast-cell-related Ang-II may explain, at least in part, the link between migraine and cardiovascular risks and the observed benefit on migraine-related morbidity with ACEIs and ARBs when studied in patients with frequently recurring migraine.

Hypothesis Testing, Theoretical Considerations, and Future Direction.—The studies that suggested that ACEIs (lisinopril) and ARBs (candesartan) were effective in reducing the frequency of migraine attacks had a number of limitations including a small number of participants, a relatively high drop-out rate, and the potential confounding "placebo effect."[41] Even though we have put forth a constellation of observations that support the plausibility that mast-cell-related RAS activation could be an important target in migraine prevention, further hypothesis testing and confirmation of the role of the RAS in the pathogenesis of migraine is needed. The degrees to which Ang II formation in meningeal mast cells is ACE- or chymase-dependent especially in experimental models of migraine, is important to determine. A study of ACE, chymase, and Ang II levels in relationship to NF-kappaB, Inos, and cytokine levels from jugular veins in animal model of migraine would be helpful. Evaluation of levels of plasma ACE, chymase and Ang II levels in migraineurs during and outside migraine attacks and in healthy controls should also be considered.

Gender differences have been reported in the renal response to RAS blockade with men showing continued Ang II sensitivity compared to women thus requiring larger dosages of ARBs.[42] Unknown is whether gender is an important factor in determining the response to angiotensin blockade in migraineurs needing prevention. Also unknown is whether a strategy of angiotensin blockade will be helpful in patients who have both migraine with and without aura, 2 clinically and genetically, and potentially pathophysiologically distinct disorders.

Work is also needed to clarify the best dose of a particular ACE inhibitor or ARB, to determine whether the choice of a particular ACE inhibitor or ARB is important, and to answer the question whether ACE inhibitors and ARBs have similar effects in preventing migraine.

Finally, whether a strategy of long-term use of Ang II blockade in migraine prevention may lose efficacy or remain sustained over time is unknown. This issue is raised because of the observation that long-term use of an ACE inhibitor or an ARB, compared to that of another vasodilator (hydralazine), was associated with restoration of the age-related decline in calcitonin gene-related peptide (CGRP)-mRNA expression in vascular and cardiac tissues in spontaneously hypertensive rats[43] (Figure). CGRP, a neuropeptide released from activated trigeminal sensory neurons, may have an important role in migraine pathophysiology by

dilating dural blood vessels and transmitting vascular nociception.[44] CGRP receptor antagonism has been shown to have clear benefit without the risk of vasoconstriction in migraine prevention and acute treatment in an intravenous preparation.[45] Clinical studies are underway on an oral CGRP antagonist, which will be more readily usable for migraineurs, and may be more appropriate for those with cardiovascular risk factors.[46] The phase 2B study on MK-0974 just reported from the podium at the American Headache Society conference in June in Chicago and published in abstract form in *Headache* and accepted for publication in *Neurology* showed good efficacy at 2 hours and excellent efficacy at 24 hours with few adverse events and no triptan adverse events.

Another exciting approach to achieving blockade of the RAS is through the inhibition of renin and chymase.[47] Aliskiren is the first in a new class of agents known as oral renin inhibitors and is approved by the Food and Drug Administration for the treatment of high blood pressure as monotherapy or in combination with other antihypertensive medications. Whether this new class of agents proves to be helpful in migraine prevention remains to be studied.

CONCLUSIONS

Over the last decade, many new pharmacological agents have been introduced to reduce the growing morbidity associated with migraine. Angiotensin blockers, when used preventively, have been demonstrated to reduce morbidity associated with migraine, with reasonable supportive laboratory evidence especially in reference to the role of the RAS in mast cell physiology and in the pathophysiology of meningeal inflammation.

From a clinical perspective, a preventive strategy utilizing angiotensin blockade is a reasonable approach, especially in those migraineurs who remain symptomatic despite multiple other preventive interventions. It should also be considered for first line therapy in those with a comorbidity, such as hypertension, in which angiotensin blockade has been proven to be clinically beneficial with a relatively good adverse-event profile. It is, however, important to continue efforts to better understand the pathophysiology of migraine, identify potential therapeutic targets, and conduct quality clinical trials. We expect that it may well turn out that migraineurs without hypertension will benefit from angiotensin blockade to the same extent as those with hypertension, especially considering its efficacy and tolerability.

Conflict of Interest: None

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