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Neurovascular contributions to migraine: moving beyond vasodilation

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Abstract

Migraine is the third most common disease worldwide, the most common neurological disorder, and one of the most common pain conditions. Despite its prevalence, the basic physiology and underlying mechanisms contributing to the development of migraine is still poorly understood and development of new therapeutic targets is long overdue. Until recently, the major contributing pathophysiological event thought to initiate migraine was cerebral and meningeal arterial vasodilation. However, the role of vasodilation in migraine is unclear and recent findings challenge its necessity. While vasodilation itself may not contribute to migraine, it remains possible that vessels play a role in migraine pathophysiology in the absence of vasodilation. Blood vessels consist of a variety of cell types that both release and respond to numerous mediators including growth factors, cytokines, adenosine triphosphate (ATP), and nitric oxide (NO). Many of these mediators have actions on neurons that can contribute to migraine. Conversely, neurons release factors such as norepinephrine and calcitonin gene-related peptide (CGRP) that act on cells native to blood vessels. Both normal and pathological events occurring within and between vascular cells could thus mediate bi-directional communication between vessels and the nervous system, without the need for changes in vascular tone. This review will discuss the potential contribution of the vasculature, specifically endothelial cells, to current neuronal mechanisms hypothesized to play a role in migraine. Hypothalamic activity, cortical spreading depression (CSD), and dural afferent input from the cranial meninges will be reviewed with a focus on how these mechanisms can influence or be impacted by blood vessels. Together, the data discussed will provide a framework by which vessels can be viewed as important potential contributors to migraine pathophysiology, even in light of the current uncertainty over the role of vasodilation in this disorder.

1.1 Introduction

Migraine headache is the most common neurological disorder and one of the most common pain conditions. It is characterized by recurrent multiphasic symptoms, which include episodes of unilateral pulsating head pain. The entire sequence of migraine symptoms can

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last many hours to days and can vary greatly among patients. There are four distinct phases of migraine: the premonitory phase, aura phase, headache phase, and postdrome phase (Charles, 2013). Up to 80% of individuals who suffer from migraines experience premonitory symptoms hours or even days leading up to the headache attack (Becker, 2013). Premonitory symptoms including excessive yawning, food cravings, mood changes, fatigue, sore neck, and confusion among others, and are considered a reliable predictor of an impending migraine (Blau and MacGregor, 1994; Becker, 2013). Toward the end of the premonitory phase before the onset of headache, about 15-30% of migraine suffers report visual disturbances known as aura (Goadsby, 2012). Patients with aura can experience geometric patterns (e.g. fortification spectra), light oscillations of varying intensities, or partial vision loss (e.g. scotoma). The headache phase of migraine, which typically follows aura, is characterized by moderate to severe unilateral throbbing head pain that persists for longer than 4 hours but can last up to 72 hours. Additional symptoms associated with the headache phase include nausea, vomiting, enhanced sensitivity to light, sound and smell, and cutaneous allodynia (Piovesan et al., 2003; Goadsby, 2009a; Levy, 2010; Giamberardino, 2003; Burstein et al., 2004). After the headache subsides, many patients report postdrome symptoms such as cognitive impairments, fatigue, and changes in mood that can persist for 18-24 hours post-headache (Goadsby, 2009a).

Two distinct clinical states of migraine have been identified: episodic and chronic migraine. Episodic migraines are characterized as 14 or fewer headache days per month, while chronic migraine is characterized by 15 or more headache days per month for more than 3 months where at least 8 of the headaches meet the criteria for migraine (Headache Classification Committee of the International Headache Society, 2013). Clinical and epidemiological observations demonstrate that episodic migraine can progress to chronic migraine at a rate of 2.5% annually (Bigal et al., 2008). The migraine phases combined can last several days, and given their severity, migraines have a significant impact on overall quality of life by negatively affecting physical, social, and occupational function. According to the World Health Organization's Global Burden of Disease Study analysis of data collected from 1990 to 2010, migraine headache is the third most prevalent disease in the world (Vos et al., 2012). Additionally, a recent review of 4 national surveillance studies on migraine reinforces what is commonly known in the general population and also reported consistently throughout the literature, that migraine is 2-3 times more prevalent in females than males (Smitherman et al., 2013). Despite the prevalence, the basic physiology and underlying factors contributing to the development of migraine headache is still poorly understood.

Unlike other pain states, migraine sufferers report multiple distinct triggers. These triggers are innocuous in healthy patients which suggests that the sensitivity to different triggers in migraine is due to maladaptive changes within the nervous system. The higher incidence of migraine headache in females compared to males strongly suggests a role for female hormones in the onset of migraine. Before puberty, the annual incidence of migraine between males and females is similar (approximately 4%) (Bille, 1997), but at puberty, rates in females increase to 18% while only increasing to 6% in males (Lipton et al., 2001). Incidence remains higher in females until post-menopause. Further, approximately 50% of female migraineurs have attacks related to specific times of their menstrual cycle (Martin, 2004) with up to 20% of female migraineurs experiencing what are termed “pure menstrual”

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migraines, which by definition occur between days -2 and +3 from the onset of menstruation (Brandes, 2006). This implicates changes in hormone levels as an important migraine trigger in females. Besides changes in sex hormones, the most commonly reported migraine trigger is stress (Spierings et al., 1997; Martin and MacLeod, 2009; Houle and Turner, 2013). As many as 80% of patients indicate that stress is their primary trigger for migraine (Kelman, 2007). The physiological stress response involves the activation of the hypothalamic-pituitary-adrenocortical axis (HPA) and the autonomic nervous system. Possible mechanisms whereby activation of these systems evoke headache include stress hormone-mediated activation/sensitization of afferent nociceptors, changes in descending inhibitory control and alterations in immune system responses, among others (Burstein and Jakubowski, 2005; Imbe et al., 2006; Meng and Cao, 2007; Maier, 2003; Sauro and Becker, 2009). Recent reports also show that the peak susceptibility to migraine is in the 18-24 hours after a stressful event and therefore stress itself may not be the trigger, rather the consequences of the stressful event such as sleep disturbances, changes in diet, or other physiological changes that occur after the resolution of stress (Kemper et al., 2001; Lipton et al., 2014; Goadsby, 2014). Other common migraine triggers include alcohol, environmental irritants, exercise, changes in the weather, improper duration of sleep and intense sensory stimuli (Kelman, 2007). Patients who identify their individual triggers are often successful at reducing the frequency of migraine attacks by consciously decreasing their exposure to the trigger (Martin et al., 2014). Despite such interventions, migraine remains highly prevalent.

Since the discovery of elevated levels of the 5-HT metabolite 5-HIAA (5-hydroxyindoleacetic acid) in the urine of patients during migraine attacks (Sicuteri, 1972), the role 5-HT plays in migraine has been hotly debated. Although it is unclear whether levels increase, decrease, or remain unchanged during migraine attacks, the general consensus in the migraine field is that 5-HT plays an important role in this disorder (Dussor, 2014). In fact, the most widely utilized pharmacological agents for the acute treatment of migraine are 5-HT based. Triptans are a family of serotonin (5-HT) $_{1B}$, $_{1D}$, and $_{1F}$ agonists which include sumatriptan, zolmitriptan, rizatriptan, eletriptan, and naritriptan. They are taken at the onset of migraine symptoms in order to terminate attacks or at the very least to decrease headache intensity/duration. Triptans alone account for up to 80% of medications prescribed for migraine (Diener et al., 2011). Unfortunately, less than 50% of patients taking oral triptans are pain-free at 2 hours, and 30% have a reoccurrence of headache within 24 hours (Ferrari et al., 2001; Goadsby and Sprenger, 2010). Although they are the only drugs specifically developed to treat migraine headache, the exact mechanism by which triptans reduce migraine pain is unknown. They possess vasoconstrictive properties and therefore are generally not prescribed in patients with cardiovascular disease or abnormal blood pressure (Dodick et al., 2004). Moreover, repeated dosing with triptans can lead to a phenomenon known as medication-overuse headache (MOH) (Kristoffersen and Lundqvist, 2014). MOH is characterized as a headache occurring on more than 15 days per month with regular overuse (more than 3 months) of one or more drugs that can be taken for acute and/or symptomatic treatment of headache (Headache Classification Committee of the International Headache Society, 2013). Therefore, triptans are not recommended for daily use and are not prescribed as a migraine prophylactic. As a preventative measure to decrease the frequency of migraine headaches, patients will often be prescribed antiepileptics such as topiramate,

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beta-blockers such as propranolol, or anti-depressants such as amitriptyline off-label. However, these drugs can cause severe adverse effects including nausea, vomiting, weight gain, decreased cognition, and withdrawal symptoms upon discontinuation of the medication (Edvinsson and Linde, 2010; Stovner et al., 2009). Furthermore, migraine prophylactics only decrease the frequency of headache by about 50% in 40-50% of patients (Tfelt-Hansen and Olesen, 2012).

The development of new migraine compounds is long overdue. Recently, several studies have shown that selective 5-HT-$_{1F}$ agonists (e.g. lasmitidan (Nelson DL et al., 2010) have efficacy in several clinical trials as an abortive migraine treatment (for review see (Tfelt-Hansen and Olesen, 2012; Hoffmann and Goadsby, 2014). In addition, targeting calcitonin gene-related peptide (CGRP) directly has been shown to be a promising therapy. CGRP was found to be significantly elevated in the plasma of patients during acute migraines (Goadsby et al., 1990) and administration of CGRP to migraineurs can trigger attacks (Lassen et al., 2002). This led to the hypothesis that CGRP-based therapeutics may have efficacy for migraine. In a phase 3 clinical study, the CGRP-receptor antagonist telcagepant was more effective than placebo for the reduction in migraine symptoms; unfortunately elevated liver enzymes were detected and further development of this compound was halted (Ho et al., 2008). More recently, phase 2 clinical trials have shown that monoclonal antibodies to CGRP and the CGRP receptor significantly reduce the number of migraine headache days (Dodick et al., 2014a, Dodick et al., 2014b; Bigal et al., 2015a, Bigal et al., 2015b). Importantly, the CGRP antibodies by design are extremely specific, have long half-lives and are unlikely to cause liver toxicity given that they are not subject to hepatic metabolism (Mitsikostas and Rapoport, 2015). Currently, these antibodies are in phase 3 clinical trials for management and prevention of episodic and chronic migraine headache.

For many decades, the major contributing pathophysiological event thought to initiate migraine was cerebral and meningeal arterial vasodilation (Goadsby, 2009a; Shevel, 2011). Support for the vascular migraine hypothesis grew, in part, due to the use of the vasoconstrictor ergotamine, an ergot alkaloid that was found to reduce temporal artery pulsations and relieve headache pain in migraine patients (Graham, 1938; Drummond and Lance, 1983). Furthermore, other vasoconstrictors were soon discovered to abort migraine attacks including noradrenaline and 5-HT (Ostfeld and Wolff, 1955; Kimball et al., 1960; Anthony et al., 1967). Since ergotamine was a non-selective vasoconstrictor with affinity for 5-HT, noradrenaline and dopamine receptors, more selective 5-HT receptor agonists were developed to reduce the side-effect profile of perspective migraine therapies (for review see Humphrey, 2007). This resulted in the eventual development of the 5-HT-$_{1B/1D}$ agonist, sumatriptan, which was shown to cause vasoconstriction and effectively reduced migraine symptoms (Humphrey et al., 1990). Although there is a strong correlation between migraine pathology and the associated vasculature, other studies have concluded that vasodilation is an epiphenomenon and does not contribute to migraine directly (Olesen, 1990; Goadsby, 2009b). For example, vasoactive intestinal polypeptide (VIP) has been shown to dilate cranial arteries to a similar extent as pituitary adenylate cyclase activating peptide (PACAP-38), however VIP does not produce migraine in migraineurs (Rahmann et al., 2008) while PACAP-38 does (Amin et al., 2012). In addition, vasoactive substances known to trigger migraine, such as the NO donor nitroglycerine (NTG; Thomsen et al., 1994) and

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sildenafil (Kruuse et al., 2003) were reported *not* to cause cerebral and meningeal blood vessel dilation in migraineurs during attacks (Schoonman et al., 2008). Although this may be true for NTG, CGRP administration, which also triggers migraine in migraineurs, has been shown to cause blood vessel dilation at time points where headaches occur (Asghar et al., 2010). Discrepancies reported in the literature may be due at least in part to the use of different vasodilators (and the differential downstream effects of nitric oxide vs. CGRP) and/or different methods to detect changes in the vasculature. However, a recent study showed no significant changes in blood vessels during spontaneous migraines in humans (Amin et al., 2013) leading the authors to conclude that vasodilation is not the cause of migraine. Consequently, attention within the migraine field has largely shifted to the role that changes in the nervous system play in migraine pathophysiology. Moreover, it is likely that migraine is a consequence of dysfunctional neuronal networks (Edvinsson et al., 2012) as certain neurological symptoms of migraine cannot be explained solely by the vascular model of headache (e.g. VIP does not trigger migraines, but causes vasodilation).

Although the migraine field seems poised to discard the vascular hypothesis, this is primarily based on an unclear role of vasodilation in migraine. Before vessels are completely discarded however, it seems appropriate to further discuss whether vessels might contribute to migraine in the absence of vasodilation. The cells comprising blood vessels (e.g. endothelial and smooth muscle cells) do not merely exist to dilate and constrict blood vessels, and they may make an important contribution to migraine without a change in vascular diameter. Consequently, migraine symptoms may arise from a combination of dilation-independent vascular events (Tietjen and Khubchandani, 2015) and neurogenic mechanisms interacting throughout the brain and within the trigeminovascular system in the meninges (Levy, 2010). The purpose of the remainder of this review is to discuss the potential contribution of the vasculature to current neuronal mechanisms hypothesized to play a role in migraine including altered hypothalamic activity, cortical spreading depression (CSD), and dural afferent input from the cranial meninges. Focusing on dilation-independent mechanisms may help determine whether the vascular hypothesis as a whole should be laid to rest, or whether the field should simply move beyond vasodilation as the cause of migraine.

1.2 Blood vessel anatomy

Before discussing the potential role of blood vessels in several neuronal mechanisms thought to contribute to migraine, it is important to briefly review the anatomy of the blood vessel (see figure 1). The inner-most layer of the blood vessel, the tunica intima, is comprised of endothelial cells surrounded by a subendothelial layer of connective tissue and internal elastic lamina which provides a flexible barrier between the endothelium and the inner smooth muscle cell layer. The middle layer, the tunica media, is comprised of smooth muscle cells, connective tissue and a thick elastic band called the external elastic lamina, which separates the middle and outer layers. The outermost layer, tunica adventitia, consists of nerve fibers, fibroblasts, perivascular adipose tissue and collagen. Vascular smooth muscle cells within the tunica media have been shown to regulate vascular tone primarily in response to sympathetic nervous system innervation (e.g. adrenergic receptor activation), NO, as well as the local synthesis, uptake and release of 5-HT (Green, 200; Ni et al., 2008).

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The contribution of smooth muscle cells and their contribution to vascular tone in migraine has largely overshadowed the diverse functions of another major vascular cell type, endothelial cells. Endothelial cells directly contact the circulating blood in the lumen and also control vessel function. They express a variety proteins including growth factors (e.g. vascular endothelial cell growth factors, VEGF) (Breier and Risau, 1996), coagulants/anticoagulants (Stern et al., 1985), lipoproteins (e.g. low density lipoprotein, LDL) (Sawamura et al., 1997), and junction proteins (e.g. platelet endothelial cell adhesion molecule, PECAM-1) (Albelda et al., 1991) as well as metabolites (e.g. NO and 5-HT) (Palmer et al., 1988; Green, 2006), hormones (e.g. endothelin-1) (Yanagisawa et al., 1988), and cytokines (tumor necrosis factor, TNF-α) (Mantovani et al., 1997). Thus, endothelial cells are involved in the regulation a variety of functions including cell-cell barrier maintenance, vascular tone, vascular remodeling, immune surveillance, blood coagulation, and nutrient uptake among others (for review see Cines et al, 1998). Taken together, these studies demonstrate that the blood vessel does not simply provide a conduit for the movement of blood that can constrict and dilate; rather it coordinates a much more complicated web of signaling between multiple cell-types. Dysregulation of any part of this vascular signaling process may contribute to migraine pathology. The remainder of this review will highlight the potential contribution of vascular endothelial signaling to neuronal events thought to contribute to migraine.

2.1 Hypothalamus

The location of origin of migraines within the nervous system is unknown but many have speculated that this complex brain disorder may be driven by the hypothalamus. The hypothalamus, located at the base of the brain with widespread connections throughout the central nervous system, is involved in maintenance of homeostasis by controlling the endocrine system and coordinating activity within the autonomic nervous system. It regulates many physiological functions including food intake, energy balance, responses to stress, and circadian rhythms. Additionally, the hypothalamus is involved in the processing of trigeminal nociceptive signaling (Malick et al., 2000; Holland and Goadsby, 2007), a type of afferent sensory input critical for the pain phase of migraine (reviewed below). Many migraine patients experience premonitory symptoms related to dysfunction of the aforementioned systems including sleep disturbances, changes in wakefulness, mood, appetite and/or thirst. Additionally, functional imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) showed hypothalamic activation during spontaneous migraine (Afridi et al., 2005; Denuelle et al., 2007). Moreover, Goadsby and colleagues found increased activity in the posterolateral hypothalamus among other brain areas during the premonitory phase of NTG-triggered migraines (Maniyar et al., 2014). These data suggest that the hypothalamus plays a central role in the initiation/progression of migraine.

Hypothalamic regulation of hormonal cycles in women may contribute to the cyclic nature of migraine. As previously mentioned, migraine headache is three times more prevalent in females compared to males after puberty (Lipton et al., 2014). An explanation for the sexual dimorphism of migraine may be attributed to, among other events, estrogen regulation of hypothalamic networks that control the menstrual cycle (Brandes, 2006). During the

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follicular phase of the menstrual cycle, the amount of estrogens (e.g. estradiol) secreted by the growing follicle dramatically increase and act as a positive stimulus for hypothalamic-pituitary-mediated surges in polypeptides involved the progression of the menstrual cycle (Kelly et al., 2005). Evidence suggests that estradiol-mediated activation of estrogen receptors expressed by endothelial cells (Venkov et al., 1996) augments endothelial nitric oxide synthase (eNOS) activity (Caulin-Glaser et al., 1997; Simoncini and Genazzani, 2000; Martin and Behbehani, 2006) resulting in the rapid increase in NO release in human female endothelial cells, an effect that was antagonized by the 17β-estradiol antagonist, ICI 164, 384 (Caulin-Glaser et al., 1997). Moreover, there is a positive correlation between the incidence of migraine and expression of biomarkers of endothelial cell activation in women (Tiejen, GE et al., 2009). These data suggest that the increased incidence of migraine in women may be due in part to the effects of hypothalamic regulation of female hormones such as estradiol on endothelial cells.

Given the multitude of factors known to cause migraine, stress being the most common (Kelman, 2007), autonomic related symptoms may reflect normal hypothalamic responses to environmental triggers. During stress, the PVN of the hypothalamus releases hormones including vasopressin, oxytocin and corticotrophin–releasing hormone, altering the balance between parasympathetic and sympathetic tone. Importantly, hypothalamic neurons can regulate parasympathetic preganglionic neurons in the superior salivatory nucleus (SSN) and sympathetic preganglionic neurons in the spinal intermediolateral nucleus (Moulton et al., 2014). Although data assessing the role of the autonomic nervous system in migraine is conflicting, a majority of studies report sympathetic hypofunction and enhanced cranial parasympathetic tone in migraineurs between attacks (Shechter et al., 2002; Peroutka, 2004; Avnon et al., 2003). Activation of the SSN stimulates the release of acetylcholine, VIP, PACAP, and NO from postganglionic parasympathetic neurons in the sphenopalatine ganglion (SPG) (Uddman et al., 1999; Edvinsson et al., 2001) resulting in the local release of inflammatory mediators that can activate meningeal nociceptors (Burstein and Jakubowski, 2005, Csati et al., 2012a, Csati et al., 2012b). Therefore, the interaction between parasympathetic and trigeminal sensory systems following hypothalamic activation of the SSN may facilitate the progression of migraine.

PACAP, VIP and NO activate a variety of alternative signaling pathways in vessels independent of vasodilation that may contribute to migraine pathophysiology. The vasoactive intestinal peptide/pituitary adenylate cyclase activating polypeptide-receptor-1 (VPAC1R) and VPAC2 receptors are expressed in various cell types throughout the body (Wei and Mojsov, 1996) including endothelial cells (Steinhoff et al., 1999; Borsani et al., 2013) and show equal affinity for VIP and PACAP (Zhou et al., 2002). In a model of ischemia, VIP increased the expression and secretion of VEGF in endothelial cells (Yang et al., 2009, Yang et al., 2013) leading to increased angiogenesis (Potente et al., 2011). Considering the mediators of angiogenesis are thought to contribute to the development of chronic inflammation (Ribatti et al., 2007), angiogenic signaling may also contribute to inflammatory pain. During angiogenesis, VEGF recruits immune cells such as macrophages and neutrophils to the site of tissue injury where they produce various inflammatory cytokines including interleukins and chemokines thought to be involved in the pathology of pain (Miller et al., 2009; Kiguchi et al., 2012; Selvaraj et al., 2015). The release of the highly

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permeable gaseous molecule NO may also contribute to nociceptive neurotransmission. Under inflammatory conditions, vessel and nociceptor eNOS and VEGF immunofluorescence increases (Borsani E et al., 2013). Moreover, an eNOS inhibitor, L-N(5)-(1-iminoethyl)ornithine (L-NIO), was found to attenuate inflammatory hyperalgesia (Borsani et al., 2013). In addition, PACAP not only leads to de novo formation of new blood vessels, but also plasma protein extravasation (neurogenic inflammation) in human skin (Seeliger et al., 2010). Taken together these data suggest that hypothalamic regulation of parasympathetic tone may activate vascular endothelial cell signaling pathways known to contribute to inflammatory pain. Therefore, it is possible that the hypothalamus contributes to migraine via endothelial cell-dependent signaling pathways independent of vasodilation. How this leads to the specific set of symptoms characteristic of migraine, and not other pain states, is unclear.

3.1 Cortical Spreading Depression

Cortical Spreading Depression (CSD) is the widespread depolarization of neuronal and glial membranes due to sudden loss of membrane resistance and ionic gradients. Characterized as a brief burst of activity in the cortex that leads to the inhibition of all spontaneous and evoked synaptic activity within cerebral grey matter (for review see (Eikermann-Haerter and Ayata, 2010; Pietrobon and Moskowitz, 2014), CSD is thought to cause massive K^+ (Grafstein, 1956) and glutamate (Van Harreveld, 1959) efflux which contributes to the depolarization of adjacent brain tissue. The signal propagates as a wave at a velocity of about 2-5 mm/min across the cortical surface (Leao, 1945; Grafstein, 1956; Ochs, 1962; Aitken et al., 1998; Smith et al., 2006) and is associated with numerous physiological changes in the cortex including alterations in intra and extracellular ion concentrations, neurotransmitter release and changes in blood flow and oxygen levels (Somjen, 2001; Pietrobon and Moskowitz, 2014).

CSD may contribute to the pathophysiology of several diseases including migraine (Bolay and Moskowitz, 2005; Charles and Baca, 2013). It has been proposed that since the rate of aura spread across the surface of the primary visual cortex during migraine corresponds to the propagation velocity of CSD (Lashley, 1941; Leao, 1945; Milner, 1959), that the wave of neuronal excitation/inhibition may contribute to reported migraine symptoms (i.e. aura). Moreover, imaging studies show patterns of changes in blood flow in the cortex of human migraine patients corresponds to the mean cortical velocity of perceived aura across the visual field (Hansen et al., 2013; Charles and Baca, 2013).

Although CSD is thought to be the underlying basis of aura, whether it contributes to headache is less clear. Headache classically follows aura across the phases of migraine but headache is thought to be mediated by nociceptive trigeminal afferents innervating the meninges (discussed below) and not due to direct cortical events. While Leao first proposed that CSD could evoke pain neurotransmission via activation of trigeminal afferents (Leao, 1944), later studies found that CSD can activate meningeal nociceptors (Moskowitz and Macfarlane, 1993; Zhang et al., 2010) as well as second-order neurons in the spinal trigeminal nucleus, a brainstem region that processes nociceptive information (Moskowitz et al., 1993; Zhang et al., 2011a). Moskowitz and colleagues have shown expression of the

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neuronal marker c-fos in the trigeminal nucleus caudalis in a rat model of CSD. They also found that sumatriptan inhibited c-fos expression in this region, but did not alter the induction of CSD (Moskowitz et al., 1993). Taken together, these data suggest that CSD does not likely cause headache directly, rather it may contribute to headache via activation/sensitization of meningeal afferents of the trigeminal nerve by substances released as a result of CSD.

During CSD, the demand for energy increases dramatically and in order to restore ionic gradients and neuronal function, cerebral blood flow (CBF) also increases (Shinohara et al., 1979). In agreement with this observation, others have reported that after the depolarization wave, CBF and oxygen levels transiently increase (Lukyanova and Bures, 1967; Piilgaard and Lauritzen, 2009). This increase in CBF is followed by a persistent decrease in blood flow (Lambert and Michalicek, 1994; Ayata et al., 2004) and oxygen levels (Piilgaard and Lauritzen, 2009) leading to a period of tissue hypoxia (Lukyanova and Bures, 1967; Lacombe et al., 1992; Otori et al., 2003; Takano et al., 2007). Therefore, in order to restore metabolic balance, cortical neurons including interneurons and astroglia are thought to release of a variety of neurotransmitters including NO, carbon monoxide, adenosine, hydrogen ions, potassium ions, and lipoxygenase products known to alter cerebral vascular tone (Cauli et al., 2004; Vaucher et al., 2000; Zonta et al., 2003; Filosa et al., 2006; Koehler et al., 2006; Busija et al., 2008). Independent of vascular tone, these signaling molecules also directly affect endothelial cell signaling pathways (De Caterina et al., 1995; Jozkowicz et al., 2003; Erlinge and Burnstock, 2008; Dalvi et al., 2015; Mark et al., 2001). Moreover, the close association between cerebral blood vessels and neurons (Hawkins and Davis, 2005) facilitates 2-way communication between cortical neurons and endothelial cells comprising the blood vessels. Just as endothelial cells respond to substances released by neurons, neurons can respond to substances released by endothelial cells. For example, arterial endothelial cells synthesize and store peptides such as CGRP (Cai, et al., 1993; Doi et al., 2001; Luo et al., 2008). Endothelial cell release of CGRP may contribute to increased neuronal excitability within the cortex (Tozzi et al., 2012) in a similar manner as has been reported for astrocyte-mediated release of glutamate (Seidel et al., 2016). Ayata and colleagues have suggested that neuronal hyperexcitability due to neurovascular dysfunction enhances susceptibility to ischemic CSD-like depolarizations during mild changes in metabolic demand (Eikermann-Haerter et al., 2012; von Bornstadt et al., 2015). Thus, due to neurovascular mechanisms that contribute to neuronal hyperexcitability (e.g. endothelial cell release of CGRP), sensory stimulation in a specific cortical region that would otherwise go undetected in non-migraine patients (e.g. somatosensory events) may trigger a CSD event and aura in migraineurs.

4.1 Meningeal afferents

As previously mentioned, the pain phase of migraine likely requires activation of trigeminal nociceptors innervating the cranial meninges (Burstein et al., 2015). Trigeminal nociceptors are pain-sensing neurons that bifurcate from the cell body located in the trigeminal ganglion (TG), sending an axon branch to innervate intracranial and extracranial tissue and another axon branch to synapse on second order neurons in the trigeminal nucleus caudalis (TNC) or trigeminocervial complex (TCC) (Strassman et al., 1994; Hoskin et al., 1999). Stimulation

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of dura mater near blood vessels and sinuses has been shown to produce pain in humans that closely mirrors the sites of pain commonly reported during migraine (e.g. behind the eye) (Penfield, 1940; Ray, 1940). Although, numerous studies have reported that dural afferents are sensitive to noxious mechanical (Kaube et al., 1992; Strassman et al., 1996; Levy and Strassman, 2002) and chemical (Sarchielli et al., 2001; Perini et al., 2005) stimuli, it is still unclear how these neurons are activated during migraine. Meningeal arteries and veins including their extensive capillary network supply blood to the dura (Fricke B et al., 2001). Considering the close association between trigeminal afferents and cerebral/dural vasculature (Mayberg et al., 1981, Mayberg et al., 1984) it is possible that cells comprising blood vessels can sensitize and/or directly activate meningeal afferents leading to headache.

During migraine, intracranial and circulating levels of various inflammatory mediators, which are known to sensitize primary afferent nociceptors are elevated (Sarchielli et al., 2001; Perini et al., 2005). Thought to be a consequence of neurogenic inflammation in the meninges, immune cells including dural mast calls and macrophages release a host of proflammatory mediators including 5-HT, histamine, prostaglandins, and cytokines (Mekori and Metcalfe, 2000; Levy, 2009; Reuter et al., 2001), which are known to sensitize meningeal nociceptors (Levy et al., 2007; Zhang et al., 2007, Zhang et al., 2011b, Zhang et al., 2012, Yan et al., 2012). Neuronal receptors are thought to mediate the sensitizing actions of inflammatory cytokines (Yan et al., 2012; Nicol et al., 1997; Czeschik et al., 2008), however other non-neuronal cell types may also be involved as ablation of neuronal TNF receptors in the ganglia does not inhibit peripheral sensitization (Parada et al., 2003). Levy and colleagues have shown that local application of TNF-α to the meninges evokes TNF receptor-mediated activation of p38 MAP kinase in dural blood vessels, and that the p38 antagonist SB203580 inhibits TNF-α-mediated meningeal afferent sensitization (Zhang et al., 2011b). Other factors released by endothelial cells may also contribute to meningeal afferent sensitization as Levine and colleagues have recently reported that endothelial cell-mediated release of endothelin-1 (ET-1), a potent vasodilator and mediator elevated in human plasma at the onset of migraine attacks (Kallela et al., 1998), sensitizes nociceptors to mechanical-stimuli via endothelial cell-mediated release of ATP leading to hyperalgesia (Joseph et al., 2011, Joseph et al., 2014, Joseph et al., 2015). Further, sumatriptan and a β-adrenergic receptor antagonist, ICI118551, inhibited ET-1-induced hyperalgesia (Joseph and Levine, 2013). Although, the vasoconstrictive properties of ET-1 mediated primarily by ETA receptors are not associated with changes in cerebral blood flow during CSD (Goadsby et al., 1996), others have reported that ET-1 mediates neurogenic inflammation in rat dura mater via ETB receptors (Brandli et al., 1996) and that gene variants encoding both ET receptor subtypes are associated with migraine in humans (Tzourio et al., 2001; Lemos et al., 2011; Tikka-Kleemola et al., 2009). While promising, results from a clinical trial indicate that the mixed ETA/ETB antagonist, Bosentan, was not efficacious for aborting migraine attacks and therefore, it is unclear what role ET release from endothelial cells may have in migraine pathophysiology (May et al., 1996). In addition, c-type natriuretic peptide (CNP), an endothelium-derived hyperpolarizing factor (EDHF) which is secreted from endothelial cells (Lumsden et al., 2010; Moyes et al., 2014) induces thermal hyperalgesia in mice (Loo et al., 2012). This CNP-induced thermal hypersensitivity is mediated by PKC phosphorylation-dependent potentiation of TRPV1 via the natriuretic peptide receptor

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(NPR)-C on peripheral sensory neurons (Loo, L et al., 2013). These new data suggest that cells comprising blood vessels (e.g. endothelial cells) can contribute to afferent sensitization via the release of factors such as ET-1 and CNP. Admittedly, these studies have been conducted in tissues outside of the head and are thus not directly relevant to migraine but they could provide important information on mechanisms that may similarly occur within the brain and meninges. It is also possible that during a migraine attack, changes in metabolic demand or other stimuli such as mechanical stimulation (Bodin and Burnstock, 2001) can cause neurons and other vascular cell types to release ATP. Activation of purinergic receptors located on endothelial cells causes endothelial cell-mediated release of NO, which diffuses readily to smooth muscle cells and leads to subsequent vasodilation (Burnstock, 2015). In addition to NO-mediated vasodilation however, NO released from endothelial cells may also mediate meningeal afferent sensitization, as NO donors that are known to cause headache in migraineurs (Olesen and Jansen-Olesen, 2000) have recently been shown to promote delayed meningeal nociceptor sensitization as well as ERK phosphorylation in meningeal arteries (Zhang et al., 2013). This latter study also showed that blockade of ERK phosphorylation inhibited NTG-mediated afferent sensitization. Further, new data from Levine and colleagues implicate a role for mast cells and endothelial cells in NTG-induced hyperalgesia (Ferrari et al., 2016). The activation of purinergic receptors on endothelial cells also stimulates proflammatory pathways (Erlinge and Burnstock, 2008) including the release of interleukins (Seiffert et al., 2006) known to sensitize meningeal afferents (Zhang et al., 201; Yan et al., 2012). Purinergic receptors have been shown to mediate increases in endothelial cell surface expression of intercellular adhesion molecule-1 (ICAM-1) (Seiffert et al., 2006) and vascular cell adhesion molecule-1 (VCAM-1) (Seye et al., 2004), which are important for the recruitment of immune cells such as neutrophils (Dawicki et al., 1995) and monocytes (Seye et al., 2003) to endothelial cells. The release of proflammatory mediators by the recruited immune cells further amplifies meningeal afferent sensitization. Taken together, vasodilation may be an epiphenomena that has previously overshadowed concurrent endothelial cell-mediated signaling pathways contributing to sensitization of meningeal afferents and migraine pain.

Just as endothelial cell-mediated signaling influences primary afferent nociceptors, nociceptor-mediated signaling can also influence blood vessels (see figure 2). The release of vasoactive neuropeptides such as substance P and CGRP from meningeal afferents (Edvinsson et al., 1983; Ebersberger et al., 1999; Harrison and Geppetti, 2001) causes vasodilation (Brain and Grant, 2004; Smillie and Brain, 2011) and plasma protein extravasation (PPE) in the dura (Markowitz et al., 1987; O'Shaughnessy and Connor, 1994; Moussaoui et al., 1993), the latter due to alterations in blood vessel permeability. Enhanced blood flow and leakage of plasma constituents protects the brain and meninges by quickly diluting and clearing out noxious stimuli. However, the increase in vascular permeability may also allow for cytokines and other proflammatory mediators secreted and recruited by the endothelial cells to readily move through the vessel and potentiate meningeal nociceptor activation (Figure 2). In addition to sensory neurons, sympathetic neurons originating from the superior cervical ganglion (SCG) also innervate the meninges (Keller, JT et al., 1989; Andres, KH et al., 1987). The release of sympathetic neurotransmitters such as neuropeptide Y and norepinephrine from sympathetic fibers can directly act on vessels in the meninges

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(Edvinsson and Uddman, 1981; Edvinsson et al., 1983; Edvinsson, 1985; Keller, JT and Marfurt, CF, 1991). For example, NPY has been shown to contribute to ET-1 release in human endothelial cells (Abdel-Samad, et al., 2012) as well as increased adhesion of leukocytes to endothelial cells (Sung et al., 1991). Additionally, norepinephrine has been shown to induce endothelial cell IL-6 production (Stohl et al., 2012; Gornikiewicz et al., 2000). Thus, bi-directional communication between meningeal nerve fibers (sensory and sympathetic) and endothelial cells comprising the associated vasculature may facilitate the headache phase of migraine, further suggesting that endothelial cells play a central role in the pathology of migraine.

Meningeal afferents express numerous ion channels including transient receptor potential (TRP) channels, acid-sensing ion channels (ASICS), glutamate-gated channels, ATP-gated channel, and K^+ channels that when activated may contribute to the pain of migraine (for revew see Yan and Dussor, 2014). Among the stimuli capable of activating or sensitizing dural afferents are capsaicin (via TRPV1), mustard oil (via TRPA1), hypotonic solutions (via TRPV4), or an inflammatory soup (Strassman et al., 1996; Bove and Moskowitz, 1997; Wei et al., 2011; Edelmayer et al., 2012). Vascular endothelial cells also express a number of channels including the recently identified mechano-sensing channel, Piezo2 (Ferrari et al., 2015), sodium channels such as Nav1.7 (Rice et al., 2015), and various TRP channels including TRPA1 (Earley, 2012) and TRPV4 (Yao and Garland, 2005). Therefore, just as nociceptors detect numerous noxious stimuli including changes in temperature, pH, and pressure, recent reports suggest that endothelial cells express the machinery to detect similar noxious stimuli. Of late, Levine and colleagues demonstrated that Piezo2 channels expressed on endothelial cells mediate inflammatory hyperalgesia (Ferrari et al., 2015). It is possible that Piezo2 channels located on endothelial cells are able to detect mechanical forces such as shear stress within the vessel leading to the release of substances capable of activating meningeal afferents. Additionally, a situation could exist for example where activators of TRPA1 including environmental irritants (e.g. cigarette smoke, chlorine gas) which are well-known migraine triggers (for review see Dussor et al., 2014) are released into the blood and initiate signaling between meningeal nociceptors and endothelial cells. The full extent to which different ion channels expressed on endothelial cells contribute to processes culminating in nociceptor sensitization is currently unknown. However, bidirectional signaling between meningeal nociceptors and endothelial cells could further amplify an inflammatory process leading to a positive feedback loop potentiating nociceptive signals to the CNS and causing headache.

5.1 Conclusions

Before the migraine field abandons the theory of a vascular contribution to the disorder, it is important to consider that the cells comprising the blood vessel may contribute to the initiation and progression of migraine attacks independent of vasodilation. The strong positive correlation between the effects of migraine triggers (e.g. NO, PACAP-38, and CGRP) and migraine therapies (e.g. ergotamine, triptans) on changes in blood vessel diameter have contributed greatly to the idea that vasodilation plays a critical role in migraine. However, recent reports indicate that during spontaneous migraine there is little to no dilation of vessels. And importantly, the reverse is also true; blood vessel dilation does

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not always produce a migraine. But the unclear role of blood vessel dilation during migraine attacks is not evidence of a lack of communication between vessels and surrounding neuronal structures, it may simply be evidence of a lack of vasodilation in migraine pathophysiology. Alternatively, blood vessel dilation may be an epiphenomenon masking a chain of events leading to the development of migraine hours later. Although there may be no vasodilation during the migraine attack, vessels may dilate at time points well before the attack and this may leave a series of signaling events within the vessel in its wake. Of particular interest, CNP a potent vasodilator released by endothelial cells was recently reported to cause no change in the diameter of cerebral arteries in guinea pigs and humans (Gus, et al., 2015), but produced a pain phenotype via potentiation of TRPV1 on peripheral sensory neurons (Loo et al., 2012). Although, CNP did not produce migraine in healthy volunteers (Gus, et al., 2015), it has yet to be tested in migraineurs (this is especially relevant since NO/CGRP do not produce migraines in healthy volunteers, but do in migraineurs). These recent developments point to the possibility that signaling events within/between vascular cells, not the presence of vasodilation, may be critical to the progression of the attack. Ultimately, whether CNP and other known headache agents cause cerebral vasodilation may be irrelevant. Blood vessels are more than just a conduit for blood that can contract and dilate; they are comprised of a variety of cell types that generate numerous molecules and mediators important for intra- and intercellular processes. Endothelial cells mediate immune cell recruitment and downstream inflammatory signaling pathways, which may be critical to the pathophysiology of migraine. They also express a variety of channels and receptors (e.g. TRP channels and purinergic receptors) thought to be involved in the detection of noxious stimuli, and along with neurons, endothelial cells may potentiate the responses to noxious stimuli. Any of these processes may be critical for the development of a migraine attack regardless of whether vasodilation is present.

In order to further determine whether vessels play a role in migraine, several important questions should be answered. First, it is important to determine whether vasodilation occurs at any time point before the onset of migraine e.g. during the interictal phase leading up to an attack or during the premonitory phase. Prior reports assessing changes in vessel diameter were performed after the onset of migraine or at time points immediately following administration of the trigger (where there is clearly vasodilation from NO or CGRP). As mentioned above, there may be no vasodilation at the peak of a migraine attack, but prior vasodilation may contribute to a cascade of signaling events that long outlasts the changes in vessel diameter. Determining whether or not vasodilation is present even at very early time points, or whether the signaling cascade is the only relevant component, is important to know before the dilation hypothesis is discounted. Second, migraine triggers that may not produce cerebral vasodilation (e.g. sildenafil, Kruuse et al., 2003) should be examined more closely to better understand their mechanisms. If indeed these triggers act independently of dilation at any time point, this would provide clear evidence that vasodilation is not necessary and the more relevant mechanisms downstream of these triggers can be identified. Finally, mediators like CNP produce hypersensitivity in preclinical models but may not cause cerebral vasodilation in humans. This peptide should be examined more closely for its ability to trigger attacks in migraineurs. CNP may represent an important, endothelial-derived molecule that is capable of triggering attacks independent of vasodilation.

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Understanding how CNP and potentially other vessel-derived mediators promote attacks may provide important insights into dilation-independent vascular contributions to migraine. Ultimately, there are many connections between vessels and migraine and many potential mechanisms by which they can contribute to the disorder. While it may be reasonable at this point to discard vasodilation as a direct cause of migraine, it seems far too premature to completely eliminate vessels from the list of factors contributing to the pathophysiology of migraine.

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Highlights

- Migraine is the 3rd most common and 8th most disabling disease on earth.
- Neuronal mechanisms play a key role in migraine pathophysiology.
- Human studies have lead to increased scrutiny of the vascular theory of migraine.
- Vasodilation may not be necessary or sufficient for migraine.
- Vascular endothelial cells may contribute to migraine without vasodilation.

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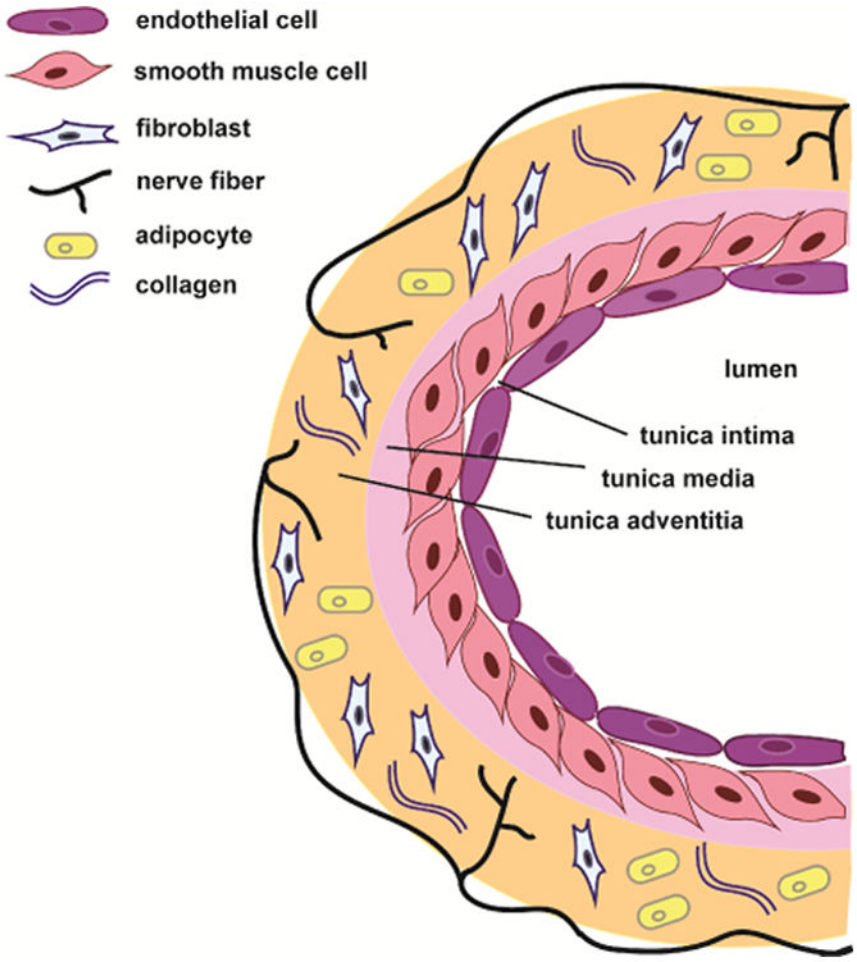

Fig. 1.

Anatomy of a blood vessel. Bloods vessels are comprised of 3 layers: the tunica intima, tunica media, and tunica adventitia. The innermost layer, the tunica intima, is comprised of a single layer of endothelial cells. The middle layer, the tunica media is predominately comprised of smooth muscle cells. The outermost layer, the tunica adventitia, consists of nerve fibers, fibroblasts, perivascular adipose tissue and collagen. Compared to smaller vessels (as depicted here), large vessels have increased tunica intima/media/adventitia thickness due to increased numbers of cells in each layer.

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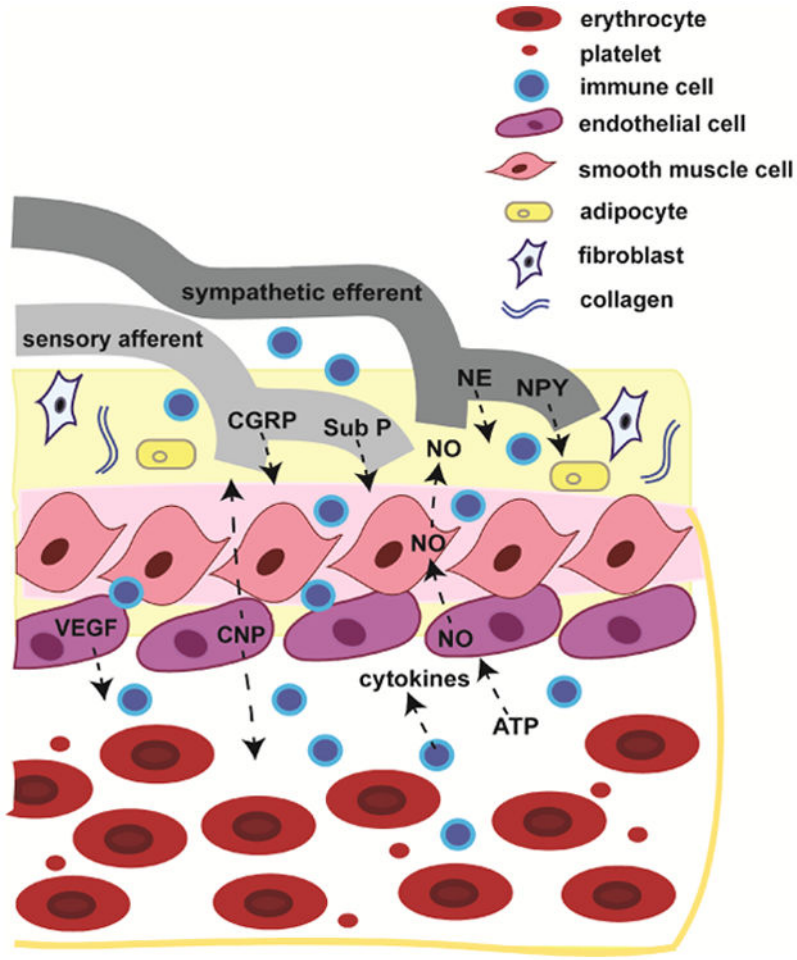

Fig. 2.

Bidirectional signaling between meningeal nerve fibers, immune cells and cells comprising the associated blood vessels. Meningeal sensory afferents originating from the trigeminal ganglia innervate the meningeal vasculature and release vasoactive neuropeptides including substance P (Sub P) and calcitonin gene- related peptide (CGRP). In addition, sympathetic efferents from the superior cervical ganglion release neurotransmitters including neuropeptide Y (NPY) and norepinephrine (NE) that can act on vessels in the meninges. Conversely, cells comprising the blood vessel as well as those in the vascular lumen can influence meningeal sensory afferents. Endothelial cells can release c-type natriuretic peptide (CNP) and potentiate sensory afferent neuronal firing. During angio- genesis, endothelial cells release vascular endothelial cell growth factor (VEGF), which recruits immune cells such as macrophages and neutrophils. The recruited immune cells infiltrate the nearby tissue and release cytokines known to sensitize sensory afferents. In addition, changes in metabolic demand and other stimuli such as shear stress can cause the release of adenosine triphosphate (ATP) from multiple cell types within the vessel. Endothelial cell purinergic receptor activation causes the release and diffusion of nitric oxide (NO) throughout the vessel and surrounding tissue resulting in a wide range of effects including sensory afferent sensitization.