Headache
© 2019 American Headache Society

ISSN 0017-8748
doi: 10.1111/head.13591
Published by Wiley Periodicals, Inc.

Views and Perspectives

CGRP and Brain Functioning: Cautions for Migraine Treatment

Jonathan M. Borkum, PhD

Background.—Calcitonin gene-related peptide has emerged as a therapeutic target in migraine. Monoclonal antibodies and small molecule receptor antagonists (gepants) directed against CGRP have been approved or are in Phase II or III clinical trials. For monitoring the long-term safety of these drugs, it is helpful to consider the role of CGRP in brain functioning.

Methods.—Qualitative review of the preclinical literature on CGRP in brain physiology and pathophysiology.

Results.—Within the brain, CGRP is upregulated by stresses such as ischemia, injury, hyperthermia, and seizure, and activates neuroprotective processes. Thus, CGRP buffers intracellular calcium, triggers antiapoptotic signaling, upregulates a number of neurotrophins (including insulin-like growth factor-1/IGF-1, basic fibroblast growth factor/bFGF, and nerve growth factor/NGF), reduces brain edema, and likely increases antioxidant defenses. When released outside the blood-brain barrier, CGRP likely protects the endothelium, upregulates growth factor signaling from the endothelium to the brain parenchyma, strengthens the blood-brain barrier, protects the immune privilege of the brain by inhibiting the movement of neutrophils and monocytes, and facilitates neurogenesis and angiogenesis at stem cell niches.

Conclusions.—CGRP participates in a wide range of neuroprotective processes. In theory, migraineurs with comorbid brain pathology might be at increased risk from CGRP inhibition. However, the extent of compensating processes is unknown and will determine whether these risks materialize in practice.

Key words: migraine, calcitonin gene-related peptide, ischemic stroke, traumatic brain injury, multiple sclerosis, oxidative stress

Abbreviations: BBB blood-brain barrier, Bcl-2 B cell lymphoma 2 survival protein, BDNF brain-derived neurotrophic factor, bFGF basic fibroblast growth factor, cAMP cyclic adenosine monophosphate, CGRP calcitonin gene-related peptide, CLR calcitonin receptor-like receptor, CREB cyclic AMP response element-binding transcription factor, eNOS endothelial nitric oxide synthase, GDNF glial cell line-derived neurotrophic factor, IGF-1 insulin-like growth factor-1, mAbs monoclonal antibodies, MCP-1 monocyte chemoattractant protein-1, MS multiple sclerosis, NGF nerve growth factor, NMDA N-methyl-D-aspartate glutamate receptor, PI3K phophoinositide 3-kinase, PACAP pituitary adenylate cyclase-activating polypeptide, RAMP receptor activity-modifying protein, RCP receptor component protein, TRPV1 transient receptor potential vanilloid 1 receptor, VEGF vascular endothelial growth factor

(*Headache* 2019;59:1339-1357)

From the Department of Psychology, University of Maine, Orono, ME, USA (J.M. Borkum); Health Psych Maine, Waterville, ME, USA (J.M. Borkum).

Address all correspondence to: J.M. Borkum, Department of Psychology, University of Maine, Orono, ME, 04469-5782 USA, email: jborkum@hpmaine.com

Accepted for publication May 9, 2019.

Migraines, comprised of moderate-to-severe head pain accompanied by nausea, vomiting, and/or painful sensitivity to light and sound, and often exacerbated by routine daily activities[1,2] affect 17% of women and 6% of men in the United States in any given year[3]

Conflicts of Interest: None
Funding: None

and 1.06 billion people globally.[4] For the individual, migraines are the sixth leading cause of disability,[4] the fifth leading cause of emergency room visits,[5] and add an average of $1705 (episodic migraines) or $4943 (chronic migraines) to annual medical expenses.[6] Societally, they are estimated to entail $13 billion in costs per year in the United States, mostly due to lost productivity.[7] Thus, finding more effective treatments is imperative.

Recent efforts have focused on the role of α-calcitonin gene-related peptide (CGRP) in migraine. CGRP is a 37-amino acid (5 KDa) peptide produced in the body by an alternative splicing of the calcitonin gene. It is transduced by a receptor complex comprised of (1) the calcitonin receptor-like receptor (CLR), (2) receptor activity-modifying protein 1 (RAMP1), which confers a degree of substrate specificity for CGRP, and (3) receptor component protein (RCP), which helps connect the receptor to intracellular signaling mechanisms.[8] In particular, the receptor is coupled to a G protein that activates adenylyl cyclase, raising levels of cyclic AMP (cAMP), and influencing an array of downstream targets.[9] Effects include relaxation of arterial smooth muscle with resulting vasodilation, sensitization of the NMDA receptor in pain pathways,[10] and direct and indirect activation of growth factor and antiapoptotic signaling.[9,10]

Several lines of evidence implicate CGRP as a key effector molecule in the migraine attack.[9,11,12] Outside of the brain, CGRP is released by sensory nerve terminals, including in the perivascular meninges and around the extracranial vessels,[13] thought to be the peripheral site of migraine pain. It is a potent vasodilator, causes mast cells to release inflammatory mediators, and thereby may sensitize peripheral nociceptors.[14] CGRP is also an important neuromodulator in the trigeminal ganglion and, within the brain, in the trigeminal nucleus caudalis, an early processing center for pain from the head,[15] as well as the periaqueductal grey, and possibly the cerebellum. In pain pathways, CGRP intensifies glutamatergic signaling[16] and activates microglia to a proinflammatory state.[17,18] Thus, CGRP is thought to contribute to sensitization to sensory input and to the pain of the migraine attack.[19]

Its concentration is elevated in the plasma of people with episodic and, more so, chronic migraine between[20] and during[21] migraine attacks. Administration of CGRP elicits a headache and sometimes a delayed migraine in migraineurs.[22,23] Conversely triptans, by activating presynaptic 5-HT_{1B} and 5-HT_{1F} receptors,[24] inhibit release of CGRP in the trigeminal ganglion[25] and normalize plasma levels during a migraine in concert with a reduction in headache pain.[26-28]

Thus, 2 categories of CGRP blockers have been introduced or are in late-stage trials for migraine:[29] (1) Monoclonal antibodies (mAbs) against the CGRP receptor (erenumab) or against CGRP itself (eptinezumab, fremanezumab, and galcanezumab). (2) Traditional CGRP receptor antagonists ("gepants") – ubrogepant, rimegepant, and atogepant – which are in clinical trials for acute migraine treatment or prevention.

These 2 categories differ in half-life (21-32 days for mAbs, 3-6 hours for gepants), route of elimination (lysis into peptides and amino acids by the reticulo-endothelial system for mAbs, hepatic metabolism, and/or renal or biliary excretion for gepants), and targeting for acute treatment (rimegepant, ubrogepant) or prevention (atogepant and all of the mAbs).[29,30] In addition, while mAbs are likely far too large to cross the blood-brain barrier (BBB), at least some of the CGRP antagonists likely do.[29,31]

The clearest data so far are for the mAbs. In phase 3 clinical trials, these molecules reduced migraine frequency, had very few reported side effects, and caused no changes in vital signs, blood chemistry, or EKG.[32,33] Erenumab had only a small effect on angina during treadmill exercise in patients with coronary artery disease[34] (however, see Maassen van den Brink et al[35]). Drug-drug interactions are very unlikely with mAbs.[36] Nonetheless, identifying subtle effects that may become consequential under particular circumstances or with long-term use will require more experience with the drugs.[37] To know where to look for potential adverse reactions it is helpful to consider the physiological role of CGRP.

Long-term theoretical risks to the body of CGRP inhibition – the cardiovascular system from impaired vasodilation, the gastrointestinal tract from inflammation and impaired tissue homeostasis, and the skin and bones from impaired healing – have been

reviewed in depth elsewhere.[36,38,39] However, except for the possibility of ischemic stroke from impaired vasodilation, the potential risks to the brain do not seem to have been reviewed. Therefore, in what follows we will consider a number of such risks, drawing on what is known or can be deduced about the normal functions of CGRP in the central nervous system. The goal will be to understand the place of CGRP in brain functioning beyond its role in generating migraine.

CGRP AND THE BLOOD-BRAIN BARRIER

The actions of CGRP in migraine take place peripherally in the meninges and trigeminal ganglion (neurogenic inflammation, vasodilation, and pain sensitization)[13,14] and centrally in the brain (pain transmission and sensory processing).[15] As mAbs and some of the gepants function outside of the BBB, they directly block only the peripheral effects of CGRP. However, whether these are truly 2 separate systems, and if so, whether they influence each other, is not yet known. Hinging on this is the question of whether CGRP and its blockade in the blood vessels and meninges have downstream effects in the brain. The simplest way for this to occur would be if CGRP, released during a migraine, itself crosses the blood-brain barrier. Several factors have bearing on this possibility.

Ordinarily, molecules have free passage through the BBB only if they are both lipophilic and small (<400 Da). However, this is not absolute. A member of the calcitonin family, amylin which, like CGRP, consists of 37 amino acids, shows some passive diffusion[40] and active transport[41] into the brain, potentially accounting for central effects of the peptide.[42]

Similarly in the rat, after intravenous injection, modest amounts of radiolabeled CGRP reach the cerebrospinal fluid, as well as the cortex, the hippocampus, and presumably other regions of brain parenchyma.[43] Interestingly, peripheral (intraperitoneal) injection of CGRP is sufficient to elicit mild photophobia in mice, a central effect, although this may be from propagation of neural signaling rather than actual brain penetrance of CGRP.[44] Alternatively, circulating CGRP may enter the brain at places such as the circumventricular organs, where the BBB is absent.[45]

Nonetheless, it is unclear that the amount of brain penetrance is sufficient to have an effect. The BBB remains intact to a gadolinium-based contrast agent during migraine with[46] and without aura.[47] In fact, applying CGRP seems to further strengthen the BBB.[48] Moreover, there is currently no evidence for active transport of CGRP into the brain.

Therefore, in what follows we will consider the intracerebral and extracerebral functions of CGRP as separate systems. The intracerebral will most likely be relevant to prospective small molecule CGRP antagonists which cross the BBB. Of relevance to mAbs, we will then discuss those functions of CGRP outside the BBB that may have downstream effects within the brain. We will also consider pathologies in which the BBB may be compromised.

NEUROPROTECTIVE PROPERTIES OF CGRP WITHIN THE BRAIN

The distribution of CGRP has been studied primarily in rats, where it is widespread throughout the brain. In particular, CGRP and/or its receptor have been found in the cortex, hippocampus, thalamus, hypothalamus, pituitary, striatum, amygdala, cerebellum, and such migraine-relevant sites in the brainstem as the locus ceruleus, raphe nuclei, and the trigeminal nucleus caudalis.[29,45]

Fluctuations in the amount of CGRP have been studied mostly in the hippocampus, where CGRP is markedly induced by such stresses as injury, ischemia, hyperthermia, adrenalectomy, kainic acid-induced seizure, and exposure to a toxin.[49-52] Based on studies of heat stress, CGRP likely increases in the cortex, striatum, and cerebellum as well.[52,53] There, it may protect neurons by buffering intracellular calcium to prevent excitotoxicity, apoptosis, and lysis.[54]

Moreover, CGRP seems to set in motion an array of other neuroprotective processes: It activates antiapoptotic signaling via the cyclic AMP response element-binding transcription factor (CREB) and B cell lymphoma 2 survival protein (Bcl-2),[55] promotes neurotrophic signaling via insulin-like growth factor-1 (IGF-1), basic fibroblast growth factor (bFGF), and nerve growth factor (NGF),[53,56,57] reduces brain edema by inhibiting overexpression of aquaporin-4[53] and, as noted, strengthens the BBB.[48,58]

Elsewhere in the body, CGRP downregulates the production of oxidants and upregulates antioxidant enzymes.[59] Thus, in ischemia and subsequent reperfusion, CGRP protects the heart muscle by reducing oxidative stress, maintaining mitochondrial membrane potential, and preventing apoptosis.[60] This type of protection might occur in the brain as well. CGRP receptors in the cerebellum, when stimulated by the related compound adrenomedullin, reduce the production of oxidants.[61] Presumably, stimulation by their primary ligand, CGRP, has the same effect.

An effect on the brain is suggested by antidepressant properties of CGRP, administered into a cerebral ventricle, in psychosocial stress.[57,62] The antidepressant properties seem to be mediated by increased NGF and markedly increased angiogenesis in the hippocampus.[57] Further, the CGRP-mediated release of hippocampal IGF-1 improves neurogenesis and cognition.[56,63] Conversely, CGRP knockout mice seem to have impaired spatial learning, apparently because of lower IGF-1 levels.[56]

In addition to neurons, other types of brain cells including astrocytes, oligodendrocytes, and microglia have receptors for CGRP.[64] In particular, microglia appear to be partially deactivated by CGRP injected directly into cerebrospinal fluid, leading to reduced neuroinflammation and disease severity in an animal model of multiple sclerosis (MS).[64,65] This effect is stimulus- and tissue-specific. CGRP is anti-inflammatory when microglia are activated through toll-like receptors [innate immunity, as in the MS model] but proinflammatory in pain pathways when microglia are activated by nociceptive signaling.[66]

Moreover, CGRP has shown promise *in vitro* for supporting the survival of adipose-derived stem cells and their differentiation into neurons[67] and, *in vivo*, for chemotaxis, attracting intrathecally injected human umbilical cord stem cells to the site of spinal cord injury.[68] It is unknown whether CGRP functions endogenously in brain repair. However, the neurotrophic and chemotactic properties of CGRP have been implicated in physiologic regeneration of peripheral nerves.[69,70]

CGRP is a strong vasodilator, suggesting that it is a defense against ischemia.[71,72] However, vasodilation by itself would not be a sound protective strategy by the body because the reperfusion would cause oxidative damage to the endothelium and ischemic tissue.[60] By pairing vasodilation with antioxidant defense and growth factor signaling, CGRP can protect against both ischemia and reperfusion injury.

Surprisingly, CGRP seems to facilitate the excitotoxic death of hippocampal neurons in a kainic acid seizure model.[73] However, facilitation of apoptosis under conditions in which necrosis would otherwise occur may be neuroprotective, because without it, the debris from necrotic cells would elicit microglial activation and an acute phase response.[51] This function of CGRP is reminiscent of brain-derived neurotrophic factor (BDNF), which protects against apoptosis when the damage is mild and potentiates it when the damage is severe.[74,75] Similarly, the antidepressant effect of CGRP may be bivalent: When psychosocial stress is combined with ischemia – a particularly severe constellation – CGRP may exacerbate depression.[76]

Of note, all of these effects are due to intracerebral CGRP, which may not be relevant in migraine. As we have seen, CGRP is traditionally not thought to cross the BBB and thus its release during a migraine may not lead to it entering the brain.[13] However, these effects may indeed be relevant to CGRP blockers that do cross the blood-brain barrier. Moreover, while the BBB is intact in normal conditions and most likely in migraine, it is disrupted in a wide range of brain pathologies, including multiple sclerosis, ischemic or hemorrhagic stroke, traumatic brain injury, prolonged hyperthermia, cold injury, Alzheimer's disease, and possibly depression and schizophrenia.[77,78] BBB disruption also may contribute to epilepsy that follows head injury or stroke.[78]

NEUROPROTECTIVE CONSEQUENCES OF CGRP OUTSIDE THE BLOOD-BRAIN BARRIER

Let us, therefore, consider the ways in which CGRP outside of the BBB can have impact on cerebral functioning. In fact, there are 5 potential mechanisms by which CGRP released in the periphery during a migraine may have neuroprotective effects in the brain:

CGRP as a Defense Against Ischemia.—In the body, production and release of CGRP are likely increased by ischemia[79,80] and help defend against

it.[71,72] Similarly, in animal models of cerebral ischemia-reperfusion, intraperitoneal or intravenous administration of CGRP decreases the extent of tissue damage and behavioral deficit.[53,55,81] Intravenous CGRP also decreases the lesion size in a mouse model of permanent ischemia.[82] Presumably, these central effects of peripherally administered CGRP are facilitated by breakdown of the BBB in ischemia.

Several mechanisms seem at work. As a potent vasodilator, CGRP may help preserve and restore blood flow.[55] Thus, CGRP appears to protect against vasospasm and resulting ischemia following subarachnoid hemorrhage[83] and helps to maintain cerebral blood flow (cerebrovascular autoregulation) when there is a fall in systemic blood pressure.[84] CGRP also binds to platelets, inhibiting their aggregation.[85]

In addition, CGRP seems to reduce NMDA-mediated excitotoxicity.[81] By inhibiting glycogen synthase kinase-3β, CGRP can prevent hyperphosphorylation of tau and the consequent neural degeneration.[55] Further, by activating the CREB transcription factor, growth factor signaling cascades, and the protein Bcl-2, CGRP prevents apoptosis.[55,81,82,86]

A CGRP knockout model suggests additional mechanisms. Mice genetically lacking CGRP show increased inflammation, astroglial activation, oxidative DNA damage, decreased expression of vascular endothelial growth factor (VEGF) and IGF-1, and reduced compensatory formation of new capillaries.[87] Of note, this was found not only in an acute ischemic event but also in chronic, low-grade ischemia from experimental carotid artery stenosis.[87]

VEGF also increases capillary density in healthy brain tissue in regions of increased neural activity, an effect that may be set in motion by local hypoxia.[88] As CGRP facilitates VEGF expression, it may be relevant to this neurovascular coordination.

It should be noted in this regard that migraine with aura confers a twofold increased risk for ischemic stroke, an effect that is higher in females, in people younger than 45, and, markedly, with oral contraceptive use, smoking, and their combination.[89] Leaving migraine aside, women who use combined oral contraceptives are at greater risk of myocardial infarction and ischemic stroke than non-users (RR ≈ 1.6).[90]

CGRP in the Neurotrophic Support of the Brain.— BDNF, the most abundant growth factor in the brain, is important in antioxidant defense, protecting neurons from apoptosis, facilitating the formation and plasticity of synapses, and promoting neurogenesis and neural repair.[91] Thus, BDNF is neuroprotective in animal models.[92,93]

Of note, approximately 50% of BDNF in brain tissue is produced in the blood vessel endothelium.[94,95] Endothelial production of BDNF is set in motion by nitric oxide.[94] Conversely, in a positive feedback cycle, BDNF increases the endothelial production of nitric oxide.[96] Thus, the endothelium helps to maintain not only cerebrovascular integrity but the functioning of brain tissue as well.

CGRP appears relevant to this neuroprotection in part because it protects the endothelium from oxidative stress. It prevents damage and apoptosis of human umbilical vein endothelial cells from oxidized low-density lipoprotein.[97] CGRP also protects endothelial cells from the effects of angiotensin II by reducing the production of oxidants and preserving antioxidant defenses, thus maintaining the expression of endothelial nitric oxide synthase (eNOS).[98] By similar mechanisms, and upregulation of the anti-aging protein klotho, CGRP prevents the accelerated senescence of endothelial *progenitor* cells caused by angiotensin II.[99] These antioxidant processes likely also have a sparing effect on nitric oxide, increasing its availability for facilitating BDNF.

In addition, by increasing blood flow to a region, CGRP may intensify sheer stress and thus the production of nitric oxide by the endothelium.[100]

Moreover, CGRP has been directly implicated in production of VEGF[101] and bFGF[53,80] by the endothelium. VEGF protects endothelial cells by inducing antiapoptotic genes and cytoprotective signaling pathways via the Akt/PI3K pathway.[102-104] Moreover, VEGF is thought to stimulate the expression of eNOS and the production of nitric oxide.[105] Under most conditions, nitric oxide then stimulates VEGF gene expression in a positive feedback loop.[106]

Of note, the VEGF phase of CGRP signaling is likely time-limited, as high levels of nitric oxide feed back and reduce VEGF activity.[106] This, too, may be

protective, as excessive VEGF signaling can disrupt the BBB.[102]

Thus, CGRP protects the endothelium and, through VEGF and, likely, sheer stress, increases production of nitric oxide and presumably BDNF. CGRP may also directly raise plasma levels of BDNF as, at least *in vitro*, it causes neurons in the trigeminal ganglion to secrete BDNF.[107,108]

In these ways, CGRP outside the BBB may maintain and increase the brain's supply of BDNF.

Further, VEGF is itself neurotrophic. It readily crosses the BBB, at least at neural stem cell niches, where angiogenesis and neurogenesis appear to be coordinated. There, VEGF is responsible for the increased level of neurogenesis induced by physical exercise or an enriched environment.[109-111] In a model of adult neurogenesis, the seasonal development of a vocal center in male songbirds, VEGF also triggers endothelial cells to produce BDNF.[112] Of note, the role of VEGF seems restricted to induced rather than basal levels of neurogenesis.[109]

Of course, an even more direct mechanism would be for CGRP, as a vasodilatory molecule, to itself phosphorylate eNOS and increase the production of nitric oxide. CGRP receptors have been found in the endothelium of the basilar and pial arteries and the cerebral microvasculature.[113,114] Moreover, in the human brain, CGRP receptors may be more common in the venous endothelium than in the arterial.[115] Further, endothelial CGRP receptors are induced by CGRP.[101] As migraineurs have higher plasma levels of CGRP between[20] and during[21] migraine attacks, their cerebral endothelium might be more sensitive to CGRP.

However, CGRP receptors have not been found in the endothelium of human meningeal, middle cerebral, or superficial temporal arteries.[116,117] In the cerebral arteries, removing the endothelium or blocking the activity of eNOS does not affect the magnitude of the vasodilation, suggesting that if there is a vasodilatory effect from the endothelium, it is swamped by the effect of CGRP in relaxing the smooth muscle layer.[113] In all, in the human brain, vasodilation by CGRP is thought to be mediated by the smooth muscle layer of the arteries, while the actions of CGRP on the endothelium involve growth factor signaling.

Through a number of mechanisms, then, CGRP very likely preserves and potentiates downstream neurotrophic signaling from the endothelium to the brain.

CGRP in the Immune Privilege of the Brain.—The effect of CGRP on the trafficking of leukocytes is complex, with some studies suggesting that CGRP, released from sensory axons, may help guide leukocytes to the site of injury.[118] Nonetheless, CGRP reduces production by the endothelial cells of CCL2 (also termed monocyte chemoattractant protein-1/MCP-1) and certain other chemokines such as CXCL1 and CXCL8.[119,120]

CGRP, a key effector molecule for neurogenic inflammation, downregulates Th1-type classical inflammation, decreasing the production of tumor necrosis factor-α, interleukin-2, and interferon-γ, and the innate immune response in macrophages.[121] Administration of CGRP is protective in a mouse model of sepsis[122] by limiting the movement of neutrophils and monocytes from blood vessels into the mouse peritoneal cavity.[122] CGRP also inhibits neutrophil chemotaxis in barrier tissues such as the lung and skin.[123,124]

Similarly, CGRP may protect the immune privilege of the brain by preventing movement of leukocytes through the BBB. In particular, CCL2/MCP-1 is constitutively expressed in small amounts by brain microvascular endothelial cells and by neurons, astrocytes, and microglia.[125] When its expression is upregulated by inflammatory stimuli such as lipopolysaccharides, or by axonal damage, CCL2 weakens the BBB and attracts monocytes into brain tissue.[125] In so doing, CCL2 plays an important role in the early stages of MS.[126] Similarly, the chemokine CXCL8 is constitutively expressed in brain endothelial cells.[127] It attracts neutrophils into the brain, exacerbating the reperfusion injury following ischemia and increasing the severity of focal traumatic brain injuries.[125] Thus, CGRP, administered outside the BBB, by inhibiting the expression of CCL2 and CXCL8,[119] helps strengthen and preserve the immune privilege of the brain.[128]

This might be relevant clinically for people with MS, a condition in which the prevalence of migraines is three times greater than in the general population,[129] and in which the BBB is compromised for up to several months after a flare-up.[77] As we have seen, CGRP, injected into a cerebral ventricle, reduces disease severity in an animal model of MS.[64,65]

CGRP likely strengthens the BBB in other ways as well, under pathological conditions such as heat stress[128] and ischemia-reperfusion.[58] That is, in ischemia-reperfusion injury, CGRP attenuates ultrastructural damage to the capillary endothelial cells, the tight junctions between them, and the surrounding basement membrane, thereby preserving the BBB.[58] CGRP protects endothelial cells under oxidizing conditions, and thus at least part of the endothelial protection may be through CGRP's antioxidant activities.[130] Moreover, as neutrophils damage the endothelium when they adhere to it,[131] the above-noted downregulation of CXCL8 is also likely protective.

As we have seen, the BBB is disrupted in various other conditions that might occur, by accident or as a comorbidity, in someone with migraines, including sepsis and traumatic brain injury. In these, CGRP is thought to play a protective role.

Note, however, that this neuroprotective effect of CGRP pertains to pathological states, when chemokine production is enhanced. There is no evidence that the low-level constitutive expression of brain endothelial chemokines is harmful. Indeed, CXCL8 has neurotrophic properties *in vitro*, although whether and how this is relevant *in vivo* is not yet known.[125]

In inflammation as well, however, there is suggestion of bivalent actions: In an animal model of amyotrophic lateral sclerosis, CGRP preserves the neuromuscular junction at early stages by releasing glial cell line-derived neurotrophic factor (GDNF), but accelerates the decline in later stages by intensifying neuroinflammation.[132]

CGRP in Cognition and Adult Neurogenesis.—CGRP is involved in pain transmission from the periphery through the trigeminal ganglion to the trigeminal nucleus caudalis within the brain. However, capsaicin-sensitive pain fibers from the periphery also transmit signals to the parabrachial nuclei, which in turn relay the signal to the dentate gyrus of the hippocampus, increasing neurogenesis, angiogenesis, synaptic function, and cognitive performance.[56] That is, there is a rather direct link between nociceptive stimulation in the periphery and neurogenesis in the hippocampus. To the extent that CGRP contributes to episodic pain transmission and sensitization, directly or through activation of mast and glial (satellite) cells, it presumably participates in this neuroregenerative process.

Elsewhere, the role of CGRP in information processing is not well understood. In pain circuits in the brain, such as between the parabrachial nucleus and the central nucleus of the amygdala, CGRP causes a sustained increase of glutamatergic signaling by sensitizing the NMDA receptor.[10] CGRP is distributed widely in the brain, including the cortex,[29,45] but it is unknown whether it participates in glutamatergic neurotransmission outside of pain pathways. Any such role would be within the brain and thus relevant primarily to gepant antagonists that cross the BBB.

It is also possible, however, that the vasodilatory actions of CGRP, outside the BBB, play a role in information processing, consistent with the hemo-neural hypothesis.[100] The nitric oxide and BDNF likely produced by the endothelium in response to CGRP, may help fine-tune nearby neural circuits.[100] The temperature changes and mechanical pressure on neurons from dilated arterioles can activate ion channels and change electrochemical dynamics. The voltage gradient across the BBB may introduce fluctuations in the electrical environment of neurons that change with blood vessel diameter.[133] Moreover, changes in brain arteriolar diameter are transduced by adjacent astrocytes, which inhibit the firing of nearby neurons in response to vasoconstriction and facilitate it in response to vasodilation.[134] Such vasculo-neuronal coupling might play a role in brain homeostasis at rest, adjusting neuronal activity to match blood supply, or it might indicate an active contribution of vasomotor changes to information processing.

CGRP as a Component of a Neuroprotective Program.—Implicit in the choice of CGRP as a therapeutic target in migraine is the assumption that the migraine attack is a disorder to which treatment should be directed. An alternative possibility is that the attack is a physiologic response to threats to the brain, serving to restore homeostasis.[135-138]

While the focus of the current article has been on CGRP, the migraine attack involves many other components, including platelet activation, release of substance P, plasma protein extravasation, activation of eNOS, production of BDNF, release of serotonin and, in migraine with aura, cortical spreading depression.[139] Each of these processes can decrease the production of oxidants, increase antioxidant defenses and antiapoptotic and growth factor signaling, decrease microglial activation, increase neurogenesis, recruit endothelial progenitor cells, downregulate energy-demanding pathways, and/or facilitate mitochondrial biogenesis.[136,140] Thus, through its release during a migraine, CGRP may facilitate a number of other processes that are neuroprotective.

A related issue is whether CGRP blockers, which prevent the migraine attack clinically, are also preventive physiologically, that is, whether they intervene in the poorly understood sequence of events that culminates in an attack.[14] In favor of such an effect, release of CGRP seems necessary for cortical spreading depression, thought to underlie the migraine aura, *in vitro*.[141] The *in vivo* animal evidence is mixed,[142,143] but 28% of migraineurs reported aura symptoms after infusion of CGRP.[22] Moreover, fremanezumab has been shown clinically to reduce photophobia and phonophobia.[144] As both can also be prodromal symptoms of migraine, this suggests a capacity of the antibody to intervene physiologically prior to the attack. However, in migraineurs, the interictal period is characterized by progressive alterations in electrophysiology, and in serotonergic neurotransmission, particularly in the dorsal raphe nucleus. These changes are then reset by the migraine attack. For example, the latency of the P3 component of the visual evoked potential shows a progressive loss of inhibition, beginning at least 8 days before an attack.[145] In the dorsal raphe nucleus, the availability of 5-HT_{1B} receptors increases, possibly indicating reduced synthesis of serotonin, throughout the interictal period.[146] These changes may represent a vulnerability of the brain to migraine. There is no data so far that CGRP antagonism can mitigate them.

Table 1.—Protective Processes Facilitated by CGRP

Endothelium	Blood-Brain Barrier	Intracerebral
Antioxidant ↓ Oxidant production ↑ Antioxidant defenses Nitric oxide ↑ eNOS Neurotrophic ↑ VEGF ↑ BDNF ↑ bFGF ↓ Apoptosis	Structural Preserve tight junctions (in ischemia-reperfusion) ↓ Ultrastructural damage (in heat stress) Immune/chemotactic ↓ Neutrophil entry into brain (in TBI, reperfusion) ↓ Monocyte entry into brain (in MS)	Antioxidant ↓ Oxidant production ↑ Antioxidant defenses Neuroprotection ↓ Edema/aquaporin-4 ↓ Excitotoxicity ↓ Hyperphosphorylation of tau ↓ Neuroinflammation Neurotrophic ↑ IGF-1 ↑ bFGF ↑ NGF ↓ Apoptosis (↑ CREB, ↑ Bcl-2) Neural repair ↑ Angiogenesis ↑ Neurogenesis ↑ Homing and survival of neural stem cells Behavioral ↓ Depressive behaviors ↑ Learning and memory

Bcl-2 = B cell lymphoma 2 survival protein; BDNF = brain-derived neurotrophic factor; bFGF = basic fibroblast growth factor; CREB = cyclic AMP response element-binding transcription factor; eNOS = endothelial nitric oxide synthase; IGF-1 = insulin-like growth factor-1; MS = multiple sclerosis; NGF = nerve growth factor; TBI = traumatic brain injury; VEGF = vascular endothelial growth factor.

It should be emphasized that migraines themselves are not risk factors for accelerated cognitive decline.[147] Indeed, when an effect has been found, the data have suggested a protective role of migraines. Thus, in the Baltimore Epidemiologic Catchment Area Study, a diagnosis of migraine with aura was associated with slower decline in immediate and delayed recall with age.[148] In the Epidemiology of Vascular Aging study, diagnosis with migraine protected against decline in scores on the Digit Symbol Substitution test of the Wechsler Adult Intelligence Scale-Revised.[149]

The neuroprotective processes of CGRP are summarized in the Table 1.

PITUITARY ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE (PACAP)

Although the focus here is on CGRP, similar considerations may emerge as blockade of PACAP is developed as a therapeutic strategy in migraine.[150] Like CGRP, PACAP is a vasodilator and contributes to peripheral and central pain sensitization. [151] Its blood levels rise in spontaneous migraine attacks.[152] Its infusion causes headache in healthy subjects, reversible by sumatriptan,[153] and a delayed migraine in 58% of migraineurs without aura.[154]

Like CGRP, PACAP activates adenylyl cyclase and cAMP-dependent downstream pathways.[155] Not surprisingly, then, *in vitro* and animal models suggest that PACAP elicits similar neuroprotective processes.[150] These include antiapoptotic signaling,[156] production of BDNF[157,158] and nitric oxide,[158] adult neurogenesis,[159,160] and antioxidant defenses.[161,162] PACAP may confer resistance to excitotoxicity by facilitating the uptake of glutamate by astrocytes,[163] and by changing the configuration of NMDA receptors.[157] PACAP appears to strengthen the BBB under conditions of glucose deprivation and oxidative stress[164] and it facilitates angiogenesis and capillary formation by cerebral microvessel endothelial cells.[165] In a head injury model, PACAP reduced brain edema[156] and blunted the activation of microglia.[156] Not surprisingly, PACAP has shown promise in animal models of traumatic brain injury, transient or permanent ischemia, and Parkinson's, Alzheimer's, and Huntington's Diseases.[161] Interestingly, IV administration of PACAP also improved memory in normal rats.[159] PACAP crosses the BBB through active transport.[166]

That two different effector molecules of the migraine attack would have broad neuroprotective properties is consistent with the idea that the attack itself is neuroprotective. As with CGRP, however, it will be important to establish whether PACAP blockade outside the BBB has an intracerebral effect.[167]

PROCESSES THAT MIGHT COMPENSATE FOR LOSS OF CGRP

Despite these theoretical concerns, reported side effects in clinical trials have been mild-to-moderate and generally infrequent.[33,36,168-171] The concerns noted above would be more likely to emerge with long-term exposure or if the CGRP blockade were present during a pathological event – head injury, transient ischemic attack, bone fracture, or MS, among others.

Still, the data so far do not point to long-term harm. Decreased activation of eNOS through CGRP blockade should increase the probability of hypertension,[172] yet no increases in blood pressure were seen in clinical trials.[33] Similarly for the hypothesized reduction in VEGF-mediated neurogenesis: Decreased neurogenesis is an essential feature of clinical depression,[173] yet there have been no reports of new or worsened mood disorder in clinical trials.[33]

In fact, the long-term effects of CGRP inhibition depend particularly on 3 unknown factors. The first is the extent of compensating mechanisms. αCGRP is part of a family of peptides comprised also of βCGRP, adrenomedullin, adrenomedullin II (also termed intermedin), amylin, and calcitonin itself.[8] In αCGRP knockout mice, expression of the genes encoding βCGRP, which differs by only 3 amino acids from αCGRP, and adrenomedullin, were upregulated.[87,98] βCRGP is a strong agonist and adrenomedullin is a weak agonist at the CGRP receptor.[8] Adrenomedullin itself seems to decrease the production of oxidants in the brain.[61,174] Thus, overlapping functions among different peptides in the calcitonin family presumably allow for some degree of compensation when CGRP is disabled.

There is also overlap among the receptors for these peptides. As discussed above, the CGRP

receptor consists of 3 parts: the calcitonin receptor-like receptor (CLR), receptor component protein (RCP), and receptor activity-modifying protein 1 (RAMP1).[8] Substituting RAMP2 or RAMP3 for RAMP1 yields the receptor for adrenomedullin or intermedin, respectively. Combining the calcitonin receptor, rather than CLR, with RAMP1, RAMP2, or RAMP3 gives the amylin I, II, or III receptors.[8] As a result, some effects of CGRP may be mediated by the amylin and adrenomedullin receptors.[8] Except for the amylin 1 receptor this effect may be very weak when the downstream measure is cAMP and smooth muscle vasodilation; however, it may be stronger when Akt signaling and growth factor production is the measure.[8] Presumably, this allows for some compensation when the CGRP receptor is blocked.

The second factor is whether the neuroprotective functions of CGRP are partially constitutive, ie, part of normal neural housekeeping, or are elicited only paroxysmally by a threat to the brain such as ischemia, heat shock, sepsis, or head injury. By analogy, CGRP seems to be constitutively active in protecting the gastric mucosa,[175] possibly in neurogenesis in the hippocampus,[56] and in pain transmission at the dorsal horn.[16] In contrast, it is likely not constitutive as a vasodilator, as blocking CGRP does not cause significant vasoconstriction.[176]

The third factor is whether frequent migraine attacks are a reflection of frequent threats to the brain (eg, from poor antioxidant defenses) or an overly sensitive migraine response system. These might represent different subtypes of migraine disorder.

Of note, certain effects of CGRP develop over time. In an animal model of hind limb ischemia, a CGRP-mediated increase in capillary density and blood flow peaked at 7 days post-injury.[80] Therefore, some of the protective effects of CGRP could likely be maintained if short half-life CGRP antagonists were rapidly discontinued. This would not be possible for mAbs, however, with half-lives of 3-4 weeks.

POTENTIAL BENEFITS OF BLOCKING CGRP

The contention here is not that CGRP antagonism is inherently harmful. Indeed, there may be conditions in addition to migraine in which blocking CGRP is therapeutic.

In the nervous system, CGRP likely contributes to pain sensitization on sensory and affective levels.[15] The evidence is strongest for synovial fluid and tissue in osteoarthritis, and blood in muscle and ligament pain.[177] In animal models of pain, CGRP in the spinal cord and trigeminal nucleus caudalis contributes to hyperalgesia by way of microglial activation.[17,18] That is, CGRP may contribute to classical inflammation in pain processing regions and may attenuate such inflammation elsewhere in the brain. CGRP has also been implicated in signaling cascades in neurons, microglia, and astrocytes underlying tolerance to morphine.[178]

Moreover, CGRP, while suppressing cell-mediated (Th1) immunity, may facilitate the humoral (Th2) response. In particular, CGRP seems to activate the immune system in complex regional pain syndrome, leading to autoimmunity, which may contribute to the disorder.[179] Similarly, via neurogenic inflammation and local immune activation, CGRP may participate in psoriasis and possibly rosacea and atopic dermatitis.[180] As there may be pathophysiological links between migraine and atopic dermatitis,[181] there could be dual benefit in CGRP blockade.

Abnormal sprouting of CGRP-containing fibers may underlie the autonomic dysreflexia and proneness to severe hypertension seen in spinal cord injuries above the T5 level.[15]

CGRP is part of the signaling network by which the skin regulates its microbiome.[182] CGRP helps constrain the invasiveness of Staphylococcus epidermidis, under normal conditions a harmless commensal bacterium on the skin.[182] Blocking CGRP might alter this balance. However, the effect is strain- and measure-dependent. In necrotizing fasciitis, certain bacteria such as Streptococcus pyrogenes exploit the immunosuppressant properties of CGRP against neutrophils and monocytes.[124] Possibly, CGRP blockers might prevent limb amputations in this otherwise hard-to-treat illness. CGRP-based immunosuppression has also been implicated in septic peritonitis[183] and lethal Staphylococcus aureus pneumonia.[123] In these conditions, too, blocking CGRP might help in clearing the infection.

The upregulation of growth factor signaling by CGRP is not necessarily benign; it has been implicated in renal fibrosis.[184] Moreover, the combination of growth factors, anti-apoptotic signaling, angiogenesis, and immunosuppression might contribute to the growth of tumors.[185]

Thus, there are circumstances besides migraine in which CGRP blockade may be therapeutic. Indeed, genetically deleting the TRPV1 ion channel preserves metabolic heath and extends lifespan in mice, effects that seem dependent on reduced CGRP levels.[186] Similarly, blocking CGRP seems to have an anti-aging effect.[186] These results are striking, with the longest-lived mice reaching exceptional ages. Note, however, that mortality in laboratory mice is disproportionately from cancer (chiefly, lymphoma), while of course in people it is primarily from heart disease. A molecule such as CGRP, which may protect against heart disease but potentiate cancer, can theoretically reduce lifespan in mice while extending it in people.

CONCLUSIONS

From animal studies, within the brain CGRP is upregulated by physiological threats and in turn activates a wide range of neuroprotective processes. This may be relevant to small molecule antagonists that cross the BBB and in conditions such as ischemia, brain injury, and MS, in which the BBB is disrupted. Outside the BBB, CGRP protects the endothelium and the immune privilege of the brain, and may facilitate neurogenesis and the supply of growth factors to the brain. Post-marketing surveillance should include monitoring for neurological side effects, particularly depression (from decreased neurogenesis), ischemic events, and cognitive decline. Nonetheless, the risks noted here are theoretical and depend on the unknown extent of compensating mechanisms. If actual risk emerges, it would be more likely in migraineurs with neurological comorbidities.

Acknowledgment: The author would like to thank Jennifer Williams for discussions of topics related to this article.

REFERENCES

1. Headache Classification Committee. International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.
2. Borkum JM. *Chronic Headaches: Biology, Psychology, and Behavioral Treatment*. Mahwah, NJ: Lawrence Erlbaum Associates; 2007.
3. Buse DC, Loder EW, Gorman JA, et al. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: Results of the American Migraine Prevalence and Prevention (AMPP) Study. *Headache*. 2013;53:1278-1299.
4. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390:1211-1259.
5. Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: Figures and trends from government health studies. *Headache*. 2018;58:496-505.
6. Messali A, Sanderson JC, Blumenfeld AM, et al. Direct and indirect costs of chronic and episodic migraine in the United States: A web-based survey. *Headache*. 2016;56:306-322.
7. Hu XH, Markson LE, Lipton RB. Stewart WF, Berger ML. Burden of migraine in the United States: Disability and economic costs. *Arch Intern Med*. 1999;159:813-818.
8. Hay DL, Garelja ML, Poyner DR, Walker CS. Update on the pharmacology of calcitonin/CGRP family of peptides: IUPHAR Review 25. *Br J Pharmcol*. 2018;175:3-17.
9. Edvinsson L, Haanes KA, Warfvinge K, Krause DN. CGRP as the target of new migraine therapies – Successful translation from bench to clinic. *Nat Rev Neurol*. 2018;14:338-350.
10. Okutsu Y, Takahashi Y, Nagase M, Shinohara K, Ikeda R, Kato F. Potentiation of NMDA receptor-mediated synaptic transmission at the parabrachial-central amygdala synapses by CGRP in mice. *Mol Pain*. 2017;13:1-11.
11. Karsan N, Goadsby PJ. Calcitonin gene-related peptide and migraine. *Curr Opin Neurol*. 2015;28:250-254.

12. Edvinsson L, Warfvinge K. Recognizing the role of CGRP and CGRP receptors in migraine and its treatment. *Cephalalgia*. 2019;39:366-373.
13. Messlinger K. The big CGRP flood – Sources, sinks and signaling sites in the trigeminovascular system. *J Headache Pain*. 2018;19:22.
14. Burstein R, Noseda R, Borsook D. Migraine: Multiple processes, complex pathophysiology. *J Neurosci*. 2015;35:6619-6629.
15. Benarroch EE. CGRP: Sensory neuropeptide with multiple neurologic implications. *Neurology*. 2011;77:281-287.
16. Yu Y, Lundeberg T, Yu LC. Role of calcitonin gene-related peptide and its antagonist on the evoked discharge frequency of wide dynamic range neurons in the dorsal horn of the spinal cord in rats. *Regul Pept*. 2002;103:23-27.
17. Cady RJ, Glenn JR, Smith KM, Durham PL. Calcitonin gene-related peptide promotes cellular changes in trigeminal neurons and glia implicated in peripheral and central sensitization. *Mol Pain*. 2011;7:94.
18. Nieto FR, Clark AK, Grist J, Chapman V, Malcangio M. Calcitonin gene-related peptide-expressing sensory neurons and spinal microglia reactivity contribute to pain states in collagen-induced arthritis. *Arthritis Rheumatol*. 2015;67:1668-1677.
19. Ho TW, Edvinsson L, Goadsby PJ. CGRP and its receptors provide new insights into migraine pathophysiology. *Nat Rev Neurol*. 2010;6:573-582.
20. Ashina M, Bendtsen L, Jensen R, Schifter S, Olesen J. Evidence for increased plasma levels of calcitonin gene-related peptide in migraine outside of attacks. *Pain*. 2000;86:133-138.
21. Gallai V, Sarchielli P, Floridi A, et al. Vasoactive peptide levels in the plasma of young migraine patients with and without aura assessed both interictally and ictally. *Cephalalgia*. 1995;15:384-390.
22. Hansen JM, Hauge AW, Olesen J, Ashina M. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. *Cephalalgia*. 2010;30:1179-1186.
23. Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J. CGRP may play a causative role in migraine. *Cephalalgia*. 2002;22:54-61.
24. González-Hernádez A, Marichal-Cancino BA, Lozano-Cuenca J, et al. Heteroreceptors modulating CGRP release at neurovascular junction: Potential therapeutic implications on some vascular-related diseases. *Biomed Res Int*. 2016;2016:1-17.
25. Durham PL, Masterson CG. Two mechanisms involved in trigeminal CGRP release: Implications for migraine treatment. *Headache*. 2013;53:67-80.
26. Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: Studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Ann Neurol*. 1993;33:48-56.
27. Sarchielli P, Pini LA, Zanchin G, et al. Clinical-biochemical correlates of migraine attacks in rizatriptan responders and non-responders. *Cephalalgia*. 2006;26:257-265.
28. Juhasz G, Zsombok T, Jakab B, Nemeth J, Szolcsanyi J, Bagdy G. Sumatriptan causes parallel decrease in plasma calcitonin gene-related peptide (CGRP) concentration and migraine headache during nitroglycerin induced migraine attack. *Cephalalgia*. 2005;25:179-183.
29. Maasumi K, Michael RL, Rapoport AM. CGRP and migraine: The role of blocking calcitonin gene-related peptide ligand and receptor in the management of migraine. *Drugs*. 2018;78:913-928.
30. Voss T, Lipton RB, Dodick DW, et al. A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine. *Cephalalgia*. 2016;36:887-898.
31. Holland PR, Goadsby PJ. Targeted CGRP small molecule antagonists for acute migraine therapy. *Neurotherapeutics*. 2018;15:304-312.
32. Ashina M, Dodick D, Goadsby PJ, et al. Erenumab (AMG 334) in episodic migraine: Interim analysis of an ongoing open-label study. *Neurology*. 2017;89:1237-1243.
33. Hou M, Xing H, Cai Y, et al. The effect and safety of monoclonal antibodies to calcitonin gene-related peptide and its receptor on migraine: A systematic review and meta-analysis. *J Headache Pain*. 2017;18:42.
34. Depre C, Antalik L, Starling A, et al. A randomized, double-blind, placebo-controlled study to evaluate the effect of erenumab on exercise time during a treadmill test in patients with stable angina. *Headache*. 2018;58:715-723.
35. Maassen van den Brink A, Rubio-Beltrán E, Duncker D, Villalón CM. Is CGRP receptor blockade cardiovascularly safe? Appropriate studies are needed. *Headache*. 2018;58:1257-1258.

36. Deen M, Correnti E, Kamm K, et al. Blocking CGRP in migraine patients – A review of pros and cons. *J Headache Pain*. 2017;18:96.
37. Paemeleire K, MaassenVanDenBrink A. Calcitonin-gene-related peptide pathway mAbs and migraine prevention. *Curr Opin Neurol*. 2018;31:274-280.
38. Chan KY, Vermeersch S, de Hoon J, Villalón CM, MaassenVanDenBrink A. Potential mechanisms of prospective antimigraine drugs: A focus on vascular (side) effects. *Pharmacol Ther*. 2011;129: 332-351.
39. MaassenVanDenBrink A, Meijer J, Villalón CM, Ferrari MD. Wiping out CGRP: Potential cardiovascular risks. *Trends Pharmacol Sci*. 2016;37:779-788.
40. Kastin AJ, Pan W. Brain influx of endogenous peptides affecting food intake. In: Sharma HS, Westman J, eds. *Blood-Spinal Cord and Brain Barriers in the Health and Disease*. Boston, MA: Elsevier Academic Press; 2004:57-62.
41. Banks WA, Kastin AJ, Maness LM, Huang W, Jaspan JB. Permeability of the blood-brain barrier to amylin. *Life Sci*. 1995;57:1993-2001.
42. Banks WA, Kastin AJ. Differential permeability of the blood-brain barrier to two pancreatic peptides: Insulin and amylin. *Peptides*. 1998;19:883-889.
43. Sun B-L, Shen F-P, Wu Q-J, et al. Intranasal delivery of calcitonin gene-related peptide reduces cerebral vasospasm in rats. *Front Biosci*. 2010;E2:1502-1513.
44. Mason BN, Kaiser EA, Kuburas A, et al. Induction of migraine- like photophobic behavior in mice by both peripheral and central CGRP mechanisms. *J Neurosci*. 2017;37:204-216.
45. Hendrikse ER, Bower RL, Hay DL, Walker CS. Molecular studies of CGRP and the CGRP family of peptides in the central nervous system. *Cephalalgia*. 2019;39:403-419.
46. Hougaard A, Amin FM, Christensen CE, et al. Increased brainstem perfusion, but no blood-brain barrier disruption, during attacks of migraine with aura. *Brain*. 2017;140:1633-1642.
47. Amin FM, Hougaard A, Cramer SP, et al. Intact blood-brain barrier during spontaneous attacks of migraine without aura: A 3T DCE-MRI study. *Eur J Neurol*. 2017;24:1116-1124.
48. Hu DE, Easton AS, Fraser PA. TRPV1 activation results in disruption of the blood-brain barrier in the rat. *Br J Pharmacol*. 2005;146:576-584.
49. Bulloch K, Prasad A, Conrad CD, McEwen B, Milner TA. Calcitonin gene-related peptide level in the rat dentate gyrus increases after damage. *Neuroreport*. 1996;7:1036-1040.
50. Bulloch K, Milner TA, Pierce J, McEwen BS. Kainic acid induction of CGRP-LI in the hippocampal formation of rats: Regional regulation of the CNS injury/immune response. *Neurosci Abstr*. 1997;23:716.
51. Bulloch K, Milner TA, Prasad A, Hsu M, Buzsaki G, McEwen BS. Induction of calcitonin gene-related peptide-like immunoreactivity in hippocampal neurons following ischemia: A putative regional modulator of the CNS injury/immune response. *Exp Neurol*. 1998;150:195-205.
52. Sharma HS, Westman J, Nyberg F. Selective alteration of calcitonin gene related peptide in hyperthermic brain injury. An experimental study in the rat brain using immunohistochemistry. *Acta Neurochir*. 2000;76(Suppl.):541-545.
53. Cai H, Xu X, Liu Z, et al. The effects of calcitonin gene-related peptide on bFGF and AQP4 expression after focal cerebral ischemia reperfusion in rats. *Pharmazie*. 2010;65:274-278.
54. Wang FZ, Feng CH, Liu ZP. The role of calcium in changes of membrane function and the protection of CGRP in hippocampal slice during hypoxia. *Abstr Soc Neurosci*. 1993;16:479.
55. Zhang Z-H, Fang X-B, Xi G-M, Li W-C, Ling H-Y, Qu P. Calcitonin gene-related peptide enhances CREB phosphorylation and attenuates tau protein phosphorylation in rat brain during focal cerebral ischemia/reperfusion. *Biomed Pharmacother*. 2010; 64:430-436.
56. Harada N, Narimatsu N, Kurihara H, Nakagata N, Okajima K. Stimulation of sensory neurons improves cognitive function by promoting the hippocampal production of insulin-like growth factor-1 in mice. *Transl Res*. 2009;154:90-102.
57. Hashikawa-Hobara N, Ogawa T, Sakamoto Y, et al. Calcitonin gene-related peptide pre-administration acts as a novel antidepressant in stressed mice. *Sci Rep*. 2015;5:12559.
58. Liu Z, Liu Q, Cai H, Xu C, Liu G, Li Z. Calcitonin gene-related peptide prevents blood-brain barrier injury and brain edema induced by focal cerebral ischemia reperfusion. *Regul Pept*. 2011;171:19-25.
59. She F, Sun W, Mao J-M, Wang X. Calcitonin gene-related peptide gene therapy suppresses

reactive oxygen species in the pancreas and prevents mice from autoimmune diabetes. *Acta Physiol Sin*. 2003;55:625-632.
60. Guo Z, Liu N, Chen L, Zhao X, Li M-R. Independent roles of CGRP in cardioprotection and hemodynamic regulation in ischemic postconditioning. *Eur J Pharmacol*. 2018;828:18-25.
61. Figueira L, Israel A. Adrenomedullin and angiotensin II signaling pathways involved in the effects on cerebellar antioxidant enzymes activity. *Brain Res Bull*. 2017;128:83-91.
62. Schorscher-Petcu A, Austin J-S, Mogil JS, Quirion R. Role of central calcitonin gene-related peptide (CGRP) in locomotor and anxiety- and depression-like behaviors in two mouse strains exhibiting a CGRP-dependent difference in thermal pain sensitivity. *J Mol Neurosci*. 2009;39:125-136.
63. Narimatsu N, Harada N, Kurihara H, Nakagata N, Sobue K, Okajima K. Donepezil improves cognitive function in mice by increasing the production of insulin-like growth factor-1 in the hippocampus. *J Pharmacol Exp Ther*. 2009;330:2-12.
64. Sardi C, Zambusi L, Finardi A, et al. Involvement of calcitonin gene- related peptide and receptor component protein in experimental autoimmune encephalomyelitis. *J Neuroimmunol*. 2014;271:18-29.
65. Rossetti I, Zambusi L, Finardi A, et al. Calcitonin gene-related peptide decreases IL-1beta, IL-6 as well as Ym1, Arg1, CD163 expression in a brain tissue context-dependent manner while ameliorating experimental autoimmune encephalomyelitis. *J Neuroimmunol*. 2018;323:94-104.
66. Carniglia L, Ramírez D, Durand D, et al. Neuropeptides and microglial activation in inflammation, pain, and neurodegenerative diseases. *Mediators Inflamm*. 2017;2017:1-23.
67. Yang Q, Du X, Fang Z, et al. Effect of calcitonin gene-related peptide on the neurogenesis of rat adipose-derived stem cells in vitro. *PLoS One*. 2014;9:e86334.
68. Zhang Y, Yang J, Zhang P, et al. Calcitonin gene-related peptide is a key factor in the homing of transplanted human MSCs to sites of spinal cord injury. *Sci Rep*. 2016;6:27724.
69. Chung AM. Calcitonin gene-related peptide (CGRP): Role in peripheral nerve regeneration. *Rev Neurosci*. 2018;29:369-376.
70. Toth CC, Willis D, Twiss JL, et al. Locally synthesized calcitonin gene-related peptide has a critical role in peripheral nerve regeneration. *J Neuropathol Exp Neurol*. 2009;68:326-337.
71. Gherardini G, Evans GRD, Theodorsson E, et al. Calcitonin gene-related peptide in experimental ischemia. Implication of an endogenous anti-ischemic effect. *Ann Plast Surg*. 1996;36:616-620.
72. Goadsby P. What is the physiological role of the trigeminovascular system? *Cephalalgia*. 1995;15:333.
73. Park S-H, Sim Y-B, Kim C-H, Lee J-K, Lee J-H, Suh H-W. Role of α-CGRP in the regulation of neurotoxic responses induced by kainic acid in mice. *Peptides*. 2013;44:158-162.
74. Shu Y-H, Lu X-M, Wei J-X, Xiao L, Wang Y-T. Update on the role of p75NTR in neurological disorders: A novel therapeutic target. *Biomed Pharmacother*. 2015;76:17-23.
75. Wu Y, Liu W-Z, Liu T, Feng X, Yang N, Zhou H-F. Signaling pathway of MAPK/ERK in cell proliferation, differentiation, migration, senescence and apoptosis. *J Recept Signal Transduct Res*. 2015 ;35:600-604.
76. Shao B, Zhou YL, Wang H, Lin YS. The role of calcitonin gene-related peptide in post-stroke depression in chronic mild stress-treated ischemic rats. *Physiol Behav*. 2015;139:224-230.
77. Cramer SP, Simonsen H, Frederiksen JL, Rostrup E, Larsson HB. Abnormal blood-brain barrier permeability in normal appearing white matter in multiple sclerosis investigated by MRI. *Neuroimage Clin*. 2013;4:182-189.
78. Schoknecht K, Shalev H. Blood-brain barrier dysfunction in brain diseases: Clinical experience. *Epilepsia*. 2012;53(Suppl. 6):7-13.
79. Manzini S, Perretti F, De Benedetti L, Pradelles P, Maggi CA, Geppetti P. A comparison of bradykinin- and capsaicin-induced myocardial and coronary effects in isolated perfused heart of guinea-pig: Involvement of substance P and calcitonin gene-related peptide release. *Br J Pharmacol*. 1989;97:303-312.
80. Mishima T, Ito Y, Hosono K, et al. Calcitonin gene-related peptide facilitates revascularization during hindlimb ischemia in mice. *Am J Physiol Heart Circ Physiol*. 2011;300:H431-H439.
81. Yang SI, Yuan Y, Jiao S, Luo Q, Yu J. Calcitonin gene-related peptide protects rats from cerebral ischemia/reperfusion injury via a mechanism of action in the MAPK pathway. *Biomed Rep*. 2016;4:699-703.

82. Abushik PA, Bart G, Korhonen P, et al. Pronociceptive migraine mediator CGRP provides neuroprotection of sensory, cortical and cerebellar neurons via multi-kinase signaling. *Cephalagia*. 2017;37:1373-1383.
83. Schebesch K-M, Herbst A, Bele S, et al. Calcitonin-gene related peptide and cerebral vasospasm. *J Clin Neurosci*. 2013;20:584-586.
84. Shin HK, Hong KW. Importance of calcitonin gene-related peptide, adenosine and reactive oxygen species in cerebral autoregulation under normal and diseased conditions. *Clin Exp Pharmacol Physiol*. 2004;31:1-7.
85. Matsumoto Y, Ueda S, Matsushita S, Ozawa T, Yamaguchi H. Calcitonin gene-related peptide inhibits human platelet aggregation. *Jpn Circ J*. 1996;60:797-804.
86. Zhang J-Y, Yan G-T, Liao J, et al. Leptin attenuates cerebral ischemia/reperfusion injury partially by CGRP expression. *Eur J Pharmacol*. 2011;671:61-69.
87. Zhai L, Sakurai T, Kamiyoshi A, et al. Endogenous calcitonin gene-related peptide suppresses ischemic brain injuries and progression of cognitive decline. *J Hypertens*. 2018;36:876-891.
88. Argandona EG, Bengoetxea H, Ortuzar N, Bulnes S, Rico-Barrio I, Lafuente JV. Vascular endothelial growth factor: Adaptive changes in the neuroglial-vascular unit. *Curr Neurovasc Res*. 2012;9:72-81.
89. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Tobias Kurth T. Migraine and cardiovascular disease: Systematic review and meta-analysis. *BMJ*. 2009;339:b3914.
90. Roach REJ, Herlmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: The risk of myocardial infarction and ischemic stroke. *Cochrane Database Syst Rev*. 2015;CD011054.
91. Lipsky RH, Marini AM. Brain-derived neurotrophic factor in neuronal survival and behavior-related plasticity. *Ann N Y Acad Sci*. 2007;1122:130-143.
92. Radecki DT, Brown LM, Martinez J, Teyler TJ. BDNF protects against stress-induced impairments in spatial learning and memory and LTP. *Hippocampus*. 2005;15:246-253.
93. Larsson E, Nanobashvili A, Kokaia Z, Lindvall O. Evidence for neuroprotective effects of endogenous brain-derived neurotrophic factor after global forebrain ischemia in rats. *J Cereb Blood Flow Metab*. 1999;19:1220-1228.
94. Guo S, Kim WJ, Lok J, et al. Neuroprotection via matrix-trophic coupling between cerebral endothelial cells and neurons. *Proc Natl Acad Sci USA*. 2008;105:7582-7587.
95. Marie C, Pedard M, Quirié A, et al. Brain-derived neurotrophic factor secreted by the cerebral endothelium: A new actor of brain function? *J Cereb Blood Flow Metab*. 2018;38:935-949.
96. Meuchel IW, Thompson MA, Cassivi SD, Pabelick CM, Prakash YS. Neurotrophins induce nitric oxide generation in human pulmonary artery endothelial cells. *Cardiovasc Res*. 2011;91:668-676.
97. Luo D, Zhang YW, Peng WJ, et al. Transient receptor potential vanilloid 1-mediated expression and secretion of endothelial cell-derived calcitonin gene-related peptide. *Regul Pept*. 2008;150:66-72.
98. Smillie S-J, King R, Kodji X, et al. An ongoing role of α-calcitonin gene-related peptide as part of a protective network against hypertension, vascular hypertrophy, and oxidative stress. *Hypertension*. 2014;63:1056-1062.
99. Zhou Z, Hu CP, Wang CJ, Li TT, Peng J, Li YJ. Calcitonin gene-related peptide inhibits angiotensin II- induced endothelial progenitor cells senescence through up-regulation of klotho expression. *Atherosclerosis*. 2010;213:92-101.
100. Moore CI, Cao R. The hemo-neural hypothesis: On the role of blood flow in information processing. *J Neurophysiol*. 2008;99:2035-2047.
101. Tuo Y, Guo X, Zhang X, et al. The biological effects and mechanisms of calcitonin gene-related peptide on human endothelial cell. *J Recept Signal Transduct Res*. 2013;33:114-123.
102. Dragoni S, Turowski P. Polarised VEGFA signalling at vascular blood-neural barriers. *Int J Mol Sci*. 2018;19:1378.
103. Gerber HP, Dixit V, Ferrara N. Vascular endothelial growth factor induces expression of the antiapoptotic proteins Bcl-2 and A1 in vascular endothelial cells. *J Biol Chem*. 1998;273:13313-13316.
104. Mason JC, Steinberg R, Lidington E, et al. Decay accelerating factor induction on vascular endothelium by vascular endothelial growth factor (VEGF) is mediated via a VEGF receptor-2 (VEGF-R2)- and protein kinase C-a/e(PKCa/e)-dependent cytoprotective signaling pathway and is inhibited by cyclosporin A. *J Biol Chem*. 2004;279:41611-41618.
105. Bussolati B, Dunk C, Grohman M, et al. Vascular endothelial growth factor receptor-1

modulates vascular endothelial growth factor-mediated angiogenesis via nitric oxide. *Am J Pathol*. 2001;159:993-1008.
106. Kimura H, Esumi H. Reciprocal regulation between nitric oxide and vascular endothelial growth factor in angiogenesis. *Acta Biochim Pol*. 2003;50:49-59.
107. Simonetti M, Giniatullin R, Fabbretti E. Mechanisms mediating the enhanced gene transcription of $P2X_3$ receptor by calcitonin gene-related peptide in trigeminal sensory neurons. *J Biol Chem*. 2008;283:18743-18752.
108. Buldyrev I, Tanner NM, Hsieh HY, Dodd EG, Nguyen LT, Balkowiec A. Calcitonin gene-related peptide enhances release of native brain-derived neurotrophic factor from trigeminal ganglion neurons. *J Neurochem*. 2006;99:1338-1350.
109. Fabel K, Fabel K, Tam B, et al. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur J Neurosci*. 2003;18:2803-2812.
110. Licht T, Keshet E. Delineating multiple functions of VEGF-A in the adult brain. *Cell Mol Life Sci*. 2013;70:1727-1737.
111. Cao L, Jiao X, Zuzga DS, et al. VEGF links hippocampal activity with neurogenesis, learning and memory. *Nat Genet*. 2004;36:827-835.
112. Louissaint A Jr, Rao S, Leventhal C, Goldman SA. Coordinated interaction of neurogenesis and angiogenesis in the adult songbird brain. *Neuron*. 2002;34:945-960.
113. Jansen-Olesen I, Jørgensen L, Engel U, Edvinsson L. In-depth characterization of CGRP receptors in human intracranial arteries. *Eur J Pharmacol*. 2003;481:207-216.
114. Moreno MJ, Cohen Z, Stanimirovic DB, Hamel E. Functional calcitonin gene-related peptide type I and adrenomedullin receptors in human trigeminal ganglia, brain vessels, and cerebromicrovascular or astroglial cells in culture. *J Cereb Blood Flow Metab*. 1999;19:1270-1278.
115. Hagner S, Stahl U, Knoblauch B, McGregor GP, Lang RE. Calcitonin receptor-like receptor: Identification and distribution in human peripheral tissues. *Cell Tissue Res*. 2002;310:41-50.
116. Edvinsson L, Chan KY, Eftekhari S, et al. Effect of the calcitonin gene-related peptide (CGRP) receptor antagonist telcagepant in human cranial arteries. *Cephalalgia*. 2010;30:1233-1240.
117. Oliver KR, Wainwright A, Edvinsson L, Pickard JD, Hill RG. Immunohistochemical localization of calcitonin receptor-like receptor and receptor activity-modifying proteins in the human cerebral vasculature. *J Cereb Blood Flow Metab*. 2002;22:620-629.
118. Talme T, Liu Z, Sundqvist K-G. The neuropeptide calcitonin gene-related peptide (CGRP) stimulates T cell migration into collagen matrices. *J Neuroimmunol*. 2008;196:60-66.
119. Huang J, Stohl LL, Zhou X, Ding W, Granstein RD. Calcitonin gene-related peptide inhibits chemokine production by human dermal microvascular endothelial cells. *Brain Behav Immun*. 2011;25:787-799.
120. Russell FA, King R, Smillie S-J, Kodji X, Brain SD. Calcitonin gene-related peptide: Physiology and pathophysiology. *Physiol Rev*. 2014;94:1099-1142.
121. Assas BM, Pennock JI, Miyan JA. Calcitonin gene-related peptide is a key neurotransmitter in the neuro- immune axis. *Front Neurosci*. 2014;8:23.
122. Gomes RN, Castro-Faria-Neto HC, Bozza PT, et al. Calcitonin gene-related peptide inhibits local acute inflammation and protects mice against lethal endotoxemia. *Shock*. 2005;24:590-594.
123. Baral P, Umans BD, Li L, et al. Nociceptor sensory neurons suppress neutrophil and γδ T cell responses in bacterial lung infections and lethal pneumonia. *Nat Med*. 2018;24:417-426.
124. Pineho-Ribeiro FA, Baddal B, Haarsma R, et al. Blocking neuronal signaling to immune cells treats streptococcal invasive infection. *Cell*. 2018; 173:1083-1097.
125. Semple BD, Kossmann T, Morganti-Kossmann MC. Role of chemokines in CNS health and pathology: A focus on the CCL2/CCR125 and CXCL8/CXCR125 networks. *J Cereb Blood Flow Metab*. 2010;30:459-473.
126. Mahad D, Callahan MK, Williams KA, et al. Modulating CCR126 and CCL2 at the blood-brain barrier: Relevance for multiple sclerosis pathogenesis. *Brain*. 2006;129:212-223.
127. Subileau EA, Rezaie P, Davies HA, et al. Expression of chemokines and their receptors by human brain endothelium: Implications for multiple sclerosis. *J Neuropathol Exp Neurol*. 2009; 68:227-240.
128. Lu C-X, Qiu T, Liu ZF, Su L, Cheng B. Calcitonin gene-related peptide has protective effect on brain injury induced by heat stroke in rats. *Exp Ther Med*. 2017;14:4935-4941.

129. Pakpoor J, Handel AE, Giovannoni G, Dobson R, Ramagopalan SV. Meta-analysis of the relationship between multiple sclerosis and migraine. *PLoS One*. 2012;7:e45295.
130. Ye F, Deng P-Y, Li D, et al. Involvement of endothelial cell-derived CGRP in heat stress-induced protection of endothelial function. *Vascul Pharmacol*. 2007;46:238-246.
131. Zarbock A, Ley K. Mechanisms and consequences of neutrophil interaction with the endothelium. *Am J Pathol*. 2008;172:1-7.
132. Ringer C, Tune S, Bertoune MA, et al. Disruption of calcitonin gene-related peptide signaling accelerates muscle denervation and dampens cytotoxic neuroinflammation in SOD1 mutant mice. *Cell Mol Life Sci*. 2017;74:339-358.
133. Nikulin VV, Fedele T, Mehnert J, et al. Monochromatic ultra-slow (~0.1 Hz) oscillations in the human electroencephalogram and their relation to hemodynamics. *Neuroimage*. 2014;97:71-80.
134. Kim KJ, Diaz JR, Iddings JA, Filosa JA. Vasculo-neuronal coupling: Retrograde vascular communication to brain neurons. *J Neurosci*. 2016;36:12624-12639.
135. Borkum JM. Migraine triggers and oxidative stress: A narrative review and synthesis. *Headache*. 2016;56:12-35.
136. Borkum JM. The migraine attack as a homeostatic, neuroprotective response to brain oxidative stress. *Headache*. 2018;58:118-135.
137. Cortelli P, Montagna P. Migraine as visceral pain. *Neurol Sci*. 2009;30:s19-s22.
138. Loder E. What is the evolutionary advantage of migraine? *Cephalalgia*. 2002;22:624-632.
139. Goadsby PJ. Pathophysiology of migraine. *Ann Indian Acad Neurol*. 2012;15(Suppl. 1):s15-s22.
140. Borkum JM. Harnessing migraines for neural regeneration. *Neural Regen Res*. 2018;13:609-615.
141. Tozzi A, de Iure A, Di Filippo M, et al. Critical role of calcitonin gene-related peptide receptors in cortical spreading depression. *Proc Natl Acad Sci USA*. 2012;109:18985-18990.
142. Wang Y, Li Y, Wang M. Involvement of CGRP receptors in retinal spreading depression. *Pharmacol Rep*. 2016;68:935-938.
143. Filiz A, Tepe N, Eftekhari S, et al. CGRP receptor antagonist MK-8825 attenuates cortical spreading depression induced pain behavior. *Cephalalgia*. 2019;39:354-365.
144. Silberstein SD, Rapoport AM, Loupe PS, et al. The effect of beginning treatment with fremanezumab on headache and associated symptoms in the randomized phase 2 study of high frequency episodic migraine: Post-hoc analyses on the first 3 weeks of treatment. *Headache*. 2019;59:383-393.
145. Evers S, Quibeldey F, Grotemeyer K-H, Suhr B, Husstedt I-W. Dynamic changes of cognitive habituation and serotonin metabolism during the migraine interval. *Cephalalgia*. 1999;19:485-491.
146. Deen M, Hansen HD, Hougaard A, et al. Low 5-HT1B receptor binding in the migraine brain: A PET study. *Cephalalgia*. 2018;38:519-527.
147. Rist PM, Kurth T. Migraine and cognitive decline: A topical review. *Headache*. 2013;53:589-598.
148. Kalaydjian A, Zandi PP, Swartz KL, Eaton WW, Lyketsos C. How migraines impact cognitive function: Findings from the Baltimore ECA. *Neurology*. 2007;68:1417-1424.
149. Rist PM, Dufouil C, Glymour MM, Tzourio C, Kurth T. Migraine and cognitive decline in the population based EVA study. *Cephalalgia*. 2011;31:1291-1300.
150. Reglodi D, Vaczy A, Rubio-Beltran E, MaassenVanDenBrink A. Protective effects of PACAP in ischemia. *J Headache Pain*. 2018;19:19.
151. Edvinsson L, Tajti J, Szalárdy L, Vécsei L. PACAP and its role in primary headaches. *J Headache Pain*. 2018;19:21.
152. Tuka B, Helyes Z, Markovics A, et al. Alterations in PACAP-38-like immunoreactivity in the plasma during itcal and interictal periods of migraine patients. *Cephalagia*. 2013;33:1085-1095.
153. Amin FM, Asghar MS, Guo S, et al. Headache and prolonged dilatation of the middle meningeal artery by PACAP38 in healthy volunteers. *Cephalalgia*. 2012;32:140-149.
154. Schytz HW, Birk S, Wienecke T, Kruuse C, Olesen J, Ashina M. PACAP38 induces migraine-like attacks in patients with migraine without aura. *Brain*. 2009;132:16-25.
155. Vaudry D, Falluel-Morel A, Bourgault S, et al. Pituitary adenylate cyclase- activating polypeptide and its receptors: 20 years after the discovery. *Pharmacol Rev*. 2009;61:283-357.
156. Mao S-S, Hua R, Zhao X-P, et al. Exogenous administration of PACAP alleviates traumatic brain injury in rats through a mechanism involving the TLR4/

MyD88/NF-κB pathway. *J Neurotrauma*. 2012; 29:1941-1959.
157. Kaneko Y, Tuazon JP, Ji X, Borlongan CV. Pituitary adenylate cyclase activating polypeptide elicits neuroprotection against acute ischemic neuronal cell death associated with NMDA receptors. *Cell Physiol Biochem*. 2018;51:1982-1995.
158. Ladjimi MH, Barbouche R, Barka ZB, et al. Comparison of the effects of PACAP-38 and its analog, acetyl-[Ala^{15}, Ala^{20}] PACAP-38-propylamide, on spatial memory, post-learning BCNF expression and oxidative stress in rat. *Behav Brain Res*. 2019;359:247-257.
159. Ohta S, Gregg C, Weiss S. Pituitary adenylate cyclase-activating polypeptide regulates forebrain neural stem cells and neurogenesis in vitro and in vivo. *J Neurosci Res*. 2006;84:1177-1186.
160. Mercer A, Ronnholm H, Holmberg J, et al. PACAP promotes neural stem cell proliferation in adult mouse brain. *J Neurosci Res*. 2004;76:205-215.
161. Rivnyak A, Kiss P, Tamas A, Balogh D, Reglodi D. Review on PACAP-induced transcriptomic and proteomic changes in neuronal development and repair. *Int J Mol Sci*. 2018;19:1020.
162. Miyamoto K, Tsumuraya T, Ohtaki H, et al. PACAP38 suppresses cortical damage in mice with traumatic brain injury by enhancing antioxidant activity. *J Mol Neurosci*. 2014;54:370-379.
163. Reglodi D, Tamas A, Somogyvari A, et al. Effects of pretreatment with PACAP on the infarct size and functional outcome in rat permanent focal cerebral ischemia. *Peptides*. 2002;23:2227-2234.
164. Wilhelm I, Fazakas C, Tamás A, Tóth G, Reglődi D, Krizbai IA. PACAP enhances barrier properties of cerebral microvessels. *J Mol Neurosci*. 2014;54:469-476.
165. Banki E, Sosnowska D, Tucsek Z, et al. Age-related decline of autocrine pituitary adenylate cyclase-activating polypeptide impairs angiogenic capacity of rat cerebromicrovascular endothelial cells. *J Gerontol A Biol Sci Med Sci*. 2015;70:665-674.
166. Banks WA, Kastin AJ, Komaki G, Arimura A. Passage of pituitary adenylate cyclase activating $polypeptide_{1-27}$ and pituitary adenylate cyclase activating $polypeptide_{1-38}$ across the blood-brain barrier. *J Phamacol Exp Ther*. 1993;267:690-696.
167. Rubio-Beltrán E, Correnti E, Deen M, et al. PACAP38 and PAC_1 receptor blockade: A new target for headache? *J Headache Pain*. 2018;19:64.
168. Dodick DW, Ashina M, Brandes JL, et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia*. 2018;38:1026-1037.
169. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim B-K, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia*. 2018;38:1442-1454.
170. Camporeale A, Kudrow D, Sides R, et al. A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine. *BMC Neurol*. 2018;18:188.
171. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med*. 2017;377: 2113-2122.
172. González J, Valls N, Brito R, Rodrigo R. Essential hypertension and oxidative stress: New insights. *World J Cardiol*. 2014;6:353-366.
173. Micheli L, Ceccarelli M, D'Andrea G, Tirone F. Depression and adult neurogenesis: Positive effects of the antidepressant fluoxetine and of physical exercise. *Brain Res Bull*. 2018;143:181-193.
174. Figueira L, Israel A. Adrenomedullin and angiotensin II in rat cerebellar vermis: Reactive oxygen species production. *Focus Sci*. 2017;3:1-6.
175. Ohno T, Hattori Y, Komine R, et al. Roles of calcitonin gene-related peptide in maintenance of gastric mucosal integrity and in enhancement of ulcer healing and angiogenesis. *Gastroenterology*. 2008;134:215-225.
176. Rubio-Beltrán E, Labastida A, De Vries R. Effects of AMG 334 on human isolated coronary artery [abstract]. *Cephalalgia*. 2016;36:S41.
177. Schou WS, Ashina S, Amin FM, Goadsby PJ, Ashina M. Calcitonin gene-related peptide and pain: A systematic review. *J Headache Pain*. 2017; 18:34.
178. Carniglia L, Ramirez D, Durand D, et al. Neuropeptides and microglial activation in inflammation, pain, and neurodegenerative diseases. *Mediators Inflamm*. 2017;5048616.
179. Li W-W, Guo T-Z, Shi X, et al. Neuropeptide regulation of adaptive immunity in the tibia fracture model of complex regional pain syndrome. *J Neuroinflammation*. 2018;15:105.
180. Choi JE, Nardo AD. Skin neurogenic inflammation. *Semin Immuunopathol*. 2018;40:249-259.

181. Özge A, Uluduz D, Bolay H. Co-occurrence of migraine and atopy in children and adolescents: Myth or a causal relationship? *Curr Opin Neurol*. 2017;30:287-291.
182. Feuilloley MGJ. Antidromic neurogenic activity and cutaneous bacterial flora. *Semin Immunopathol*. 2018;40:281-289.
183. Jusek G, Reim D, Tsujikawa K, Holtzmann B. Deficiency of the CGRP receptor component RAMP1 attenuates immunosuppression during the early phase of septic peritonitis. *Immunobiology*. 2012;217:761-767.
184. Yoon SP, Kim J. Exogenous CGRP upregulates profibrogenic growth factors through PKC/JNK signaling pathway in kidney proximal tubular cells. *Cell Biol Toxicol*. 2018;34:251-262.
185. Toda M, Suzuki T, Hosono K, et al. Neuronal system-dependent facilitation of tumor angiogenesis and tumor growth by calcitonin gene-related peptide. *Proc Natl Acad Sci USA*. 2008;105:13550-13555.
186. Riera CE, Huising MO, Follett P, et al. TRPV1 pain receptors regulate longevity and metabolism by neuropeptide signaling. *Cell*. 2014;157:1023-1036.