



# Glutamate and Its Receptors as Therapeutic Targets for Migraine

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There is substantial evidence indicating a role for glutamate in migraine. Levels of glutamate are higher in the brain and possibly also in the peripheral circulation in migraine patients, particularly during attacks. Altered blood levels of kynurenes, endogenous modulators of glutamate receptors, have been reported in migraine patients. Population genetic studies implicate genes that are involved with glutamate signaling in migraine, and gene mutations responsible for familial hemiplegic migraine and other familial migraine syndromes may influence glutamate signaling. Animal studies indicate that glutamate plays a key role in pain transmission, central sensitization, and cortical spreading depression. Multiple therapies that target glutamate receptors including magnesium, topiramate, memantine, and ketamine have been reported to have efficacy in the treatment of migraine, although with the exception of topiramate, the evidence for the efficacy of these therapies is not strong. Also, because all of these therapies have other mechanisms of action, it is not possible to conclude that the efficacy of these drugs is entirely due to their effects on glutamate receptors. Further studies are needed to more clearly delineate the possible roles of glutamate and its specific receptor subtypes in migraine and to identify new ways of targeting glutamate for migraine therapy.

**Key Words** Glutamate · Migraine · Aura · Headache · Cortical spreading depression

## Introduction

Migraine involves alteration in the excitability of multiple regions of the central nervous system (CNS). Glutamate is the most important and widely distributed excitatory neurotransmitter in the CNS, and therefore likely plays a crucial role in migraine pathophysiology [1]. Glutamate exerts diverse and complex effects in the CNS by binding to a large range of receptors with distinct structural and functional properties. Glutamate receptors are broadly divided into two groups, the cation-permeable ionotropic glutamate receptors (iGluR) and the G protein-coupled metabotropic glutamate receptors (mGluR). The iGluRs are subdivided into *N*-methyl-D-

aspartate (NMDA),  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), and 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine (kainate) receptors and each of these comprises several receptors that are permeable to sodium ( $\text{Na}^+$ ) or calcium ( $\text{Ca}^{2+}$ ). The mGluRs are subdivided into three groups (groups I–III) [2, 3]. Receptors belonging to group I are predominantly located postsynaptically, activate phospholipase C and thereby increase excitability. However, they are also found presynaptically where they induce the activation of protein kinase C enhancing the exocytotic release of glutamate [4]. In contrast, the mGluRs belonging to groups II and III, which are predominantly located presynaptically, activate adenylyl cyclase and thereby reduce the release of glutamate. Based on these functions of mGluR, they possess distinct effects on neuronal activity with receptors belonging to group I being predominantly pronociceptive and those belonging to groups II and III being predominantly antinociceptive. In addition, the different groups may interact with each other, as for example mGluR belonging to group I may prime NMDA receptors to enhance their excitability. This mechanism may be relevant for the induction of central sensitization, a neuronal phenomenon that may affect peripheral and central neurons and is characterized by a reduction in the activation threshold of nociceptive neurons so that usually non-nociceptive stimuli induce a nociceptive neuronal response. This phenomenon is the pathophysiological

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correlate of the cutaneous allodynia that is frequently observed in migraine [5].

## Evidence for a Role for Glutamate in Migraine

A large body of preclinical and clinical evidence suggests that glutamate and its receptors are involved in migraine pathophysiology [1].

### Elevated Levels of Glutamate in Migraine Patients

Elevated blood levels of glutamate have been recorded both interictally and ictally in migraine patients [6–8], although the results of these measurements have not been consistent across all studies. Effective migraine preventive therapies with distinct mechanisms of action have been reported to reduce plasma glutamate levels [9]. Increased levels of glutamate have also been reported in the cerebrospinal fluid in migraine patients during the ictal and interictal periods [8, 10, 11], as well as in saliva in episodic and chronic migraine patients [12, 13]. A proton magnetic resonance spectroscopy study has found that glutamate in the occipital cortex was increased in patients with migraine without aura compared with controls [14].

Studies demonstrating increased levels of glutamate in migraine patients are supported by the effects of orally administered monosodium glutamate. Although the reported effects of monosodium glutamate vary considerably, multiple studies have found that administration of monosodium glutamate can evoke headache [15, 16]. This observation that glutamate may act as a headache trigger in some individuals is consistent with elevated levels of glutamate playing a causative role in migraine.

### Endogenous Glutamate Receptor Modulators in Migraine

Kynurenines are products of the major metabolic pathway of the amino acid tryptophan. Kynurenines have direct effects on both iGluRs and mGluRs, as well as influencing synaptic glutamate release. It has been hypothesized that kynurenines could play a role in migraine by modulating glutamatergic activity [17]. In animal models of migraine, nitroglycerine downregulates the kynurenine pathway [18] while kynurenines have been shown to reduce nitroglycerine-evoked hyperalgesia [19] and cortical spreading depression [20]. Altered levels of kynurenines have been reported in chronic migraine patients [21]. An intriguing aspect of kynurenines is that they could represent a link between systemic metabolism and glutamatergic signaling. Fluctuating levels of kynurenines could lead to episodic changes in glutamate signaling that could be involved in episodic neurological

disorders such as migraine. The kynurenine pathway therefore represents an interesting potential therapeutic target.

## Migraine-Associated Genes and Glutamate Signaling

Population genetic studies have identified multiple migraine-associated polymorphisms in genes that could be involved in glutamate signaling. Polymorphisms of genes encoding AMPA receptors have been associated with migraine in multiple population studies, although the results of these studies have not been consistent in different populations [22–26]. Population studies have also identified other migraine-associated polymorphisms of genes encoding potential regulators of glutamate receptor trafficking or glutamate release including LRP1, IGSF89, CARF, REST, JPH3, PHACTR1, and PRDM16 [27, 28]. A polymorphism of the glutamate transporter EAAT2 has been reported to be associated with progression of migraine from episodic to chronic [29]. Familial hemiplegic migraine (FHM) genes and other familial migraine genes may also influence glutamatergic signaling. Mutations in the genes encoding the P/Q type calcium channel in FHM1 and the voltage-gated sodium channel in FHM3 have been hypothesized to increase neuronal glutamate release [30], whereas mutations in the ATP1A2 sodium-potassium ATPase in mice have been hypothesized to reduce glutamate uptake by astrocytes [31]. Mutations in the genes encoding PRRT2, which are associated with hemiplegic migraine in some families, have also been reported to result in altered glutamatergic signaling [32]. Mutations in casein kinase 1 delta that are associated with migraine and advanced sleep phase syndrome [33, 34] could result in increased glutamatergic signaling via alterations in the phosphorylation and processing of glutamate receptors [35].

## The Role of Glutamate in Pain Transmission and Central Sensitization

Given its excitatory action on nociceptive neurons along the trigeminovascular pathway glutamate has long been discussed as a crucial neurotransmitter in the pathophysiology of migraine headache and migraine-related central sensitization. All three classes of iGluR as well as the mGluR are located in the superficial laminae I and II of the trigeminocervical complex (TCC) [36] forming the basis for a complex interaction and modulation of neuronal pain signals. The TCC is of crucial importance in migraine pathophysiology as it represents the key relay center that integrates the peripheral and central elements of the trigeminovascular pathway and activates during the pain phase of a migraine attack [37]. In addition to the TCC and to the trigeminal ganglion, glutamate receptors are

found on other pain-modulating structures including the thalamus and hypothalamus as well as the periaqueductal gray [38, 39]. Beyond this neuroanatomical distribution, a functional role in these nociceptive pathways has been proven as noxious; painful stimulation leads to an increase in glutamate concentration in these structures including the TCC [40, 41]. In line with these observations, the microiontophoretic administration of glutamate into the Sp5C of the TCC induced a facilitation of neuronal activity in this region [42]. Stimulation of intracranial structures such as the middle meningeal artery or superior sagittal sinus in the dura mater as well as stimulation of other areas with afferent trigeminal innervation such as the cornea and the temporomandibular joint induce a neuronal facilitation of nociceptive fibers in the TCC [41, 43–45] emphasizing the potential importance of glutamate in the central transmission of nociceptive trigeminal signals. Triptans, which are serotonin agonists at the 5-HT<sub>1B/D/F</sub> receptors, may act, at least in part, through a modulation of glutamate release [46]. Based on this strategic receptor distribution and the described functional properties in key centers along the trigeminovascular pain pathway, targeting glutamate receptors is an attractive pharmacological approach for the treatment of migraine.

### The Role of Glutamate in Cortical Spreading Depolarization

There is strong evidence that glutamate plays a primary role in cortical spreading depolarization (CSD, classically referred to as cortical spreading depression), which is believed to be the physiological substrate of the migraine aura. CSD is associated with the release of glutamate into the extracellular space. Glutamate release in CSD has been reported to be a regenerative process, whereby released glutamate acts on presynaptic NMDA receptors to elicit further release of glutamate [47]. Multiple inhibitors of glutamate receptors, particularly NMDA receptor antagonists including the MK801, APH [48], ifenprodil [49], memantine [50], ketamine [51], and others have been reported to inhibit the initiation and propagation of CSD, indicating that activation of NMDA receptors play a key role in generating CSD. Topiramate, a kainate receptor antagonist, has also been reported to inhibit CSD [52]. Conversely, “unblocking” NMDA receptors by lowering extracellular magnesium can evoke CSD [53]. In contrast to NMDA receptors, activation of AMPA receptors has been reported to suppress CSD [54]. CSD can also be inhibited by systemic administration of the endogenous glutamate receptor modulator L-kynurenine [20], supporting a potential role for kynurenines in migraine as discussed above.

## Glutamate Receptor Subtypes as Therapeutic Targets in Migraine

### NMDA Receptors

NMDA receptors are widely distributed in the CNS. Under resting conditions, the channel pore is blocked by magnesium ( $Mg^{2+}$ ) preventing the flow of ions through the receptor channel. During neuronal depolarization,  $Mg^{2+}$  leaves the pore allowing the influx of  $Ca^{2+}$  [55].

A number of preclinical studies indicate a potential role for the action of  $Mg^{2+}$  on NMDA receptors as a migraine mechanism. These studies revealed that large groups of glutamate receptors are located on the superficial laminae of the trigeminal nucleus caudalis (TNC) [36]. Local stimulation of these receptors with microiontophoretically administered glutamate induces a postsynaptic facilitation of neuronal activity within the TNC [42]. In rats, chemical activation of corneal nociceptors with mustard oil induced a significant increase in Fos protein immunoreactivity, a marker for neuronal activation, in the TNC (Sp5C) [43]. This effect was attenuated by intravenous pretreatment with the NMDA receptor antagonist dizolcypine maleate (MK-801) [43] indicating the importance of NMDA receptors in the transmission of trigeminal nociceptive information in the centrally located TNC. These observations were reproduced in electrophysiological experiments in cats in which nociceptive electrical stimulation of the superior sagittal sinus also had a facilitating effect in the TCC which could be inhibited by the intravenous administration of MK-801 [44]. A similar effect is observed in the TCC when electrical stimulation is performed on the occipital nerve as it converges with trigeminal input into the same nuclei in the brainstem [56]. In contrast to the inhibitory effects observed when the antagonists or channel blockers are administered microiontophoretically, the attenuation of a stimulus-evoked response in the TCC is not observed after intravenous administration of the NMDA channel pore blockers magnesium and memantine suggesting that the permissible doses given through this route of administration do not achieve a sufficient channel blocking effect at NMDA receptors located in the TCC [45].

In contrast to what is seen in the TCC, MK-801, may also increase neuronal activity in certain regions of the midbrain involved in the descending inhibitory modulation of the trigeminal pain processing pathway, such as the periaqueductal gray and the nucleus raphe magnus [57].

Beyond its role in mediating neuronal activation, NMDA receptors play a significant role in peripheral and central neuronal sensitization, the pathophysiological correlate of allodynia. Cutaneous allodynia is a common symptom during an acute migraine attack and describes a nociceptive response under normal conditions non-nociceptive stimulus [5, 58]. This phenomenon can be reproduced in preclinical studies.

For example, intense, repetitive, and sustained neuronal stimuli may induce central sensitization and there is a large body of evidence indicating a substantial role of NMDA receptors in the establishment of this condition [59–62]. The same phenomenon can be induced in animal models of peripheral inflammation, in which allodynia and hyperalgesia are induced by the local injection of carrageenan or glutamate and, as observed in electrically induced sensitization, treatment with the NMDA channel blocker MK-801 or the NMDA receptor antagonist AP7 ((±)-2-amino-7-phosphonoheptanoic acid) effectively reverses these neuronal phenomena [63, 64].

In the context of migraine, even more important than the establishment of allodynia, is the possibility that central sensitization may play a major role in the chronification of this disorder [65–67]. More research is needed in this area to elucidate the role of central sensitization and NMDA receptors in the chronification of migraine but if this assumption should become well accepted, it could represent a promising target to treat this disabling condition. In this case, one may even speculate of a therapeutic potential of similar or associated conditions involving neuronal sensitization such as medication overuse headache [68].

### AMPA Receptors

As described above, AMPA receptors are located in the superficial laminae of the TCC [36]. Given the known interaction between NMDA and AMPA receptors and the fundamental importance of the TCC in migraine pathophysiology, it seems likely that these receptors play a role in the pathophysiology of migraine. Through a specific arrangement of their subunits as well as a significant membrane trafficking, AMPA receptors are dynamically regulated adjusting their synaptic strength [3]. These properties of AMPA receptors and their functional interaction with NMDA receptors form the molecular basis for their role in normal nociception as well as in injury-induced synaptic plasticity, hyperalgesia, and allodynia. Their functional relevance in nociceptive trigeminovascular neurotransmission and therefore possibly in migraine pathophysiology was demonstrated in preclinical studies conducted by Storer et al. in which stimulus-evoked nociceptive neuronal activity in the TCC could be inhibited by the specific AMPA receptor antagonist GYKI52466 [44]. These electrophysiological studies are in line with the observations made in an animal model of capsaicin-induced neuronal activation which revealed that in the TCC (Sp5C) capsaicin-induced increase in *c-fos* expression, which reflects an increase in neuronal activation, is reduced by the AMPA/kainate receptor antagonists 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzol[f]quinoxaline-7-sulphonamide and 6-cyano-7-nitroquinoxaline-2,3-dione [69]. As this antinociceptive effect was not observed with the selective kainate receptor antagonists gamma-(R-)glutamylaminomethanesulphonic acid and 6,7,8,9-tetrahydro-5-nitro-1H-benz[g]indole-2,3-dione-3-

oxime, it may be assumed that the capsaicin-induced facilitation in the TCC is mediated through AMPA receptors [69]. In this context, the AMPA/kainate receptor antagonist LY293558, which effectively inhibits *c-fos* expression in the TCC in a preclinical model of migraine [70], is effective in the acute treatment of migraine [71]. However, the design of these preclinical experiments does not allow any conclusion if the clinical efficacy relies on an action at AMPA or kainate receptors.

Taken together, the results suggest a therapeutic potential in targeting AMPA receptors. Given the lack of more AMPA-selective agonists and antagonists, it is still challenging to dissect further the distinct effects at AMPA receptors and their clinical significance compared to other iGluRs, in particular kainate receptors.

### Kainate Receptors

Kainate receptors consist of several subunits named iGluR5, 6, and 7 and KA1 and KA2. Homo- and heteromeric assemblies of these subunits create the functional receptor [72–74]. Within the peripheral part of the trigeminovascular system, functional kainate receptors have been detected within the trigeminal ganglion [75, 76] whereas in central regions that modulate and process trigeminal nociceptive signals, kainate receptors are found in laminae I and II of the TNC (Sp5C) [36, 76] as well as in the sensory thalamus [39]. Given that kainate receptors are localized pre- [77, 78] and postsynaptically [79–81], they may exert their functional actions through a presynaptic regulation of neuropeptide and neurotransmitter release [77, 78, 82, 83] as well as through a postsynaptic regulation of neuronal currents [82].

In regard to their functional role in pain, activation of kainate receptors at both locations, pre- and postsynaptic, has been shown to influence nociceptive neurotransmission [81, 83]. In animal models investigating peripheral pain, activation of the kainate receptor induced mechanical [84] and thermal [63] hyperalgesia and allodynia as well as pain behavior [84]. Studies investigating plasma protein extravasation (PPE) in rodents, a mechanism that in the past had been thought to be predictive for clinical efficacy, showed that the receptor antagonists LY293558, LY382884, and LY435735, which have varying degrees of selectivity and affinity to the kainate receptors, effectively inhibit PPE [70]. As the selective AMPA receptor antagonist LY300168 did not block PPE [70], it may be assumed that the PPE-inhibiting effect of the combined AMPA/kainate receptor antagonists relies mainly on an antagonism at the kainate receptor. However, given that the NK-1 receptor antagonist lanepitant, which effectively blocks PPE, failed to show clinical efficacy in migraine treatment [85, 86], the value of PPE as a predictive marker for clinical efficacy in migraine has been dismissed.

Beyond its effect on PPE, the AMPA/kainate receptor antagonist LY293558 has been shown to inhibit *c-fos* expression

in the TCC elicited by electrical stimulation of the trigeminal ganglion [70]. Based on this observation, a randomized placebo-controlled trial was conducted in migraineurs which proved this compound to be effective in the acute treatment of migraine [71, 87] but, as described above, whether the relevant effect is mediated through AMPA or kainate receptors remains unclear. However, even if it remains to be clarified if AMPA or kainate receptors play the prominent role in these mechanisms, it seems likely that the responsible receptor is located within the CNS as antagonizing kainate receptors in the peripheral part of the trigeminal pain pathway does not affect vessel diameter after electrical [83] or CGRP-induced [88] stimulation. This is supported by the observation that the GluK1 receptor antagonist LY466195 inhibits nociceptive neuronal activity in the TCC, possibly at the postsynaptic GluK1 receptor [76]. In line with these results, topiramate, which is effective and widely used for the preventive treatment of migraine [89–91], acts at least partially on kainate receptors in the TCC and the ventroposteromedial nucleus (VPM) of the thalamus [92].

In summary, the results suggest that targeting kainate receptors may offer an effective strategy for the treatment of migraine. Further studies with kainate-selective agonists and antagonists are required to further elucidate the underlying mechanisms and confirm the clinical utility of kainate receptor antagonists in migraine.

## Metabotropic Glutamate Receptors as a Pharmacological Target in Migraine

The role of the mGluRs in migraine is largely unknown. In general, it is well established, that the mGluRs belonging to group I are predominantly pronociceptive as they are located postsynaptically and, if activated, increase excitability, while those belonging to groups II and III are located presynaptically reducing glutamate release thereby mainly creating an antinociceptive effect [2]. While, in the context of migraine, the functional relevance of mGluRs belonging to group I is beginning to be understood, the role of mGluRs belonging to groups II and III remains largely unknown.

### Group I mGluR

In relationship to migraine and trigeminal pain, mGluRs belonging to group I, in particular mGluR5, are the most investigated. The mGluR5 are located in trigeminal sensory afferents [93, 94], the trigeminal ganglion [95], and in the TCC [96–99]. From a functional perspective, the receptor has been shown to be involved in several types of pain including inflammatory and neuropathic pain [100, 101]. In this context beyond enhancing neuronal activation, the receptor is involved in creating neuronal sensitization causing allodynia

and hyperalgesia [100–102]. It may also interact with other receptor systems involved in the modulation of pain signals including opioid [47, 103] and TRPV1 [100, 101] channels and in this way even play a significant role in the chronification of pain. In the context of migraine, targeting these receptors in an *in vivo* rodent model with the negative allosteric modulator ADX10059 has revealed that the compound attenuates neurogenic dural vasodilation induced by electrical stimulation of the middle meningeal artery as well as stimulus-evoked and spontaneous central nociceptive transmission through the TCC [96] indicating an action at peripheral and central receptors. As these results suggested a therapeutic potential in migraine, a randomized controlled trial has been conducted which demonstrated clinical efficacy [96].

In contrast to the mGluR5, the mGluR1 is much less explored in the context of migraine. In the periphery, mGluR1 receptors are found in peripheral sensory afferents [93], the meningeal vasculature [94], and in the trigeminal ganglion [104]. Within the CNS, the receptor has been identified in the TCC as well as in the thalamus, hypothalamus, and in inhibitory structures belonging to the descending modulating network such as the periaqueductal gray [105]. As observed in mGluR5 receptors, stimulation of mGluR1 receptors on peripheral nociceptive trigeminal neurons induces a facilitation within the TCC [97]. In addition, the mGluR1 may be involved in the establishment of central sensitization [102]. These two observations demonstrate the functional influence of mGluR1 on central structures modulating and processing trigeminally mediated pain signals [97]. Interestingly, this connection may be influenced by estrogens [97]. In contrast to the mGluR5, the mGluR1 is much less expressed in the TCC compared to the other central areas, in particular, the thalamus [105]. Thalamic mGluR1 interact functionally with NMDA receptors creating synergistic effects enhancing neuronal activity [106]. This anatomical distribution and functional interaction suggests, that centrally located mGluR1s are particularly involved in the modulation of neuronal traffic in higher pain processing areas.

### Group II mGluR

The group II mGluRs comprise the mGluR2 and mGluR3 and have been identified in the meningeal vasculature [94], trigeminal ganglion [104], as well as in the TCC and the thalamus [98, 106–110]. Functionally, group II mGluRs are located presynaptically and reduce the release of glutamate upon activation. It is therefore assumed that this group exerts mainly antinociceptive effects [2]. In addition to its direct effect on glutamate release, the mGluRs belonging to group II interact and modulate gamma-aminobutyric acid (GABA) mediated inhibitory transmission in the thalamus causing a functional disinhibition [108–110].

Their role in migraine pathophysiology is largely unknown, in part owned to the lack of highly selective agonists and antagonists for their subtypes. However, their anatomical distribution suggests an involvement in the modulation of trigeminal nociceptive signals. Therefore, a potential relevance in the pathophysiology of migraine seems likely.

### Group III mGluR

The mGluRs belonging to group III comprise the mGluR4–6. Group III mGluRs have been identified in the meningeal vasculature and trigeminal ganglion as well as in the trigeminal complex (in particular in laminae I and II), thalamus, hypothalamus, and inhibitory structures including the periaqueductal gray [94, 104, 111–114]. This particular anatomical distribution suggests that group III mGluRs may play a role in migraine pathophysiology. As is the case in group II mGluRs, group III mGluRs are located mainly pre-synaptically, reducing the exocytotic release of glutamate and are therefore characterized by a predominantly antinociceptive effect [2]. However, as described for group II mGluRs, group III mGluRs may also induce a neuronal disinhibition in the thalamus as they modulate GABA-mediated inhibition. These findings highlight the complexity of the actions and interactions of some of the mGluRs in neuronal communication. Unfortunately, preclinical research in this area is still hampered by the lack of highly selective agonists and antagonists to each of the single receptor subtypes that would allow to further elucidate these complex mechanisms.

## Glutamate Receptor Modulators in the Treatment of Migraine

### Magnesium

As discussed above, magnesium is an activity-dependent blocker of NMDA receptors that has been shown to be involved in both pain transmission and cortical spreading depression. There is also human evidence that  $Mg^{2+}$  may play a role in migraine. Reduced  $Mg^{2+}$  levels have been reported in cerebrospinal fluid [115] serum [116] and saliva [116] during the ictal and interictal phases in migraine patients. An MR spectroscopy study also suggested  $Mg^{2+}$  concentration within the brain may be reduced in patients with migraine [117].

Oral magnesium is commonly used as a non-prescription preventive therapy in migraine, and both oral and intravenous migraine are used as acute therapies, although the evidence for these approaches is not strong [118, 119]. The use of magnesium is driven in large part by its reasonable tolerability. It is important to consider that magnesium has numerous effects on the nervous system apart from its effects on NMDA receptors, including inhibition of voltage-gated calcium channels,

connexin channels, and other ion channels. These other mechanisms could also be involved in any role that magnesium may play in migraine.

### Topiramate

Topiramate has been shown in large clinical trials to be effective in the prevention of both episodic and chronic migraine [120, 121]. It has been shown to inhibit cortical spreading depression and nitroglycerin-evoked hyperalgesia in animal models. Topiramate has multiple potential mechanisms of action as a therapeutic agent for epilepsy and migraine. One of these is the inhibition of iGluR receptors, specifically kainate receptors [122]. Other potential mechanisms of action of topiramate include inhibition of voltage-gated sodium and calcium channels, activation of GABA receptors, and inhibition of carbonic anhydrase [123, 124].

### Memantine

Memantine is an activity-dependent blocker of NMDA receptors that is approved for the treatment of Alzheimer's disease [125]. Memantine has also been reported to block other ligand-gated ion channels including the 5HT<sub>3</sub> receptor [126] and a subtype of the nicotinic acetylcholine receptor [127]. Memantine inhibits cortical spreading depolarization in animal models [50]. Two observational studies [128, 129] and one randomized, double-blind, placebo-controlled study [130] have reported efficacy of memantine as a migraine preventive therapy. It is not approved for migraine prevention. However, given its tolerability, possibly due to the fact that it is an activity-dependent blocker of NMDA receptors that could inhibit hyper-excitability without affecting normal function, it may be worth considering in migraine patients in whom standard therapies have been ineffective or poorly tolerated.

### Ketamine

Ketamine is a selective antagonist of the NMDA receptor, which is believed to be a primary mechanism of action. It has numerous other complex pharmacological actions, however, including effects on extracellular glutamate and dopamine and opioid receptors [131, 132]. It has been reported to inhibit cortical spreading depression [51]. Two case series have reported transient improvement in headache severity with infusion of ketamine, but neither reported statistically significant sustained improvement [133, 134]. Ketamine has also been reported to stop or reduce the severity of prolonged migraine aura in some patients [135, 136]. At this stage, there is insufficient evidence to endorse the use of ketamine for migraine, particularly because of the challenges associated with its administration and the potential for adverse effects.

## Summary

There is strong indirect evidence for a role for glutamate in migraine based on anatomical and physiological studies in animal models and genetic, biochemical, and imaging studies in humans. Thus far, however, there is no definitive pharmacological evidence that specifically targets glutamate or its receptors as an effective strategy for acute or preventive migraine therapy. This may be in part due to the lack of the appropriate pharmacological agents. In addition to different glutamate receptor modulators, treatments that target glutamate release or uptake, or endogenous modulators of glutamate signaling such as kynurenines may be more effective therapeutic strategies for migraine. Another factor may be that because of its crucial role in normal function of the nervous system, it may be difficult to therapeutically target glutamate or its receptors without causing unacceptable adverse effects. Future therapies may need to be refined to more specifically target abnormal migraine-related glutamatergic signaling without altering normal neurological function.

## Compliance with Ethical Standards

**Required Author Forms** Disclosure forms provided by the authors are available with the online version of this article.

**Disclosures** Jan Hoffmann has consulted for and/or serves on an advisory board of Allergan, Autonomic Technologies Inc., Chordate Medical AB, Novartis, and Teva. He received honoraria for speaking from Allergan, Chordate Medical AB, Novartis, and Teva. Andrew Charles has served as a consultant for Amgen, Alder, Biohaven, Eli Lilly, and eNeura. He has received grant funding from Takeda Pharmaceuticals.

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