Editorial

Glutamate and migraine: From Ikeda to the 21st century

Nabih M Ramadan

Introduction

The discovery of glutamate (Glu) is more than 100 years old, dating from when Ikeda isolated this natural amino acid from seaweed broth. Discoveries of neurotransmitter function, the role of Glu as a neurotransmitter, and Glu receptors and receptor types and functions followed over the subsequent century. To date, it is well established that Glu is the major neurotransmitter in the mammalian brain, and it participates in a myriad of functions in brain physiology and pathophysiology; migraine is no exception.

Glu receptors

Glu receptors are divided into two major types. The so-called ionotropic Glu receptors are ligand-gated channels that mediate fast receptor transmission and use-dependent plasticity by allowing nonselective exchange of monovalent (Na⁺ and K⁺) and sometimes divalent Ca²⁺ cations (GluA2(Q) or glutamine-edited AMPA receptor subunit-2) across neurons and glial cells (1). Known ionotropic Glu receptor subtypes are named after their agonists. They are: N-methyl-D-aspartate (NMDA) receptor family (GluN); α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) family (GluA); and 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine or kainate (KA) family (GluK). Both NMDA and non-NMDA ionotropic receptors exist in different subunits. Discussion of the structure, function, and pharmacology of the ionotropic receptor subunits is beyond the scope of this editorial and excellent reviews can be found in the literature (1).

The other type of Glu receptors are G-protein coupled receptor channels (GPCR) called metabotropic receptors and they modulate Glu release thereby modulating postsynaptic excitability (2). The metabotropic Glu receptors are grouped based on their messenger coupling, pharmacology, and sequence homology (Group I: mGlu1 and mGlu5; Group II: mGlu2 and mGlu3; Group III: mGlu4 and mGlu6-8).

Glu and migraine

The role of Glu in migraine can be traced back to the discovery that spreading cortical depression (SCD) can be induced by topical Glu in experimental animals (3) and the link between SCD and migraine (4,5). Other indirect evidence of glutamatergic involvement in migraine (Table 1) stems from clinical observations, physiologic experiments, localization studies, and preclinical models relevant to migraine mechanisms (6,7), and from genetic studies (8). Such experimental discoveries sparked worldwide interest in targeting Glu transmission in migraine therapeutics and the subject has been reviewed in several recent publications (6,7,9,10).

Clinical trials of Glu modulation in migraine

Uncontrolled and randomized controlled clinical trials (RCTs) using Glu receptor subtype modulators have been published in the last two decades. The results of an open-label study indicated that intranasal ketamine—an NMDA receptor antagonist—was effective in reducing the severity and duration of aura symptoms of migraine but ineffective on pain (11).

Prior to publication of the BGG492 study (current issue of Cephalalgia), data on three recent RCTs of selective Glu receptor modulators in the treatment of acute attacks of migraine were presented publicly (Table 2). The first RCT tested intravenous (IV) LY293558 (tezampanel)—a non-NMDA ionotropic receptor antagonist (12). Primary (response rate at

Department of Developmental Disabilities, Nebraska Department of Health and Human Services (DHHS), NE, USA

Corresponding author:
Nabih M Ramadan, Department of Developmental Disabilities, Nebraska Department of Health and Human Services, 3000 Lincoln St., Beatrice, NE 68310, USA.
Email: nabih.ramadan@nebraska.gov
two hours) and secondary efficacy measures (pain-free rate at two hours) significantly favored the study drug (69% and 54%, respectively; \( p < 0.05 \) vs placebo) and the active control 6 mg subcutaneous (SC) sumatriptan (86% and 60%, respectively) over placebo (25% and 6%, respectively). Central nervous system (CNS) adverse events of dizziness, sedation, and drowsiness were common among subjects who were treated with LY293558.

Ramadan et al. tested the efficacy and safety of LY466195—a GluK5 receptor sub-type selective antagonist—in treating acute attacks of migraine, using 1-mg and 3-mg IV doses; 6-mg SC sumatriptan was the active control (7). Dose selection was based on preclinical data, predicted tolerability from phase I studies of study drug, and clinical experience with LY293558. LY466195 did not demonstrate superiority over placebo for the primary efficacy measure at any dose. Response rates were 50% for 3 mg LY466195, 74% for SC sumatriptan, and 39% for placebo (\( p > 0.05 \) vs placebo). However, pain-free rates were statistically significantly higher for 3 mg LY466195 (29%) and sumatriptan (50%) as compared to placebo (0%). The major, clinically reversible, adverse effects of LY466195 were visual disturbances (21% at the highest dose).

Goadsby and Keywood studied the efficacy and safety of ADX10059, a negative allosteric modulator of mGlu5 receptor subtype, for the treatment of acute attacks of migraine (13). This RCT, proof-of-concept phase II study of 129 migraineurs (128 subjects in the intent-to-treat population) met its primary efficacy objective when it showed that pain-free rates were 16.1% with ADX10059 and 4.5% with placebo (\( p < 0.05 \)). Similar to LY466195, no significant advantage was observed for the two-hour response rate. Subjects who received ADX10059 reported adverse events more frequently than those who took placebo (73% vs 36%). Similar to LY293558, adverse events were more commonly related to the CNS in the ADX10059 (71%) vs the placebo group (14%). CNS adverse events on ADX10059 included dizziness (48%), vertigo (14%) and blurred vision (13%).

In this issue of *Cephalalgia*, Gomez-Mancilla et al. report on the results of a placebo-controlled RCT using BGG492, a GluA receptor selective (no appreciable affinity to GluK or GluN human or rat receptors) and GluA subunit nonselective antagonist, to treat acute attacks of migraine (14). One dose (250 mg) of oral BGG492 was used in the study, sumatriptan 100 mg was the positive control, and the trial was designed as a proof of concept with inclusion of both interim and final analyses of efficacy outcomes. In summary, the trial failed to meet its pre-stated efficacy objectives while demonstrating that BGG492 had significant CNS adverse events, similar to trials of the

### Table 1. Indirect evidence for glutamatergic role in migraine.

<table>
<thead>
<tr>
<th>Experimental setting</th>
<th>Example(s) of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiologic</td>
<td>Glu induces cortical spreading depression</td>
</tr>
<tr>
<td></td>
<td>Glu activates trigeminal neurons</td>
</tr>
<tr>
<td></td>
<td>Glu plays a key role in sensitization mechanisms</td>
</tr>
<tr>
<td>Localization</td>
<td>Abundance of Glu-positive neurons and glia cells in pain relay centers of the brain</td>
</tr>
<tr>
<td>Genetic</td>
<td>Polymorphism of genes encoding for GluA receptor subunits in people with migraine with aura</td>
</tr>
<tr>
<td>Preclinical models</td>
<td>Effectiveness of ionotropic and metabotropic Glu receptor modulators in preclinical models with relevance to migraine mechanisms</td>
</tr>
<tr>
<td>Clinical</td>
<td>Elevated extracellular (plasma, CSF) and intracellular (e.g. white blood cells, erythrocytes) Glu levels in migraineurs</td>
</tr>
</tbody>
</table>

Glu: glutamate; GluA: \( \alpha \)-amino-3-hydroxy-5-methyl-4-isozolepropionic acid (AMPA) glutamate receptor type; CSF: cerebrospinal fluid. See text for references.

### Table 2. Randomized controlled trials of glutamate receptor-specific experimental drugs in the treatment of acute migraine attacks.

<table>
<thead>
<tr>
<th>Study drug</th>
<th>Dose, route</th>
<th>Active control</th>
<th>Primary efficacy (Measure)</th>
<th>Common AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY293558</td>
<td>1.2 mg/kg IV</td>
<td>Sumatriptan</td>
<td>Demonstrated (two-hour response)</td>
<td>CNS</td>
</tr>
<tr>
<td>LY466195</td>
<td>1, 3 mg IV</td>
<td>Sumatriptan</td>
<td>Not demonstrated (two-hour response)</td>
<td>Visual</td>
</tr>
<tr>
<td>ADX10059</td>
<td>375 mg PO</td>
<td>None</td>
<td>Demonstrated (two-hour pain free)</td>
<td>CNS</td>
</tr>
</tbody>
</table>

IV: intravenous; PO: oral; AE: adverse event; CNS: central nervous system. See text for references.
other Glu receptor selective modulators mentioned earlier. Notwithstanding, several points are worth highlighting: They are:

1. The mean duration between onset of symptoms and study drug administration was approximately three hours across all treatment arms, which raises concerns about oral absorption of drugs.
2. A numerically higher number of subjects who received the experimental drug had severe headache and nausea at time of treatment. In addition, pharmacokinetic (PK) and pharmacodynamic (PD) analyses indicated a large intersubject variance (as estimated by the percentage coefficient of variance (% CV)) in BGG492 plasma level concentrations and no PK-PD relationship between levels and measures and efficacy; this was not the case for sumatriptan. Theoretically and clinically, these results may have impacted the efficacy outcomes.
3. The predefined interim analysis rule was set for 15 evaluable subjects in each treatment arm. It is puzzling to note that the interim analyses included 16 subjects who received BGG492 and 23 of the 25 subjects who took placebo and completed the study.
4. CNS adverse events (dizziness, vertigo, gait disturbance) were more common in the experimental study drug arm of the study than in the other two groups. Also, two subjects who received BGG492 experienced serious adverse events, albeit reversible, requiring hospitalization. These differences in adverse event profiles between study groups could have impacted study blinding. Interestingly, however, the relatively low rates of adverse events in the placebo group compared to subjects who were treated with BGG492 would have been expected to lower the placebo response, which was not the case.
5. The use of an active comparator (sumatriptan in the current study) in early clinical trials is important to evaluate the so-called assay sensitivity. It can be argued from the study results that sumatriptan truly did not separate from placebo at the predefined primary efficacy endpoint as the p value 0.0502 or >0.05.

Where do we go from here?

Whether in the next few years, decade or century, we should not doubt that advances in migraine therapeutics will continue. Refinements in clinical trials methodology, multiple shots on targeted migraine mechanisms, including the glutamatergic system, and pharmaco-genomic discoveries, to name only a few, likely will yield better therapy for the millions of migraine sufferers worldwide. Specifically, modulating the Glu receptor family with improved therapeutic index and testing Glu receptor modulators in migraine prevention warrant further exploration. To this end, both topiramate and botulinum toxin, two therapies with proven efficacy in migraine prevention and relatively good therapeutic indices, modulate central glutamatergic tone (15,16). Therefore, it is suggested, conceptually at least and indirectly from preclinical experiments, that modulators of Glu receptors can prove more beneficial in migraine prevention than in the treatment of acute attacks. Indeed, a phase II trial of ADX10059 in migraine prevention was initiated but the study was terminated because of concerns with liver damage. More should be coming! Only time, concerted research efforts, and perhaps good luck will prove or disprove this hypothesis.

Conflict of interest

None declared.

References

6. Ramadan NM. The link between glutamate and migraine. CNS Spectr 2003; 8: 446–449.
12. Sang CN, Ramadan NM, Wallihan RG, et al. LY293558, a novel AMPA/GluR5 antagonist, is efficacious and


