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Review article

Genetic insights into migraine and glutamate: a protagonist driving the headache

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ABSTRACT

Migraine is a complex polygenic disorder that continues to be a great source of morbidity in the developed world with a prevalence of 12% in the Caucasian population. Genetic and pharmacological studies have implicated the glutamate pathway in migraine pathophysiology. Glutamate profoundly impacts brain circuits that regulate core symptom domains in a range of neuropsychiatric conditions and thus remains a "hot" target for drug discovery. Glutamate has been implicated in cortical spreading depression (CSD), the phenomenon responsible for migraine with aura and in animal models carrying FHM mutations. Genotyping case-control studies have shown an association between glutamate receptor genes, namely, GRIA1 and GRIA3 with migraine with indirect supporting evidence from GWAS. New evidence localizes *PRRT2* at glutamatergic synapses and shows it affects glutamate signalling and glutamate receptor activity *via* interactions with GRIA1. Glutamate-system defects have also been recently implicated in a novel FHM2 ATP1A2 disease-mutation mouse model. Adding to the growing evidence neurophysiological findings support a role for glutamate in cortical excitability. In addition to the existence of multiple genes to choreograph the functions of fast-signalling glutamatergic neurons, glutamate receptor diversity and regulation is further increased by the post-translational mechanisms of RNA editing and miRNAs. Ongoing genetic studies, GWAS and meta-analysis implicate neurogenic mechanisms in migraine pathology and the first genome-wide associated locus for migraine on chromosome X. Finally, in addition to glutamate modulating therapies, the kynurenine pathway has emerged as a candidate for involvement in migraine pathophysiology. In this review we discuss recent genetic evidence and glutamate modulating therapies that bear on the hypothesis that a glutamatergic mechanism may be involved in migraine susceptibility.

Contents

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1. Glutamatergic mechanisms in migraine

There has been ongoing interest in the involvement of glutamate in migraine pathophysiology. Biochemical studies of migraine patients have shown significant differences of glutamate in a range of biological fluids relative to controls, particularly in migraineurs with aura [1–3]. Evidence for this idea, the 'glutamate hypothesis', was discussed by Ramadan [4] and more recently Gasparini [5]. The glutamate hypothesis of migraine is centered on the subset of pathologic mechanisms linked to glutamatergic signalling and is based on genetic, biochemical and clinical findings pointing to a hypofunction of glutamatergic signalling [6]. Glutamate is a ubiquitous neuro-messenger that can be likened to a 'handle with care explosive' stored in intracellular vesicles at high concentration (10 mM) and is a key player in numerous metabolic pathways [7].

Glutamate is toxic to neurons in the brain can kill them when it persists in and around synapses, and is also able to initiate migraine by cortical spreading depression (CSD) the lynchpin of migraine aura [8–10]. CSD has been studied experimentally and waves of CSD promoted by a wide range of stimuli including local mechanical stimulation, local injury, high frequency electrical pulses, potassium chloride, potassium ions, hypo-osmotic medium, metabolic inhibitors, ouabain, glutamate receptor agonists, glutamate, acetylcholine and endothelin [11,12]. These noxious stimuli perturb the neuronal environment leading to glutamate-induced excitotoxicity. During CSD, glutamate contributes to a loss of membrane potential and disruption of ionic gradients (Ca^{2+}, Na^{+}, K^{+}) [13,14]. Ca^{2+} and Na^{+} channels, as well as glutamatergic and/or GABAergic transmissions are active in CSD and targeted by antiepileptic drugs [9]. *N*-methyl-D-aspartate (NMDA) receptors, which are activated by glutamate, play an essential role in CSD mechanisms and antagonists of NMDA receptors have been shown to reduce CSD [15,16].

Poor glutamate processing results in a build-up of extracellular glutamate which is toxic to neurons [17]. Overstimulation of glutamate receptors triggers a flood of Ca^{2+} into cells which leads to uncontrolled continuous depolarization of neurons, a toxic process termed excitotoxicity first introduced by Olney [18]. Unregulated Ca^{2+} influx in turn activates a destructive cascade of events that triggers a number of enzymes, including phospholipases, endonucleases, and proteases such as calpain which destroy cell structures and components of the cytoskeleton, membrane, and DNA leading to the demise of the cells [19]. This situation can occur when not enough glutamate transporters are present to clean up the extracellular spaces or transporters are sluggish because of CNS injury or genetic defects that decrease the functionality of glutamate transporters. Alterations in the expression, distribution, synaptic levels, recycling and autoregulation of glutamate receptors and transporters can result in altered glutamatergic function [20].

2. Glutamate genetic evidence

Glutamate action is governed by a number of genes involved in its reception; transport and synthesis (see Table 1). Interest in the role of glutamate in migraine at the molecular genetic level was instigated by Formicola et al., in 2010 who reported an allelic association between intronic variants of the GRIA1 and GRIA3 AMPA receptor gene subunits and migraine with aura [21]. Since this initial study a handful of subsequent studies have examined the relationship between glutamatergic dysfunction and migraine. Notably, a replication study by Maher et al. [22] identified association in 1 of 3 *GRIA3* polymorphisms (rs3761555) and none of the *GRIA1* variants tested in the Formicola et al. study [21]. The positive association was observed in the *GRIA3* promoter polymorphism (rs3761555) [22] in an Australian case-control cohort of 500 migraineurs, this is double the size of the Italian population (250 migraineurs) used in the study by Formicola [21]. The *GRIA3* SNP is in a promoter binding site and the T allele, which was over-represented in the Australian case cohort, reduces the promoter activity and therefore affects the expression of the gene [22]. In addition a positive association between the X-linked gene, *GRIA3* (rs1034428, A allele) and schizophrenia was reported in female patients [23]. These results are supported by studies by Ibrahim et al., [24] and by Meador-Woodruff et al. [25] reporting decreased expression levels of the AMPA receptor.

Two studies, one by Gasparini et al. [26] and a study by Cargnin et al. [27] genotyped polymorphisms in the *GRIA2* and *GRIA4* genes in an Australian case-control cohort and in the *GRIA1* gene in an Italian case-control cohort, respectively. Although both these studies indicated that GRIA genotypes and haplotypes did not influence migraine susceptibility, a recent study by Fang et al. [28] detected an association of GRIA1 (rs2195450) to female migraine (MA, MO) susceptibility in the Chinese Han population. Investigation into other glutamate related genes have also shown connections with migraine. The activity of the enzyme

Table 1
Gene and protein constituents of the glutamatergic system adapted from [53].

Gene name	Protein - enzymes
PDP1	PDH, pyruvate dehydrogenase
GLS2	PAG, phosphate activated glutaminase
ME3	mME, mitochondrial malic enzyme
GAD1	GAD, glutamic acid decarboxylase
GLUL	GS, glutamine synthetase
PC	PC, pyruvate carboxylase
ME1	cME, cytosolic malic enzyme
GOT1	AAT, aspartate aminotransferase
GLUD1	GDH, glutamate dehydrogenase

Gene name	Protein - ionotropic glutamate receptors (iGluRs)	Antagonists
GRIA1	AMPA	BGG492
GRIA2	AMPA	LY293558 AMPA/kainate
GRIA3	AMPA	
GRIA4	AMPA	
GRIK1	Kainate	LY466195
GRIK2	Kainate	
GRIK3	Kainate	
GRIK4	Kainate	
GRIK5	Kainate	
GRIN1	NMDA	Memantine
GRIN2A	NMDA	Ketamine
GRIN2B	NMDA	Topiramate AMPA/kainate
GRIN2C	NMDA	
GRIN2D	NMDA	
GRIN3A	NMDA	
GRIN3B	NMDA	
GRID1	Orphan	
GRID2	Orphan	

Gene name	Protein - metabotropic glutamate receptors (mGluRs)	Antagonists
GRM1	mGluR1	
GRM2	mGluR2	
GRM3	mGluR3	
GRM4	mGluR4	
GRM5	mGluR5	ADX10059
GRM6	mGluR6	
GRM7	mGluR7	
GRM8	mGluR8	

Gene name	Protein - transporter type	Antagonists
SLC1A3	EAAT1	
SLC1A2	EAAT2	
SLC1A1	EAAT3	
SLC1A6	EAAT4	
SLC1A7	EAAT5	
SCL17A7	VGLUT1	Botulinum toxin type A
SCL17A6	VGLUT2	Lamotrigine
SCL17A8	VGLUT3	

Note: Some enzymes are composed from individual subunits that assemble to form larger multimeric complexes and therefore the same enzyme name will appear to have multiple chromosomal locations in the databases.