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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.

glutamate oxaloacetate transaminase (GOT) was shown to be reduced in blood in a case-control study of 45 episodic migraine patients and 16 control subjects [20]. Recently mutations in glutamate receptor genes have also been reported for their involvement in the aetiology of epilepsy, intellectual disability and mental retardation [29–33]. In addition to the genetic evidence, biochemical studies add credence to a glutamatergic mechanism for migraine reviewed in Gasparini et al. [5].

Imbalance in glutamate regulation including glutamate release and clearance, has also been postulated in the pathogenesis of familial hemiplegic migraine (FHM), whereby mutations in causal ion channel genes *CACNA1A*, *ATP1A2* or *SCN1A* are linked to neuronal excitability and have been correlated with increased glutamate [34–38]. In the last few years the PRRT2 gene (proline rich transmembrane protein 2) has attracted attention due to reports of heterozygous mutations in the PRRT2 gene identified in patients diagnosed with hemiplegic migraine and other forms of migraine [39–42]. *PRRT2* is also a candidate gene for epilepsy, contributing to a broad range of seizure subtypes [43]. *PRRT2* encodes a protein distributed in brain and spinal cord that is predicted to regulate presynaptic release of neurotransmitters in a calcium-triggered process that also requires synaptosomal associated protein 25 (SNAP-25) [44,45]. Heron et al., pointed out that perturbation of this process due to mutations in the *PRRT2* gene is likely to be the cause of seizure and movement disorder phenotypes including paroxysmal kinesigenic dyskinesia (PKD), benign familial infantile epilepsy (BFIE), infantile convulsions and choreoathetosis (ICCA) and hemiplegic migraine (HM) [46]. PRRT2 has thus been dubbed "a gene with remarkable pleiotropy" due to its involvement in a spectrum of paroxysmal neurological disorders.

Interestingly, a recent study by Li et al., demonstrated that PRRT2 is located at glutamatergic synapses by double immunostaining neurons of mouse cortex with a pre-synaptic marker (vGlut1) and a post-synaptic marker (PSD-95) of glutamatergic neurons [47]. Greater levels of PRRT2 expression were demonstrated in this study in the mouse cerebral cortex, hippocampus and cerebellum [48]. They also showed that wild type PRRT2 remains anchored in the membrane whilst mutated PRRT2 detaches and disperses in the cytoplasm of COS-7 cells. The authors confirmed interactions between PRRT2 and SNAP-25 as previously demonstrated and that these are disturbed by the presence of mutations in PRRT2 [47,49]. The SNAP-25 protein participates in the regulation of synaptic-vesicle exocytosis and association studies have suggested that some SNAP-25 gene polymorphisms may be implicated in psychiatric diseases including schizophrenia and attention deficit hyperactivity disorder [50,51]. Most importantly, the authors demonstrated protein-protein interactions between mouse PRRT2 and GRIA1 both *in vitro* and *in vivo* and that these were weakened in the presence of mutant PRRT2. GRIA1 is 1 of 4 subunits that assemble to form the ligand-gated AMPA receptor which is integral to fast excitatory transmission and common variants in the *GRIA1* gene have previously been associated with migraine patients with and without aura [21,52]. PRRT2 knock down gene expression with shRNA-PRRT2 lentivirus resulted in increased glutamate levels in neural cell culture. This was the first study to verify that PRRT2 can affect glutamate signalling and glutamate receptor activity and that this event may be connected with neuronal hyperexcitability [47].

3. Novel FHM2 ATP1A2 disease-mutation mouse model

Perturbed glutamate neurotransmission is demonstrated in a myriad of psychiatric diseases including schizophrenia, Parkinson's disease, Alzheimer's disease, epilepsy and diseases of addiction [54,55]. Models are needed to characterize and explore the key molecular events at the core of the neurobiological base of neuropsychiatric disorders. Animal models are useful for two main reasons: one is to study the pathophysiology and progression of a disease and second to identify and validate drug targets and for developing and testing new drugs for use in human patients [56]. Models of glutamate involve studying glutamatergic signalling and up until now, have focused on glutamate excitotoxicity induced by acute exposure of neurons, either *in vitro* or *in vivo*, to sudden large excesses of extracellular glutamate [17]. Cell model systems have been used to study glutamate excitotoxicity and in particular the end result of activating intracellular signalling cascades initiated by the excitotoxic insult [57]. In addition, cloning of the receptors has enabled the expression of proteins in expression systems, *Xenopus* oocytes or in mammalian cell lines for biochemical characterization, structure analyses, subunit composition and electrophysiological studies [57]. Pharmacological models of the single receptors can help derive knowledge of structure-function relationships and of glutamate function, kinetics of response, different doses, downstream signalling [58,59]. In recent times, X-ray crystal structures of glutamate receptors have helped define structure-function relationships based upon co-crystals of the ligand-binding for a myriad glutamate receptors as well as with positive allosteric modulators [57,60–62]. These studies have provided insight into the mechanism of action of glutamate receptor antagonists and the molecular interactions between receptor and modulator. Finally, animal localization studies have also identified NMDA, AMPA, Ka receptors in the trigeminal system [63,64].

Recently Bøttger et al. described a completely novel familial hemiplegic migraine (FHM), FHM2 disease-mutation mouse that exhibits glutamate-system defects and psychiatric manifestations, mood depression and obsessive-compulsive disorder (OCD) [65]. FHM2 (FHM2; MIM602481) is a rare form of migraine with hemiplegia and partial paralysis during the aura phase and, in some cases, accompanied by seizures or cognitive dysfunction [35]. Familial hemiplegic migraine (FHM) is a disorder that lends itself more easily to functional analysis in animal models due to well characterized mutations in large effect genes. FHM2 is caused by mutations in the *ATP1A2* gene. The ATP1A2 gene encodes the α2 isoform of the major subunit of the Na^+/K^+-ATPase pump and is located at 1q21–23 [35]. The product of the ATP1A2 gene is a sodium-potassium pump ($\alpha 2Na^+/K^+$-ATPase) that aids in establishing and maintaining the electrochemical gradients of Na^+ and K^+ ions across the plasma membrane of astrocytes. Mutations in the *ATP1A2* gene were first identified in two Italian families in 2003 and account for approximately 20% of FHM in families [66,67].

Most recently in the Lykke-Hartmann lab, Bøttger et al., introduced the FHM2-associated G301R-mutation in knock-in mice [65]. This new knock-in mouse builds upon previous work, including two separate groups, the Lingrel lab [68] and Kawakami lab [69] who created FHM2 knock-outs through disruption of the ATP1A2 gene at two different locations, exon 4 and exon 21 respectively. Conversely the Casari lab generated the first FHM2 knock-in mouse by inserting the T2763C mutation, which causes the amino acid substitution W887R in exon 19 of the gene [70]. In cell-based studies, a complete loss of pump function is observed due to misfolding of the protein in the β subunit binding site [71]. The Lykke-Hartmann lab is the second group to create an FHM2 knock-in mouse [65]. Mice heterozygous for the FHM2-associated G301R-mutation show impaired glutamate uptake in *in vitro* hippocampal-derived matured mixed cultures of astrocytes and neurons established from embryos (E17) compared to WT mice. Following a series of behavioural tests the mice were found to suffer stress-induced depression and reduced sociability. The observed behavioural phenotypes are thought to be linked to ineffective handling of glutamate in the synaptic cleft and seem to be more pronounced in female mice $\alpha^{2+/G301R}$ due to an interplay with the female sex hormone cycle.

In addition pharmacological treatment of mice with NMDA receptor antagonists, amantadine and memantine, which act to decrease NMDA receptor signalling, was found to rescue marble burying behaviour. Marble burying is typically used as a measure of compulsive behaviour of OCD, and in this instance amantadine and memantine counteracted the glutamate-system defects induced by the presence of the mutation in the ATP1A2 [65]. Electrophysiological recordings demonstrated prolonged recovery phase after induction of CSD in males due to compromise and impairment of Na^+/K^+-ATPase pump activity. This is in

line with other FHM mutations where the phenomenon CSD has been studied and glutamate has been implicated [72]. FHM gene mutations play a role in synaptic transmission and brain excitability by affecting the neuronal current and facilitating CSD ignition in FHM [38,73,74]. Deregulated handling of glutamate is hypothesized to play a role in facilitating CSD due to increased probability of glutamate release as shown in FHM1 R192Q, S218L knock-in mice [37,72]. Recently new evidence from a transgenic mouse model of migraine, reveals that CSD in addition to initiating a series of neural and vascular events can also modulate inflammatory processes [75]. In the cortex of FHM1 R192Q mutant brains, specific genes in interferon-mediated inflammatory signalling were shown to be up-regulated in response to CSD [75]. Altogether these results are novel and add to our current understanding of FHM and migraine and co-morbid psychiatric manifestations.

In the future with the advent of the genome-editing toolbox, using transcription activator-like effector nucleases (TALEN) or clustered regularly interspaced short palindromic repeats that rely on RNA-guided DNA endonuclease Cas9 (CRISP/Cas9) in mammalian cells will surely be exploited for functional studies based on GWAS findings to generate cellular and animal models in a more efficient manner. Innovative methods such as non-viral (siRNA) or viral (shRNA) delivery techniques may enable more subtle genetic manipulations. These methods can achieve more sensitive down-regulation or completely silencing genes in more subtle ways than by complete knock-down. These can be useful to study time dependent gene expression and can be engineered in all cells of the body or in a tissue specific manner and may be manipulated to alter their activity in response to specific stimuli.

4. Neurophysiological evidence

The aim of neurophysiology studies was originally to aid in diagnosis and then characterization of cortical excitability in the migraine brain in the search for biomarkers [76]. Cortical excitability refers to the reactivity of the brain to diverse exogenous and endogenous stimuli and is measured as the "global output of cortical neurons to external stimuli" [77,78]. Neurophysiological interactions are typically assessed by techniques that measure the excitability of the brain and include evoked potentials (EPs) techniques and non-invasive brain stimulation methods such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) [79]. Most studies support changes in cortical excitability throughout the migraine cycle and that migraineurs display an impairment of habituation to repeated sensorial stimulation which may represent a neurophysiological marker of migraine [77,80–82]. Deficit of habituation seems to be the most consistent response found in migraineurs for many stimulation modalities: visual, auditory and somatosensory [83]. Habituation is a behaviour that refers to the inability of migraine patients to habituate or adapt to repeated sensory stimulation [84]. The goal of studies measuring visual evoked potentials (VEPs) in migraine is to determine if specific alterations in visual function may be present. Many of these studies have reported that different subgroups of migraineurs, in particular those with migraine with aura, have distinct visual evoked potential profiles and a lack of habituation [85–90]. Recently a study assessed differences of pattern-reversal visual evoked potential parameters and migraine in a teenage migraine with aura and without aura cohort [91]. In this cohort, migraine with aura patients had longer N2 wave latencies relative to migraine without aura patients and healthy controls. Results have not always been consistent and a clear consensus regarding habituation, which was considered to be a neurophysiological hallmark of migraine, is lacking. This has been attributed to sources of methodological heterogeneity that prevent exact conclusions to be drawn. In addition, migraine is a multifaceted and cycling disease and the type of migraine studied and the stage of illness can also have a bearing on the results obtained.

The level of neuronal excitability (excited or inhibited) is determined by multiple neurotransmitter systems including glutamate-dopamine-serotonin which converge in their signalling circuits and cellular receptors [92]. The trio of primary neurotransmitters including serotonin, dopamine, and glutamate affect each other in complex ways, overlapping in their neurotransmitter circuits and hyperactive glutamate neurotransmission may account for the dysfunctions observed in migraine (see Fig. 1). Glutamate and its actions on *N*-methyl-D-aspartate (NMDA), and non-NMDA receptors facilitate excitation [93]. Certain groups support glutamatergic dysfunction as the culprit of cortical excitability [81,94,95]. In summary, neurophysiological studies have shown evidence of cortical dysfunction and a deficit of habituation to repeated stimuli that fluctuates with the migraine cycle. Moreover, a disequilibrium between intracortical inhibitory and excitatory neuronal circuits [96] is present in the migraine brain and neurophysiological testing may help reveal additional clues to understand brain dysexcitability. Inconsistencies in results, however, still leave some questions in this area to be answered. Future studies will need to replicate one another and arrive at standardised methodologies in order to further our neurophysical understanding of migraine.

Genetic, biochemical and pharmacological studies support the involvement of the neurotransmitters serotonin, dopamine and glutamate in migraine aetiology. Genetic studies have focused on the receptors, transporters and enzymes involved in the synthesis and metabolism of neurotransmitters. Genetic variation in the gene constituents of neurotransmitter systems may cause dysfunctional signalling and neurotransmission leading to an imbalance in the way the neurotransmitter is handled at the synapse *i.e.*, released and recycled and may lead to a higher susceptibility to migraine. The hypothesis is based on the idea that disturbances in circulating levels of neurotransmitters or in the function of the receptors, transporters and enzymes that synthesise and metabolise the neurotransmitters due to an aberrant combination of genes may express the biochemical phenotype of migraine.

5. RNA editing of AMPA glutamate receptors

In addition to the existence of multiple genes to choreograph the functions of fast-signalling glutamatergic neurons, glutamate receptor diversity is further increased by the post-translational mechanisms of alternative splicing and RNA editing [98]. Adenosine-to-Inosine (A-to-I) RNA editing of the GRIA2 subunit of glutamate AMPA receptors at the coding region glutamine/arginine (Q/R607) site (in the pore forming second transmembrane (M2) domain) epitomizes genetic regulation of glutamate receptors [99]. The Q/R site of the GRIA2 subunit undergoes extensive (>99.9%) editing and this editing is important for gating Ca^{2+} entry through the AMPA receptor channels [100,101]. In a healthy state, effective RNA editing at the Q/R site results in the production of GRIA2-(R) (arginine amino acid) whilst in a diseased state, defective RNA editing at the Q/R site results in the production of GRIA2-(Q) (glutamine amino acid) [102]. Inefficient editing of the GRIA2 subunit results in AMPA glutamate receptor channels that are permeable to Ca^{2+} [103], resulting in cell death due to flooding with Ca^{2+} and this event has been linked to the disease amyotrophic lateral sclerosis (ALS) [104,105]. Targeted RNA editing also controls the heteromeric assembly of the AMPA receptors by holding the GRIA2 subunits in the endoplasmic reticulum and delaying transport to the synaptic surface [106]. Consequently RNA editing at this site is an essential mechanism that indirectly contributes to the effective functioning of glutamatergic neurotransmission. RNA editing is an enzymatic process that is carried out by two enzymes of the adenosine deaminase family *ADARB1* and *ADARB2* that mostly target neurotransmitter receptors and ion channels [102,107]. These two genes have also been investigated as plausible candidates in migraine [108] because they are most prevalent in the central nervous system and fit criteria for migraine neuropathology [109]. Further illustrating the importance of these two RNA-editing enzymes ADARB1 knockout mice die approximately 20 days post-birth and manifest epileptic seizures [99] whilst ADARB2 knockout mice die embryonically, exhibit a high interferon signature,

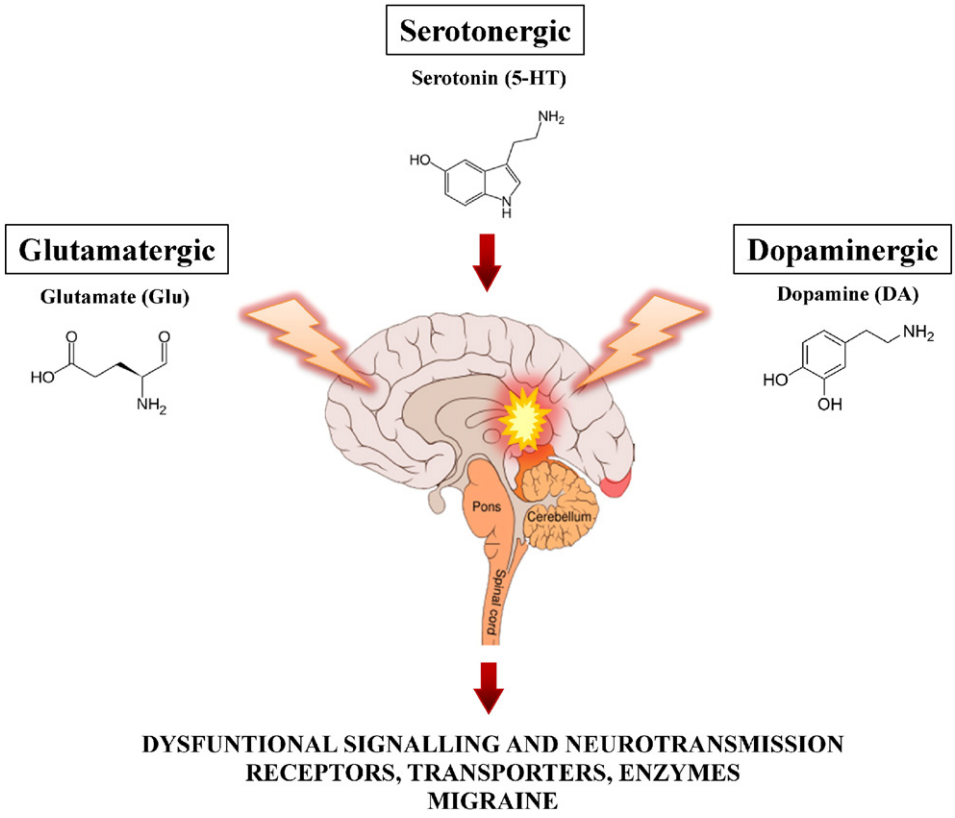

Fig. 1. Neurotransmitter systems implicated in migraine adapted from [97].

increased apoptosis and hematopoietic defects [110–112]. Additionally a few studies suggest a role for ADARB1 in the pathophysiology of mental disorders [113,114].

6. miRNAs and implications for migraine

Introducing another dimension to current migraine research is modification of gene expression *via* microRNAs (miRNAs). miRNAs are small non-coding RNA molecules (19–24 nucleotides) encoded in our genome that modulate gene expression by actively targeting mRNAs post-transcriptionally [115]. miRNAs interact with mRNAs by complementary binding by different mechanisms to inhibit their translation and expression of the encoded genetic information [116]. They act like silencing tags that regulate genome activity and protein levels and thus fine tune numerous modalities of the cell including differentiation, proliferation, apoptosis in symphony with other gene regulatory processes [117].

The extent to which miRNAs are involved in brain development and in the aetiology of neuro-psycho and degenerative disorders remains to be quantified. miRNA expression has been studied in a variety of neurological disorders including Alzheimer's, Parkinson's, and Huntington's diseases, amyotrophic lateral sclerosis epilepsy [118–120], schizophrenia, autism, cognitive dysfunction and drug addiction [121]. Recently miRNAs have been implicated in bipolar disorder [122,123] and it is not unlikely that these regulatory RNAs might have some usefulness in migraine diagnosis as well. miRNA are important regulators of gene expression with important functions, yet to be understood, in brain development and in regulating many aspects of neuronal morphology, such as neurite outgrowth and synapse formation [124]. miRNAs display a brain-specific expression pattern and the majority of proteins are regulated by miRNAs [125,126].

A point in case is miRNA regulation of the main CNS glutamate transporter EAAT2/GLT1 of the glutamatergic system. In 2013, Morel et al., demonstrated that exogenously delivered miR-124a can up-regulate EAAT2 (excitatory amino acid transporter 2) protein expression both *in vitro* and *in vivo* [127]. This is an interesting finding with potential to be turned into a therapy to regulate EAAT2 activity in disease states and in addition reveals a novel regulatory mechanism. In a study by Harraz et al., miR-223 was reported to regulate the expression of AMPAR subunit GluR2 and NMDAR subunit NR2B 3-UTR [128]. miR-223 deficiency increases expression of GluR2 and NR2B and consequently miR-223 is a key regulator of glutamate receptor expression and function. There are other examples whereby miRNAs have been shown to regulate NMDA receptors in schizophrenia and other conditions but it is beyond the scope of this review [129,130].

Thus far two studies have directly explored the nexus between miRNAs and migraine. Andersen et al., profiled microRNAs using serum from migraine sufferers during attack periods and pain-free periods, comparing these to healthy control subjects [131]. This study identified four microRNAs to be differentially expressed out of 372 (miR-34a-5p, miR-29c-5p, miR-382-5p and miR-26b-3p) and these were selected for further investigation [131]. Expression of these miRNAs was significantly altered between migraineurs and healthy controls in two independent validation cohorts ($n = 16$ and $n = 24$). The authors could not account for the structures/tissues from which the miRNAs originate, however *in silico* target predictions suggested the miRNAs may target components of GABAergic and anti-inflammatory signalling pathways. The second study by Tafuri et al. [132] in contrast, screened 175 miRNAs most commonly detected in plasma exosomes and analysed the expression of miRNAs in the blood of 15 MO patients and matching controls by qRT-PCR. In this study four miRNAs were differentially expressed: miR-27b was significantly up-regulated, while miR-181a, let-7b, and miR-22 were significantly down-regulated. The miRNAs reported in this study appear to have some connection with cardiovascular disease and may provide a circulating exosome miRNA profile specific to MO patients.

The significance and relevance of this layer of genetic regulation on the occurrence of migraine remains to be discerned. Currently there is

insufficient data to correlate a definite relationship between miRNAs and migraine. From the evidence of involvement of miRNAs in other diseases co-morbid with migraine like epilepsy, however, it is clear these regulatory molecules may hold potential to be used as migraine biomarkers. Although miRNA research is still in its infancy the field is blossoming with an increase in the number of biomarker studies investigating the potential use of miRNAs as a diagnostic tool in different biological fluids for different neurological disorders [133]. This is due to the fact that miRNAs are found in all body tissues and fluids such as plasma, serum, urine, saliva, milk and CSF and different organs express different miRNAs, allowing specific profiles to be obtained [134,135].

7. GWAS

Additional associations in SNPs located in genes that act to regulate glutamate turn over have been uncovered in Genome Wide Association Studies (GWAS). Comprehensive GWAS studies have been instrumental in revealing a number of interesting and novel potential candidate loci without *a priori* assumptions that implicate glutamate in migraine aetiology [136–138]. The main hit from the first migraine GWAS was an intergenic SNP (rs1835740) at locus 8q22.1 identified in migraineurs from three European headache clinics that is in linkage disequilibrium (LD) with two candidate genes: plasma glutamate carboxypeptidase (*PGCP*) and; the astrocyte elevated gene 1 (*MTDH/AEG-1*) [136]. The enzymatic function of the PGCP gene is to cleave *N*-acetyl-L-aspartyl-L-glutamate into *N*-acetyl aspartate (NAA) and glutamate and *via* this function *PGCP* may contribute to a rise in extracellular glutamate concentrations [139]. Meta-analysis of GWAS results by Ligthart et al., replicated the association with the MTDH/AEG-1 gene [138]. In cultured lymphoblastoid cell lines the risk allele A of SNP rs1835740 was found to correlate with the transcript levels of *MTDH/AEG-1*. Furthermore, experiments in cultured astrocytes documented an inverse correlation between expression levels of *MTDH/AEG-1* and *EAAT2* [140–142]. *MTDH/AEG-1* can decrease the expression of the glutamate transporter *EAAT2* (also called GLT1 and SLC1A2) in neurons and this fault is thought to lead to excess glutamate in the synapse which could potentiate migraine by making cells more susceptible to glutamate excitotoxicity [143,144].

More recently, a study by Lee et al. [145] provided evidence of the ability of MTDH/AEG-1 to downregulate the expression of EAAT2 in the setting of glioma-induced neurodegeneration. The proposed pathological mechanism is that too much glutamate in the synaptic cleft due to an increase in PGCP activity or MTDH/AEG-1 or both may contribute to migraine attacks. EAAT2 is the major transporter of glutamate in neurons whose importance to neural biology is further exemplified in knockout mice. The lack of functional EAAT2 produces a fatal phenotype leading to progressive neurodegeneration and spontaneous epileptic seizures [146–148]. Glutamate transporters serve critical physiological functions such as terminating fast synaptic neurotransmission and as such they are subject to tight spatio-temporal expression and regulation [149]. In addition mutations in the related EAAT1 transporter have shown up in other episodic disorders such as episodic ataxia 6 [150,151], and a non-familial hemiplegic migraine type 1 or 2 (FHM1/2) hemiplegic migraine/episodic ataxia/seizure phenotype [152].

In a GWAS by Chasman et al., the three most significant GWAS hits that reached genome-wide significance and withstood replication in three replication data sets were rs2651899 in *PRDM16*, rs10166942 in *TRPM8* and rs11172113 in *LRP1* [137]. The proteins produced by *PRDM16* (PR domain containing 6), *TRPM8* (transient receptor potential melastatin 8) and *LRP1* (low density lipoprotein receptor 1) indirectly affect glutamate turnover. The product of the *PRDM16* gene is involved with the development of brown fat but its function and relation to migraine aetiology remains to be established [153]. *TRPM8* is an ion channel related to neuropathic pain but its complete range of functions is not fully understood [154]. The *LRP1* protein has been found to interact with *N*-methyl-D-aspartate (NMDA) receptors, suggesting a more direct role in the glutamate pathway providing support for a glutamatergic mechanism in migraine [137,155]. Two of the loci, rs10166942 in the *TRPM8* gene and rs11172113 in the LRP1 gene identified in the Chasman study were confirmed in German and Dutch individuals as being involved with the MO phenotype [156]. Meta-analysis of clinic-based Danish and Icelandic migraineurs identified a similar association [157].

Recently, replication studies in Spanish, Swedish, Chinese and Indian populations independently replicated some of the top-ranking SNPs from GWAS data [158–161]. Replicating GWAS hits is important as the risk imparted by the variants may vary and be population specific. In the Spanish study nominal associations were identified for single nucleotide polymorphisms rs2651899 (within the *PRDM16* gene), rs10166942 (near *TRPM8*), rs12134493 (close to *TSPAN2*) and rs10504861 (near *MMP16*) in a migraine with aura sample [158]. In the Swedish study association in rs2651899 was identified [160]. The Indian study reports association in rs1835740, *LRP1* rs11172113 and *PRDM16* rs2651899 polymorphisms [159]. In the Chinese Han study the association of *PRDM16* to migraine susceptibility was reaffirmed [161].

A recent GWAS conducted in 460 bipolar migraineurs with 914 bipolar patients without migraine from the Bipolar Genome Study (BiGS) identified a genome-wide significant association with migraine in these patients and rs1160720, an intronic SNP in the *NBEA* gene [162]. The NBEA protein plays a role in trafficking neurotransmitter receptor filled vesicles but since the association of this SNP did not replicate in data from the GWAS migraine meta-analysis consortium and a smaller sample of 289 migraine cases, the authors concluded that this may be an association specific to migraine co-morbid with bipolar disorder.

Altogether GWAS have thus far identified 13 risk loci of genome-wide significance to modulate susceptibility to migraine [136,137,156,163]. These loci show enriched functions in glutamatergic neurotransmission (*MTDH*, LRP1, MEF2D), neuron and synapse development (*MEF2D*, *ASTN2*, *PRDM16*, *FHL5*, *PHACTR1*, *TGFBR2* and *MMP16*), brain vasculature (*PHACTR1*, *TGFBR2*, C7orf10), extracellular matrix (*MMP16*, *TSPAN2*, *AJAP1*), and pain-sensing (*TRPM8*) supporting neurogenic mechanisms [164]. These findings are corroborated by another recent GWAS implicating astrocytes and oligodendrocytes in migraine pathophysiology with different genetic backgrounds for MA and MO [165]. Functional and biochemical characterization of these proteins will be needed to further decipher their involvement in migraine processes. Despite GWAS proving to be a powerful tool to identify genes of small effect sizes it does not answer questions about disease-mechanisms, nor gene expression or biochemical questions to inform the underlying processes of a disease.

Based on the generally accepted view that "functionally related genes show coordinated expression in order to perform their cellular functions" [166] a recent GWAS used two statistical methods to identify modules of gene expression to identify brain regions, cell types and pathways involved in migraine pathophysiology [167]. In this GWAS based study the authors used gene expression data from the Allen Human Brain Atlas enriching for migraine associated genes. Secondly, drawing from the largest migraine GWAS dataset currently available [163] they used high-confidence migraine genes to build a migraine-related co-expression gene network [167]. Importantly, this study highlighted genes involved in mitochondrial function and common migraine which is not surprising given that synapses of neurons are regions of high energy demand and abundant in mitochondria [168]. Glutamatergic alterations and mitochondrial impairments are closely interrelated [169–172]. Mitochondrial variants were hypothesized to be involved in migraine after morphological, biochemical, imaging and genetic studies identified some mitochondrial abnormalities that may be related to mitochondrial dysfunction at least in some individuals [173–177]. Noteworthy is a study Zaki et al., who identified two polymorphisms in the mitochondrial genome, C16519T and G3010A, associated with migraine and cyclic vomiting syndrome CVS [174]. In addition, recently an association for a locus in the mitochondrial DNA

with migraine, both with and without aura was reported by Guo et al. [178], and Anttila et al., for a mitochondrial ATP synthase, ATP5B [163].

Most recently the largest meta-analysis of migraine consisting of 59,674 cases and 316,078 controls of European ancestry identified 38 susceptibility loci that map to factors in vascular and smooth muscle tissues for migraine from 22 GWA studies [179]. Not surprisingly, ten of the 13 GWAS hits identified in this meta-analysis replicate previous GWAS results [179]. Surprisingly, only two of 38 genomic loci are in ion channel genes (KCNK523 and TRPM824) and three other loci (SLC24A326, ITPK127, and GJA128) are involved more generally in ion homeostasis [179]. This result is in contrast to prevalent notions of migraine pathogenesis that support the involvement of ion channel genes and the grouping of migraine into a channelopathy but is in agreement with the idea that the expression of multiple genes of modest effect in the so called 'migraine polygenic model' perpetuates the migraine phenotype [180].

8. X chromosome

The meta-analysis by Gormley et al. also identified the first genome-wide associated locus for migraine on chromosome X [179]. This finding is in line with previous genetic studies of the X chromosome which have implicated three distinct susceptibility loci at *Xp22*, *Xq13*, *Xq24–28* with stronger evidence in support of the *Xq24–q28* region [181–183]. The hypothesis that genomic factors on the X-chromosome may play a part in migraine aetiology is due to the uneven gender distribution observed in epidemiological data (gender ratio 3:1 of female migraine sufferers) [184,185]. In particular, the observed female preponderance is ascribed to hormonal influences which correlate with reproductive milestones and possible gene dosing effects, as females inherit two copies of the X chromosome while males only inherit one X. In addition, the proportion of male probands with affected first-degree relatives is notably higher with respect to relatives of female probands [186].

Although a number of candidate genes in the Xq24–Xq28 region including 5-hydroxytryptamine (serotonin) receptor 2C (*5HT2C*), Glutamate Receptor ionatropic AMPA3 (*GRIA3*), gamma-aminobutyric acid A receptor epsilon (*GABRE*), gamma-aminobutyric acid receptor theta (*GABRQ*) and gamma-aminobutyric acid A receptor 3 (*GABRA3*) have been investigated for association with migraine in a number of ethnically different populations [187–190], apart from the *GRIA3* subunit of AMPA glutamate receptors at Xq24 implicated in an Italian migraine cohort, no specific causal gene on the X chromosome has yet been identified [21]. Interestingly, a common theme that links all these candidate genes together is that they have a neurological role and belong to the neurotransmitter class of genes supporting current concepts of neurological dysfunction in migraine.

9. Glutamate modulating therapies

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. Current evidence that supports a role of the glutamatergic system in migraine comes from randomized controlled trials of modulators of glutamatergic signalling and biochemical studies since the early 1990s that have identified increased levels of glutamate in CSF or in the blood among migraineurs compared with controls. Much progress has been made in characterizing, cloning and crystallizing the receptors and developing antagonists since the first functional ionotropic glutamate receptor was cloned in 1989 [191]. Despite the number of glutamate receptor subtypes, their varied functions, and complex neurochemistry, to date there are only a handful of modulators of glutamatergic signalling in preclinical development [192]. Modulators that have undergone preclinical development for the treatment of migraine include BGG492, LY293558, LY466195, ADX10059 [193–196]. FDA approved modulators of glutamatergic signalling in clinical use include drugs lamotrigine, ketamine, topiramate, memantine, and BoNTA [197–201]. The upside of these compounds is that because they are neurally based they do not have the vasoconstrictive side-effects of other regimens and thus may benefit some patients who have cardiovascular risk factors or co-morbidities [202,203].

Recently the kynurenine pathway (KP) has emerged as a candidate for involvement in migraine pathophysiology with growing interest in the literature [204]. The kynurenine pathway encompasses neuroactive compounds produced from metabolism of the essential amino acid tryptophan [205]. Targets of KP metabolites include both ionotropic and metabotropic glutamate receptors and some of these molecules have recently been linked to migraine [204,206]. Curto et al. report decreased levels of kynurenine metabolites in serum samples from 21 chronic headache patients [207]. They also suggest that biochemical studies exploring serum kynurenine level may be warranted in parallel with genotypic/phenotypic profiles of the kynurenine pathway in migraine to better understand the importance of this pathway in migraine patients [208]. Thorough assessment of the genetic background of the KP and pharmacological interactions with the KP in migraine is missing and consequently if this pathway is to be targeted for migraine therapy more establishing studies would need to be performed. In addition, it may be worthwhile to determine if an association exists between KP metabolites, mitochondrial function and oxidative stress in the migraine brain and if these intracellular functions are brain-specific and if there are regional differences between glial cells and neurons [204].

10. Conclusion

Migraine is a multi-factorial genetic disorder that evolves in adulthood and whose clinical presentation is dependent on the patient's genetic background and environmental factors. In agreement with biochemical studies, genetic studies provide evidence that malfunctioning of the glutamatergic system may contribute to symptoms of migraine. Although it is not yet determined if any one component of the glutamatergic system plays a dominant role in migraine aetiology further studies in conjunction with recent GWAS will enhance our understanding of the pathway. What is definite at present is that genetic data implicating the glutamate hypothesis exists and is growing. The hypothesis of a glutamatergic deficit in migraine is supported by genetic evidence implicating SNPs in GRIA subunit genes in migraine aura patients, glutamatergic abnormalities in plasma, platelets, urine and CSF in migraine aura patients and FHM mutations induce CSD and enhance glutamate release. Additionally, glutamate may be involved in cortical excitability and consequently perturbation of the glutamatergic system and other neurotransmitter systems that interplay at multiple levels may play a role in migraine. Specific animal models of glutamate are lacking, currently the most studied are cell based models of glutamate excitotoxicity. Nevertheless, progress will continue, particularly with multicenter collaborations making use of large patient cohorts and well-defined case material. The application of novel genome-editing technologies also will help harvest recent genetic discoveries in GWASs, which is needed to have a more complete understanding of the disease mechanisms in migraine. The molecular mechanisms regulating glutamate receptor expression and function including RNA editing and miRNAs remain unexplored. This represents fertile terrain for more in depth study of how the gene and protein constituents of the glutamatergic system are regulated that could be developed into therapies. Glutamate modulating therapies and the kynurenine pathway are under-investigated from a genetic standpoint and further study may hasten development of novel drugs for treating migraine. Deciphering the glutamatergic cross-talk in the brain is central to understanding how disruption of glutamatergic circuits leads to neurological and psychiatric diseases. In conclusion, understanding the glutamatergic system is crucial for understanding basic brain functions such as learning and memory which might be applicable in the research for

other neurodegenerative disorders than migraine, where glutamatergic proteins are additionally involved.

Competing interests

The authors declare that there is no conflict of interest.

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