Austin Journal of Clinical Neurology

Open Access

Austin Publishing Group

Review Article

Biochemical Studies of the Neurotransmitter Glutamate: A Key Player in Migraine

Gasparini CF[1], Smith RA[2] and Griffiths LR*

[1]Menzies Health Institute Queensland, Griffith University Gold Coast, Australia

[2]Genomics Research Centre, Queensland University of Technology, Australia

***Corresponding author:** Griffiths LR, Genomics Research Centre, Institute of Health and Biomedical Innovation, Queensland University of Technology, Musk Ave, Kelvin Grove, QLD, 4059, Australia

Received: August 10, 2015; **Accepted:** October 30, 2015; **Published:** November 20, 2015

Abstract

Susceptibility to migraine is influenced by a multitude of factors including gene-environment and gene-gene interactions. The emerging picture of migraine pathogenesis is that it is a complex polygenic and heterogeneous disorder at both the population and molecular levels. Causes of migraine are not very clearly understood and therefore research into the aetiology of migraine takes several different approaches including genetic, pharmacological and biochemical to integrate disease based information on multiple levels. Neurotransmitters have been implicated in migraine pathogenesis, in particular the excitatory transmitter glutamate with supporting evidence from GWAS and genotyping case-control studies. The brain contains large amounts of glutamate, a plentiful excitatory amino acid neurotransmitter necessary to the integrity of synaptic plasticity and memory in CNS functioning, which is highly toxic to neurons if present for prolonged periods. Glutamate has been implicated in cortical spreading depression (CSD) in animal models and the ingestion of glutamate in the form of monosodium glutamate in predisposed individuals can elicit sensitivity and migraine-like headache (the MSG Symptom Complex). Comparisons between migraine patients and normal controls on biochemical measures in a range of biological fluids have shown significant differences between these groups particularly in migraineurs with aura. Despite the observation of notable biochemical alterations, specific diagnostic markers are lacking. In this review we discuss biochemical findings in plasma, platelets, saliva, cerebrospinal fluid, and urine that support the conception that a component of glutamate receptor disruption may contribute to migraine susceptibility.

Keywords: Migraine; Migraine with aura; Migraine without aura; Glutamate; Neurotransmitters; Platelets

Abbreviations

CSD: Cortical Spreading Depression; MSG: Monosodium Glutamate; TCA: Tricarboxylic Acid; GS: Glutamine Synthetase; CRS: Chinese Restaurant Syndrome; NMDA: N-Methyl-D-aspartate; CSF: Cerebrospinal Fluid; MA: Migraine with Aura; MO: Migraine without Aura; TH: Tension Headache Patients; PRP: Platelet-rich Plasma; HVA: Homovanillic Acid; 5-HIAA: 5-Hydroxyindoleacetic Acid; FM: Fibromyalgia; CDH: Chronic Daily Headache; CM: Chronic Migraine; CH: Cluster Headache; CMF: Chronic Migraine with Fibromyalgia; PLTS: Platelets; RBC: Red Blood Cells

Introduction

Glutamate, like serotonin and dopamine is a prominent neurotransmitter in the CNS that mediates fast excitatory synaptic neurotransmission via ionotropic and metabotropic receptors [1]. Glutamatergic receptors are the molecular mediators through which glutamate acts and are found in the trigeminovascular system and its structures [2,3]. Glutamate is stored intracellularly inside synaptic vesicles where the concentration may be as high as 100 millimolars and is inactive until released into the synapse [4]. Glutamate is believed to be required for cortical spreading depression and to activate the trigeminovascular system and central sensitization [5-7] is a substrate for various enzymes at glutamatergic synapses and is at a crossroads of metabolic pathways acting as a precursor of the inhibitory neurotransmitter GABA and being involved in brain energy metabolism and nitrogen homeostasis [8]. There are two pathways through which glutamate can be synthesized: the majority is synthesised from glutamine deamidation via the enzyme glutaminase and to a lesser extent approximately one-third is derived from glucose via tricarboxylic acid (TCA) cycle intermediates (α- ketoglutarate) and transamination with GABA [9]. In addition to glutamate receptors and transporters, there are enzymes, such as glutamine synthetase (GS) that control the levels of intracellular glutamate, for example through the conversion of glutamate to glutamine [10].

Accumulating data from genetic studies demonstrate that migraineurs have a perturbed glutamatergic system, which may be reflected in the brain as neuronal hyperexcitability [11]. There is also accumulating evidence that glutamate receptors exhibit a modulatory effect in migraine mechanisms and glutamate modulating therapies have shown promise on migraine symptoms [12]. The glutamatergic system in migraine patients may be compromised and this may occur as a consequence of polymorphisms in genes that regulate glutamatergic signalling. Currently there is only evidence to implicate the *GRIA3* gene of the AMPA receptor, but time will tell if there are more polymorphisms in these or other genes to be identified [13,14]. The peripheral metabolism of glutamate which includes the production,

Citation: Gasparini CF, Smith RA and Griffiths LR. Biochemical Studies of the Neurotransmitter Glutamate: A Key Player in Migraine. Austin J Clin Neurol 2015; 2(9): 1079.

storage, expression, trafficking and function of ionotropic glutamate receptors and glutamate is just as important as is the neuronal component of glutamate in the brain and may also have a bearing on migraine. The hypothesis is that migraineurs have a propensity for genetically disordered glutamatergic neurotransmission.

Migraine is a multi-system disorder with vascular, inflammatory, neurological and biochemical components that culminate in central neuronal hyperexcitability, which is the underlining mechanism most often targeted in pharmacological intervention [15]. The ideal situation for diagnosis and treatment of migraine would be to have biomarkers which can reliably distinguish those with disease from healthy individuals [16]. The genetic evidence for glutamate's involvement in migraine and our knowledge of its biochemical role gives it potential to be such a biomarker for migraine. At present, however, the development and adoption of glutamate or glutamate-related biomarkers is slow and currently there are no validated biomarkers for measuring glutamate pathology in CNS injuries or disorders, including migraine [16-18]. More precise characterization of the glutamate molecular-signaling pathways in glutamatergic cells is warranted as a prerequisite for understanding the potential involvement of the glutamatergic system in the aetiology of migraine. The goal of this short review is to summarize the biochemical findings of the neurotransmitter glutamate in migraine to help facilitate further research which may enable its use as a migraine biomarker.

Glutamate Biochemical Studies

Monosodium glutamate

Glutamate produced outside of the human body is best known as "monosodium glutamate" (MSG) which is sodium salt of glutamic acid [19]. MSG is a well-known food additive and flavor enhancer that has been used for more than 100 years in Asian cuisine due to the umami (savory) taste it gives to food [20]. Binding of MSG to a specific metabotropic glutamate receptor, different from the receptors for sweet, salty, sour, and bitter, is thought to be responsible for this fifth gustatory sensation [21]. Aside from being synthesized as a food additive, MSG is also naturally occurring at high levels in some foods such as tomato and cheese. The human body prefers to use L-glutamic acid which is the naturally-occurring predominant form of glutamate. The second form of glutamic acid, the D-enantiomeric form D-glutamic acid, is found naturally only in the cell walls of certain bacteria [22]. Manufactured/processed MSG typically contains L-glutamic acid in addition to the D-enantiomer D-glutamic acid and a mixture of impurities of pyroglutamic acid, mono and dichloro propanols and heterocyclic amines [23,24]. Further research regarding the impact of D-amino acid metabolism with the normal metabolism of L-amino acids is necessary in view of the fact that some studies have shown that when D-glutamate is given to mice in large doses it can suppress immunological activity [25].

Early reports claimed that MSG may be the cause of headache and Alfred Scopp in 1991 published a study "MSG and hydrolyzed vegetable protein induced headache: review and case studies" questioning the connection between MSG and headache [26]. According to this study, MSG, tyramine and aspartame were found to be migraine triggers in susceptible individuals [26]. This observation is supported by discussion in the published literature of the Chinese Restaurant Syndrome (CRS) now better known as the MSG symptom complex [27]. MSG symptom complex refers to a triad of symptoms first reported in 1968 after ingestion of a Chinese meal [28]. The symptoms experienced were described as "numbness at the back of the neck and arms gradually radiating to the arms and the back, general weakness, and palpitations" and were thought to be brought on by ingestion of food rich in MSG in particular Chinese cuisine [29]. Based on these observations researchers have investigated the potential relationship between MSG and headache and the MSG symptom complex in various studies in animals and humans.

MSG injected intravenously into rats has been shown to raise intramuscular tissue concentrations of glutamate through activation of N-methyl-D-aspartate (NMDA) receptors [6,30]. Elevated tissue concentrations of glutamate have been shown to contribute to pain and sensitivity in certain musculoskeletal pain conditions [31]. Baad-Hansen et al., 2009 investigated the influence of an oral dose of MSG based on each individual subject's body weight, administered to 14 young healthy male volunteers and the occurrence of headache, side-effects, sensitivity to pressure pain in masseter and temporalis muscles, blood pressure and heart rate were assessed [32]. This study reported a significant increase in subjects' self-reported symptoms of headache and pericranial muscle tenderness after ingestion of MSG, as well as increased systolic blood pressure. Similarly and more recently Shimada et al., 2013 [33] conducted a double-blind, placebo-controlled, crossover study to look at the effect of MSG intake on spontaneous headache. The conclusion reached was that subjects consuming MSG had higher systemic levels of glutamate and that this is the reason participants were more likely to suffer from headache and have accompanying masseter muscle sensitivity. Overall, neurotoxicity by MSG has been demonstrated in animals and various studies in humans have investigated reports of adverse reactions to MSG with high doses however, the symptoms reported in these studies are neither persistent nor serious. Consequently, the data on the relationship between MSG and migraine headache is still inconclusive and a causal relationship has not explicitly been identified and further investigation is warranted [27,34-36]. Although a subset of the population react adversely to MSG and are termed "MSG sensitive individuals" who have experienced adverse reactions which include skin rash, tachycardia, migraine headache, depression, and seizures, altogether the literature agrees there is inadequate evidence to establish MSG as a causative factor of migraine headache [23].

Plasma

In the last 30 years, biochemical studies investigating glutamate levels in plasma, platelets, CSF and urine of migraine patients have reported significantly higher glutamate concentrations particularly in patients with migraine with aura. The main source of glutamate is from neurons however, in the periphery, plasma glutamate mostly derives from freely circulating platelets which accumulate glutamate [37]. Blood plasma is the pale yellow liquid portion of blood in which blood cells are suspended and nutrients are dissolved, contributing 55% of the body's total blood volume [38].

Thus far, five studies out of seven have reported higher plasmatic levels of glutamate in migraine patients between and during attacks with the study by Alam et al., 1998 [39] having the largest sample size consisting of 80 migraine with aura (MA), 9 migraine without

Table 1: Biochemical studies of Glutamate in migraine patients and controls.

Reference	Migraine Classification	Controls/Cases	Total Sample Size Cases	Sample & Levels
(Ferrari et al., 1990) [75]	(ICHD-I, 1988) [76]	**Controls: 9**	40	Plasma
		MA: 10		↑
		MO: 21		↑
		TH: 9		=
(Martinez et al., 1993) [44]	(ICHD-I, 1988) [76]	**Controls: 21**	27	Plasma : CSF
		MA: 11		↓↑:
		MO: 16		↓↑:
(Cananzi et al., 1995) [54]	(ICHD-I, 1988) [76]	**Controls: 19**	57	Plasma : PLTS
		MA: 32		=↑:
		MO: 25		↑: =
(Deufemia et al., 1997) [45]	(ICHD-I, 1988) [76]	**Controls: 16**	34	Plasma : RBCs
		MA: 15		↓: =
		MO: 19		↓: =
(Alam et al., 1998) [39]	(ICHD-I, 1988) [76]	**Controls: 62**	103	Plasma
		MA: 80		↑
		MO: 9		↑
		TH: 14		↑
(Vaccaro et al., 2007) [55]	(ICHD-II, 2004) [77]	**Controls: 20**	50	Plasma : PLTS
		MA: 25		↑↑:
		MO: 25		↑↑:
(Ferrari et al., 2009) (78)	(ICHD-II, 2004) [77]	**Controls: 24**	24	Plasma
		MO: 24		↑
(Dandrea et al., 1991) [53]	(ICHD-I, 1988) [76]	**Controls: 17**	98	PLTS
		MA: 24		↑
		MO: 22		=
		TH: 15		=
		CH: 37		=
(Zukerman, 1993) [62]	(ICHD-I, 1988) [76]	**Controls: N/A**	10	CSF
		MA: 6		↑
		MO: 4		↑
(Gallai et al., 2003) [63]	(Silberstein,1996) [79]	**Controls: 20**	25	CSF
		CDH: 10		↑
		CDH - medicated: 15		↑
(Peres et al., 2004) [64]	(Silberstein, 1996) [79]	**Controls: 20**	20	CSF
		CMF: 12		↑
		CM: 8		↑
(Vieira et al., 2007) [65]	(ICHD-II, 2004) [77]	**Controls: 19**	19	CSF
		CM: 5		↓
		CM - NSAIDS: 8		↓
		CM - Tryptans: 6		↓
(Ragginer et al., 2012) [67]	(ICHD-II, 2004) [77]	**Controls: 48**	48	Urine
		MA: 48		↑

CDH = Chronic Daily Headache; CH = Cluster Headache; CMF = Chronic Migraine with Fibromyalgia; CM = Chronic Migraine; CSF = Cerebrospinal fluid; MA = Migraine with aura; MO = Migraine without aura; PLTS = Platelets; RBC = Red blood cells; TH = Tension ↑lc Headache; Rease; ↓Decrease; = Unchanged.

aura (MO) and 14 Tension Headache (TH) patients (Table 1). The largest sample size was 103 and the smallest 24, the average sample size in the seven studies using plasma as sample was 48, showing a range of studies with various capabilities to detect alterations in glutamate metabolism. Moreover, plasma glutamate is likely to be linked to the platelet glutamate storage function, and individual differences in this mechanism may add additional variation to observed glutamate levels [40,41]. Factors which can further confound the accurate reporting of plasma glutamate levels include differences in experimental procedures, such as different concentrations of inducers, centrifugation time and pharmaceutical substances produced by different manufacturers, different timing of blood sampling (time of day, menstrual cycle, time passed since the last attack, fasting/non-fasting), blood-drawing and sample-handling protocols (venipuncture-induced platelet activation, body position, blood sample device: open system/vacutainer, operators' experience, time of stasis), patient drug history and diet [42,43].

Two out of the seven studies reported lower levels of glutamate, these included a study by Martinez et al., 1993 [44] and a study by Deufemia et al., 1997 [45]. Martinez et al., 1993 [44] considered the levels of glutamic and aspartic acid in both plasma and CSF in patients with MA and MO relative to a group of controls suffering from stress. Despite reporting lower plasma levels, Martinez et al., 1993 simultaneously reported higher CSF glutamate in migraineurs which led the authors to conclude there may be an excess of neuroexcitatory amino acids in the central nervous system which may promote a state of neuronal hyperexcitability in migraine patients. Deufemia et al., 1997 demonstrated lower plasma-glutamate levels in paediatric migraineurs than in controls and concurrently reported a significantly higher erythrocyte to plasma-glutamate ratio [45]. Differences in the results may be explained by the nature of the control group in both studies which was composed of patients under stress in the Martinez study and a group of paediatric controls in the Deufemia study.

The sum of these studies suggest that plasma glutamate could serve as a diagnostic tool for monitoring disease status in migraine patients and as a biomarker of response to treatment however more studies utilizing the latest diagnostic criteria are needed to make a more solid conclusion and develop accurate and standardised sampling. These findings do support a link between high plasma glutamate levels in migraine patients and cortical neuronal hyperexcitability which may be mediated via NMDA-glutamatergic transmission and may be connected with the pathobiology of migraine. Additionally, increased plasma levels of glutamate have been reported in some neuropsychiatric disorders in which glutamate excitotoxicity is thought to play a role in their pathophysiology, including epilepsy [46], Alzheimer's disease [47] and amyotrophic lateral sclerosis [48].

Platelets

Platelets are the primary source of neurotransmitters in human blood [49]. The accessibility of platelets has made them a viable cellular tool with which to study the aetiology of neurological disorders. Platelets have been considered a useful model for studying glutamatergic dysfunction and neurological disorders because they possess high-affinity glutamate transporters similar to glutamatergic neurons and contain platelet-dense granules that store and release the neurotransmitter glutamate [40,50] through similar pathways to those described in the brain. The rationale for investigating peripheral sources of glutamate is that platelet glutamate metabolism may contribute to the accumulation of glutamate in the brain and its vasculature through the blood brain barrier and hence peripheral levels of glutamate/glutamine may correlate with those of the central nervous system [51]. In addition platelets possess many molecules and receptors which have functional similarities with neuronal elements and endothelial cells, for example the up-taking, storing and releasing of neurotransmitters such as glutamate, serotonin, GABA and dopamine, through expression of their specific receptors and/or transporters. These functions may play a role in platelet activation and/or aggregation and hence platelets have been used as surrogate models for the investigation of peripheral neurotransmitter function [52].

Three studies have evaluated glutamate levels in platelets (Table 1) [53-55]. In each study, platelets were isolated from a sample of whole blood, with a minimum of 8mL and a maximum of 25mL, collected after overnight fasting from the antecubital vein of each study participant. In every study platelet-rich plasma (PRP) was the portion of plasma used to determine platelet counts and from which the platelet-rich pellet was harvested. Cananzi et al., 1999 found that migraine with aura patients had higher platelet levels than migraine without aura patients [54]. D'andrea et al., 1991 measured platelet glutamate, aspartate and glycine levels in groups of patients with migraine with aura, migraine without aura, tension headache and cluster headache [53]. Glutamate, aspartate and glycine levels were reported to be highest in migraine with aura patients in this study. Vaccaro et al., 2007 in addition reported that platelet glutamate uptake, assessed as 3H-glutamate intake, was increased in MA, while it was reduced in MO with respect to the control group [55]. These studies were consistent, all reporting higher levels of glutamate in the platelets of the MA group. Different authors have suggested there may be a glutamate metabolic profile specific to a migraine phenotype suggesting unique pathophysiological characteristics that may explain the observed differences between the two types of migraine MA and MO.

Saliva

The justification for utilizing saliva as a fluid for evaluating neurotransmitter function is that as fluid saliva is stable and easy to obtain and the salivary glands are innervated by the nerve terminals of the trigeminovascular system [56]. These nerves innervate the mucosal bucca (buccal nerve) and the parotid gland (from the mandibular nerve, parotid branches convey secretomotor fibers to the gland) [57]. The advantage of using saliva to assay central nervous system function is that it is non-invasive to collect and it contains a wide array of neuropeptides that might highlight certain clues about the pathophysiology of neurological disease [58]. There is one study to date that has evaluated free amino acids in saliva of patients with migraine and found these to be elevated relative to controls [59]. Rajda et al., 1999 tested the saliva of 23 migraineurs without aura and 14 migraineurs with aura and 20 healthy controls [59]. The amino acids tested glutamic acid; serine, glycine, arginine, and tyrosine were all found significantly elevated in the saliva samples of both groups of migraineurs relative to the control group. These results are in line with previous studies investigating glutamate levels in plasma and cerebrospinal fluid supporting that a dysfunction of the glutamatergic

brain metabolism may exist in migraine. More studies using saliva as a sample are needed to ascertain its potential as a fluid to detect metabolic abnormalities.

Cerebrospinal fluid

Cerebrospinal fluid (CSF) has been proposed as a source of biomarkers because it is within the blood-brain barrier and neurotransmitter levels in CSF may correspond to those in the ventricular system. Therefore, CSF from lumbar puncture might accurately reflect glutamate-mediated excitotoxicity in the CNS [60]. The earliest study investigating CSF as a source of biomarkers in migraine was by Kovacs et al., 1989 measuring homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations, CSF pressure, total protein content and protein fractions of MA and MO patients as well as controls [61]. That study found an increased 5- HIAA level in migraineurs compared to controls. Since then five independent studies [44,62-65] have investigated glutamate levels in CSF of migraine patients with results showing migraine patients have a significant increase in CSF glutamate levels compared to controls. Martinez et al., 1993 [44] identified higher concentrations of glutamate in CSF and concluded that high levels of glutamate in the CSF may participate in triggering of attacks by contributing to a state of neuronal hyperexcitability. The fact that both amino acids glutamate and aspartic acid have been co-involved in the pathophysiology of epilepsy and ischemic and hypoglycemic neuronal death is further evidence to support the concept that they may promote a state of central neuronal hyperexcitability [44]. Similarly a study by Rothrock et al., 1995 [66] found high levels of amino acids (glycine, taurine, glutamine) in CSF in migraine patients and a study by Zukerman et al., 1993 [62] identified similar results but in a smaller cohort of patients.

The study by Peres et al., 2004 [64] used Silberstein classification criteria and chronic daily headache patients. This study differed to the others as they included migraine patients with and without fibromyalgia, a muscular condition co-morbid with migraine. Fibromyalgia (FM) is a common syndrome of musculoskeletal pain and fatigue, which occurs mostly among middle-age women. Peres et al., 2004 demonstrated CSF glutamate to be significantly higher in migraine patients with fibromyalgia compared to migraine patients without fibromyalgia.

The study by Gallai et al., 2003 [63] and Vieira et al., 2007 [65] considered the influence of different acute medications on the levels of glutamate in CSF. In both these studies patients were divided into different treatment groups either using or not using medication. Gallai et al., 2003 [63] subdivided patients into two groups, Group 1 chronic daily headache (CDH) patients without analgesic overuse (n = 10) and Group 2 medication overuse patients (n = 15). The results of this study indicated that both treatment groups of CDH patients with and without analgesic overuse had significantly higher CSF glutamate levels than the control group but that there was no difference between the two treatment groups, indicating the use of acute medications did not influence glutamate levels overall. As the authors did not observe high levels of glutamate in healthy controls, they concluded that the high level of glutamate in migraine patients may represent a biochemical marker of neuronal hyperexcitability.

Vieira et al., 2007 [65] determined CSF glutamate levels of chronic migraine patients and found that patients overusing triptans had significantly lower CSF glutamate levels than in non-over users but CSF glutamate levels were still significantly higher than in healthy controls suggesting the glutamatergic system is likely to be altered in the migraine brain. The study by Vieira et al., [65] considered chronic migraine (CM) patients divided into the following groups: Group 1 comprised patients overusing analgesics (NSAIDs); Group 2 comprised patients not overusing medications; and Group 3 comprised patients overusing triptans. Vieira et al., 2007 found that CM patients in all three treatment groups showed higher CSF glutamate levels when compared with control subjects. No difference was found between Group 1 patients overusing analgesics (NSAIDs) compared to Group 2 those not overusing. However Group 3 patients overusing triptans had lower glutamate levels in CSF when compared to Group 2 non-overuse patients, though levels were not significantly different to Group 1 patients. The authors suggest the decrease of glutamate in CSF in the Group 3 patients overusing triptans may be connected with the action of triptans as glutamate levels were found to be lower after triptan treatment. These data suggest, although indirectly, the involvement of excitatory amino acids in central nociception in migraine patients and that inhibiting excitatory amino acid transmission in central neuronal circuits invol secretomotor ved in the processing of nociceptive information could be a route to follow for improved treatments.

Although analysis of glutamate levels in CSF is concordant with five out of five studies reporting the same result it is important to point out that the sample size in each of the studies using CSF was small in comparison to studies performed with other fluids. At present no specific characteristic or biochemical marker has been consistently recognized in affected individuals and therefore future replications of these studies will be needed to confirm and strengthen the power of these findings. Nevertheless the identification of biochemical and genetic mechanisms that control the homeostatic milieu is essential to sustained progress in migraine research.

Urine

In 2012 a study by Ragginer et al. [67] reported a significant decrease in the urinary glutamate levels of female migraineurs with respect to healthy controls, a result which was associated with a 4.04-fold higher risk for migraine. The authors hypothesized that migraine patients are more prone to suffer metabolic dysfunctions and consequently in addition to investigating glutamatergic homeostasis in the urine concomitantly investigated parameters of insulin and lipid metabolism, inflammatory and anthropometric parameters. Commercial ELISA kits and Roche analysers were used for determining urinary glutamate levels and various glucose and lipid measurements. Migraine has been associated with metabolic dysfunctions; in particular, regarding the insulin- and glucose-metabolism [68,69]. In this study, however, no significant correlation was identified in the urinary glutamate levels and metabolic and anthropometric parameters in migraineurs. This is the only study so far evaluating glutamate in urine as a sample, but it shows that urine may have potential as a source of glutamate biomarkers for migraine. Analysis of metabolites obtained from different body fluids can help inform the course and progression of a disease, but more complete descriptions of the biochemical irregularities must first be established before urine can be used in migraine management.

Glutamate pharmacotherapy

Current migraine therapies work at differing efficacies and often have several side-effects; therefore more safe and effective treatment options for migraine are a high priority for future research. This is because migraine is a multifactorial disorder caused by several factors and genetic polymorphisms that together contribute to the variety of symptoms and triggers reported by migraineurs [15]. Consequently gaining an in depth understanding of the genotypic profile of migraineurs is an active area of research that is necessary to improve the effectiveness of migraine treatment. Given the broad phenotypic expressivity of migraine and variable patient response and presence of co-morbidities, a pharmacological repertoire is necessary to target the multitude of symptoms exhibited by different migraine patients.

As mentioned above, genetic studies have implicated glutamate in migraine pathogenesis [11,13,14]. Deficiency in glutamatergic neurotransmission due to genetic mutation in any of the gene constituents of the glutamatergic system may result in a disturbed balance of synaptic activity and may play a key role in the pathophysiology of migraine. Many studies have examined pharmacological treatment variation in relation to genetically different populations and seek to evaluate the association of specific gene polymorphisms to patient response to medication. Pharmacogenomics, the hybrid union of pharmacology and genetic research, is an expanding discipline that addresses how diseases of different genetic make-up respond to treatments. It holds promise in the future to design more efficacious pharmaceutical treatments to address the specific needs of individual patients based on their genetic profile and has already had some notable successes in fields such as cancer treatment.

Research into the peripheral metabolism of glutamate, its agonists and antagonists has provided the substrate for the development of focused modulators of the glutamatergic system. Glutamatergic receptors NMDA, AMPA, ka are all potential targets for the development of modulators. Preclinical experiments with glutamate antagonists have provided experimental evidence for pursuing modulators in the treatment of migraine and support the hypothesis that blocking glutamate receptor subtypes is a potential logical approach. Modulators that have undergone preclinical development for the treatment of migraine include BGG492, LY293558, LY466195, and ADX10059 [70-73]. Modulators of the glutamatergic system already in clinical use include drugs topiramate, memantine, ketamine and BoNTA. Such compounds may benefit the patient in situations where other regimens have been unsuccessful. The advantage of targeting the glutamatergic system is that if offers a neurally based non-vasoactive approach that can bypass the vasoconstrictive side-effects that currently plague acute anti-migraine therapies [74].

A holistic understanding of the specific receptors and/or cellular signalling mechanisms and how drugs affect the functioning of neurons in the nervous system is required to make drug design targeted and effective. There are some clear difficulties however with the use of glutamatergic modulators that must be overcome, such as neurotoxicity. Well-designed clinical studies using larger and well stratified migraine cohorts will further our current understanding of the role of modulators of the glutamatergic system in migraine and aid in the development of therapies to prevent and/or abort migraine attacks.

Conclusion

Migraine is a complex disorder marked by variability in severity and clinical phenotypic expression. The majority of the biochemical evidence suggests that glutamate levels play a role in the pathogenesis of migraine. The biochemical studies performed to date have highlighted that glutamate levels are elevated in migraineurs as detected in a range of biological fluids including plasma, platelets, saliva, CSF and urine. Although the studies typically involved a small number of subjects, they offer insight into the biochemical phenotype of migraine and are concordant with recent genetic findings implicating the neurotransmitter glutamate in migraine pathogenesis. Moreover analyses of glutamate in plasma and platelets have revealed that the uptake and release of glutamate is altered in migraine patients, particularly those with aura. The most supported result is the elevated glutamate levels in CSF reported in five out of five studies, indicating an excess of neuroexcitatory amino acids in the central nervous system that could reflect a state of neuronal hyperexcitability.

Collectively, these studies indicate that there may be a biochemical abnormality of glutamate in migraine and therefore treatments modulating this system are plausible candidates to be pursued. Dysregulation of brain glutamate systems through changes in glutamate mechanisms may result in symptoms of migraine. Although a clear biochemical cause is lacking, biochemical evidence supports the involvement of neurotransmitters serotonin, dopamine and glutamate in migraine aetiology. Follow up studies into the underlining disrupted mechanism of glutamatergic metabolism and activity may highlight more consistent markers. Newer studies with larger numbers of subjects and utilizing more modern laboratory equipment and methods are needed to more thoroughly establish the potential involvement of glutamate and other biochemical metabolites in migraine. Biochemical approaches interwoven with studies in other disciplines are necessary to discern the biochemical milieu and to identify the proper utility of glutamate and a migraine biomarker. Creative approaches are needed to complement current research strategies to continue to unravel piece by piece the molecular, genetic and biochemical substrate of migraine.

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Austin J Clin Neurol - Volume 2 Issue 9 - 2015
ISSN : 2381-9154 | www.austinpublishinggroup.com

Citation: Gasparini CF, Smith RA and Griffiths LR. Biochemical Studies of the Neurotransmitter Glutamate: A Key Player in Migraine. Austin J Clin Neurol 2015; 2(9): 1079.