Chapter 6
Glutamate in Migraine Neurobiology and Treatment

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Abstract Migraine is a disabling chronic condition characterised by recurrent episodes of head pain accompanied by other sensory disturbances. Its pathophysiology is complex and involves both the peripheral and central nervous systems. Glutamate is believed to play an important role in migraine pathophysiology, as it is involved in multiple processes of migraine's neurobiology. Glutamate is the main neurotransmitter of the trigeminal system and along the ascending trigeminothalamic pathways. It is also involved in the initiation and progression of cortical spreading depression, the underlying biological processes of migraine aura. Its levels are increased during attacks and in chronic migraine patients. Increased glutamate excitation is believed to be at least partly responsible for the clinical symptoms of allodynia in patients during an attack, as well as in the transformation of episodic migraine to chronic migraine. Some of the current migraine treatments include in their mechanism of action, at least partly, modulation of glutamatergic signalling. While some attempts have been made to directly block glutamate receptors, these were abandoned due to the development of significant side effects. Future glutamatergic therapeutics that could indirectly block glutamatergic signalling may present a viable effective tool in migraine patients.

Keywords Glutamate · Migraine · Aura · Spreading depression · Trigeminal · CGRP · Central sensitization

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6.1 Introduction

Migraine is a common, chronic neurological disease characterised by recurrent episodes of intense headache, that can worsen with activity, accompanied by nausea, sensitivity to light, noise or even smells (IHS 2018). A proportion of patients also experiences migraine with aura—transient neurological symptoms that usually occur just before the onset of a migraine headache. About 1–2% of migraine patients develop chronic migraine, characterised by at least 15 headache days per month (Buse et al. 2012). The majority of these patients may actually develop a daily or nearly daily migraine headache. Migraine pathophysiology is now believed to be triggered by, or at least include, dysfunctional processes at the level of the hypothalamus (Peres et al. 2001; Schulte et al. 2017; Schulte and May 2016), making migraine a brain disorder. However, many of the successful treatments of migraine involve drugs that do not cross the blood brain barrier, with their mechanism of action identified at the peripheral nervous system, mainly the trigeminal nerve and the trigeminal ganglion (Andreou and Edvinsson 2019; Lambru et al. 2018).

The pain of migraine was initially thought to be driven by the cephalic vasculature, potentially through excess vasodilation (Moskowitz and Macfarlane 1993; Wolff 1948). More recent research in migraine pathophysiology suggests that dysfunctional brain networks are involved in the disorder's predisposition and potentially in driving attack initiation (Andreou and Edvinsson 2019). However, central and peripheral neuronal pathways involved in pain signalling, as well as inflammation, are equally important drivers of disease biology and offer targets for the development of future therapeutics. Glutamate is the excitatory neurotransmitter that drives activation of the both the peripheral and central arms of the trigeminal pain pathway, making it a key player in the manifestation of migraine. Migraine pain-relay centres, including the trigeminal ganglion, trigeminocervical complex (TCC) and sensory thalamus, contain glutamate-positive neurons (Alam et al. 1998; van Dongen et al. 2017), while glutamate has been shown to excite neurons in the TCC and thalamus (Ferrari et al. 1990; Martinez et al. 1993). The presence of glutamate in the transmission of sensory information implicates the involvement of glutamate receptors that modulate glutamate responses, in migraine neurobiology. Thus, glutamate receptors and glutamatergic signalling offer a great potential in the development of novel, migraine-specific treatments.

In the present chapter we will discuss the neurobiology and pathophysiology of migraine and the current evidence on the involvement of glutamate signalling in the development of different migraine symptoms. We will further discuss interactions with the glutamatergic signalling of current migraine treatments and how we could effectively target the glutamate system in the future in order to develop more effective, tolerable, migraine-specific treatments.

6.2 Plasma, Cerebrospinal Fluid (CSF) and Brain Levels of Glutamate in Migraine Patients

Migraine patients have interictal elevated plasma levels of neuronal amino acids, including glutamate, glutamine, glycine, cysteic acid and homocysteic acid (van Dongen et al. 2017). The plasma levels of glutamate were found to be further increased during a migraine attack (Alam et al. 1998; Ferrari et al. 1990). Increased peripheral glutamate, if correlated with increased brain levels, suggests that migraine biology involves a persistent neuronal hyperexcitability that becomes heightened during a migraine attack.

Indeed, during migraine attacks cerebrospinal fluid (CSF) concentrations of glutamate were found to be higher in patients than in controls, suggesting an excess of neuroexcitatory amino acids in the CNS (Martinez et al. 1993). The increased levels of glutamate, particularly in migraine with aura patients may be relevant to their neurological symptoms (D'Andrea et al. 1991). Additionally, glutamate concentrations were increased in CSF from chronic migraine patients (Gallai et al. 2003; Peres et al. 2004; van Dongen et al. 2017), further supporting the concept of excess neuroexcitation in the CNS. In support of this theory is the finding that migraine patients exhibit signs of central sensitization during an attack (Burstein et al. 2000), which is a process of excessive activation of second order dorsal horn neurons and/or third order thalamic neurons, which occurs following peripheral sensitization in the trigeminal ganglion (Woolf and Decosterd 1999). Glutamate release in the spinal dorsal horn and glutamate receptor activation mediates central sensitization (Burstein 2001). Allodynia and hypersensitivity is a common clinical observation of chronic migraine (Bigal et al. 2008a; Kitaj and Klink 2005) and is regarded as the result of central sensitization (Andreou and Edvinsson 2019).

Brains of patients with migraine differ pharmacologically from those of non-migraine sufferers (Mathew 2011), with glutamate playing a major role in such differences. A small magnetic resonance spectroscopy study found glutamatergic abnormalities in the anterior cingulate cortex and insula in migraine patients during their interictal period compared to healthy controls (Prescot et al. 2009). Bigger magnetic resonance spectroscopy studies of the cortex and the thalamus found higher interictal glutamate levels in the visual cortex and thalamus of migraine patients (Bathel et al. 2018; Zielman et al. 2017), but no group differences in GABA levels supporting the hypothesis of cortical and thalamic hyperexcitability in migraine driven by excess availability of glutamate (Bathel et al. 2018).

6.3 Genetics of Migraine and the Glutamatergic System

The increased glutamate levels, both during a migraine attack and in chronic migraine, may suggest a defective cellular reuptake mechanism for glutamate in migraine patients at the neuronal/glial level, predisposing the pain pathway to excess excitation. Increased cortical glutamate levels may also drive the development of cortical spreading depression during migraine aura. To date, our knowledge on migraine genetics is not complete, but some genetic modification findings may support this theory.

Migraine is a multifactorial disorder and genetic factors play an important role in the development of the disorder. Studies examining the genetic basis of migraine are complicated by the heterogeneous nature of the condition and the lack of objective clinical or diagnostic tests. Family and twin studies showed increased risk in the family members of migraine patients (Noble-Topham et al. 2003; Ziegler et al. 1998), indicating that genetic factors are a major contribution to the pathogenesis of both migraine with and without aura. Genome-wide association studies (GWAS) failed to shed light on the actual molecular changes that are responsible for the genetic susceptibility of migraine. It is understood that multigenetic variants, rather than individual genes, influence the susceptibility to migraine (Gormley et al. 2016). Regardless of these outcomes, due to their small effect size, no single nucleotide polymorphisms has any clinical use in predicting the risk of developing migraine (Andreou and Edvinsson 2019). Potentially, more knowledge on the function of these variants could highlight which molecular pathways are involved in migraine susceptibility (van den Maagdenberg et al. 2019). With respect to the glutamatergic system, one of the chromosomal regions with significant linkage for non-hemiplegic migraine with aura is the 11q24 locus (Cader et al. 2003), which maps, among other candidates, the GRIK4 gene of the KA1 kainate receptor subunit (Mayer 2007). Polymorphisms in the glutamate receptor ionotropic amino-3-hydroxy-5-methyl-4-isoxazole-propionin acid 1 (GRIA1) and GRIA3 genes that code for two of the four subunits of the AMPA ionotropic glutamate receptor have been previously associated with migraine in an Italian and Australian population (Fang et al. 2015; Formicola et al. 2010; Maher et al. 2013), further supporting the plethora of evidence suggesting that glutamate dysfunction may contribute to migraine susceptibility. Furthermore, genetic screening of a patient with hemiplegic migraine, seizures and episodic ataxia revealed a mutation on the excitatory amino acid transporter 1 (EAAT1) (Jen et al. 2005), which reduces the glial cell's ability to clear glutamate from the synaptic cleft (Ramadan and Buchanan 2006). The resultant increased availability of synaptic glutamate would contribute to post-synaptic hyperexcitation, which would further lead to the development of central sensitization and the prominent neurological symptoms seen during migraine attacks. Another small study demonstrated that polymorphism of the glutamate transporter protein excitatory amino acid transporter 2 (EAAT2) are potentially involved in the development of medication-overuse headache and migraine transformation into chronic daily

headache, as *EEAT2* polymorphisms were significantly higher in patients with frequent analgesic usage (Shin et al. 2011).

Familial Hemiplegic Migraine (FHM) is a rare monogenic form of migraine with prominent aura symptoms (Ferrari et al. 2015) that is inherited in an autosomal dominant manner. The molecular linkage of FHM involves three mutations (van den Maagdenberg et al. 2007): FHM 1 mutation affecting the *CACNA1A* calcium channel gene mapped to chromosome 19p13 (Ophoff et al. 1996). FHM 2 mutation affecting the *ATP1A2* gene on chromosome 1q23 (De Fusco et al. 2003). FHM 3 mutation affecting the *SCN1A* gene on chromosome 2q24, which is a rarer cause of FHM (Dichgans et al. 2005; Vanmolkot et al. 2007). Interestingly a common consequence of these mutations is an increase in glutamate availability at the synaptic cleft (Andreou and Goadsby 2009a). The FHM 1 mutation on the pore-forming A1 subunit of $Ca_v2.1$ (P/Q-type) voltage-gated neuronal calcium channels that modulate release of neurotransmitters at peripheral and central synapses (van den Maagdenberg et al. 2007; Wessman et al. 2004) can have as a consequence enhanced glutamate release due to enhanced calcium flux at the pre-synaptic terminal (Schneggenburger and Neher 2005). The FHM2 mutation affecting the A2 subunit of sodium-potassium pump ATPases, which transport potassium and sodium ions across the cell membrane, has as a consequence a dysfunction on the reuptake of potassium and glutamate from the synaptic cleft into glial cells (De Vries et al. 2006). The FHM 3 mutation affects the A1 subunit of neuronal voltage-gated sodium ($Na_v1.1$) channels that normally modulate generation and propagation of action potentials, and has as a consequence the facilitation of high-frequency discharges that might also increase synaptic glutamate levels (Dichgans et al. 2005). The increased glutamate availability at the synaptic cleft caused by these mutations could potentially explain the increased susceptibility to cortical spreading depression, the underlying mechanism of migraine aura (van den Maagdenberg et al. 2004; Wessman et al. 2007).

6.4 Pathophysiology of the Migraine Attack and Glutamate Involvement

To date, through brain imaging studies we have a clear understanding of the bulk brain structures involved in migraine pathophysiology, however, the exact molecular mechanisms are not understood. Glutamate, as the main excitatory neurotransmitter in the brain, and the major neurotransmitter of the peripheral trigeminal system, has been implicated in all phases of a migraine attack. A migraine attack is characterised by different phases, the premonitory phase, migraine aura phase, the headache phase and the postdrome. Each phase is thought to involve functional changes in different brain structures.

6.4.1 The Premonitory Phase

Before the onset of any neurological symptoms or head pain, the majority of migraine patients can recognise the onset of the "premonitory phase". During the premonitory phase, which can last between few hours to days, patients experience excessive yawning, thirst, somnolence, food craving, cognitive difficulties and mood changes (Laurell et al. 2016). Early hypothesis on the brain areas involved in the preliminary phase of migraine suggested an association with hypothalamic function, given that the symptoms described are strongly associated with homeostatic functions regulated by the hypothalamus, such as arousal, sleep and feeding (Alstadhaug 2009). Additionally, a disturbance in homeostatic function, such as changes in sleep or eating patterns is a significant trigger of attacks (Kelman 2007). In the past years, few brain imaging studies provided stronger evidence for hypothalamic activation in migraine patients. These studies demonstrated increased blood flow in the posterior region of the hypothalamus during the very early stages of spontaneous migraine attacks (Denuelle et al. 2007; Schulte and May 2016) and during the premonitory phase of nitroglycerin (nitric oxide-NO donor)-induced migraine attacks (Maniyar et al. 2014). One of the fMRI studies, which scanned daily a migraine patient and captured all phases of migraine within a period of one month, reported, in addition to hypothalamic activation, increased activity at the occipital cortex (Schulte and May 2016), which has been long recognised as an area of hyperexcitability both in episodic and in chronic migraine (Aurora et al. 1999; Mulleners et al. 2001). Although it has been suggested that dysrhythmia along the thalamo-cortical axis in migraine patients may be responsible for abnormal cortical responses (Coppola et al. 2007), no such theory or evidence has been shown to date for hypothalamic-cortical dysrhythmia. Hence, through which networks, neurotransmitters and molecular changes the occipital cortex and the hypothalamus may influence each other remains unknown. A role for glutamate is possible, as preclinical studies demonstrated the participation of glutamatergic efferent pathways from the cortex to the posterior hypothalamus in the modulation of pain and anxiety and highlighted a role for ionotropic glutamate receptors (Falconi-Sobrinho et al. 2017).

Importantly, to date we do not understand the actual hypothalamic nuclei and their pharmacology involved in the development of the premonitory phase of migraine and potentially the triggering of a migraine attack. The hypothalamus, although a small region in the brain, consists of a number of different subnuclei that play a crucial role in many important functions, including releasing hormones, regulating body temperature, sleep and arousal. Although imaging studies suggest it is mostly its posterior area that could be implicated in the premonitory phase of migraine, several subnuclei, neurotransmitters and neuropeptides may be involved. Mainly animal studies suggest that these include dopaminergic mechanisms (Akerman and Goadsby 2007; Barbanti et al. 1998; Charbit et al. 2010; Marmura 2012; Shepherd et al. 2002), potentially from the dopaminergic A11 nucleus of the hypothalamus which has been shown to project to the TCC (Bjorklund and Skagerberg 1979). Interestingly, vesicular glutamate transporter 2 (VGluT2)

mRNA-expressing neurons are observed within different hypothalamic nuclei and on each midbrain dopamine system, suggesting that at least a subset of neurons might release dopamine and glutamate separately from different varicosities in many of their single axons (Kawano et al. 2006; Morales and Root 2014). To date, no concrete data in humans suggest the actual involvement of any specific hypothalamic nucleus or hypothalamic neurotransmitters/neuropeptides in migraine pathophysiology, although it remains an interesting area to explore for the development of future migraine therapeutics.

6.4.2 The Migraine Aura

The occipital cortex has been strongly linked to the development of migraine aura. This phase of a migraine attack occurs in about 20% of patients (Rasmussen and Olesen 1992) and it is characterised by transient neurological symptoms, most commonly visual alterations, that occur just before, or at the onset the actual migraine headache (IHS 2018; Zhang et al. 2016). Visual symptoms are the most common and are usually described as zigzag or scintillating figures mostly affecting one hemifield of both eyes. In some patients, sensory symptoms affecting the hand and gradually spreading to the whole arm and the perioral region occur alone or in conjunction with visual aura (Russell and Olesen 1996). Motor aura is less frequent and not well recognised by patients and is usually described as motor weakness (Jensen et al. 1986; Silberstein et al. 2001). Speech disturbances may also occur in some patients during the aura phase.

The underlying phenomenon that drives the migraine aura is now believed to be a wave of cortical spreading depression (CSD) which spreads out from the cortex, resulting in an initial hyperaemic phase followed by an oligaemic phase, and linked with a wave of cortical neuronal depolarisation (Lauritzen 1994; Leão 1944; Olesen 1998; Olesen et al. 1990). CSD, described first by Leão in the rabbit cortex in 1944, is a self-propagating depolarisation of neurons and glia linked with depressed neuronal electrical activity (Leão 1944) that moves at a rate of about 2–3 mm/min across the cerebral cortex. Leão first observed that CSD leads to transient dilatation of pial arteries. Following this transient hyperperfusion, hypoperfusion ensues, which persists long after CSD waves have passed. Spreading depression has been demonstrated in almost all the grey matter regions of the central nervous system (CNS) (Somjen 2001), although the cortex of primates, especially in humans, is relatively more resistant to CSD. Early observations from Lashley (Lashley 1941) suggested an association between CSD and the migraine aura and several imaging and blood flow studies of patients during migraine with aura showed unilateral regions of occipital hypoperfusion that tend to spread rostrally from the occipital cortex and persist into the headache phase (Sanchez-del-Rio and Reuter 2004). Actual clinical evidence supporting that a cerebral blood flow altering event such as CSD generates the aura in human visual cortex came only with the use of high-field functional MRI with near-continuous recording during migraine visual aura in

humans. With this method Hadjikhani and colleagues (2001) observed blood oxygenation level-dependent (BOLD) signal changes that demonstrated characteristics of CSD as time-locked to percept onset of the aura. For ethical reasons, direct electrophysiological recordings in the migraine brain have not been contacted, as for example in traumatic brain injury (Hartings et al. 2011; Lauritzen et al. 2011).

It is not yet clear how CSD is triggered in human cortex during migraine aura. A number of diverse stimuli trigger CSD in animal models, including direct cortical trauma, exposure to high concentrations of excitatory amino acids, including glutamate, or K^+, direct electrical stimulation, inhibition of Na^+/K^+-ATPase and energy failure (Somjen 2001). CSD in the neocortex of a variety of species, including man, has been demonstrated to be dependent on activation of the N-methyl-D-aspartate (NMDA) receptor (Faria and Mody 2004). Local release of glutamate by neurons is thought to initiate CSD and the subsequent activation of post-synaptic central glutamate receptors is argued to explain its propagation (Vinogradova 2018; Zandt et al. 2013). Volume-sensitive organic anion channels (VSOACs) in astrocytes are activated by cell swelling and release glutamate which contributed further to the propagation of spreading depression (Basarsky et al. 1999). NMDA receptor antagonists reduce the rate of propagation of SD (Basarsky et al. 1999). Furthermore, inhibition of CSD by memantine, an NMDA receptor antagonist, also suggests a key role for activation of neuronal glutamate receptors in the initiation of CSD (Peeters et al. 2007). As previously mentioned genetic predispositions and environmental factors may modulate individual susceptibility by lowering the CSD threshold (van den Maagdenberg et al. 2004), and cortical excitation may cause sufficient elevation in extracellular K^+ and glutamate to initiate CSD (De Fusco et al. 2003).

Although no obvious aura symptoms are reported by the majority of migraine patients, the presence of silent auras has been proposed (Dahlem and Isele 2013; Purdy 2008), based on observations of increased cortical blood flow in migraine without aura patients at the onset of a migraine attack (Denuelle et al. 2008; Woods et al. 1994). This theory however remains a matter of debate, as it is yet unclear if CSD can trigger a migraine attack in humans. Clinically, this hypothesis is not supported as aura without headache is not uncommon, and migraine aura is not always contralateral to the headache (Goadsby 2001). On the other hand, increased cortical excitability, potentially due to elevated glutamatergic activity, has been seen in migraine without aura patients controls (Aurora et al. 1999; Mulleners et al. 2001). In animals, CSD has been shown to induce activation of second order neurons in the TCC, and the authors suggested this is due to sensitization of pial emended trigeminal fibres from ions released from the cortex during a CSD (Zhang et al. 2010, 2011). However, if indeed the ascending trigeminothalamic pathway can be modulated by CSD, this could also be through activation of cortico-spinal projections or cortico-thalamic activation (Andreou et al. 2012, 2013), at least in animal models of migraine.

6.4.3 The Headache Phase

The headache phase of migraine is the most disabling phase of the attack. The actual pain in an untreated migraine attack may last between 4 and 72 h and it is characterised as moderate or severe. Head pain is often accompanied by nausea and other sensory symptoms, including photophobia and phonophobia. The pathophysiology of the headache phase in migraine is believed to include activation of trigeminal fibres, that innervate the dura matter and intracranial vasculature (Edvinsson et al. 2020; Olesen et al. 2009; Penfield and McNaughton 1940; Ray and Wolff 1940; Wolff 1948). These primary fibres have their cell body in the trigeminal ganglion and project centrally in the trigeminocervical complex (TCC; trigeminal nucleus caudalis, C1 and C2 spinal levels) (Edvinsson et al. 2020). The axons of the second order neurons in the TCC are part of the ascending trigeminothalamic pathway which projects and transmits nociceptive information to third order neurons, mainly in the ventroposteromedial thalamic nucleus (VPM) (Andreou and Edvinsson 2019).

A number of evidence over the decades suggest that activation of peripheral trigeminal fibres and subsequently of the ascending trigeminothalamic pathway during the headache phase may drive the nociceptive signals of the migraine headache (Andreou and Edvinsson 2019). First, stimulation of the dura matter and its vasculature in humans during awake brain surgery induces head pain that resembles the migraine headache and its frequent localisation on the temporal region (Olesen et al. 2009; Penfield and McNaughton 1940; Ray and Wolff 1940; Wolff 1948). Activation of the trigeminal fibres in migraine is mostly evident by the release of the neuropeptide calcitonin-gene related peptide (CGRP). CGRP levels have been shown to be elevated in cranial circulation during a migraine attack and in chronic migraine patients. Animal studies suggest that the origin of the CGRP is indeed the trigeminal nerve (Goadsby et al. 1988, 1990; Lambert et al. 1988). Additionally, substances like calcitonin gene-related peptide and histamine, that do not cross the blood brain barrier (BBB), can trigger a migraine attack (Hansen et al. 2010; Lassen et al. 1995). Final evidence and perhaps the most important is that therapeutics, like triptans (5HT1B/D agonists),—the migraine-specific acute treatments, that do not cross the BBB can stop a migraine attack (Millson et al. 2000; Tfelt-Hansen 2010). Other preventive migraine treatments that also do not cross the BBB, like the new CGRP monoclonal antibodies (mAbs) and botulinum toxin A (BOTOX) are amongst the most effective treatments in reducing the frequency of headache in chronic migraine patients (Andreou et al. 2018; Lambru et al. 2018).

The trigeminothalamic pathway includes the second order neurons located in the TCC and their projections to third order neurons, mainly in the VPM nucleus. Both the TCC and the thalamus are important relay centres of the migraine pathophysiology and prominent sites of action of migraine therapeutics (Andreou et al. 2010; Andreou and Goadsby 2009a; Andreou and Goadsby 2011; Shields and Goadsby 2006). The thalamic area has been further implicated in the development of

associated symptoms, such as hypersensitivity to visual (Noseda et al. 2010) and auditory stimuli (Filippov et al. 2008).

The major neurotransmitter in the trigeminal ganglion neurons, TCC neurons and third order neurons in the VPM is glutamate (Andreou and Goadsby 2009a). VGLUT1 and VGLUT2 positive neurons in the TCC provide collateral projections to the thalamus (Zhang et al. 2018). In vivo studies using microdialysis and blood flow measurements demonstrated increased levels of glutamate in the TCC during and post stimulation of trigeminal fibres in dural structures (Bereiter and Benetti 1996; Goadsby and Classey 2000). Glutamate plays a crucial role in the transmission of nociceptive information in the VPM. It is involved in signalling from spinothalamic tract and lemniscal pathways and from cortico-thalamic afferents (Broman and Ottersen 1992). Extracellular levels are increased following experimentally produced pain (Silva et al. 2001).

Glutamate triggers post-synaptic excitatory action potentials both in second TCC and third order VPM neurons, by activating multiple glutamate receptors (Andreou et al. 2015; Dougherty et al. 1996; Li et al. 1996; McCormick and von Krosigk 1992; Salt et al. 1999a, b; Salt and Eaton 1995; Salt and Turner 1998). Subunits of all three ionotropic glutamate receptors, namely NMDA, AMPA and kainate receptors, which are involved in fast synaptic signalling, have been found in trigeminal ganglia neurons or on their primary axons on the dura matter (Andreou et al. 2009, 2015; O'Brien and Cairns 2016; Quartu et al. 2002; Sahara et al. 1997; Watanabe et al. 1994). A study in rodents showed that peripherally administrated monosodium glutamate lowers the mechanical threshold of activation of trigeminal fibres in the dura matter, an effect blocked by NMDA receptor antagonists (O'Brien and Cairns 2016). In humans, anecdotal reports exist on the role of dietary monosodium glutamate as a migraine trigger, potentially acting on peripheral glutamate receptors (Borkum 2016; Jinap and Hajeb 2010). Intramuscular injection of glutamate in the masseter muscle which is also innervated by trigeminal fibres evokes pain, potentially through activation of the NMDA receptor (Cairns et al. 2003; Castrillon et al. 2007). These studies further support a role of peripheral glutamate receptors in trigeminal nociception.

On the other hand, earlier brain imaging studies demonstrated increased blood flow in the region of the dorsal rostral pontine and brainstem in both episodic (Afridi et al. 2005; Weiller et al. 1995) and chronic migraine patients (Matharu et al. 2004). The brainstem is known to project a number of descending modulatory circuits to the spinal cord (Akerman et al. 2011), and potentially a malfunction of this modulatory tone may amplify normal sensory processing along the ascending trigeminothalamic pathway (Andreou and Edvinsson 2019).

Within the TCC, microiontophoresis of selective NMDA, AMPA and kainate agonists was shown to excite second order neurons that respond to trigeminovascular stimulation (Andreou et al. 2006; Storer and Goadsby 1999). On the other hand, selective antagonists of NMDA, AMPA and kainate receptors have been shown to inhibit nociceptive trigeminovascular activation of these neurons (Storer and Goadsby 2009a, b), including magnesium, which can block the NMDA receptor (Furukawa et al. 2005). Likewise, within the VPM, agonists of the

ionotropic glutamate receptors were found to excite third order neurons, and selective antagonists were found to inhibit these neurons and trigeminovascular stimulation (Andreou et al. 2008; Salt 2002; Salt and Eaton 1989). Of interest, topiramate, an anti-convulsant approved for the preventive treatment of migraine has been shown to inhibit third order neurons responding to trigeminovascular stimulation, and to selectively block excitation induced by kainate receptor agonists but not by NMDA or AMPA agonists (Andreou and Goadsby 2011).

Some members of the metabotropic glutamate receptors (mGLuRs), which *act by coupling to G-proteins* and modulate differentially activation of sensory fibres, are also found in the trigeminal ganglion. Activation of group I mGluRs (mGluR1 and mGluR5) can increase neuronal excitation through phospholipase C calcium mobilisation (Abe et al. 1992; Pin et al. 2003). Activation of group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7 and mGluR8) mGluRs decreases neuronal excitation by inhibiting adenylyl cyclase (AC) resulting in reduction of intracellular cyclic adenosine monophosphate (cAMP) levels (Boye Larsen et al. 2014; Pin et al. 2003; Tanabe et al. 1993). Studies in rats showed that trigeminal neurons express mGluR1α, mGluR2/3 and mGluR8, while satellite glial cells (SGCs) express mGluR1α and mGluR8 (Boye Larsen et al. 2014). The role of mGluRs has been studied extensively in animal models of somatic pain (Pereira and Goudet 2018), however, very few studies investigated their function in trigeminal nociception and in migraine models. The mouse TCC has been shown to express at least the mGluR1, mGluR5, mGluR3 and mGLuR4. These receptors have been also found in the sensory thalamus and in midbrain and medulla sections involved in descending modulation of pain, notably in the periaqueductal grey (PAG) and rostroventral medulla (RVM) (Pereira and Goudet 2018).

Within the thalamus, microiontophoretic studies demonstrated that selective mGLuR1 and mGluR5 agonists can excite third order thalamic neurons (Salt et al. 1999b; Salt and Eaton 1995). Acute thalamic nociceptive responses are found to be mediated by a combination of mGlu1, mGlu5 and NMDA receptor activation, and that co-activation of these receptors produced a synergistic excitatory effect (Salt et al. 1999a; Salt and Binns 2000). On the other hand, agonists that are active at Group II and Group III mGluRs were shown to reduce sensory-evoked synaptic inhibition by a pre-synaptic mechanism (Salt and Eaton 1995; Salt and Turner 1998). A small clinical trial on the acute actions on migraine attack of a selective mGluR5 agonist, ADX-10059, was discontinued due to unacceptable side effects, despite some promise on its efficacy versus placebo (Marin and Goadsby 2010).

The glutamate transporters (GLT) have been also found on trigeminal fibres in the periphery and in the dorsal horn of the TCC (Alvarez et al. 2004; Kim et al. 2015, 2018; Li et al. 2003; Persson et al. 2006). High affinity excitatory amino acid transporters (EAATs) are essential to terminate glutamatergic neurotransmission and to prevent excitotoxicity. So far, five structurally distinct transporters have been identified from animal and human tissues: glutamate/aspartate transporter (GLAST; EAAT1 in human), glutamate transporter-1 (GLT-1; EAAT2 in human), excitatory amino acid carrier-1 (EAAC1; EAAT3 in human), excitatory amino acid transporter 4 (EAAT4) and excitatory amino acid transporter 5 (EAAT5). In the

TCC, it was shown that EAAC1 like-immunoreactivity was present in lamina II. GLAST like-immunoreactivity was also present in lamina II, in both astroglia and neurons and around the central canal (lamina X). GLT-1 was highly expressed in astroglial cells in laminae I-III and the area around the central canal (Tao et al. 2005), and finally, though EAAT4 was initially found to be neuronal in the brain, it has been co-localised with astroglia in the spinal cord (Hu et al. 2003; Rothstein et al. 1994). EAAC1, in addition to its expression in the spinal cord neurons, is detected in dorsal root ganglia (DRG) and distributed predominantly in small DRG neurons (Tao et al. 2005). Some of these EAAC1-positive DRG neurons are positive for CGRP or are labelled by isolectin B4 (Tao et al. 2005), a marker of non-peptidergic neurons. As mentioned earlier, polymorphisms of EAAT2 have been proposed to be involved in the development of chronic migraine (Shin et al. 2011).

Vesicular glutamate transporters (VGLUTs) are considered as the best glutamate markers for staining glutamatergic cells; their presence is a strong indication that glutamate is accumulated in vesicles from which it can be released. Staining studies found these transporters in populations of axons that are known to be glutamatergic and their expression in cultured cells results in glutamate uptake and the subsequent conversion of neurons to a glutamatergic phenotype (Bellocchio et al. 2000; Todd et al. 2003). In the spinal cord both the VGLUT1 and VGLUT2 are expressed, though the spinocervical tract, including the TCC, was found to contain dense labelling for VGLUT2 (Persson et al. 2006). This suggests that VGLUT2 is the transporter responsible for the vesicular accumulation of glutamate at the spinocervical tract terminals, and thus most glutamatergic fibre systems in the spinal cord should display high probability of release, because of their use of VGLUT2 as vesicular transporter (Fremeau Jr et al. 2001; Persson et al. 2006). Spinal, and subsequently TCC, glutamate transporters might play an important role in normal sensory transmission. Intrathecal application of the selective glutamate transporter blocker DL-threo-β-Benzyloxyaspartic acid (TBOA) resulted in significant and dose-dependent spontaneous nociceptive behaviours, and in remarkable hypersensitivity in response to thermal and mechanical stimuli (Liaw et al. 2005). TBOA on the dorsal surface of the spinal cord also resulted in a significant elevation of extracellular glutamate concentrations (Liaw et al. 2005). These findings indicate that a decrease of spinal glutamate uptake can lead to excessive glutamate accumulation in the spinal cord, which might, in turn, result in over-activation of glutamate receptors, and production of spontaneous nociceptive behaviours and sensory hypersensitivity (Tao et al. 2005). However, the glutamate transporters seem to also have opposing actions in pathological pain in animal models. Inhibition or transient knockdown of spinal GLT-1 led to a significant reduction of nociceptive behaviour in the formalin model, whereas different glutamate transporter inhibitors (TBOA, dihydrokainate, threo-3-hydroxyaspartate) reduced formalin-induced nociceptive responses and complete Freund's adjuvant-evoked thermal hyperalgesia (Tao et al. 2005). Different potential mechanisms by which glutamate transporters are involved in pathological pain have been suggested; however, their exact function is not completely understood.

6.4.4 *The Postdrome Phase*

The postdrome phase is the last phase of a migraine attack, which is recognised by at least 80% of patients (Giffin et al. 2016). The postdrome phase occurs after the end of the headache phase and its duration may be between few hours to days. It is mainly characterised by symptoms of fatigue, difficulties in concentration and comprehension, neck stiffness and high disability scores (Giffin et al. 2016). The migraine postdrome is the least studied and least understood phase of migraine. A couple of functional imaging studies showed widespread reduction in brain-blood flow during this phase, but persistent blood flow increase in the occipital cortex (Bose and Goadsby 2016; Schulte and May 2016).

6.5 Pathophysiology of Chronic Migraine and Glutamate Involvement

Chronic migraine is defined by the International Classification of Headache Disorders (ICHD3) of the International Headache Society, as a disorder with headache occurring on at least 15 days per month, which on at least 8 days have the features of a migraine headache (IHS 2018). In chronic migraine it is often impossible to distinguish the individual episodes of headache attacks and the headache appears as a continuous state. About 2.5% of episodic migraine patients progress into chronic migraine (Manack et al. 2011). Chronic migraine is disabling, underdiagnosed and undertreated, affecting about 1–2% of the general population (Buse et al. 2012; Natoli et al. 2010). Factors identified to increase the risk for migraine chronification include de novo increased migraine attack frequency, overuse of acute migraine medication, ineffective acute treatment that could lead to medication overuse, depression and lifestyle factors such as stress, high caffeine intake and obesity (Ashina et al. 2012; Bigal and Lipton 2006; Katsarava et al. 2004; Lipton et al. 2015; Mathew et al. 1990; May and Schulte 2016; Scher et al. 2003).

Chronic migraine appears to induce neuroplastic changes in patients' brain. A number of brain imaging studies showed changes in grey matter volume, as well as in white matter hyperintensities in CM patients, compared to episodic migraine patients (Aradi et al. 2013; Chiapparini et al. 2010; Rocca et al. 2006; Valfre et al. 2008; Zheng et al. 2014), as well as large-scale reorganisation of functional cortical networks and interactive neuronal networks (Coppola et al. 2019). Similar to episodic migraine, cortical excitability appears to be abnormal in chronic migraine patients, but whether this contributes to migraine chronification remains uncertain (Coppola and Schoenen 2012; Cosentino et al. 2014).

The physiological mechanisms that underlie the development of chronic migraine from its episodic form are not understood (Andreou and Edvinsson 2019). However, central sensitization, occurring from peripheral sensitization, has been proposed to play a key role in the development of chronic migraine, similar to other chronic pain

conditions. Central sensitization refers to increased excitability of second order neurons and could even include sensitization of third order thalamic neurons, characterised by increased synaptic strength and enlargement of receptive fields (McMahon et al. 1993; Woolf and Doubell 1994; Woolf and Salter 2000). Central sensitization occurs following repeated activation of peripheral fibres that are at a state of peripheral sensitization leading to the establishment of hyperexcitability in second order neurons in the TCC. Multiple studies in different animal models of pain showed that activity-dependent central sensitization is induced by intense, repeated, or sustained nociceptor inputs. Central sensitization can then persist in the absence of further nociceptor input. Clinically, central sensitization is manifested as a state of either hyperalgesia—an exaggerated pain in response to a stimulus that normally causes mild pain, or of allodynia—a pain response to a normally nonpainful stimulus, and exaggerated pain response referred outside the original pain site (Dodick and Silberstein 2006). Indeed, during a migraine headache about 80% of migraine patients develop cutaneous allodynia, characterised by increased skin sensitivity, mostly within the referred area of pain of the ipsilateral head, but other parts of the body may be also affected, especially if the attack remains untreated (Burstein et al. 2000; Selby and Lance 1960; Su and Yu 2018). Allodynia in non-cephalic areas has been proposed to include sensitization of both second order neurons in the TCC and of third order neurons in the thalamus (Burstein et al. 2000; Dodick and Silberstein 2006). Hence, repeated episodes of peripheral and central sensitization could lead to the development of chronic migraine.

Central sensitization is a glutamate-dependent process and at least, NMDA receptor activation seems to be pivotal for the induction and maintenance of central sensitization in neuronal fibres innervating the dura matter (Woolf and Thompson 1991). Hence, treatment of chronic migraine could target glutamatergic transmission in brain pathways involved in central sensitization, or the peripheral cause in the trigeminal system that induced glutamatergic-driven peripheral sensitization.

Central sensitization requires activation of NMDA receptors for its induction, which leads to elevation in intracellular calcium, activating multiple calcium-dependent kinases that act on receptors and ion channels to further increase synaptic efficacy (Latremoliere and Woolf 2009). AMPA receptors may also participate in the elevation of calcium in the synapse. Studies in multiple pain models suggest that central sensitization includes multiple mechanisms of synaptic plasticity caused by changes in the density, nature and properties of ionotropic and metabotropic glutamate receptors (Latremoliere and Woolf 2009). Ionotropic glutamate receptors can be phosphorylated by intracellular kinases, inducing changes in their activity and trafficking to the membrane, which manifest central sensitization by boosting synaptic efficacy (Carvalho et al. 2000; Lau and Zukin 2007). Stimulation of group I mGluRs also participate, along with NMDA and AMPA receptors, in the activation of the intracellular pathways that sustain central sensitization (Ferguson et al. 2008; Guo et al. 2004; Hu et al. 2007).

In animal models of migraine, inflammatory agents on the dura matter induced long-lasting activation of the trigeminovascular pathway (Burstein et al. 1998; Ebersberger et al. 1997; Schepelmann et al. 1999), which provoked long-lasting

sensitization in trigeminocervical neurons manifested as increased responsiveness and expansion of dural and cutaneous receptive fields (Burstein et al. 1998). These changes were recorded in parallel to an increase of the extracellular glutamate concentration of second order neurons in the TCC (Oshinsky and Luo 2006), indicating an important contribution of glutamate and its receptors in trigeminal allodynia (Oshinsky and Luo 2006). The increased glutamate concentrations in the CSF of chronic migraine patients (Gallai et al. 2003; Peres et al. 2004; van Dongen et al. 2017) indeed support the presence of central sensitization (Burstein et al. 2000).

6.6 CGRP in Migraine and its Modulation of Glutamatergic Transmission

What may initiate peripheral sensitization of the trigeminal nerve that could then lead to the development of central sensitization in chronic migraine remains uncertain, however a role for peripheral inflammation seems plausible (Andreou and Edvinsson 2019; Edvinsson et al. 2019). Calcitonin gene-related peptide (CGRP), of trigeminal origin, is a neuropeptide shown to be increased in the circulation of patients during migraine attacks (Goadsby et al. 1988, 1990) and in between attacks (Ashina et al. 2000). Its levels were shown to be normalised following treatment with sumatriptan (Goadsby and Edvinsson 1993), a $5HT1_{B/D}$ agonist designed as a migraine-specific acute treatment. Intravenous infusion of CGRP has been shown to induce migraine attacks without aura in migraine patients (Hansen et al. 2010). Importantly, CGRP has emerged as a therapeutic target in migraine, since CGRP receptor antagonists and mAbs against CGRP itself or against its receptor are effective preventive treatments for episodic and chronic migraine patients (Andreou et al. 2020; Lambru et al. 2018).

In the peripheral neural tissue, CGRP is found in the trigeminal, dorsal root and vagal ganglia, and their nerve endings, including peri-vasculature nerve terminals in the dura matter (Edvinsson et al. 2020). Centrally, CGRP is found mainly in nerve fibres in the dorsal horn laminae I/IIo of the spinal cord and the TCC, and in some acetylcholine neurons of the ventral horn (Piehl et al. 1991). Small populations of neurons expressing CGRP are also found in the brain (Hokfelt et al. 1992). In migraine animal models, stimulation of trigeminal fibres innervating the superior sagittal sinus increases CGRP circulating levels (Goadsby et al. 1988; Zagami et al. 1990). In humans CGRP levels are increased during stimulation of the trigeminal ganglion, further supporting a trigeminal origin of CGRP in migraine patients (Goadsby et al. 1988).

CGRP is expressed in many human VGLUT1 and VGLUT2 positive trigeminal axons, as well as in rat glutaminase positive neurons (Miller et al. 1993) but not in VGLUT1 positive trigeminal neurons (Cho et al. 2021). However, in immunohistochemistry studies using an anti-glutamate glutaraldehyde antibody in rat and rhesus

monkey trigeminal ganglia found only few neurons co-expressing CGRP and glutamate (Eftekhari et al. 2015). CGRP has been found however to co-release with glutamate, and its release is regulated by voltage-dependent calcium channels (Xiao et al. 2008). Upon its release, CGRP acts on the CGRP receptor which consists of heterodimers of CLR/RAMP1 subunits. Functional CLR/RAMP1 receptors require intracellular interactions with receptor component protein (RCP) and its activation induces stimulation of adenylyl cyclase (AC) and production of *cyclic* adenosine monophosphate (cAMP) (Russell et al. 2014). Recently, the calcitonin receptor CTR/RAMP1 heterodimer (AMY1 receptor) is also believed to be a functional CGRP receptor (Hay et al. 2008; Walker et al. 2015). Functional CGRP receptor(s) have similar distribution patterns as with CGRP neurons and fibres (Russell et al. 2014).

While peripherally, the vascular actions of CGRP as the most potent vasodilator are well characterised (Brain et al. 1985), its modulatory function in somatosensory neurons received considerable attention only recently. Growing evidence indicates that CGRP plays a key role in the development of peripheral sensitization and in the development of neurogenic inflammation. In animals, sustained CGRP release may induce peripheral sensitization of the trigeminal system (Nakamura-Craig and Gill 1991), likely due to the release of pre-synaptic inflammatory mediators, such as bradykinin or prostaglandins from nerve endings and potentiation of post-synaptic glutamate responses (Birrell et al. 1991; Schaible and Schmidt 1988; Wang et al. 2006). CGRP induces release of pro-inflammatory mediators from inflammatory cells (Walsh et al. 2015). Direct application of CGRP on trigeminal fibres on the dura matter does not sensitize second order neurons (Levy 2012; Levy et al. 2005). When CGRP is applied microiontophoretically onto second order neurons in the TCC, in the absence of any other stimulus, it also has little effect on spontaneous neuronal firing (Leem et al. 2001; Miletic and Tan 1988). However, in the presence of glutamate, CGRP can facilitate, inhibit or have no effect on glutamate-evoked firing in second order neurons (Leem et al. 2001; Yu et al. 2002). CGRP was shown to potentiate mainly NMDA, but also AMPA-evoked firing, while in some neurons CGRP showed reciprocal changes, inducing potentiation of NMDA-evoked firing and suppression of AMPA-evoked firing (Leem et al. 2001). Given that CGRP is co-released with glutamate, its role as a glutamatergic modulator is thus of significant importance. Importantly, CGRP can facilitate nociceptive activation of second order neurons and contributes to the development and maintenance of central sensitization (Biella et al. 1991). In animal models of migraine, CGRP antagonists have been shown to inhibit trigeminovascular nociceptive information in parallel to reducing glutamate-evoked activation of second order neurons in the TCC (Storer et al. 2004).

6.7 Current Migraine Treatments Acting as Modulators of Glutamatergic Signalling

Migraine treatment involves acute (abortive) and preventive therapies. Acute treatments are used for relieving migraine headache upon occurrence of a migraine attack. Preventive treatments on the other hand aim to reduce frequency and severity of migraine attacks. A wide range of medications have been used for the preventive treatment of migraine, including beta-adrenoceptor blocking drugs, antidepressants, calcium channel blockers, antiepileptics, botulinum toxin A and the newly developed anti-CGRP mAbs and CGRP antagonists. Acute treatments include triptans, non-steroidal anti-inflammatory drugs, acetaminophen and other over-the-counter pain killers. These treatments exhibit different mechanisms of actions and their efficacy in migraine is variable.

6.7.1 Triptans and Glutamatergic Modulation

Triptans are $5HT1_{B/D}$ agonists specifically developed for the acute treatment of migraine. Part of their anti-nociceptive mechanism of action is believed to be due to the modulation of glutamate release from primary afferents, similar to endogenous serotonin's actions (Travagli and Williams 1996). Triptans have been shown to modulate the release of glutamate from primary afferents in the TCC, by decreasing the amplitude of glutamatergic excitatory post-synaptic currents and reduce the frequency of spontaneous miniature excitatory post-synaptic currents. These actions are potentially mediated by the presence of $5\text{-}HT1_D$ and/or $5\text{-}HT1_B$ receptors on the pre-synaptic terminal, activation of which affects pre-synaptic Ca^{2+} influx (Choi et al. 2012; Hwang and Dun 1999; Jennings et al. 2004). Similar actions of triptans on glutamatergic transmission have been shown in brain neurons (Maura and Raiteri 1996; Stepien et al. 1999), however triptans are unlikely to cross the blood brain barrier (Kaube et al. 1993; Liktor-Busa et al. 2020). Regardless, CSF levels of glutamate in chronic migraine patients who overuse triptans are lower than in CM who overuse other abortive treatments suggesting that triptans mechanism of action may include in part reduction of extracellular glutamate levels in the brain (Vieira et al. 2007).

6.7.2 Preventive Migraine Treatments Acting as Modulators of Glutamatergic Signalling

Topiramate is an anti-epileptic drug used in the preventive treatment of migraine. Its mechanism of action is complicated and rather unclear. Several targets have been proposed to be relevant to the therapeutic activity of topiramate (Aboul-Enein et al.

2012) including voltage-gated sodium channels, high-voltage-activated calcium channels, $GABA_A$ receptors and AMPA/kainate receptors. Although all the above-mentioned mechanisms of action may be relevant to its therapeutic efficacy in migraine, preclinical studies in animal models of migraine showed that topiramate can block nociceptive-evoked activation of second and third order neurons in the TCC and thalamus, respectively (Andreou and Goadsby 2010, 2011; Storer and Goadsby 2004), by selectively blocking kainate agonists-evoked currents (Andreou and Goadsby 2010, 2011). Topiramate's modulatory action on the glutamatergic system may be more complicated as in healthy subjects it was found to increase the cortical levels of glutamine, possibly by acting on the metabolic pathway of glutamate and GABA (Moore et al. 2006). Although topiramate was shown to inhibit CSD in animal models, it was not found effective in preventing migraine aura in patients (Lampl et al. 2004).

Lamotrigine is an anti-convulsant which reduces glutamate release possibly through modulation of voltage-sensitive sodium channels (Lee et al. 2008; Wang et al. 2001). A role for lamotrigine in the prophylactic treatment of migraine has been suggested by small studies, although conflicting outcomes are available (D'Andrea et al. 1999; Gupta et al. 2007; Lampl et al. 1999, 2005; Smeralda et al. 2020; Steiner et al. 1997). Clinically, lamotrigine seems to be an effective treatment option in chronic migraine patients with allodynia, prominent aura and vertigo (Bisdorff 2004; Cologno et al. 2013; D'Andrea et al. 1999).

Ketamine is a medication primarily used for the induction of sedation; however, it can be used for the acute management of pain under controlled conditions (Rocchio and Ward 2021). Ketamine is a non-competitive antagonist at the NMDA receptor which has been used in small studies in migraine patients and found to be effective as an abortive treatment of migraine, especially in patients accessing the emergency department (Bilhimer et al. 2020). It has been also used in FHM migraine with aura patients and found to be effective in reducing the aura symptoms in about 50% of the patients without significant improvement of the migraine headache (Kaube et al. 2000). Ketamine in migraine animal models attenuated neurogenic dural vasodilation (NDV) in rats, demonstrating an additional role for NMDA receptors on the peripheral trigeminovascular system (Chan et al. 2009). Its use has limitations however as its overall efficacy and dosage in relation to the risk of undesirable side effects remain uncertain. Of interest in a small, randomised study, intranasal ketamine was not found to be superior to standard therapy among patients with primary headache syndromes (Benish et al. 2019).

Memantine is another non-competitive NMDA receptor channel blocker which demonstrated significant effects in reducing the headache frequency and the mean disability scores when given as a preventive treatment of refractory migraine (Assarzadegan and Sistanizad 2017; Charles et al. 2007; Krymchantowski and Jevoux 2009; Noruzzadeh et al. 2016; Shanmugam et al. 2019). In a small randomised double-blind placebo-controlled trial memantine was found a tolerable and efficacious preventive treatment in patients with migraine without aura (Noruzzadeh et al. 2016). Its side effects were generally mild (Bigal et al. 2008b; Noruzzadeh et al. 2016). Memantine was shown to inhibit nociceptive

trigeminovascular transmission in second order neurons in the TCC of animal models of migraine (Hoffmann et al. 2019).

Activation of NMDA requires simultaneous binding of both glutamate and the co-agonist glycine (Johnson and Ascher 1987; Kleckner and Dingledine 1988) in conjunction with the removal of Mg^{2+} blockage in a voltage-dependent manner (Mayer and Westbrook 1987). Oral magnesium is commonly used as a non-prescription preventive therapy in migraine (Orr 2016), although appropriate studies providing strong evidence on its efficacy are lacking (Andreou and Goadsby 2009a). It is worth mentioning that Mg^{2+} efficacy may include other mechanisms of action beyond the NMDA receptor. A role for Mg^{2+} in migraine pathophysiology has been suggested as reduced Mg^{2+} levels have been reported in the serum and CSF during and between attacks (Nischwitz et al. 2008; Ramadan et al. 1989; Sarchielli et al. 1992). An older MR spectroscopy study also showed reduced Mg^{2+} concentration within the brain of migraine patients (Ramadan et al. 1989). In animal models of migraine, Mg^{2+} was shown to inhibit nociceptive trigeminovascular transmission in second order neurons in the TCC of (Hoffmann et al. 2019).

Subcutaneous/intramuscular injections of botulinum toxin A (BoNT/A) in the head, neck and shoulders (PREEMPT protocol) is one of the most effective preventive treatments in migraine (Andreou et al. 2018; Aurora et al. 2014; Dodick et al. 2010). BoNT/A cleaves SNAP-25, preventing the correct assembly of the SNARE complex which leads to potent blockade of neurotransmitter and neuropeptide release. At the neuromuscular junction, BoNT/A-induced cleavage of SNAP-25 inhibits the release of acetylcholine from the nerve endings, resulting in muscle paralysis (Binz et al. 2010). Similarly, by cleaving SNAP-25, BoNT/A can interfere with sensory neuronal secretion by blocking pre-synaptic release of glutamate and neuropeptides (Durham et al. 2004; Gazerani et al. 2010; Meng et al. 2009). In animal models of migraine, BoNT/A was shown to block the release of CGRP and of glutamate from trigeminal ganglion neurons (Durham et al. 2004; Gazerani et al. 2010; Meng et al. 2009). In the trigeminovascular model of migraine, BoNT/A was shown to block mechanical activation and sensitization of nociceptors (Burstein et al. 2014; Gazerani et al. 2010). Interestingly, the SNARE complex is also used for the vesicular transport and exocytosis of NMDA and other glutamate receptors on the neuronal membrane (Woo et al. 2020). BoNT/A has been shown to reduce the expression of these receptors, representing an additional anti-nociceptive mechanism of action (Cheng et al. 2013; Woo et al. 2020).

6.8 Future Developments and Perspectives for Glutamate Modulating Treatments

Glutamate is clearly implicated in migraine pathophysiology. Being the major neurotransmitter that drives activation of the ascending trigeminovascular pathway, ultimately a glutamate blocker will be the “cure” of at least the disabling migraine

headache. However, given the abundance of glutamate and its receptors in the brain and their significant function in excitatory neurotransmission, such an option is unacceptable.

Some attempts have been made in the past to block ionotropic glutamate receptors in clinical trials. In a randomised, double-blind, proof-of-concept study which assessed the efficacy of an AMPA receptor antagonist, BGG492, in the acute treatment of migraine, BGG492 was found superior to placebo, but not superior to sumatriptan. However, adverse effects were reported by 80% of patients on the active arm (Gomez-Mancilla et al. 2014). In a randomised double-blind study, a selective GluK1 kainate antagonist LY466195 (Weiss et al. 2006) was effective in relieving acute migraine (Johnson et al. 2008), however, patients reported significant visual side effects. In preclinical studies using selective ionotropic glutamate receptor agonists, Andreou and colleagues identified in addition to kainate, NMDA antagonist actions of this compound on second order neurons in the TCC (Andreou and Goadsby 2009a, b). A possibility is that the visual disturbances reported by patients were mediated by the NMDA antagonism, while both receptors may have participated in the clinical efficacy of this drug. With that in mind, amongst the ionotropic glutamate receptors, the kainate receptor may represent a potential glutamatergic target for future therapeutics, providing that more selective antagonists will become available for clinical trials.

Kainate receptors are not as abundant as NMDA or AMPA receptors, however they are expressed in key structures of the trigeminal nociceptive pathway, including the trigeminal ganglion, trigeminal fibres innervating the dura matter, pre-synaptically and post-synaptically in the TCC and ventroposteromedial thalamus. Their expression within the trigeminal ganglion has been shown to increase after injection of nitroglycerin (Sankaran et al. 2019), which in humans triggers a migraine attack (Iversen and Olesen 1996). In vitro experiments have demonstrated that kainate receptors function as modulators of synaptic transmission and plasticity by regulating post-synaptic currents and pre-synaptic neurotransmitters' release (Andreou and Goadsby 2009a; Bortolotto et al. 1999; Kerchner et al. 2002). Microiontophoretic ejection of selective GluK1 antagonists in the TCC caused a differential response with both inhibition and facilitation in different subpopulations of neurons, activated in response to dural vessel electrical stimulation, by acting at either post-synaptic or pre-synaptic sites (Andreou et al. 2015). Intravenous administration of an iGluR5 agonist inhibited neurogenic dural vasodilation, whereas an antagonist had no effect (Andreou et al. 2009). Direct ejection of an iGluR5 antagonist in the VPM, using microiontophoretic electrode, attenuated activation of third order neurons in response to dural vessel electrical stimulation (Andreou and Goadsby 2009a).

Migraine treatment with metabotropic glutamate receptors has been also attempted in small clinical trials, based on outcomes from preclinical studies on the efficacy of mGluR antagonists in the reduction of hyperalgesia and allodynia in animal models of chronic pain (Fundytus 2001). A potent, selective, negative allosteric modulator of the mGluR5 receptor, ADX10059, was used in small randomised, placebo-controlled clinical trial for the acute treatment of migraine.

ADX10059 showed a statistically significant higher number of patients pain-free 2 h after dosing compared to placebo, however the reported side effects, including hallucinations and vivid dreaming, were discouraging (Marin and Goadsby 2010). Further to this group I mGluR5 antagonist, group II mGluR antagonists have been also advanced into clinical trials in the past for the treatment of acute migraine, however their outcomes have not been published (Johnson et al. 2008). These concerned an mGluR3 antagonist, and a dual mGluR2/cysteinyl-leukotriene 1 (CysLT1) antagonist which entered a Phase II placebo-controlled proof-of-concept study in patients with migraine. This molecule was found to have low brain penetration and was found effective in a preclinical rodent model of migraine, and well tolerated in rat and dog toxicological studies (Célanire et al. 2012). Moving forward, group II mGluRs may still offer a potential therapeutic opportunity, given their important role in pain modulation (Mazzitelli et al. 2018). mGluR2 and mGLuR3 are couple negatively to adenylyl cyclase through Gi/Go proteins, mainly expressed pre-synaptically, and typically their activation has been shown to inhibit the release of neurotransmitters, including glutamate and GABA. Although more knowledge is needed around their function, pharmacological studies in pain models have shown anti-nociceptive effects of group II mGluR agonists, and not of antagonists (Mazzitelli et al. 2018). The availability of orthosteric and new selective allosteric modulators acting on mGluR2 and mGluR3 may provide valuable tools for investigating the role of these receptors in migraine pathophysiology and their potential as therapeutic targets (Mazzitelli et al. 2018).

Any new pharmacological agents that target the glutamatergic system will also have to possess acceptable safety profiles along with clinical efficacy. This is illustrated by the recent discontinuation of clinical trials involving the mGluR5 receptor modulator ADX10059. Perhaps, targeting the glutamatergic system indirectly is an approach that deserves further investigations. For example, the kynurenic acid, a product of the tryptophan-kynurenic pathway, may present such a possibility. Kynurenic acid has been shown to act as an antagonism of NMDA receptors (Stone and Darlington 2002). Studies in chronic migraine patients found altered serum levels of all kynurenine metabolites (Curto et al. 2015). In animal models pre-treatment with kynurenic acid was shown to prevent the nitroglycerine-induced neuronal activation and sensitization in the TCC (Fejes-Szabo et al. 2014), to supress nociceptive activation of the trigeminal pathway (Csati et al. 2015; Lukacs et al. 2016; Veres et al. 2017), and to reduce the release of glutamate (Lukacs et al. 2016). Additionally, the expanding engineering of recombinant BoNT molecules (Dolly et al. 2011), which have been shown to be effective in animal models of migraine (Andreou et al. 2021), could offer in the future the opportunity to selectively block VGLUT1/2 trigeminal fibres, in order to selectively block glutamatergic transmission along the trigeminal system.

Despite the number of studies on pain pathways involved during the headache phase, the molecular changes that actually trigger a migraine attack in the brain remain unknown. The lack of such knowledge had significantly hampered the design of migraine-specific and effective preventive treatments for a long time. Certainly, designing brain acting glutamate modulators could offer a significant therapeutic

value in migraine patients, however any attempt will have to minimise the occurrence of significant side effects, that limited the advancement of glutamate antagonists in migraine clinic.

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