Drug targets of migraine and neuropathy: treatment of hyperexcitability

Abstract : Migraine and neuropathic pain are common causes of chronic pain. The exact pathomechanism has not been fully clarified for either disorder, but their pathophysiological backgrounds involve several similar mechanisms. Peripheral sensitization occurs in the neuronal elements of the dorsal root ganglion or the trigeminal ganglion, while central sensitization appears in the second-order neurons in the dorsal horn of the spinal cord or the trigeminal nucleus caudalis. Central neuronal hyperexcitability has been implicated in both disorders, and the emerging evidence suggests alterations in the glutamatergic neurotransmission and NMDA-receptor activation. Migraine and neuropathic pain additionally share certain clinical features, such as enhanced sensitivity to sensory stimuli and cutaneous allodynia. The pharmacotherapy of both diseases is often challenging, but several antiepileptic drugs that target hyperexcitability are beneficial for both migraine and neuropathic pain. Kynurenine pathway metabolites are capable of influencing the glutamate receptors, and might therefore be novel candidates for future drug development.

Keywords : allodynia, glutamate, hyperexcitability, migraine, neuropathic pain, sensitization

Introduction

Migraine is a common, highly disabling neurovascular disorder with a high socioeconomic impact, but its effective therapeutic management still poses a considerable challenge. The overall prevalence of migraine is around 16%; in the adult population, the prevalence is 3-fold higher in women than in men. Migraine attacks are characterized by a unilateral, throbbing or pulsating, often severe headache concomitant with autonomic symptoms such as nausea or vomiting, photophobia and phonophobia. Among the subtypes differentiated on the 2013 criteria of the International Headache Society, the most frequent are migraine with aura (MA) and migraine without aura (MoA). In patients with MA, focal neurological symptoms develop before the beginning of the headache phase; these may include visual disturbances such as blurred vision, tunnel vision or scintillating scotomas, and less frequently motor symptoms or speech difficulties. Cephalic and extracephalic cutaneus allodynia is also a common sign, which together with photophobia and phonophobia suggests a hyperexcitability state. The altered function is present in the central nervous system (CNS) at the level of the cortex and brainstem and at the periphery too, e.g. the trigeminal ganglion.

Neuropathic pain, another common cause of chronic pain, has a deteriorating effect on the overall quality of life. The prevalence of chronic pain with neuropathic characteristics is in the general population 6-10% . The latest definition of neuropathic pain by the International Association for the Study of Pain is a ,,pain caused by a lesion or disease of the somatosensory system” . Neuropathic pain syndromes include a variety of different conditions, which may have very heterogenous etiological factors. The main common feature is an abnormal pain

sensation with sensory disturbances without any nociceptive stimuli. The most common causes of neuropathic pain are diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia and spinal cord injury, but stroke, multiple sclerosis, cancer and several other conditions may also result in neuropathic pain. Neuropathic pain conditions result in similar symptoms, independently of the etiology: spontaneous and evoked types of pain, paresthesia, dysesthesia, allodynia, hyperpathia and hyperalgesia may all occur. The exact pathophysiological mechanisms underlying the development of neuropathic pain syndromes have not been fully elucidated, but the sensitization process is widely accepted to play an important role. Alterations in the peripheral nervous system, in the spinal cord and at the brain level may all contribute to the pathomechanism.

The pharmacological management of both migraine and neuropathic pain is often a serious challenge. Neuropathic pain syndromes and migraine share a common pathomechanism of hyperexcitability, which might comprise a therapeutic target. This review presents an overview of the role of hyperexcitability in these disorders, with an account of the current therapeutic options and the future possibilities.

Hyperexcitability and sensitization in migraine

The exact pathomechanism behind repeated migraine attacks is still unclear, but an alteration in the normal brain function has been suggested, especially as concerns the sensory information processing . In the early 1980s, it was suggested that hyperexcitability occurs in migraineurs, characterized by an increased response to different sensory stimuli. The first study demonstrated several visual evoked potential (VEP) abnormalities in migraine patients . Wilkins et al. later described more intense illusions caused by grating patterns in migraineurs as compared with healthy subjects, this phenomenon exhibiting similarities to photosensitive epilepsy . Another study confirmed prolonged VEP latencies and an increased P100 amplitude in both MA and MoA patients . An increased P100 amplitude has likewise been observed in another study, and was suggested to correlate with a low serum magnesium (Mg^{2+}) level . In MA patients, the increased P100 amplitudes displayed a side-difference, and were significantly higher on the side contralateral to the aura symptoms . In accordance with these data, an increased evoked cortical response was detected after auditory stimuli in migraine patients versus controls , and migraineurs demonstrated a strong intensity dependence. A magnetoencephalographic study provided evidence of hyperexcitability in the primary somatosensory cortex too, which correlated with the migraine attack frequency . A transcranial magnetic stimulation (TMS) study revealed a lower threshold for phosphene generation in MA patients, reflecting occipital cortex hyperexcitability . This finding was later confirmed by several other investigations . Moreover, TMS is a valuable tool for assessment of the effects of migraine-prophylactic drugs . Similarly, migraineur women reported increased sensitivity even to environmental light stimuli, such as glare, flicker or patterns, which was more expressed in MA patients as regards both the frequency and the severity . The mechanism of how lights

stimulation triggers migraine pain has still not been fully clarified, but a number of studies have suggested that light might have a modulatory role in different brain regions. A pressure algometry study, which measured pain perception thresholds over the emergence of the trigeminal branches and over the greater occipital nerve in migraineurs, revealed significant lower thresholds after light stimulation, indicating hypersensitivity in the visual afferents of migraine patients, and suggesting that this influences the trigeminal and cervical nociception . In an interesting study, Noseda et al. observed that retinal photoactivation is able to modulate the nociceptive pathway at the level of the thalamus by specific dura/light-sensitive thalamic neurons .

The findings of electrophysiological studies were later confirmed by modern neuroimaging methods. A PET study involving migraineurs with olfactory hypersensitivity demonstrated a higher cortical activation in the temporal pole in the patients than in healthy controls . An interictal PET study investigated the visual cortex responses after luminous stimulation, and demonstrated bilateral visual cortex activation only in migraineurs and not in controls. Moreover, concomitant trigeminal pain stimulation caused a potentiated activation in the patients , reflecting cortical hyperexcitability.

Another important aspect of migraine pathomechanism is a habituation deficit. Repeated sensory stimulation normally results in a decrement of responses, this phenomenon being referred to as habituation. There is growing evidence of habituation deficits in response to various sensory stimuli, including visual, auditory and somatosensory evoked responses in migraineurs . The first evidence of a habituation deficit was proved by an increase in the amplitude of contingent negative variation (CNV) in migraine patients . In the first VEP study describing a similar pattern, migraine patients exhibited increases in N1-P1 and P1-N2 amplitudes; in contrast, healthy participants displayed a habituation with decreases in the same components . A habituation deficit was also confirmed by magneto-encephalographic (MEG) studies . Similarly, migraineurs show a potentiation of cortical auditory evoked potential amplitudes (AEPs) versus the habituation detected in healthy controls , while for brainstem AEPs a lack of habituation has also been described in waves IV-V . A lack of habituation has similarly been reported in median nerve somatosensory evoked potentials as well . The same phenomenon was later confirmed not only in MoA patients, but also in subjects with medication-overuse headache . In 2003, Katsarava et al. presented the first account of a reduced habituation interictally in the nociceptive blink reflex, which describes the responses of the trigeminal system . In migraine patients, reduced habituation to laser-evoked experimental pain has also been described . The habituation in migraine patients displays a fluctuation related across the migraine cycle (ictal-interictal) . A MEG study detected normalization of the visual cortex excitability periictally . In another study, VEPs and AEPs were recorded in migraine patients at different time points, before, during and after an attack. The habituation deficit recorded interictally normalized just before and during a migraine attack, and the VEP amplitudes even showed a potentiation 2 days after the attack . Kropp et al. observed higher CNV amplitudes in migraineurs

interictally as compared with the recordings during an attack. This finding reflects a habituatian deficit in the interictal phase, which normalizes during the headache phase . Similarly, a loss of cognitive habituation was detected interictally in another study, while the P300 latency increased during an attack, and habituation normalized . The same phenomenon was described as concerns the nociceptive blink reflex, where the habituation also normalizes during a migraine attack .

These studies confirming increased responses to sensory stimuli and reduced habituation point to the concept of an increased excitability of migraineurs. The exact pathobiochemical basis of this hyperexcitability is not yet fully understood. MR-spectroscopically Sandor et al. detected an increased baseline lactate level in the visual cortex of migraineurs with pure visual aura, which did not change after visual stimulation. In contrast, healthy controls and migraineurs with complex neurological aura displayed a normal lactate level, which was significantly elevated after stimulation. This phenomenon reflects the lack of habituation, and the authors suggesedt that the increased lactate level in the occipital cortex could be a consequence of a mitochondrial dysfunction .

Another important aspect of migraine is the development of aura symptoms. The concept of cortical spreading depression (CSD), first put forward by Leao in 1944, is thought to be the pathomechanistic basis of the aura symptoms. Functional magnetic resonance imaging (fMRI) and MEG provided evidence of a connection between migraine aura and electric and metabolic alterations in the brain consistent with CSD. Barkley et al. provided the first description of large-amplitude waves and direct current (DC)-shifts observed in the MEG of migraine patients . In a later study, Bowyer et al. demonstrated DC-MEG-shifts both in migraine patients with spontaneous aura and in those with visually triggered aura versus controls . In the occipital cortex of migraine patients, several regions of hyperexcitability have been identifed, which form the basis of an increased susceptibility to CSD. An fMRI-BOLD study in migraine patients revealed the presence of a spreading suppression of initial neuronal activation in visual triggered headache . Hadjikhani et al. subsequently demonstrated BOLD signal changes during spontaneus migraine aura, which propagate through the visual cortex and resemble CSD . Moreover, fMRI studies have indicated activation in brainstem nuclei during both spontaneous and visually triggered migraine attacks .

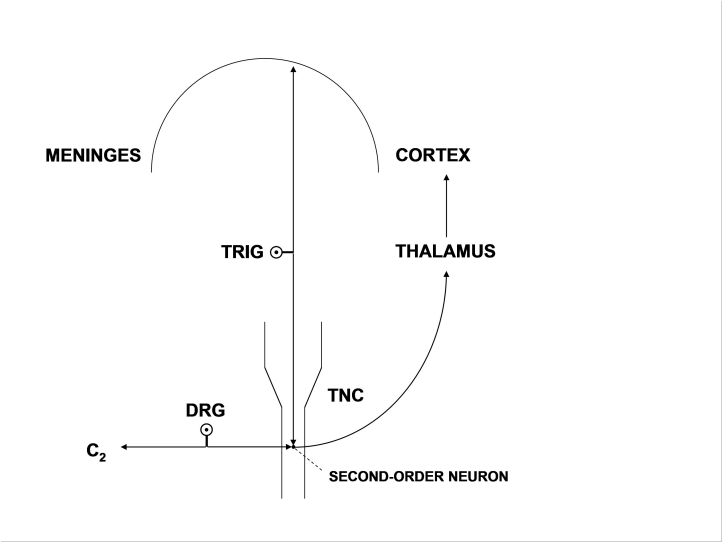
All of these neurophysiological and neuroimaging observations revealed neuronal hyperexcitability in the brain of migraineurs both during and between attacks, especially in the neuronal cell membranes of the occipital cortex . The pathomechanisms underlying this have not been fully elucidated, but several mechanisms may contribute to the altered function. An impaired energy metabolism, channelopathies, reduced $Mg2+$ levels and alterations in the serotoninergic system may all play a role in this process . One of the first phosphorus magnetic resonance spectroscopy (^{31}P-MRS) studies of the brain energy metabolism demonstrated an impaired phosphate energy metabolism ictally . Another early study described low brain $Mg2+$ levels during a migraine attack . Later, an impaired energy metabolism was confirmed by the finding of a decreased adenosine triphosphate (ATP) level in the occipital cortex of

MoA patients in the interictal period . A reduced phosphocreatine to inorganic phosphate ratio, which reflects the cellular energy status, was revealed by multiple studies in different subtypes of migraine patients . An impaired energy metabolism proved to be associated with low Mg^{2+} levels in migraineurs, and low Mg^{2+} levels also correlated with the severity of the disease . Low Mg^{2+} levels may contribute to neuronal hyperexcitability, possibly by influencing excitatory receptors .

The concept of hyperexcitability was confirmed by measurements of neuroexcitatory amino acids. the levels of glutamic and aspartic acid were significantly higher in the plasma, platelets and cerebrospinal fluid (CSF) of migraine patients as compared with controls, and the plasma glutamate level was elevated even further during a migraine attack . Chronic migraine patients also have significantly higher CSF glutamate levels . Another study detected increased concentrations of glycine, cysteic acid and homocysteic acid . Similar data were found in the saliva of migraine patients, where significant elevations of glutamic acid, serine, glycine, arginine and tyrosine were measured . Alterations in excitatory neurotransmitter distribution have been demonstrated in the anterior cingulate cortex and insula by proton magnetic resonance spectroscopy (^{1}H-MRS) data as well . These data indicate that a predominance of neuroexcitatory aminoacids in migraine patients may lead to an increased activation of glutamate receptors, and reflect a hyperexcitability of the CNS. Several studies have revealed lower Mg^{2+} levels in the blood, saliva and cortex of migraine patients, which might further enhance the sensitivity of the N-methyl-D-aspartate (NMDA) receptors . Glutamate, the main excitatory aminoacid in the brain, exerts its effect on the ionotropic NMDA and AMPA receptors and on the metabotropic G-protein-coupled receptors. Experimental data indicate that glutamate is involved in trigeminovascular nociception, and antagonists of NMDA receptors are able to block trigeminovascular nociception .

One of the leading theories relating to the pathomechanism of migraine is the activation of the trigeminovascular system (TS) . The anatomy of the TS is based on the pseudounipolar neurons in the trigeminal ganglion, whose peripheral branches innervate the meningeal tissues and the intracranial vasculature, while their central afferents project to the nociceptive second-order neurons of the trigeminal nucleus caudalis . The nociceptive second-order neurons receive convergent synaptic input from the supratentorial dura mater (trigeminal part) and from the greater occipital nerve (second cervical spinal nerve). An altered function of the TS plays a crucial role in the pathomechanism of migraine: sensitization .

Fig1.: Scheme of the trigeminovascular system



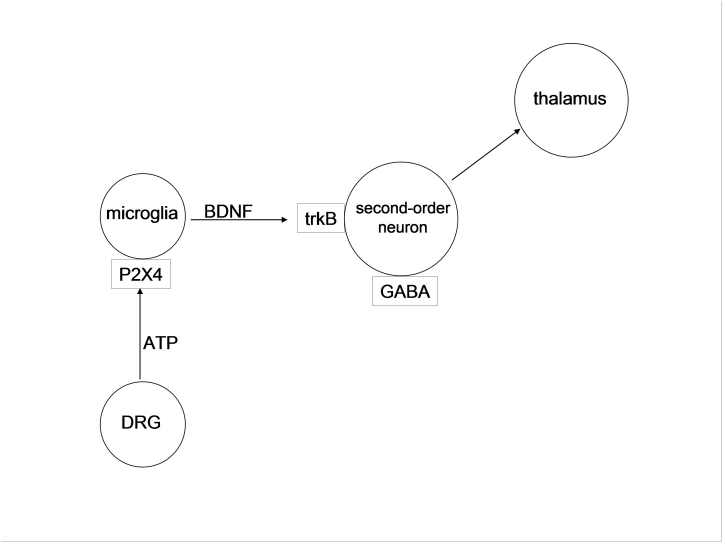
The term sensitization refers to an increased afferent activity as a response to an unchanged stimulus. The main forms of sensitization are peripheral and central sensitization and disinhibition . Peripheral sensitization is a process of functional plasticity, when high-threshold nociceptors are converted to a low-threshold neurons . It occurs when meningeal nociceptors of the trigeminal neuron afferents are soaked with the „inflammatory soup", e.g. inflammatory mediators, such as prostaglandin E2, bradykinin, histamine, serotonin, tumor necrosis factor alpha (TNFα) and other cytokines . This mechanism is responsible for the clinically observed intracranial hypersensitivity, which results in the throbbing nature of the headache and the observation of the pain worsening after physical activity. These signs are based on the hyperresponsiveness of the sensitized nociceptors to the fluctuation of intracranial pressure . Besides the local dural stimulation by the „inflammatory soup", an important element in the central sensitization process is the increased activity of the NMDA receptors in the second-order neurons and a self-amplifying process induced by nitric oxide . The clinical consequence of this process is cutaneous allodynia of the face and scalp, and extracranial tenderness . The central sensitization process is induced by the release of glutamate in the trigeminal nucleus caudalis from the C-fibers of the pseudounipolar neurons of the trigeminal ganglion. Increased intracellular calcium levels activate protein kinase C, which leads to the phosphorylation of the NMDA receptors. The phosphorylated NMDA receptors have an increased glutamate sensitivity, which results in the hyperexcitability of the neurons .

Hyperexcitability and sensitization in neuropathic pain

The exact pathomechanism of neuropathic pain has not yet been completely clarified, but a sensitization process seems to play a key role. The neuronal elements of peripheral sensitization in neuropathic pain are the pseudounipolar neurons of the dorsal root ganglion (DRG). Damage to the peripheral nerves results in macrophage infiltration from the endoneural blood vessels into the nerve and the release of an

„inflammatory soup” . A peripheral nerve lesion additionally initiates alterations in the innervated skin area. The Langerhans cells, keratinocytes and mast cells are activated in the skin and release pro-inflammatory cytokines, growth factors and nitric oxide . When the continuity of the nerve fibers is interrupted, Wallerian degeneration begins. In the course of Wallerian degeneration the proliferating Schwann cells secrete chemokines in the vicinity of the peripheral nerve lesion, and this results in the accumulation of leukocytes around them, which release proinflammatory cytokines . Damage to the primary sensory neuron afferents is followed by an increased expression of voltage-gated sodium channels $Na_v1.8$ and $Na_v1.9$, which are the sources of ectopic impulse generation. The upregulation of sodium channels is a consequence of nerve growth factor release . The consequence of this process is a decreased action potential threshold, resulting in hyperactivity . Ectopic primary afferent firing is associated clinically with a spontaneous burning pain and electric-shock like sensations . A peripheral nerve injury initiates an inflammatory response in the DRG and spinal cord . The central terminals of the damaged primary sensory neurons release various important substrates, such as ATP, brain-derived neurotrophic factor (BDNF) and fractalkine to the DRG. ATP is a key molecule which is able to influence the activity of the microglia, which causes the release of BDNF from the microglia through the activation of the P2X4 receptors on the cell surface . BDNF activates the tropomyosin receptor kinase (TrkB) receptors, which results in the down-regulation of the K^+-Cl^--cotransporter (KCC2) of the second-order neurons in spinal lamina I, which convey information to the thalamus . The consecutive rise in Cl^- in the neurons causes the inhibitory function of the GABA- and glycine channels to be less effective, and in some cells even depolarization may occur . The consecutive change in the membrane potentials reduces the Mg2+-blockade and thereby facilitates NMDA-mediated currents. The disinhibitiory process may lead to an excess activation of the NMDA receptors, leading to the hyperexcitability of the spinal neurons . This central sensitization process is associated with the development of allodynia.

Fig.2. Neuronal-glial interactions in the dorsal horn of the spinal cord



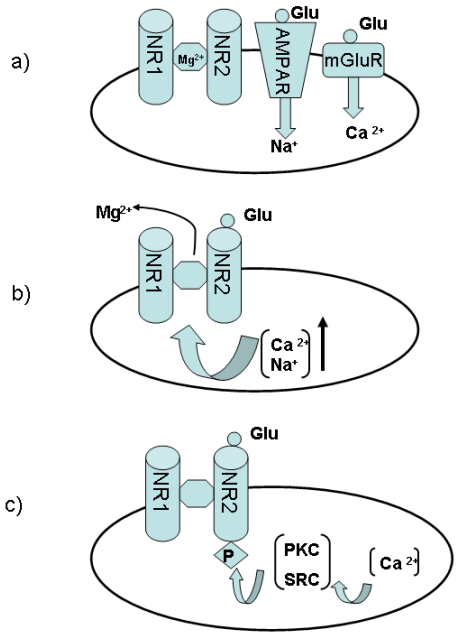
In a ^{1}H-MRS study of neuropathic patients, a decreased N-acetylaspartate (NAA) concentration was detected in the third-order neurons of the thalamus. This result could be explained by a decreased activity of the inhibitory neurons in the thalamus and a consecutive increase in the excitatory neuron activation . Another study has revealed that NAA levels correlate negatively with the intensity of pain in patients with neuropathic pain . In another study involving patients with trigeminal neuropathic pain, a significant reduction of the gray matter volume of the thalamus and a reduced NAA/creatine ratio were detected in the thalamus. These alterations were observed only in the case of trigeminal neuropathic pain, and not in trigeminal neuralgia . A PET study of patients with peripheral nerve injury (limb amputation) showed glial cell activation in the contralateral thalamus . Imaging studies revealed alterations in the highly organized cortical structures. An MRI investigation indicated a significantly reduced gray matter volume of the thalamus and prefrontal cortex in patients with chronic low back pain with a neuropathic component . Similar anatomical changes have been demonstrated in fibromyalgia patients, where a diminished gray matter volume was found to be present in different brain regions (the cingulate gyrus, insula, frontal cortex and parahippocampal gyrus), and the changes in gray matter density correlated with the dopamine metabolism . Furthermore, in an animal model of diabetic neuropathic pain, an enhanced glutamatergic neurotransmission was revealed in the anterior cingulate cortex .

NMDA receptors and glutamate have been implicated in the pathomechanism of neuropathic pain at multiple levels. NMDA receptors are present at all levels of the somatosensory system and at the levels of the peripheral nervous system on both myelinated and unmyelinated axons, in the spinal cord and at a supraspinal level . The activation of glutamate receptors proved to induce hyperalgesia, allodynia and characteristic behavioral responses in animal studies, reflecting their involvement in peripheral nociceptive transmission. Accordingly, the antagonism of glutamate receptors reduced allodynia and hyperalgesia in the same animal models . It was later also described that inflammation

results in a significant increase in the sensory axons containing ionotropic glutamate receptors, which may contribute to the peripheral sensitization process under inflammatory conditions . NMDA receptors have additionally been shown to be involved in the process of central sensitization, through the development of spinal hyperexcitability . Under normal conditions, NMDA receptors do not participate in synaptic transmission, because extracellular Mg2+ results in a voltage-dependent block. A constant nociceptive stimulus induces a strong membrane depolarization, which permits NMDA receptor-mediated synaptic transmission. A calcium influx into the cells activates the non-receptor tyrosine kinase, which leads to phosphorylation of the NMDA receptors. The Mg2+ blockade of phosphorylated NMDA receptors is decreased, and therefore the receptors can be activated even under a resting membrane potential .

Sensitization and hyperexcitability are common mechanisms in the development of migraine and neuropathic pain. Both processes involve alterations in the glutamatergic neurotransmission and the increased activity of NMDA receptors.

Fig.3. The role of NMDA receptors in the central sensitization process



Therapeutic opportunities

1. Migraine

As discussed above, a neuronal hyperexcitability is demonstrated in migraine sufferers, at both the cortical and the brainstem level. Accordingly, there is a need for therapeutic approaches that target CNS hyperexcitability, and several drugs are already available. The pathomechanism of epilepsy is well known to involve hyperexcitability of

the brain, and several antiepileptic drugs also display marked efficacy in migraine .

The first widely used antiepileptic drug in the prophylaxis of episodic migraine was valproate. There is strong evidence that valproic acid or sodium valproate or their combination (divalproex sodium) effectively prevents the occurrence of migraine attacks . The ventroposteromedial thalamic nucleus (VPM) is a key thalamic structure receiving trigeminal nociceptive transmission, which subsequently conveys sensory information to the primary somatosensory cortex , and the VPM might therefore be a potential therapeutic target. Valproate effectively blocks trigeminovascular nociception and the ongoing activity in the VPM . It has been demonstrated to exert its effect at the level of the trigeminal nucleus caudalis, where it can inhibit capsaicin-induced c-fos immunoreactivity . It effectively inhibits CSD too .

Another antiepileptic drug which is widely accepted for migraine prevention is topiramate, the efficacy of which is well established . It has diverse pharmacological effects: besides glutamate receptor antagonism, it influences the GABA-ergic neurotransmission and modulates of ion channels . Evidence from TMS studies revealed that topiramate is able to decrease cortical excitability . Accordingly, a TMS study demonstrated that topiramate effectively reduces the cortical excitability of the motor and visual cortices in migraine patients, and also lessens the frequency of migraine attacks. Its reduction of headache frequency proved to be strongly correlated with the decrease in cortical excitability, which can probably be explained by modulation of the glutamatergic neurotransmission . There are several potential mechanisms as concerns how topiramate can influence the development of migraine attacks. It has been revealed that topiramate exerts its effect in the trigeminocervical complex and the VPM through the antagonism of kainate receptors . Moreover, topiramate is capable of blocking CSD, the underlying mechanism of migraine aura . In an *in vitro* study, topiramate inhibited the high-voltage-activated Ca^{2+}-currents in cortical pyramidal cells and periaqueductal gray neuronal elements .

The efficacy of other antiepileptic drugs has not yet been fully established. Lamotrigine reduced the frequency only of migraine auras . Carbamazepine exhibited efficacy in diminishing the attack frequency as compared with placebo in only one study . Another antiepileptic drug, pregabalin, has demonstrated good efficacy in reducing headache frequency and severity in both episodic and chronic migraine. Although relatively few data are available, the promising results suggest the need for further large-scale investigations . A few studies have demonstrated the good efficacy of levetiracetam in reducing the frequency and intensity of migraine attacks . Similarly to other antiepileptic drugs, it resulted in an increase in the phosphene threshold in a TMS study, and in a reduction of the cortical excitability correlating with the decrease in headache frequency .

A relatively new therapeutic option is memantine, which was earlier approved for the treatment of Alzheimer's disease. Memantine is a noncompetitive NMDA antagonist, which inhibits NMDA receptor overactivation, but does not interfere with the normal baseline activity. A

small study suggested that memantine could be beneficial for migraine prevention, efficiently reducing headache frequency; this was later confirmed by others . Multicenter studies are still required to support this observation.

2. Neuropathic pain

In the management of neuropathic pain, antiepileptic drugs targeting hyperexcitability are widely used. The antinociceptive effect of this medication may by explained by different mechanisms: the inhibition of neuronal ion channels, the enhancment of the GABA-mediated inhibition of glutamate release or direct glutamate-receptor antagonism.

Pregabalin and gabapentin have been demonstrated to be effective in several animal models of neuropathic pain, and are currently first-line treatments in the EFNS guideline for the different neuropathic pain syndromes . Both substances exert their effects by binding to the $\alpha 2$-$\delta 1$ subunit of the presynaptic voltage-dependent Ca^{2+} channels and reducing the release of several neurotransmitters .

Carbamazepine and oxcarbazepine are the first line of treatment for trigeminal neuralgia, and the efficacy of carbamazepine has also been demonstrated in other chronic neuropathic pain conditions . Valproate has been reported to display an antiallodynic effect in an animal model of neuropathic pain, and its efficacy has been demonstrated against painful diabetic neuropathy in humans .

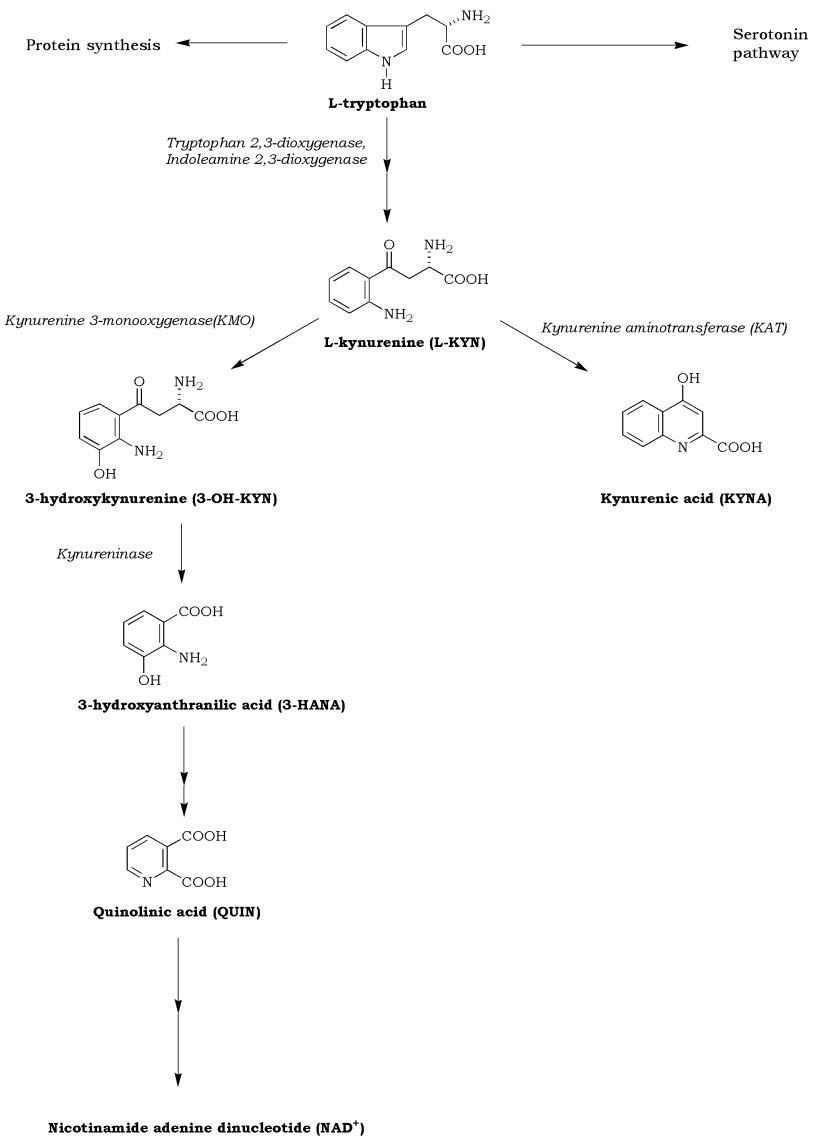
As NMDA receptors are considered to have a pivotal role in the development and maintenance of neuropathic pain, direct NMDA-receptor antagonists seem to be reasonable therapeutic options. Ketamine has been demonstrated to have beneficial effects in neuropathic pain conditions by reducing hyperalgesia, allodynia and pain . However, ketamine may induce severe side-effects, especially in higher doses, and its use is therefore currently limited. Memantine, a low-affinity uncompetitive NMDA antagonist has a favorable pharmacological profile with less side-effects. It proved capable of alleviating neuropathic pain development in a rat model and exhibited a significant antinociceptive effect in a diabetic neuropathic pain animal model . Complete NMDA antagonism is associated with severe side-effects, but NR2B-subtype-specific antagonists of NMDA receptors have a favorable pharmacological profile. Thus, two different NR2B antagonists both increased the nociceptive threshold in animal models of neuropathic pain, without any motor side-effect . Ralfinamide, another compound that inhibits NMDA receptors andalso Na^{+} and Ca^{2+} channels, exhibited good efficacy in a rat model of neuropathic pain .

Several clinical trials with promising novel drugs are currently ongoing, targeting neuronal hyperexcitability or neuron-glia interaction in neuropathic pain . In a recent phase 3 study, dextromethorphan/quinidine was effective in diabetic neuropathic pain patients .

Future therapeutic possibilities with kynurenines

The kynurenine pathway is the main metabolic route of the tryptophan catabolism, being responsible for more than 95% of tryptophan degradation in the human brain . The first and rate-limiting step of tryptophan degradation is the synthesis of L-kynurenine, through the action of indoleamine- 2,3-dioxygenase. L-Kynurenine can be converted in two distinct metabolic ways: it can serve as a precursor of kynurenic acid (KYNA) or it can be transformed into 3-hydroxy-kynurenine. KYNA is a broad-spectrum endogenous antagonist of excitatory aminoacid receptors, and therefore has a neuroprotective effect. KYNA is able to prevent the overexcitation of glutamate receptors and excitotoxic neuronal death. Its neuroprotective effect is mainly due to the blockade of NMDA receptors, but it is able to bind to AMPA and to the α7-nicotinic acetylcholine receptors . Interestingly, its effect on the AMPA receptors are concentration-dependent: in the low concentration range it may facilitate these glutamate receptors while at a higher concentration level it inhibits them . The experimental data indicate that KYNA has a modulatory role in the CNS, because it is implicated in the regulation of glutamate and dopamine release . The neuroprotective effect of KYNA might also be related to the inhibition of the α7-nicotinic acetylcholine receptors, because it can thereby modulate presynaptic glutamate release . The kynurenine pathway produces several other neuroactive metabolites, including the potent neurotoxin quinolinic acid, an NMDA receptor agonist, whose neurotoxic properties may also be a consequence of its capacity to induce lipid peroxidation or to lead to an elevation of the extracellular glutamate level, which can further induce excitotoxicity . Alterations in the delicate balance of the neuroprotective and neurotoxic metabolites have been described in multiple neurological diseases, including Alzheimer's disease, stroke, Parkinson's disease and multiple sclerosis . Synthetic derivatives of KYNA might provide therapeutic options for the treatment of neurodegenerative diseases, one of such molecule was already patented for the treament of Huntington's disesease (P1000343).

Fig.4. The knyurenine pathway of tryptophan metabolism



Kynurenines in migraine

Metabolites in the kynurenine pathway have been implicated in the modification of the trigeminovascular activation processes. As a consequence of electrical stimulation of the trigeminal ganglion, the kynurenine aminotransferase immunoreactivity decreased significantly in the Schwann cells and macrophages . Further, kynurenine in combination with probenecid prior to nitroglycerine treatment or electrical stimulation effectively reduced the c-fos immunoreactivity in the rat trigeminal ganglion . Kynurenine with probenecid or a novel kynurenic acid derivative also prevented nitroglycerine- induced expression of n-nitric oxide synthase . The kynurenine derivative was able to block calmodulin-dependent protein kinase II alpha (CamKIIalpha) and calcitonin gene-

related peptide (CGRP) expression in the same animal model . L-Kynurenine or KYNA treatment was also capable of suppressing CSD in a rat model . KYNA additionally inhibits higher brainstem nuclei activation, e.g. the locus coeruleus . KYNA administered into the periaqueductal gray matter potentiates the effect of morphine .

Kynurenines in neuropathic pain

Treatment with KYNA proved to be antinociceptive, reducing allodynia in a rat model of inflammatory pain . In a recent study, L-Kynurenine + probenicid treatment diminished allodynia in an animal model of neuropathic pain by giving rise to an increased KYNA concentration . In those works, it was suggested that the antinociceptive effect could be due to NMDA receptor antagonism. Notably, NMDA antagonism in this model did not result in any motor side-effect. However, in another interesting animal study of inflammatory pain, another possible mechanism of action was put forward. In this model, activation of the previously orphan GPR35 receptor by KYNA was able to result in an antinociceptive effect . In this setting, the effect of KYNA could be due to the inhibition of Ca^{2+} channels and glutamate release . Further studies are needed to clarify the potential therapeutic options of kynurenines in neuropathic pain conditions.

Conclusions

Hyperexcitability and sensitization are common mechanisms in migraine and neuropathic pain, glutamate and its receptors playing a pivotal role in these processes. The targeting of ionotropic and metabotropic glutamate receptors may therefore be a promising therapeutic possibility both in migraine and in neuropathic pain condiitions. Curent therapeutic options which influence hyperexcitability are mainly antiepileptic drugs. Kynurenines might offer valuable therapeutic options for future drug development.

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Figure legend

Fig. 1. Scheme of the trigeminovascular system

The peripheral branches of the pseudounipolar neurons in the TRIG innervate the meningeal vasculature, while the central branches project to the nociceptive second-order neurons in the TNC. The second-order neurons receive convergent synaptic input from the C2 DRG too. From the TNC sensory information is conveyed to the thalamus and the cortex.

TRIG: trigeminal ganglion, TNC: trigeminal nucleus caudalis, DRG: dorsal root ganglion, C2: second cervical spinal nerve.

Fig. 2. Neuronal-glial interactions in the dorsal horn of the spinal cord

After an injury of the peripheral nerve fibers of the pseudounipolar neurons of the dorsal root ganglion, ATP is released via the central part to the dorsal horn of the spinal cord. ATP acts on the P2X4 receptor on the microglia, and the stimulated glia releases BDNF. BDNF binds to the trkB receptors and induces the downregulation of the K^+C^- contransporter. The resultant rise in the Cl^- level attenuates the inhibitory action of GABA, leading to hyperexcitability of the neurons.

BDNF: brain-derived neurotrophic factor, trkB: tropomyosin-receptor kinase (family of the tyrosine kinase receptors), GABA: gamma-amino-butiric acid, ATP: adenosin-triphosphate, DRG: dorsal root ganglion, P2X4: purinergic receptor P2X, ligand-gated ion channel, 4

Fig.3. The role of NMDA receptors in the central sensitization process

a) In a resting state, NMDA receptors on the second-order neurones are blocked by Mg^{2+}, and do not participtae in synaptic transmission. Glutamate, released from the primary afferent terminals exerts its effect on the AMPA and G-protein-coupled metabotropic glutamate receptors, and results in Na^+ and Ca^{2+} influx to the cells.

b) A constant noxious stimuli results in a strong membrane depolarization, which removes the Mg^{2+} blockade and permits the NMDA receptors to participate in synaptic transmission.

c) The calcium influx activates the PKC and SRC, which phosphorylates the NMDA receptors. Phosphorylation of the NMDA receptors results in an enhanced glutamate sensitivity and hyperexcitability of the cells.

NMDA: N-methyl-D-aspartate, Ca^{2+} : calcium, $Mg^{2+:}$ magnesium, PKC: protein kinase C, SRC: protein tyrosine kinase

Fig. 4. The kynurenine pathway of tryptophan metabolism

The KP is a sequence of enzymatic steps leading to the formation of NAD. The rate-limiting step is the coversion of TRP by IDO. The metabolic cascade divides into two branches at L-KYN, the key intermediate of the KP. One branch consists of the synthesis of KYNA via the action of KATs,

while the other branch produces several neuroactive metabolites including the NMDA receptor agonist QUIN, and the free radical generator 3-OH-KYN.

KP: kynurenine pathway, TRP: tryptophan, L-KYN: L-kynurenine, IDO: indoleamine-2,3,-dioxygenase, KYNA: kynurenic acid, QUIN: quinolinic acid, 3-OH-KYN: 3-hydroxy-kynurenine, KAT: kynurenine-aminotransferase, NAD: nicotinamide adenine dinucleotide, NMDA: N-methyl-D-aspartate