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Review

Stress-Induced Alteration in Chloride Transporters in the Trigeminal Nerve May Explain the Comorbidity between Depression and Migraine

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Abstract: Migraine is frequently comorbid with depression and anxiety disorders. In the case of depression and panic disorder, the associations seem to be bidirectional. Stress (activation of the hypothalamic-pituitary-adrenal axis) is thought to be involved in increasing the attack frequency. In the current review, it is argued that elevated levels of cortisol increase the function of chloride-ion transporter NKCC1 and decrease the function of chloride-extruder KCC2 in the trigeminal nerve. This leads to a diminished inhibitory effect of gamma-aminobutyric acid (GABA) and an enhanced likelihood of a migraine attack. Since migraine attacks themselves are stressful, and since brain areas are activated that could contribute to panic, anxiety and depression, a number of self-sustaining circular processes could occur that would explain the bi-directionality of the associations. On the basis of this hypothesis, several novel therapeutic approaches to counter the pathological process can be proposed. These include inhibition of corticotrophin releasing factor by CRF1 receptor antagonists, blockade of adrenocorticotropic hormone (ACTH) at the MC2 receptor, and inhibition of the hyperactive NKCC1 chloride-transporter.

Keywords: GABA disinhibition; NKCC1; KCC2; learned helplessness; ACTH; migraine; major depressive disorder; panic disorder; trigeminal nerve

1. Introduction

Migraine is characterized by recurring, disabling headache attacks that last somewhere between four and 72 h. The moderate to severe pain has a pulsating quality, is intensified by physical activity, and is often associated with nausea, photophobia, or phonophobia [1]. During migraine, nociceptive information from cranial blood vessels in the pia-, dura-, and arachnoid mater is transmitted via Aδ- and C-type sensory fibers [2,3]. These fibers originate from the trigeminal ganglion and project to an area in the medulla and brainstem designated as the trigeminocervical complex, including the trigeminal nucleus caudalis [3]. Aδ and C sensory neurons express several peptide neurotransmitters, including calcitonin gene-related peptide, substance P and pituitary adenylate cyclase activating peptide [4,5], as well as glutamate [6,7]. It is hypothesized that an altered processing of sensory input into the trigeminal nucleus caudalis accounts for many of the temporal and symptomatic features of migraine [3,8]. Certain branches of the trigeminal nerve innervate extracranial tissues and since information-processing by sensory nerves is bidirectional, central activation of the trigeminus is noticeable in the skin of the head and neck [3].

2. Migraine Is Co-Morbid with Panic Disorder and Depression

Migraine is frequently comorbid with depression and anxiety disorders [9–12]. At least in the case of depression and panic disorder, the associations seem bidirectional [13,14]. A psychiatric

comorbidity may promote the transformation from episodic migraine to chronic (or even daily) migraine [10,11,15,16] and worsens the pain of other types of headache as well [17]. Stress (activation of the hypothalamic-pituitary-adrenal (HPA) axis and cortisol release) may be involved in early onset, gradual worsening, and "chronification" of migraine [12–14,18–20]. Compared to patients with episodic migraine and healthy subjects, patients with chronic migraine had significantly higher serum levels of cortisol [21]. Remission of the chronic migraine was associated with a reduction of the cortisol levels, whereas in non-remitting chronic migraine the cortisol levels remained unaltered [21]. Endogenous cortisol levels may therefore serve as biomarker for migraine chronification [21]. Migraine attacks themselves can act as a stressor, thereby potentially promoting an increase in migraine frequency [22]. A hypothesis, referred to as the "central sensitization theory", postulates that stress induces an abnormal activation of the trigeminal nerve [8,18]. Unfortunately, a mechanistic understanding of the process that purportedly fuels the central sensitization process is still lacking.

3. GABA Receptors and Functional Responses of the Trigeminal Nerve

In whole-cell patch clamp experiments in rats, gamma-aminobutyric acid (GABA) application induced inward Cl^- currents in trigeminal neurons [23]. GABA, acting via GABA-A receptors inhibited the activity of trigeminal neurons in the trigeminal ganglion [23]. In addition, in cats, GABA inhibited 2nd order neurons in the trigeminocervical complex via GABA-A receptor activation [24]. These data suggest that GABA, at least under resting conditions, may reduce the activity of the trigeminal nerve and its upstream response.

Sensitization refers to increased neural activity in response to repeated stimulation [25]. In epilepsy research, repeated low grade neural stimulation "kindles" the development of spontaneous seizures; an effect that could relate to a loss of selective types of interneurons, alteration of GABA function, and/or decrease in dendritic inhibition [26]. For this reason, the levels of GABA and its inhibitory effects could be relevant for migraine too. GABA levels have been measured in patients with depression, and in patients with migraine (acute, chronic, with and without aura). Cerebrospinal fluid levels of GABA were significantly lower in patients with chronic migraine with depression than in chronic migraine without concomitant depression [27]. Reduced levels of GABA were also observed in the ventroposterior thalamus of subjects with neuropathic pain of the trigeminal nerve [28]. These data are at variance with results from magnetic resonance studies in migraine patients. A meta-analysis found quite consistently higher GABA concentrations in a variety of cortical brain areas, independent of the type and duration of the migraine [29]. It is important to note that in certain pain syndromes GABA may cause neuro-*excitation*, not the commonly described neuro-*inhibition* [30]. It is therefore unclear what the functional consequence of the altered GABA levels in migraine patients will be.

4. Stress Modifies the Activity of Chloride Transporters

Under normal circumstances the opening of GABA-channels causes an influx of chloride ions that evokes a hyperpolarization of the neuronal membrane. The expression and activity of the chloride transporters, NKCC1 (Na-K-Cl cotransporter-1) and KCC2 (K-Cl cotransporter-2) modulate intracellular chloride levels. KCC2 extrudes chloride ions, whereas NKCC1 promotes a chloride influx [30]. Data from several animal experiments indicate that stress or glucocorticoid treatment increases the expression and function of NKCC1 and decreases the function of KCC2. The functional consequence is an increase in intracellular chloride concentrations [31–33]. Opening of the GABA chloride-channel by a GABA-A agonist then results in a diminished net chloride influx and consequently neuronal hyperpolarization is diminished, which means that GABA is less inhibitory [30]. Acute and prolonged stress thus have the propensity to weaken the neuronal inhibitory effect of GABA. In extreme situations like in neuropathic pain and stroke, there may be a net efflux of chloride, which means that GABA becomes an excitatory neurotransmitter. Data from a study by Wei et al. [34] indicate that it is conceivable, that such a response can occur in the trigeminal nerve too. The authors reported that in a rat model of trigeminal neuropathic pain, generated by chronic constrictive ligation of the infraorbital

nerve, chloride homeostasis in trigeminal neurons collapsed, while GABA inhibition was impaired [34]. Indeed, the nerve ligation increased the pain responses to mechanical stimulation. In situ hybridization and immunohistochemical analysis showed that NKCC1 mRNA and protein levels were upregulated in primary neurons in the injured side of the trigeminal ganglion and in the peripheral terminal [34]. Moreover, the outward-directed KCC2 transporter mRNA and protein levels were downregulated in secondary relay neurons on the injured side of the trigeminocervical complex. Optical imaging of evoked synaptic responses using a voltage- sensitive dye, revealed that post-synaptic GABA actions at the injured side were excitatory. This down-regulation of KCC2 in the trigeminocervical complex may result in an excitatory switch by impairing postsynaptic GABA inhibition [34]. Although this is a model of neuropathic pain and not of migraine, it is conceivable that in patients with chronic migraine the trigeminal nerve might become hyperexcitable owing to a GABA-disinhibitory effect of cortisol.

5. Discussion

The available data suggest that the increased recurrence of migraine attacks seen in patients with depression or panic disorder, could be mediated by activation of the HPA axis and an excess release of cortisol (see Figure 1). The action of cortisol presumably alters the expression of chloride transporters in the trigeminal nerve, which diminishes the inhibitory activity of GABA and even revert it to excitation. During migraine attacks, structures such as the periaqueductal gray (PAG) and the Bed Nucleus of the Stria Terminalis (BNST), which are upstream of the trigeminal nerve, become activated [2]. They respectively play a role in panic behavior [35] and activation of the HPA axis [2]. In addition, the repeated stress of poorly-controllable migraine pain may purportedly lead to an attitude that in animals is coined as "learned helplessness" [36]. In helpless rats, circulating levels of corticosterone are increased, while there was non-suppression in the dexamethasone suppression test [37,38]. Moreover, in animals with learned helplessness, the BNST and the amygdala are activated [37], which again could relate to HPA axis activation and panic behavior. Learned helplessness has been conceptualized as a process that enhances the risk of depression [36,37]. These processes give rise to several positive feedback loops, whereby depression and panic enhance the frequency of migraine attacks, and this, in turn, enhances depression and/or panic. This would explain why the associations between depression or panic disorder and migraine are bi-directional [13,14] (see Figure 1).

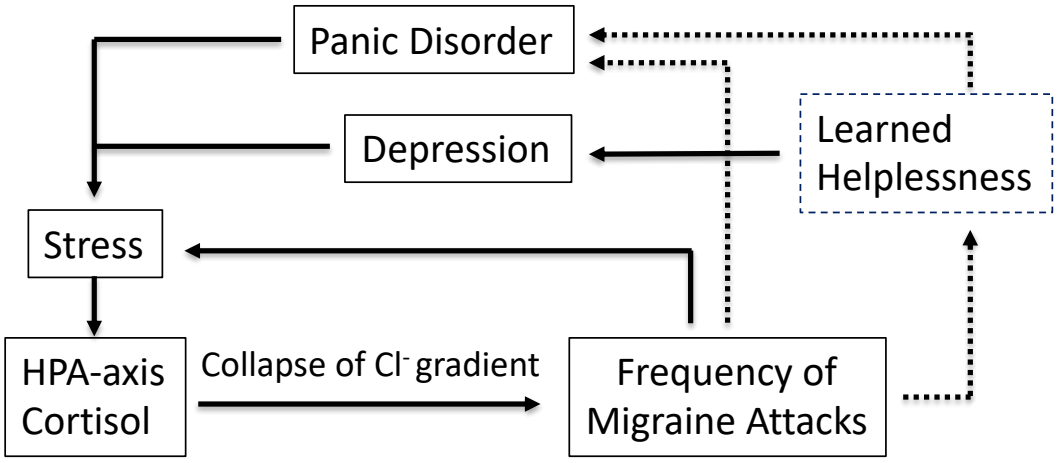

Figure 1. Schematic representation of the potential mechanisms that are assumed to play a role in the bidirectional associations between migraine, and respectively depression or panic disorder. Both psychiatric disorders are associated with stress, activation of the hypothalamic-pituitary-adrenal (HPA) axis, and elevated circulating levels of cortisol. The glucocorticoid cortisol alters the activity of neuronal chloride-transporters, which would diminish the chloride-ion gradient across the neuronal membrane, and this in turn would reduce the inhibitory activity of GABA at the GABA-A ion- channel.

It is speculated that this process occurs, amongst others, in the trigeminal nerve. The increased ratio between excitation and inhibition would raise the likelihood of a further migraine attack. Activation of brain centers involved in learned helplessness, panic, and HPA axis-activation might close the vicious circular process, and would provide an explanation for the bidirectional associations of migraine, and depression or panic disorder. Dashed lines indicate limited evidence.

Based on this interpretation, one may propose several novel therapeutic approaches to counter this pathophysiological process. The excess activity of the HPA axis may be reduced by CRF-, ACTH- or glucocorticoid receptor blockade [39]. CRF-antagonists have been developed [40], but were found to be insufficiently effective as antidepressants [39]. One could eventually try these compounds as migraine prophylactic agents. Although inhibition of ACTH at the MC2 receptor would be another attractive approach, ACTH MC2-antagonists have not been developed [41]. The development of ACTH-antagonists has proven difficult until quite recently, when the obligatory accessory-protein MRAP (melanocortin-receptor accessory-protein) was discovered [41]. With the currently available knowledge of the MC2 receptor/MRAP complex, it should be possible to develop low-molecular weight receptor antagonists and inhibitors [42]. ACTH-inhibition would take place at the adrenal, so brain penetration would not be a requirement.

OnabotulinumtoxinA blocks neurotransmitter-release from nerves [43]. Subcutaneous injection of this compound near trigeminal nerve endings in the cranio-facial-cervical region not only reduced the headache frequency, but also improved depression scores in patients with comorbid depression and chronic migraine [44,45]. However, as these were open label studies without a contemporaneous control group, the results require confirmation in double-blind studies. Nevertheless, the data with onabotulinumtoxinA support the contention that prevention of migraine helps to break the vicious circle between migraine and depression.

A further logical approach would be to target the altered chloride-gradient, for instance by inhibiting the NKCC1-ion transporter. The diuretic bumetanide might serve as a proof of concept molecule [31,46]. Since a large section of the trigeminal nerve is outside of the blood brain barrier [47], it could be that profound brain penetration of NKCC1-inhibitors is not required. On the other hand, there is also evidence that disinhibition of the GABA response might occur in the circuitry that is upstream of the trigeminal nerve [24], or even at the level of the HPA-axis [31]. In that case, a compound that crosses the blood brain barrier would be required.

6. Conclusions

The literature cited in this review suggests that stress worsens migraine because it reduces the inhibitory effect of GABA at the trigeminal nerve. Since stress and as consequence GABA-disinhibition seems to aggravate numerous psychiatric disorders, targeting the function of NKCC1 and KCC2 may be a particularly relevant approach, not only for migraine, but also for mental health disorders.

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