Of generators, networks and migraine attacks

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Purpose of review
One of the most discussed topics in migraine pathophysiology is where migraine attacks originate. Although recent evidence suggests central attack generating loci, there is an ongoing debate about the involved centres of the brain and brainstem.

Recent findings
Recent neuroimaging studies focussing on the preictal stage of migraine attacks suggest a predominant role of the hypothalamus and its functional connectivity shortly before the beginning of migraine headaches. In interictal migraineurs, changes in resting state functional connectivity of the dorsal pons and the hypothalamus have been found.

Summary
Based on the clinical presentation of the premonitory phase of migraine, the hypothalamus and changes within the dopaminergic system have been discussed as likely candidates for attack generation. Neuroimaging studies however suggested the dorsal pons as attack generator. Taking into account the recent findings of hypothalamic involvement and changing connectivity in the preictal stage, the available evidence suggests that the idea of a single migraine generator within the human brain is probably too simplistic. More likely, spontaneous oscillations of complex networks lead to activity changes in certain subcortical and brainstem areas. This in turn might constitute functional changes of descending pain-modulating pathways, and thus the generation of migraine pain.

Keywords
connectivity, dopamine, dorsal pons, hypothalamus, migraine generator

INTRODUCTION

In contrast to earlier hypotheses of migraine attacks being of extracranial provenance, evidence of the past 20 years supports the existence of central processes leading to the evolution of migraine pain. The first brain region to be identified using neuroimaging in spontaneous human migraine attacks was a region of the dorsal pons. Due to the rather low spatial resolution of common neuroimaging techniques, however, the distinct anatomical structure has still not been identified. Recent evidence as well as the clinical presentation of migraine nowadays suggests other parts of the central nervous system to play a more prominent role in migraine-attack generation – among these the central dopaminergic system and the hypothalamus. If one wants to interpret the most recent findings in migraine pathophysiology, it is important to again discuss the clinical presentation of the premonitory phase of a migraine attack.

MIGRAINE-ATTACK GENERATION: WHAT CAN WE LEARN FROM THE CLINICAL PRESENTATION OF MIGRAINE?

Migraine is clinically characterized by a specific succession of various symptoms, the most salient of which is the headache with its typical characteristics (unilaterality, throbbing and pulsating) and accompanying symptoms: nausea and vomiting, photophobia, phonophobia and sometimes osmophobia. The headache exacerbates during physical exercise, and patients often feel the need to withdraw from activities and disturbing stimuli [1]. Debilitating as it may be, the headache is not the only clinical feature of a migraine attack: up to about 80% of migraine patients might experience – at least from time to time – so-called migraine premonitory symptoms including changes in appetite (food craving or nausea), in sleep–waking rhythms (yawning, fatigue and sleep disturbances), hypersensitivity to certain stimuli (photophobia, osmophobia and phonophobia), mood changes, changes in liquid tolerance and others [2–8]. Most

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KEY POINTS

- Typical migraine premonitory symptoms suggest hypothalamic and dopaminergic involvement in migraine-attack generation.
- The dorsal pons has long been discussed as a migraine generator but might more be involved in migraine-pain sustainment than in migraine-attack generation.
- Recent evidence suggests more complex connectivity and network changes as the key attack-generating mechanisms.

of these premonitory symptoms can occur days to hours before the beginning of the actual migraine headache and are seen as early symptoms of a migraine attack.

After headache remission, a great percentage of patients experience a postdromal phase characterized by freedom of pain but still altered physiological and psychological functioning: fatigue might be present as well as euphoria or dysphoria or again alterations in appetite or liquid tolerance [9–11]. Putting those clinical characteristics of a typical migraine attack in a timely order, migraine appears to be not an isolated event of headache but as a cyclic up and down of certain sensory and bodily functions, with headache just being one of many symptoms. This model of migraine as a swinging system has first been proposed by Blau [12]. Nearly all symptoms in the premonitory phase, but also the circadian rhythmicity of attacks [13] and their association with hormonal states and the menstrual cycle, already point towards hypothalamic involvement. Some of the typical premonitory symptoms (e.g. yawning and nausea) point towards dopaminergic involvement. The pain phase with the typical hypersensitivity towards different stimuli might involve certain brainstem nuclei, including pain-processing and pain-modulating areas. Finally, the postdromal phase of migraine might still involve changes in hypothalamic activity and also possibly certain brainstem centres, whereas trigeminal pain-processing areas are not involved anymore.

THE HYPOTHALAMUS AS A MEDIATOR OF MIGRAINE ATTACKS

Due to the specific clinical presentation of the premonitory phase of migraine with symptoms pointing directly to hypothalamic involvement, the hypothalamus has long been hypothesized to play an important role in migraine-attack generation. The hypothalamus has various neuroanatomical connections to pain-modulating systems and also to the spinal trigeminal nuclei. The orexinergic system, which is known to regulate – among others – arousal and nociceptive processing as well as thermoregulation and autonomic functions, has only recently become a site of interest in migraine research [14,15]: pharmacological blockade of orexine receptors attenuated meningeal artery dilation caused by nociceptive afferent trigeminal activation and inhibit cortical spreading depression in rats [16]. Consequently, it has been suggested that orexinergic processing might be involved in migraine-attack generation and sustainment of migraine pain. Another neurotransmitter system involving the hypothalamus is the central dopaminergic system. Typical premonitory symptoms, such as excessive yawning and fatigue as well as changes in appetite and nausea, often reported to already start in the late premonitory and early headache phase indeed involve the dopaminergic system [17,18] and dopaminergic agonists such as apomorphine clinically increase yawning, dizziness, nausea and vomiting in migraine patients [17,19–22]. Dopamine antagonists such as metoclopramide are also effective in the treatment of headache itself in acute migraine attacks [23–28]. In animal models, especially the A-11 cell group within the posterior hypothalamus has been shown to inhibit trigeminonociceptive firing within the trigeminocervical complex, and this effect could be reversed by application of the dopamine-receptor antagonist Eticlopride. Furthermore, projections from this cell group to thalamic regions possibly involved in photophobia and whole body allodynia (posterior and lateroposterior thalamus) indicate yet another possible role of this hypothalamic cell group in migraine [29]. In addition, projections from other parts of the hypothalamus usually involved in regulation of food intake to the same thalamic areas further corroborate a role of the hypothalamus for migraine premonitory and accompanying symptoms, such as craving or anorexia [29]. Neuroimaging studies in migraine patients could further undermine hypothalamic involvement in the premonitory and acute pain phase of migraine: Early PET studies showed enhanced hypothalamic activation within the pain phase of migraine as compared with the pain-free interval [30,31]. Interestingly, this activation persisted even after pain relief by sumatriptan, thus suggesting a role of the hypothalamus going beyond simple pain processing [30]. To date, there are two recent neuroimaging studies showing enhanced hypothalamic activity during the premonitory phase of migraine: Maniyar *et al.* [32] investigated the pain-free interval between initial headache after administration of NO and onset of migraine like headaches as a human model of the premonitory phase and found

increased activity of the hypothalamus and the dorsal rostral pons. Another study from our group investigated one migraine patient daily over a whole month and also found increased hypothalamic activation as a response to pain within the last 24 h before headache onset as compared with the interictal state. In this study, pain-related hypothalamic functional connectivity to the spinal trigeminal nuclei was increased during the preictal phase as compared with the interictal phase [33▪]. All of these data corroborate an important role of the hypothalamus for the generation of migraine premonitory symptoms but also attack generation and sustainment.

THE PAIN PHASE: REVISITING THE DORSAL PONS

The one region that is traditionally termed the migraine generator is the rostral part of the dorsal pons. It was the first region to be identified as being specifically activated during spontaneous human migraine attacks and the only one that persisted after complete relief from headache due to sumatriptan administration in an early PET study. It was thus concluded that this region could not only have a function related to pain processing during headaches but might also have attack-generating properties [34]. Activation within the dorsal half of the pons has since been shown in multiple neuroimaging studies using different modalities: further PET studies showed a similar region being more active during migraine pain than within the pain-free interval both in spontaneous [30,35,36] and NO-triggered migraine headaches [32,37]. Even the persisting activation of this region after pain relief by sumatriptan could be replicated in a further study [30]. Task-related functional magnetic resonance imaging (fMRI) studies further replicated stimulus-dependent pons activations during spontaneous migraine attacks [33▪,38,39]. It might even be functionally stronger coupled to the hypothalamus during spontaneous migraine attacks [33▪]. Although the important role of this region for the pain phase is out of question, given the overwhelming evidence, there are still many questions as how this region might be involved in migraine-attack generation [40]. The commonly reported sustained activation of this area even after pain relief by sumatriptan strongly suggests attack-sustaining properties and that triptans do not terminate migraine attacks but merely lead to a headache relieve for a certain time. The frequently reported recurrence of headache some hours after triptan intake would then be explained with the short half-life of triptans with the activity in the brainstem ongoing. However, a strong indicator for an attack-generating function of this area is the fact that a specific activation of this region could be shown for the premonitory phase of nitroglycerin triggered migraine attacks even before onset of migraine-like headaches in a recent PET study [32]. The exact anatomical correlate corresponding to such activations, however, has to date not been clearly identified: the spatial resolution of common neuroimaging approaches is usually too low to allow for a distinct attribution of found activations to certain distinct brainstem nuclei and certainly not to specific neuronal populations within these areas. Likely candidates however are – the caudal part of the periaqueductal grey area (PAG), the cuneiforme nucleus, the Locus Coeruleus, the lateral parabrachial nucleus and the dorsal Raphe – areas that are commonly involved in trigeminal pain processing and are thought to be parts of the descending pain-modulating system [40]. Altered function of these brainstem areas might thus indicate a deficit in descending pain control and possibly disinhibition of lower pain-processing areas, such as the spinal trigeminal nucleus. The locus coeruleus and the lateral parabrachial nucleus are also important relay stations for dopaminergic projections from the mesostriatal and the mesocorticolimbic dopaminergic systems. The dorsal raphe, on the other hand, is involved in regulation of arousal and sleep – altered activation of this area even before headache onset might thus explain the changes in alertness often experienced in the premonitory phase of migraine – activation of the same area during headache might account for similar changes in the headache phase.

MIGRAINE ATTACK AS A CHANGE IN NETWORK ARCHITECTURE?

Comparing activity levels of certain brain regions during the different stages of the migraine cycle has had tremendous impact on our understanding of migraine pathophysiology within the past 20 years. Recent work suggests that single activation changes in specific brain regions may be the correlate of specific symptoms of headache but does not easily explain any cycling changes or indeed the generation of attacks. It is rather likely that the observed changes in netto activity within for example the dorsal pons or the hypothalamus might be the result of changes in functional connectivity and that this, in turn, might lead to changes in functional coupling with again other brain areas. Various studies have investigated network architecture in interictal migraineurs and have found alterations in common resting state networks and seed-based connectivity [41–51,52▪,53]. Connectivity studies using areas as seeds that are known to play an

important role in migraine pathophysiology are especially apt to contribute to a deeper understanding of the interictal state of this disease: The dorsal pons showed increased functional connectivity with the anterior insula [52▪], the PAG showed stronger coupling to various brain areas involved in somatosensation and nociception [43] and the hypothalamus was functionally stronger connected to the locus coeruleus, the parahippocampal gyrus and other brain areas [54]. Studying the interictal state of migraine can thus provide insight into basic differences between migraineurs and nonmigraineurs and thus contribute to the pathophysiological understanding of migraine. Studies investigating different stages of the migraine cycle comparing them with each other are however scarce. Amin *et al.* investigated changes in resting state functional connectivity during PACAP-38 (pituitary adenylate-cyclase activating polypeptide 38)-induced migraine attacks and found alterations within the salience network, the sensorimotor network and the default mode network. Interestingly, connectivity of the sensorimotor network with the visual network was decreased during PACAP-38-induced migraine attacks and might thus explain the pronounced visual accompanying symptoms of migraine headache [55▪]. Another very recent study from our own group on one migraineur scanned daily over a whole month and three untreated migraine attacks revealed alteration in pain-related hypothalamic functional connectivity. Although in the preictal phase, the hypothalamus was functionally coupled with the spinal trigeminal nuclei, it showed increased functional coupling with the dorsal rostral pons during the ictal phase. These data strongly point towards the hypothalamus as the true attack initiator, or more precisely, its role in initiating alterations in functional connectivity over time with other brain regions typically involved in migraine pathophysiology. However, these data are based on a single-patient analysis and urgently need confirmation in an adequate study sample. Taken together, the available data suggest a more complex picture of migraine attack generation: distinct changes in connectivity involving the hypothalamus and the dorsal pons might thus be the underlying mechanism.

CONCLUSION

Recent evidence from neuroimaging draws a complex picture of the evolution of a migraine attack: distinct changes within the dopaminergic system account for typical migraine premonitory and accompanying symptoms by modulating and evoking activity changes in certain networks, including the hypothalamus and the dorsal rostral pons with a rather specific pattern during different stages of the migraine cycle. These activity changes contribute to the typical clinical presentation of migraine attacks: the classic premonitory symptoms can be mainly explained by changes in dopaminergic and hypothalamic networks, whereas later changes in pontine activity and networks probably maintain specific migraine symptoms and sustain migraine pain. Thus, the current understanding of migraine-attack generation is developing from the hypothesis of one single migraine generator to a more complex perspective of oscillating neurotransmitter networks and time-dependent changes in network connectivity.

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Conflicts of interest

There are no conflicts of interest.

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