Biochemistry in different phases of the migraine attack

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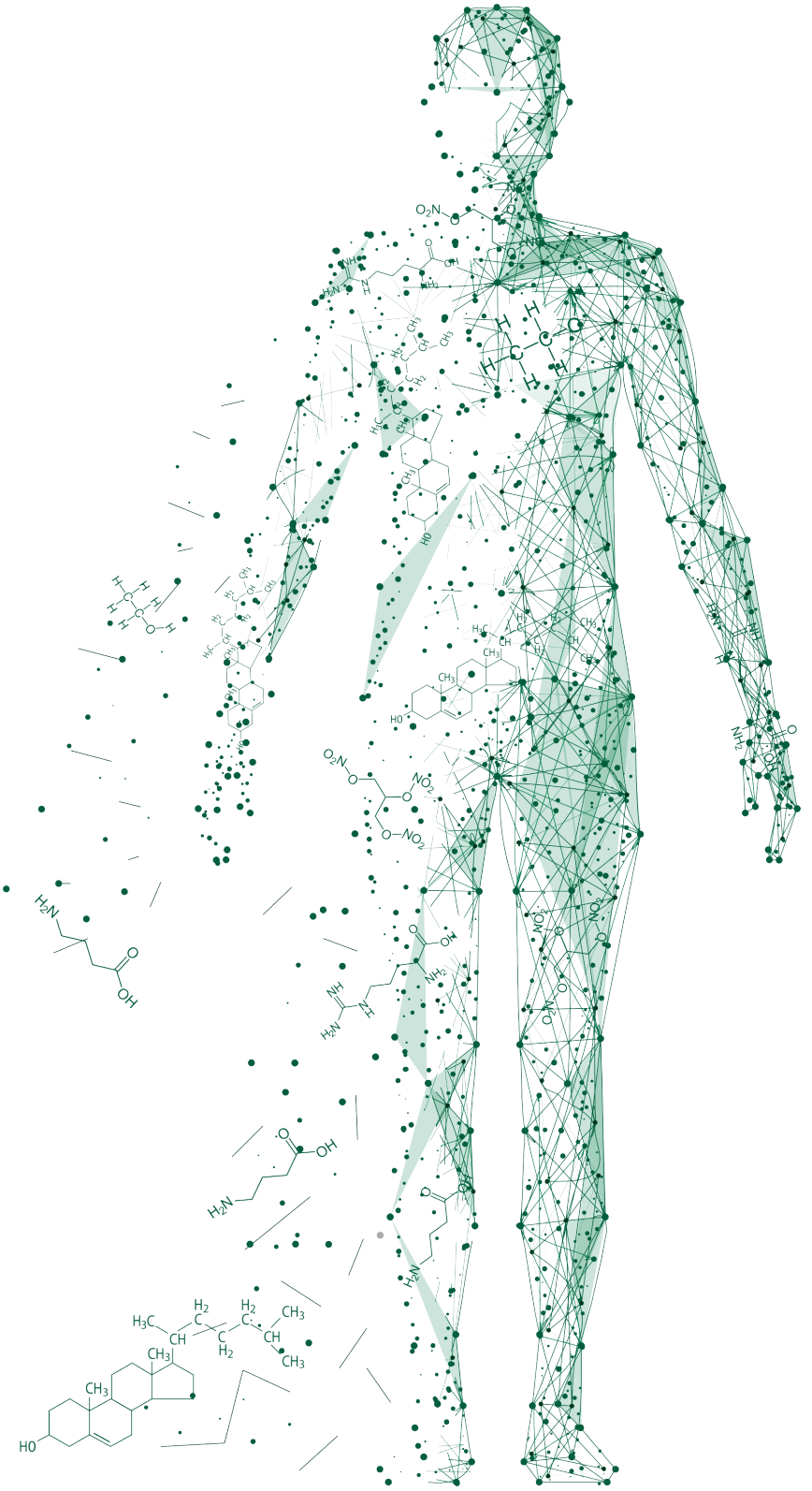

Chapter 1

General introduction

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Primary and secondary headaches

Characterizing and diagnosing headache disorders has been particularly challenging in the past as they can present as diverse phenotypes based on associated signs and symptoms. A phenotype of a specific disorder can vary not only between individuals but also intra-individually over time. In order to standardize the diagnosis of headache disorders the International Headache Society published the International Classification of Headache Disorders (ICHD).[1] The ICHD increased accuracy of diagnoses in population-based surveys and has proven to be an important tool for patient selection in clinical trials and scientific research. For instance, the use of standardized homogenous patient groups to study physiology or biochemistry and has greatly improved validity, reproducibility and agreement between clinicians in diagnosing headaches.

The current third edition of the ICHD recognizes a vast array of headache disorders that are divided into two main groups: primary and secondary headaches. Primary headache disorders are by definition not the result of any other underlying disease or process. There are three main primary headache disorders: (1) migraine, (2) tension-type headache, and (3) trigeminal autonomic cephalalgias.[1] Most of the biochemical and provocation research in primary headache disorders has focused on migraine.[1] A secondary headache disorder is defined as a new headache that occurs for the first time in close temporal relation to another disorder that is known to cause headache (e.g. trauma, (non-)vascular disorders, substance or its withdraw, or infection), or fulfills other criteria for causation by that disorder.[1]

Migraine

Migraine is a highly prevalent and disabling paroxysmal neurovascular brain disorder.[2,3] Studies from throughout the world consistently report lifetime migraine prevalence ranging from 17% to 33% in women and from 8% to 22% in men.[4–6] For migraine, the median attack frequency is about 1–2 attacks per month with a median attack duration of one day. At least 10% of patients have weekly attacks lasting 2–3 days each. The burden of migraine is tremendous as it is associated with a deteriorated health-related quality of life and lost productivity and has a large impact on patients and their families.[7,8] Consequently, migraine was rated the second most disabling chronic disorder in 2016.[3] There are two main subtypes of migraine: migraine with and migraine without aura.[9] Clinically, the following two terms are used to described a headache patient's status: interictal (outside an attack) and ictal (during an attack). Over the course of a migraine attack four distinct phases can be distinguished: the preictal premonitory phase, the ictal aura and headache phases, and the postictal postdromal phase.

Almost ninety percent of patients with migraine experience certain nonheadache symptoms warning them of an impending migraine attack.[7,10–13] These symptoms, called premonitory or prodromal symptoms, can occur hours even days before the headache during the so-called premonitory or prodromal phase.[1] In patients reporting premonitory symptoms their occurrence led to an actual migraine attack in 72% of cases.[12] Variation in recognition of premonitory symptoms is mostly due to differences in monitoring (prospective versus retrospective) of these symptoms between studies, the populations studied (clinic-based versus population-based) and the definition of premonitory symptoms versus precipitating or trigger factors.[7,10,11] Frequently reported symptoms include specific food cravings, irritability, concentration difficulties, excessive yawning, tiredness/fatigue, phonophobia, and neck stiffness.[1,12,13] Given the nature and often circadian rhythmicity of premonitory symptoms the hypothalamus with among others orexinergic (sleep regulation, feeding) and dopaminergic (yawning, nausea) systems have been proposed to be implicated.[14] Support comes from neuroimaging findings showing involvement of the hypothalamus preceding and during spontaneous[15,16] and pharmacologically triggered attacks.[17] Interestingly, these symptoms have been reported to endure and persist during aura (if applicable), headache and even postdromal phases.[12,14,18]

In about one-third of patients the headache phases of attacks are preceded by transient neurological symptoms, which are known as migraine aura. The most prevalent is the visual aura (80-90%) which can vary from simple flashes or lights to fortification scotoma or complex hallucinations.[7,19] Other well-known aura symptoms are sensory paresthesia's (30%), aphasic speech disturbances (17%), and motor weakness (10%).[9] Duration of the aura symptoms typically ranges from 5 until 60 minutes.[20–22] The migraine aura is likely caused by cortical spreading depolarization (CSD), a wave of intense neuronal and glial depolarization that starts in the occipital cortex and propagates frontally, until it hits upon a less sensitive part of the brain.[23–25] The wave front travels at a speed of 2-5 mm per minute and leaves affected neurons depolarized for several minutes to up to an hour.[25] A rare and clinically heterogeneous monogenic subtype of migraine with aura, characterized by attacks associated with transient motor weakness and various other neurologic features, is hemiplegic migraine.[1] If a patient has at least one first- or second-degree relative who also has migraine aura with motor weakness, this patient is labeled as having familial hemiplegic migraine (FHM). So far, three genes have been identified for FHM: *CACNA1A* (FHM1), *ATP1A2* (FHM2), and *SCN1A* (FHM3).[26] The discovery of gene mutations in FHM has led to the concept that the migraine brain is hyperexcitable and more vulnerable to CSD compared to non-migraine patients.[26–28] In migraine there are, however, no signs of neuronal damage that trigger CSD events, as is the case for other known causes of spreading depolarization, such as ischemic or hemorrhagic stroke and traumatic brain injury.[26,29] All three mutated FHM genes ultimately lead to increased concentrations of the excitatory neurotransmitter glutamate in the synaptic cleft, at least in the cortex.[27]

Studies in transgenic FHM mouse models have confirmed a reduced triggering threshold, an enhanced traveling speed, and subcortical propagation of the spreading depolarization waves.[28,30] Although glutamate has been primarily implicated in CSD because of the FHM mutations, other mediators have been linked to CSD as well (figure 1).

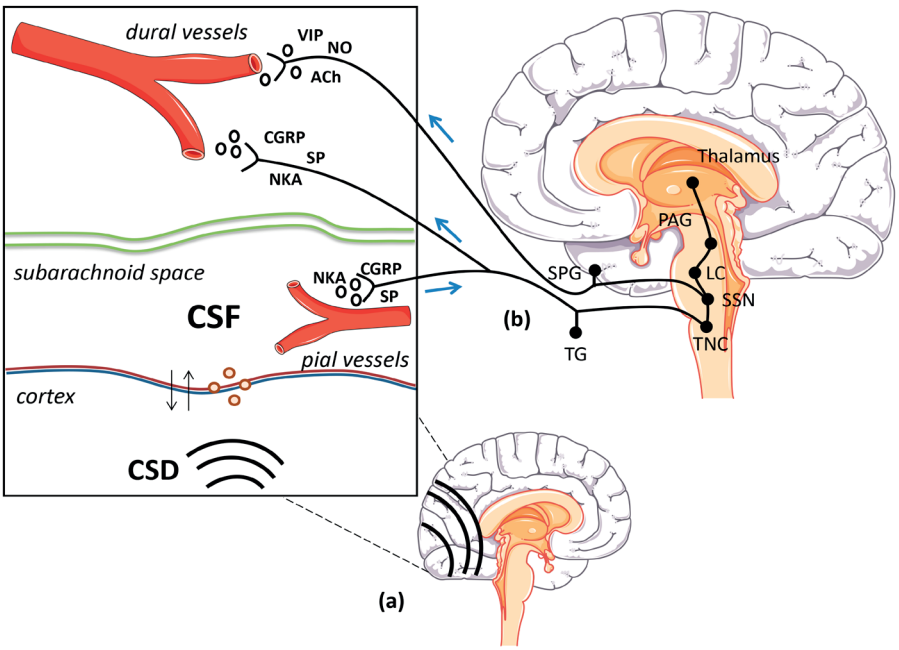

Figure 1. CSF is highly interesting for studying migraine mechanisms, because of its close contact with the brain interstitium. In the ventricles there is free diffusion of molecules between CSF and the interstitium after fetal development (not shown here); at the cortex the glial limitans and pia mater (see box, red line) do not tightly limit molecular exchange. [78,79] (a) Migraine aura is caused by CSD, originating in the occipital cortex. Although the exact biochemical changes leading to CSD are still unknown, glutamate is thought to play an important role. The depolarization wave, typical for a CSD, causes major disturbances in ions and other mediators. In experimental animal models, there is evidence that CSD might lead to delayed activation of trigeminal afferents. For instance, neuronal Panx1 channels release HMGB1 proteins upon CSD, thereby stimulating astrocytes in the glia limitans to release inflammatory mediators.[37] (b) Migraine headache is caused by activation of the trigeminovascular system. Perivascular trigeminal afferents transmit signals via the trigeminal ganglion to the brainstem, with CGRP as the main neurotransmitter. In the brainstem the signal is modulated and transmitted to the thalamus. Activation of the trigeminal afferents also leads to perivascular release of proinflammatory neuropeptides and other mediators via trigeminal fibers (CGRP, SP, NKA) and parasympathic fibers (VIP, NO, ACh). This release leads to sustained activation and therefore sensitization of the primary afferents. Further sensitization along the pain pathway can cause accompanying symptoms such as allodynia, photophobia and phonophobia. SP=substance P, NKA=neurokinin A, VIP=vasoactive intestinal peptide, NO=nitric oxide, ACh=acetylcholine, TG=trigeminal ganglion, TNC=trigeminal nucleus caudalis, SSN=superior salivatory nucleus, SPG=sphenopalatine ganglion, LC=locus coeruleus, PAG=periaqueductal gray. (From: Chapter 16- Primary Headaches in Handbook of Clinical Neurology[80]; adapted from several figures courtesy of Servier Medical Art.)

The migrainous headache phase is typically characterized by severe, often unilateral, headache that is accompanied by associated symptoms of photophobia and phonophobia, and/or nausea which may lead to vomiting.[31] When left untreated these attacks can last between four hours up to multiple days and are very disabling for patients.[32,33] The migraine headache is thought to be caused by activation of the trigeminovascular system (TGVS). The TGVS consists of nociceptive trigeminal afferents surrounding different types of meningeal blood vessels (figure 1). After stimulation, the trigeminal afferents transmit nociceptive signals through the trigeminal ganglion to the trigeminocervical complex where it is modulated by different brainstem regions before being processed in the thalamus and ultimately the cortex. Associated symptoms such as photophobia, phonophobia and allodynia are likely caused by sensitization of neurons along this pain pathway.[26,34–36]

Several neuropeptides and other mediators are known to be released by the trigeminal fibers after they become activated. However, the mechanisms causing the actual activation are still unclear. In migraine with aura, the aura typically precedes the headache and it is therefore hypothesized that CSD activates the TGVS. Through the opening of Pannexin1 mega-channels CSD can indeed lead to subsequent activation of inflammatory pathways and trigeminal afferents, at least in animal models.[37] Whether this also applies to humans, and if so, how the TGVS is activated in migraine without aura remains an enigma.[26]

Up to eighty percent of patients recognize a postdromal phase which occurs after the headache subsides.[18] Frequently reported symptoms include concentration difficulties, tired/weary feeling, stiff neck, irritable or intolerant, and light sensitivity.[12] Interestingly, these symptoms are similar to the ones experienced in the prodromal phase.[10,12,13] As mentioned above, premonitory symptoms have also been reported during the headache phase, therefore it remains to be elucidated when specific symptoms are initiated and if they indeed persist until the postdromal phase.[12,14] Table 1 lists the complete ICHD-3 criteria for migraine with and without aura.

Migraine treatment is divided in attack treatment and prophylactic treatment.[38,39] The first step in attack treatment is the use of simple analgesics (acetaminophen/acetylsalicylic acid) and non-steroidal anti-inflammatory drugs (NSAIDs) for the headache; if necessary in combination with anti-emetics for nausea. If unsuccessful, triptans (5-HT1B/1D receptor agonists) can be used. Development of future attack treatments with selective 5-HT1F receptor agonists (ditans) and first and second-generation calcitonin gene-related peptide (CGRP) agonists (gepants) may offer additional treatment possibilities.[40,41] While a number of triptans also bind to the 5-HT1F receptor, their efficacy has been attributed to their binding to 5-HT1B and 1D receptors.[40] Selective

affinity for the 5-HT1F receptor may however result in fewer vasoconstrictive side effects compared to triptans in patients suffering from cardiovascular disease.[40] When a patient has on average two or more migraine attacks per month, prophylaxis should be considered. Betablockers, anti-epileptic drugs (topiramate and sodium valproate), pizotifen, flunarizine, and candesartan are commonly used, and botulinum toxin-A for the chronic form of migraine, although the specific mechanisms of action in migraine are unclear. On average, two-third of the patients on prophylaxis will experience a 50% reduction in attack frequency.[38,39] Recently, the first prophylactic therapy specifically developed for the treatment of migraine, CGRP antibodies, have been approved as a possible option.[42–44] An important advance, since a number of these drugs have been developed toward a suspected underlying pathophysiological mechanism for migraine headache.[44] With advances in neuroimaging, biomarker identification, and genomic analysis further unraveling of the mechanisms behind migraine additional compounds and treatment targets are expected to be identified in the future.[44]

Biomarker identification in migraine

Identification of biochemical compounds in body fluids (e.g. cerebrospinal fluid (CSF), urine, and blood) or the brain itself may act as a disorder-specific biomarker with great potential in migraine. A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".[45] Biomarkers can: (1) provide insight into pathophysiological mechanisms, (2) quantify the degree of change over time (for instance, over the different phases of a migraine attack), (3) distinguish subgroups of primary headache disorders from one another or from controls, (4) discriminate what may be clinically overlapping disorders, (5) help to define more homogeneous groups of patients for genetic and other headache research, (6) predict or monitor treatment response, (7) predict or monitor risk for chronification, and (8) eventually perhaps serve as a widely used diagnostic marker.

Whereas routine biofluid measurements in CSF or blood are not helpful in migraine,[46] the usage of high-throughput proteomics, peptidomics and metabolomics that allows for the rapid simultaneous identification and quantification of a large number of biochemical measures may provide more detailed pathophysiological insights, that is beyond traditional biofluid measurements. With these advanced techniques a large number of proteins, peptides and metabolites can be quantitatively measured from minimal amounts of biological material. However, not all molecules can be measured on a single platform. Therefore, different analytical approaches and platforms have to be employed.[47]

Table 1. Criteria for migraine without aura and migraine with aura according to the International Classification of Headache Disorders, third edition (ICHD-3)[1]

ICHD-3 criteria
Migraine without aura
A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
1. nausea and/or vomiting
2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.
Migraine with aura
A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal
C. At least three of the following six characteristics:
1. at least one aura symptom spreads gradually over ≥5 minutes
2. two or more aura symptoms occur in succession
3. each individual aura symptom lasts 5-60 minutes
4. at least one aura symptom is unilateral
5. at least one aura symptom is positive
6. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis.

[1]ICHD=International Classification of Headache Disorders

Biofluid biological molecule measurements

Biomarker research can be performed from various tissues and biofluids,[48] however, in most cases blood is the biofluid of choice. Due to the minimally invasive nature of its collection it is understandable that blood is the most commonly used biofluid for clinical chemistry analyses and diagnoses in healthcare. However, the rich metabolome in blood is a reflection of the overall metabolic state of the entire organism.[49,50] Instead, CSF may represent a more specific and selective matrix of metabolites for diseases of the central nervous system (CNS) since it is in direct contact with the brain interstitial fluid and may therefore better represent the brains neurochemical state.[49,51] It is likely

that the biochemical constitution of CSF in migraine patients reflects somehow the susceptibility to develop migraine attacks.[26,52] Over 70 biochemical measurements have been determined in CSF of migraine patients.[46,53] These measurements represent various molecular classes, i.e. neuropeptides, neurotransmitters, hormones, cytokines, and ions.[46,53] Amines involved in pathways implicated in migraine pathophysiology, such as glutamate, glutamine, GABA and serotonin, have been frequently studied.[26,46,54] However, study quality varied greatly, i.e. frequently there are issues regarding the measurement techniques and the selection and matching of controls.[46] Also the studies focused on single molecular measurements, which did not allow for global biochemical profile and/or pathway analyses.[46]

Brain biological molecule measurements

An advantage of measuring biological molecules in biofluids is that a large number of biochemical measurements can be performed in a single run, however, even CSF acts as a representative of processes that are thought to occur in the brain of migraine patients. Magnetic resonance spectroscopy (MRS) is a noninvasive method well-suited for the *in vivo* analysis of a limited set of metabolites in specific brain areas. The aforementioned enhanced cerebral excitability may directly increase susceptibility to develop a CSD event or increase brain reactivity in certain areas to migraine-relevant stimuli (such as light during attacks).[26,55,56] Biofluid measurements revealed elevated glutamate levels in patients with chronic migraine, in CSF and elevated blood glutamate levels in patients with episodic migraine.[46] Earlier investigations of the glutamatergic system using proton MRS (^{1}H-MRS), generally reported as “glx”, referring to the combined measure of excitatory neurotransmitter glutamate and its major non-neuroactive precursor glutamine.[57,58] Recently a study using 7 Tesla (7T) ^{1}H-MRS, allowing for the independent measurement of glutamate and glutamine, identified elevated glutamate concentrations in the visual cortex of interictal migraine without aura patients.[59] Apart from glutamine, glutamate is also metabolically intertwined with the inhibitory neurotransmitter GABA, for which glutamate serves as precursor.[60] Therefore, measuring the concentration of each of these three metabolites separately is essential to detect metabolic changes between them in the glutamatergic system. Such information is currently lacking and almost all of this research using ^{1}H-MRS focused on the interictal phase which does not look into whether glutamate changes are indeed involved in the initiation of a migraine attack as hypothesized.

Migraine provocation

The pathophysiological mechanisms behind the triggering and consecutive initiation of migraine attacks remain to be elucidated. The susceptibility to develop attacks has been suggested to depend on the dysregulation of cortical excitability that influences the way the brain (e.g. brainstem, deep brain nuclei and cortex) reacts to certain stimuli.[61,62] This dysregulation is thought to be due to a continues dynamic process made up of a contribution from of non-modifiable genetic factors (e.g. aforementioned changes in glutamatergic neurotransmission) and modifiable internal (e.g. comorbidities and hormonal fluctuations) and external (e.g. alcohol and food consumption, and weather changes) risk modulation factors.[26,63–67] External risk modulation factors, also called trigger factors, might be more easily modified compared to internal factors. A trigger factor, if indeed proven to be reliable in provoking attacks might be used either by patients to possibly avoid attacks or for research purposes to study attack onset, so as to enhance knowledge of pathophysiological mechanisms involved in the initiation of attacks. A trigger factor frequently reported by patients are various types of alcoholic beverages.[63,66,68,69] Headaches occurring after exposure to some of these trigger factors are listed in the ICHD as secondary headaches.[1] For instance the ICHD recognizes immediate and delayed alcohol-induced headache or immediate and delayed nitric oxide donor-induced headache or phosphodiesterase inhibitor-induced headache provoked by well-known pharmacological migraine provocation models.[1] The distinction is made as these headaches respond to a non-physiological stimulus and might be due to be another mechanism.[1] Therefore, when migraine attacks are provoked for study purposes they are often referred to as migraine-like attacks. However, investigating the initiation of spontaneous attacks is difficult as these attacks strike unexpected. Furthermore, associated disability frequently inhibits patients from traveling to the hospital to be studied or when patients arrive at the hospital and the attack has already progressed to the headache phase.[70] Pharmacological migraine models such as intravenous infusion with the nitric oxide donor glyceryl trinitrate (GTN) gives rise to immediate and delayed nitric oxide donor-induced headache.[70,71] Such a model can be used to investigate attack initiation under precisely monitored and regulated conditions.[70,72] Hypothalamic, brainstem and occipital cortex activation[17] have been demonstrated in GTN-triggered attacks and spontaneous attacks,[15,16,26,73–76] as well as premonitory symptoms,[77] illustrating the possibility of using such a model to study the early processes involved in the onset of attacks.

Outline of the thesis

This thesis is divided in two parts. **Part 1**, which consists of **Chapters 2 and 3**, describes biofluid investigations in interictal migraine patients aimed at the validation of known and the discovery of new compounds related to migraine pathophysiology using metabolomics. **Part 2** of this thesis, which consists of **Chapters 4, 5, and 6**, describes the transition towards research during the preictal and ictal phases of migraine attacks. The research in these chapters investigates methods for triggering attacks, and the use of GTN in provoking migraine-like attacks to investigate biochemical changes related to the preictal and ictal phase with ^{1}H-MRS.

Part 1: Migraine biochemical profiling in biofluids

Chapter 2 describes the biochemical profiling of plasma samples from interictal migraineurs and healthy controls from eight Dutch cohorts with a proton nuclear magnetic resonance (^{1}H-NMR)-based metabolomics platform. The research aimed to identify a plasma metabolomic biomarker signature for migraine. In **Chapter 3** CSF and plasma samples from interictal patients with migraine with aura, patients with migraine without aura, and healthy volunteers, were profiled using an ultra-performance liquid chromatography mass spectrometry (UPLC-MS) platform for amine measurements, as multiple amines have been implicated in migraine pathophysiology.

Part 2: Triggering migraine and biochemical profiling of upcoming attacks

Alcoholic beverages are frequently reported migraine triggers. The aim of **Chapter 4** was to assess the potential of various alcohol beverages as a migraine attack trigger using a questionnaire study in a large cohort of migraine patients. In **Chapter 5**, the frequently used pharmacological migraine trigger GTN was studied in migraineurs and healthy controls to investigate whether previously reported premonitory symptoms are indeed specific to migraine patients. In **Chapter 6** elements of the glutamatergic system, i.e., glutamate, glutamine, and GABA, were assed in the visual cortex of migraineurs before and over the course of a GTN-provoked attack to detect possible involvement of the glutamatergic system in the onset of attacks.

Finally, **Chapter 7** provides a general discussion of the thesis, reviewing the results and discussing future possibilities for research into migraine biochemistry and triggering of migraine attacks.

References

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* **38**, 1–211 (2018).
2. Jensen, R. & Stovner, L. J. Epidemiology and comorbidity of headache. *Lancet Neurol.* **7**, 354–361 (2008).
3. Global Burden of Disease Study 2016 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* **390**, 1211–1259 (2017).
4. Launer, L. J., Terwindt, G. M. & Ferrari, M. D. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. *Neurology* **53**, 537–542 (1999).
5. Stovner, L. J., Zwart, J. A., Hagen, K., Terwindt, G. M. & Pascual, J. Epidemiology of headache in Europe. *Eur. J. Neurol.* **13**, 333–345 (2006).
6. Buse, D. C. *et al.* Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: Results of the American Migraine prevalence and prevention (AMPP) study. *Headache* **53**, 1278–1299 (2013).
7. Rasmussen, B. K. & Olesen, J. Migraine with aura and migraine without aura: an epidemiological study. *Cephalalgia* **12**, 221–228 (1992).
8. Lipton, R. B., Diamond, S., Reed, M., Diamond, M. L. & Stewart, W. F. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache* **41**, 638–645 (2001).
9. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* **33**, 629–808 (2013).
10. Waelkens, J. Warning symptoms in migraine : characteristics and therapeutic implications. *Cephalalgia* **5**, 223–8 (1985).
11. Russell, M., Rasmussen, B., Fenger, K. & Olesen, J. Migraine without aura and migraine with aura are distinct clinical entities: a study of four hundred and eighty-four male and female migraineurs from the general population. *Cephalalgia* **16**, 239–245 (1996).
12. Giffin, N. J. *et al.* Premonitory symptoms in migraine: an electronic diary study. *Neurology* **60**, 935–940 (2003).
13. Schoonman, G. G., Evers, D. J., Terwindt, G. M., van Dijk, J. G. & Ferrari, M. D. The prevalence of premonitory symptoms in migraine: a questionnaire study in 461 patients. *Cephalalgia* **26**, 1209–13 (2006).
14. Goadsby, P. J. *et al.* Pathophysiology of migraine: a disorder of sensory processing. *Physiol Rev* **97**, 553–622 (2017).
15. Denuelle, M., Fabre, N., Payoux, P., Chollet, F. & Geraud, G. Hypothalamic activation in spontaneous migraine attacks. *Headache* **47**, 1418–1426 (2007).
16. Schulte, L. H. & May, A. The migraine generator revisited: Continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain* **139**, 1987–1993 (2016).
17. Maniyar, F. H., Sprenger, T., Monteith, T., Schankin, C. & Goadsby, P. J. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain* **137**, 232–241 (2014).
18. Giffin, N. J., Lipton, R. B., Silberstein, S. D., Olesen, J. & Goadsby, P. J. The migraine postdrome: An electronic diary study. *Neurology* **87**, 309–313 (2016).
19. Wilkinson, F. Auras and other hallucinations: windows on the visual brain. *Prog. Brain Res.* **144**, 305–320 (2004).

20. Manzoni, G. C., Farina, S., Lanfranchi, M. & Solari, A. Classic migraine--clinical findings in 164 patients. *Eur. Neurol.* **24**, 163–9 (1985).
21. Queiroz, L. P. *et al.* Characteristics of migraine visual aura. *Headache* **37**, 137–41 (1997).
22. Viana, M., Sprenger, T., Andelova, M. & Goadsby, P. J. The typical duration of migraine aura: a systematic review. *Cephalalgia* **33**, 483–490 (2013).
23. Goadsby, P. J., Charbit, A. R., Andreou, A. P., Akerman, S. & Holland, P. R. Neurobiology of migraine. *Neuroscience* **161**, 327–341 (2009).
24. Tfelt-Hansen, P. C. History of migraine with aura and cortical spreading depression from 1941 and onwards. *Cephalalgia* **30**, 780–792 (2010).
25. Charles, A. C. & Baca, S. M. Cortical spreading depression and migraine. *Nat. Rev. Neurol.* **9**, 637–644 (2013).
26. Ferrari, M. D., Klever, R. R., Terwindt, G. M., Ayata, C. & van den Maagdenberg, A. M. J. M. Migraine pathophysiology: lessons from mouse models and human genetics. *Lancet Neurol.* **14**, 65–80 (2015).
27. Tolner, E. A. *et al.* From migraine genes to mechanisms. *Pain* **156**, S64–S74 (2015).
28. van den Maagdenberg, A. M. J. M. *et al.* A Cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression. *Neuron* **41**, 701–710 (2004).
29. Ayata, C. & Lauritzen, M. Spreading Depression, Spreading Depolarizations, and the Cerebral Vasculature. *Physiol. Rev.* **95**, 953–993 (2015).
30. Eikermann-Haerter, K., Negro, A. & Ayata, C. Spreading depression and the clinical correlates of migraine. *Rev. Neurosci.* **24**, 353–363 (2013).
31. Moskowitz, M. A. & Buzzi, M. G. Migraine general aspects. *Handb. Clin. Neurol.* **97**, 253–266 (2010).
32. Charles, A. The evolution of a migraine attack- a review of recent evidence. *Headache* **53**, 413–419 (2013).
33. Lipton, R. B. & Bigal, M. E. Ten lessons on the epidemiology of migraine. *Headache 47 Suppl* **1 SRC-G**, S2–S9 (2007).
34. Burstein, R., Yarnitsky, D., Goor-Aryeh, I., Ransil, B. J. & Bajwa, Z. H. An association between migraine and cutaneous allodynia. *Ann. Neurol.* **47**, 614–624 (2010).
35. Louter, M. A. *et al.* Cutaneous allodynia as a predictor of migraine chronification. *Brain* **136**, 3489–3496 (2013).
36. Pietrobon, D. & Moskowitz, M. a. Pathophysiology of migraine. *Annu. Rev. Physiol.* **75**, 365–91 (2013).
37. Karatas, H. *et al.* Spreading depression triggers headache by activating neuronal Panx1 channels. *Science* **339**, 1092–1095 (2013).
38. Goadsby, P. J. Migraine — Current Understanding and Treatment. *N. Engl. J. Med.* **346**, 257–270 (2002).
39. Goadsby, P. J. Recent advances in the diagnosis and management of migraine. *Bmj* **332**, 25–9 (2006).
40. Rubio-Beltrán, E., Labastida-Ramírez, A., Villalón, C. M. & MaassenVanDenBrink, A. Is selective 5-HT1F receptor agonism an entity apart from that of the triptans in antimigraine therapy? *Pharmacol. Ther.* **186**, 88–97 (2018).
41. Negro, A., Lionetto, L., Simmaco, M. & Martelletti, P. CGRP receptor antagonists: an expanding drug class for acute migraine? *Expert Opin. Investig. Drugs* **21**, 807–818 (2019)
42. Goadsby, P. J. *et al.* A controlled trial of erenumab for episodic migraine. *N. Engl. J. Med.* **377**, 2123–2132 (2017).
43. Silberstein, S. D. *et al.* Fremanezumab for the preventive treatment of chronic migraine. *N. Engl. J. Med.* **377**, 2113–2122 (2017).
44. Hershey, A. D. CGRP- The next frontier for migraine. *N. Engl. J. Med.* **377**, 2190–2191 (2017).
45. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and

conceptual framework. *Clin. Pharmacol. Ther.* **69 SRC**-, 89–95 (2001).

46. van Dongen, R. M. *et al.* Migraine biomarkers in cerebrospinal fluid: A systematic review and meta-analysis. *Cephalalgia* **0**, 1–15 (2016).
47. Patti, G. J., Yanes, O. & Siuzdak, G. Innovation: Metabolomics: the apogee of the omics trilogy. *Nat. Rev. Mol. Cell Biol.* **13**, 263–269 (2012).
48. Johnson, C. H., Ivanisevic, J. & Siuzdak, G. Metabolomics: Beyond biomarkers and towards mechanisms. *Nat. Rev. Mol. Cell Biol.* **17**, 451–459 (2016).
49. Wishart, D. S. *et al.* The human cerebrospinal fluid metabolome. *J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci.* **871**, 164–173 (2008).
50. Psychogios, N. *et al.* The human serum metabolome. *PLoS One* **6**, e16957 (2011)
51. Brown, P. D., Davies, S. L., Speake, T. & Millar, I. D. Molecular mechanisms of cerebrospinal fluid production. *Neuroscience* **129**, 957–970 (2004).
52. Stankewitz, A. & May, A. The phenomenon of changes in cortical excitability in migraine is not migraine-specific – A unifying thesis. *Pain* **145**, 14–19 (2009).
53. Zielman, R. *et al.* Metabolomic changes in CSF of migraine patients measured with 1 H-NMR spectroscopy. *Mol. BioSyst.* **12**, 3674–3682 (2016).
54. Humphrey, P. P. A. *et al.* Serotonin and Migraine. *Ann. N. Y. Acad. Sci.* **600**, 587–598 (1990).
55. Boulloche, N. *et al.* Photophobia in migraine: An interictal PET study of cortical hyperexcitability and its modulation by pain. *J. Neurol. Neurosurg. Psychiatry* **81**, 978–984 (2010).
56. Maniyar, F. H., Sprenger, T., Schankin, C. & Goadsby, P. J. Photic hypersensitivity in the premonitory phase of migraine- a positron emission tomography study. *Eur. J. Neurol.* **21**, 1178–1183 (2014).
57. Danbolt, N. C. Glutamate uptake. *Prog. Neurobiol.* **65**, 1–105 (2001).
58. Waagpetersen, H. S., Sonnewald, U. & Schousboe, A. *Handbook of neurochemistry and molecular neurobiology*. (2007).
59. Zielman, R. *et al.* Cortical glutamate in migraine. *Brain* **140**, 1859–1871 (2017).
60. Walls, A. B., Waagepetersen, H. S., Bak, L. K., Schousboe, A. & Sonnewald, U. The Glutamine–Glutamate/GABA Cycle: Function, Regional Differences in Glutamate and GABA Production and Effects of Interference with GABA Metabolism. *Neurochem. Res.* **40**, 402–409 (2014).
61. Cosentino, G., Fierro, B. & Brighina, F. From different neurophysiological methods to conflicting pathophysiological views in migraine: A critical review of literature. *Clin. Neurophysiol.* **125**, 1721–1730 (2014).
62. Bolay, H. The first phase of a migraine attack resides in the cortex. *J. Neural Transm.* **119**, 569–574 (2012).
63. Hoffmann, J. & Recober, A. Migraine and triggers: Post hoc ergo propter hoc? *Curr. Pain Headache Rep.* **17**, 370 (2013).
64. Burstein, R., Noseda, R. & Borsook, D. Migraine: Multiple Processes, Complex Pathophysiology. *J. Neurosci.* **35**, 6619–6629 (2015).
65. Polderman, T. J. C. *et al.* Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat. Genet.* **47**, 702–709 (2015).
66. Kelman, L. The triggers or precipitants of the acute migraine attack. *Cephalalgia* **27**, 394–402 (2007).
67. Gormley, P. *et al.* Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. *Nat. Genet.* **48**, 856–866 (2016).

68. Peroutka, S. J. What turns on a migraine? A systematic review of migraine precipitating factors. *Curr. Pain Headache Rep.* **18**, 454 (2014).
69. Zaeem, Z., Zhou, L. & Dilli, E. Headaches: a Review of the Role of Dietary Factors. *Curr. Neurol. Neurosci. Rep.* **16**, 101 (2016).
70. Ashina, M., Hansen, J. M. & Olesen, J. Pearls and pitfalls in human pharmacological models of migraine: 30 years' experience. *Cephalalgia* **33**, 540–53 (2013).
71. Schytz, H. W., Schoonman, G. G. & Ashina, M. What have we learnt from triggering migraine? *Curr. Opin. Neurol.* **23**, 259–65 (2010).
72. Ashina, M., Hansen, J. M., á Dunga, B. O. & Olesen, J. Human models of migraine — short-term pain for long-term gain. *Nat. Rev. Neurol.* **13**, 713–724 (2017).
73. Weiller, C. *et al.* Brain stem activation in spontaneous human migraine attacks. *Nat. Med.* **1**, 658–60 (1995).
74. Bahra, A., Matharu, M. S., Buchel, C., Frackowiak, R. S. & Goadsby, P. J. Brainstem activation specific to migraine headache. *Lancet* **357**, 1016–7 (2001).
75. Afridi, S. *et al.* A positron emission tomographic study in spontaneous migraine. *Arch Neurol* **62**, 1270–5 (2005).
76. Hadjikhani, N. *et al.* Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc. Natl. Acad. Sci. U. S. A.* **98**, 4687–4692 (2001).
77. Afridi, S. K., Kaube, H. & Goadsby, P. J. Glyceryl trinitrate triggers premonitory symptoms in migraineurs. *Pain* **110**, 675–80 (2004).
78. Saunders, N. R., Liddelow, S. A. & Dziegielewska, K. M. Barrier mechanisms in the developing brain. *Front. Pharmacol.* **3 MAR**, 1–18 (2012).
79. Cipolla, M. J. Barriers of the CNS. in *The cerebral circulation* (2009).
80. Onderwater, G. L. J., van Dongen, R. M., Zielman, R., Terwindt, G. M. & Ferrari, M. D. Primary Headaches. in *Handbook of clinical neurology* **146**, 267–28 (2017).