# Trigger factors and mechanisms in migraine

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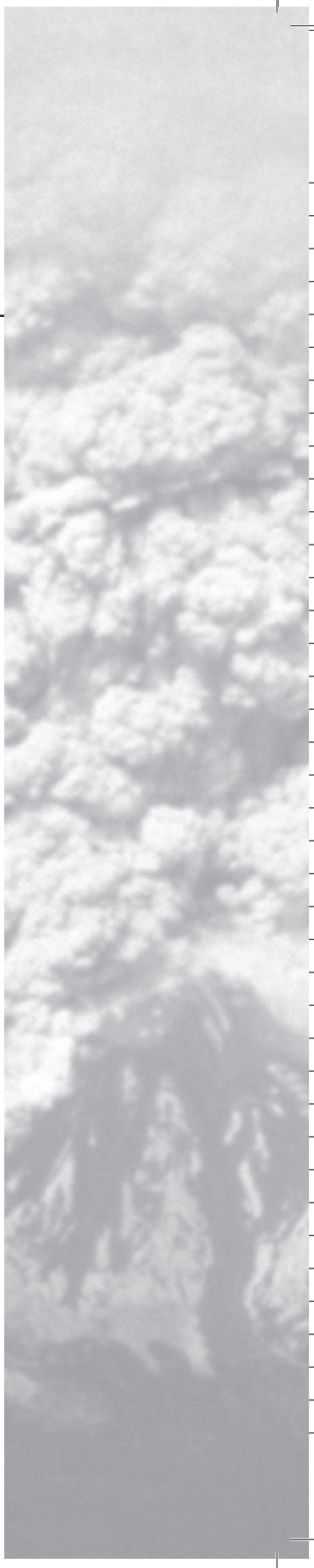



# GENERAL DISCUSSION AND CONCLUSIONS

This thesis deals with the association between potential trigger factors and the occurrence of a migraine attack as well as the action mechanism of trigger factors in migraine. We have focused our research on three trigger factors; mental stress, normobaric hypoxia and nitroglycerin. The most remarkable findings will be summarized and discussed.

### *Premonitory symptoms are frequently reported by migraine patients in a clinic based sample (chapter 1)*

In a clinic based sample of 374 migraine patients we found that 86.9% of patients reported at least one symptom and 71.1% reported two or more. Forty-nine patients (13.1%) reported no premonitory symptoms. Other clinic based studies found prevalence rates for premonitory symptoms of 79%[133] and 84%[7], although rates of around 33% also have been found[134,135]. The most frequently reported premonitory symptoms were fatigue (46.5%), phonophobia (36.4%) and yawning (35.8%). This is in accordance with other studies assessing premonitory symptoms. In a prospective study in 100 migraine patients the most frequent symptoms were anxiety, phonophobia, irritability, unhappiness and yawing[7]. Several important questions regarding premonitory symptoms in migraine remain to be answered. For instance how specific are premonitory symptoms for migraine? Many possible premonitory symptoms are rather a-specific and are also associated with other conditions such as premenstrual syndrome[136] and depression[140]. Future studies could try to assess the occurrence of possible premonitory symptoms in combination with other migraine symptoms in a prospective design using electronic diaries in an unselected migraine population[131].

### *The association between mental stress and the occurrence of a migraine attack is less clear than previously assumed (chapter 2)*

In chapter 2 we described findings of a prospective longitudinal study. We failed to find any objective evidence for a temporal relationship between changes in perceived stress, biological indicators for a stress-response, and the onset of a migraine attack. Although stress-sensitive patients indeed reported an increase in perceived stress in the days before an attack, this was not accompanied by objective signs indicating a biological stress response. These findings are in accordance with previous stress studies. Retrospective and prospective questionnaire studies suggest an increase in the perception of potential stressors around the migraine attack[27,42]. On the other hand stress provocation studies including biological stress response measures during and outside a migraine attack are either negative or not conclusive[141]. Furthermore, there is also no association between migraine and major life stressors[251]. Possibly mental stress is not a trigger factor for migraine but do migraine patients perceive daily hassles as

stressful due to the development of a migraine attack. The lack of a biological stress response (eg cortisol) in patients who perceived more stress could be the result of the temporal resolution of our measurements as discussed in chapter 2. Future studies will have to answer the question whether mental stress is a trigger factor for migraine or not. An option could be to design an experimental provocation study using a mental stressor sufficient enough to trigger migraine attacks.

### *Normobaric hypoxia is a possible trigger factor for migraine (chapter 3)*

A high altitude environment causes acute mountain sickness in healthy volunteers [97] and might be able to trigger migraine in susceptible patients[126], mainly through hypoxia, although an additional effect of hypobaria can not be excluded[179]. Several symptoms in acute mountain sickness are comparable to migraine including headache, nausea, fluid retention and disturbance of sleep[97] and as we have shown in chapter 3 normobaric hypoxia triggered a migraine attack in 6 out of 14 migraine patients. The results for hypoxia were not significant but in the light of a very low response after the positive control nitroglycerin it could be that the studied population was not very susceptible for migraine. Combined with previous studies in mountaineers[99] it was concluded that hypoxia is a possible trigger factor for migraine. For the dutch migraine population there are no direct consequenses of this finding, since the highest mountain in the Netherlands is only 321 meters. Airflights might cause a problem; current regulations require that cabin air pressure must be no lower than the air pressure that naturally occurs at 2400 meter. In our experiments subjects were exposed to hypoxia corresponding to 4500m. Whether 2400m would be enough to trigger migraine is unclear.

### *The migraine response after NTG infusion is variable ranging between 20% and 83% (chapter 3 and 6)*

The migraine response after infusion of a nitric oxide donor ranges from 20% to 83% between studies. The reason for the observed variability is unclear. A low baseline attack frequency could be a likely explanation. A study comparing the migraine response in patients with <4 attacks per year with patients 12 attack per year showed a trend towards more migraine attacks in frequent sufferers.[252] The second explanation could be the occurence of aura's. Two studies found a lower migraine response in patients with aura; 67% MA vs 83% MO[56] and 31.8% MA vs 78% MO[55]. A third factor could be age. In the three studies with the lowest migraine response the mean age is rather low ranging from 29.1[126] to 34.3 years.[123,129] Also in our second NTG study in migraine patients the mean age in non-responders was 34 year whereas the mean age in responders was 45.5 year (chapter 6). Whether there are other factors involved in migraine susceptibility for NTG is unclear.

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### *Normobaric hypoxia causes cerebral edema in healthy volunteers (chapter 4)*

Research in acute mountain sickness has mainly focused on the development of cerebral edema. Severe AMS is associated with high altitude cerebral edema[104]; whether edema also occurs in mild cases of AMS was unclear. In chapter 4 we have shown that hypoxia caused vasogenic edema in healthy volunteers irrespective of AMS symptoms and that cytotoxic edema might be associated with severe AMS. Our findings are in accordance with other studies which have been published while our study was drafted[167]. These findings in AMS might have implications for migraine. Approximately 30% of healthy climbers develop AMS at 3000m altitude[97]. Whether migraine patients are more susceptible for AMS is unclear. One of the mechanisms involved in the development of vasogenic and/or cytotoxic edema is Na(+)-K(+)-ATPase[190]. A mutation in the Na(+)-K(+)-ATPase gene was found in familial hemiplegic migraine[253], possibly causing blood brain barrier disruption and cerebral edema[254]. Future studies in migraine using hypoxia as a trigger will have to show whether cerebral edema is involved in the pathophysiology of the common types of migraine.

### *Nitroglycerin induced vasodilatation in both healthy volunteers and migraine patients (chapter 5 and 7) can be measured reliably with MRA*

Nitroglycerin is an exogenous donor of nitric oxide[255] and causes vasodilatation either through relaxation of vascular smooth muscles or through the release of CGRP[114]. A common technique to measure the diameter of cerebral blood vessels in vivo in humans is using trans-cranial Doppler. The advantages of TCD are that it is a continuous, cheap and non-invasive measurement, however, the outcome is operator dependent and TCD is an indirect measurement of the blood vessel diameter since it measures blood flow velocity[237]. To study blood flow diameters in migraine patients the aim was to have a direct and non-invasive method which would enable us to study blood vessel as small as the middle meningeal artery. Using magnetic resonance we have been able to reliably measure blood vessel diameters as shown in chapter 5 and 6. MRA images were measured by two independent observers and the agreement between observers was 0.74 (an intra class correlation of 0.7 or more is considered acceptable).The MMA diameter increase during NTG in healthy volunteers in chapter 5 was 20.1%, whereas the diameter increase in an other sample of healthy volunteers in chapter 6 was 19.9%.

### *The blood flow response but not vasodilatory response to nitroglycerin in migraine is related to the development of a delayed migraine attack (chapter 6)*

Nitroglycerin caused a decrease in ICA blood flow without affecting BA blood flow. The ICA blood flow decreased significantly more in healthy volunteers as compared to migraine patients. Previous NTG studies in migraine showed either no difference in blood velocity decrease in the middle cerebral artery between migraine and controls[118], or a more pronounced decrease in migraine patients[117]. An explanation for the difference in results could be that these studies did not take into account the occurrence of a provoked attack. As shown in this study the patients without an attack (several hours after NTG infusion) showed a decrease in ICA blood flow similar to healthy volunteers whereas in patients with an attack ICA blood flow did not decrease. Blood flow in the ICA is affected by several parameters; i) ICA blood vessel diameter, ii) cardiac output and iii) vasomotor tone in small resistance vessels. The ICA diameter increased during NTG infusion, but there was no difference between groups. Nitroglycerin has shown to decrease cardiac output[216]. In this study we did not measured cardiac output but we did not observe a difference in blood pressure response during NTG infusion between groups (data not shown), suggesting that there was no difference in decrease of cardiac output between groups. So a difference in vasomotor tone of small resistance vessels might be the main explanation for the observed difference between patients with and without an attack.

### *There is no vasodilatation during the headache phase of a nitroglycerin provoked migraine attack (chapter 7)*

This is the most important conclusion in this thesis. For many years there has been debate concerning vasodilatation in meningeal and cerebral arteries during the headache phase of a migraine attack. Studies by Wolff et al. showed that stimulation of cerebral and meningeal arteries caused headache and it was suggested that vasodilatation of cranial blood vessels was the cause for headache during a migraine attack[198]. Vasoactive substances such as nitroglycerin can trigger migraine in susceptible patients[78] and triptans might exert their anti-migraine effect through vasocontriction of cranial blood vessels[75]. However, in vivo measurements in humans using transcranial Doppler (TCD) are not conclusive[204,226,227,243-246]. In chapter 7 we have shown that there is no vasodilatation or change in cerebral blood flow during the headache phase of a provoked migraine attack as a model for spontaneous attacks. This finding does imply that future anti-migraine drugs do not have to constrict cerebral or meningeal blood vessels to treat the headache during a migraine attack.

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## Conclusions and future perspectives

Based on the studies presented in this thesis several conclusions can be drawn. The most important conclusion is that there is no vasodilatation of cranial arteries during the headache phase of a migraine attack. Future drug development research should focus on non-vascular structures to treat migraine headache. The second conclusion is that there is no clear association between mental stress and the occurrence of a migraine attack in spite of previous reports. Based on this study it does not make sense to advise migraine patients to avoid potential mental stressors as part of there therapeutic plan. The discrepancy between objective and subjective stress measures needs further study. The third conclusion is that hypoxia might trigger migraine in susceptible patients through a process which may involve development of cerebral edema. This conclusion is rather speculative and needs more study in migraine patients using hypoxia as an experimental trigger factor.