Trigger factors and mechanisms in migraine

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CHAPTER 3

NORMOBARIC HYPOXIA AND NITROGLYCERIN AS TRIGGER FACTORS FOR MIGRAINE

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Abstract

Migraine prevalence is increased in high-altitude populations and symptoms of acute mountain sickness mimic migraine symptoms. Here we tested whether normobaric hypoxia may trigger migraine attacks. As positive control we used nitrolgycerine (NTG), which has been shown to induce migraine attacks in up to 80% of migraineurs. Sixteen patients (12 females, mean age 28.9 ± 7.2 years) suffering from migraine with (n=8) and without aura (n=8) underwent 3 different provocations (normobaric hypoxia, NTG and placebo) in a randomized, cross-over, double dummy design. Each provocation was performed on a separate day. The primary outcome measure was the proportion of patients developing a migraine attack according to the criteria of the International Headache Society within 8 hours after provocation onset. Fourteen patients completed all three provocations. Migraine was provoked in 6 (42%) patients by hypoxia, 3 (21%) by NTG and 2 (14%) by placebo. The differences among groups were not significant (p=0.197). The median time to attacks was 5 hours. In conclusion, the (remarkably) low response rate to NTG is surprising in view of previous data. Further studies are required to fully establish the potency of hypoxia in triggering migraine attacks.

Introduction

Migraine is a common neurovascular disorder that affects 15 to 20 % of the population[11]. Several substances are known to induce migraine attacks in susceptible patients. Nitroglycerin (NTG) is the most frequently studied trigger factor and has been shown to induce migraine attacks in 60 to 80% of migraineurs within 5 to 6 hours [55,56,78]. Hypoxia may also be a trigger factor for migraine. Firstly, acute exposure to high altitude may induce acute mountain sickness (AMS), which is characterized by headache, insomnia, dizziness, lassitude, fatigue and gastrointestinal symptoms such as anorexia, nausea, or vomiting in an unacclimatized person who has recently reached an altitude above 2500 m [97]. Up to one third of subjects with acute AMS also fulfill the criteria for migraine [3,98,99]. Secondly, chronic exposure to high altitude is associated with an increased migraine prevalence [100,101] and thirdly, sumatriptan is an established drug for the acute treatment of migraine [75], and was also shown to be effective in some studies in AMS [102,103]. In the present study we tested whether normobaric hypoxia may trigger migraine attacks in migraine patients under experimental conditions. We used NTG as a positive control.

Methods

Patients

Patients with a history of migraine with (MA) or without (MO) aura, aged 18-65 years, with a baseline attack frequency of 1 to 9 per 3 months in the last six months were recruited from the outpatient clinic, among hospital staff and university students. Exclusion criteria were headache on more than 10 days per month, pregnancy, lactation, psychiatric disorders including substance and drug abuse, neurological diseases other than migraine, and a medical disease that could, according to the judgment of the investigators, interfere with the study. Before each provocation it was made sure that no migraine attack had occurred within the previous 3 days, no pain or migraine medications were taken the previous 24 hours, and that the patient did not suffer from sinusitis or coryza. The study was approved by the local ethical committee.

Experimental Design

Patients were subjected to three different provocations (normobaric hypoxia, NTG and placebo) in a randomized, double-dummy controlled fashion using a cross-over design. The NTG and placebo part were double blind, and the hypoxia part was single blind, because arterial oxygen saturation (SaO_2) had to be monitored continuously.

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Each of the three provocations was performed on a different day. At the beginning of each provocation, the supine patient obtained a well fitting facial mask, which was connected with a tube for the administration of air with reduced or normal (placebo) oxygen content. Then an antecubital vein was cannulated for the infusion of NTG or saline (placebo). As soon as the patients stated that they became familiar with the facial mask and the attached tube, the provocation was started. An independent physician carried out randomization.

Exposure to normobaric hypoxia: An investigator progressively increased the concentration of nitrogen (N_2) in the inspired air to obtain SaO_2 values of 75 to 80% within 20 minutes. During exposure to normobaric hypoxia, intravenous (IV) saline was administered. The NTG provocation consisted of IV administration of 0.5 microgram / kg body weight NTG within 20 minutes using a free infusion set (Codan, the Netherlands), while the patient was breathing normal air. Placebo provocation: The participants breathed normal air during the whole provocation, whereas only IV saline was administered during the first 20 minutes of the provocation.

Headache Response to the Different Provocations

Migraine symptoms according to the criteria of the International Headache Society (IHS)[3] and headache severity on a visual analogue scale (VAS) ranging from 0 to 100 were assessed every 30 minutes. Each provocation was terminated after 5 hours, or earlier, if headache symptoms fulfilled the IHS criteria for migraine, or the experiment was not tolerated by the patient. The presence of headache symptoms was re-assessed 8 hours after the beginning of each provocation, because the time-course of migraine attacks induced by hypoxia might differ from those induced by NTG. After termination of every provocation the patient was asked which provocation they thought they were exposed to.

SaO_2 measurements

SaO_2 was measured using a fingertip pulse oximeter (Datex-Ohmeda, Helsinki, Finland).

Statistical analysis

The primary outcome measure was the migraine response, defined as the proportion of patients developing a migraine attack fulfilling the IHS criteria [3] for migraine within 8 hours after the start of the experiment. Differences in response between groups were tested using Friedman's test. Patients who did not complete all provocations were analyzed on a worst-case scenario basis (meaning an attack after placebo and no attack after provocation). Fourteen patients were required to detect a difference in migraine

response of 40% between hypoxia and placebo (alpha 0.05, beta 90%). The secondary outcome measure was the difference in headache response categorized as (1) absent, (2) mild, (3) moderate or severe headache not fulfilling the criteria for migraine or (4) migraine fulfilling the IHS criteria.

Results

A total of 16 patients (12 females, mean age 29 ± 7 years) were included in the study. The mean baseline attack frequency was 1.2 attacks per month (SD 0.76). Fourteen patients completed all three provocations, and two patients completed only two (Table 1).

Table 1 Patient characteristics (demographic and migraine)

Subject	Sex	Age	Migraine (IHS)	Migraine attacks per month	Attack positive provo-cations	Migraine characterics of provoked attacks								
						HS	UH	AH	PH	N	V	PT	PN	VAS
1	F	25	MO	0.33	Hypoxia	2	-	-	yes	yes	-	yes	-	59
2	M	26	MA	0.33										
3	M	36	MA	0.33	Placebo	2	-	yes	yes	yes	-	yes	yes	43
4	F	23	MO	3	Hypoxia	3	yes	yes	yes	yes	yes	yes	-	60
5	F	25	MO	1	Hypoxia	3	-	yes	yes	yes	-	yes	-	65
6	M	24	MO	2										
7	F	23	MO	1	Hypoxia	2	-	yes	yes	yes	-	-	-	49
					NTG	2	-	yes	yes	yes	-	-	-	31
8	F	28	MO	1	NTG	2	-	yes	yes	yes	-	-	-	61
9*	F	42	MO	1	NTG	2	yes	yes	yes	yes	-	yes	yes	38
10	F	33	MA	1	Hypoxia	2	yes	yes	yes	yes	-	-	-	70
11*	F	44	MA	2										
12	M	36	MA	2	Hypoxia	2	yes	yes	yes	yes	-	yes	yes	28
					NTG	3	yes	-	yes	yes	yes	yes	yes	29
13	M	23	MO	1										
14	F	29	MA	1										
15	F	22	MA	0.5										
16	F	22	MA	2	Hypoxia	2	yes	yes	yes	-	-	yes	yes	51
					Placebo	3	yes	yes	yes	-	-	yes	yes	61

F denotes female, M male, MA migraine with aura, MO migraine without aura, NTG nitroglycerine, HS headache severity (2=moderate, 3 =severe), UH unilateral headache, AH aggravation of headache during physical activity, PH pulsating headache, N nausea, V vomiting, PT photophobia and PN phonophobia

Out of the 14 patients who underwent all three provocations, six patients (43%; 95% confidence interval (CI) 27% to 69%) developed a MO attack during exposure to normobaric hypoxia, three patients (21%; 95%CI 0% to 42%) after the administration of NTG, and two patients (14%; 95%CI –4% to 32%) after the administration of placebo. The frequency of migraine attacks did not differ among groups (p= 0.197). Both patients with incomplete provocations developed a MO attack, one after exposure to normobaric hypoxia and the other after administration of NTG. The inclusion of the two patients who underwent just two provocations did not change the study results (p=0.150). The median time to migraine attacks was five hours (4 hours for placebo, 4.5 hours for hypoxia and 6 hours for NTG). Headache responses (Figure 1) did not differ between groups (p=0.094). Both in the hypoxia and NTG group there were 4 patients who developed moderate to severe headache, but did not fulfull IHS criteria for migraine (no accompanying symptoms such as nausea, phonophobia or photophobia). The subjects' rating of whether they had been exposed to hypoxia, NTG or placebo was no better than by chance. Four patients guessed all three provocations correct, five guessed all three provocations and four were correct in one provocation (2 placebo and 2 hypoxia). Ratings were missing in one patient.

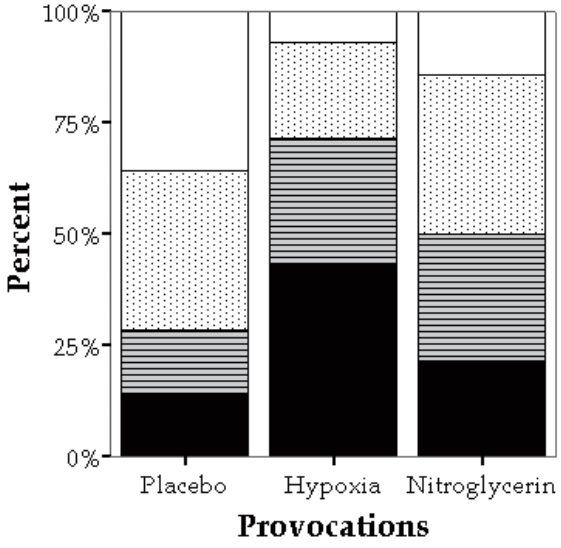

Figure 1 Headache and migraine response to placebo, normobaric hypoxia and nitroglycerin. Black bars represent migraine response, dark gray is moderate or severe headache not fulfilling migraine criteria, light gray is mild headache and white bars is no headache.

Discussion

The first remarkable finding in this study is the low migraine response of 21% after NTG. This is in line with a recent study in English subjects where the migraine response rate after NTG was only 20% [123]. However in most other studies NTG provoked migraine attacks in 60% to 80% of subjects [55,78,123,125]. The low response in our study could have been due to either differences in methodology or in study population. Although we administered the same NTG dose and used the same infusion systems (PVC free) as was done in previous studies [78], the experimental design of our study was entirely different [55,78]. Due to the double dummy design, the patients had to breathe through a facial mask during the whole duration of all experimental conditions, which was considered rather stressful, but tolerable by most participants. The stress could have prevented the occurrence of migraine attack [25,26]. Alternatively, our study population could have been less susceptible to NTG. We had 50% of MA patients in our study and such patients may have a lower migraine response to NTG than MO patients [55,56,162]. Why MA patients would be less susceptible to NTG is not known. A third explanation could be the clinical scoring system. In our study four patients in both the hypoxia and the NTG group had moderate to severe headache but did not fulfill the criteria for migraine.

Normobaric hypoxia provoked a migraine attack in 6 out of 14 patients as compare to only two after placebo and three after NTG. Although this difference between groups was not significant, the relatively high migraine response after hypoxia is remarkably and seems compatible with the results of a large study in mountaineers at high altitude. Of 1213 mountaineers 589 developed headache within 2 to 6 hours after arrival at 4559 m of altitude [99]. In 112 (19%) subjects the symptoms fulfilled the criteria for migraine whereas only 78 (13%) subjects had a history of migraine at sea level. We conclude that the migraine response to NTG was remarkably low in view of previous data , and normobaric hypoxia might be a trigger factor for migraine, but this requires further research.