Triptan-induced disruption of trigemino-cortical connectivity

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ABSTRACT

Objective: The 5-HT1B/D agonists (triptans) are specific headache medications that have no effect on pain as such. Although they are routinely used in the treatment of acute migraine attacks, the underlying mechanisms of action are still a matter of debate.

Methods: Forty-three healthy participants underwent fMRI while receiving trigemino-nociceptive stimulation and control stimuli in a standardized fMRI paradigm. Using a crossover, double-blind, placebo-controlled design, 21 participants (10 women, mean age 26.9, range 20–37 years) received sumatriptan and 22 participants (11 women, mean age 25.5, range 22–32 years) received acetylsalicylic acid (ASA). Administration of medication and saline was randomized between participants of each group resulting in half of the participants receiving saline and the other half receiving the respective medication during the first fMRI data acquisition.

Results: While mean pain intensity ratings did not differ significantly between control and medication nor between medications, we found a significant blood oxygen level-dependent signal increase in the trigeminal nuclei and the thalamus after sumatriptan treatment compared with placebo or ASA. In addition, we specifically looked for the pharmacologic modulation of functional coupling between trigeminal nuclei and higher brain areas, i.e., trigemino-cortical pathways, and found a strong coupling during the saline condition, which was altered by sumatriptan but not after ASA administration.

Conclusion: These data suggest that a specific functional inhibition of trigemino-cortical projections is one of the reasons that triptans, unlike pain killers, act highly specifically on headache and migraine but not pain as such.

GLOSSARY

ASA = acetylsalicylic acid; BOLD = blood oxygen level-dependent; CGRP = calcitonin gene-related peptide; FWE = family-wise error; gPPI = general psychophysiological interaction; SVC = small volume correction; VAS = visual analog scale.

Migraine is effectively treated by the administration of 5-HT1B/D receptor agonists, so-called triptans, and their mechanisms of action have been of major interest in recent years. However, until now, only a few imaging studies indirectly investigated pharmacologic modulations in headache by comparing brain activations of migraineurs experiencing a triggered migraine attack before and after triptan administration. Nevertheless, most of our understanding of mechanisms of action of triptan treatment derives from animal studies. Triptans exert their clinical effect peripherally by blocking 5-HT1B receptors, resulting in slight vasoconstrictive properties as well as blocking calcitonin gene-related peptide (CGRP) release and centrally by blocking trigeminal transmission via binding at 5-HT1D receptors in the trigeminal nuclei of the brainstem. Emphasizing the role of the trigeminal nuclei for migraine pathophysiology, a recent fMRI study revealed that activity in the trigeminal nuclei is not an all-or-nothing reaction to a nociceptive input but shows a cycling behavior throughout the migraine interval. Moreover, an inhibitory effect of triptans on the transmission of painful sensory information within the ventroposteromedial nucleus of the thalamus could be demonstrated using an animal model for trigeminovascular nociception.
We focused on the central mode of actions of triptans comparing the effect of sumatriptan with saline and acetylsalicylic acid (ASA) treatment on stimulus-evoked blood oxygen level–dependent (BOLD) responses to pain vs no pain using fMRI. In addition, we examined the coupling of pain-related brain structures during sumatriptan treatment compared with saline and ASA. Results concerning the general effect of ASA on pain-processing brain structures have been published elsewhere.18

METHODS Standard protocol approvals, registrations, and patient consents. This crossover, randomized, placebo-controlled, and double-blind fMRI study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (PV4084). Volunteers gave written informed consent before study participation.

Participants. We scanned in total 45 healthy volunteers in 2 sessions. One-on-one volunteers were investigated in the sumatriptan group (n = 10 women, mean age 26.9, range 20–37 years) and 22 participants in the ASA group (n = 11 women, mean age 25.5, range 22–32 years). Volunteers had no history of migraine or any neurologic, internal, or psychiatric disease and especially no history of pain syndrome. They were instructed not to take any pain medication while participating in the study. We also controlled for any possible contraindication for the medication investigated. Before fMRI data acquisition, all volunteers were informed in detail about the purpose of the study and that they could withdraw from the experiment at any time. Participants were remunerated for participation.

Substances. Administration of medication and saline was randomized between participants of each group resulting in half of the participants receiving saline during the first fMRI scan and the second half of the volunteers receiving sumatriptan or ASA. The correspondent substance (medication or saline) was administered subcutaneously in the thigh or abdomen. The correspondent substance (medication or saline) was administered subcutaneously in the thigh or abdomen. Participants in the second session. Volunteers in the sumatriptan group received sumatriptan (6 mg) or a corresponding volume of saline (0.9%) administered subcutaneously in the thigh or abdomen. For blinding reasons, all participants were told that each injection of saline could irritate C-fibers and that the injection might therefore hurt, regardless of the substance used. Participants in the ASA group obtained either 500 mg ASA or a corresponding volume of saline (0.9%) administered subcutaneously in the thigh or abdomen.

Study design/stimuli. Pre-experimental phase. Before the fMRI experiment, volunteers underwent one training session outside the scanner to acclimatize to the paradigm.

Experimental phase. The fMRI data acquisition took place on 2 separate days at least 8 to 14 days apart from each other. The design and equipment used in this study are a slightly extended version of a successfully used paradigm described in detail elsewhere.19 Briefly, volunteers perceived 15 standardized trigemino-nociceptive stimuli (gaseous ammonia) while olfactory stimulation in the form of rose odor, an odorless (air puffs) stimulation, and a visual stimulus (flickering checkerboard) served as control conditions. The study design was pseudo-randomized and controlled for nociceptive stimuli being always followed by a control stimulus. Before the stimulation, volunteers underwent a short reaction task (reaction to cross changing color). After stimulation, volunteers were instructed to rate the stimulus intensity (from 0 [no pain/no sensation] to 100 [highest pain imaginable/highest intensity imaginable]) and pleasantness (from −50 [very unpleasant] to 50 [very pleasant]) on a visual analog scale (VAS).

Image acquisition. All scanning procedures were performed on a Siemens Trio 3T scanner (Siemens, Erlangen, Germany) using a 32-channel head coil. We obtained a high-resolution T1-weighted structural image (voxel size 1 × 1 × 1 mm) for every participant using a magnetization-prepared rapid gradient echo sequence. For functional imaging scans of every session, 855 to 1,202 volumes (mean 953 volumes) were acquired using an echo planar imaging sequence (repetition time 2.62 seconds, echo time 30 milliseconds, flip angle 80°, field of view 220 × 220 mm). Each volume consisted of 40 axial slices (slice thickness 2 mm, gap of 1 mm).

Behavioral data analysis. Psychophysiological data analysis was performed using SPSS Statistics version 22.0 (IBM Corp., Armonk, NY). Average pain ratings obtained by the VAS were calculated for every participant in every session. Paired t-tests compared pain intensity ratings of medication vs saline. A t-test for independent samples tested for significant differences in pain intensity ratings between medications (sumatriptan vs ASA). Statistical threshold was set to p < 0.05.

Statistical analysis for imaging data. Data processing and statistical analysis were performed using statistical parametric mapping (SPM8; Wellcome Department for Imaging Neuroscience, London, UK). The first 5 functional scans of each run were discarded. Subsequently, the remaining data preprocessing included slice time correction, data realignment of all volumes to the first volume, as well as spatial normalization into the MNI (Montreal Neurological Institute) stereotaxic space. Finally, the data were smoothed with an 8-mm (full width at half maximum) Gaussian kernel. The first-level model of each participant consisted of the following 5 regressors: “ammonia” (trigemino-nociceptive stimulation), “rose odor,” “air puffs,” “visual stimulation,” and “button presses.” All of these event types were convolved with the SPM8 canonical hemodynamic response function. In addition, 6 motion regressors were included as regressor of no interest for each session. Consequently, the first-level design matrix for every participant included both sessions with 11 regressors each.

Based on an earlier study,22 condition contrast images of the parameter estimates of ammonia > baseline were estimated for every participant comparing medication and saline sessions (medication session [“ammonia > baseline”] > placebo session [“ammonia > baseline”]) and raised to the following second-level random-effect analyses:

1. One-sample t-test for the sumatriptan group to investigate differences in BOLD signal changes in response to painful stimulation compared with saline

2. Two-sample t-test between participants of the 2 different medications to investigate differential group effects regarding painful stimulation (sumatriptan > saline vs ASA > saline)

3. A general psychophysiological interaction (pPPI) analysis

Analyzes 1 and 2. Based on earlier results12,13,17,24 we were specifically interested in the effect of sumatriptan on the trigeminal
nuclei and the thalamus. Therefore, we performed a small volume correction (SVC) using the family-wise error (FWE) correction for multiple comparisons \((p < 0.05)\) for these regions. For the trigeminal nuclei, we used a sphere of 6 mm on the coordinates of an independent previous study (right: \(x = 6, y = -39, z = -45\); left: \(x = -9, y = -39, z = -45\))^16 adjusted to our scanner setting (left: \(x = -10, y = -40, z = -46\); right: \(x = 6, y = -40, z = -46\)). For analyses of the thalamus, we performed SVC \((p < 0.05\) FWE-corrected) using a mask of the right and left thalamus cortex from the Harvard-Oxford cortical/subcortical structural atlas (http://www.cma.mgh.harvard.edu/fs_l_atlas.html). For completeness, whole-brain analysis for the sumatriptan data is also reported using an uncorrected threshold of \(p < 0.001\) and a minimum cluster size of \(>20\) voxels.

**Analysis 3.** A gPPI analysis as described by McLaren et al.\(^{24}\) was performed to assess whether increased activation in the trigeminal nuclei (as region of interest obtained from analyses 1 and 2) within sumatriptan treatment compared with the saline condition interacted with activity patterns in other brain structures related to nociceptive stimulation. The same analysis was performed for the ASA application run compared to its saline condition. For detailed information regarding the gPPI analysis, see appendix e-1 on the Neurology® Web site at Neurology.org. Results are reported with a threshold of \(p < 0.001\) uncorrected, once a cluster threshold of 20 was reached.

**RESULTS** Because the region of the brainstem was of major interest for our data analysis, the dataset of 2 volunteers in the sumatriptan group had to be excluded from the study because imaging slices down to \(z = -50\) (MNI space) were not available. Therefore, our analysis including behavioral and imaging data of the sumatriptan group was restricted to 19 volunteers.

One participant in the ASA group withdrew from the experiment. Two volunteers had to be excluded from further analysis because of too low pain ratings (mean pain rating in both sessions <30).

To compare results of both medications, we performed a 2-sample \(t\) test. Because of the participation of 5 volunteers in both medication groups, we randomly assigned them to either the sumatriptan or the ASA group to allow group comparisons. Hence, our 2-sample \(t\) test was restricted to 17 participants in the ASA group and 16 volunteers in the sumatriptan group. Deleting analyses of all 5 participants before performing the 2-sample \(t\) test did not change the results significantly.

**Psychophysics.** Average pain intensity ratings obtained by the VAS (± SEM) for the sumatriptan group were 66.3 ± 1.9 and 67.0 ± 2.1 for the saline session. Mean pain intensity perception within the ASA session remained at 61.7 ± 2.73, whereas during the saline session, mean pain ratings were 62.1 ± 2.71.\(^{18}\)

No significant difference of the sumatriptan condition compared with the saline session or between ASA and the saline session could be found. No significant difference in mean pain intensity ratings could be obtained between the 2 medications.

**Imaging data. Main effects of trigemino-nociceptive stimulation.** Independent of the fMRI session (medication and saline session pooled together), we found that trigemino-nociceptive stimulation led to statistically significant increases in BOLD signal changes (FWE-corrected) in several cortical and subcortical areas including the insular cortex, putamen, thalamus, amygdala, middle and anterior cingulate cortex, brainstem, the cerebellum, and somatosensory cortices. These brain areas have been reported previously using the same trigemino-nociceptive stimulation method.\(^{16,21,22}\)

**Differences in fMRI signal intensity during trigemino-nociceptive stimulation between sumatriptan and the saline session.** An increase of activation of the trigeminal nuclei (left: \(x = -8, y = -36, z = -50\); \(t_{18} = 3.35, p < 0.05\) SVC; right: \(x = 6, y = -44, z = -50, t_{18} = 3.59, p < 0.05\) SVC) after the administration of sumatriptan compared with saline was found (figure, A). In addition, a trend toward an
increased activation of the left thalamus ($x = -20, y = -26, z = 8, t_{18} = 3.56, p = 0.083$ SVC) in the sumatriptan group compared with saline could be obtained. For a full list of activations obtained from the whole-brain analysis, see table 1. The opposite contrast (saline $>$ sumatriptan) did not reveal significant results.

Differences in fMRI signal intensity during trigemino-nociceptive stimulation between ASA and sumatriptan groups ($2$-sample $t$-test). The SVC for the trigeminal nuclei revealed an increased activation with a peak activity at $x = -8, y = -38, z = -50, t_{51} = 2.8, p < 0.05$ SVC, for the sumatriptan group compared with ASA. Increased BOLD signal intensity could be found in the thalamus ($x = -20, y = -24, z = 6, t_{11} = 3.59, p < 0.05$ SVC) of the sumatriptan group compared with ASA. The opposite contrasts for both analyses (ASA $>$ sumatriptan) showed no significant results in the a priori-defined regions of interest.

Results for gPPI analysis. Increased coupling of the trigeminal nucleus with several cortical and subcortical brain areas including the bilateral putamen, bilateral insular cortex, red nucleus, middle cingulate, and the secondary somatosensory cortex under saline treatment compared with sumatriptan administration could be revealed (figure, B). Leaving out the extended voxel threshold of $20$ contiguous voxels, we also found an increased functional connectivity between trigeminal nuclei and the thalamus (see table 2 for full list of results). For the contrast ASA $>$ saline, no increased functional connectivity could be revealed between the trigeminal nuclei and other brain regions choosing an extended voxel threshold of $20$ voxels. However, lowering this threshold to $10$ voxels, an increased functional connectivity between the trigeminal nuclei and the putamen ($x = -16, y = 12, z = -6, t_{18} = 4.55$) could be revealed. The opposite contrast did also not reveal any significant results.

DISCUSSION The present study shows an increased response to trigemino-nociceptive stimulation in the trigeminal nuclei of the brainstem and the thalamus after sumatriptan administration compared with saline. These BOLD signal changes were highly specific for sumatriptan and were not shown after ASA application. Hence, sumatriptan seems to increase BOLD signal intensity within the trigemino-thalamo-cortical pathway, and specifically in $2$ crucial hubs of this system. This finding is somewhat counterintuitive because several animal studies demonstrated an inhibitory effect of triptans on trigeminovascular neurons. However, an increase in BOLD signal only indicates a change in neuronal activation without making any inference about this change being excitatory or inhibitory. Therefore, the increased BOLD signal intensity observed in the trigeminal nuclei and the thalamus during painful stimulation after sumatriptan injection could very likely be an inhibitory effect of sumatriptan on the trigeminal nuclei and thalamus per se or on inhibitory interneurons within this...
One could argue that the increased BOLD activation represents some state of initiating sensitization that is found in migraineurs during an attack. Of note, the time between administering the drug and scanning was 20 minutes and the scanning, i.e., sampling of data, took another 40 minutes. It is therefore very unlikely that an initial sensitization, which has been discussed with triptans, is the reason for the BOLD activation.

A possible inhibitory effect of triptans on trigeminal nociceptive transmission in the thalamus would also be in line with results of an earlier animal study.17 Moreover, a very recent study showed an inhibitory effect of CGRP on mechanically evoked activity in the spinal trigeminal nuclei after pretreatment with glyceryl trinitrate, while the CGRP antagonist olcegepant led to an increase of activity in the trigeminal nuclei.26 It was proposed that a CGRP-triggered increase in CA2+ could lead to a release of inhibitory peptides such as somatostatin, which is known to attenuate activation of trigeminal afferents and suggested to inhibit CGRP release not only from dorsal root cultures27 but possibly also from the trigeminal ganglion.26 This inhibitory effect is then blocked by the CGRP antagonist olcegepant resulting in an increased activation within the trigeminal nuclei.26 Sumatriptan also inhibits potassium-stimulated CGRP release in the trigeminovascular system11,28 and thereby interrupts the feedback loop in which neurogenic inflammation due to CGRP release leads to additional CGRP transmission.11 Therefore, the increase in BOLD signal changes after sumatriptan administration in the present study could be attributable to an inhibition of the inhibitory action of CGRP on trigeminal neurons in the brainstem. This disinhibition (i.e., increase in "firing" rate of neurons usually

<table>
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Abbreviation: gPPI = general psychophysiologic interaction.

Results of the gPPI analysis for the comparison saline > sumatriptan (MNI [Montreal Neurological Institute] space). All results shown are presented at a threshold of \( p < 0.001 \), uncorrected, and a minimum cluster size of 20 contiguous voxels (except the thalamus + nucleus subthalamicus). Blood oxygen level-dependent activation not reaching a \( t \) value of at least >4 is not presented in the table.

*Voxel threshold <10 voxels.
Comment: How do triptans work in migraine?

Triptans, serotonin 5-HT$_{1D}$/1D receptor agonists, represent a milestone in migraine therapeutics; they are effective acute attack therapies with a clear pharmacology and no substantial nonheadache indications. Their mechanism of action has never been entirely defined despite widespread use and the potential utility for medicine development in understanding the effect.

Kroger and May used blood oxygenation level–dependent (BOLD) functional MRI and an olfactory stimulation paradigm to examine the effects of sumatriptan, aspirin, and saline on brain processing of trigeminal nociceptive inputs. They found no difference in pain ratings between aspirin and sumatriptan, and no antinociceptive effect of either treatment. They identified an increased BOLD signal in the trigeminal nuclei tracking the pain stimulus when comparing the sumatriptan and saline sessions. When comparing the sumatriptan and aspirin sessions, there was an increase in trigeminal nucleus activity and thalamic activity in the sumatriptan session. These data demonstrate a unique effect of sumatriptan on head pain pathways not seen with aspirin.

The study provides as many questions as answers since the authors tackle a hitherto underaddressed issue. The nature of the change in the BOLD signal—an increase in metabolic activity—does not allow the inference that activations represent sumatriptan’s direct effect. The lack of an effect of aspirin is interesting and needs further exploration. The data overall point to a network, or systems effect, of triptans on migraine, which would be consistent with their ability to terminate the sumatriptan session. These data demonstrate a unique effect of sumatriptan on pain intensity perception.

Contrary to the main analysis, the PPI analysis focuses on the functional connectivity between the seed region (trigeminal nuclei) and other pain-related brain areas during pain. In the present study, we show a downregulatory mechanism of sumatriptan on functional connectivity between the nociceptive trigeminal nuclei and pain-related brain structures, such as the red nucleus, the putamen, the insula cortex, the thalamus, and the secondary somatosensory cortex. It seems that sumatriptan initiates a central regulatory mechanism resulting in an attenuated coupling, i.e., functional connectivity between brain regions known to be altered in migraineurs. Of note, we could not reveal such an inhibitory mechanism on functional connectivity for ASA based on the trigeminal nuclei as a seed region.

Several recent imaging studies (but not investigating medication) suggested an altered coupling between brain areas in migraineurs. However, these studies used several different methods (e.g., resting state) to investigate functional connectivity between cortical regions and are therefore not directly comparable to each other and our own results. We specifically looked for the pharmacologic modulation of functional coupling between trigeminal nuclei and higher brain areas, i.e., trigemino-cortical pathways rather than pain-transmitting systems per se and found a strong coupling during the saline condition, which was exclusively altered by sumatriptan but not by nonsteroidal anti-inflammatory drug administration. One could speculate that this specific inhibition of trigemino-cortical functional coupling is one of the reasons that sumatriptan, unlike pain killers, acts more specifically on headache and migraine than pain...
as such. Of interest, brain areas such as the putamen or the red nucleus, which we found to be less coupled with the trigeminal nuclei during painful stimulation after sumatriptan treatment, are known to be relevant for migraine pathophysiology.99 Thus, the present study revealed an increase in BOLD signal intensity in the trigeminal nuclei and the thalamus during painful stimulation that is specific for sumatriptan but not ASA. Furthermore, we identified an attenuated coupling between the trigeminal nuclei and higher pain-processing brain structures under sumatriptan treatment, which may be the reason why triptans are headache-specific medications.

AUTHOR CONTRIBUTIONS
Inga L. Kröger: acquisition of data, analysis and interpretation of data, drafting of the manuscript. Arne May: conception and design of the study, analysis of data, interpretation of data, revising the manuscript critically for important intellectual content. Both authors discussed the results and commented on the manuscript.

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