Abnormal central serotonin turnover and an associated increase in serotonin receptor sensitivity may compromise pain modulation and increase susceptibility to migraine.\(^1,2\) Conversely, serotonergic drugs have therapeutic and prophylactic effects,\(^2\) possibly by inhibiting neurotransmitter release from the peripheral or central projections of trigeminal afferent neurons or by activating pain-modulation pathways that inhibit trigeminal nociceptive input from cranial blood vessels.

In this study, a tryptophan-free amino acid drink was used to restrict the entry of tryptophan into the brain, thereby reducing the synthesis of serotonin.\(^3,4\) We sought to determine whether tryptophan depletion would aggravate symptoms of motion sickness provoked by optokinetic stimulation (the visual illusion of movement). Migraineurs are unusually susceptible to symptoms induced by optokinetic stimulation,\(^5\) but the basis of this susceptibility is unknown. Because serotonergic drugs block emesis during motion sickness,\(^6\) low levels of serotonin in the vestibular or emetic pathways of migraineurs might increase susceptibility to nausea. If so, tryptophan depletion should reproduce this susceptibility in controls.

**Method.** Subjects. Thirty-three women and six men aged 18 to 57 years (mean ± SD, 34.7 ± 13.8 years), who experienced migraine with aura (eight patients) or without aura (31 patients) at least monthly, were compared with 28 healthy women and nine men aged between 19 and 59 years (mean age 36.8 ± 14.3 years) without a history of migraine and who experienced six or fewer headaches per year. Women were tested between menstrual periods, and migraineurs were tested 9.2 ± 7.4 days after their most recent headache. Apart from the oral contraceptive, none of the participants took preventative medicine for migraine or for any other condition, and no subject had taken medication on the day of the experiment. Each subject provided informed consent for the procedures, which were approved by the University Ethics Committee.

**Procedures.** This was a randomized, placebo-controlled, double-blind trial of tryptophan depletion. Subjects had a light protein-free breakfast without caffeine and reported to the laboratory (maintained at 22.8 ± 1.1°C) at approximately 8 AM. Tryptophan depletion was accomplished by consuming capsules and a drink containing 100 g amino acids without tryptophan.\(^1\) In the balanced amino acid condition, 2.3 g \(\ell\)-tryptophan was added to the drink. Blood samples were taken before the subject ingested the amino acids, 276 ± 27 minutes later, and straight after optokinetic stimulation (461 ± 27 minutes after ingesting the amino acids). The platelet serotonin concentration and levels of unbound tryptophan in blood plasma were later measured using high-pressure liquid chromatography.

During optokinetic stimulation, subjects sat on a stationary chair with their head and shoulders inside a drum (50 cm wide and 70 cm high), painted internally with 24 pairs of vertical black and white stripes.\(^2\) The drum revolved 10 times per minute for 15 minutes or until vomiting was imminent. To enhance the illusion of movement created by the moving stripes, subjects focused on a point. They rated nausea, dizziness, and headache on a 0 to 10 scale of intensity before and every 3 minutes during optokinetic stimulation, starting 1 minute after the drum began to rotate. Subjects also rated the extent to which they felt that they were spinning and the drum was still as “no movement” (0), “some” (1), or “a lot” (2).

**Statistical approach.** The effect of the drink content on the platelet serotonin concentration and the free (unbound) plasma tryptophan level was investigated in group (migraine, control) × drink content (with or without tryptophan) × time (baseline, 4.5 hours after ingesting the drink, and after optokinetic stimulation) analyses of variance. The multivariate solution was used for effects that involved factors with more than two levels. Mean ratings of the illusion of spinning were investigated in a group × drink content analysis. Analyses for mean ratings of nausea, dizziness, and headache had an additional factor of block (before vs during optokinetic stimulation).

**Results.** Tryptophan depletion. Free plasma tryptophan levels decreased substantially in the tryptophan depletion condition but increased transiently in the balanced amino acid condition [drink content × time interaction, \(F(2,56) = 55.1, p < 0.001\)] (table). Levels remained low in the tryptophan depletion condition throughout the experiment, and did not differ between migraineurs and controls. Platelet serotonin levels fell slightly over the course of the experiment \([F(2,57) = 7.61, p < 0.001]\), but did not differ between the tryptophan depletion and balanced amino acid conditions or between migraineurs and controls (see table). Symptoms induced by optokinetic stimulation. Controls in the balanced amino acid condition were less susceptible than other groups to motion sickness during optokinetic stimulation (see table and figure). The group × drink content interaction for time spent in the drum \([F(1,72) = 3.16, p < 0.08]\) was investigated with planned
Serotonin, nmol/10^9 platelets

Headache over the next 24 h

Optokinetic stimulation

Plasma tryptophan, μg/mL ± SD

Serotonin, nmol/10^9 platelets ± SD

Optokinetic stimulation

Duration, min ± SD

No. who withdrew (%)

Headache over the next 24 h

Discussion. During optokinetic stimulation, tryptophan depletion boosted nausea and dizziness in controls to levels that approached those reported by migraineurs. In animals, 5-HT_{1A} agonists prevent motion sickness and also inhibit emesis provoked by toxins by inhibiting activity in the vestibular nuclei and in the emetic motor pathway; in humans, selective serotonin reuptake inhibitors suppress vertigo and dizziness. Thus, serotonin may inhibit central vestibular disturbances. Serotonin may also suppress conflict between visual cues of movement and vestibular cues of stability because tryptophan depletion enhanced the illusion of movement during optokinetic stimulation in controls. In contrast, neither tryptophan supplementation nor depletion had any effect on the heightened illusion of movement or搖

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**Table Effects of tryptophan depletion in migraineurs and controls**

<table>
<thead>
<tr>
<th></th>
<th>Controls Without tryptophan, n = 18</th>
<th>Controls With tryptophan, n = 19</th>
<th>Migraineurs Without tryptophan, n = 17</th>
<th>Migraineurs With tryptophan, n = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma tryptophan, μg/mL ± SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.9 ± 0.5</td>
<td>0.8 ± 0.6</td>
<td>0.8 ± 0.4</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>After 4.5 h</td>
<td>0.1 ± 0.1</td>
<td>2.6 ± 1.6</td>
<td>0.1 ± 0.1</td>
<td>2.4 ± 1.1</td>
</tr>
<tr>
<td>After optokinetic stimulation</td>
<td>0.1 ± 0.1</td>
<td>1.1 ± 0.7</td>
<td>0.2 ± 0.1</td>
<td>1.1 ± 0.4</td>
</tr>
<tr>
<td><strong>Serotonin, nmol/10^9 platelets ± SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.4 ± 1.0</td>
<td>3.7 ± 0.8</td>
<td>3.2 ± 1.1</td>
<td>3.9 ± 1.5</td>
</tr>
<tr>
<td>After 4.5 h</td>
<td>3.4 ± 0.8</td>
<td>3.6 ± 0.8</td>
<td>3.2 ± 1.0</td>
<td>3.8 ± 1.5</td>
</tr>
<tr>
<td>After optokinetic stimulation</td>
<td>3.4 ± 0.9</td>
<td>3.5 ± 0.7</td>
<td>3.1 ± 1.1</td>
<td>3.7 ± 1.5</td>
</tr>
<tr>
<td><strong>Optokinetic stimulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, min ± SD</td>
<td>11.5 ± 4.8</td>
<td>14.1 ± 2.0</td>
<td>11.9 ± 4.2</td>
<td>11.0 ± 5.3</td>
</tr>
<tr>
<td>No. who withdrew (%)</td>
<td>8 (44)</td>
<td>4 (21)</td>
<td>7 (41)</td>
<td>10 (45)</td>
</tr>
<tr>
<td>Headache with nausea, n (%)</td>
<td>1 (6)</td>
<td>0</td>
<td>7 (41)</td>
<td>8 (36)</td>
</tr>
<tr>
<td>Headache without nausea, n (%)</td>
<td>2 (11)</td>
<td>1 (5)</td>
<td>4 (24)</td>
<td>3 (14)</td>
</tr>
</tbody>
</table>

Contrasts. As expected, migraineurs in the balanced amino acid condition withdrew from the drum earlier than controls in the balanced amino acid condition (p < 0.05). In addition, controls in the tryptophan depletion condition withdrew from the drum earlier than controls in the balanced amino acid condition (p < 0.05). However, withdrawal times were similar in migraineurs and controls in the tryptophan depletion condition.

Tryptophan depletion boosted ratings of the illusion of spinning in controls (p < 0.01) but not migraineurs [group × drink content interaction, F(1,72) = 11.4, p < 0.001] (see figure, A). Ratings of nausea, dizziness, and headache were greater in migraineurs than controls both before and during optokinetic stimulation [F(1,71) = 20.0 to 25.0, p < 0.001] and increased in both groups during optokinetic stimulation [F(1,71) = 6.18 to 124.6, p < 0.05] (figure, B through D). Increases in dizziness were greater in migraineurs than controls [group × block interaction, F(1,71) = 13.2, p < 0.001], and there were similar trends for nausea [F(1,71) = 3.06, p = 0.085] and headache [F(1,71) = 3.58, p = 0.062]. Tryptophan depletion heightened dizziness in controls (p < 0.01) but not migraineurs during optokinetic stimulation [group × drink content × block interaction, F(1,71) = 4.12, p < 0.05] (see figure, B). Although the three-way interaction was not significant for nausea, nevertheless tryptophan depletion boosted nausea in controls (p < 0.05) but not migraineurs during optokinetic stimulation (see figure, C). Tryptophan depletion did not affect headache during optokinetic stimulation (see figure, D) or over the next 24 hours (see table).

![Figure. Mean ratings (± SE) of the illusion of spinning (A) and symptoms (B through D) induced by optokinetic stimulation in controls with (stippled columns) and without (hatched columns) tryptophan, and in migraineurs with (open columns) and without (filled columns) tryptophan. Tryptophan depletion enhanced the illusion of spinning and ratings of dizziness and nausea in controls. *p < 0.05, but not in migraineurs.](image-url)
vestibular symptoms in migraineurs. Because tryptophan depletion had no effect on platelet serotonin concentrations, central serotonin levels (e.g., in vestibular or emetic pathways) may be chronically low in migraineurs. Alternatively, serotonergic receptors might be less sensitive to serotonin in migraineurs than controls.

Serotonin elicits a range of pro- and antinociceptive effects due to contrasting actions at different receptor subtypes on multiple targets within the CNS (e.g., the central terminals of primary nociceptive afferents, projection neurons, excitatory and inhibitory pain modulation interneurons). This might explain why tryptophan depletion had no effect on headache, either during or after the experiment in migraineurs or controls. Although reduced production of serotonin is unlikely to be the primary stimulus for migraine, the present findings suggest that low levels of brain serotonin promote dizziness and nausea during optokinetic stimulation. Because head pain also triggers nausea in migraineurs, trigeminal nociceptive discharge during attacks of migraine could induce nausea by stimulating vestibular or emetic pathways rendered sensitive by low levels of serotonin.

**Acknowledgment**

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**References**


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This issue of *Neurology* has an online-only NeuroImage that has a video:

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* T. Hölischer, S.-E. Olson, P.-D. Lyden, R.-F. Mattrey, W.-G. Wilkening, and C.-W. Kerber

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Effect of tryptophan depletion on symptoms of motion sickness in migraineurs
Peter D. Drummond
Neurology 2005;65:620-622
DOI 10.1212/01.wnl.0000172339.15577.a6

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