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μ-Opiate receptor agonists – a new pharmacological approach to prevent motion sickness?

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Aims
Stress hormones might be involved in motion sickness. The influence of loperamide on kinetosis-induced nausea and stress hormone release was investigated in a placebo-controlled, cross-over study.

Methods
Standardized rotation around the vertical axis combined with head movements was used to induce nausea 3 h after 16 mg loperamide or placebo ($n = 8$). Plasma antidiuretic hormone (ADH), adrenocorticotropic hormone (ACTH) and nausea ratings were investigated.

Results
After loperamide nausea was significantly lower ($P < 0.02$). ACTH ($P < 0.05$) and ADH levels ($P < 0.02$) increased significantly in both settings, but were lower after loperamide.

Conclusions
The susceptibility to develop kinetosis-induced nausea and stress hormone release is decreased by loperamide, although the site of action remains speculative.

Introduction

Motion sickness remains a persistent problem, while drugs show variability and are limited by side-effects [1]. The aetiology of motion sickness is not fully understood, but stress hormones might be involved [2].

Loperamide, a mainly peripheral acting μ-opiate receptor agonist [3] used for symptomatic treatment of diarrhoea [4], was reported to suppress adrenocorticotropic hormone (ACTH) release in human [5] and vagal-cholinergic mechanisms, including those activated by afferent vagal pathways [6]. As afferent gastrointestinal signals reach the 'vomiting centre', loperamide might also influence kinetosis-induced nausea and stress hormone release.

Methods

Subjects and test procedure

After giving written informed consent, eight healthy subjects [four female, four male, age 27 years (range 25–29)] were single-blinded in a cross-over design and instructed that they receive either drug (16 mg Imodium® lingual; Janssen-Cilag, Neuss, Germany) or pla-

cebo on one of the two occasions (at least 2 days apart) after an overnight fast in a randomized sequence. Placebo/loperamide was applied orally 3 h before the test, to reach sufficient concentrations [7]. Using a rotating chair, subjects were rotated for 2 min around the vertical axis (120° s^{1}) and asked to move their heads forwards and backwards (angle 90°) every 6 s with closed eyes (coriolis stimulus). After a break (4 min) the procedure was repeated (maximum 6 rotation units). Subjects without nausea symptoms under both conditions were excluded. The study protocol was approved by the local ethics committee.

Nausea ratings

Nausea was scored before rotation, during each break, and immediately as well as 30 min after rotation according to a system to rate the severity of nausea as previously described [8]. The rating scale contains seven symptoms, related to the development of nausea: dizziness, headache, nausea, urge to vomit, tiredness, sweating and stomach awareness. Each symptom was rated on a scale between 0 and 10, and the sum score ('cumulative nausea') was used for analysis. Nausea per rotation unit was calculated from 'cumulative nausea' adjusted to rotation tolerance by dividing through the number of rotation units.

Plasma samples and assay procedures

Blood samples were drawn before, immediately and 30 min after rotation. Samples were immediately centrifuged (4 °C), and aliquots were frozen until assayed. Antidiuretic hormone (ADH) and ACTH plasma levels were measured in duplicate (IBL, Hamburg, Germany; Nicols, Bad Nouheim, Germany).

Statistics

Increases of hormone levels were obtained by subtraction of baseline values from post-rotation levels. The relative increase was calculated by the quotient of increase and baseline levels. For statistical evaluation Wilcoxon tests for paired data were performed to compare hormonal levels before and after rotation as well as nausea ratings for both conditions (loperamide and placebo). Correlation coefficients were calculated by the linear regression method. All values are given as median and range. Changes were considered significant at a level of $P < 0.05$.

Results

Nausea

One subject was symptom free under both conditions and was excluded. Rotation procedure after placebo forced three subjects to stop earlier – after loperamide each of them tolerated one further rotation period. Median rotation units under loperamide did not reach significance ($P = 0.083$) compared with placebo, as more than half of the subjects were able to finish 6 rotation units. After loperamide nausea per rotation unit was found to be lower compared with placebo (see Table 1), showing a significant reduction of kinetosis-induced nausea ($P = 0.018$). Nausea per rotation unit was not different between day 1 and day 2 ($P = 0.085$).

ACTH plasma levels

After placebo ACTH levels increased with rotation compared with baseline ($P = 0.018$) and remained elevated 30 min thereafter ($P = 0.043$). Upon loperamide basal ACTH levels before rotation were lower compared with placebo ($P = 0.018$). ACTH levels increased immediately ($P = 0.018$), and 30 min after rotation ($P = 0.028$), but each elevation remained lower compared with placebo ($P = 0.018$) (see Table 2).

ACTH increase was lower after loperamide compared with placebo ($P = 0.043$). No significant correlation between relative ACTH increase after rotation and nausea was found.

ADH plasma levels

After placebo ADH levels increased immediately ($P = 0.043$). After loperamide, basal ADH levels were not significantly different from placebo, increased after

Table 1
Nausea per rotation unit showed a significant reduction of kinetosis-induced nausea after loperamide to placebo (unaffected subject no. 7 was excluded; $n = 7$)

Affected subjects (no.)	Placebo rotation units	Placebo nausea/ rotation units	Loperamide rotation units	Loperamide nausea/ rotation units
1	2	7.0	3	5.0
2	1	10.0	2	4.0
3	3	9.3	4	8.3
4	6	2.7	6	2.3
5	6	3.5	6	3.2
6	6	5.3	6	4.5
8	6	1.2	6	0.5
Median	6.0	5.3*	6	4.0*
Range	2–6	1.2–10.0	1–6	0.5–8.3

**P = 0.02 (placebo compared with loperamide).*

Table 2
Adrenocorticotropic hormone (ACTH) and antidiuretic hormone (ADH) plasma levels in affected subjects after placebo and loperamide ($n = 7$, median and range)

	Placebo ACTH (pmol l^{-1})	Loperamide ACTH (pmol l^{-1})	Placebo ADH (pmol $^{-1}$l)	Loperamide ADH (pmol l^{-1})
Before rotation	10.8 (7.9–24.9)	3.9 (0.5–16.6)	35.9 (26.5–82.7)	31.4 (22.5–64.7)
After rotation	129.8** (8.2–766-3)	15.5** (2.9–596.6)	123.8* (34.2–195.6)	34.2* (28.5–176.8)
30 min after rotation	50.1* (5.2–458)	8.1* (2.6–287.0)	60.5 (30.8–93.2)	46.1 (28.6–83.5)
Increase after rotation	120.9* (0.3–741.4)	13.1* (0.2–580.0)	81.8 (–2.6–169.1)	4.1 (–2.9–154.3)

*$P < 0.05$ and **$P < 0.02$ (compared with baseline in each setting).*

rotation ($P = 0.043$), but remained lower compared with placebo (Table 2).

ADH increase after rotation was lower upon loperamide; however, the difference did not reach significance. After placebo relative ADH increase after rotation was significantly positively correlated to nausea per rotation unit ($n = 7$; $r = 0.81$; $P = 0.027$). This effect was abolished after loperamide.

Side-effects

Two subjects had slight constipation for 2 days after loperamide.

Discussion

The present study shows that nausea per rotation unit was significantly lower after loperamide, indicating an inhibiting effect on kinetosis-induced nausea (Table 1). An effect of habituation to rotating cannot be fully excluded ($P = 0.085$) but appears unlikely: it was found to occur with daily repetitions of rotation but differentially in men and women [9]. In our study design only two rotation procedures were performed at least 48 h apart and in an equal number of male and female subjects, thus making habituation an unlikely explanation for the current results.

Opiate receptors in the chemoreceptor trigger zone [10] and in the dorsolateral medullary reticular formation (so called 'vomiting centre') are able to stimulate (δ-opiate-receptors) and inhibit the emetic response (κ-, μ-opiate-receptors), respectively [11]. Loperamide, an opiate agonist of high affinity for μ-receptors [3], crosses the blood–brain barrier in minimal amounts [7], which might be sufficient to act at the 'vomiting centre'. Loperamide inhibits efferent vagal-cholinergic pathways including those activated by afferent vagal fibres [6]. As afferent gastrointestinal signals influence the 'vomiting centre' and μ-opiate receptors are present on afferent vagal fibres [12], loperamide might reduce motion sickness by this site.

We found that ADH release is correlated with nausea. But ADH and ACTH were also released in the unaffected subject, thus indicating that ADH is not a causal factor. Stress hormones during motion sickness were released due to the general stress reaction [13], but whether the known ACTH-reducing effect of loperamide [5] modulates nausea ratings is unclear. While μ-opiate agonists generally induce nausea accompanied with an increase of ADH [14], loperamide shows a suppressing effects on ADH release and nausea symptoms.

Despite the sites of action being speculative, our results show that the μ-opiate receptor agonist loperamide exerts a beneficial effect on nausea.

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