ELSEVIER

European Journal of Pharmacology 309 (1996) 33–35

ejp

Short communication

Prophylactic effect of serotonin uptake inhibitors against motion sickness in *Suncus murinus*

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Received 24 April 1996; revised 20 May 1996; accepted 24 May 1996

Abstract

The prophylactic effect of serotonin uptake inhibitors, imipramine and fluoxetine, against motion sickness was investigated in *Suncus murinus*. Imipramine (s.c.) and fluoxetine (i.p.) inhibited motion-induced emesis dose dependently with ID_{50} values of 1.7 and 26 mg/kg, respectively. The results suggest that increasing the concentration of serotonin in the synaptic cleft can prevent motion-induced emesis and that serotonin uptake inhibitors are effective as anti-motion sickness drugs.

Keywords: 5-HT (5-hydroxytryptamine, serotonin) uptake inhibitor; Imipramine; Fluoxetine; Motion sickness

1. Introduction

The involvement of the serotonergic system in at least some types of emetic response has been shown. Perhaps, the most important clinical finding is the prevention of cancer chemotherapeutic drug-induced emesis by 5-HT_3 receptor antagonists (Sanger, 1990). The drugs probably act peripherally to prevent the activation of 5-HT_3 receptors on vagus afferents. However, recent studies have suggested that serotonergic nervous systems in the brain may be involved in the emetic pathway. Several 5-HT_{1A} receptor agonists (e.g. 8-hydroxy-2-(di-*n*-propylamino)tetralin: 8-OH-DPAT, buspirone) can inhibit the emesis elicited by motion stimulus or by emetic drugs in cats (Lucot and Crampton, 1987, 1989) and in *Suncus murinus* (Okada et al., 1994). Furthermore, a 5-HT_2 receptor agonist, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), also blocks the emesis induced by motion or by cisplatin (Okada et al., 1995). These agonists probably act in the central nervous system and cause an anti-emetic effect. Therefore, it is possible that an increase in the serotonin level in the brain could attenuate the emetic reflex.

The present study was designed to examine the role of central serotonergic neurons in the emetic response. We investigated the effects of fluoxetine and imipramine on motion sickness in *S. murinus*. Fluoxetine and imipramine are serotonin uptake inhibitors and widely used in the treatment of mental depression (Hollister and Claghorn, 1993). The inhibition of the uptake carrier on serotonin nerve terminals is expected to amplify serotonergic function by increasing the concentration of serotonin in the synaptic cleft.

2. Materials and methods

Experiments were performed on 3–6-month-old male *S. murinus* weighing 50–90 g. The animals were purchased from the Central Institute for Experimental Animals (Kanagawa, Japan) and housed in a temperature-controlled room at 24 ± 1°C under a 12-h light/dark cycle at the Animal Care Institute (University of Tokyo). They were allowed free access to pellet chow, supplied by the Central Institute for Experimental Animals, and tap water.

Experimental conditions were similar to those reported previously by our laboratory (Okada et al., 1994). Motion sickness was elicited by reciprocal shaking (amplitude of 40 mm, frequency of 1.0 Hz, duration of 5 min). Each animal was placed in a transparent cage ($10^W \times 15^L \times 12^H$ cm) fixed on a reciprocal shaker (TAITEC R-30mini, Taiyo Scientific Industrial Co., Japan). After a 5-min acclimation, the motion was started. The number of vomiting episodes and the latency to the first vomiting were recorded for 5 min. Animals were beforehand selected for

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PII S0014-2999(96)00407-4

susceptibility to motion sickness. Generally, more than 90% of naive animals vomited during the motion. An interval longer than 1 week was kept between the motion tests to avoid the possible involvement of habituation to the motion.

Fluoxetine hydrochloride (Eli Lilly Co., Indianapolis, USA) and imipramine hydrochloride (Wako Pure Chemical Industries, Osaka, Japan) were used in the experiments. Doses refer to the base form of drugs. Imipramine was dissolved in saline. Fluoxetine was suspended in saline. Motion was started 30 min after subcutaneous (s.c.) injection of imipramine and 30 or 60 min after intraperitoneal (i.p.) injection of fluoxetine. The injection volumes of imipramine and fluoxetine were adjusted to 0.1 and 0.5 ml/50 g body weight, respectively. ID_{50} values were calculated using Brownlee's up-and-down method (Brownlee et al., 1953).

3. Results

S.c. injection of imipramine 30 min prior to the motion prevented emesis dose dependently in *S. murinus* (Table 1). The ID_{50} value of imipramine was 1.7 mg/kg s.c. However, i.p. injection of fluoxetine 30 min prior to the motion did not show an anti-emetic effect against motion-induced emesis. At the dose of 32 mg/kg, two out of four animals vomited in response to the motion. We examined the effect of the time interval between administration of fluoxetine and motion. One out of five animals vomited with a 60-min interval and one out of four animals vomited with a 90-min interval between administration of 32 mg/kg fluoxetine and motion. Therefore, we concluded that a 60-min interval was sufficient to detect anti-emetic effect of fluoxetine against motion-induced emesis. When the interval was fixed at 60 min, fluoxetine inhibited the emesis elicited by the motion in a dose-dependent manner with an ID_{50} value of 26.0 mg/kg i.p. (Table 1). At doses above 16 mg/kg, fluoxetine apparently decreased spontaneous motor activity, an effect which lasted for 15–30 min. However, all animals recovered completely when motion was applied, eliminating the possibility that the anti-emetic effect of the drug is due to its apparent sedative effect. Imipramine within the dose range used in the experiment did not cause significant behavioral change.

4. Discussion

We have already reported that 5-HT_{1A} receptor agonists, e.g. 8-OH-DPAT, buspirone and ipsapirone, and a 5-HT_2 receptor agonist, DOI, can block emesis induced by motion or by several emetic drugs in *S. murinus* (Okada et al., 1994, 1995). These agonists exert anti-emetic effects probably through an action in the central nervous system because they are effective against various types of emetic stimuli. Therefore, endogenous serotonin in the central nervous system may play an inhibitory role against at least some types of emetic response. In the present study, pretreatment with imipramine and fluoxetine dose dependently prevented motion-induced emesis in *S. murinus*. These results suggest that an increase of the serotonin concentration in the synaptic cleft in the central nervous system causes the suppression of the motion-induced emesis, confirming our hypothesis.

When ID_{50} values were compared, s.c. injection of imipramine was more potent against motion-induced emesis than i.p. injection of fluoxetine. One possibility is that imipramine has wide pharmacological actions. Tricyclic antidepressants including imipramine inhibit not only serotonin uptake but also neural uptake of noradrenaline, and antimuscarinic and antihistaminergic effects are also known (Hall and Ögren, 1981). We have already reported that methamphetamine, which has the ability to release catecholamines, and antihistaminergics, e.g., diphenhydramine, chlorpheniramine and dimenhydrinate, have a prophylactic effect against motion-induced emesis in *S. murinus* (Ueno et al., 1988, Kaji et al., unpublished data). However, scopolamine, which is a classic antimuscarinic agent, showed less prophylactic effect against motion-induced emesis in *S. murinus* (Ueno et al., 1988). Therefore, the prophylactic effect of imipramine in the present study may

Table 1
Anti-emetic effects of imipramine and fluoxetine on motion-induced emesis in *Suncus murinus*

Drug	Dose (mg/kg)	No. of *S. murinus* vomiting/tested	No. of vomiting episodes	Latency (s)	ID_{50} value (mg/kg)
Imipramine (s.c.)	0.5	3/3	8.3 ± 2.0	89.3 ± 15.9	1.7
	1.0	5/5	5.4 ± 2.0	106.6 ± 33.2	
	2.0	1/5	2	221	
	4.0	0/3	–	–	
Fluoxetine (i.p.)	16.0	4/4	5.8 ± 2.3	79.3 ± 12.4	26.0
	32.0	1/5	2	31	
	64.0	0/1	–	–	

Values for the number of vomiting episodes and the latency to vomit per vomiting animal are means ± S.E.M., but actual values are indicated when the number of vomiting animals was less than three. ID_{50} values were calculated using the Brownlee's up-and-down method.

result from a combination of an antihistaminergic action and inhibition of uptake of both serotonin and noradrenaline but not from an antimuscarinic action.

Fluoxetine is a selective serotonin uptake inhibitor and has no effect on the uptake of catecholamine and has low affinity for adrenaline, histamine, muscarine, $GABA_B$ or 5-HT receptors (Hollister and Claghorn, 1993). The inhibition of the uptake of serotonin is expected to amplify serotonergic function by increasing the concentration of serotonin in the synaptic cleft. Recently, direct evidence for an increased serotonin concentration in the synaptic cleft after administration of fluoxetine has been obtained (Fuller and Wong, 1990). Furthermore, Perry and Fuller (1992) have demonstrated an increased serotonin concentration in rat striatum after systemic administration of fluoxetine to rats by using a microdialysis method. After the injection of fluoxetine, the serotonin concentration increased quickly and reached a new plateau level, more than 4 times the mean basal level, within 90 min and maintained this level for longer than 3 h. These findings accord with the present results that more than a 60-min interval between the administration of fluoxetine and the motion was necessary to suppress the motion-induced emesis by fluoxetine.

Recently, Angel et al. (1993) reported that fluoxetine did not show an anti-emetic effect against the cisplatin-induced emesis in ferrets. The reason for the inconsistency with our results may be that the doses used in their study were lower than those of our experiments. The other possibility is that the emetic stimulus caused by cisplatin is too strong to be modified by the serotonergic system. When ID_{50} values are compared, $5\text{-}HT_{1A}$ and $5\text{-}HT_2$ receptor agonists are less effective against cisplatin than against the motion (Okada et al., 1994, 1995).

Antihistamines and anticholinergics are clinically used as the main medication for motion sickness. However, the prophylactic effects of these drugs are still not satisfactory, and their unwanted side effects, such as the drowsiness of antihistamines, restrict application of these drugs. The present findings that fluoxetine and imipramine were effective against motion-induced emesis suggest that serotonin uptake inhibitors have the potential to be a new type of anti-motion sickness drug.

In conclusion, the results in the present study suggest that an increase of serotonin concentration in the synaptic cleft in the central nervous system attenuates the emetic response and that serotonin uptake inhibitors can be new prophylactic drugs against motion sickness.

Acknowledgements

The authors are grateful to Eli Lilly Co. for the gift of fluoxetine.

References

Angel, I., H. Schoemarker, M. Prouteau, M. Garreau and S.Z. Langer, 1993, Litoxetine: a selective 5-HT uptake inhibitor with concomitant $5\text{-}HT_3$ receptor antagonist and antiemetic properties, Eur. J. Pharmacol. 232, 139.

Brownlee, K.A., J.R. Hodges, Jr. and M. Rosenblatt, 1953, The up-and-down method with small samples, J. Am. Stat. Assoc. 48, 262.

Fuller, R.W. and D.T. Wong, 1990, Serotonin uptake and serotonin uptake inhibition, Ann. N.Y. Acad. Sci. 600, 68.

Hall, H. and S.O. Ögren, 1981, Effects of antidepressant drugs on different receptors in the brain, Eur. J. Pharmacol. 70, 393.

Hollister, L.E. and J.L. Claghorn, 1993, New antidepressants, Annu. Rev. Pharmacol. Toxicol. 32, 165.

Lucot, J.B. and G.H. Crampton, 1987, Buspirone blocks motion sickness and xylazine-induced emesis in the cat, Aviat. Space Environ. Med. 58, 989.

Lucot, J.B. and G.H. Crampton, 1989, 8-OH-DPAT suppresses vomiting in the cat elicited by motion, cisplatin or xylazine, Pharmacol. Biochem. Behav. 33, 627.

Okada, F., Y. Torii, H. Saito and N. Matsuki, 1994, Antiemetic effects of serotonergic $5\text{-}HT_{1A}$-receptor agonists in *Suncus murinus*, Jpn. J. Pharmacol. 64, 109.

Okada, F., H. Saito and N. Matsuki, 1995, Blockade of motion- and cisplatin-induced emesis by serotonergic $5\text{-}HT_2$ receptor agonist in *Suncus murinus*, Br. J. Pharmacol. 114, 931.

Perry, K.W. and R.W. Fuller, 1992, Effect of fluoxetine on serotonin and dopamine concentration in microdialysis fluid from rat striatum, Life Sci. 50, 1683.

Sanger, G.J., 1990, New antiemetic drugs, Can. J. Physiol. Pharmacol. 68, 314.

Ueno, S., N. Matsuki and H. Saito, 1988, *Suncus murinus* as a new experimental model for motion sickness, Life Sci. 43, 413.