Jpn. J. Pharmacol. **89**, 324 – 326 (2002) Rapid Communication

Vasopressin Induces Emesis in *Suncus murinus*

Yuji Ikegaya* and Norio Matsuki

Laboratory of Chemical Pharmacology, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113-0033, Japan

Received May 20, 2002 Accepted June 5, 2002

ABSTRACT—This paper reports that vasopressin is emetogenic in the house musk shrew *Suncus murinus*. Either intravenous or intracerebroventricular administration of vasopressin caused vomiting within a few minutes. The ED_{50} of intravenous vasopressin was as high as 4.67 μg/kg, whereas intracerebroventricularly injected vasopressin was effective at a low dose of 20 ng/brain. The emetogenic target of vasopressin may therefore be present in the central nervous system. We propose the *Suncus* as a useful animal for investigation of vasopressin-mediated emesis, including motion sickness.

Keywords: Vomit, *Suncus*, Vasopressin

Arginine vasopressin (AVP) is a posterior pituitary hormone, which is assigned pleiotropic functions, e.g., vascular regulation, osmoregulation, stress responses, renal regulation and neuromodulation. Recent evidence implies an involvement of AVP in vomiting and nausea of humans and animals. For instance, the level of plasma AVP is rapidly elevated in response to diverse emetic stimuli such as motion stimuli (1) and cisplatin (2). The intravenous injection of AVP per se results in vomiting and retching in several species (1, 3, 4). Treatment with antagonists of the AVP receptor V_1 efficiently prevents motion sickness (5, 6), which suggests an involvement of endogenous AVP in naturally occurring emesis. However, our understanding for how the endogenous AVP causes emetic responses is still rudimental. To elucidate the action of AVP, a simple animal model should be established. In the present study, we examined whether or not AVP induces vomiting in the house musk shrew *Suncus murinus*, a small-size, thus handy, animal, which is an insectivore (Fig. 1).

Experiments were performed on male *Suncus murinus* weighing 50 – 80 g (Central Institute for Experimental Animals, Kawasaki), in accordance with the Guiding Principles for the Care and Use of Laboratory Animals approved by The Japanese Pharmacological Society. The experiment procedures used have been described elsewhere (7). After sampling about 1 ml of blood, plasma levels of AVP were measured by radioimmunoassay (Mitsubishi Chemical Corporation, Tokyo). For intravenous (i.v.) injection of AVP (Research Biochemicals, Natick, MA, USA), an indwelling transvenous jugular catheter was implanted (2 ml/kg of injection volume). For intracerebroventricular (i.c.v.) injection, an indwelling guide cannula was stereotaxically implanted into the left lateral cerebral ventricle (9.8-mm anterior, 0.8-mm lateral, 3.5-mm ventral to the lambda) (3 μl of injection volume). The latency from the AVP injection to the first vomiting episode and the total number of vomiting episodes were manually recorded.

The baseline level of plasma AVP in *Suncus* was 106.1 ± 27.4 pg/ml (mean ± S.E.M. of 10 animals). Thus, AVP was intravenously injected at a dose of 0.02 μg/kg because the maximal concentration of the injected AVP immediately after its distribution in the whole blood should be simply estimated at about 400 pg/ml on the assumption that the body weight and the total blood volume are 50 g and 2.5 ml, respectively, and that the rapid metabolism of

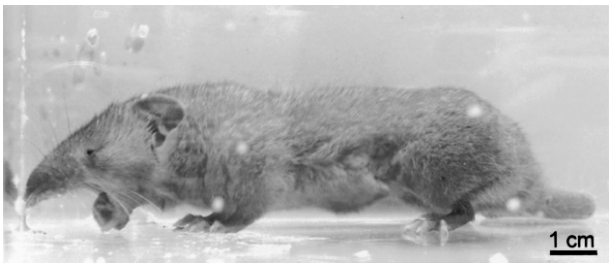

Fig. 1. Photograph of a vomiting *Suncus murinus*. The insectivore *Suncus* is a small-size animal that is useful for investigation of vomiting and nausea and for development of antiemetic drugs. Note that rodent species, e.g., rats and mice, are incapable of vomiting.

*Corresponding author. FAX: +81-3-5841-4784
E-mail: ikegaya@tk.airnet.ne.jp

Table 1. AVP-induced emesis in Suncus murinus

Dose	No. of *Suncus* (vomiting/tested)	Latency (min)	No. of vomiting episodes
i.v. injection			
100 μg/kg	2/2	1, 2	8, 6
20	3/3	1.7 ± 0.3	6.3 ± 3.0
10	3/3	1.9 ± 0.7	6.2 ± 3.6
5	3/5	2.0 ± 0.6	5.3 ± 2.0
2.5	0/4	—	—
0.02	0/3	—	—
i.c.v. injection			
20 ng/brain	4/4	0.7 ± 0.4	6.8 ± 4.2
2	0/3	—	—

Data represent means ± S.E.M., but when the number of vomiting animals was <3, the actual values are indicated. —: no animal vomited. By Brownlee's method, the ED_{50} value was estimated to be 4.67 μg/kg (i.v.).

AVP could be ignored. The animals treated with 0.02 μg /kg AVP displayed no characteristic behaviors including vomiting during an observation period of up to 120 min (Table 1). At much higher doses, however, AVP could reproducibly induce vomiting. The first vomiting episode was observed 1 – 3 min after the i.v. injection, and the total number of vomiting episodes ranged from 3 to 8 (Table 1). The vomiting behavior was brought to completion within 7 min. The ED_{50} was calculated to be 4.67 μg/kg by Brownlee's up-down method.

One of the major actions of plasma AVP is to elevate the blood pressure via its potent vasoconstrictive effect. Such an acute rise in blood pressure is, however, an unlikely cause of emesis because the flush i.v. injection of 0.5 ml saline (almost equivalent to 20% of the total blood volume), which might produce an abrupt increase in blood pressure, failed to induce vomiting (n = 3, data not shown). Undoubtedly, there was no guarantee that such a rapid injection of saline evoked a similar increase in blood pressure to AVP-induced hypertension, but it should also be noted that the ED_{50} value was about 10^5 times higher than the basal level of plasma AVP as obtained above. Considering that when megadosed, AVP can partly pass through the blood-brain barrier (8), we assumed that AVP-induced emesis is mediated by the central action of AVP. Indeed, this idea is consistent with a report on humans (1). We therefore examined the effect of the i.c.v. injection of AVP and found that 20 ng/brain, but not 2 ng/brain, of AVP elicited vomiting with a short latency of less than 1 min (Table 1).

AVP has recently been implicated in vomiting and nausea, yet how AVP contributes to emesis is incompletely understood. Here we have shown for the first time that both the i.v. and i.c.v. injections of AVP rapidly cause vomiting in the insectivore *Suncus murinus*.

The ED_{50} value of the emetic effect of intravenous AVP was considerably higher than the physiological range of plasma AVP levels. Other reports also demonstrated that high doses of AVP (>100 μg/kg, i.v.) are required for the induction of emesis in humans (3) and dogs (4). This may be partly because plasma AVP is easily metabolized in the kidney or liver. In the present study, however, we demonstrated that vomiting is more efficiently elicited by the i.c.v. injection of AVP. The effective dose was 20 ng/brain. Assuming that the *Suncus* weighs 50 g, it corresponds to a systemic dose of 0.4 μg/kg, being tenfold less than the intravenous ED_{50} value. In this case, the final concentration in the cerebrospinal fluid is estimated to be about 500 – 700 pg/ml, closely corresponding to previously reported concentrations of AVP in the cerebrospinal fluid (8). Therefore, we conclude that central AVP is emetogenic. Of course, our data do not exclude the possible contribution of peripheral AVP to emesis. In humans, indeed, motion sickness is often associated with increases in tachygastric activity and plasma AVP (1). There may be a possible difference in the involvement of peripheral and central AVP between *Suncus* and other species. In the brain, vasopressin and its receptors are widely distributed in the hypothalamus, medulla oblongata, hippocampus, amygdala and thalamus (9, 10). In particular, the medulla oblongata, hypothalamus and thalamus are believed to play pivotal roles in motion sickness and chemically evoked emesis. These areas are potential targets of emetogenic AVP.

To our knowledge, the *Suncus* is the smallest experimental animal that displays AVP-induced vomiting. This species can be a practically useful model for studying of the involvement of AVP in emesis and for development of anti-emetic drugs.

REFERENCES

1 Kim MS, Chey WD, Owyang C and Hasler WL: Role of plasma vasopressin as a mediator of nausea and gastric slow wave dysrhythmias in motion sickness. Am J Physiol **272**, G853 – G862 (1997)
2 Cubeddu LX, Lindley CM, Wetsel W, Carl PL and Negro-Vilar A: Role of angiotensin II and vasopressin in cisplatin-induced emesis. Life Sci **46**, 699 – 705 (1990)
3 Sirinek KP and Thomford NR: The hemodynamic response of cirrhotic patients to the combined administration of vasopressin and isoproterenol. Rev Surg **32**, 217 – 220 (1975)
4 Carpenter DO, Briggs DB and Strominger N: Behavioral and electrophysiological studies of peptide-induced emesis in dogs. Fed Proc **43**, 2952 – 2954 (1984)
5 Kohl RL and MacDonald S: New pharmacologic approaches to the prevention of space/motion sickness. J Clin Pharmacol **31**, 934 – 946 (1991)
6 Cheung BS, Kohl RL, Money KE and Kinter LB: Etiologic significance of arginine vasopressin in motion sickness. J Clin Pharmacol **34**, 664 – 670 (1994)

7 Kakimoto S, Saito H and Matsuki N: Antiemetic effects of morphine on motion- and drug-induced emesis in *Suncus murinus*. Biol Pharm Bull **20**, 739 – 742 (1997)
8 Nagao S: Vasopressin and blood-brain barrier. Brain Nerve **50**, 809 – 815 (1998)
9 Hawthorn J, Ang VT and Jenkins JS: Localization of vasopressin in the rat brain. Brain Res **197**, 75 – 81 (1980)
10 Tribollet E, Barberis C, Jard S, Dubois-Dauphin M and Dreifuss JJ: Localization and pharmacological characterization of high affinity binding sites for vasopressin and oxytocin in the rat brain by light microscopic autoradiography. Brain Res **442**, 105 – 118 (1988)