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P152602.PDF [Page: 3 of 10]

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Etiologic Significance of Arginine Vasopressin in Motion Sickness

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There is abundant evidence implicating the role of arginine vasopressin in motion sickness. The effects of AVP analogs on motion sickness were investigated in squirrel monkeys. Two specific V_1 antagonists (SK&F 100273 and SK&F 103561) and three mixed V_1/V_2 antagonists (SK&F 101926, SK&F 105494, and SK&F 104146-D) were tested on six highly susceptible monkeys. Intravenous injections of 200 ug of a V_1 antagonist abolished emesis in all six monkeys, and few prodromal symptoms remained (latency to emesis > 120 minutes, $P < .001$). Mixed V_1/V_2 antagonists failed to abolish emesis in all monkeys. However, there was a slight increase in the latency to the first bout of emesis/retching with the mixed antagonists when compared with the baseline. The dose-response relationship and rate of onset of action of the V_1 antagonists (SK&F 100273) were explored. Latency to the first bout of emesis/retching increased to about twice that of the baseline when half of the effective antiemetic dose was used. The efficacy demonstrated by the specific V_1 antagonists indicates that V_1 receptors may modulate emesis.

Pharmacologic management is still the most convenient approach to the problem of motion and space sickness. Current literature reveals that there appear to be three main categories of antimotion-sickness drugs: H_1 antihistamines (diphenhydramine and promethazine), anticholinergics (scopolamine), and psychostimulants (amphetamine). The majority of existing antimotion-sickness drugs are depressants with the main site of action in the central nervous system (CNS). The psychostimulants, although effective when used alone, are predominantly combined with the other agents to counteract CNS depression. Their use has undesirable consequences on functions associated with motion, particularly with respect to the integrity of the visual and vestibular systems. For example, promethazine impaired dynamic tracking performance and reduced the ability to maintain visual fixation.[1] Interferences with visual acuity and visual tracking ability have potentially adverse consequences for spatial orientation and flight safety, and reduce operational proficiency. Similarly, the administration of scopolamine as an antimotion-sickness drug is often associated with side effects, such as drowsiness, sedation, blurred vision, cycloplegia, inability to concentrate, and short-term memory loss.[2,3]

New antihistamines referred to as "second-generation H_1 antagonists" act peripherally, and are free of central antihistaminic and anticholinergic actions. However, the potent and highly selective H_1 antagonist astemizole, with a half life of 4.5 days, did not appear to exhibit any antimotion-sickness effects.[4] Terfenadine, another peripherally active H_1 antagonist, was found to have marginal efficacy at a single large dose of 300 mg, and exhibited pronounced individual response differences.[5] There have been anecdotal reports and retrospective studies from the astronaut corps that intramuscular injection and intravenous (IV) infusion of promethazine is highly effective, without the side effect of sedation.[6-8] However, no systematic studies have been published to quantify the effectiveness of the treatment and documentation of side effects of this alternative administration procedure. The metabolism of histamine in orbit must be investigated to elucidate the absence of sedation. It is encouraging to note that IV infusion

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P152602.PDF [Page: 4 of 10]

and intramuscular injection are operationally feasible on a routine basis in orbital flights. The objective in seeking an agent that effectively prevents motion/space sickness without notable side effects has not been met.

In this study, we investigated an alternative pharmacologic approach based on the hormonal response of significant release of arginine vasopressin (AVP) to stressful motion environment and to nausea/emesis. Preliminary studies indicated that two potent and highly specific AVP V_1 antagonists delay the onset of severe symptomatology and emesis in squirrel monkeys at IV doses of 100 to 240 ug/kg.[9] The efficacy of six AVP analogs in preventing motion sickness was investigated.

METHODS

Subjects

A group of six (10–12 years of age) male squirrel monkeys (*Saimiri sciureus*) of the Bolivian subspecies served as subjects. Care and handling of the animals were in accordance with recommendations specified in the *Guide to Care and Use of Experimental Animals*, provided by the Canadian Council on Animal Care. All were fed with a commercially prepared high-protein diet, supplemented with fresh fruit. Water was available at all times. The integrity of their vestibular function was examined by visual and electronystagmographic observations of spontaneous and positional nystagmus, and they exhibited normal rotation-induced nystagmus.

Procedure

All testing took place in the morning to standardize possible circadian variations in drug sensitivity. The squirrel monkeys were fed 20 g of banana 30 minutes before the motion stimulation to standardize stomach loading. Test animals were placed inside a transparent, well-ventilated Lucite chamber, 30.5 x 30.5 x 35.6 cm in size, bolted onto the test platform. The motion stimulus consisted of simultaneous horizontal angular rotation of 25 rpm with a constant 0.5-Hz vertical sinusoidal excursion of 15 cm. The resulting motion was a helix up and a helix down. The duration of each test was 120 minutes, during which time the behavioral responses of the monkeys were recorded in detail, according to a rating scale described previously (Table I), allowing a maximum sickness score of 31 points.[9] Severity of sickness was primarily determined by the latency of vomiting and cumulative sickness scores. The baseline susceptibility level of each monkey was established from the average of five trials (one trial every 10 days) with an IV injection of saline. All postdrug tests were based on a single trial.

To avoid the possibility of habituation to the motion, and to avoid the effects of one drug that may contaminate the assessment of other drugs administered later, an intertrial interval of 10 days was allowed. At the end of the series of tests of each drug treatment, and after an additional 2 weeks, the monkeys were subjected to a single trial using the same motion profile with placebo (saline) treatment. All six test monkeys were selected from a group of 13 monkeys, and were found to be highly susceptible to this specific motion stimulus. They demonstrated a consistent response to the motion stimulus, with a mean latency to the first bout of vomiting around 30 minutes, and an average of three bouts of vomiting within the 120-minute testing period. Because of the small supply of some of the test compounds, we were unable to employ a larger group of monkeys. Response/time characteristics of the most effective AVP analogs were investigated, based on the behavioral responses of emesis/retching as an index of blood level. Our laboratory was not equipped to measure the plasma or cerebral spinal fluid (CSF) level of AVP antagonist, nor to distinguish analogs from AVP in a conscious, unrestrained monkey.

Drugs and Their Administration

Each of the following arginine vasopressin analogs were tested for their effectiveness in preventing motion sickness in the squirrel monkeys. Their receptor affinity and potency as cited were based on available *in vitro* human data.

1. SK&F 100273, $d(CH_2)_5$Tyr(Me)AVP, a highly potent and specific V_1 antagonist, chemically defined as [1-(beta-mercapto-beta-cyclopentamethylenepropionic acid), 2-(O-methyl)tyrosine]-8-arginine vasopressin. V_2K_I (potency) = 283 nM;[10] V_2K_B (receptor affinity) = 2.23 nM.[11]
2. SK&F 103561, a highly potent and specific V_1 antagonist, chemically defined as [1-(deaminopenicillamine),2-(O-ethyl)D-tyrosine, 7-desproline, 8-arginine, 9-desglycine]vasopressin. V_1K_B = 1.5nM, V_2K_B = 317 nM.[12]
3. SK&F 101926, desGlyd$(CH_2)_5$D-Tyr(Et)VAVP, a potent V_2 antagonist; like most V_2 antagonists, it is nonselective in that it is a potent antagonist of V_1, V_2, and oxytocin receptors, and is chemically defined as [1-(beta-mercapto-beta, beta-cyclopentamethylene propionic acid), 2-(O-ethyl)D-tyrosine, 4-valine, 8-arginine, 9-desglycine]vasopressin. For V_1,K_B = 1.2 nM; for V_2, K_B = 3.6 nM.[13,14]

P152602.PDF [Page: 5 of 10]

TABLE

Diagnostic Criteria for Acute Motion Sickness in the Squirrel Monkey*

Pathognomonic	Major	Minor	Minimal	Qualifying Symptoms
16 points Vomiting or retching	8 points Frequent vigorous chewing	4 points Salivation occasional chewing	2 points Reduced activity and alertness (drowsiness), occasional licking of lips	1 point Reduced activity and inquisitiveness, unusual postures

* *Based on Graybiel's diagnostic criteria for acute motion sickness in humans.* *Maximum sickness scores: 31 points.*

4. SK&F 104146-D, $C_{52}H_{79}N_{15}O_{10}S_2$, a potent V_1/V_2 antagonist, chemically defined as O-ethyl-N-[(1-mercaptocyclohexyl)acetyl]-D-Tyr-L-Ala-L-Val-Asn-L-Cys-L-Arg-D-Arg Amide, cyclic[1,5] disulfide hydrogen phosphate. For V_1, K_B = 2.4 nM; for V_2, K_B = 1.7 nM.[14]
5. SK&F 105494, $C_{54}H_{83}N_{15}O_{10}$, a potent V_1/V_2 antagonist, chemically defined as O-ethyl-D-tyrosine-L-phenylalanyl-L-Valyl-L-Asparginyl-5-[1-(carboxylmethyl)cyclohexyl]-L-norvalyl-L-Argin-D-Argininamide cyclic (5-1)-peptide. For V_1, K_B = 2.5 nM; for V_2, K_B = 3.9 nM.[13,14]
6. dDAVP 1-Deamino 8-D-Arg vasopressin (Desmopressin), a V_2 agonist that may act via stimulation of CNS receptors referred to as V_3 that are not well characterized. K_B = 540 nM.[15]

Before parenteral administration, sterile isotonic saline was added to dissolve the compounds. A fixed dose of 200 ug each was employed, disregarding the weight differences among the monkeys (body weight varied from 820 to 900 g). In the case of SK&F 100273, doses of 100 and 50 ug were also used. Strict antiseptic precautions were observed, and care was taken to avoid extravasation. All injections were administered IV through the ventral surface of the tail vein of the conscious animal in a restraining chamber. Repeated-measures design and multiple-comparison tests were employed for the analysis of all the data obtained.

RESULTS

The behavioral response of the susceptible squirrel monkeys to motion stimulation has been discussed in detail in previous studies.[9,16,17] Susceptible animals consistently exhibited varying degrees of sickness, starting with reduced inquisitiveness, prodromal signs such as licking of lips, salivation, occasional and frequent chewing, and, in the final stage, retching and emesis. Effectiveness of the different arginine vasopressin analogs in preventing motion sickness was best reflected by the latency to the first bout of vomiting. Changes in water balance were not quantified, and no diuresis was noticed in any of the tests.

The quantitative data for each drug treatment were subjected to repeated-measures ANOVA to determine their effectiveness against motion sickness and the subsequent dose-response relationship of the various compounds. Visual inspection of the data indicated an unexpectedly large difference between the effectiveness of V_1 and mixed V_1/V_2 antagonists. Scheffe's test for multiple comparisons was chosen for further test of significance, because it is more stringent. This statistical test allows us to test any number of comparisons that are selected by inspection, and the probability of finding an erroneous significant result (Type I error) is minimized. This control of the experiment error rate seems appropriate in our study.

The effectiveness of AVP analogs in preventing motion sickness in the squirrel monkey is shown in Figure 1. There was a significant effect with SK&F 100273 (Scheffe's test, $F(5,40) = 13.781$, $P < .001$) and SK&F 103561 (Scheffe's test, $F(5,40) = 13.373$, $P < .001$) in abolishing emesis and severe symptoms of motion sickness in the squirrel monkeys. Without treatment, the monkeys vomited with a mean latency of 29.9 ± 2.7 minutes and mean cumulative sickness scores of 22.2 ± 0.56. No emesis was observed 150 minutes after the IV injection of either SK&F 100273 and 103561, and the mean cumulative sickness scores were 2.3 ± 0.33 and 2.0 ± 0.25, respectively (Figure 2). Antagonists with both V_1 and V_2 receptor affinity (SK&F 101926, 104146-D, and 105494) did not prevent emesis; although the latency to emesis increased slightly, it was not statistically significant. When the monkeys were retested after all the drug treatments, the mean latency to emesis was 28.8 ± 4.4 minutes and the mean cumulative sickness score was 23.8 ± 1.2, not significantly different from the baseline. Desmopressin (dDAVP), a V_2 agonist, shortened the latency of emesis compared

P152602.PDF [Page: 6 of 10]

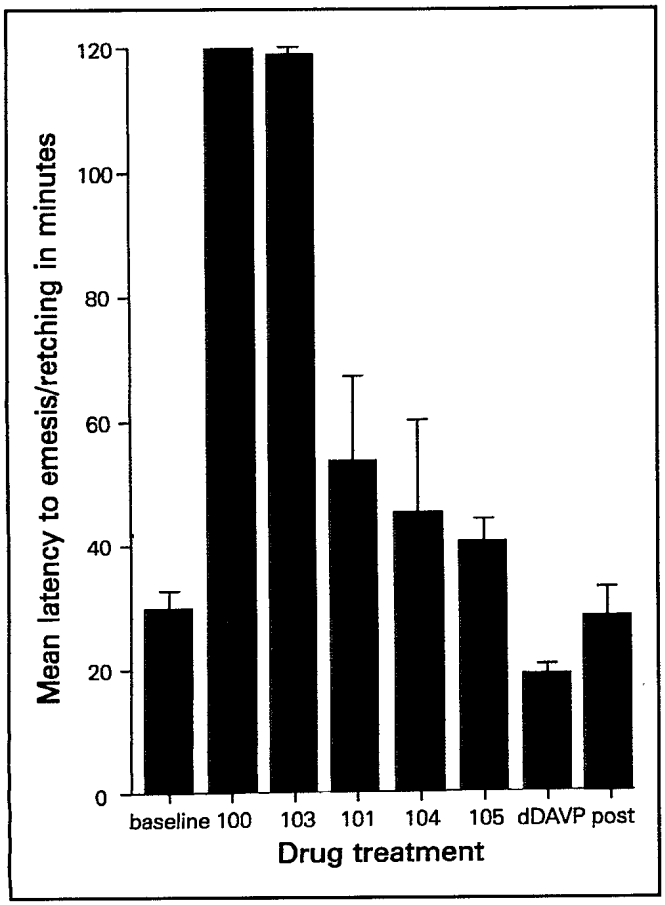

Figure 1. Effectiveness of AVP analogs in delaying the onset of the first bout of emesis. 100 = SK&F 100273; 103 = SK&F 103561; 101 = SK&F 101926; 104 = SK&F 104146-D; 105 = SK&F 105494; dDAVP = desmopressin; post = posttreatment injection. Error bars = SEM, n = 6. A significant effect of SK&F 100273 and 103561 in preventing emesis was shown: latency to emesis > 120 minutes (P < .001) and latency to emesis = 118.6 minutes (P < .001), respectively. Antagonists with V_1 and V_2 receptor affinity lengthened the latency to emesis, while dDAVP a V_2 agonist shortened the latency to emesis; however, they were not significant statistically.

with the baseline (not significant statistically), and demonstrated a comparable mean sickness score of 24.7 ± 0.88.

The dose-response relationship of SK&F 100273 is shown in Figure 3. Compared with the baseline, there was no significant effect demonstrated at 50 ug. At 100 ug, the latency to vomiting was approximately twice that of the baseline (Scheffe's test, $F(5,18) = 7.777$, $P < .001$). At 200 ug, emesis was completely abolished within the duration of the test (latency to emesis > 120 minutes). The response/time characteristics of 100 ug SK&F 100273, using the behavioral response of emesis as an index of blood level, is shown in Figure 4. It appeared that, at this intermediate dose level, the optimal time between drug injection and onset of motion stimulation was between 30 and 60 minutes. Results from the test of significance are as follows: between 30 and 0 minutes, Scheffe's test, $F(5,18) = 8.986$, $P < .001$; between 60 and 0 minutes, Scheffe's test, $F(5,18) = 5.902$, $P < .005$; between 30 and 120 minutes, Scheffe's test, $F(5,18) = 8.76$, $P < .001$; and between 60 and 120 minutes, Scheffe's test, $F(5,18) = 5.902$, $P < .005$.

DISCUSSION

Our results demonstrated that IV injections of 200 ug of specific and highly potent vasopressinergic V_1 an-

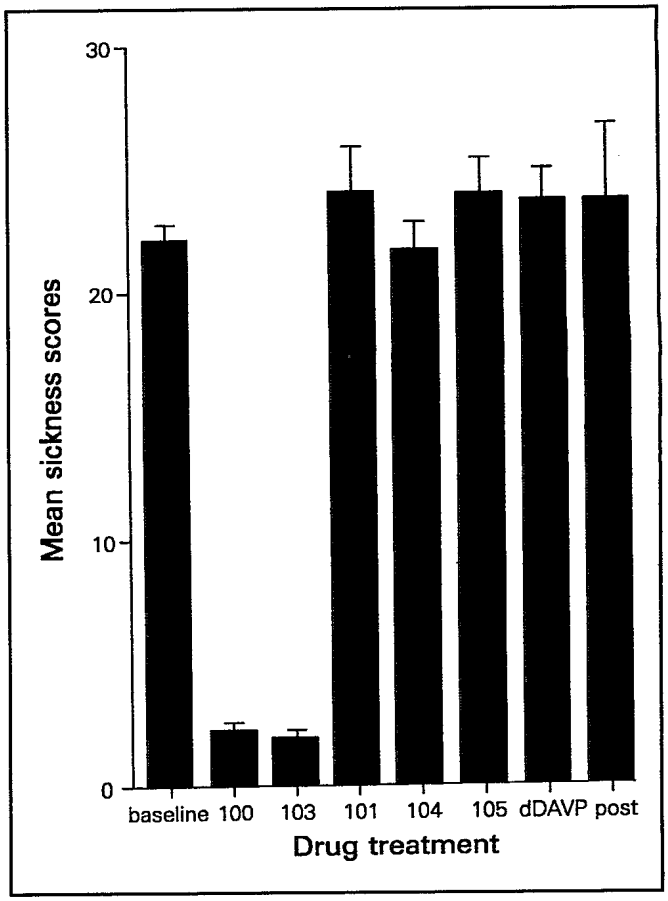

Figure 2. The effect of AVP analogs on the mean cumulative sickness scores. 100 = SK&F 100273; 103 = SK&F 103561; 101 = SK&F 101926; 104 = SK&F 104146-D; 105 = SK&F 105494; dDAVP = desmopressin; post = posttreatment injection. Error bars = SEM, n = 6. Specific V_1 antagonists SK&F 100273 and SK&F 103561 abolished severe symptoms of motion sickness and emesis; only a few prodromal symptoms remained.

P152602.PDF [Page: 7 of 10]

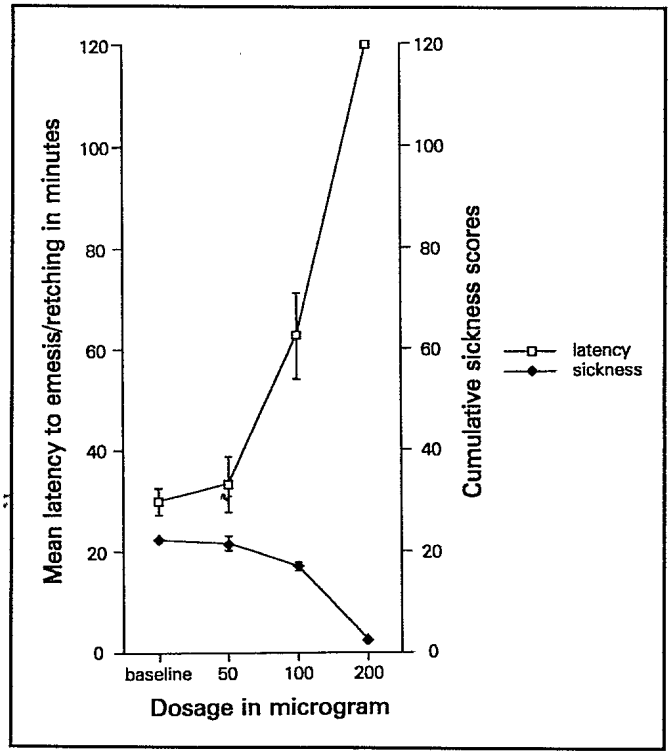

Figure 3. Dose-response relationship of SK&F 100273. Error bars = SEM, n = 6. No significant effect at 50 ug. A dose of 200 ug completely abolished emetic response within the duration of the test (latency to emesis > 120 minutes). At 100 ug, the mean latency to emesis was 62.4 minutes, approximately twice that of baseline (29.8 minutes) (P < .005).

tagonists (SK&F 100273 and SK&F 103561) were very effective in abolishing emesis and the development of significant symptomatology of motion sickness in a group of highly susceptible squirrel monkeys. The specific action could be accounted for by the specific receptor affinity and potency against the V_1 receptor. The efficacy of V_1 antagonists in the squirrel monkeys strongly indicates that rising levels of AVP directly contribute to emesis and that V_1 receptors play a critical role, although the mechanism of action of AVP in motion-induced emesis is not completely understood.

There is abundant evidence implicating the role of vasopressin in motion sickness. It has been known for a long time that inhibition of water diuresis consistently accompanies laboratory-induced motion sickness in humans and dogs.[18] There was a correlation between the severity of the symptoms and the degree of the antidiuresis. Subjects who failed to become motion sick exhibited a much smaller inhibition of diuresis or none at all. This study indicated that an enhanced secretion of AVP leads to a decrease of urine flow in experimentally provoked motion sickness. Eversmann et al[19] demonstrated that, during the development of motion-sickness symptomatology, there was a 21-fold increase in plasma levels of AVP. The release of AVP was the earliest and most pronounced endocrine marker of motion sickness. Subsequent studies confirmed the above finding.[20–22] Kohl et al[22] were first to report the susceptibility-related differences in AVP and ACTH in human subjects exposed to Coriolis stimulation. Motion-induced elevation of plasma levels of vasopressin has been shown to correlate with individual differences in susceptibility to stressful motion.[23,24] The latter findings were explained in terms of V_1 receptor stimulation and individual differences in V_1 receptor sensitivity or number. A pronounced rise in plasma AVP was also observed in subjects with apomorphine-induced nausea/emesis, to levels 80-fold above normal.[25]

Results from experiments with cats also indicated that changes in systemic AVP were related to vomit-

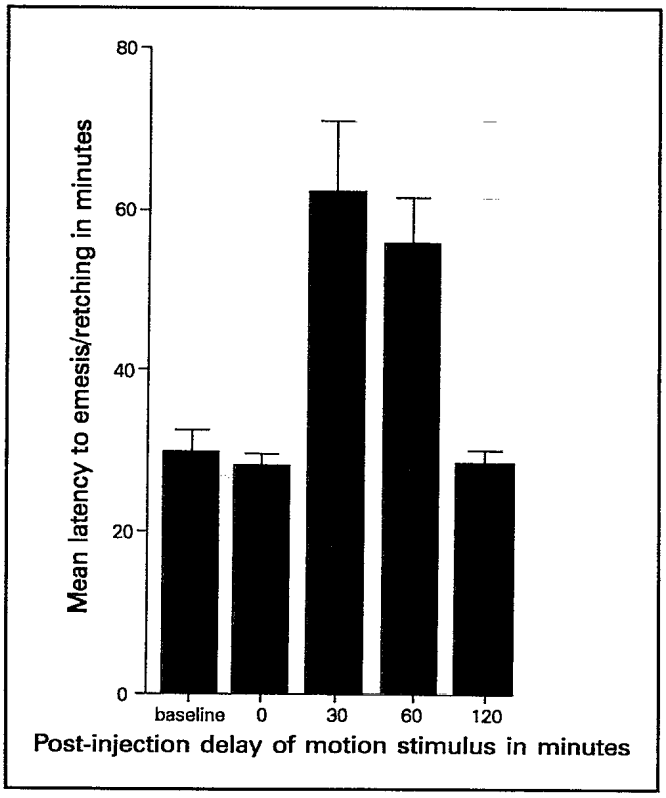

Figure 4. Response/time characteristics of (100 ug) SK&F 100273. Error bars = SEM, n = 6. Response/time characteristics based on the behavioral response of emesis as an index of blood level. The optimal effect appeared to be between 30 and 60 minutes postinjection (P < .01).

P152602.PDF [Page: 8 of 10]

ing induced by motion.[26] Plasma AVP levels, but not the AVP in the cerebral spinal fluid (CSF), increased significantly in both susceptible and resistant cats exposed to motion. When vomiting occurred, plasma AVP levels were increased 27-fold. In agreement with the human data, there were no differences in resting levels of plasma AVP between the susceptible and the resistant group, but higher levels of AVP in CSF have been found in cats that are more resistant to stressful motion.

The principal physiologic function of vasopressin is the regulation of body fluid tonicity and volume. Two types of receptors have been identified: the antidiuretic V_2 receptor, located on the basolateral membranes of renal collecting duct; and the pressor V_1 receptor, located in the vasculature, the adenohypophysis, and the hippocampus in the CNS. Stimulation of V_1 receptors leads to an array of activities in the CNS. The release of AVP in response to stressful motion indicated that the paraventricular nucleus of the hypothalamus (PVH) may play a central role in coordinating endocrine and autonomic responses to motion sickness. Sawchenko and Swanson[27] reported cell bodies within the PVH containing high concentrations of AVP. Other AVP-containing cell bodies were found in the limbic system, which has direct outputs to the PVH, which, in turn, sends projections to the pituitary to control the release of AVP. It was reported that PVH plays a dominant role in neuronal coupling of autonomic, endocrine, and somatomotor responses to environmental stresses.[28] The PVH is one of the highly vascularized areas of the brain, a rich network for the forebrain, limbic system, and other hypothalamic nuclei.[29] It is also connected to the brain stem autonomic centers, such as the nucleus of the solitary tract and the dorsal vagal complex.[30,31] The major signs and symptoms of motion sickness are indicative of autonomic involvement, although motion sickness cannot be considered as simply a development of the autonomic effects caused by vestibular stimulation. The autonomic nervous system is activated by the brain stem and hypothalamic centers. Visual, vestibular, and somatosensory inputs (spatial orientation information) eventually pass through the cerebral cortex, in particular the limbic system, which can directly or indirectly influence autonomic activities. However, it is not clear what role AVP plays in autonomic function that is relevant to the etiology of nausea and emesis.

It is possible that pharmacologic intervention in the squirrel monkey may not be relevant to human motion sickness because of species differences. Recent research with cats, dogs, and squirrel monkeys demonstrated that animal models sometimes do respond to drugs that are effective in humans. Animal models have the advantage of allowing the use of wide dose ranges for testing with emesis as the end point. This often is not possible in human studies. Sufficient data has been provided in this study to warrant further investigation on the effectiveness of these specific V_1 antagonists as preventive measures for motion sickness in human subjects.

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