Neural mechanisms of motion sickness

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Abstract: Three kinds of neurotransmitters : histamine, acetylcholine and noradrenaline, play important roles in the neural processes of motion sickness, because antihistamines, scopolamine and amphetamine are effective in preventing motion sickness. Histamine H_1-receptors are involved in the development of the symptoms and signs of motion sickness, including emesis. On provocative motion stimuli, a neural mismatch signal activates the histaminergic neuron system in the hypothalamus, and the histaminergic descending impulse stimulates H_1-receptors in the emetic center of the brainstem. The histaminergic input to the emetic center through H_1-receptors is independent of dopamine D_2-receptors in the chemoreceptor trigger zone in the area postrema and serotonin $5HT_3$-receptors in the visceral afferent, which are also involved in the emetic reflex. Antihistamines block emetic H_1-receptors to prevent motion sickness. Scopolamine prevents motion sickness by modifying the neural store to reduce the neural mismatch signal and by facilitating the adaptation/habituation processes. The noradrenergic neuron system in the locus coeruleus is suppressed by the neural mismatch signal. Amphetamine antagonizes mismatch-induced suppression of noradrenergic neural transmission, resulting in preventing motion sickness. J. Med. Invest. 48 : 44-59, 2001

Keywords **:** *motion sickness, space motion sickness, histamine, antihismamine, acetylcholine, scopolamine, noradrenaline, amphetamine*

INTRODUCTION

Motion sickness is observed in humans exposed to unfamiliar motion (1-3). The characteristic symptoms and signs of motion sickness are nausea, vomiting, pallor and cold sweating. Virtually all humans are susceptible to motion sickness on exposure to unfamiliar motion of sufficient intensity and duration, and many other animal species also exhibit susceptibility.

The vestibular end-organs, the semicircular canals and otolith organs, play a significant role in the genesis of motion sickness (4). Many motions that cause vigorous stimulation of the vestibular end-organs are very effective in causing motion sickness. Patients without vestibular function do not experience motion sickness. However, it is difficult to accept the hypothesis that motion sickness is due to vestibular overstimulation, because it does not account for space motion sickness.

More than half of astronauts who have flown in spacecrafts have experienced symptoms similar to those that are characteristic of terrestrial motion sickness (5, 6). Space motion sickness appears within the first few hours in the microgravity environment, but is not seen at launch, when the astronaut is exposed to linear acceleration. Space motion sickness is frequently precipitated by active head movement, which does not produce terrestrial motion sickness. These phenomena are clearly inconsistent with the vestibular overstimulation hypothesis of motion sickness. Nor can it account for visually-induced motion sickness, such as simulator sickness.

The neural mismatch hypothesis in the development

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of motion sickness is the most plausible (7-9). In this review, the theoretical basis of the neural mismatch model of motion sickness is presented. Based on our results in experiments in a rat model, proposed neural mechanisms of motion sickness in the course of sensory processing, generating the neural mismatch signal and the emetic linkage, and the factors influencing susceptibility to motion sickness are then presented. Finally, the prevention and treatment of motion sickness are discussed.

AETIOLOGY OF MOTION SICKNESS

Essential to the neural mismatch hypothesis of motion sickness is the neural mismatch signal. The converging sensory inputs from the otolith organs, semicircular canals, eyes and somatosensory receptors are mismatched with the expected sensory patterns in the neural store calibrated by past experience, and spatial orientation is disturbed, leading to motion sickness. The essential components of the neural mismatch model of motion sickness are illustrated in Fig. 1. When a body movement is commanded, the efference copy is transmitted to the neural store (memory directory) where it retrieves and reactivates the stored afference previously associated with it (expected afference). The function of the comparator is to match the converging sensory inputs (re-afference) with the expected afferenee selected from the neural store by the efference copy. If there is a discrepancy between the expected patterns and current inputs, the mismatch signal is generated, triggering the neural mechanisms mediating autonomic nervous symptoms. A component of the neural mismatch signal also updates the neural store where a new association of re-afference and efference copy is registered. When the association is consolidated, the comparator accepts the match, and the adaptation/habituation processes are terminated. The neural mismatch hypothesis explains many of the known characteristics of motion sickness, including space motion sickness and visually-induced motion sickness. It can be equally applicable in understanding such autonomic reaction as nausea and vomiting associated with pathological (e.g., Meniere's disease) or surgical (e.g., labyrinthectomy) disturbances of vestibular function (10, 11).

NEURAL MECHANISMS OF MOTION SICKNESS

1. Emetic linkage and histamine

Antihistamines, which block histamine H_1-receptors, are effective in preventing motion sickness in humans (12-14), but new H_1-receptor antagonists such as astemizole, which cannot cross the blood-brain barrier, are not effective against motion sickness (15).

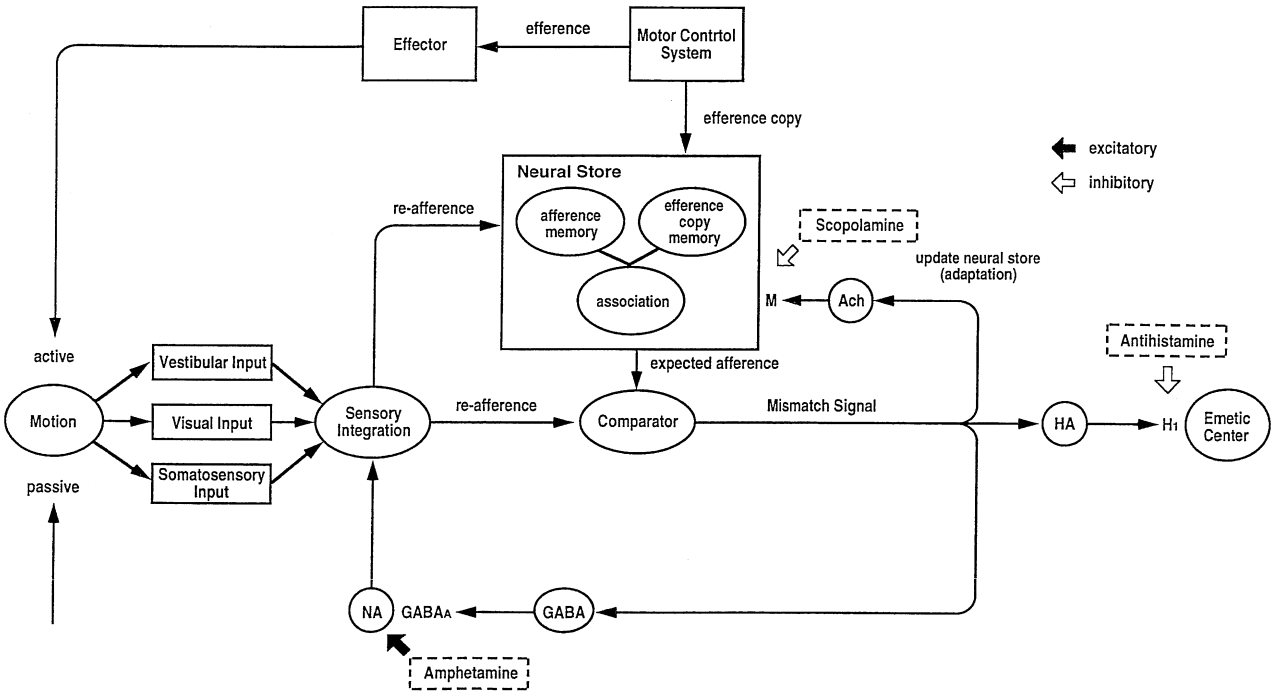

Fig. 1. The neural mismatch hypothesis and neural mismatch mechanisms of motion sickness. HA : histaminergic neuron system ; H_1 : histamine H_1-receptor ; Ach : cholinegic neuron system ; M : acetylcholine muscarinic receptor ; NA : noradrenergic neuron system ; GABA : GABAergic neuron system ; $GABA_A$: $GABA_A$ receptor.

Therefore, the histaminergic neuron system in the brain has been suspected to play an important role in the neural processes of motion sickness. Takeda *et al.* (16) and Morita *et al*. (17) developed a rat model of motion sickness and examined the neuropharmacological involvements of the histaminergic neuron system in motion sickness. Rats cannot vomit, but pica, the ingestion of non-nutritive substances such as kaolin (hydrated aluminum silicate), is an illness-response behavior in rats, which is analogous to vomiting (18). Morita *et al.* (17) showed that pica is an index of motion sickness in rats. Rotation around two axes (double rotation) with continuously changing centrifugal and angular accelerations was found to induce kaolin intake in rats (Fig. 2a), suggesting that these rats suffered from motion sickness. In contrast, after rotation around one axis (single rotation), rats consumed only a small amount of kaolin (Fig. 2b). Moreover, double rotation did not increase kaolin intake in bilaterally labyrinthectomized rats. Since double rotation presents an unusual pattern of sensory inputs to the otolith organs and semicircular canals which could cause neural mismatch, these findings demonstrate that rats, like humans, suffer from motion sickness due to the neural mismatch signal generated by the vestibular information passed through the inner ear.

The double rotation-induced pica is suppressed by diphenhydramine, an antagonist of H_1-receptor, showing that the histaminergic mechanisms involved in human motion sickness are apparently also involved in the development of motion sickness in rats (19). However, the possibility that the prophylactic effect of antihistamines is due to their anti-cholinergic activity (13) cannot be excluded. Takeda *et al.* (16, 20) used the rat model and found α-fluoromethylhistidine (FMH), which is an irreversible inhibitor of the histidine decarboxylase (HDC), is an effective anti-motion sickness agent. FMH depletes brain neural components of histamine and specifically blocks neural transduction of the histaminergic neuron system (21). In rats treated with FMH, double rotation-induced pica was suppressed, suggesting that FMH prevents motion sickness in the rat. FMH also suppresses motion-induced vomiting in the cat (22) and the suncus (23). These findings that FMH prevents motion sickness suggest that the histaminergic neuron system is specifically involved in the development of motion sickness.

Takeda *et al.* (16) examined the effects of double and single rotation on the histaminergic neuron systemic the rat model. Immunohistochemical studies have demonstrated that histaminergic neurons are concentrated in the hypothalamus, and the pons-medulla oblongata, one of the most important regions of the brain in motion sickness, contains histaminergic fibers (24, 25). Double rotation significantly increased

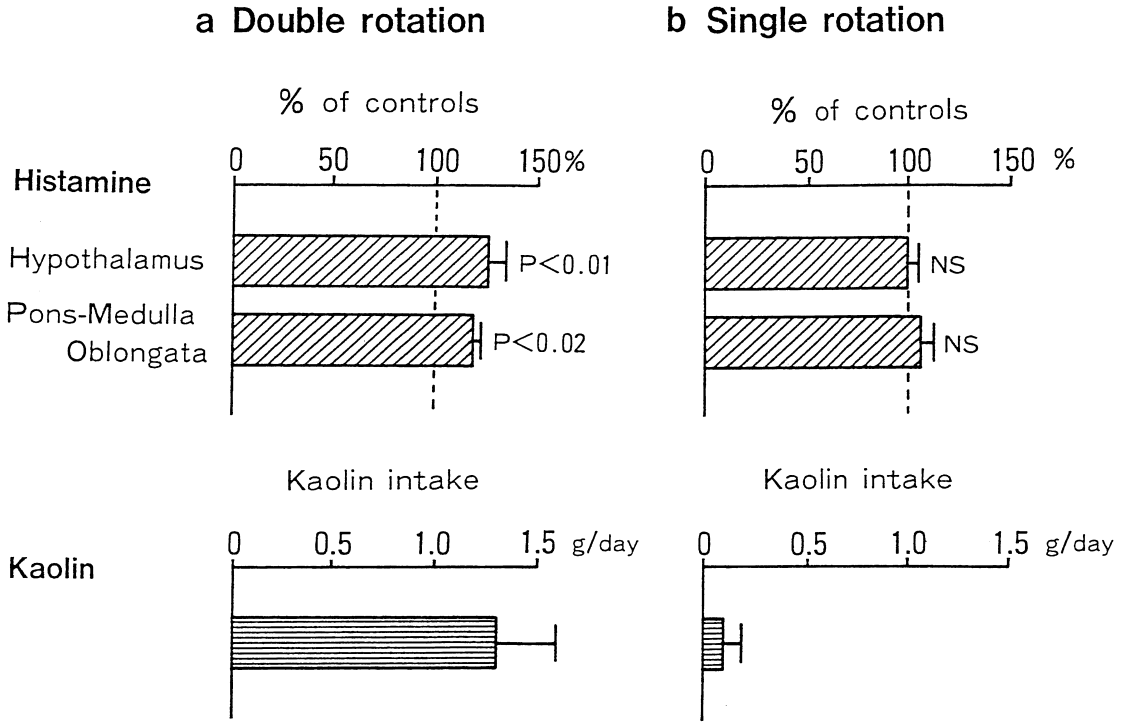

Fig. 2 a, b. Effects of double rotation (a) and single rotation (b) on histamine levels in the hypothalamus and pons-medulla oblongata, and kaolin intake as an index of motion sickness in rats. Double rotation increased the histamine levels in these regions and kaolin consumption. (From Takeda et al., 1986 (16) with permission)

the histamine contents in both regions (Fig. 2a), suggesting that double rotation, which produces motion sickness, changes the activity of the histaminergic neuron system. On the other hand single rotation, which does not induce motion sickness, does not increase the histamine content of these regions (Fig. 2b). Recently, using *in vivo* brain microdialysis technique, Horii *et al.* (26) measured endogenous histamine release from the hypothalamus of rats during unilateral caloric stimulation. Hot water irrigation of the middle ear, which activates the lateral semicircular canal afferents, increased histamine release from the hypothalamus. However, ice water irrigation, which inhibits the canal afferents, also increased histamine release (Fig. 3). Thus, caloric stimulation both hot and cold water activates the histaminergic neuron system in the brain. Even though the initial causes of motion sickness and of emesis induced by unilateral vestibular dysfunction (caloric stimulation) may differ, both are considered to be generated by the neural mismatch signal arising from mismatch of the converging sensory inputs and expected sensory pattern (10, 11). Taken together with the neuropharmacological finding that FMH prevents motion sickness, the neurochemical findings therefore suggest that the neural mismatch signal activates the histaminergic neuron system, resulting in motion sickness.

Recently, Takeda *et al.* (27) developed an animal model of space motion sickness. Uno *et al.* (28) used the animal model and reported that histamine release from the hypothalamus of freely moving rats exposed to negative change in gravity with *in vivo* brain microdialysis technique. It is suggested that histaminergic activation in the development of motion sickness induced by negative change in gravity is underlying mechanisms of space motion sickness.

According to the neural mismatch hypothesis, the repeated arrivals of the neural mismatch signals update the neural store, which registers a new re-afference and efference copy association. The comparator then accepts the match, and adaptation/habituation to the provocative motion is acquired. Takeda *et al.* (29) examined the effects of FMH on the development of habituation to double rotation in rats. Based on their hypothesized effects of anti-motion sickness drugs on the development of habituation to provocative motion, they classified the anti-motion sickness drugs into the following three classes : Class A drugs that block the sensory input which is responsible for neural mismatch ; Class B drugs that modify the neural store to reduce the neural mismatch signal ; and class C drugs that inhibit the subsequent mechanisms which bring about the symptoms and signs of motion sickness. While all these types of drugs have protective effects against motion sickness, their effects on the development of habituation to provocative motion probably differ. It was hypothesized that class A drugs would retard the acquisition of habituation, since they block the sensory input to be habituated (Fig. 4 a), Class B drugs would accelerate the processes of habituation (Fig. 4b), and class C drugs would not affect habituation, since they block only the final processes in motion sickness (Fig. 4c). Rats were rotated in the double rotation mode once a day for 10 days. After day 8, kaolin intake gradually decreased with habituation to double rotation. On days 4 to 6, test animals were treated with FMH before exposure to double rotation. Controls were received

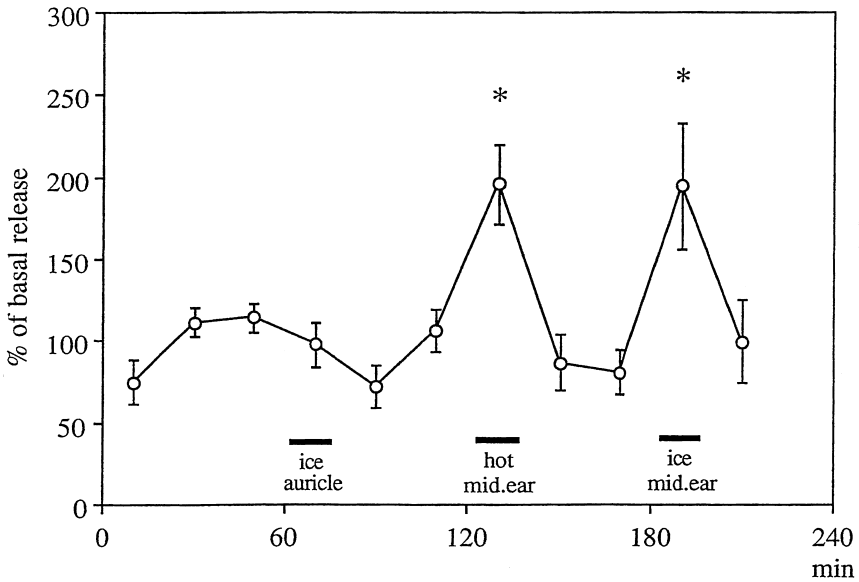

Fig. 3. Effects of caloric stimulation on histamine release from the hypothalamus in rats. Irrigation with hot water or ice water of the middle ear, but not that with ice water of the auricle, increased the histamine release. *$p<0.05$ vs. the release before the evoked release. (From Horii et al., 1993 (26) with permission)

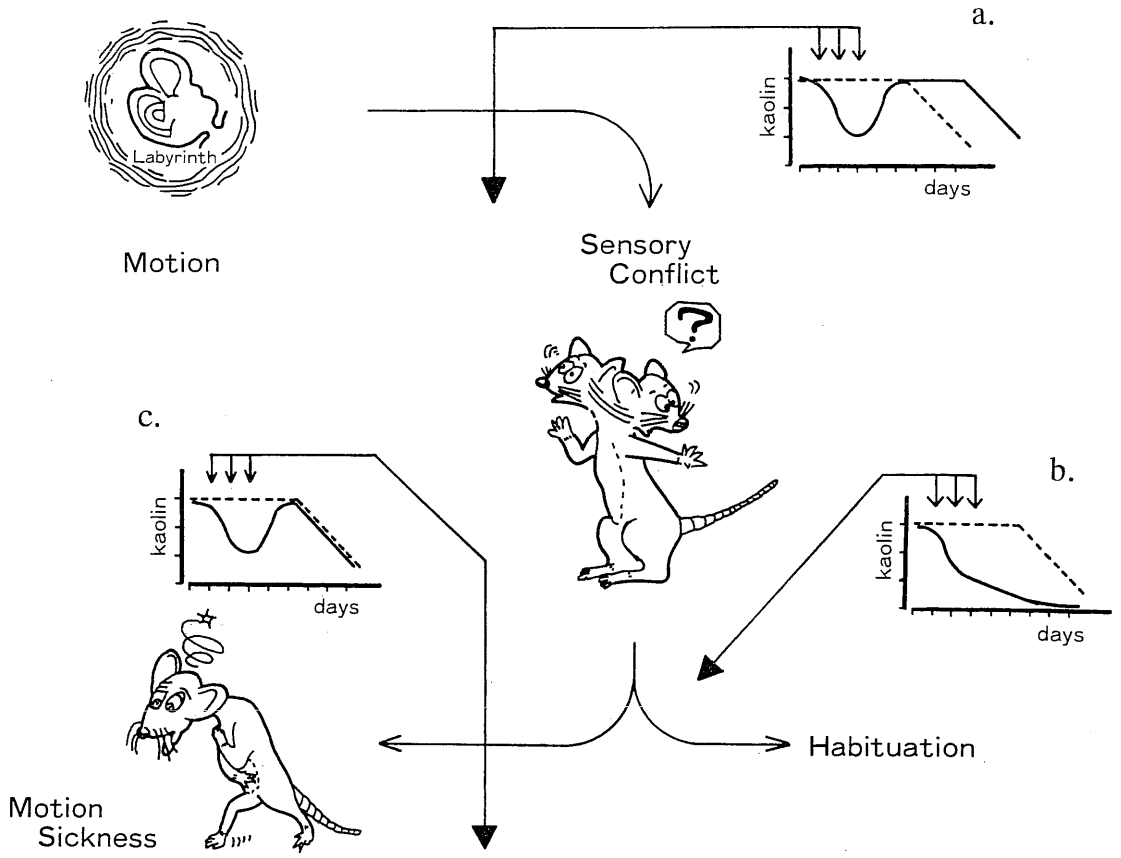

Fig. 4 a, b, c. Hypothesized effects of drugs classes A, B and C on the development of habituation to provocative motion. In the insert graphs (a, b and c) for drugs A, B and C, respectively, the solid line indicates the kaolin intake as an index of motion sickness in rats treated with each drugs on the days indicated by arrows over daily rotations ; the dashed line shows the kaolin intake of controls. (From Takeda et al., 1993 (29) with permission)

saline only. Although FMH decreased kaolin intake on days 4 to 6, the residual habituation of the FMH-treated rats at day 10 was almost the same as that of the control rats (Fig. 5). This finding indicates that the rate of habituation in the rats that showed reduction of motion sickness due to FMH was the same as that in controls. Since the curve for the effect of FMH on the development of habituation is similar to the solid line in Fig. 4c, FMH is a class C drug. Therefore, it is suggested that the histaminergic neuron system is involved in the symptomatic mechanism of motion sickness.

Immunohistochemical studies have demonstrated that the histaminergic neurons are located in the tuberomammillary nucleus (El-5) in the posterior hypothalamus and that their axons project both rostrally and causally (30). It has also been suggested that the emetic center encompasses the neural interactions among the parvicellular reticular formation, the nucleus tractus solitarii, the dorsal motor nucleus of the vagi and the nucleus ambiguous (31). Immunohistochemical and autoradiographic studies have demonstrated that histaminergic fibers (30) and H_1-receptors (32) are

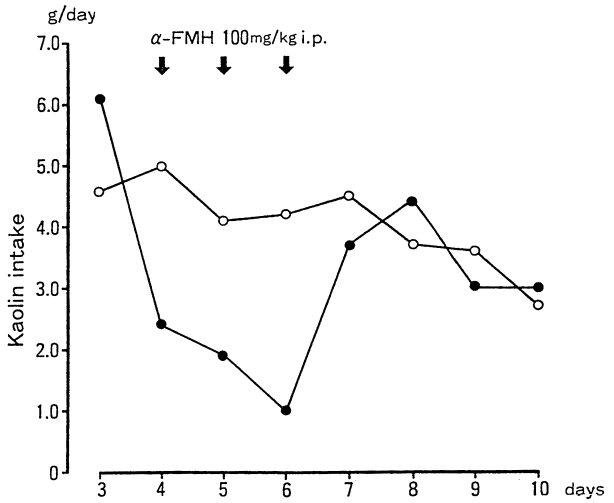

Fig. 5. Effects of FMH on habituation to double rotation in highly susceptible rats. ● : Rats with FMH ; ○ : Control rats. Although FMH decreased kaolin intake on day 4 to 6, the rate of habituation in FMH-treated rats was the same as that in the controls. (Data from Takeda et al., 1993 (29))

distributed in the emetic center. Bhargava *et al.*(33) reported that the intracerebroventricular administration of histamine in dogs caused vomiting via H_1-receptors.

Therefore, it seems likely that histaminergic descending impulses induced by the neural mismatch signal stimulate H_1-receptors in the emetic center, resulting in motion sickness (Fig. 1). The clinical observation that H_1-antagonists reduce the severity of motion sickness symptoms, even if administered after nausea or vomiting has developed (34), support the hypothesis of histaminergic involvement in the mechanism underlying the development of symptoms and signs of motion sickness. The hypothesis may also account for the oliguria associated with motion sickness. The plasma vasopressin level is increased in humans suffering from motion sickness (35), and histaminergic fibers innervate the paraventricular nucleus, which contains vasopressinergic neurons (36). Vasopressin release can be increased by intracerebroventricular administration of histamine, utilizing H_1-receptor (37). Therefore, it also seems likely that mismatch-induced histaminergic ascending input to the paraventricular nucleus causes the oliguria in motion sickness.

2. Mismatch signal and acetylcholine

The efficacy of scopolamine, an antagonist of acetylcholine muscarinic receptors, has been shown to prevent motion sickness in humans (12-14). Accordingly, acetylcholine has been considered to be one of the most important neurotransmitters involved in motion sickness. Morita *et al.* (38) used the rat model of motion sickness and examined the effect of scopolamine on the development of habituation to motion. Rats were rotated in the double rotation mode once a day for more than 10 days. Rats treated with one eighth of a clinical-sized patch of TTS (transdermal therapeutic system)-scopolamine on days 4 to 7 showed progressive decrease of kaolin intake after double rotation, which is an index of motion sickness of rats. When the TTS-scopolamine patch was removed just after rotation on day 7, the residual habituation was more marked than that in the control rats. On day 10, the kaolin intake was still decreased relative to that of the controls (Fig. 6). These findings demonstrate that scopolamine accelerated the processes of habituation to double rotation and is a class B drug (solid line in Fig. 4b). Conversely, physostigmine, a centrally acting cholinesterase inhibitor which increases cholinergic transmission in the brain, was found to delay habituation to double rotation in rats, while the cholinesterase inhibitor neostigmine, which does not act centrally, had no such effect (38). In humans, scopolamine buthylbromide, which cannot cross the blood-brain barrier, is ineffective against motion sickness (12). All of these findings suggest that the cholinergic neuron system in the brain is involved in the processes of habituation to motion sickness.

TTS-scopolamine affords better protection against sea sickness when the period of exposure is longer (39). Clinical trials of long-term use of TTS-scopolamine to prevent sea sickness indicate that its benefical effect is increased when it is applied in the early stage of the trip, before adaptation occurs (40). These clinical observations are consistent with the experimental conclusion that scopolamine facilitates habituation

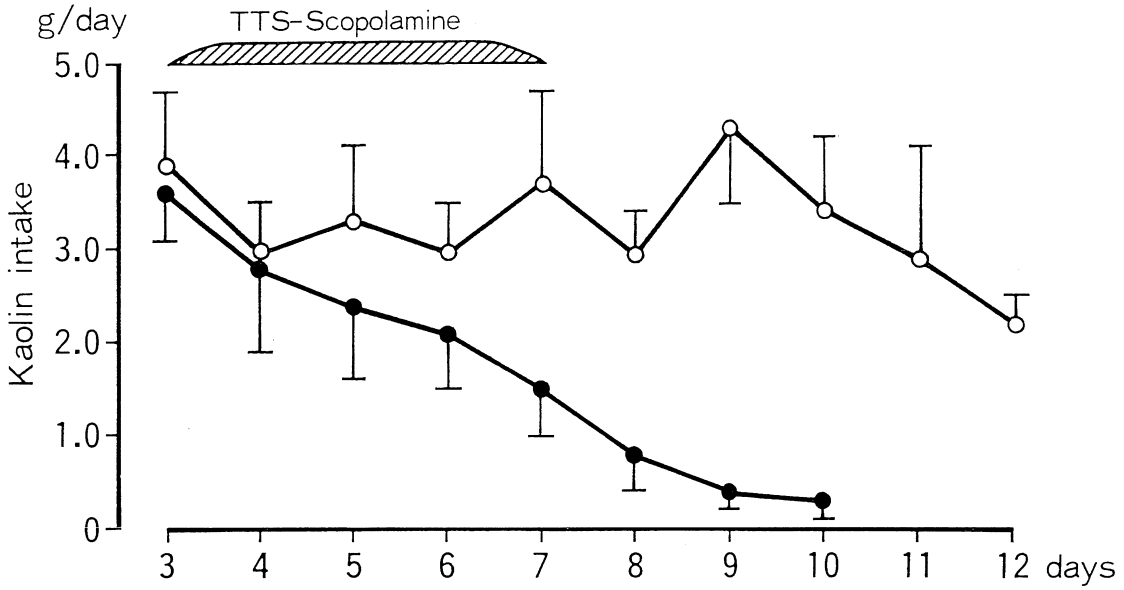

Fig. 6. Effects of TTS-scopolamine on habituation to double rotation in highly susceptible rats. ● : Rats with TTS-scopolamine ; ○ : Control rats. TTS-scopolamine decreased kaolin intake on day 4 to 7. After the TTS-scopolamine patch removed, the kaolin intake of treated rats remained lower than that in the controls. (From Morita et al., 1990 (38) with permission)

to the provocative motion. However, Wood *et al.* (41) reported a controversial set of results regarding the effects of scopolamine on habituation to rotation in humans: the drug was found to accelerate habituation, but a rebound of sensitivity to vestibular stimulation was observed after withdrawal of scopolamine. On the other hand, the clinical finding that scopolamine is much less effective when administered after symptoms have appeared (42) may exclude cholinergic involvement in the symptomatic mechanism of motion sickness.

The two main cholinergic pathways in the brain are the projection from the magnocellular forebrain nuclei to the cerebral cortex and the septo-hippocampal pathway (43, 44). The cerebral cortex and limbic system, particularly the hippocampus, are major sites of spatial orientation information processing (45, 46). It has been shown that the hippocampal cholinergic neuron is activated by auditory and somatosensory stimulation, while the cortical cholinergic system is unaffected (47). Recently, Horii *et al.* (48) using *in vivo* brain microdialysis technique, demonstrated that electrical vestibular stimulation increases the release of acetylcholine from the hippocampus. Thus, the cholinergic septo-hippocampal pathways have an important role in sensory input processing (49).

Although the neural mismatch signal is generated in the region of the brain subserving spatial orientation, the anatomical location is unknown (50-52). Several lines of evidence suggest that the hippocampus can process both spatial and nonspatial information (53). The sensory information processing in the hippocampus, in which novel information is compared with the stored sensory memory (54), seems likely to be responsible for the generation of the neural mismatch signal. Moreover, O'Keefe (55, 56) found "place units" in the hippocampus, which are strongly correlated with the animal's location and proposed the hypothesis that the hippocampus contains a spatial map. There may be an analogy between the neural store and the spatial map in the hippocampus.

Several lines of evidence suggest that the cholinergic neuron system in the hippocampus is involved in learning and memory (57). In a recently proposed model of cholinergic modulation of cortical associative memory function, activation of the cholinergic system facilitates the acquisition of associative memory by enhancing a new input pattern and suppressing previous stored patterns (58, 59). The model can be applied to the neural mismatch hypothesis of motion sickness. The cholinergic neuron system activated by the neural mismatch signal stimulates the acquisition of a new pattern of re-afference and efference copy, resulting in the development of adaptation/habituation (updating the neural store) (Fig. 1). In fact, Horii *et al.* (48) demonstrated that both unilateral stimulation of the canal by hot water irrigation of the middle ear and unilateral suppression of the canal by ice water increased the acetylcholine release from the hippocampus (Fig. 7), suggesting that the neural mismatch signal activates the hippocampal cholinergic neuron system.

The model also indicates that cholinergic antagonists would impair the discrimination of stored sensory patterns (58, 59). In the case of scopolamine, the drug would prevent identification of the expected afference previously associated with efference copy from the neural store. Re-afference without the expected afference

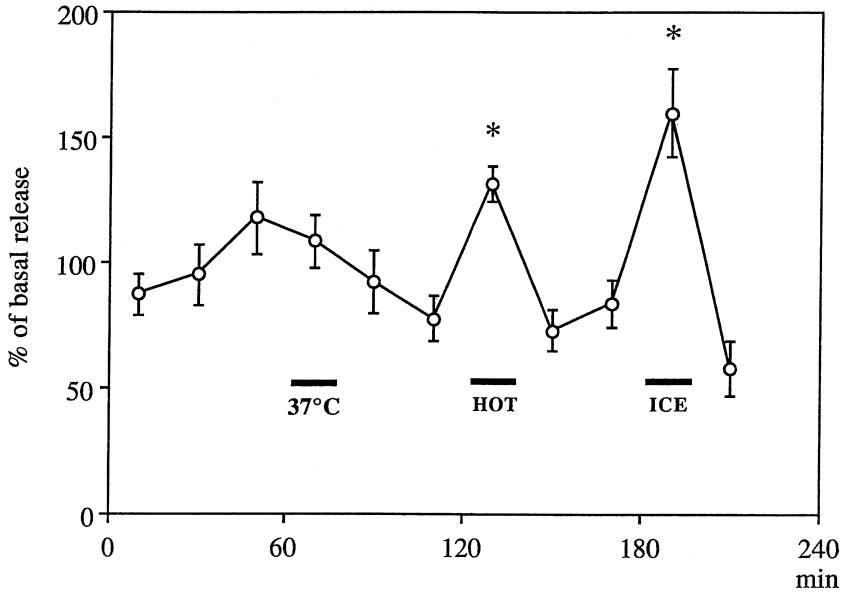

Fig. 7. Effects of caloric stimulation on acetylcholine release from the hippocampus in rats. Irrigation with hot water or ice water, but not that with 37°C water, of the middle ear increased the acetylcholine release. *p<0.01 vs. the release before the evoked release. (From Horii et al., 1994 (48) with permission)

does not activate the comparator nor generate the neural mismatch signal. Thus, it is likely that scopolamine prevents motion sickness by reducing the neural mismatch signal (Fig. 1). In the adaptation/habituation processes in motion sickness, unpredictable passive motion generates the neural mismatch signal, which updates the neural store. On the other hand, during the acquisition of motor skills and control in early childhood, the newly acquired but as yet unfamiliar locomotion does not generate the neural mismatch signal, because the expected afference associated with the efference copy of the locomotion command is not yet available in the neural store. Re-afference without the neural mismatch signal would be directly registered in the neural store in association with the efference copy, leading to the developmental acquisition of locomotion observed in infancy. If the suggestion that scopolamine reduces the neural mismatch signal is correct, then the neural store acquisition of a new association of re-afference and efference copy induced by scopolamine would more rapid than that resulting from mismatch-induced updating. Thus, the cholinergic model of associative memory could also account for the prevention of motion sickness and facilitation of the processes of adaptation/habituation induced by scopolamine.

The ventral tegmental nucleus (VT) is a midbrain core structure of the limbic system and is responsible for the transfer of sensory information arising from the brain stem to limbic forebrain structures (60). Irle *et al*. (61) reported monosynaptic innervation from the vestibular nuclei to the VT in mice, rats and cats. Therefore, vestibular information may enter the hippocampus via the VT. On the other hand, Erickson *et al*. (62) reported that the afferent connections of the hypothalamic tuberomammillary nucleus, which contains histaminergic neurons, arise from the limbic system. This pathway may transmit the neural mismatch signal generated in the hippocampus to the hypothalamic histaminergic system as the trigger in the emetic linkage processes. Preliminary experiments have demonstrated that AF64A, which degenerates cholinergic neurons, suppresses the vestibular-evoked histamine release from hypothalamus, while depletion of histamine by FMH does not affect acetylcholine release from the hippocampus induced by vestibular stimulation in rats (63). The findings suggest transmission from cholinergic to histaminergic processes in the development of motion sickness.

Another candidate as the comparator and neural store is the cerebellum, which receives signals from the vestibular nuclei and other sensory inputs (52). Recent immunohistochemical study demonstrated that cholinergic mossy afferents to the vestibular cerebellum arise from the medial vestibular nucleus and prepositus hypoglossal nucleus (64). Since muscarinic receptors are concentrated in the vestibular cerebellum (65), scopolamine as an anti-motion sickness drug may act on the cerebellum. However, it is unclear whether the cerebellum is (66) or is not (67) essential in the development of motion sickness. Recently, Uno *et al*. (68) used a rat model of motion sickness and examined the effects of vestibular cerebellum lesion on the development of motion sickness. Their findings that surgical ablation of the bilateral cerebellar flocculus and the cerebellar vermis had no effects indicated that the vestibular cerebellum does not play an essential role in the development of motion sickness.

3. Sensory processing and noradrenaline

Amphetamine is used clinically as an anti-motion sickness drug (12-14), and has also been observed to prevent motion-induced pica as an index of motion sickness in rats (19). Because amphetamine activates the catecholaminergic neuron system with resulting increase in the release of noradrenaline and dopamine from the nerve terminals (69), the noradrenergic and dopaminergic neuron system in the brain has been thought to contribute to the therapeutic effect of amphetamine on motion sickness. Wood and Graybiel (13) have hypothesized that the action of noradrenergic neuron system in the brain is antagonistic to the development of motion sickness. However, there is no direct evidence for their hypothesis. Takeda *et al*. (70) used the rat model to examine the neurochemical effects of motion sickness-inducing rotational stimulation on the activity of the noradrenergic neuron system in the brain stem. They found that both single and double rotation increased the turnover of noradrenaline, suggesting that rotational stimulation activates the noradrenaline system in the brain stem. However, as double rotation induces motion sickness whereas single rotation does not, increased noradrenergic activity in the brain stem seems unlikely to be directly related to the development of motion sickness. These findings do not support the hypothesis of Wood and Graybiel (13). Histochimical studies indicate that the vestibular nuclei and brain stem reticular formation contains only a few noradrenergic fibers (25, 71). Electrophysiologically, conditioning stimulation of the locus coeruleus (LC), which is the largest nucleus of central noradrenergic neurons in the brain, has no effect on the neural activity in the lateral vestibular nucleus in cats (72). These

findings are further evidence that the noradrenergic neuron system in the brain stem is not important in the development of motion sickness.

Recently, Nishiike *et al*. (73) recorded the electrical activity of noradrenergic neurons of the LC in rats and examined the effects of unilateral caloric stimulation on their activity. Both activation of the canal by hot water irrigation and inhibition by cold water irrigation suppress LC neuronal activity (Fig. 8). On the other hand, it has been reported that noradrenergic neurons in the LC are periodically activated during sinusoidal body tilt in cats (74). Since unilateral caloric stimulation causes nausea and vomiting like the symptoms of motion sickness, while sinusoidal body tilt does not, it is suggested that the neural mismatch signal suppresses the noradrenergic neurons of the LC (Fig. 1). Nishiike *et al*. (73) also reported that the inhibitory response of LC neurons to caloric stimulation is blocked by iontophoretic application of bicuculline, a $GABA_A$-receptor antagonist, indicating that the inhibition of LC neurons by caloric stimulation is mediated by $GABA_A$-receptors. Anatomical and electrophysiological studies have demonstrated GABAergic input from the prepositus hypoglossal nucleus (PrH) to the LC via $GABA_A$-receptors (75, 76). Since PrH neurons receive vestibular input, it is possible that GABAergic neurons in PrH contribute to the LC neuronal inhibition. However, the possibility is unlikely, because lesions in PrH did not attenuate the inhibitory response of LC neurons induced by caloric stimulation (77). Another major input to the LC is the pathway from the ventrolateral medulla (VLM) (75, 76). Recently, Nishiike *et al*. (78) reported that electrical and chemical lesions in VLM attenuated the LC inhibition in response to caloric stimulation, suggesting that VLM is the origin of inhibitory vestibular input to the noradrenergic neurons in LC. Therefore, it is suggested that the neural mismatch signal activates the VML, leading to inhibition of noradrenaline-containing LC neurons via $GABA_A$-receptors (Fig. 1).

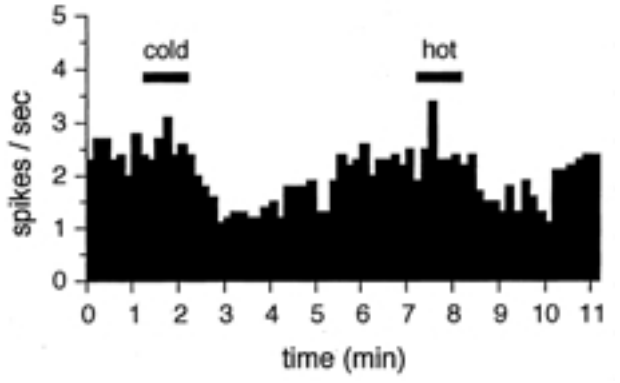

Fig.8. Effects of caloric stimulation on the neural activity of the locus coeruleus (LC) in rats. LC neural activity was suppressed in response to both hot and cold water irrigation of the middle ear.

In addition to nausea and vomiting, drowsiness is an important symptom commonly associated with motion sickness. A symptom complex concerning around drowsiness has been termed the sopite syndrome (79). Drowsiness of the sopite syndrome of motion sickness persists long after the nausea and vomiting have subsided. The LC participates in inducing arousal (80). The long-lasting inhibition of LC neurons is induced by caloric vestibular stimulation (73). Therefore, the suppression of the noradrenergic neuron system during vestibular stimulation may account for the sopite syndrome.

In addition to amphetamine, central nervous system stimulants, which facilitate noradrenergic transmission, such as pemolin and methylphenidate, are also effective in preventing motion sickness (81). Nonspecific sources of arousal, which activate the noradrenergic neuron system, are also effective (1). Therefore, it is likely that amphetamine or other psychostimulants antagonize mismatch-induced suppression of the noradrenergic neuron system and induce recovery of the arousal state, resulting in prevention of motion sickness.

Why does the neural mismatch signal suppress the noradrenergic neuron system? Electrophysiological studies have demonstrated that LC neurons are activated by many kind of sensory stimuli, including visual, auditory and somatosensory stimuli (82). This broad spectrum of sensory responses, together with the widespread efferent projections from the LC, suggests that the noradrenergic neuron system plays an important role in central sensory information processing. Moreover, recent studies have suggested that LC neurons are involved in the selective attention in selective sampling of sensory stimuli (83). According to an evolutionary hypothesis of motion sickness (84), the mechanisms underlying motion sickness constitute a warning system, which protects the body against neurotoxins, such as toadstool. Treisman (84) postulates that absorbed neurotoxins affect sensory inputs or motor coordination, leading to generation of the neural mismatch signal. An emetic response as a protective reflex would be induced by neurotoxins ingested by chance, but also inadvertently by provocative stimuli, such as vehicular travel. If this suggestion is correct, suppression of the noradrenergic neuron system induced by the neural mismatch signal would shift attention from discordant sensory inputs, which

are not novel stimuli to be attended, but disturbances to be ignored.

Dopamine D_2-receptor in the chemoreceptor trigger zone (CTZ) in the area postrema has been established to play a role in vomiting and nausea (85) (Fig. 9). Domperidone and metochropramide, which are D_2-antagonists, inhibit emesis by inhibiting the CTZ. However, these D_2-antagonists have no effect on motion sickness in humans (86) or in rats (87). Nevertheless, the possibility of the involvement of the dopaminergic neuron system in motion sickness cannot be excluded, because amphetamine, an effective anti-motion sickness drug, enhances dopaminergic transmission as well as noradrenergic transmission (69). Takeda, *et al*. (70) examined the effect of rotation on the turnover of dopamine in the rat brain stem. Both double rotation, which induces motion sickness, and single rotation, which do not, increased the turnover of dopamine. Thus, the dopaminergic neuron system in the brain stem seems unlikely to play a role in motion sickness.

INDIVIDUAL SUSCEPTIBILITY

Considerable individual differences have been found in susceptibility to motion sickness upon exposure to provocative motion (1, 2). In the general population, age and sex are known to contribute to this variation in susceptibility : motion sickness is rare in those below the age of 2 years and above the age of 50 years, but is more common in women than in men of the same age. However, there are also individual differences in susceptibility within groups of men or women of the same age.

Three hypothetical factors, i.e., receptivity, adaptability, and retentivity, have been proposed to account for variation in susceptibility to motion sickness (88) (Table 1). Receptivity refers to the processing of information in the brain. In persons with high receptivity, transduction and processing of sensory stimuli are thought to be more effective. Hence, when receptive individuals are exposed to provocative motion, the intensity of the neural mismatch signal is thought to be greater, with greater likelihood of develop-

Table 1. Factors influencing individual differences of susceptibility to motion sickness

1. Receptivity
2. Adaptability
3. Retentivity
4. Sensitivity of the emetic center

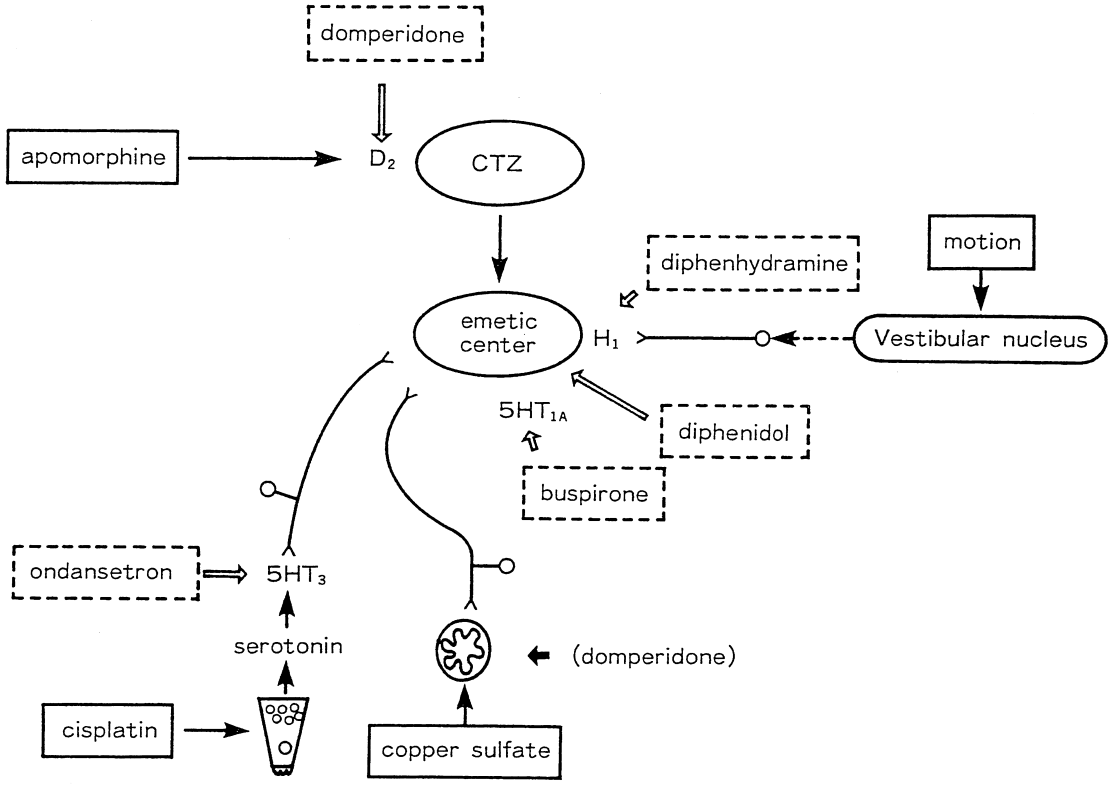

Fig. 9. Neuropharmacological mechanisms underlying the emetic reflex. CTZ : chemoreceptor trigger zone ; H_1 : histamine H_1-receptor ; D_2 : dopamine D_2-receptor ; $5HT_{1A}$: serotonin $5HT_{1A}$-receptor ; $5HT_3$: serotonin $5HT_3$-receptor. (From Takeda et al., 1993 (29) with permission)

ment of motion sickness than that in non-receptive individuals. Adaptability refers to the rate at which the individual adapts to provocative motion. Those who low adaptability would be more likely to suffer from motion sickness than those with high adaptability. Retentability refers to the duration of retention of adaptation after exposure to provocative motion. Having once adapted to provocative motion, persons with high retentability would remain less susceptible than those with low retentability. Hasegawa *et al*. (89) added recently the sensitivity of the emetic center as another factor which may influence susceptibility to motion sickness (Table 1). They found a wide variation in susceptibility to motion sickness using the rat model. They then found significant positive correlations between susceptibility to motion sickness and to emesis induced by apomorphine and copper sulfate. Since motion, apomorphine and copper sulfate induce emesis through different receptors (Fig. 9), the findings suggest that the sensitivity of a common locus of emesis, presumably the emetic center in the brain stem, is one determinant of individual differences in susceptibility to motion sickness. When exposed to many kinds of emetic stimuli, including provocative motion, persons with high sensitivity of the emetic center may have low threshold for the emetic response, and may vomit or feel nausea more frequently than persons with low sensitivity. Clinically, Morrow (90) reported that patients with a history of motion sickness were significantly more susceptible to chemotherapy-induced nausea and vomiting than those without such a history. These four factors may all contribute to various degrees to the susceptibility to motion sickness of a given individual.

PREVENTION AND TREATMENT

The development of motion sickness involves the three steps of sensory processing, generation of the neural mismatch signal, and the emetic linkage. Blockade of any step can be used to prevent or treat motion sickness (Table 2).

Table 2. Prevention and treatment of motion sickness

1. Blockade of the emetic linkage
Antihistamines (H_1-receptor antagonist), diphenidol
2. Reduction of mismatch signal size
TTS-scopolamine
Training for adaptation to provocative motion
3. Modification of sensory input
Restriction of head movement
Learned postural adjustment
Avoidance of discordant visual cue
Amphetamin or other psychostimulants

1. Blockade of the emetic linkage

Antihistamines (H_1-antagonists) have been demonstrated to be effective in preventing and controlling motion sickness. The effective dose is 50 mg for diphenhydramine or 25 mg for promethazine (13). Since the histaminergic neuron system is involved in the symptomatic mechanism of motion sickness via H_1-receptors, antihistamines reduce the severity of the symptoms and signs of motion sickness by blocking the emetic linkage between the neural mismatch signal and the emetic center (Figs. 1 & 9). Therefore, antihistamines are effective, even if administered after nausea or vomiting has developed. The side effect of antihistamines at effective dose is sedation, which is to be avoided in crew-members but may be useful in passengers.

If an anti-emetic drug inhibits the emetic center itself, it would be effective in preventing emesis due to all causes, including motion sickness. It is conceivable that diphenidol may be a drug of this kind (Fig. 9). Takeda *et al*. (91) demonstrated that diphenidol suppressed all motion-, apomorphine and cisplatin-induced pica analogous to emesis in rats. Diphenidol is clinically effective in preventing motion sickness (13) and emesis induced by levodopa, which acts on the CTZ (92). Diphenidol has also been found to be beneficial in patients receiving cisplatin (93). However, the specific receptor for diphenidol remains unknown. Diphenidol used at the dose of 50 mg is as effective as antihistamines. Lucot & Crampton (94) have shown that 8-OH-DPAT, a serotonin $5HT_{1A}$-receptor agonist, suppressed the vomiting induced by motion, cisplatin, and xylazine in cats, suggesting that this agent acts on the emetic center (Fig. 9). However, the efficacy in motion sickness of buspirone, a clinically used $5HT_{1A}$ agonist, has not been reported.

Dopamine D_2-receptor antagonists such as domperidone and metochropramide are clinically used as anti-emetic drugs. D_2-antagonists inhibit emesis by inhibiting the CTZ in the area postrema. However, these D_2-antagonists have no effect on motion sickness in humans (86) or in rats (87). Serotonin $5HT_3$-receptor antagonists such as ondansetron and granisetron are effective for preventing emesis induced by anti-cancer therapy (95). However, $5HT_3$-antagonists have no prophylactic effect against motion-induced emesis in humans (96) and rats (97). Thus, H_1-, D_2- and 5 HT_3-receptors are

independently involved in the emetic reflex (Fig. 9).

2. Reduction of mismatch signal size

Scopolamine has been shown to have a prophylactic effect against motion sickness, but it is less useful in controlling established motion sickness. Scopolamine administered orally or intramuscularly is less effective, because of its short half-life in the serum. The disadvantage has been overcome with the development of a transdremal therapeutic system for administration of scopolamine in the form of TTS-scopolamine (97). The effect of TTS-scopolamine is like that of continuous intravenous infusion : scopolamine is released into the systemic circulation gradually and an effective serum concentration is maintained. The incidence of side effects (such as dry mouth and drowsiness etc.) associated with TTS-scopolamine is lower than that associated with orally or intramuscularly administered scopolamine, and it is equally efficacious in preventing motion sickness. The cholinergic model of associative memory suggests that scopolamine prevents motion sickness by reducing the neural mismatch signal and by facilitating the adaptation/habituation processes. Therefore, scopolamine should be administrated prior to exposure to provocative motion to obtain better protection.

The most potent therapeutic measure, at least in the long term, is adaptation to the provocative motion, and it is the preferred method of preventing motion sickness, particularly for crew-members (2, 98). For the acquisition and maintenance of protective adaptation, the individual should be gradually exposed to the provocative motion. Once adaptation is achieved, regular and repeated exposure to the motion stimuli should be maintain. Anti-motion sickness drugs, especially scopolamine, may aid the adaptation method by accelerating the acquisition of protective adaptation.

3. Modification of sensory input

Some behavioral measures prevent motion sickness by modifying the sensory pattern, which is responsible for the neural mismatch signal. Head movement should be reduced to a minimum. The restriction of head movements during acceleration in vehicles helps to prevent motion sickness because additional complex set of stimulation, such as cross-coupled acceleration, are avoided. Learned postural adjustment, which counter-regulates the body oscillations induced by vehicular acceleration, is also helpful (99). Discordant visual cues should also be minimized. For example, reading a book or looking at a map in a moving vehicle should be avoided, because visual/vestibular conflict inputs are responsible for the neural mismatch signal.

Amphetamine and psychostimulants have been demonstrated to be effective in preventing motion sickness. In particular, the combination of methamphetamine with scopolamine (13) or with promethazine (14) is the most effective for prophylaxis. It is suggested that general arousal activated by amphetamine prevents motion sickness. Amphetamine is especially effective in relieving the drowsiness of sopite syndrome of motion sickness (100).

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