Basic and Applied Aspects of Vestibular Function
J.C. Hwang, N.G. Daunton and V.J. Wilson (Eds.)

THE EFFECTS OF AREA POSTREMA LESIONS AND SELECTIVE VAGOTOMY ON MOTION-INDUCED CONDITIONED TASTE AVERSION

R.A. Fox*, R.L. Sutton** and S. McKenna*

**Department of Psychology, San Jose State University, San Jose, CA 95192, U.S.A.;*
*** Mental Retardation Research Center, Center for the Health Sciences, 760 Westwood Plaza, University of California, Los Angeles, CA 90024, U.S.A.*

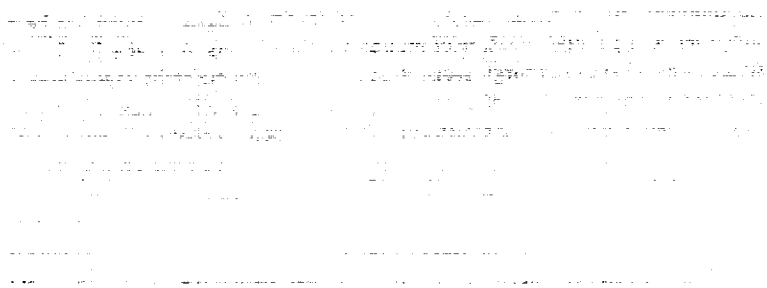
Abstract

Conditioned taste aversion (CTA) is one of several behaviors which has been suggested as a putative measure of motion sickness in rats. A review is made of studies which have used surgical disruption of area postrema or the vagus nerve to investigate whether CTA and vomiting induced by motion may depend on common neural pathways or structures. When the chemoreceptive function of the area postrema (AP) is destroyed by complete ablation, rats develop CTA and cats and monkeys develop CTA and vomit. Thus the AP is not crucially involved in either CTA or vomiting induced by motion. However, after complete denervation of the stomach or after labyrinthectomy rats do not develop CTA when motion is used as the unconditioned stimulus. Studies of brainstem projections of the vagus nerve, the area postrema, the periaqueductal grey, and the vestibular system are used as the basis for speculation about regions which could mediate both motion-induced vomiting and behavioral food aversion.

Introduction

Animals commonly avoid the ingestion of foods treated with non-lethal doses of poison. The laboratory study of this phenomenon has led to the development of specialized procedures for investigating the role learning plays in this behavioral aversion to poisoned food. These procedures commonly are referred to as the 'conditioned taste aversion paradigm'. In typical applications of this paradigm a previously novel food is ingested just prior to poisoning. This 'pairing' of food with the effects of poisoning results in a strong, long-lasting avoidance of

Keywords: conditioned taste aversion, vomiting, area postrema, vagus nerve, reticular formation, vestibular system, periaqueductal grey, nucleus tractus solitarius



Neural Structures

Surgical lesions have been used in numerous experiments to investigate the neural structures crucial to CTA and vomiting. Usually, such studies have been used to investigate the effects of lesions on vomiting or on CTA independently, but not upon both responses simultaneously. Many of these studies have focused upon the AP and the vagus nerve. Thus, in independent studies it has been shown that the AP is critically involved in the emetic and in the conditioning efficacy of certain toxins. These effects commonly are attributed to a chemoreceptive function of the AP (Coil and Norgren, 1981; Carpenter *et al.*, 1983; Borison *et al.*, 1984). In addition, involvement of the vagus nerve has been shown in both vomiting (Borison, 1952) and CTA (Coil *et al.*, 1978; Rabin *et al.*, 1985) induced by intra-gastric copper sulfate.

Studies conducted as direct examinations of the role of the AP and the vagus nerve in motion-induced CTA and as simultaneous evaluations of the relationship been CTA and vomiting have occurred only recently. It has been known for some time that rotation could be used as a US to induce CTA in rats (Braun and McIntosh, 1973; Green and Rachlin, 1973). Because the AP had long been thought necessary for motion-induced vomiting in dog, cat, and monkey, and because the AP was known to be involved critically in the induction of CTA by certain toxins and radiation, the role of the AP in motion-induced CTA was investigated first. Ossenkopp (1983) reported that rats with the AP ablated formed a stronger CTA than unoperated rats when saccharin was paired with motion. He proposed that this enhanced CTA could have occurred because ablation of AP influenced the intake of the saccharin (a preferred fluid) which was used as a CS. A second study (Sutton *et al.*, in press) also demonstrated that motion can be used to induce CTA in rats with the AP ablated, but did not find enhanced CTA in ablated rats when a cider vinegar solution was used as the CS. In these two studies conditioning failed to occur when blood-borne toxins were used as the US (scopolamine methyle nitrate and lithium chloride, respectively), thereby indicating that the chemoreceptive function of the AP was eliminated by the ablations. Thus, in rats, the AP apparently is not a chemoreceptive site of action for a neurohumoral substance critical to motion-induced CTA.

Recent ablation studies have demonstrated clearly that the AP is not required for motion-induced vomiting in cats (Corcoran *et al.*, 1985; Borison and Borison, 1986) or squirrel monkeys (Elfar *et al.*, 1986; Wilpizeski *et al.*, 1986). Vomiting and CTA have been assessed in the same animals after ablation of the AP in three experiments. After ablation of the AP in cats, neither vomiting nor CTA was produced by a dose of xylazine which reliably produces vomiting in cats (Corcoran *et al.*, 1985). Vertical linear acceleration did produced vomiting on some trials, and CTA was produced when this motion was used as the US with these same AP-ablated cats. In squirrel monkeys with AP ablated, CTA was not produced by an intraperitoneal injection of LiCl, a chemical which requires an intact AP to produce CTA in rats (Ritter *et al.*, 1980; Sutton *et al.*, in press). However, these same monkeys vomited in some tests when exposed to vertical axis rotation, and CTA was produced by this motion stimulation (Elfar *et al.*, 1986). In the second study with squirrel monkeys, conditioned aversion was not investigated with chemical toxicosis, but rotation did produce CTA in monkeys with the AP ablated (Wilpizeski *et al.*, 1986). These studies provide additional support for an important chemoreceptive function of the AP in both emesis and CTA induced

by certain chemicals, and they simultaneously demonstrate that the emetic and taste aversion-producing properties of motion are not crucially dependent upon this chemoreceptive function of the AP.

The effect of disruption of the vagus nerve upon motion-induced CTA has been reported only in rats (Fox and McKenna, in press). In this experiment gastric denervation was accomplished by sectioning the anterior branch of the vagus distal to the hepatic branch, ligating and sectioning the posterior branch and the gastric artery proximal to the esophagogastric junction and then sectioning vagal branches in the region of the cardiac sphincter and along the greater curvature of the stomach. After this selective gastric vagotomy CTA was not produced when vertical axis rotation was the US. Animals in a control group subjected to ligation of the gastric artery and posterior vagus developed a CTA equal in magnitude to the aversion developed in unoperated animals. Becuase of this effect, it was proposed that either the anterior vagus, the sympathetic fibers, or both are crucial for motion to be an effective US for CTA in rats. Thus, while ablation of the AP has no apparent effect upon CTA produced by motion in rats, cats, or squirrel monkeys, the efficacy of rotation as a US for CTA in rats is disrupted after complete gastric denervation. The possibility that vagal pathways might be shared by CTA and vomiting could not be addressed directly in this experiment because rats are incapable of vomiting.

These investigations have shown that the AP plays no critical role in motion-induced CTA or vomiting. In some studies it was shown that motion produced both vomiting and CTA after the chemosensory function of the AP was eliminated by ablation. Thus, as has been asserted for vomiting (Borison, 1985), CTA induced by motion apparently does not depend upon a humoral factor acting on the AP. The question of whether CTA and vomiting depend upon common neural structures remains unanswered by these studies because both responses were unaffected by ablation of the AP.

Inferences regarding a role for gastric innervation can be only speculative at this time. Gastric denervation eliminates the efficacy of motion as a US for CTA in the rat, but the processes underlying this effect are unclear. Both afferent and efferent vagal functions were eliminated by gastric denervation, and secondary effects of this disruption on the CNS were not assessed. In addition, the magnitude of CTA produced by motion is reduced greatly when the labyrinth is destroyed in rats (Hartley, 1977). Thus, both labyrinthine and gastric systems contribute critically to the support of CTA induced by motion, and neither vestibular nor gastric inputs to the CNS alone is adequate for the production of CTA when motion in the US in the rat. Because CTA can be produced by motion only when both systems are intact, it seems that vagal and labyrinthine circuity either must converge in some CNS region which is necessary for the support of motion-induced CTA, or alternatively, some form of modulation occurs between the two systems. Caloric stimulation of the labyrinth influences the rate of efferent activity in the vagus nerve of rats (Niijima *et al.*, 1988), and, in man, gastric emptying is delayed and duodenal motility is reduced by vestibular stimulation (Thompson *et al.*, 1982), further indicating interaction of the two systems.

A CNS locale where vagal and vestibular fibers may interact is unknown. Vagal afferents project to the subnucleus gelatinosus, the medial NTS, and the commissural NTS (Leslie *et al.*, 1982; Shapiro and Miselis, 1985). Dendrites of dorsal motor nucleus neurons have been reported to be co-distributed with these afferent projections and to penetrate the ependyma of the fourth ventricle and the ventral aspect of the AP. This co-distribution of afferent and

efferent components of the gastric vagus has been suggested as a possible locale for monosynaptic vagovagal interactions (Shapiro and Miselis, 1985). It has also been shown that cells in the medial half of the medullary parvicellular reticular formation (PCRF) project to the caudal solitary and vagal nuclei in the cat (Mehler, 1983). The PCRF is a site of origin of efferent fibers projecting to the vestibular sensory epithelium and it has been speculated that these efferents may contribute to a vomiting trigger zone circuit via the generation of a mismatch signal with vestibular afferent signals (Goldberg and Fernández, 1980; Mehler, 1983). The PCRF also receives projections from the periaqueductal grey, a necessary structure for the production of CTA when morphine is the US (Blair and Amit, 1981).

Conclusions

These studies demonstrate that neural fibers associated with the periaqueductal grey, the vestibular system, the AP, and the stomach, four structures which have been demonstrated to be important to CTA produced by various USs, are found in the NTS and PCRF. The NTS and PCRF are characterized by complicated interconnections locally, and with higher brain structures as well, so the neural events critical to the formation of CTA could interact in these regions. However, specific interconnections important to such interaction have not been identified. This area of the PCRF also is the general region identified as a vomiting trigger zone (Borison and Wang, 1949; see also Miller and Wilson, 1983). Thus, neural pathways or structures important to both CTA and vomiting could coexist in this general region. Whether common neural pathways or a discrete nuclear group of cells co-ordinating these two responses to motion exist remains to be demonstrated. Both responses are complex, involving many muscular events, and it may not be possible to identify a 'neural center' co-ordinating such responses. However, multidisciplinary research employing present technology for immunohistochemistry, electron microscopy, electrophysiology, biochemistry, and neuroanatomy portends the opening of new vistas for the understanding of the neural events underlying these behaviors.

Acknowledgements

This work was supported in part by NASA-Ames Cooperative Agreement NCC 2-167 to the San Jose State University Foundation.

References

1. Ashe, J.H. and Nachman, M. (1980). Neural mechanisms in taste aversion learning. *Progress in Psychobiology and Physiological Psychology*, 9, 233-62.
2. Blair, R. and Amit, Z. (1981). Morphine conditioned taste aversion reversed by periaqueductal gray lesions. *Pharmacol. Biochem. Behav.*, 15, 651-53.
3. Borison, H.L. (1952). Role of gastrointestinal innervation in digitalis emesis. *J. Pharmacol. Exp. Ther.*, 104, 396-403.

4. Borison, H.L. (1985). A misconception of motion sickness leads to false therapeutic expectations. *Aviat. Space. Environ. Med.*, 56, 66-68.
5. Borison, H.L. and Borison, R. (1986). Motion sickness reflex arc bypasses the area postrema in cats. *Exp. Neurol.*, 92, 723-37.
6. Borison, H.L., Borison, R. and McCarthy, L.E. (1984). Role of the area postrema in vomiting and related functions. *Fed. Proc.*, 43, 2955-58.
7. Borison, H.L. and Wang, S.C. (1949). Functional localization of central co-ordinating mechanism for emesis in cat. *J. Neurophysiol.*, 12, 305-13.
8. Braun, J.J. and McIntosh, H., Jr. (1973). Learned taste aversions induced by rotational stimulation. *Physiol. Psychol.*, 1, 301-304.
9. Carpenter, D.O., Briggs, D.G. and Strominger, N. (1983). Responses of neurons of canine area postrema to neurotransmitters and peptides. *Cell. Mol. Neurobiol.*, 3, 113-26.
10. Coil, J.D. and Norgren, R. (1981). Taste aversions conditioned with intravenous copper sulfate: Attenuation by ablation of the area postrema. *Brain. Res.*, 212, 425-33.
11. Coil, J.D., Rogers, R.C., Garcia, J. and Novin, D.L. (1978). Conditioned taste aversions: Vagal and circulatory mediation of the toxic unconditioned stimulus. *Behav. Biol.*, 24, 509-19.
12. Corcoran, M., Fox, R., Brizzee, K., Crampton, G. and Daunton, N. (1985). Area postrema ablations in cats: Evidence for separate neural routes for motion- and xylazine-induced CTA and emesis. *Physiologist*, 28, 330.
13. Elfar, S., Brizzee, K., Fox, R., Corcoran, M., Daunton, N. and Coleman, J. (1986). Recovery of the vomiting reflex following area postrema ablation in squirrel monkeys. *Soc. Neurosci. Abstr.*, 12, 885.
14. Fox, R.A. and McKenna, S. Conditioned taste aversion induced by motion is prevented by selective vagotomy in the rat. *Behav. Neural Biol.* (In press).
15 Garcia, J. and Ervin, F.R. (1968). Gustatory-visceral and telereceptor-cutaneous conditioned adaptation in internal and external milieus. *Communications in Behavioral Biology*, 1, 389-415.
16. Garcia J., Hankins, W.G. and Rusiniak, K.W. (1974). Behavioral regulation of the milieu interne in man and rat. *Science*, 185, 824-31.
17. Goldberg, J.M. and Fernández, C. (1980). Efferent vestibular system in the squirrel monkey: Anatomical location and influence on afferent activity. *J. Neurophysiol.*, 43, 986-1025.
18. Green, L. and Rachlin, H. (1973). The effect of rotation on the learning of taste aversions. *Bull. Psychon. Soc.*, 1, 137-38.
19. Hartley, P.L. (1977). Motion-induced learned taste aversions in rats and the role of the area postrema. Riverside: University of California. (Unpublished dissertation).
20. Leslie, R.A., Gwyn, D.G. and Hopkins, D.A. (1982). The central distribution of the cervical vagus nerve and gastric afferent and efferent projections in the rat. *Brain Res.*, 8, 37-43.
21. Mehler, W.R. (1983). Observations on the connectivity of the parvicellular reticular formation with respect to the vomiting center. *Brain Behav. Evol.*, 23, 63-80.
22. Miller, A.D. and Wilson, V.J. (1983). 'Vomiting center' reanalyzed: An electrical stimulation study. *Brain Res.*, 270, 154-58.

23. Mitchell, D., Krusemark, M.L. and Hafner, E. (1977a). Pica: A species relevant behavioural assay of motion sickness in the rat. *Physiol. Behav.*, 18, 125-30.
24. Mitchell, D., Laycock, J.D. and Stephens, W.F. (1977b). Motion sickness induced pica in the rat. *Am. J. Clin. Nut.*, 30, 147-50.
25. Niijima, A., Jiang, Z.-Y., Daunton, N.G. and Fox, R.A. (1988). Experimental studies on gastric dysfunction in motion sickness: The effect of gastric and vestibular stimulation on the vagal gastric efferents. In J.C. Hwang, N.G. Daunton and V.J. Wilson (Eds.), *Basic and Applied Aspects of Vestibular Function*. Hong Kong: Hong Kong University Press, pp. 133-42.
26. Ossenkopp, K-P. (1983). Area postrema lesions in rats enchance the magnitude of body rotation-induced conditioned taste aversions. *Behav. Neural Biol.*, 38, 82-96.
27. Rabin, B.M., Hunt, W.A. and Lee, J. (1985). Intragastric copper sulfate produces a more reliable conditioned taste aversion in vagotomized rats than in intact controls. *Behav. Neural Biol.*, 44, 364-73.
28. Ritter, S., McGlone, J.J. and Kelley, K.W. (1980). Absence of lithium-induced taste aversion after area postrema lesion. *Brain Res.*, 201, 501-506.
29. Roy, M.A. and Brizzee, K.R. (1979). Motion sickness-induced food aversions in the squirrel monkey. *Physiol. Behav.*, 23, 39-41.
30. Shapiro, R.E. and Miselis, R.R. (1985). The central organization of the vagus nerve innervating the stomach of the rat. *J. comp. Neurol.*, 238, 473-88.
31 Sutton, R.L., Fox, R.A. and Daunton, N.G. Role of the area postrema in three putative measures of motion sickness in the rat. *Behav. Neural Biol.* (In press).
32. Thompson, D.G., Richelson, E. and Malagelada, J-R. (1982). Perturbation of gastric emptying and duodenal motility through the central nervous system. *Gastroenterology*, 83, 1200-1206.
33. Wallace, P. (1976). Animal behavior: The puzzle of flavor aversion. *Science*, 193, 989-91.
34. Wilpizeski, C.R., Lowry, L.D. and Goldman, W.S. (1986). Motion-induced sickness following bilateral ablation of area postrema in squirrel monkeys. *Laryngoscope*, 96, 1221-25.

Basic and Applied Aspects of Vestibular Function
J.C. Hwang, N.G. Daunton and V.J. Wilson (Eds.)

EXPERIMENTAL STUDIES OF GASTRIC DYSFUNCTION IN MOTION SICKNESS: THE EFFECT OF GASTRIC AND VESTIBULAR STIMULATION ON THE VAGAL AND SPLANCHNIC GASTRIC EFFERENTS

A. Niijima*, Z.Y. Jiang*, N.G. Daunton** and R.A. Fox***

**Department of Physiology, Niigata University School of Medicine, Niigata 951, Japan;*
***Neurosciences Branch, National Aeronautics and Space Administration (NASA) – Ames Research Center, Moffett Field, CA 94035, U.S.A.; and*
**** Department of Psychology, San Jose State University, San Jose, CA 95192, U.S.A.*

Abstract

The experiments were conducted in anaesthetized rats. In the first part of the experiments, the effect of $CuSO_4$ on the afferent activity in the gastric branch of the vagus nerve was investigated. Gastric perfusion of $CuSO_4$ solution (0.04% and 0.08%) provoked an increase in afferent activity. In the second part of the experiments, the reflex effects of gastric perfusion of $CuSO_4$ solution, repetitive stimulation of the gastric vagus nerve, and caloric stimulation of the right vestibular apparatus (5-18°C water) on gastric autonomic outflow were investigated. The results of these experiments showed that these three different types of stimulation caused an inhibition in efferent activity of the gastric vagus nerve and a slight activation of the splanchnic gastric efferents. The summation of the effect of each stimulation was also observed. These results, therefore, provide evidence for a possible integrative inhibitory function of the vagal gastric center as well as an excitatory function of gastric sympathetic motoneurons in relation to motion sickness.

Introduction

It has been generally recognized that nausea and emesis with gastric dysfunction are the main symptoms of space and motion sickness. It is assumed that vestibular as well as gastric

Keywords: gastric afferents, gastric efferents, vestibulo-vagal reflex, vestibulo-sympathetic reflex, gastrosensory-vestibular-autonomic interactions

stimulation can be the major sources of these symptoms. It is also well known that caloric stimulation of the vestibular apparatus can cause emesis and nystagmic responses. Wang and Borrison (1951) reported that the intragastric administration of copper sulfate induced emetic responses, and that the surgical interruption of the vagi had a more profound effect on the threshold and latency of vomiting than did sympathectomy, which caused no remarkable changes in these parameters. They stressed that the vagal gastric afferents play a more important role than splanchnic gastric afferents in the mediation of the gastric effects of copper sulfate. The present experiments were designed to study the effects of individual and combined vestibular and gastric stimulation on the reflex change in gastric autonomic outflow. Portions of the data describing the effects of copper sulfate on the rate of afferent discharges in the gastric branch of the vagus nerve have been reported elsewhere (Niijima *et al.*, 1987).

Methods

Male Wistar rats weighing 300-400 g were used. Food, but not water, was removed 5 hours before the experiment. Rats were anesthetized with 700 mg/kg of urethane and 50 mg/kg of chloralose, given i.p. A tracheal cannula was inserted.

The stomach could be perfused with copper sulfate ($CuSO_4$) or physiological saline through a catheter which was placed in the oesophagus and directed toward the cardiac portion of the stomach. Another catheter was placed in the pyloric portion of the stomach through the duodenum as an outlet for the perfusate.

Before starting the experimental perfusion, the stomach was washed with isotonic saline. Copper sulfate solutions (0.04% and 0.08%) and isotonic saline were used for the experimental perfusions. For each perfusion 4 ml of solution at 38°C were injected by syringe into the stomach over a 1-min period. The solution was kept in the stomach for 5-30 min, after which time the stomach was flushed for 1 min with isotonic saline. To stimulate the vestibular apparatus, the right external auditory meatus was irrigated for 3-10 min with cold water (5-18°C) and then flushed with warm water (34-35°C).

Afferent nerve activity was recorded from a nerve filament isolated from the peripheral cut end of the gastric branch of the vagus nerve, or of the splanchnic nerve. Efferent nerve activity was made from a filament isolated from the central cut end of the ventral gastric branch of the vagus nerve or the gastric branch of the splanchnic nerve. Nerve activity was amplified by means of a condenser-coupled differential amplifier, and stored on magnetic tape. Analysis of the nerve activity was performed after conversion of raw data to standard pulses by a window discriminator that distinguished the nerve discharges from the background noise. To monitor the time course of changes in neural activity the rate of neural discharge was determined by a ratemeter with a reset time of 5 sec. The output of this ratemeter was displayed on a pen recorder. Normal animal body temperature was maintained by means of a heating pad. The ECG was monitored throughout the experiment.

Results and Discussion

The Effect of Copper Sulfate on the Afferent Activity of the Gastric Branches of the Vagus Nerve

The perfusion of 4 ml of two different concentrations (0.04% and 0.08%) of $CuSO_4$ solution provoked an increase in afferent activity of the gastric branch of the vagus nerve (Niijima *et al*, 1987). After the onset of the perfusion with $CuSO_4$ the activity increased gradually and the increase lasted until after flushing of the gastric canal with isotonic saline. The stimulating effect of 0.08% solution of $CuSO_4$ was stronger than that of the 0.04% solution, and lasted for a longer period of time, as shown in the upper trace of Figure 1. With

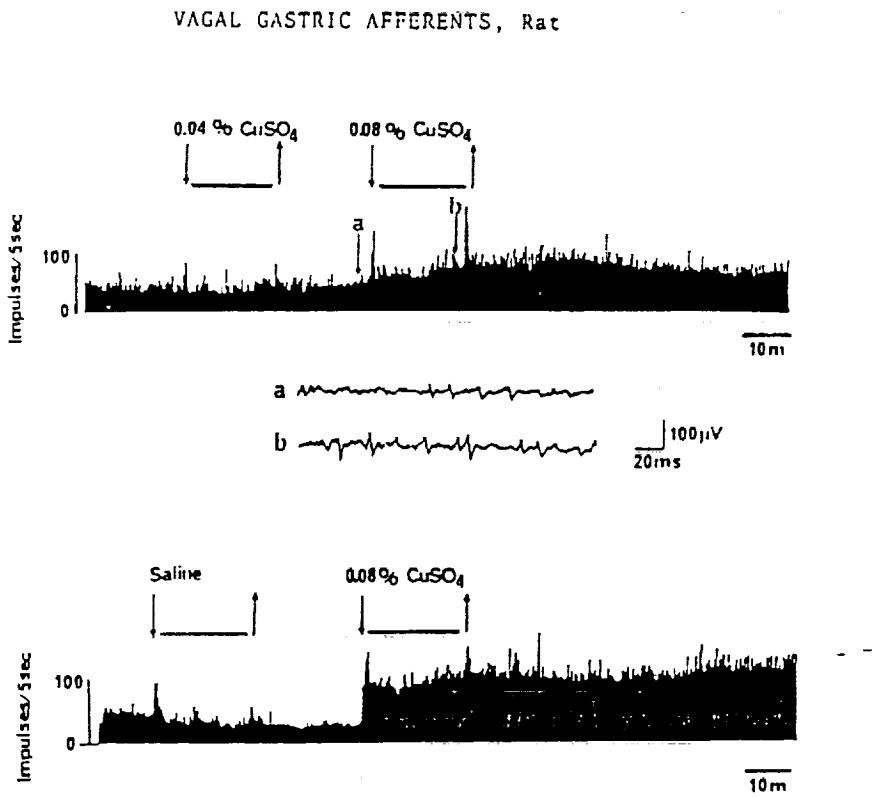


Fig. 1. Effect of gastric perfusion by 0.04% and 0.08% $CuSO_4$ solution and physiological saline on the afferent discharge rate of a vagal gastric nerve filament (from Niijima *et al.*, 1987). Downward arrows show time of onset of perfusion. Upward arrows show the end of rinsing with saline. Horizontal bars indicate the duration of perfusion with $CuSO_4$ solution and physiological saline. (*a*): sample of nerve activity taken at time indicated by arrow a, before perfusion with 0.08% $CuSO_4$;.(*b*): sample of nerve activity obtained at time indicated by arrow b, during perfusion with 0.08% of $CuSO_4$.

the 0.08% solution the increase in vagal activity lasted in general for more than 1 hour, even though the stomach was flushed after 20 min of exposure to the $CuSO_4$. The peak of activity provoked by the $CuSO_4$ was reached after perfusate had been flushed out of the stomach (Fig. 1, upper and lower trace). It is unlikely that these changes in neural activity resulted from mechanical effects of the infusion of solution into the stomach, because the perfusion of 4 ml of saline resulted in no noticeable change in discharge rate beyond the transient increase that was observed at the onset of perfusion and flushing of $CuSO_4$ solutions and saline (Fig. 1, lower trace).

Figure 2 shows the mean discharge rate in spikes/sec of five different preparations just before (control), 20 min after the onset of 0.08% $CuSO_4$ solution, and 30 min after flushing with saline. Those discharge rates are 6.4 ± 0.3 (S.E.M.), 13.4 ± 1.8 (S.E.M.) and 18.8 ± 2.3 (S.E.M.) respectively. The difference between firing rates obtained during the control period and the period 20 min after onset of perfusion, as well as between the control period and the period 30 min after flushing were statistically significant (Student's t-test).

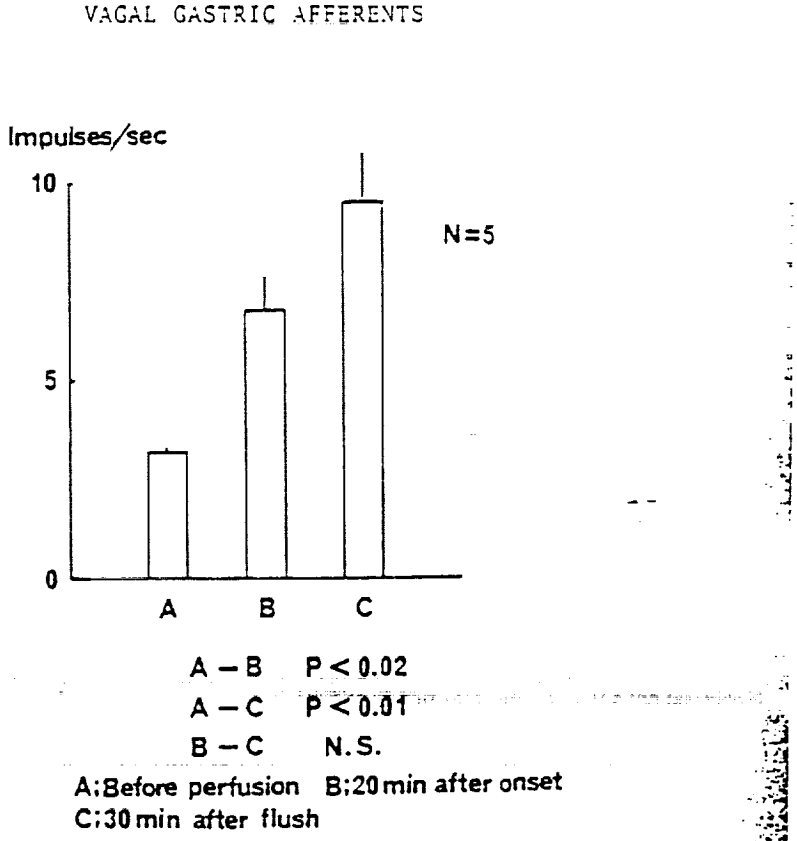


Fig. 2. Mean discharge rate of the gastric vagal afferents before A, 20 min after B and 30 min after rinsing C of perfusion by 0.08% $CuSO_4$ solution. (From Niijima *et al.*, 1987.)

C-2

The Effect of Copper Sulfate on the Afferent Activity of the Gastric Branches of the Splanchnic Nerve

Figure 3 shows a typical change in the discharge rate of afferent fibers of the gastric branch of the splanchnic nerve. Except for the transient increases at the time of the onset of perfusion and rinsing, no remarkable change was found in the rate of afferent discharge during perfusion with the 0.08% $CuSO_4$ solution for 30 min or after flushing out by saline. These effects, in combination with those reported in the preceding section, indicate that the gastric effects of $CuSO_4$ were mainly mediated through gastric vagal afferents but that splanchnic afferent activity was not greatly altered by these stimuli.

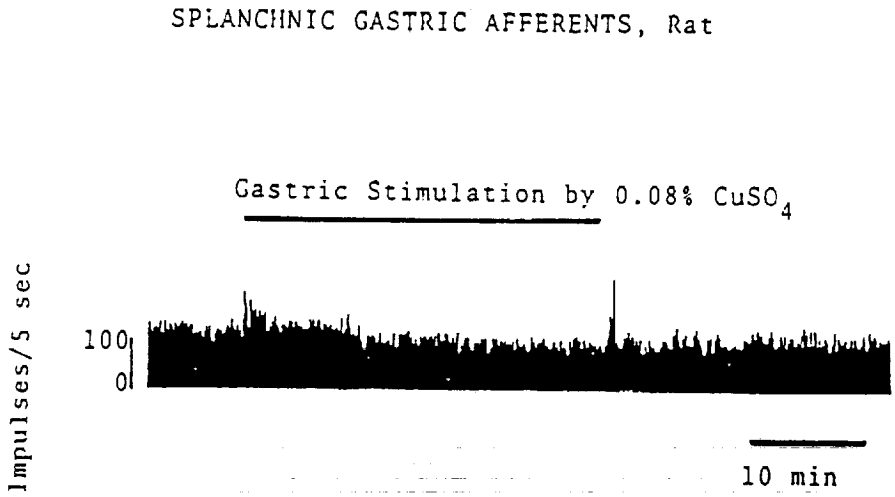


Fig. 3. Effect of gastric perfusion by 0.08% $CuSO_4$ solution on the afferent discharge rate of a splanchnic gastric nerve filament. Horizontal bar indicates the duration of perfusion with 0.08% solution.

It was established by Wang and Borison (1951) that the effective emetic concentration of $CuSO_4$ for oral administration was 0.08% in the dog and cat. The effect of intragastric $CuSO_4$ on the firing rate of gastric afferents is consistent with this in that the 0.08% solution produced a larger and more reliable change in the rate of firing than that produced by the 0.04% solution.

The specific receptors mediating the gastric vagal afferent response to $CuSO_4$ have not yet been identified, although several candidates exist. Mei (1985) has demonstrated the existence of vagal chemoreceptors in the intestinal wall, while Iggo (1957) has suggested that gastric pH receptors exist. Mei (1970) has also reported the existence of receptors in the mucous membrane of the gastrointestinal wall. While any of these receptors might be stimulated by $CuSO_4$ solutions, the exact source of the stimulating effect of $CuSO_4$ on gastric vagal afferents is not known.

The Effect of Caloric Stimulation of Vestibular Apparatus and Gastric Stimulation by Copper Sulfate on the Activity of the Vagal Gastric Efferent Nerve Fibers

As caloric stimulation of the vestibular apparatus, and gastric stimulation by $CuSO_4$ can cause the vomiting response in man (Wang and Borrison, 1951; Mano *et al*, 1988), a change in efferent activity in the vagal gastric nerve by these stimuli can be expected. Recordings of the efferent discharges were made from a ventral gastric branch of the vagus nerve.

The upper trace of Figure 4 shows the effect of caloric stimulation of the right vestibular apparatus on the rate of efferent discharges in the vagal gastric nerve. An application of cold water (10°C) on the right external meatus for 3 min caused a clear suppression in the rate of efferent discharge. The suppression continued even after the flushing of the meatus with warm water (34-35°C). It lasted about 17 min after cessation of the cold stimulation. A nadir was reached about 15 min after the onset of cold stimulation in this particular experiment. The lower trace of Figure 4 shows the effect of gastric stimulation by $CuSO_4$ and that of caloric

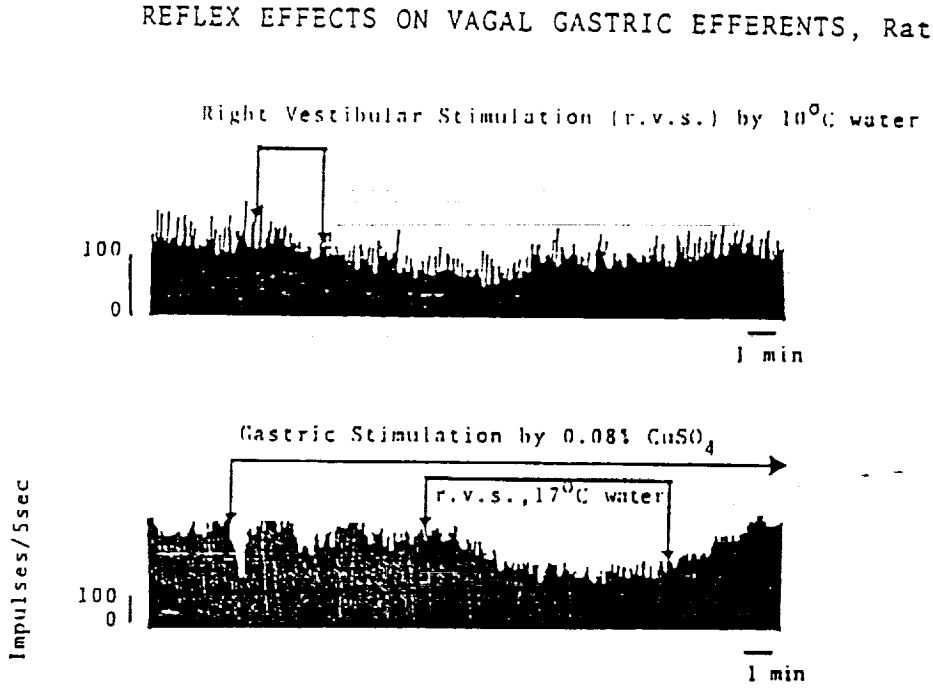


Fig. 4. Effects of gastric perfusion with 0.08% $CuSO_4$ solution and caloric stimulation of the right vestibular apparatus on the efferent discharge rate of the gastric branch of the vagus nerve. Vertical arrows in upper trace show time of onset and end of caloric stimulation of the right vestibular apparatus. First vertical arrow in lower trace indicates time of onset of gastric perfusion with 0.08% $CuSO_4$ solution. Second and third arrows show time of onset and end of caloric stimulation. Horizontal arrow shows duration of gastric perfusion.

stimulation on the vagal gastric efferent activity. At first, gastric stimulation with 0.08% $CuSO_4$ was applied, which caused a wave-like suppression in vagal activity. About 8 min after the onset of gastric stimulation, caloric stimulation of the right vestibular apparatus with 17°C water was applied for 11 min. This caloric stimulation caused a further stronger suppression in discharge rate. A nadir of suppression was reached about 7 min after the onset of caloric stimulation. As observed in the trace, the effects of gastric stimulation and caloric stimulation appeared to summate, and the effect of caloric stimulation was apparently stronger than that of gastric stimulation. Observations from two other preparations were consistent with the results. No remarkable suppressive response was elicited by gastric stimulation with 2% $CuSO_4$ (Fig. 5).

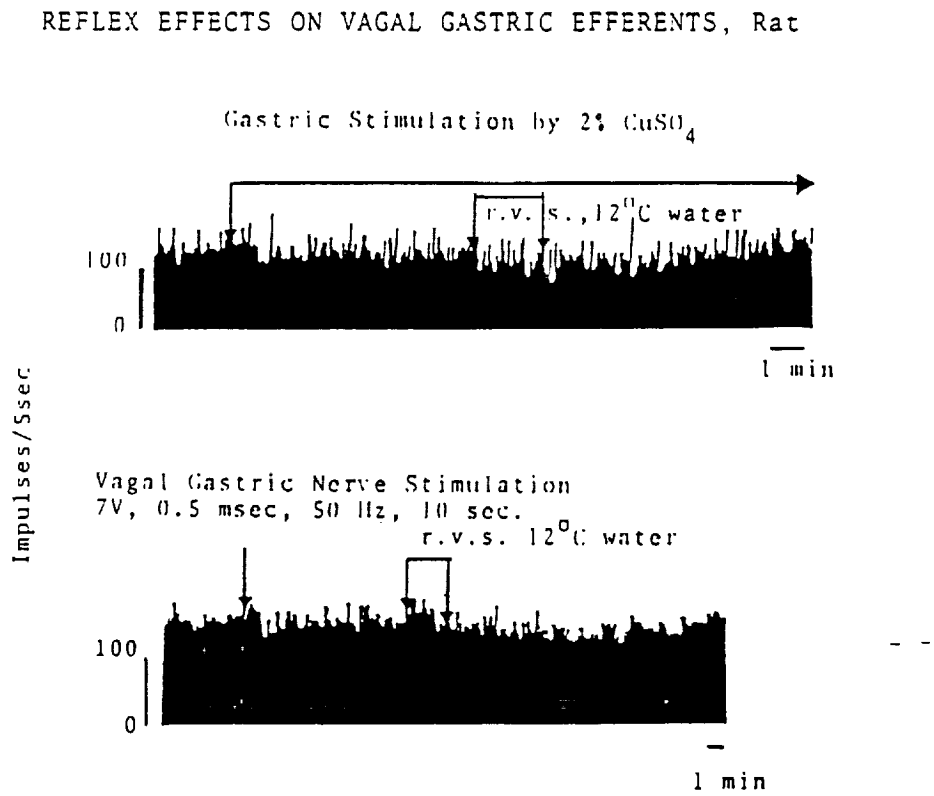


Fig. 5. Effects of gastric perfusion with 2% $CuSO_4$ solution, repetitive electrical stimulation of the gastric vagus nerve and caloric stimulation of the right vestibular apparatus on the efferent discharge rate of the gastric branch of the vagus nerve. Vertical arrows in upper trace indicate time of onset of gastric perfusion with 2% $CuSO_4$, and time of onset and end of caloric stimulation. Horizontal arrow indicates the duration of the gastric perfusion. First vertical arrow in lower trace shows time of electrical stimulation of the gastric branch of the vagus nerve, and second and third arrows indicate time of onset and end of caloric stimulation.

The lower trace of Figure 5 shows the effect of electrical stimulation of the gastric vagus nerve on the activity of the gastric vagal efferents. Two branches of the ventral gastric vagus nerve were used after sectioning. A pair of stimulation electrodes were placed on the central cut end of one branch, and recordings were made from the nerve filament dissected from the central cut end of another branch. As shown in the trace, a repetitive stimulation (7 V, 0.5 msec, 50 Hz for 10 sec) caused a long lasting inhibition in the rate of efferent discharge, lasting about 12 min. Caloric stimulation (12°C water) of the right vestibular apparatus for 3 min also resulted in a suppression lasting approximately 20 min.

The Effects of Caloric Stimulation of the Vestibular Apparatus and Gastric Stimulation by Copper Sulfate on the Activity of the Splanchnic Gastric Efferent Nerve Fibers

The top trace of Figure 6 shows the effects of gastric stimulation, as well as caloric stimulation of the right vestibular apparatus, on the efferent discharge rate of the gastric splanchnic nerve. These two stimulations for 5 min resulted in a slight facilitation in efferent discharge activity. The middle and lower traces show the effects of caloric stimulation for 5 min in different preparations. Caloric stimulation with water (5°C) of the right vestibular apparatus caused slight acceleration in splanchnic nerve activity in these two preparations.

These observations indicate that caloric stimulation of the vestibular apparatus as well as gastric stimulation with $CuSO_4$, resulted in a slight facilitation of gastric splanchnic efferent nerve activity.

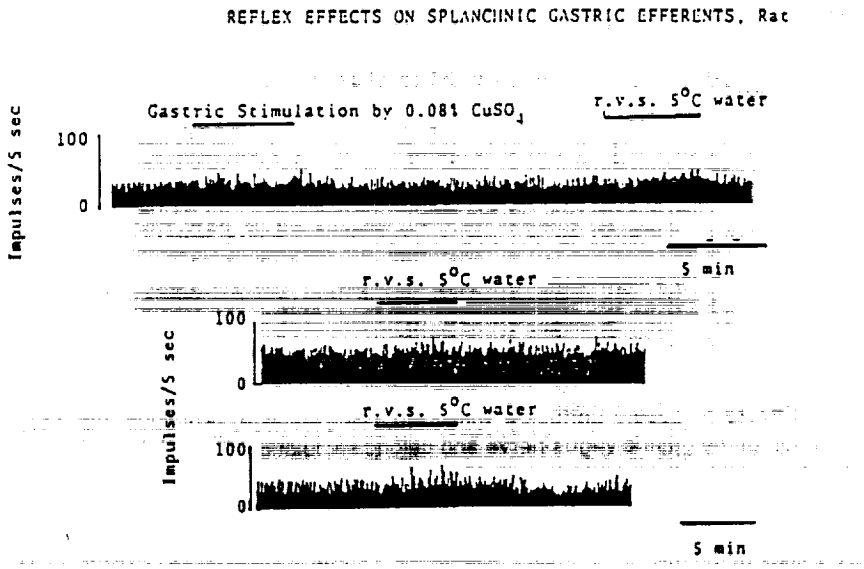


Fig. 6. Effects of gastric perfusion with 0.08% $CuSO_4$ solution and caloric stimulation of the right vestibular apparatus on the efferent discharge rate of the gastric branch of the splanchnic nerve. First horizontal bar on the top trace indicates time of gastric perfusion and second bar shows time of caloric stimulation. Horizontal bars on the middle and lower traces indicate time of caloric stimulations.

The results of these experiments can be summarized as follows: the different types of stimulation, such as gastric stimulation by $CuSO_4$, repetitive stimulation of the gastric vagus nerve and caloric stimulation of vestibular apparatus, caused an inhibition in efferent activity of the gastric vagus nerve and a slight activation of the splanchnic gastric efferents. This report therefore, provides evidence for a possible integrative inhibitory function of the vagal gastric center as well as a possible excitatory function of the gastric sympathetic motoneurons, which may play a role in space and motion sickness (Fig. 7).

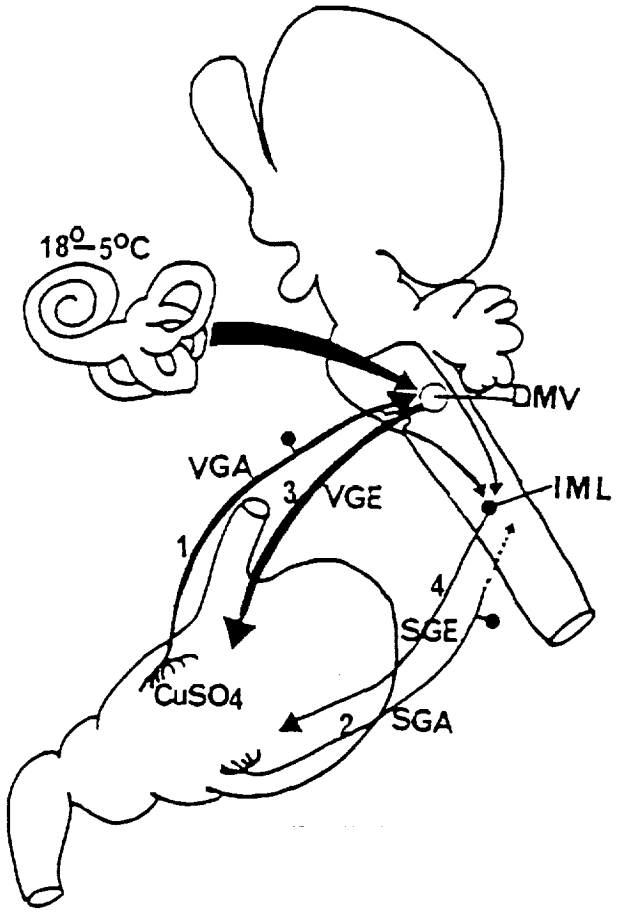


Fig. 7. Schematic illustration of the effects of gastric and vestibular stimulations on the activities of vagal and splanchnic gastric efferent outflows. *VGA*, vagal gastric afferents; *VGE*, vagal gastric efferents; *SGE*, splanchnic gastric efferents; *SGA*, splanchnic gastric afferents; *DMV*, dorsal motor nucleus of the vagus; *IML*, intermediolateral cell column (sympathetic preganglionic neuron group); *Inh.*, inhibition; *Exc.*, excitation.

Wang and Borrison (1951) reported that complete blockage of the emetic response to intragastric $CuSO_4$ required vagotomy combined with sympathectomy, and further suggested that the gastric splanchnic afferent pathway may play a role in the emetic response. However, our observations indicate that the chemical effect of gastric stimulation by $CuSO_4$ is not mediated by the gastric splanchnic afferents but by the gastric vagal afferents. It is suggested that the effects of mechanical stimulation such as distension of the gastric wall, can be mediated by the gastric splanchnic afferents and may play some role in the emetic response.

In relation to our observation of an increase in gastric sympathetic outflow following caloric stimulation of the vestibular apparatus, Mano *et al.* (1988) reported an increase in muscle sympathetic nerve activity (MSA) to the gastrocnemius-soleus muscle due to caloric stimulation of the vestibular apparatus in man. These findings may suggest the general activation of the sympathetic system and inhibition of the parasympathetic system in space motion sickness (however, see Akert and Gernandt, 1962; Megirian and Manning, 1967; Uchino *et al.* 1970, for reports of an opposite effect of vestibular stimulation).

References

1. Akert, K. and Gernandt, B.E. (1962). Neurophysiological study of vestibular and limbic influences upon vagal outflow. *Electroenceph. Clin. Neurophysiol.*, 14, 904-14.
2. Iggo, A. (1957). Gastric mucosal chemoreceptors with vagal afferent fibers in the cat. *Q. J. Exp. Physiol.*, 42, 398-409.
3. Mano, T., Iwase, S., Saito, M., Koga, K., Abe, H., Inamura, K., Matsukawa, Y. and Mashiba, M. (1988). Somatosensory-vestibular-sympathetic interactions in man under weightlessness simulated by head-out water immersion. In J.C. Hwang, N.G. Daunton and V.J. Wilson (Eds.), *Basic and Applied Aspects of Vestibular Function*. Hong Kong: Hong Kong University Press, pp. 193-203.
4. Megirian, D. and Manning, S.W. (1967). Input-output relations of the vestibular system. *Arch. ital. Biol.*, 105, 15-30.
5. Mei, N. (1970). Mecanorecepteurs vagaux digestifs chez le chat. *Exp. Brain Res.*, 11, 502-14.
6. Mei, N. (1985). Intestinal chemosensitivity. *Physiol. Rev.*, 65, 211-37.
7. Niijima, A., Jiang Z.-Y., Daunton, N.G. and Fox, R.A. (1987). Effect of copper sulphate on the rate of afferent discharge in the gastric branch of the vagus nerve in the rat. *Neurosci. Lett.*, 80, 71-74
8. Uchino, Y., Kudo, N., Tsuda, K. and Iwamura, Y. (1970). Vestibular inhibition of sympathetic nerve activities. *Brain Res.*, 22, 195-206.
9. Wang, S.C. and Borrison, H.L. (1951). Copper sulphate emesis: A study of afferent pathways from the gastrointestinal tract. *Amer. J. Physiol.*, 1265, 520-26.