pneumonitis following chronic ganglionic blockade[6], oxygen toxicity[7,8], epinephrine-induced injury[9], desquamative interstitial pneumonia[10], pulmonary alveolar proteinosis[11], monocrotaline-induced pulmonary lesions[12], etc. Nevertheless the combination of features appears to be quite characteristic of a drug-induced disorder of lipid metabolism, as it can be seen in anorogenic drug-induced lipidosis[13–15].

Before a pathogenetic mechanism can be proposed for the lesions observed by us, some points have to be referred to: a) it has been found that rat lung tissue is capable of completely oxidizing alcohol and utilizing alcohol in the synthesis of fatty acids[16]; b) studies on the fate of alcohol in the organism have shown that alcohol metabolites in the form of total lipids and fatty acids accumulate in the lung[17]; c) alcohol has a lipolytic action by mobilizing the fat deposits of the body[18,19], probably due to its sympathomimetic properties[20–22]; d) it is well known that alcoholism is associated with hyperlipidemia[23–26]; and e) the lungs are an important route of excretion of lipids in rats[27,28].

According to these facts, it seems likely that alcohol-dependent metabolic derangements may well be the basic mechanism of the pulmonary pathological changes mentioned above. It is clear that further studies are needed before these observations can be fully understood, which may also contribute to the understanding of certain aspects of cellular function in the lung.

Zusammenfassung. Bei normaler Ernährung und täglichem Trinken von beliebigen Mengen 40%igem Zuckerrohrschnaps wurden bei weissen Laboratoriumsratten diverse anatomische und ultrastrukturelle Lungenveränderungen nachgewiesen: Hypertrophie und Hyperplasie der Pneumocyten vom Typ 2, Anhäufung intraalveolärer Makrophagen und Verdickung der Alveolarwände.

M. A. Rossi

Department of Pathology, Medical School of Ribeirão Preto, Caixa Postal 301, 14100–Ribeirão Preto (S.P., Brazil), 5 December 1974.

[6] H. M. Perry, R. M. O'Neal and W. A. Thomas, Am. J. Med. *22*, 37 (1957).
[7] F. Schaffner, P. Felig, W. Patterson and E. Trachtenberg, Arch. Path. *83*, 99 (1967).
[8] Y. Kapanci, E. R. Weibel, H. P. Kaplan and F. R. Robinson, Lab. Invest. *20*, 101 (1969).
[9] N. S. Wang, S. N. Huang, H. Sheldon and W. M. Thurlbeck, Am. J. Path. *62*, 237 (1971).
[10] G. H. Farr, R. A. Harley and G. R. Hennigar, Am. J. Path. *60*, 347 (1970).
[11] C. Kuhn, F. Györkey, B. E. Levine and J. R. Garcia, Lab. Invest. *15*, 492 (1966).
[12] C. F. Chesney and J. R. Allen, Cardiovasc. Res. *7*, 508 (1973).
[13] G. Franken, H. Lüllmann and A. Siegfriedt, Arzneimittel-Forsch. *20*, 417 (1970).
[14] G. Magnusson and O. Magnusson, Beitr. Path. *146*, 79 (1972).
[15] Z. Hruban, A. Slesers and I. Aschenbrenner, Toxic. appl. Pharmac. *26*, 72 (1973).
[16] E. J. Masoro, H. Abramovitch and J. R. Birchard, Am. J. Physiol. *173*, 37 (1953).
[17] H. Casier, Q. Jl. Stud. Alcohol *23*, 529 (1962).
[18] R. H. Schapiro, R. L. Scheig, G. D. Drummer, J. H. Mendelson and K. J. Isselbacher, New Engl. J. Med. *272*, 610 (1965).
[19] C. S. Lieber, N. Spritz and L. M. DeCarli, J. clin. Invest. *45*, 51 (1966).
[20] S. Mallow, Am. J. Physiol. *189*, 428 (1957).
[21] B. B. Brodie, W. M. Butler jr., M. G. Horning, R. P. Maickel and H. M. Maling, Am. J. clin. Nutr. *9*, 432 (1961).
[22] L. A. Pohorecky, J. Pharmac. exp. Ther. *189*, 380 (1974).
[23] D. P. Jones and E. A. Greene, Am. J. clin. Nutr. *18*, 350 (1966).
[24] C. S. Lieber and N. Spritz, J. clin. Invest. *45*, 1400 (1966).
[25] J. J. Barboriak and R. C. Meade, Am. J. med. Sci. *255*, 245 (1968).
[26] P. E. Wilson, P. H. Schreibman and A. C. Brewster, J. Lab. clin. Med. *75*, 264 (1970).
[27] S. Bernick and P. R. Patek, Arch. Path. *72*, 310 (1961).
[28] F. D. Bertalanffy, Int. Rev. Cytol. *17*, 213 (1964).

Motion-Modulated Vestibular Neurons: Central versus Peripheral Effects of Cholinergic Blocking Agents

Studies in many laboratories have indicated the effectiveness of the belladonna alkaloids, scopolamine and atropine[1,2] and the antihistaminics, diphenhydramine and dimenhydrinate[3], in the prevention of motion sickness. Some recent studies have indicated that the effectiveness of these drugs in treating motion sickness is due to their anticholinergic action possibly mediated through a locus in the brainstem[4], rather than at the vestibular end organs.

However, several recent reports suggest that acetylcholine is the neurotransmitter at efferent nerve fibres innervating the hair cells of the inner ear. Both acetylcholine esterase and choline acetyltransferase have been localized at these efferent synapses and inhibitory post synaptic potentials recorded in hair cells can be blocked by D-tubocurarine[5]. The existence of an efferent component of the vestibular nerve mediated by acetylcholine indicates that the site of action of anticholinergic agents used clinically for the prevention of motion sickness may be peripheral rather than central.

The purpose of the work presented here was to assess the effectiveness of scopolamine methyl bromide and other quaternary compounds with muscarinic blocking activity in the vestibular nuclei and compare it with that of scopolamine hydrochloride. Because of the lack of access of quaternary ammonium compounds to the CNS, this comparison should distinguish between possible central or peripheral modes of action.

Materials and methods. 12 cats (3.5 to 4.5 kg) of either sex were anesthetized with halothane. Cannulae were inserted in the trachea, femoral vein and artery for adequate ventilation, i.v. injections and recording arterial blood pressure, respectively. After the animal's head was fixed in a stereotaxic apparatus, a midcollicular decerebration was performed. The lower brain stem was exposed by an occipital craniotomy and the cerebellum was left intact. Body temperature was maintained at 37 ± 1.0 °C.

A platinum-iridium microelectrode was advanced through the cerebellum and into the vestibular nucleus according to the stereotaxic coordinates of Berman[6].

[1] E. M. Glaser, Proc. R. Soc. Med. *52*, 965 (1959).
[2] C. D. Wood and A. Graybiel, Aerospace Med. *39*, 1341 (1968).
[3] L. N. Gay and P. E. Carliner, Science *109*, 359 (1949).
[4] E. B. Kirsten and E. P. Schoener, Neuropharmacology *12*, 1167 (1973).
[5] Å. Flock and D. M. K. Lam, Nature, Lond. *249*, 142 (1974).
[6] A. Berman, *A Cytoarchitectonic Atlas with Stereotaxic Coordinates* (University of Wisconsin Press, Madison, Wisc., USA 1968).

Controlled stimulation of the vestibular apparatus was produced by sinusoidal acceleration of the animal in a horizontal plane as previously reported[7]. Stimulation of the otolith organs of the utricle by accelatory motion proved a very effective physiological procedure for activation and modulation of afferent impulses to the vestibular nucleus. Hence, a functionally homogeneous population of vestibular neurons responding to accelatory motion were selected for pharmacological testing. The monitoring and processing of unit activity have previously been described[4].

Results and discussion. Administration of scopolamine methyl bromide (100 µg/kg, i.v.) in 3 experiments had no effect on the spontaneous discharge rate of vestibular neurons as illustrated in Figure 1. Other quaternary compounds exhibiting antimuscarinic activity, including atropine methyl nitrate (500 µg/kg) and lachesine chloride[8] (5 mg/kg) were tested in 5 experiments and also proved ineffective in altering vestibular unit discharge. In some experiments neuronal discharge was monitored for 30–60 min after drug injection without any depression of discharge. Subsequent administrations of scopolamine (100 µg/kg) always depressed neuronal activity as shown in Figure 1. As in earlier investigations[4], the discharge rate was reduced following scopolamine to a new stable level at approximately 50% of control. In no experiments did the quaternary compound combined with scopolamine even completely block neuronal activity.

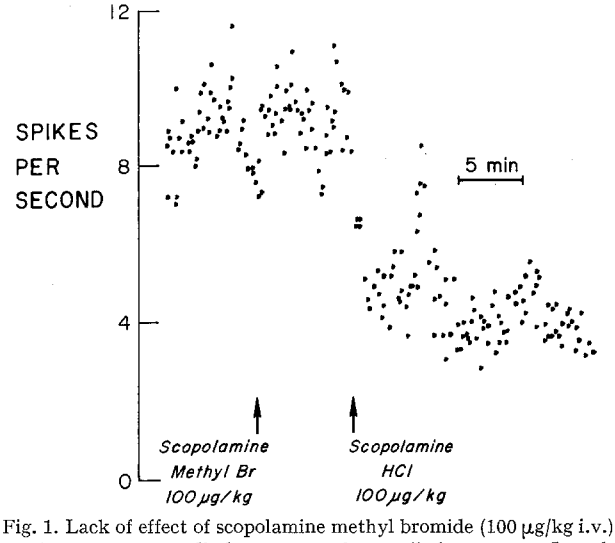

Fig. 1. Lack of effect of scopolamine methyl bromide (100 µg/kg i.v.) on the spontaneous discharge rate of a vestibular neuron. Scopolamine hydrochloride (100 µg/kg i.v.) produces a rapid decline in spike discharge from a rate of 8 spikes/sec to 4 spikes/sec. Each point represents summated activity for a 10 sec period.

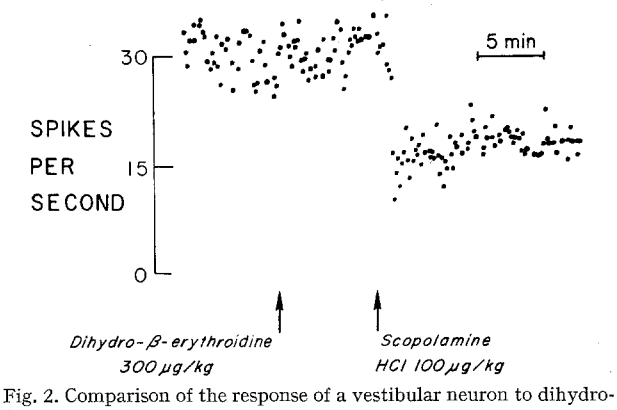

Fig. 2. Comparison of the response of a vestibular neuron to dihydro-β-erythroidine (300 µg/kg i.v.) with that of scopolamine hydrochloride (100 µg/kg i.v.). Dihydro-β-erythroidine has no effect on the spontaneously discharging neuron while scopolamine produces a 50% depression of discharge rate.

Because of the reported effectiveness of the nicotinic antagonist D-tubocurarine in blocking efferent vestibular impulses[5], we performed several studies with dihydro-β-erythroidine[9] to determine possible central or peripheral actions. The nicotinic blocking agent dihydro-β-erythroidine (300 µg/kg) was studied in 4 experiments and found to produce no excitation or inhibition of vestibular units when followed up to 40 min (Figure 2). Scopolamine was subsequently injected and, regardless of the time after dihydro-β-erythroidine, scopolamine always produced a significant depression of the discharge rate. This decrease was rapid in onset and its duration was notably prolonged.

These observations indicate a general ineffectiveness of muscarinic cholinergic antagonists which, because of quaternary ammonium substituents, do not have access to putative central sites of action. However, in every case it was found that scopolamine, a potent antimuscarinic agent, caused depression of the same vestibular units. Scopolamine appears to elevate the threshold for neuronal excitation produced by natural activation of the peripheral end organ, that is, a greater stimulus of the end organ is required to produce an equivalent response in the vestibular nucleus. The effect of scopolamine seems to be limited to a central neuronal mechanism with little or no involvement of muscarinic cholinergic receptors in the vestibular apparatus.

Spontaneous efferent activity exists in the vestibular nerve[10, 11] and probably acts to inhibit afferent discharge[12]. Dihydro-β-erythroidine, a nicotinic blocking agent with access to both peripheral and central synapses, had no effect on afferent activity as reflected by monitoring central vestibular discharge. This ineffectiveness of dihydro-β-erythroidine may be due to the small number of efferent fibres influencing afferent discharge[10, 12]. Based on pharmacological intervention studies, it would appear that the excitatory synaptic modulation governing the discharge of central vestibular neurons is at least partly muscarinic[13].

Zusammenfassung. Die Aktivität der Vestibular-Neurone in der decerebralisierten Katze wird durch Scopolamin, nicht aber durch Scopolamin-Methylbromid oder andere quaternäre Ammoniumanaloga des Scopolamins mit muscarinartigem Effekt, gehemmt. Es scheint, dass nur zentralangreifende antimuscarine Substanzen bei der Behandlung der «Bewegungskrankheit» (motion sickness) wirksam sind.

E. B. KIRSTEN and E. P. SCHOENER

Columbia University, College of Physicians and Surgeons, Department of Pharmacology, 630 West 168th Street, New York (N. Y. 10032, USA), 6 January 1975.

[7] J. H. LICKING, E. B. KIRSTEN and S. M. Ross, J. appl. Physiol. *29*, 391 (1970).

[8] Lachesine chloride was kindly donated by Gerhardt-Penick, Ltd. Croyden, England.

[9] Dihydro-β-erythroidine was supplied by Merck, Sharp & Dohme Research Laboratories, Rahway, New Jersey, USA.

[10] W. PRECHT, R. LLINÁS and M. CLARK, Expl. Brain Res. *13*, 378 (1971).

[11] O. SALA, Acta Otolaryng. suppl. *197*, 5 (1964).

[12] R. LLINÁS and W. PRECHT, Expl. Brain Res. *9*, 16 (1969).

[13] Supported in part by NIH Grant No. RO1 NS 11858. E. B. KIRSTEN is the recipient of Career Developments Award No. K4-GM 70179. E. P. SCHOENER is presently in the Dept. of Pharmacology, Wayne State Univ. Detroit, Mich., USA 48202.