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NATURE OF HISTAMINE RECEPTORS IN THE EMETIC CHEMORECEPTOR TRIGGER ZONE

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1 The protective effects of the intracerebroventricular (i.c.v.) administration of the H_1-receptor antagonist, mepyramine and the H_2-receptor antagonists, burimamide and metiamide on centrally induced histamine-emesis were studied in unanaesthetized dogs.

2 The PD_{50} values of intraventricular mepyramine, burimamide and metiamide against the 100% emetic dose of histamine (3.0 mg i.c.v.) were found to be approximately 200 μg, 20 μg and 20 μg respectively.

3 Although burimamide (i.c.v. or i.v.) afforded protection against histamine-induced emesis, there was no protection against intravenous apomorphine- or oral copper sulphate-induced emesis.

4 The results suggest that both H_1- and H_2-histamine receptors in the emetic chemoreceptor trigger zone of the area postrema are concerned in histamine-induced emesis.

Introduction

The region of the area postrema in the medulla oblongata is highly vascular and there is an abundance of nerve terminals in the region (Cammermeyer, 1949; Brizzee & Neal, 1954). This is compatible with the concept of chemoreceptors for the emetic action of various chemicals (Borison & Wang, 1953). The area postrema is very rich in biogenic amines, including histamine (Adam, 1961) but their precise role in the emetic chemoreceptor trigger (ECT) zone is not known. However, intraventricular administration of histamine in dogs elicited emesis which was completely blocked after surgical ablation of the ECT zone (Bhargava & Dixit, 1968). Histamine receptors for emesis were therefore proposed in the ECT zone but they were not classified. With the availability of specific H_1- and H_2-receptor antagonists, it is now possible to assess the receptor type involved in the central emetic action of histamine. The present work was designed to determine the protective effects of the H_1-receptor antagonist, mepyramine and the H_2-receptor antagonists, burimamide and metiamide on histamine-induced emesis.

Methods

The investigation was carried out in mongrel dogs weighing between 8 and 14 kg of either sex. Chronic implantation of stainless steel cannulae into either of the lateral cerebral ventricles was performed aseptically under pentobarbitone sodium anaesthesia (25 mg/kg, i.v.) according to the technique of Bhargava, Gupta & Chandra (1961). Streptomycin 0.25 g plus procaine penicillin 200,000 u, intramuscularly, was given post-operatively for 5 days. The correct placement of cannulae was ascertained by withdrawal of clear cerebrospinal fluid from the implanted cannulae, by a positive emetic response to an injection of apomorphine (2 μg) into the cannulated lateral ventricle 3 to 4 days after the implantation and finally on autopsy.

Experiments were designed to study the effect of mepyramine, burimamide and metiamide on the emetic response to parenterally and intracerebroventricularly (i.c.v.) administered histamine. For studying the emetic response, the dogs were fed 30 min before the injection and observed till they vomited, or for a period of 2 hours. The volume of drug solutions injected into the lateral cerebral ventricle never exceeded 0.5 ml. Tests were made at intervals of at least 3 days.

Drugs employed in the study were histamine dihydrochloride (Ward, Blenkinsop Co.), apomorphine hydrochloride (Mallinckrodt Chemicals, New York), copper sulphate, mepyramine maleate (May & Baker, Bombay), burimamide and metiamide (SK & F). The doses of histamine refer to the base, those of other drugs to their salts.

Results

The protective effects of mepyramine, burimamide and metiamide against the emesis induced by intracerebroventricular histamine are summarized in

Table 1. The doses of each histamine antagonist (i.c.v.) which protected 50% of the animals (PD_{50}) against the 100% emetic dose (3 mg) of histamine were determined. The PD_{50} of mepyramine (200 μg) was found to be approximately ten times that of burimamide and metiamide (20 μg).

It was found in a series of dogs, that the 100% emetic dose of histamine (i.c.v.) had to be increased four-fold to overcome the effect of the PD_{50} doses of burimamide and mepyramine given 30 min before histamine challenge.

The antiemetic activity of intravenous as well as intraventricular burimamide was tested against the emetic response induced by intravenous and intraventricular histamine and apomorphine and oral copper sulphate. The results (Table 2) show that whereas burimamide given either intravenously or intraventricularly was effective in protecting against intraventricular histamine-induced emesis, intraventricular burimamide offered only partial protection against intravenous histamine. Intravenous apomorphine (50 μg/kg) as well as oral copper sulphate (300 mg)-induced emesis was unaffected by intravenous or intraventricular burimamide treatment.

Discussion

Although it has been proposed that histamine receptors in the ECT zone of the area postrema of the dog may fully account for the emesis induced by intraventricular histamine (Bhargava & Dixit, 1968), the nature of these receptors was not known. The present study has clearly shown the importance of both H_1- and H_2-receptors in the emetic action of centrally administered histamine. Several investigators (Black, Duncan, Durant, Ganellin & Parson, 1972; Saxena, 1975) have reported roles for H_1- and H_2-receptors in the peripheral vasculature. Similarly in the brain, histamine-induced cyclic adenosine 3′,5′-

Table 1 Antiemetic action of mepyramine, burimamide and metiamide against 100% emetic dose (3.0 mg i.c.v.) of histamine in dogs

Antiemetic agent (μg, i.c.v.)		*No. of dogs that vomited*	*% Vomited*	*Approximate 50% protective dose (μg)*
Mepyramine	125	2/3	66	200
	250	1/3	33	
	500	1/5	20	
	1000	0/5	0	
Burimamide	10	2/3	66	20
	25	2/4	50	
	50	1/5	20	
	100	0/6	0	
Metiamide	10	3/4	75	20
	25	3/6	50	
	50	1/5	20	
	100	0/6	0	

Table 2 Antiemetic activity of burimamide

Burimamide pretreatment		*100% Emetic challenge*		*No. of dogs*	*%*
Route	*Dose (μg/kg)*	*Route*	*Dose*	*that vomited*	*Protection*
	Nil	Histamine i.v.	1 mg/kg	7/7	0
i.v.	100	Histamine i.v.	1 mg/kg	1/5	80
i.v.	200	Histamine i.v.	1 mg/kg	0/5	100
i.c.v.	100 (total)	Histamine i.v.	1 mg/kg	2/4	50
i.v.	100	Histamine i.c.v.	3 mg (total)	0/4	100
i.v.	200	Apomorphine i.v.	50 μg/kg	5/5	0
i.c.v.	100 (total)	Apomorphine i.v.	50 μg/kg	3/3	0
i.v.	500	Copper sulphate orally	300 mg (total)	3/3	0
i.c.v.	100–5000 (total)	Copper sulphate orally	300 mg (total)	2/2	0

monophosphate activity (Schwartz, 1975) and temperature changes (Lomax, Green & Cox, 1975) are mediated through H_1- and H_2-receptors.

Our PD_{50} studies, against histamine-induced emesis, with the antagonists of H_1- and H_2-receptors revealed that the H_2 antagonists, burimamide and metiamide were approximately 10 times more potent than mepyramine which is a H_1 antagonist. However, since a four-fold increase in the 100% emetic dose of intraventricular histamine overcomes the effects of equipotent (PD_{50}) doses of both H_1- or H_2-receptor blocker, it is possible that both receptors have an equal significance in the emetic response to histamine.

The selective antiemetic action of burimamide is shown by its ineffectiveness against intravenous apomorphine- and oral copper sulphate-induced emesis. These results rule out a general non-specific depressant action of the H_2 antagonist on the emetic centre. Furthermore, the lack of antagonism of burimamide against intravenous apomorphine- or oral copper sulphate-induced emesis suggests that histamine receptors are not involved in all types of emesis. It is interesting to note the failure of burimamide (i.c.v) to offer full protection against intravenously induced histamine emesis. Although not studied in a quantitative fashion this could indicate that part of the emesis induced by parenterally administered histamine (Peng & Pi, 1967) is mediated through central pathways not involving histamine. Neither histamine nor burimamide is believed to cross the blood-brain barrier (Halpern, Neveu & Wilson, 1959; Cross, 1973). However, the results of the present study show that intravenous burimamide antagonizes intraventricular histamine and that intravenous histamine can be counteracted by intraventricular burimamide. Thus, these agents probably pass from the blood to the region of the area postrema in adequate concentrations to produce pharmacological responses. Possibly the area postrema, where the emetic ECT zone is situated, does not have a normal blood-brain barrier.

These experiments suggest that H_2-receptor antagonists may have clinical significance in conditions where histamine may play a role in emesis such as anaphylaxis, motion-sickness and pregnancy and in which H_1-receptor antagonists have some activity (Bhargava, 1974).

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