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Studies on the possible role of brain histamine in behaviour

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Summary

1. The possible role of brain histamine in behavioural performance was studied in rats using thirst-induced water consumption, continuous (Sidman) avoidance, and reinforcement withdrawal test systems.

2. Parenteral administration of a variety of antihistamines to rats decreased thirst-induced water consumption; this effect could be antagonized by administration of histamine directly into the brain by a ventricular cannula.

3. When intraventricular doses of histamine were administered to rats at weekly intervals, an adaptation was seen in the effects of the amine on continuous avoidance behaviour. With succeeding doses, the initial period of depression of avoidance responding was shortened and the subsequent rebound stimulation disappeared.

4. The results support the hypothesis that histamine in the brain is involved in several behavioural phenomena.

Introduction

The scientific literature contains few reports on the possible relationships between brain histamine and animal behaviour. This is surprising in light of reports on differential distribution of histamine in brain areas (Adam & Hye, 1966), the presence of enzymes in the brain for synthesis and degradation of the amine (Green, 1964; Green, 1970; White, 1966), and the presence of histamine in brain nerve ending particles (Kataoka & DeRobertis, 1967).

The most important side effects of antihistamines are those affecting the central nervous system (Wyngaarden & Seevers, 1951). Overdosage evokes excitation and convulsions in children, and depression and coma in adults. Recently, Goldstein, Murphree & Pfeiffer (1968) used electroencephalograph techniques to confirm that therapeutic doses of most antihistamines induce depression of the central nervous system in adult subjects. Hollister (1969) has reviewed the use of various antihistamines as mild sedative agents (minor tranquillizers, antianxiety agents) in the psychotherapy of anxiety states.

Notwithstanding well documented clinical studies demonstrating that antihistamines have definite effects on the central nervous system, few animal behavioural studies have been conducted examining this class of drugs. Rosenberg & Savarie (1964) have reported that several (but not all) antihistamines, histamine and amino-

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guanidine (a diamine oxidase inhibitor) are all able to reverse chlorpromazine-induced depression in mice. Cesare, Carlini & Carlini (1963) have observed that histamine potentiates reserpine—or tetrabenazine-induced catatonia.

The present paper reports on the effects of antihistamines on three types of behaviour: thirst-induced water consumption, continuous (Sidman) avoidance and reinforcement withdrawal.

Methods

All animals used were adult, male Sprague-Dawley rats, obtained at 60–75 days of age (200–250 g) from Hormone Assay Laboratories, Chicago, Illinois. The rats were maintained on Purina lab chow and tap water *ad libitum* for 7–10 days before use in experiments. For animals to be used in experiments requiring injections directly into the brain, cannulae were implanted in the lateral hypothalamus or lateral ventricle (Hayden, Johnson & Maickel, 1966); these animals were used in experiments 7–10 days after surgery.

Drugs were administered as solutions of their respective salts in distilled water. Placebo runs were performed using injections of 0·9% saline or distilled water. For intraperitoneal dosage, concentrations were adjusted so that animals received 0·1 ml/100 g body weight; for intraventricular or lateral hypothalamus dosage, injections were delivered in a volume of 5 μl.

Thirst-induced water consumption was measured as described by Gerald & Maickel (1969). Rats were placed in cages $28 \times 28 \times 56$ cm, identical to the home cages of the animals. The cages were in individual compartments of a soundproofed box with uniform fluorescent lighting. Constant circulation of air by blowers maintained uniform temperatures in the compartments; the noise level of the blowers was used as a uniform white noise. Each cage contained a drinking tube connected to an external 50 ml stoppered buret filled with tap water at the start of each run. As the animal consumed water, the change in volume was visually estimated to the nearest 0·1 ml. The front door of each compartment was fitted with an eye-piece lens to permit visual observation of the rats without disturbing their behavioural performance. For at least one week before the first drug day, rats were deprived of water for 23 h before the testing, then placed in the drinking cages and allowed to drink for one hour. Food was available *ad libitum* in the home cages but not in the drinking cages.

Drug trials were started only after the animals demonstrated stable water intake baselines (less than 5% daily variation). The schedule for drug studies was arranged so that the rats were run daily, with drugs administered every fourth day, and placebo (saline) dosage on the intervening days. Water intake was recorded at 15, 30 and 60 min of the test sessions; the greatest proportion of drinking occurred in the first 15 min in all cases. Drug doses were selected so that each compound was tested at three dosages, having the proportions n, 2n and 4n, with the stipulation that the dose of 4n should not produce any abnormal gross behaviour on visual observation. All drugs were administered by injection as solutions in distilled water 10 min before placement of the animals in the drinking cages. The results presented in the Tables depict the volume consumed after 60 minutes.

Single-lever continuous avoidance was measured as described by Maickel, Cox, Miller, Segal & Russell (1969). Experiments were carried out in standard

behavioural boxes with metal sides, back and top, a Plexiglass door, and a floor (29 × 26 cm) made up of 1 cm grids placed 2·0 cm apart (centre to centre) for delivering shock. A lever was mounted on one end, 7·8 cm above the floor and 7·8 cm from the back wall. Shock (350 V, 1·0 mA shortcircuit current) was provided by a Grason-Stadler E-1064 shock generator and delivered to the grids via a scrambler circuit. The boxes were enclosed in insulated shells for isolation from external stimuli, white noise was provided continuously.

The response-shock interval was 40 s ; shock onset was delayed for 40 s each time the rat pressed the lever when the shock was not being delivered. Forty seconds after the last avoidance response, a 3 s shock period was instituted which could be terminated by the rat pressing the lever in an escape response. The shock-shock interval was 20 s, that is, further shocks were presented at 20 s intervals until the animal inserted an avoidance response to return the schedule to the 40 s response-shock interval.

Rats were trained and tested at 4-day intervals allowing 0·5 h of warmup, removal for injection of drug or placebo, followed by a 4 h session. Six sessions were usually required to produce stable avoidance baselines, at which time each animal's avoidance response rate varied by less than 10% during a session. Since the animals respond well, they get very few shocks, usually less than six per hour and often only one or two in the entire 4·5 h session. Drugs were administered every eighth day with intervening placebo runs ; results are expressed as percentage of placebo avoidance response rate.

For reinforcement withdrawal, the system used was that described by Heise, Laughlin & Keller (1970). The apparatus used was similar to that used for continuous avoidance, except that the box contained a Skinner valve, located adjacent to the response lever, programmed to present drops of 9% sucrose solution. After training 23 h water-deprived rats to bar press for 9% sucrose, the following schedule was instituted. Twenty consecutive reinforced (S+) trials were presented concurrently with a signal light. After the twentieth subject response, the subject was trained to refrain from responding to three successive non-reinforced (S−) trials. At this time, a tone (1,000 Hz, 80 decibels) was presented, signalling the start of a second S+ session. Ten such sessions were presented in each day's run, affording the subject the opportunity to receive 200 S+ ; the volume of fluid so obtained (10 ml) was not sufficient to satiate the animal. The maximum duration of each S+ trial was 10 s unless terminated by a response. Each trial alternated with an intertrial-interval of 10 seconds. A response by the rat during the intertrial-interval reset the timer for an additional 10 seconds. The S− trials were of 10 s duration, regardless of the response made by the subject. A perfect animal would make one response for each of twenty consecutive S+ presentations, a twenty-first response on the first S− trial, then allow the next three S− trials to pass without a response before responding again to the next twenty consecutive S+ trials. Thus, this ideal animal would make 200 S+ responses and ten S− responses in each session. Animals were trained to reach a stable intra-animal baseline of responding with placebo injections before beginning drug testing. After each session, rats were permitted free access to water (for about 15 min) until satiated, thus enabling subjects to maintain a constant body weight (±5%).

TABLE 1. *Effect of antihistamines, atropine and promazine on thirst-induced water consumption in rats*

Drug	Dose (mg/kg)	*n*	Volume consumed Placebo (ml)	Drug (ml)	% Placebo	Slope of regression	Relative potency
Bromodiphenhydramine	12·5	6	22·0±0·8	17·8±3·1	80·8*		
	25·0	8	18·9±2·7	12·6±2·6	68·2*	−2·17	31
	50·0	6	19·0±1·8	1·8±2·4	8·6*		
Cyproheptadine	4·0	7	19·9±4·7	20·6±6·2	102·8		
	8·0	5	20·4±5·5	16·1±6·3	79·1*	−2·04	57
	16·0	6	19·0±4·1	7·2±6·2	39·7*		
Diphenhydramine	12·5	6	2·18±3·7	18·0±2·0	84·1		
	25·0	8	20·2±2·1	11·5±3·6	57·7*	−1·85	23
	50·0	6	22·8±2·2	4·8±4·7	22·5*		
Methapyrilene	2·5	8	19·0±3·4	18·5±3·3	97·5		
	5·0	8	19·6±4·4	14·5±3·7	73·7*	−2·07	77
	10·0	7	18·8±2·7	8·5±3·0	44·6*		
Tripelennamine	6·25	8	26·5±2·6	22·6±3·1	85·6*		
	12·5	6	22·5±2·3	17·3±3·6	77·6*	−1·93	42
	25·0	6	27·4±2·2	8·1±8·4	29·4*		
Atropine	2·5	8	21·3±4·1	19·6±7·5	90·3		
	5·0	8	23·9±3·2	15·1±4·3	63·6*	−1·91	100
	10·0	8	21·4±2·3	8·9±1·5	42·6*		
Promazine	2·5	6	20·5±1·5	17·2±2·2	84·4*		
	5·0	6	18·4±2·2	12·6±5·4	67·0*	−1·02	75
	10·0	6	21·6±2·1	10·9±6·7	50·3*		

Rats were deprived of water for 23 h and dosed with drug 10 min before the drinking period. Results are expressed as mean ± S.D. Statistical comparisons were made by the correlated *t* test for matched scores; values significantly different from placebo ($P<0·05$) are indicated by *.

TABLE 2. *Effects of central administration of histamine on water consumption in rats*

Water pretreatment	Drug	Route	Placebo (ml)	Drug (ml)	% Placebo
Satiated	Histamine (80 μg)	l.h.			
	+placebo	i.p.	1·7±1·3	5·0±3·2	294·1*
	Placebo	l.h.			
	+methapyrilene	i.p.	1·3±0·7	0·4±0·5	30·8
	Histamine (80 μg)	l.h.			
	+methapyrilene	i.p.	1·6±1·7	0·2±0·4	12·5*
Deprived	Histamine (40 μg)	l.h.			
	+placebo	i.p.	17·5±4·5	19·3±5·7	110·4
	Histamine (80 μg)	l.h.			
	+placebo	i.p.	17·8±4·4	21·7±4·5	121·9*
	Histamine (160 μg)	l.h.			
	+placebo	i.p.	17·9±4·1	22·5±6·6	125·7*
	Placebo	l.h.			
	+methapyrilene	i.p.	18·8±2·7	8·5±2·7	45·2*
	Histamine (80 μg)	l.h.			
	+methapyrilene	i.p.	16·2±4·6	13·1±3·7†	80·9†
	Placebo	l.h.			
	+atropine	i.p.	18·5±2·2	11·0±3·5	59·5*
	Histamine (80 μg)	l.h.			
	+atropine	i.p.	18·2±4·1	13·4±4·7	73·6‡

Rats were deprived of water for 23 h, then either given drugs and tested as in Table 1 or permitted to drink to satiety for 1 h and subsequently tested. Methapyrilene or atropine (10 mg/kg, i.p.) or placebo was given 10 min before lateral hypothalamus (l.h.) administration of histamine or placebo, and drinking was allowed to begin immediately. Results are expressed as mean ± S.D. for five–eight animals per group. Statistical comparisons were made by the correlated *t* test for matched scores; values significantly different from placebo ($P<0·05$) are indicated by *. † Histamine+methapyrilene significantly different from histamine alone. ‡ Histamine+atropine significantly different from histamine alone.

Results

Effect of antihistamines on thirst-induced water consumption in rats

The results obtained with intraperitoneal injections of various compounds at different dose levels are presented in Table 1. All the compounds tested produced a significant decrement in water consumption at two or more dose levels. When the data in Table 1 were plotted as the log molar dose/percent of baseline response, a series of straight lines were obtained. With the exception of promazine, computer analysed regression analyses gave slope values between $-1{\cdot}85$ and $-2{\cdot}17$; all mutually parallel at the 0·05 level of confidence. It is of particular interest that the antihistamines tested were all parallel to atropine; relative molar potency values (atropine=100) ranged from 23 to 77.

Interaction of histamine and antihistamines on water consumption in rats

Since the data in Table 1 suggests that antihistamines interfere with thirst-induced water consumption, it seemed reasonable to examine the effect of increasing brain histamine on water intake. In order to bypass the blood-brain barrier, studies were performed in which histamine was injected directly into the lateral hypothalamus of the rat brain. Under these conditions, administration of 40, 80, and 160 μg of histamine significantly increased the water consumed by deprived rats (Table 2), with 160 μg only slightly more effective than 80 μg. The effect of 80 μg dosage was magnified when tested in satiated animals enhancing water intake 3-fold. Saline solutions at pH 4·4 (the pH of solutions of histamine dihydrochloride in distilled water) were without effect. Of particular interest are the data on interaction of parenterally administered drugs and centrally administered histamine. The effects of central histamine administration were completely reversed by intraperitoneal methapyrilene in satiated rats and markedly antagonized by intraperitoneal methapyrilene or atropine in deprived rats.

Effects of antihistamines, atropine and promazine on reinforcement withdrawal in rats

Several compounds were tested in this behavioural system, yielding the results shown in Table 3. Among the antihistamines tested, only bromodiphenhydramine

TABLE 3. *Effect of antihistamines, atropine and promazine on reinforcement withdrawal responding in rats*

Drug	Dose (mg/kg, i.p.)	S- responses		Relative molar potency
		Placebo	Drug	
Bromodiphenhydramine	25	1·17±0·12	1·83±0·58	16
Cyproheptadine	4	1·20±0·22	3·55±0·50*	166
Diphenhydramine	25	1·13±0·10	2·55±0·71*	18
Methapyrilene	10	1·23±0·21	2·49±0·65*	41
Tripelennamine	12·5	1·24±0·17	2·87±0·83*	37
Atropine	10	1·10±0·14	4·90±1·01*	100
Promazine	5	1·25±0·11	1·75±0·57	62

Rats were tested as described in **Methods.** Each value is the mean ± S.D. number of non-reinforced (S-) responses per session obtained from three rats, tested in ten sessions each. Drug values significantly different from placebo ($P<0{\cdot}05$, t test) are indicated by *.

failed to produce behavioural impairment, as did promazine, a compound having weak antihistaminic activity. The relative molar potency ranking is somewhat different from that observed with the thirst-induced water consumption system, especially for cyproheptadine.

Effects of methapyrilene and various compounds in influencing histamine on continuous avoidance behaviour

Initial studies of the effects of methapyrilene on continuous avoidance produced the dose-response data shown in Table 4. The lowest doses of the drug (5–10 mg/kg, i.p.) produced an initial brief depression, with a return to normal by 2·5 h after dosage. The highest doses (20–40 mg/kg) elicited a decrease in the response rate for the entire period, with no evidence for a normal dose-response relationship.

The effects of several other compounds are presented in Table 5. Betahistine evoked an increase in avoidance response rates, whether given intraperitoneally or into the lateral ventricle, while the intraventricular administration of trimethylhistamine was without effect. L-Histidine had no effect when given intraperitoneally, in doses of 100 mg/kg, but if the rats were pretreated with the monoamine oxidase inhibitor pargyline, L-histidine caused an initial depression of avoidance responding, followed by increased responding at 2–3 hours.

Effects of centrally administered histamine on continuous avoidance behaviour in rats

To further explore the actions of histamine administered into the lateral ventricle, separate groups of rats, trained to the continuous avoidance situation, were given

TABLE 4. *Effect of methapyrilene on continuous avoidance behaviour of rats*

Time after drug (h)	Methapyrilene (mg/kg, i.p.) 5	10	20	40
0·5	81±7*	55±10*	77±15*	62±10*
1·0	91±6	84±21	75± 8*	73± 7*
1·5	106±6	85±12	77± 6*	73±10*
2·0	113±5	89±12	79± 6*	79±10*
2·5	115±6	89±10	78±11*	79± 9*

Values represent time mean ± S.E.M. of four animals given the stated dose of drug at time=0. The data are presented as % of baseline avoidance responding of each animal in single lever continuous avoidance behaviour as described in **Methods.** Values significantly different from placebo ($P<0·05$) are indicated by *.

TABLE 5. *Effects of various compounds on continuous avoidance behaviour of rats*

Treatment	*n*	Avoidance responding (% of baseline) 1 h	2 h	3 h
Atropine (10 mg/kg, i.p.)	4	150*	150*	185*
Trimethylhistamine (80 μg/rat, i.ventr.)	2	90	85	85
Betahistine (4 mg/kg, i.p.)	2	128	124	135
Betahistine (320 μg/rat, i.ventr.)	2	127	150*	129*
L-Histidine (100 mg/kg, i.p.)	4	106	120	116
Pargyline (40 mg/kg, i.p., 30 min before testing)	4	124	119	131*
Pargyline+L-histidine (as above)	8	81	147*	130*

Values represent the mean of *n* animals treated as described in **Methods.** Data presented as % of baseline avoidance responding as in Table 4. Significant effects ($P<0·05$) are indicated by *.

80 μg doses of histamine at 8 day intervals. The results, shown in Table 6, indicate that adaptation occurred to the repeated dosage schedule at 8 day intervals. In the first two drug sessions, the centrally administered histamine caused an initial depression of behaviour, lasting about 1·5 h and followed by a return to normal responding or an enhanced avoidance response rate (session II). However, in subsequent sessions only brief initial depression was observed—the histamine caused a slight stimulation in session III, whereas in the last session, after 0·5 h normal performance was observed. Repeated dosages of saline, distilled water or saline brought to pH 4·4 with diluted HCl (a pH equivalent to the solution of histamine hydrochloride) were without effect.

Discussion

As part of a project investigating the action of drugs on thirst-induced water consumption in rats, several antihistamines representing a diversity of chemical structures and pharmacological actions, all proved effective in reducing the volume of water consumed by deprived rats (Table 1). Furthermore, when the data from Table 1 were plotted in the form of dose-response curves, that is, per cent of placebo water volume consumed against the log molar dose, the straight lines obtained proved to have similar slopes. This finding, when considered in the light of concepts suggested by Ariens (1964), may suggest a common mechanism of action for all of these agents, especially since the slopes for amphetamine (Maickel & Webb, 1972) and several phenothiazine tranquillizers (Maickel, Gerald, Warburton & Mahju, 1968) are different.

The mere finding that several antihistamines have a similar effect on a behavioural test system does not demonstrate an exclusive role for brain histamine in such a behavioural pattern. Since the drugs were given intraperitoneally possible peripheral effects could not be ruled out. However, further investigation demonstrated that this antihistamine-mediated reduction in water consumption could be reversed by administration of histamine directly into the lateral hypothalamus of the rat brain (Table 2). In addition, this central histamine dosage also produced a significant increase in water intake by deprived rats. Moreover, in satiated animals, central administration of histamine evoked a 3-fold increase in water consumption, an action reversed with intraperitoneal methapyrilene (Table 2). These results suggest that central histaminergic function may be involved in the thirst-induced consumption of fluids.

These central effects of histamine should be considered in the light of reports by Grossman (1960, 1962a, 1962b) showing that administration of carbachol into sites

TABLE 6. *Effects of repeated central administration of histamine on continuous avoidance responding in rats*

No. of doses	Avoidance responding at hours after histamine dose (% of baseline) 0·5	1·0	1·5	2·0	2·5	3·0
1#	31·3±3·0*	37·7± 3·5*	56·2±17·0*	61·6±15·0*	79·5±17·6	97·7±20·3
2#	30·0±5·5*	47·0±12·2*	55·6±13·6*	121·7±16·7*	174·1±35·1*	148·8±35·1*
3#	47·6±4·4*	110·6±16·6	125·7±22·8	127·2±18·9*	140·0±23·2*	180·4±33·3*
4#	49·5±8·0*	94·1± 6·8	110·4±13·9	111·6±12·4	117·8±13·2	96·8±11·1

Values represent the mean ± S.E.M. of four animals given repeated doses of histamine (80 μg in 5 μl) in the lateral ventricle before measurement of avoidance behaviour. Data are presented as % of baseline responding as in Table 4. Values significantly different from placebo are indicated by *.

in the lateral hypothalamus induced drinking in satiated animals, an effect that could be blocked by parenterally administered atropine. Similarly, Stein & Seifter (1962) showed that injection of muscarine into the lateral hypothalamus of rats elicited drinking, also blocked by atropine.

Other types of behaviour were also shown to be altered by antihistamines. For example, in the reinforcement withdrawal system described by Heise *et al.* (1970), cyproheptadine, diphenhydramine, methapyrilene and tripelennamine produced a significant increase in non-reinforced responding (Table 3). Bromodiphenhydramine also increased non-reinforced responding, but not at a level producing statistical significance. In this regard, it is of interest that Carlton (1963) has suggested that the characteristic behaviour elicited in operant situations is the result of the choice: reward or non-reward, with unrewarded responses inhibited. Carlton has suggested that cholinergic blocking agents are capable of disrupting this behavioural system by preventing the withholding of non-rewarded responses. Khavari & Maickel (1967) demonstrated a perseveration in erroneous (non-rewarded) behaviour under the influence of atropine. Similar effects have been reported by Heise *et al.* (1970) to be evoked by cholinergic blocking agents in the reinforcement withdrawal test system. While many of the antihistamines also have cholinergic blocking activity, tripelennamine's effectiveness (a compound apparently devoid of anticholinergic potency) suggests that brain histamine as well as acetylcholine may be implicated in this behavioural response pattern.

Finally, the results obtained with continuous avoidance also support the concept that brain histamine has a role in behavioural patterns. The lowest doses of methapyrilene used (5–10 mg/kg, i.p.) caused a brief initial depression of avoidance responding. Increasing the dose of methapyrilene to 20 or 40 mg/kg, intraperitoneally, elicited a prolongation of reduced avoidance responding for 3·5–4·0 hours (Table 4). These actions of the antihistamine are in contrast to the effects of atropine which evokes an increase in avoidance responding (Table 5).

When histamine was administered directly into the lateral ventricle of the rat brain, an unusual effect was observed in avoidance responding (Table 6). The administration of a single dose of histamine (80 μg/rat) caused a depression of responding for the first 2 h, followed by a return to a normal response rate for the remainder of the test session. However, when a second dose was given 8 days later, the initial period of depression was shortened to 1·5 h and was followed by a subsequent 1·5 h of increased responding. Administration of a third dose after another 8 day period produced only a 30 min period of depression, followed by an increased responding for the remainder of the test session. A fourth test dose (after 8 days) showed that initial 30 min depression followed by normal responding. This progressive pattern of differing responses suggests an adaptation to repeated histamine administration, although at the present time we have no biochemical data to offer in explanation.

The results reported in this paper do not completely clarify the nature of brain histamine's role in behaviour. Certainly, the similarities between the effects of the acetylcholine antagonist atropine and the various antihistamines tested on thirst-induced water consumption are striking. The slopes of the molar dose-response curves are parallel, and parenteral atropine or methapyrilene have a similar antagonistic effect towards centrally administered histamine. Similarly, acetylcholine antagonists and antihistamines are capable of perturbing the behavioural perform-

ance of rats in the reinforcement withdrawal test. In contrast, promazine, a compound having little antihistaminic and cholinergic blocking potency, has a different regression slope on water consumption and is ineffective towards reinforcement withdrawal. However, in a continuous avoidance test, methapyrilene depresses avoidance responding, while atropine evokes a marked increase.

Erspamer (1961) stated that 'histamine in the CNS has been ignored for a long time by several investigators as a second-class amine. But this amine, however annoying the fact may be, has the same citizenship rights in the CNS as catecholamines and 5-HT, whose function in the CNS is approximately as obscure as that of histamine.' Unfortunately, little work has been done since 1961 on the possible functional role of brain histamine. The volume on histamine of the *Handbook of Experimental Pharmacology* (Roche e Silva, 1966), devotes only 8 pages (White, 1966) to the subject of brain histamine. More recently, Kahlson & Rosengren (1968) devoted only one page out of a 40 page review to the formation of histamine in cerebral tissues. Despite considerable clinical evidence for central nervous system or behavioural effects of antihistamines (Wyngaarden & Seevers, 1951; Goldstein *et al.*, 1968; Hollister, 1969), there is a paucity of reports on behavioural studies in animals permitting a unified hypothesis regarding the physiological role of brain histamine.

Perhaps the most appropriate conclusion to draw from the data in the present paper is that histamine and acetylcholine in the rat brain may have some common interrelated functions. Whether one considers this as suggestive of a possible histaminergic-cholinergic function or as merely the interaction of different neuronal systems and drugs with multifaceted actions, the possible role of brain histamine in behavioural patterns cannot be completely ignored.

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