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DUBRAVKA POTKONJAK and PAVAO STERN*

THE EFFECTS OF HISTAMINE, AGONISTS AND ANTAGONISTS OF H_1 AND H_2 HISTAMINE RECEPTORS ON TREMOR AND RIGIDITY IN THE RAT**

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SUMMARY

The existence of histamine H_1 and H_2 receptors in the rat brain was investigated using specific agonists and antagonists of these receptors in peripheral tissues. It seems that there are histamine H_1 receptors in the rat brain. These receptors might play a role in pathophysiology of tremor, but not rigidity in the rat.

INTRODUCTION

Mc Geer et al. (1961) advanced the hypothesis that there is an equilibrium within the brain between two groups of substances serotonin and catacholamines on the one hand, acetylcholine and histamine on the other. Rigidity and tremor would be characterized by a shift of this equilibrium in favour of acetylcholine — histamine group.

It has been apparent for some time that more than one type of histamine receptors exists. The existence of H_1 and H_2 histamine receptors as well as different agonists and antagonists of these receptor have been proposed (Ash and Schild, 1966, Black et al., 1972).

* Institute of Pharmacology and Toxicology Medical Faculty, University of Sarajevo, Yugoslavia

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Because of this, there were two aims of this work. The first aim was to investigate the existence of histamine H_1 and H_2 receptors in the CNS. The second aim was to investigate the effect of histamine, agonists and antagonists of H_1 and H_2 histamine receptors on tremor and rigidity in the rat.

METHODS

Male Wistar rats weighing 130—150 g were used in all the experiments.

Histamine, agonists (2-methylhistamine and 4-methylhistamine) and antagonists (mepyramine and burimamide) of H_1 and H_2 histamine receptors were dissolbed in Ringer solution. Drugs were injected into the head of the caudate nucleus by a stereotaxic method similar to that of H o r s l e y and C l a r k e (1908) and B r e l j a k o v i ć et al. (1964), using the stereotaxic system of coordinates* (De G r o o t, 1959). Injections were always bilateral. All injections were made under light ether anaesthesia by means of »Agla« microsyringe. The injection volume was 2 ug in 2 ul.

Control animals were injected with 2 ul of vehicle solution into the same area.

Tremor was caused by the intravenous injection of oxotremorine (0,25 mg/kg). Rigidity was induced by an intraperitoneal injection of fluphenazine (10 mg/kg). Both applications were made 30 minutes after the stereotaxic injections.

The onset, duration and intensity of both tremor and rigidity were observed in the experimental and in the control group of rats. These observations were made independently by two persons who have been working with tremor and rigidity producing drugs for many years. After tremor and rigidity symptoms having been observed, the rats were killed by decapitation and the brains were removed. After 10% formalin fixation the brains were sectioned and the sites of injections were confirmed histologically by locationg the needle track.

RESULTS

The results are shown in tables.

No obvious differences were observed between the onset and duration of both tremor and rigidity between the experimental and control groups of animals.

* A — 7,8 mm; V + 1 mm; L = 3 mm

Table 1

THE EFFECT OF HISTAMINE, AGONISTS AND ANTAGONISTS OF HISTAMINE H_1 AND H_2 RECEPTORS ON OXOTREMORINE INDUCED TREMOR IN THE RAT

Drugs	Intensity of tremor	
	Experimental groups	Control groups
Histamine	++	+
2-methylhistamine	++	+
4-methylhistamine	+	++
2-methylhistamine + 4-methylhistamine	++	+
Mepyramine	+	++
Burimamide	+	+
Mepyramine + Burimamide	++	+

\+ — weak tremor ++ — strong tremor

Tremor of higher intensity than in control groups was observed in the groups of rats injected with histamine and 2-methylhistamine alone as well as with agonists and antagonists of H_1 and H_2 histamine receptors given together. After injections of 4-methylhistamine and mepyramine (given alone) tremor of lower intensity than in the control groups could be obserevd. No differences in tremor intensity between experimental and control groups of rats was seen after injection of burimamide alone.

After application of histamine alone and antagonists of H_1 and H_2 histamine receptors which were given either alone or in combination with each other rigidity of higher intensity than in control groups was observed. No differences in intensity of that symptom between experimental and control groups of animals was observed after injection of H_1 and H_2 histamine receptors agonists given either alone or in combination.

Table 2

THE EFFECT OF HISTAMINE, AGONISTS AND ANTAGONISTS OF HISTAMINE H_1 AND H_2 RECEPTORS ON FLUPHENAZINE INDUCED RIGIDITY IN THE RAT

Drugs	Intensity of rigidity	
	Experimental groups	Control groups
Histamine	+++	++
2-methylhistamine	+++	+++
4-methylhistamine	+++	+++
2-methylhistamine + 4-methylhistamine	+++	+++
Mepyramine	+++	+

(Continuation Tab. 2)

Drugs	Intensity of rigidity	
	Experimental groups	Control groups
Burimamide	+++	+
Mepyramine + Burimamide	+++	++

+ — weak rigidity ++ — strong rigidity +++ — very strong rigidity

DISCUSSION

Increase in tremor intensity observed after injection of histamine alone supports the Mc Geer's hypothesis that within the brain there exists an increase in concentration of histamine during a state of tremor. 2-methylhistamine has been reported to stimulate histamine H_1 receptors (B l a c k et al., 1972). Mepyramine has been defined as histamine H_1 receptor antagonist (Ash and Schild, 1966). In our experiments, 2-methylhistamine produced tremor of higher and mepyramine of lower intensity than in control groups. This could probably mean that in the rat brain there also are histamine H_1 receptors and that histamine produces an increase in tremor intensity acting on that receptors.

4-methylhistamine which has been reported to stimulate histamine H_2 receptors (B l a c k et al., 1972) produced in our experiments tremor of lower intensity than controls. The same authors (B l a c k et al., 1972) found that burimamide was a specific antagonist of histamine H_2 receptors. This drug, however, in our experiments did not cause any change in tremor intensity between experimental and control groups of animals. This might mean that in the rat brain there are not histamine H_2 receptors.

Simultaneos application of both histamine H_1 and H_2 receptors agonists and antagonists produced tremor of higher intensity respectively. It has been reported that mepyramine, burimamide and 2-methylhistamine were all strong inhibitors of histamine methyltransferase (B a r t h and N i e m e y e r, 1973). This might be the possible explanation for the increase in tremor intensity after injection of these drugs. It could be pressupposed that in both cases there was an increase in histamine concentriation due to the inhibition of histamine methyltransferase by these drugs.

Histamine alone, agonists and antagonists of histamine H_1 and H_2 receptors seem to have no direct action on rigidity in rats. It might be possible that their effect on rigidity was indirect through some mechanism, a nature of which is still to be explained. S t e r n (1968) has published that an increase of histamine concentration in the mouse brain caused the potentiation of the action of acetylcholine. It might be possible that in our experiments mepyramine and burimamide inhibited histamine methyltransferase, which in turn produced an increase of histamine concentration. This increase might have caused the potentiation of acetylcholine action and rigidity of higher intensity than in control groups.

DUBRAVKA POTKONJAK i PAVAO ŠTERN

UTICAJ HISTAMINA, STIMULATORA I BLOKATORA H_1 I H_2 RECEPTORA NA EKSPERIMENTALNO IZAZVANI TREMOR I RIGOR PACOVA

KRATAK SADRŽAJ

Ustanovljeno je da zasad na periferiji postoje bar dvije vrste histaminskih receptora, koji su nazvani H_1 i H_2 receptori. Utvrđeno je da je 2-metilhistamin specifični stimulator H_1 receptora, a 4-metilhistamin specifični stimulator H_2 receptora. Specifični blokatori ovih receptora su mepiramin (H_1 receptori) i burimamid (H_2 receptori). Prije nego što je ovo bilo utvrđeno postavljena je hipoteza da u toku izraženog rigora i tremora dolazi do porasta količine ne samo acetilholina nego i histamina u mozgu obolelih ljudi i eksperimentalnih životinja.

Cilj rada bio je da se ispita uticaj histamina, stimulatora i blokatora histaminskih receptora na eksperimentalno izazvani tremor i rigor pacova.

Sve supstance bile su aplicirane stereotaktičkim putem direktno u corpus striatum. Tremor je izazvan intravenoznom primenom oksotremorina, a rigor intraperitonealnim davanjem flufenazina. Kontrolnim životinjama injiciran je fiziološki rastvor u navedenu regiju.

U poređenju sa kontrolnim grupama sam histamin, njegov agonist 2-metilhistamin dat sam za sebe i u istovremenoj kombinaciji sa 4-metilhistaminom, kao i istovremena aplikacija oba antagonista mepiramina i burimamida doveli su do pojačanja tremora. Davanje samog histamina i njegovih antagonista datih pojedinačno ili u istovremenoj kombinaciji izazvalo je pojačanje rigora u poređenju sa kontrolnim grupama.

Na osnovu dobijenih rezultata moglo bi se pretpostaviti da i u centralnom nervnom sistemu, tj. u mozgu tretiranih pacova verovatno postoje H_1 receptori, koji izgleda igraju određenu ulogu u patofiziologiji tremora, ali ne i rigora.

REFERENCES

1. Ash, A. S. F. and Schild, H. O.: — Receptors mediating some actions of histamine. Brit. J. Pharmac. Chemother. **27**, 427—439 (1966).
2. Barth, H. and Niemeyer, I.: Inhibition and activation of histamine methyltransferase by H_1 and H_2 receptor antagonists and methylated histamines. Naunyn-Schmiedeberg's Archives of Pharmacology. Suppl. to **227**, R 2 (1973).
3. Black, J. W., Duncan, W. A. M., Durant, C. J., Ganellin, C. R. and Parsons, E. M.: Definition and antagonism of histamine H_2-receptors. Nature **236**, 385—390 (1972).

4. Breljaković, B., Hadžović, S. and Stern, P.: Ein billiger und praziser stereotaktischer Apparat für Ratten und Katzen. Z. med. Labortechnik **5**, 47—48 (1964).

5. De Groot, J.: The rat forebrain in stereotaxic co-ordinates. In Verhandelingen der Köninklijke Nederlandse Akademie van Neten Schappen AFD Natuurkunde, Tweede Reeks. Deel LII, No 4, N. V. NoordlHollandsche Uttgevers Maatschappi, Amsterdam, 1959.

6. Horsley, V. and Clarke R. H.: The structure and functions of cerebellum exiamined by a new method. Brain **31**, 45—124 (1908).

7. Mc Geer, P. L., Boulding, J. E., Gibson, W. C. and Foulkes, R. G.: Drug-induced extrapyramidal reactions. Treatment with diphenylhydramine hydrochloride and dihydroxyphenylalanine, J. A. M. A. **177**, 665—670 (1961).

8. Stern, P.: Beitrag zur Wirkungsweise des Histaminis im Zentralnervensystem. Wien. klin. Wschr. **80**, 181—185 (1968).