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The Somatostatin Effect on the Turnover of Serotonin After the Stimulation and Blocking of the Histamine H_2 Receptor in the Rat's Brain

Wpływ somatostatyny na obrót serotoniny po stymulacji i zablokowaniu receptora histaminowego H_2 w mózgu szczura

Physiological effects of neuromediators, including the somatostatin, and their interactions with other neuromediator systems have been a subject to numerous examinations. Within the framework of researches on the neuromediators interactions the stimulation and blocking of the histamine H_2 receptor and the influence of somatostatin on the serotonin turnover in rat's brain were examined.

The aim of the study was to find out if histamine as well as ranitidine and somatostatin — widely used drugs in the gastroenterological diseases — have any side effects in the central nervous system after the peripheral administration.

MATERIALS AND METHODS

The studies were carried out on Wistar rats kept in standard conditions and without food for 24 hrs before experiments. The rats were divided into 9 groups depending on the administered substance (Table 1).

All used substances were administered intraperitoneally (i.p.) for three days in water solutions. Equal volumes of distilled water were administered to animals of control groups.

The turnover of serotonin in rat's brain was determined according to Tozer et al. (1) after administration of tranylcypromine (trans-2-phenylcyclopropylamine, Sigma). Serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) were assayed according to Curzon and Green (2).

The results were statistically analyzed and 5% was accepted as an error risk.

Table 1. Experimental groups of animals

Group	Number of rats	Administered substance	Administered dose
1	18	Histamine*	0.05 mg/kg
2	18	Histamine	0.5 mg/kg
3	18	Ranitidine**	3.0 mg/kg
4	18	Ranitidine	15.0 mg/kg
5	18	Somatostatin***	2.0 μg/kg
6	18	Somatostatin	10.0 μg/kg
7	18	Ranitidine + Histamine	15.0 mg/kg + 0.05 mg/kg
8	18	Histamine + Somatostatin	0.5 mg/kg + 10.0 μg/kg
9	18	Histamine + Ranitidine + Somatostatin	0.5 mg/kg + 15.0 mg/kg + 10.0 μg/kg
C	180	Control group	—

* Histaminum dihydrochloricum, Polfa, Jelenia Góra, Poland.
** Ranitidine hydrochloride, Glaxo, England.
*** Modustatin, Clin Midy, France.

RESULTS

(Figs 1—3)

There was found an acceleration of the serotonin turnover in rat's brain after both doses of histamine, but the effect noted after the lowest dose was more intense. Ranitidine, in a higher dose did not influence over the 5-HT turnover, whereas the lower dose caused a decrease of the serotonin turnover. The somatostatin effect on the 5-HT turnover was similar to histamine and it was also more intense after the lower dose. The blockade of histamine H_2 receptor with ranitidine did abolish the effect of histamine on the serotoninergic system in the rat's brain. Simultaneous administration of histamine and somatostatin increased the intensity of their action on the acceleration of the serotonin turnover. The blockade of histamine H_2 receptor with ranitidine did not abolish the effect

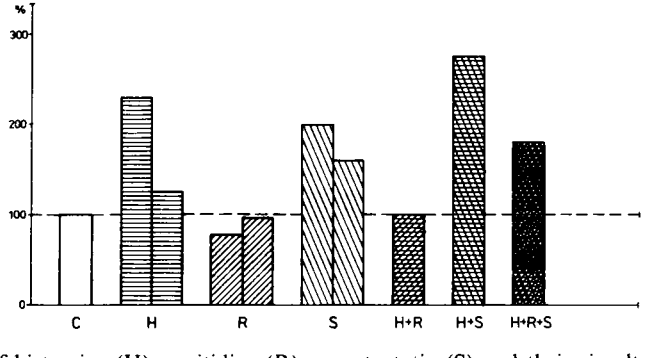

Fig. 1. Effect of histamine (H), ranitidine (R), somatostatin (S) and their simultaneous administration on the 5-HIAA decrease coefficient in the rat brain

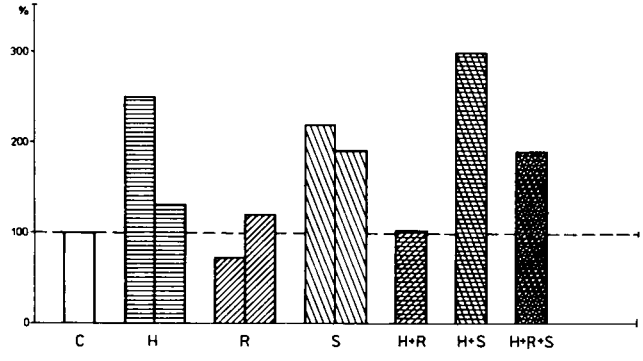

Fig. 2. Effect of histamine (H), ranitidine (R), somatostatin (S) and their simultaneous administration on the serotonin turnover rapidity in the rat brain

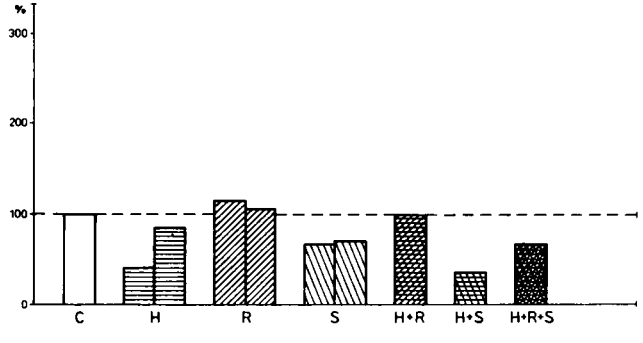

Fig. 3. Effect of histamine (H), ranitidine (R), somatostatin (S) and their simultaneous administration on the serotonin turnover duration in the rat brain

of somatostatin on the 5-HT turnover in rat's brain — it is similar to the effect of somatostatin alone.

DISCUSSION

Ranitidine as well as somatostatin are widely used drugs in gastroenterology. The inhibiting influence of somatostatin on pancreatic secretion (3) and on stomach secretion stimulated by pentagastrin and histamine has been proved (4, 5). Positive results of administering somatostatin in carcinoid syndrome have been described (6). The stimulation of the adrenergic system increases the delivery of somatostatin from D cells in the digestive system, whereas the action of cholinergic receptor agonists as well as serotonin, inhibits its delivery (7).

The biggest amount of somatostatin occurs in the digestive system and a little less in the brain. Its various interactions can be seen in this level as well. The

secretion of somatostatin by the neurosecretory cells of hypothalamus increases under the influence of the cholinergic stimulation, and this effect can be blocked by gamma-aminobutyric acid (GABA) or serotonin (8).

In our previous research we have examined an interaction between histaminergic and serotoninergic systems following the H_2 receptor stimulation with histamine and blocking with ranitidine. There was found an antagonistic action of both neurotransmitter systems in the alimentary tract and in the brain of rat (9).

In the present study we have found an influence of the peripheral administered somatostatin as well as histamine and ranitidine on the turnover of serotonin in the central nervous system. The peripheral influences of histamine and somatostatin on the rat's brain serotonin turnover are similar and result in its increase. Lakoski et al. (10) have also found the interactions between histaminergic and serotoninergic systems in the rat's brain. They observed a depression of the serotoninergic neurons activity following the microiontophoretic application of histamine to the dorsal raphe nucleus; histamine H_2 receptor antagonists attenuated this depression. But in contrast to our examinations, these interactions were observed after the central administration of drugs.

Somatostatin and histamine administered simultaneously increased their action on the acceleration of the 5-HT turnover. However, the action of somatostatin is not blocked by ranitidine. Its action on the serotoninergic cells activity is probably carried through the other receptors.

The lowest doses of histamine, ranitidine and somatostatin produce more evident changes of the serotonin turnover. Probably the action of higher doses of drugs is less specific and may change the activity of the serotonin structures by action on the other receptors.

Examination of the different neuromediator systems interaction under the influence of the drugs used in clinic can help in explanation of their side effects.

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STRESZCZENIE

W badaniach przeprowadzonych na szczurach szczepu Wistar stwierdzono przyspieszenie obrotu serotoniny w mózgu po dootrzewnowym podaniu histaminy. Ranitydyna w niskiej dawce powodowała zmniejszenie obrotu serotoniny. Zablokowanie receptora histaminowego H_2 za pomocą ranitydyny znosi wpływ histaminy na układ serotoninergiczny w mózgu szczura. Wpływ somatostatyny na obrót 5-HT był podobny jak histaminy, a jednoczesne ich podanie zwiększa intensywność działania na przyspieszenie obrotu serotoniny. Zablokowanie receptora histaminowego H_2 za pomocą ranitydyny nie znosi wpływu somatostatyny na obrót 5-HT w mózgu. Zaobserwowano interakcję tych trzech układów neuroprzekaźnikowych w mózgu po obwodowym podaniu leków.