In Vitro Effects of Pentifin on Some Neurotransmitter Systems in the Brain

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Pentifin and dopamine D_1 receptor antagonist SCH-23390 possess similar pharmacological properties. In the present work we studied *in vitro* effects of Pentifin on dopamine receptors. Experiments on rat ductus deferents showed that Pentifin acts as a weak ligand of dopamine receptors. Our results indicate that the antihaloperidol effect of Pentifin is not related to the blockade of dopamine receptors.

Key Words: *dopamine, acetylcholine, and epinephrine receptors*

New compounds belonging to a chemical group of acetylene aminoalcohols were synthesized after the search for medicinal preparations for the prevention and therapy of parkinsonism [4]. These compounds display specific activity on the model of haloperidol-induced catalepsy [1]. Pentifin (4-piperidino-1-phenyl-1-cyclopentyl butin-2-ol-1-hydrochloride) was most effective in this test. Activity of this substance in blocking muscarinic receptors is comparable with that of atropine. Published data show that the ability of Pentifin to prevent the development of haloperidol-induced extrapyramidal disorders is an order of magnitude higher that that of antiparkinsonian preparations acting as muscarinic receptor antagonists [3]. *In vivo* experiments with blockade of M_1-, M_2-, and M_3-cholinoceptors demonstrated that antihaloperidol activity of Pentifin greatly surpasses its anticholinergic activity [2]. It was hypothesized that antagonistic properties of Pentifin and haloperidol are associated not only with blockade of muscarinic receptors. The mechanism underlying action of Pentifin not related to its anticholinergic activity was extensively studied.

Here we evaluated whether the effects of Pentifin are associated with modulation of dopaminergic activity and studied its influence on dopamine receptors.

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MATERIALS AND METHODS

The effects of Pentifin on dopamine receptors were studied on ductus deferens isolated from experimental animals. Experiments were performed on 85 rats weighing not more than 200 g and kept in a vivarium under standard conditions. Highly selective dopamine D_1 receptor antagonist SCH-23390 served as the reference preparation [5].

Ductus deferens was isolated and maintained in a 20-ml well with aerated Krebs solution (load 0.65 g, 32°C). Dopamine in a concentration of 3×10^{-6} mg/ml was added to a well. Contraction of the test object was recorded on an Ugo Basile 4050 device using an isometric transducer. The test object was washed with Krebs solution. Pentifin and SCH-23390 were added in concentrations of 10^{-5}-10^{-15} M (0.2 ml). We estimated the effect of test substances on ductus deferens. Moreover, the reaction of ductus deferens to dopamine was evaluated after treatment with antagonists for 20 min. The duct was washed with Krebs solution after each treatment.

The effects of Pentifin and SCH-23390 on muscarinic receptors were studied on small intestine segments (SIS) from outbred male rats weighing 180-200 g. The samples were taken after starvation. The intestinal segment (0.4 g) was placed in a well with aerated Tyrode's solution (20 ml) at 37.5°C. The load was 0.85 g. Contraction of SIS produced by acetyl-

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choline in a concentration of 10^{-6} g/ml was recorded on an Ugo Basile 4050 device using an isometric transducer. We studied the effects of SCH-23390 and Pentifin in concentrations of 10^{-14}-10^{-6} M on SIS and their reaction to acetylcholine. The test objects were washed as described above.

The effects of Pentifin and SCH-23390 on epinephrine receptors were studied on seminal vesicles from adult male rats weighing not less than 200 g. The test object was kept in aerated Tyrode's solution at 32°C. The initial load was 0.65 g. Changes in the tone of the test objects were evaluated as described above. Norepinephrine in a concentration of 3×10^{-6} g/ml was used as the antagonist [1].

RESULTS

In vivo activity of Pentifin is comparable with that of selective dopamine D_1 receptor antagonist SCH-23390 [5]. Previous studies showed that SCH-23390 is as potent as Pentifin in preventing catalepsy produced by haloperidol. Pentifin and SCH-23390 were antagonistic to apomorphine in the open-field test. Both compounds reduced the acetylcholine release in the striatum. These data suggest that antihaloperidol activity of Pentifin is realized via the dopaminergic mechanism.

Our experiments demonstrated that unlike SCH-23390, Pentifin produced no direct blocking effect on dopamine receptors in the spermatic cord of rats (Table 1). This is consistent with published data that Pentifin blocks cholinoceptors [3].

Pentifin in high concentrations caused contraction of the spermatic cord. It should be emphasized that the concentration of Pentifin markedly surpassed that of SCH-23390 (Table 1). Experiments with the small intestine produced opposite results. Changes in rat seminal vesicles were observed only after treatment with preparations in high concentrations.

TABLE 1. Blocking Effect of Pentifin and SCH-23390 in EC_{50} (M) on Several Receptors in Isolated Rat Organs

Substance	Dopamine receptor	Epinephrine receptor	M_1-cholinoceptor
SCH-23390	3×10^{-12}	$>5\times10^{-5}$	$>5\times10^{-5}$
Pentifin	7×10^{-5}	8×10^{-6}	2×10^{-7}

Our results show that Pentifin produces no direct effects on dopamine receptors. Therefore, antihaloperidol activity of this compound is related to modulation of other neurotransmitter systems.

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