# Study of Bipathic Effect of Haloperidol

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Parallel treatment with haloperidol and ultralow-dose haloperidol significantly increased the psychotropic neuroleptic effect of traditional doses of the drug under conditions of preliminary of simultaneous administration, which attests to a bipathic effect of this preparation. Combination of ultralow and therapeutic doses of haloperidol significantly reducted its cataleptogenic side effect.

**Key Words:** *haloperidol; ultralow doses; bipathy; psychotropic activity; catalepsy*

Haloperidol, a neuroleptic widely used in clinical practice, is characterized by a number of manifest side effects. For example, long-term haloperidol therapy can lead to the development of extrapyramidal disorders, such as increased muscle tone, tremor, akinesia up to the neuroleptic syndrome associated with hyperthermia, muscle rigidity, and loss of consciousness. This necessitates the search for new drugs with pronounced neuroleptic effect and lesser number of side effects.

Ultralow-dose drugs modify activity of drugs injected in traditional doses; this phenomenon received the name of bipathy [5,6]. Experimental studies of bipathic mode of drug administration showed that phenazepam in ultralow doses ($10^{-9}$-$10^{-14}$ mol/kg) exhibited a pronounced anxiolytic effect, not accompanied by side effects characteristic of benzodiazepine tranquilizers (myorelaxant and sedative) [1,2,4].

We studied the psychotropic neuroleptic and side cataleptogenic effects of haloperidol during bipathic treatment.

## MATERIALS AND METHODS

The study was carried out on 185 male C57Bl/6 mice (20-25 g) and 45 outbred male albino rats (250-270 g) divided into experimental groups at random.

Modification of the neuroleptic effect of haloperidol during bipathic treatment was studied by the apomorphine verticalization test on mice. Injection of apomorphine (dopamine receptor agonist) causes stereotypy in mice, which is suppressed by neuroleptics blocking dopaminergic transmission [3]. The verticalization status was induced by subcutaneous injection of apomorphine hydrochloride (2.5 mg/kg) 10 min before the start of the test. After injection, the mice were placed into cylindrical wire cages (13 cm in diameter, 16 cm high) and their behavior was recorded every 2 min over 1 h. The intensity of verticalization was evaluated using a 4-point scale (by the number of paws, by which the animal clutched to the vertical drid). Summary verticalization score for each animal over the test, mean verticalization value for each group, and intensity of vertical activity in percent of the control were estimated.

The animals were divided into 5 groups, 10 per group. Control mice were injected with distilled water. Mice of experimental group 1 were simultaneously injected with apomorphine (2.5 mg/kg) and distilled water intraperitoneally 10 min before observation. Group 2 mice received simultaneously apomorphine (2.5 mg/kg) and haloperidol intraperitoneally (0.07 ml/kg). Group 3 animals were simultaneously injected with ultralow-dose haloperidol (ULDH; mixture of homeopathic dilutions

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C12+C30+C200 corresponding to a concentration of $10^{-27}$ M) in a dose of 2.5 ml/kg, haloperidol intraperitoneally (0.07 ml/kg), and apomorphine (2.5 mg/kg). Group 4 mice were injected with ULDH 10 min before apomorphine (2.5 mg/kg) and intraperitoneal haloperidol (0.07 mg/kg).

Evaluation of cataleptogenic effects of neuroleptics is a priority problem in detection of the probability of side effects presenting by extrapyramidal disorders [3]. In the next experimental series, catalepsy was induced by intraperitoneal injection of haloperidol (ampoule solution; 0.7 mg/kg) 60 min before the test. The severity of catalepsy was scored using a 6-point scale by the capacity of animal to retain preset posture during a certain period: not to put back the fore paw, elevated onto a step for 10 sec (1 point: only one paw left on the lower step; 2 points: both paws, one-by-one, are left on the lower step; 4 points: only one fore paw left on the upper step; 6 points: both fore paws one-by-one are left on the 4th step). Testing was carried out 60, 120, and 180 min after drug injection.

Side effect (cataleptogenic) was studied in 6 groups, 10 animals per group. Controls were injected with a high dose of haloperidol (0.7 mg/kg). Animals of experimental group 1 were simultaneously injected with haloperidol (0.7 mg/kg) and reference drug cyclodol (6 mg/kg). Group 2 animals were simultaneously injected with ULDH (2.5 mg/kg) and haloperidol (0.07 ml/kg). Group 3 animals were simultaneously injected (intraperitoneally) with ULDH (2.5 mg/kg), cyclodol (6 mg/kg), and haloperidol (0.07 ml/kg). Group 4 animals were injected with ULDH (2.5 mg/kg) 10 min before haloperidol (0.7 mg/kg). Group 5 animals were injected with cyclodol (6 mg/kg) and after 10 min with haloperidol (0.07 ml/kg).

The results were statistically processed using parametrical (Student's $t$ test for related and independent samplings, ANOVA) and nonparametric (Wilcoxon, Mann—Whitney, and $\chi^2$ tests).

## RESULTS

Administration of apomorphine induced verticalization (score 85.6±2.1).

Injection of haloperidol in a dose of 0.07 mg/kg sharply reduced the effect of apomorphine to 10.8± 3.5 points ($p<0.05$ compared to apomorphine group).

Simultaneous injection of ULDH and haloperidol reduced verticalization to 5±2.4 points, but the difference from haloperidol group did not reach the level of statistical significance. Injection of ULDH 10 min before haloperidol completely abolished apomorphine verticalization (0±0 points; Table 1).

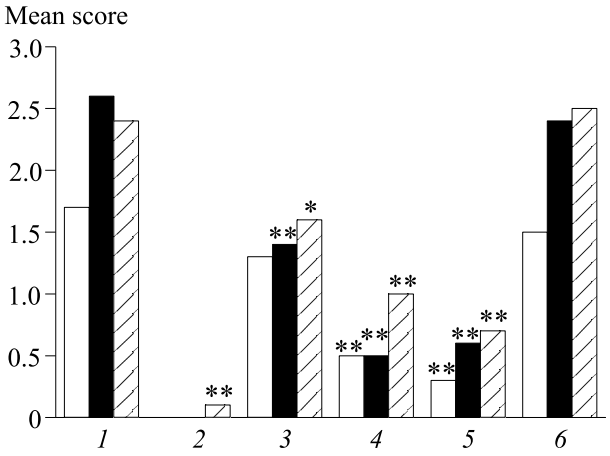


**Fig. 1.** Effects of ultralow-dose haloperidol and cyclodol on the severity of haloperidol catalepsy in rats (Morpurgo's method). *1*) haloperidol; *2*) heloperidol+cyclodol simultaneously; *3* haloperidol+ULDH simultaneously; *4*) haloperidol+cyclodol+ULDH simultaneously; *5*) cyclodol+haloperidol after 10 min; *6*) ULDH+haloperidol after 10 min. Light bars: 60 min; dark bars: 120 min; cross-hatched bars: 180 min. *$p<0.05$, **$p<0.001$ compared to haloperidol.

Injection of ULDH simultaneously with haloperidol caused a 24% reduction of catalepsy after 60 min, 46% reduction after 120 min ($p<0.001$), and 33% reduction after 180 min of observation ($p<0.05$) in comparison with animals injected with haloperidol alone (Fig. 1). Injection of ULDH 10 min before haloperidol virtually did not modify the severity of catalepsy.

Parallel injection of cyclodol and ULDH decreased the intensity of haloperidol-induced catalepsy by 71% after 60 min ($p<0.001$), by 81% after 120 min ($p<0.001$), and by 58% after 180 min ($p<0.001$).

Injection of cyclodol 10 min before haloperidol significantly reduced the intensity of catalepsy: by 82% after 60 min ($p<0.001$), by 77% after 120 min ($p<0.001$), and by 71% after 180 min ($p<0.001$).

**TABLE 1.** Effects of Haloperidol and ULDH on Intensity of Verticalization in Mice

| Group | Mean score for group, $M\pm sd$ |
|---|---|
| Intact animals | 0±0 |
| Apomorphine (2.5 mg/kg) | 85.6±2.1* |
| Haloperidol (0.07 mg/kg)+ apomorphine (2.5 mg/kg) | 10.8±3.5$^{+}$ |
| ULDH+haloperidol (0.07 mg/kg)+ apomorphine (2.5 mg/kg) simultaneously | 5±2.4$^{+}$ |
| ULDH+after 10 min haloperidol (0.07 mg/kg)+apomorphine (2.5 mg/kg) | 0±0$^{+x}$ |

**Note.** $p<0.05$ compared to *intact animals; $^{+}$apomorphine; $^{x}$haloperidol+apomorphine.

However, the effect was less pronounced than after simultaneous injection of the drugs.

Hence, bipathic injection of haloperidol and ULDH potentiated its antipsychotic effect and reduced its side cataleptogenic effects. The psychotropic neuroleptic effect was stimulated most intensely after ULDH injection before haloperidol, while the cataleptogenic effect decreased significantly after simultaneous injection of ULDH and haloperidol. Anticataleptogenic and neuroleptic effects of ULDH were less pronounced than those of the reference drug cyclodol (cholinolytic).

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