Epinephrine Potentiates Antipsychotic, but not Cataleptogenic Effect of Haloperidol in Rats

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Intramuscular injection of haloperidol or epinephrine in a minimum effective dose produces the maximum antipsychotic effect in rat model of schizophrenia, *i.e.* completely removes stereotypy, hyperlocomotion, and ataxia induced by MK-801. Haloperidol in the specified dose induces catalepsy, while epinephrine exhibits no cataleptogenic effect. Combined intramuscular injection of haloperidol and epinephrine in the threshold doses, ineffective in monotherapy, causes the maximum antipsychotic effect, but not catalepsy. Preliminary anesthesia of the gastric mucosa with 1% lidocaine and blockade of intramural ganglia in the gastric mucosa with hexamethonium completely abolished the potentiated antipsychotic effects produced by combined treatment with haloperidol and epinephrine. Hence, potentiation of the antipsychotic effect of haloperidol with epinephrine is related to stimulation of afferents in the gastric mucosa.

Key Words: *epinephrine; haloperidol; MK-801; schizophrenia; catalepsy*

Haloperidol, a neuroleptic drug easily crossing the blood-brain barrier and blocking postsynaptic dopamine receptors in the striatum [3,8], is characterized by the highest antipsychotic activity in patients with schizophrenia and in rats with experimental schizophrenia induced by dizolcipine maleate (MK-801). However, the therapeutic effect of haloperidol develops only when it is used in high doses causing severe extrapyramidal disorders, such as parkinsonism, catalepsy, and dyskinesia [3,13,15].

In contrast to haloperidol, cholecystokinin (CCK) reducing dopamine release in the striatum as a result of CCK_A receptor stimulation in the subdiaphragmatic gastric vagus afferents, is a peripheral antipsychotic causing no extrapyramidal disorders even in high doses [4,6,12]. Combined use of haloperidol and CCK potentiates their antipsychotic effects and attenuates extrapyramidal disorders due to reduction of haloperidol dose [7,10].

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Systemic treatment with epinephrine in high doses leads to the development of maximum analgesic, antidepressant, and anticonvulsant effects due to activation of the subdiaphragmatic vagus afferents, caused by the stimulatory effect of epinephrine on the gastric mucosa afferents [1,2,9]. The aim of our study was to prove that epinephrine, similarly as CCK, exhibits the maximum antipsychotic effect in systemic high-dose therapy, while in low doses potentiates the antipsychotic effects of haloperidol without the development of extrapyramidal disorders in rats.

MATERIALS AND METHODS

Experiments were carried out on the model of schizophrenia induced in outbred albino male rats (180-200 g) by intramuscular injection of MK-801 in a dose of 0.4 mg/kg [11,14]. Antipsychotic effects of epinephrine, haloperidol, and haloperidol+ epinephrine were quantitatively evaluated on the basis of their minimum effective doses preventing (after intramuscular injection) the development of

stereotypy, hyperlocomotion, and ataxia in 100% rats within 60 min after injection of MK-801. Cataleptogenic activity was evaluated by the duration of immobilization of rats placed for 3 min on wire mesh screen inclined by 45° to the horizontal plane 60 min after injection of haloperidol, epinephrine, and haloperidol+epinephrine [5]. For evaluation of the role of gastric mucosa afferents in the mechanism of the potentiating influence of epinephrine on the antipsychotic effect of haloperidol, the animals received intragastrically 1% lidocaine (0.5 ml) or hexamethonium in a dose of 0.2 mg/kg 30 min before intramuscular injection of epinephrine+haloperidol combination [1,2]. Control and experimental groups consisted of 8-10 animals. Haloperidol, epinephrine, and (+)-MK-801 (Sigma) were used in the study.

RESULTS

Intramuscular injection of MK-801 in a dose of 0.4 mg/kg caused hyperlocomotion and stereotypy after 10-12 min and ataxia after 15-20 min; these symptoms persisted for 50-70 min after injection of MK-801. These behavioral disorders (hyperlocomotion, stereotypy, ataxia) are characteristic signs of schizophrenia model in rats induced by a high dose of MK-801 [11,14]. It was shown that epinephrine and haloperidol injected intramuscularly in threshold doses of 0.01 and 0.03 mg/kg, respectively, exhibited no antipsychotic activity (did not prolong the latency from the moment of MK-801 injection to the onset of stereotypy, hyperlocomotion, and ataxia in rats). Epinephrine in a dose of 0.03-0.06 mg/kg (intramuscularly) and haloperidol in a dose of 0.1-0.2 mg/kg (intramuscularly) prolong the latency of the development of stereotypy, hyperlocomotion, and ataxia after MK-801 injection from 10-20 to 30-40 min.

Intramuscular injections of haloperidol and epinephrine in minimum effective doses of 0.15 and 0.48 mg/kg, respectively, cause the maximum antipsychotic effect, *i.e.* prevent the development of stereotypy, hyperlocomotion, and ataxia within 60 min after injection of MK-801 in 100% rats (Table 1). Haloperidol in a dose of 0.48 mg/kg exhibits not only maximum antipsychotic activity, but also causes significant catalepsy in rats, 12-fold prolonging the duration of immobilization on the inclined grid in comparison with the control (Table 1). On the other hand, epinephrine in a dose of 0.15 mg/kg does not prolong immobilization time on the inclined grid in comparison with the control (Table 1), *i.e.* in contrast to haloperidol it possesses no cataleptogenic effect.

Intramuscular injection of haloperidol in combination with the threshold dose of epinephrine (0.01 mg/kg intramuscularly) allowed 16-fold reduction of the minimum effective dose of haloperidol causing the maximum antipsychotic effect to a level of the threshold dose (0.03 mg/kg), which was ineffective in monotherapy (Table 1). Preliminary anesthesia of the gastric mucosa with 1% lidocaine and blockade of intramural gastric ganglia caused by local intragastric hexamethonium completely eliminated the potentiated antipsychotic effects of haloperidol+epinephrine combination (Table 1). Hence, potentiation of the antipsychotic effects of haloperidol with epinephrine is associated with the stimulatory effect of epinephrine on gastric mucosa afferents [1,2]. Threshold epinephrine doses potentiate only the antipsychotic, but not cataleptogenic effect of haloperidol, because the combination of haloperidol with epinephrine does not prolong the time of immobilization on the inclined grid in comparison with the control (Table 1).

Cholecystokinin is a peripheral antipsychotic reducing dopamine release in the striatum as a result of CCK_A receptor stimulation in the subdiaphragmatic gastric vagus afferents [6,12]; in low doses this agent potentiates the antipsychotic effect of

TABLE 1. Antipsychotic and Cataleptogenic Effects of Haloperidol, Epinephrine, and Their Combinations

Substance	Antipsychotic effect, mg/kg	Duration of immobilization on grid, sec
Distilled water, 0.2 ml intramuscularly (control)	No effect	10.0±1.1
Epinephrine, intramuscularly	0.150±0.017	12.0±1.5
Haloperidol, intramuscularly	0.48±0.06	120±14
+epinephrine, 0.01 mg/kg intramuscularly	0.0300±0.0036	10.0±1.2
+epinephrine, 0.01 mg/kg intramuscularly+lidocaine, 1% (0.5 ml intragastrically)	0.44±0.05	125±15
+epinephrine, 0.01 mg/kg intramuscularly+hexamethonium (0.2 mg/kg intragastrically)	0.400±0.045	130±17

Note. Epinephrine and haloperidol were injected in the minimum effective doses causing the maximum antipsychotic effect.

haloperidol, but not its extrapyramidal effects [7, 10]. However, CCK is not widely used in clinical practice because of complex technology of manufacture of its dosage form and pronounced anxiogenic and prodepressant effects [4].

We previously showed that the maximum antidepressant and analgesic effects caused by intramuscular injection of epinephrine in high doses are due to activation of the CCK_A receptors of gastric vagus afferents with endogenous CCK, whose secretion increases as a result of epinephrine stimulation of the gastric mucosa afferents [1]. Hence, systemic epinephrine in threshold doses, similarly as exogenous CCK, presumably potentiates the antipsychotic effects of haloperidol in rats with schizophrenia as a result of stimulation of gastric vagus afferents with endogenous CCK, whose secretion is stimulated because of activation of the gastric mucosa afferents with epinephrine. Similarly as CCK, epinephrine does not potentiate the cataleptogenic effect of haloperidol.

The results of our experiments indicate that compositions for systemic treatment including threshold doses of haloperidol and epinephrine can be used as highly effective and safe means for the treatment of schizophrenia, because they are not inferior to haloperidol in the maximum dose by their antipsychotic activity, but, in contrast to it, cause no extrapyramidal disorders.

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