Effects of Short-Term Exposure to Haloperidol and Reserpine on Dopamine Turnover in Nigrostriatal System in Rat Brain

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 150, No. 8, pp. 151-153, August, 2010
Original article submitted August 26, 2009

Spectrophotometric methods were employed to determine activity of dopamine metabolism enzymes, tyrosine hydroxylase and monoamine oxidase B, in nigrostriatal structures of the brain in Wistar rats after short-term (60 min) haloperidol or reserpine treatment. Activating effect of the test compounds on dopamine synthesis, more pronounced in the caudate nucleus, was demonstrated. Utilization of monoamine oxidase B transmitter was activated by haloperidol, but not reserpine. Some peculiarities of response of the nigrostriatal system structures to the test compounds were noted. We hypothesized the presence of a phase of dopamine metabolism activation, aimed at maintenance of dopamine transmission and nervous system adaptation at early terms after reserpine and haloperidol administration.

Key Words: *nigrostriatal dopaminergic structures; tyrosine hydroxylase; monoamine oxidase B; haloperidol; reserpine*

Pharmacological induction of stereotypic behavioral reactions is widely used as experimental model for studies of psycho- and neuropathological disturbances produced by some medications, the so-called "dopamine pathology" [6,9].

Administration of agents reducing dopamine transmission modulates animal behavior, impairs motor integration, and induces a depression-like condition, which to a large extent is mediated by the effects of the test compounds on dopamine (DA) metabolism, in particular by blockade of D_2-receptor (haloperidol) or by impairment of mediator incorporation into vesicles (reserpine) *etc*. These effects manifested as hypoactivity of the dopaminergic system [1,8].

In this study, modeling of dopaminergic system dysfunction was used to study changes in DA metabolism by the parameters of transmitter synthesis and utilization, in particular, activities of tyrosine hydroxylase (THL) and monoamine oxidase B (MAO B) under the influence of short-term administration of haloperidol or reserpine to rats. We also studied peculiarities of the responses of nigrostriatal structures of the brain (caudate nucleus and substantia nigra) to single treatment with the agents with different mechanism of action on dopaminergic system.

MATERIALS AND METHODS

Experiments were carried out on 24 male Wistar rats divided into 3 equal groups. The controls were injected with 0.9% NaCl and animals of two experimental groups intraperitoneally received 0.5 mg/kg haloperidol or 1.5 mg/kg body weight reserpine. The rats were decapitated under mild ether anesthesia 60 min after treatment (all procedures were performed in accordance with requirements for work with experimental animals), the brain was removed on cold, and the caudate nucleus and substantia nigra were isolated. Subcellular tissue fraction of the studied structures was isolated by differential centrifugation at 10,000*g*

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0007-4888/10/1502-0188

(20 min) and 20,000*g* (15 min) for evaluation of MAO B and THL activities, respectively.

THL activity was assessed spectrophotometrically as described previously [4]. L-tyrosine solution was used as a substrate. Enzyme activity was expressed as a change in extinction at 335 nm per mg protein in a sample over 60 min.

MAO B activity was assessed spectrophotometrically as described elsewhere [2]. Enzyme activity was expressed as ΔE450 per mg protein over 60 min.

The results were expressed in absolute values and in percent of the control (taken as 100%) and processed statistically using Statistica 6.0 software, nonparametric Wilcoxon test for paired data: control–haloperidol and control–reserpine.

RESULTS

Within the first 15-20 min after administration of haloperidol or reserpine, the rats exhibited motor anxiety of different degree, then calmed down and by the 60th minute stood still in a certain position characterized by muscle rigidity and stiffness.

Pronounced changes in activity of DA metabolism enzymes were found in rat brain structures (caudate nucleus and substantia nigra) following haloperidol or reserpine administration. Moreover, these changes were differently expressed in the studied structures and were specific for the used compounds (Table 1, Fig. 1). Thus, haloperidol significantly increased THL activity in the caudate nucleus (152%, $p<0.05$); its activity in the substantia nigra also tended to increase, but to a lesser extent (112%, $p=0.07$). The effect of reserpine on THL activity in the caudate nucleus was less pronounced (117%, $p<0.05$) and in the substantia nigra similar (127%, $p<0.05$) to the effects of haloperidole.

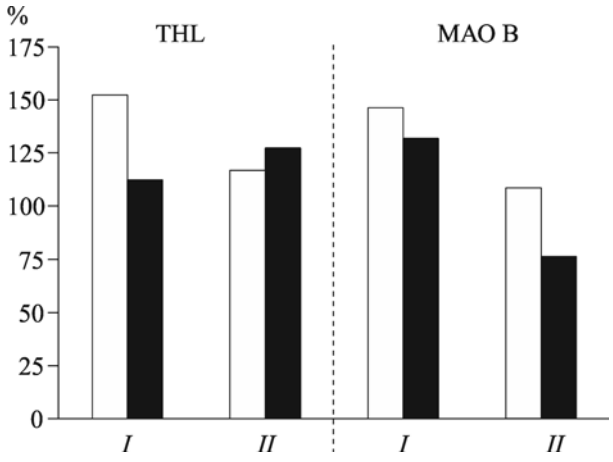

Fig. 1. Effects of haloperidol (*I*) and reserpine (*II*) on activity of DA metabolism enzymes in nigrostriatal structures of rat brain under conditions of acute dysfunction of the dopaminergic system. Light bats – caudate nucleus, dark bars – substantia nigra.

These results attest to intensification of DA synthesis in rat brain at early terms after administration of the test drugs impairing dopaminergic transmission. We previously showed a 1.5-fold increase in the content of homovanillic acid (neurotransmitter catabolism product) in rat caudate nucleus 60 min after haloperidol administration in comparison with the control [3].

Apparently, single administration of agents reducing dopaminergic transmission is followed by a short-term phase of brain metabolism stimulation. Our findings suggest that DA synthesis (THL activity) considerably increased in both nigrostriatal structures, which led to activation of the whole system of transmitter turnover.

Some peculiarities of the action of the studied compounds on DA utilization processes were noted. Thus, 60 min after haloperidol administration significant MAO B activation (146% from control, $p<0.05$)

TABLE 1. Changes in Specific Activity of THL and MAO B in Caudate Nucleus and Substantia Nigra in Rat Brain after Short-Term Treatment with Haloperidol (0.5 mg/kg) and Reserpine (1.5 mg/kg) (*M*±*m*)

Group		THL	MAO B
Caudate nucleus			
	control	1.14±0.17	1.00±0.17
	haloperidol	1.72±0.27*	1.47±0.12*
	reserpine	1.32±0.22*	1.09±0.15
Substantia nigra			
	control	1.39±0.39	1.63±0.19
	haloperidol	1.54±0.36**	2.14±0.38
	reserpine	1.77±0.48*	1.24±0.15*

Note. *$p<0.05$, **$p=0.07$ in comparison with control.

was observed in the caudate nucleus and a tendency to increase in enzyme activity (131%; Table 1; Fig. 1) was noted in the substantia nigra. Reserpine did not significantly affect MAO B activity in the caudate nucleus, and in substantia nigra even a decrease in this parameter was noted (76% from the control), *i.e*. phase of activation of the processes of transmitter utilization was virtually absent, which probably indicates that phase of total decrease in DA metabolism under the influence of reserpine appears earlier.

The processes of DA synthesis (THL activity) are more resistant to pathological influences; development of pronounced motor impairments, as a manifestation of dopamine system hypofunction and catecholamine pool depletion, appears when reserpine and haloperidol are administered for longer periods.

There are published reports on phasic effects of neuroleptic, particularly haloperidol, on animal behavior and neurotransmitter metabolism in the brain. According to physiological data, repeated haloperidol injections resulted in reduction of excitement phase and in transfer from depression-like state to the development of pronounced bradykinesis [5].

As it was mentioned, there are certain differences in the intensity of the effects of the studied compounds: reserpine induced THL less pronounced activation in the nigrostriatal system compared to haloperidol. These data is also confirmed by immunohistochemical THL detection: the number of THL-positive neurons in substantia nigra after short-term reserpine administration remained unchanged and only a tendency to an increase in the fraction of neurons with high enzyme content was noted [7].

Thus, our findings attest to different sensitivity of some components of DA metabolism system to haloperidol and reserpine, which is apparently associated with differences in the mechanism of their actualization and regulation during the dopamine system functioning.

Obtained experimental data allow assessment of the peculiarities of the response of come brain structures comprising the nigrostriatal system during modeling of DA turnover dysfunction in short periods of pathological influences and confirm conception of functionally-determined morphochemical heterogeneity of CNS.

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