EFFECT OF HALOPERIDOL ON EXTRACELLULAR CONCENTRATIONS OF DOPAMINE AND ITS METABOLITES IN THE RAT SEPTUM DURING MURICIDAL AGGRESSION

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Because of many technical difficulties the problem of the neurochemical processes taking place in the animal brain during realization of acts of aggression (attacking, biting, and so on) has not yet been adequately studied. Meanwhile it has been suggested that pharmacologic action on precisely these neurochemical events actually taking place in the course of aggression is the most effective approach to the correction of different forms of pathological aggressiveness. Neuroleptics, substances with a marked antiaggressive activity, are particularly interesting from this point of view [6]. Neuroleptics are known to block receptors of dopamine (DA), a mediator playing an important role in the initiation and maintenance of various forms of aggression in animals [6, 8]. It has been shown that nerve cells of the mesolimbicocortical dopaminergic system – a major transmitter system of the brain – have a well-developed network of synaptic endings in the amygdala, the septum, and other brain structures that constitute the principal neuroanatomical substrate of aggressive behavior [3, 8].

The aim of the investigation was to study the effect of the neuroleptic haloperidol on the dynamics of the extracellular concentrations of DA and its metabolites – 3,4-dihydroxyphenylacetic acid (DHPAA) and homovanillic acid (HVA) in the rat septum during realization of muricidal aggression.

EXPERIMENTAL METHOD

Experiments were carried out on 18 noninbred male rats weighing about 300 g, in which muricidal behavior was induced by a combination of deprivation of food for 48 h and subsequent long-term (1-1.5 months) social isolation. Animals killing mice in not more than 10 sec were chosen for the experiment. To stimulate their aggressiveness, the animals were used in the experiments after starvation for 24 h.

Under the experimental conditions the mouse was introduced into the cage of an aggressive rat by means of dressing forceps, so that the total duration of the rat's aggressive behavior could be considerably increased.

Scalping of the rats, implantation of cannulas into the septum (taking coordinates from a stereotaxic atlas of the rat brain [1]), and fixation of the cannula to the skull (with quick-hardening plastic) were carried out under ether anesthesia. The accuracy of insertion of the cannulas into the septum was confirmed macroscopically in brain sections fixed in 10% formalin solution.

The septum was perfused through a push–pull cannula with tip 0.6 mm in diameter, and with the inner barrel protruding by 0.5 mm. The choice of the push–pull cannula and not the more widely used microdialysis cannula was determined by technical limitations associated with the brevity of the act of aggression and the need to

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TABLE 1. Concentrations (in ng/ml) of DA and its Metabolites (DHPAA and HVA) in Perfusion Fluid from Rat Septum during Aggressive Acts before and during Injection of 2 mg/kg Haloperidol (M ± m)

Type of activity	Dopamine	DHPAA	HVA
Before aggression	2,10±0,35	4,88±0,84	4,81±0,63
During aggression	1,22±0,31*	3,68±0,82*	4,10±0,58*
After aggression	1,70±0,21	4,39±0,85	5,30±0,40
60 min after injection of haloperidol			
Before aggression	2,20±0,52	4,26±0,95	5,53±1,68
During aggression	0,87±0,42*	6,33±1,89*	11,52±2,60*
After aggression	1,49±0,92	5,44±1,04	6,12±1,41

Legend. *$p < 0.05$ compared with value of parameter before act of aggression (signs test).

perfuse a comparatively small structure. By using the push–pull cannula it was possible to obtain higher and more reliably detectable concentrations of the substances in the perfusion fluid. The septum was perfused with physiological saline at the rate of 5 μl/min by means of a micropump. The perfusion fluid was collected in plastic tubes every 2 min and 10 μl of 0.1 M $HClO_4$ solution was added to it. Collection of the perfusion fluid for analysis began not earlier than 5 h after the end of anesthesia. The concentrations of DA and its metabolites in perfusion fluid from the rat septum was determined by HPLC with electrochemical detection [5] before, during, and after the act of aggression, before and 1 h respectively after intraperitoneal injection of the neuroleptic haloperidol in a dose of 2 mg/kg.

The effect of haloperidol on muricidal behavior was tested in 11 animals, except that in the investigation of the dynamics of the extracellular concentration of DA and its metabolites in the rat septum during the act of aggression, before and during the action of haloperidol, seven animals were used.

The latent period of killing of the mouse and the number of rat victims in the group were chosen as indicators of muricidal behavior. The time of observation was 120 sec. If during this period the rat did not kill or even attack the mouse, complete suppression of aggressive behavior was recorded. The results were subjected to statistical analysis by the nonparametric signs test [2].

EXPERIMENTAL RESULTS

The initial mean values of the latent period of the first attack and of killing the mouse were 1.6 ± 1.2 and 3.4 ± 1.9 respectively for all 18 animals. During analysis of the antiaggressive effect of haloperidol in a separate group of rats (11 animals) values of the latent periods of the first attack and of killing of the mouse before injection of the neuroleptic were 1.5 ± 1.1 and 3.1 ± 2.1 sec respectively. Muricidal aggressiveness of the rats was considerably reduced 60 min after intraperitoneal injection of the neuroleptic in a dose of 2 mg/kg. A significant increase in the latent period of attack ($p < 0.01$, Student's test) to 13.5 ± 7.1 sec was observed. Under the influence of haloperidol only four of the 10 rats killed a mouse and the mean latent period of killing was 72 sec ($p < 0.05$, signs test).

After implantation of the cannulas all the chosen animals demonstrated elements of muricidal aggression: approaching the mouse held in the forceps, tracking it, and repeated biting. However, only in four of seven cases was the mouse killed. The latent period of attack and of killing the mouse in rats of this group was significantly longer than in intact animals, and reached 20-40 sec. Moving the mouse away from the rats with the forceps increased the duration of the aggressive actions to 1.5-2 min.

Total inhibition of muricidal aggression was observed 1 h after injection of haloperidol intraperitoneally in a dose of 2 mg/kg: none of the rats with an implanted cannula killed the mouse. In most cases, after several weak attacks the rats lost interest in the mice and subsequently hardly responded at all to them.

Data on the change in concentrations of DA and its metabolites in the perfusion fluid from the septum are given in Table 1. The initial levels of DA, DHPAA, and HVA were 0.51 ± 0.14, 2.02 ± 0.65, and 2.19 ± 0.71 ng/ml respectively. During the act of muricidal aggression, significant reductions were observed in concentrations of DA and its metabolites in the perfusion fluid compared with the initial state, or the state after aggression ($p < 0.05$, signs test). In this case, the level of release of the mediator into the septum was reduced by more than 40% compared with the initial value. Thus the results indicate lowering of the level of dopaminergic transmission in the septum during aggressive behavior.

No significant changes in concentrations of DA and its metabolites in perfusion fluid from the septum compared with the initial values could be observed 60 min after injection of haloperidol. It is well known that haloperidol, a DA receptor blocker, has a marked inhibitory action on different types of aggressive behavior of animals [6]. Since a considerable proportion of the synaptic endings of neurons of the mesolimbicocortical dopaminergic system (groups A9 and A10 [3]) are located in structures of the limbic system, it can be tentatively suggested that the neurons present in it, and which have terminals in the rat septum, are involved in the neurochemical mechanisms of muricidal aggressiveness of animals and are the cellular targets for the antiaggressive action of haloperidol.

During the aggressive act (killing the mouse) no changes in the level of reduction of the extracellular DA concentration in the septum was observed under the influence of haloperidol, whereas the concentrations of DA metabolites rose significantly (Table 1). It is generally considered that neuroleptic-induced blockade of pre- and postsynaptic DA receptors leads to an increase in the discharge activity of neurons of the mesolimbicocortical dopaminergic system, which is accompanied by acceleration of biosynthesis and of the release and turnover of DA in brain structures [7]. Hence it follows that elevation of the extracellular level of DA metabolites in the septum is the result of an increase in bioelectrical activity of nerve cells of the A9-A10 group. The antiaggressive effect of haloperidol is evidently associated with activation of those neurons of the dopaminergic system which have endings in the septum. This hypothesis is in agreement with the widely held view that the septum plays a mainly inhibitory role in the control of aggressive behavior [8].

The inability of haloperidol to increase DA release during aggression, which we found, was somewhat unexpected. However, this fact can be explained in the light of observations showing the absence of positive correlation between the increase in neuronal spike activity and DA release in vivo from its terminals under the influence of neuroleptics [9]. In addition, it was shown previously that haloperidol, in a dose of 2 mg/kg, if injected subcutaneously, does not increase DA release in the dorsal and ventral striatum of the rat brain [4].

The results confirm the inhibitory role of the septum in the realization of aggressive behavior in rats. The act of muricidal aggression is accompanied by inhibition of dopaminergic transmission in the septum. Haloperidol inhibits the aggressive reactions of the rat, and at the same time induces an increase in the extracellular concentration of DA metabolites, but not of DA itself, in the septum.

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