Effect of a Preparation of Exogenous Histone Administered by Different Routes on Intraspecific Aggression in Male Mice

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A study is made of the effect of a preparation of exogenous histone from calf thymus administered intranasally and intraperitoneally on intraspecific aggression in male mice. The histone is shown to exert a short-term suppressive effect on aggression with both routes of administration which manifests itself in a reduced number of attacks. However, the effective doses with intranasal administration are considerably lower than in the case of intraperitoneal injections.

Key Words: *exogenous histone; intranasal and intraperitoneal administration; aggressive behavior*

Cationic proteins are considered to be potential vectors for pharmaceutical delivery of drugs which cannot cross the blood-brain barrier. Some cationic proteins possess intrinsic antibacterial activity. Finally, preliminary data have been obtained on the effect of cationic proteins on animal behavior.

The ability of exogenous histone to penetrate through the blood-brain barrier into the central nervous system (CNS) was demonstrated earlier both in intravenous [1,5] and in intraperitoneal and intranasal [3] administration to experimental animals. A comprehensive study of the effect of this preparation on CNS functioning is essential. One aspect of it is discussed in the present study, using the experimental model of intraspecific aggression in male mice [4].

MATERIALS AND METHODS

We used a total preparation of histone fractions from calf thymus obtained by routine methods (extraction with 0.25 N HCl followed by ethanol precipitation) [1]. The experiments were performed on random-bred adult (2-2.5-month) male white mice. The latency of the first attack and the number of attacks carried out by each experimental mouse during the 5-min test were measured at the same time of day. The data obtained one day before administration of histone were taken as the control. Two routes of administration were used: intranasal and intraperitoneal. The doses used were 0.5, 1, 10, and 30 mg/kg for intranasal and 1, 10, 30, and 100 mg/kg for intraperitoneal administration. The histone was dissolved in physiological saline.

The animals were tested 15 min postinjection, since this interval has been found to be long enough for histone to penetrate into the CNS [1]. The testing was repeated one day after injection. The quantitative characteristics of aggressive behavior were averaged and compared with the respective parameters in control animals injected with saline. The percentage of changes in the parameters of aggressive behavior was estimated and the reliability of the changes was determined using the Student t test.

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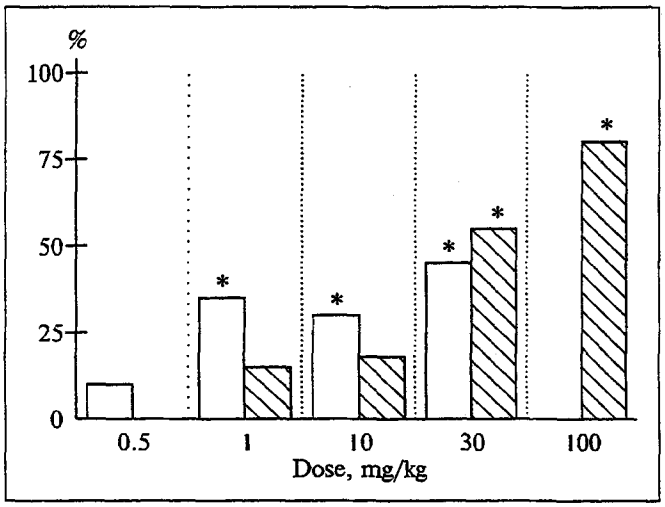

Fig. 1. Effect of intranasal and intraperitoneal administration of histone in various doses on the number of attacks in male mice. Ordinate: reduction of the number of attacks in males in comparison with intact controls. White bars: intranasal administration, dark bars: intraperitoneal administration. *$p<0.05$ in comparison with the control.

RESULTS

Physiological saline used as a vehicle for histone had no effect on the parameters of aggression in male mice in either intranasal or intraperitoneal administration. Intraperitoneal administration of exogenous histone reduced the number of attacks in experimental animals, but the changes were reliable only when high doses (30 and 100 mg/kg) were used (Fig. 1). The latencies of the first attack were also noted to be longer but these changes were unreliable. Testing the animals one day after administration showed that high doses of histone had exerted only a transient suppressive effect on aggressive behavior, because the parameters of the aggressive reaction were completely restored.

Intranasal administration of exogenous histone also suppressed aggression, but these changes were seen at concentrations one order of magnitude lower than those used in intraperitoneal administration (Fig. 1). Thus, the number of attacks was reliably decreased by one-third with the dose of 1 mg/kg. A tenfold increase in the dose did not substantially enhance the suppressive effect, which remained practically unchanged. A further increase of the dose enhanced the suppressive effect, cutting the number of attacks in half. These changes were similar to those produced by the same dose injected intraperitoneally. It should be noted that the latency of the first attack remained unchanged. One day after treatment the parameters of the aggressive reaction returned to the initial values. The higher efficacy of histone in intranasal administration is in accordance with recent reports that a number of peptides and neurotropic drugs are especially efficient when administered intranasally [2].

Thus, exogenous histone administered by either routes penetrates into the CNS and directly interacts with the systems controlling aggressive behavior. This effect manifests itself in a short-term suppression of the aggressive reaction in male mice. The comparison of different modes of administration demonstrated that the effective doses with intranasal administration were one order of magnitude lower than in the case of intraperitoneal administration, this probably indicating a more efficient transport of exogenous histone to the CNS via the intranasal route. Previous data obtained with radiolabeled histone administered intranasally do indeed confirm a more rapid accumulation of the label in certain structures of the brain, especially in the olfactory bulbs. The latter are known to be the first element of the CNS in which the signal pattern triggering aggressive behavior is formed. When histone is delivered intranasally, aggressive behavior is probably suppressed due to the interaction of the substance with the olfactory bulbs.

REFERENCES

1. D. Al-Sufi, O. A. Goryukhina, G. P. Dem'yanenko, and Yu. V. Bobryshev, *Vestn. Leningrad. Universiteta*, Ser. 3, Vol. 3, № 17, 122 (1991).
2. A. A. Kamenskii, N. Yu. Sarycheva, E. Yu. Baturina, and I. P. Ashmarin, *Vestn. Akad. Med. Nauk SSSR*, № 10, 43 (1988).
3. S. N. Novikov, in: *Pheromones and Reproduction in Mammals: Physiological Aspects* [in Russian], Leningrad (1988), p. 169.
4. V. P. Poshivalov, in: *Experimental Psychopharmacology of Aggressive Behavior* [in Russian], Leningrad (1986), p. 175.
5. W. M. Pardridge, D. Triguero, and J. Buciak, *J. Pharmacol. Exp. Ther.*, **251**, № 3, 821 (1989).