Hypothermic Effect of 5-HT$_{1A}$ Receptor Agonist: Comparison of Intranasal, Intraperitoneal, and Subcutaneous Routes of Administration

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The hypothermic effects of 5-HT$_{1A}$ serotonin receptor agonist 8-OH-DPAT after intranasal, intraperitoneal, and subcutaneous administration were compared. In a dose of 1 mg/kg 8-OH-DPAT induced similar thermal reactions after administration by all three routes. In a dose of 0.5 mg/kg 8-OH-DPAT caused no appreciable changes in body temperature after intraperitoneal injection and decreased it after subcutaneous and intranasal administration. No genotypic differences in the effects of 5-HT$_{1A}$ receptor agonist administered by different routes were detected in four inbred mouse strains.

Key Words: *5-HT$_{1A}$ receptors; 8-OH-DPAT; intranasal, subcutaneous, intraperitoneal administration*

Intranasal (IN) administration of drugs is known from ancient time; in medicine, it was primarily used in otorhinolaryngology. However, during the recent decade the attention of clinicians and scientists was attracted to this route of administration of drugs with central action due to its advantages: intranasal drug is rapidly absorbed and penetrates into the brain, does not pass through the liver; the method is atraumatic, and the patient can use the drug by him/herself. Intranasal route of administration is noninvasive, which is its important advantage, particularly in the days of rapid increase in AIDS and viral hepatitis incidence. These characteristics led to creation of an alternative to injection morphine (effective analgesic), intranasal morphine (rilomin), and awoke interest to IN administration of drugs [1,5].

Comparison of the effects of IN and injection methods of drug administration and evaluation of the role of genotype in these effects are interesting problems. Serotonin 5-HT$_{1A}$ receptor agonist 8-OH-DPAT attracts special interest. 5-HT$_{1A}$ receptors are located in the CNS and are virtually absent on the periphery, which simplifies interpretation of the results. Activation of cerebral 5-HT$_{1A}$ receptors causes clearly pronounced hypothermia [2,4], which makes possible objective quantitative comparison.

We compared the hypothermic effects of 8-OH-DPAT after its intranasal, subcutaneous (SC), and intraperitoneal (IP) administration to mice of different genotypes.

MATERIALS AND METHODS

Adult male mice of 4 strains: CBA/LacSto, C57Bl, DBA, and PT aged 3 months and weighing 23-28 g were used in the study. The animals were bred and kept under standard vivarium conditions at Institute of Cytology and Genetics. The animals were kept 6 per cage at natural light and free access to water and food. Three days before the experiment, the mice were placed into individual cages. Testing was carried out from 13.00 to 18.00 and started

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from body thermometry using a thermometer microcomputer (Hanna Instrument) with copper-constantane rectal pickups for mice (Phymep). Then the animals received 1 mg/kg 5-HT_{1A} receptor selective agonist 8-OH-DPAT dissolved in saline. In order to evaluate the effects of lesser dose of the preparation, CBA mice were injected with 0.5 mg/kg 8-OH-DPAT. Testing was carried out over 1 h; temperature was recorded every 10 min. The animals receiving saline via the same route served as controls.

For IN administration, the animal was placed into a plastic cylinder, narrowed at one end and with a special hole for the nose. Animal mobility was thus limited, and the drug could be pipetted into one of nasal sinuses with an automated pipette. The volume of fluid for SC and IP injections was 0.3 ml, for IN administration 3 μl. The animals were kept and experimental procedures were carried out in accordance with the international regulations for handling animals (Directions of the European Community of December 24, 1986; 86/309 EEC).

The results were statistically processed using dispersion analysis for repeated measurements. Paired comparisons were carried out using Newman—Keuls post-hoc test. The differences were considered significant at $p<0.05$.

RESULTS

Administration of saline by all routes caused hyperthermia (a manifestation of stress) [3]. In CBA mice, analysis of dispersions detected correlation between body temperature and route of administration ($F_{2,21}=15.4$; $p<0.001$). Body temperature increased by 2°C as soon as 10 min after IP and SC injections of saline. Hyperthermia was minimum pronounced after IN administration (Fig. 1), this indicating that this route of administration was less stressing than the injection methods.

Intranasal administration of 8-OH-DPAT in both doses caused a clear-cut body temperature drop in CBA mice ($p<0.001$). Body temperature decreased as soon as after 10 min and then gradually returned to normal over 1 h (Fig. 2). 8-OH-DPAT in a dose of 0.5 mg/kg caused no appreciable changes in body temperature after IP injection and decreased it after SC and IN administration. The hypothermic

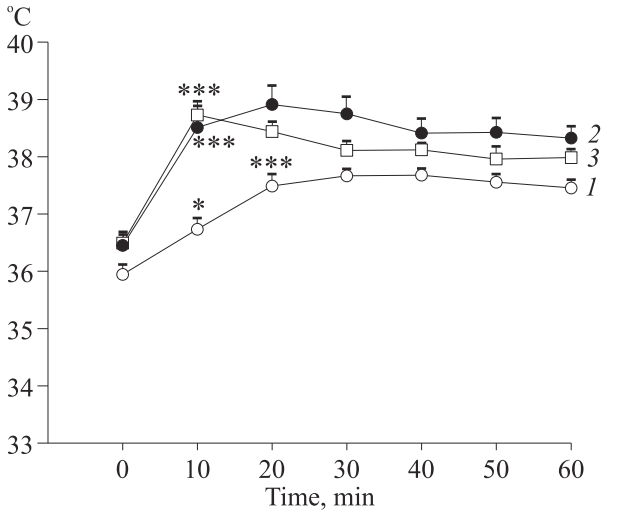

Fig. 1. Effects of IN (*1*), IP (*2*), and SC saline (*3*) on body temperature in CBA mice. Here and in Fig. 2, 3: *$p<0.05$, **$p<0.01$, ***$p<0.001$ compared to initial temperature.

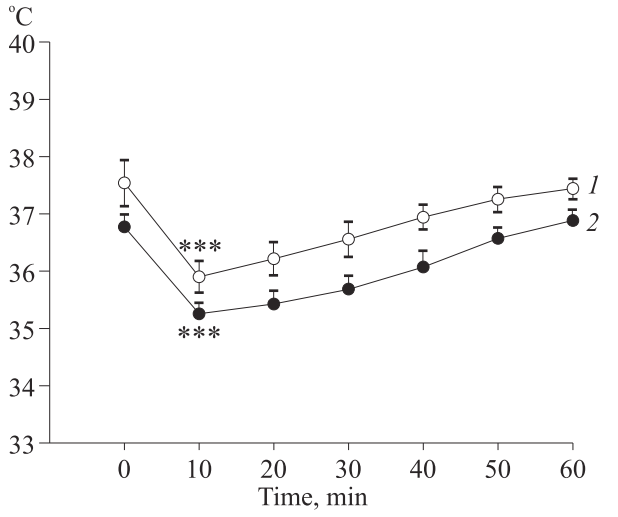

Fig. 2. Effects of intranasal administration of 8-OH-DPAT (5-HT_{1A} serotonin receptor agonist) in doses of 0.5 (*1*) and 1 mg/kg (*2*) on body temperature in CBA mice.

TABLE 1. Maximum Hypothermia in Mice of Four Strains after Administration of 8-OH-DPAT ($M\pm m$)

Mouse strain	Hypothermic effect of 8-OH-DPAT, °C		
	IN	IP	SC
CBA	1.57±0.24 (n=7)	1.10±0.18 (n=9)	1.90±0.07 (n=7)
C57Bl	0.98±0.29 (n=11)	0.67±0.29 (n=10)	2.62±0.20 (n=9)*
DBA/2	0.71±0.23 (n=10)	1.37±0.47 (n=11)	1.44±0.29 (n=10)
PT	1.80±0.35 (n=9)	1.91±0.26 (n=7)	—

Note. *$p<0.001$ compared to IN and IP.

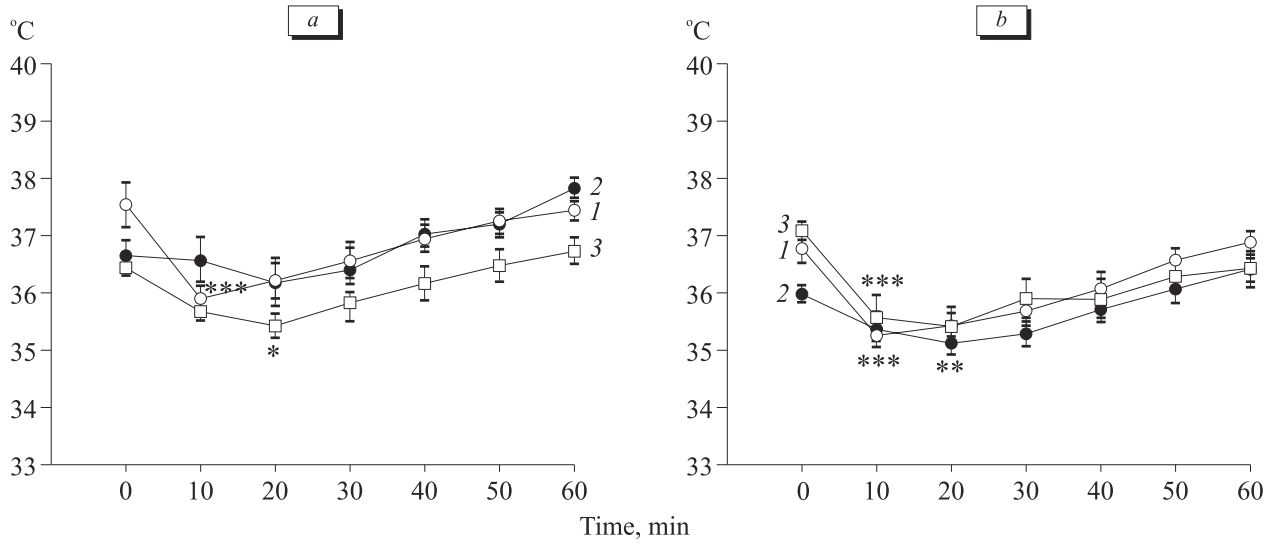

Fig. 3. Dynamics of body temperature after IN (*1*), IP (*2*), and SC 8-OH-DPAT (*3*) in doses of 0.5 mg/kg (*a*) and 1 mg/kg (*b*).

reaction to IN administration of 8-OH-DPAT manifested sooner: after 10 min *vs.* 20 min after SC injection ($p<0.05$). A clear-cut trend to more pronounced hypothermia ($p<0.001$) after IN administration of the agent was detected (Fig. 3, *a*).

Similar temperature reaction to 8-OH-DPAT was observed after administration by all three routes ($F_{2,20}=2.1$), which did not differ by the degree of hypothermia or time course of temperature reaction (Fig. 3, *b*).

No appreciable genotypical differences in the effects of 5-HT_{1A} receptor agonist administered by different routes were detected. Intranasal 8-OH-DPAT in a dose of 1 mg/kg caused a clear-cut hypothermia, not differing much from that after administration by other routes (Table 1). The only exclusion was hypothermia after SC 8-OH-DPAT in C57Bl mice, which was more pronounced than after IN and IP administration, causing virtually the same reaction. The more pronounced hypothermic effect of SC injection was presumably caused by individual peculiarities of drug penetration into the blood stream in animals of this strain.

Hence, IN 8-OH-DPAT causes a clear-cut physiological effect (hypothermia) due to its effect on brain 5-HT_{1A} receptors. Available data on the mechanism of hypothermic effect of 8-OH-DPAT indicate the involvement of cerebral presynaptic 5-HT_{1A} receptors in this effect. The effect of the drug after its IN administration in comparable doses did not differ much from its effect after SC and IP injections, though IN administration of a low dose had certain advantages over IP and SC injections in the intensity and earlier manifestation of the effect. The main advantage of IN administration is its noninvasive nature, the absence of pain, and lesser stressing effect.

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