GENETICS

Effect of Serotonin 5-HT_{1A} Receptor Agonists on Sexual Motivation of Male Mice

T. G. Amstislavskaya, S. A. Kucheryavyi, E. A. Ivanova, and N. K. Popova

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The effect of selective agonists of serotonin 5-HT_{1A} receptors on sexual arousal (its behavioral and hormonal components) in male CBA mice caused by estral females was studied. Injections of 8-OH-DPAT, flesinoxane, and ipsapirone significantly decreased the main behavioral parameter of sexual motivation (duration of the male's stay near the wall separating it from the receptive female). The activating effect of the female on the pituitary gonadal system of the male was completely blocked: the blood testosterone level did not increase. Therefore, the behavioral and hormonal components of sexual activation of males are regulated by the serotonin mechanisms alone, in which the cerebral 5-HT_{1A} receptors are involved.

Key Words: *mice; sexual motivation; serotonin 5-HT_{1A} receptors; hypothalamo-pituitary-gonadal complex; testosterone*

Cerebral serotonin inhibits sexual behavior of males in physical contact with females [5]. Recent molecular biological studies revealed considerable polymorphism of serotonin receptors; in the brain 7 types and 10 subtypes of SR have been identified [8]. The role of different types of SR in the regulation of individual components of sexual behavior and endocrine function of the hypothalamo-pituitary-testicular complex is still unknown. Sexual activation caused by respective motivation in the presence of a receptive female is the initial stage in sexual behavior of a male. The role of serotonin in the development of sexual motivation has not been studied. In this connection 5-HT_{1A} receptors attract special attention, because they are known to participate in the regulation of copulative behavior of rats [5-7].

We investigated the role of 5-HT_{1A} receptors in the behavioral and hormonal components of sexual arousal in male mice by examining the effects of specific agonists of these receptors: 8-OH-DPAT, flesinoxane, and ipsapirone.

Laboratory of Behavioral Phenogenetics, Institute of Cytology and Genetics, Siberian Division of Russian Academy of Sciences, Novosibirsk

MATERIALS AND METHODS

Experiments were performed on male CBA mice aged 2.5-3 months. The animals were kept under standard vivarium conditions. They were divided into groups 8 animals per group and given water and food *ad libitum.* The model of sexual stimulation was as follows: a receptive female placed behind the wall with small holes induced an increase in the plasma testosterone (TS) level in the male mouse [1,3]. The behavioral component of sexual motivation was evaluated by parameters used in investigations of communicative behavior: the time spent by a male near the wall and the number of approaches to the wall [9]. The method of recording the behavioral and hormonal components of sexual activation was described previously [4]. The principal behavioral parameter was the duration of the

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male's stay near the wall, while the number of approaches to the wall was the indicator of motor activity and general excitation of the animal. Five days before the experiment the males were put into cages divided with plastic walls into two compartments in order to eliminate the effect of social relationship developing in micropopulations. On the day of experiment the mice were intraperitoneally injected with 5-HT_{1A} agonists: (±)-8-OH-DPAT (0.25, 0.5, and 2 mg/kg, Research Biochemical Inc.); flesinoxan (0.05 and 0.125 mg/kg, Duphar), and ipsapirone (1 mg/kg, Tropenwerke). The controls were injected with the same volumes of physiological saline. After 10 min the cover of the cage was replaced with a transparent plastic and after 5 min an estral female was put into the free compartment of the cage for 20 min; the estrus was induced by injection of 10 U chorionic gonadotropin (prophase, Serono) 24 h before the test. Total duration of the male's stay near the wall and number of male's approaches to it were recorded for 10 min on a semiautomated Etograf device [2]. In some control experiments no females were put in order to study the behavior and TS level in a male staying alone in the cage. At the 20th minute of sexual activation the males were decapitated and the blood was collected; plasma was stored at -18°C. The level of TS, a marker of sexual activation, was radioimmunoassayed using ^{3}H-TS (Amersham) and highly specific antiserum. The results were processed using ANOVA analysis of dispersions.

RESULTS

Appearance of a receptive female induced sexual motivation and sharply modified the behavior of the male, which tried to penetrate through the wall separating the animals and spent much more time near it. The mean time spent near the wall by control CBA males staying alone in the cage was 132.5±21.82 sec, while in the presence of females this parameter increased to 391.6±22.49 sec. The number of approaches to the wall increased from 24.1±2.9 to 32.8±2.5. Injection of physiological saline did not modify these values, while injection of 8-OH-DPAT considerably reduced the time spent near the wall in a dose-dependent manner (2.5-4-fold in comparison with injection of physiological saline, Table 1). The number of approaches to the wall also decreased, but did not depend on the presence of a receptive female for all 8-OH-DPAT doses (25.0±3.3). This indicates that 8-OH-DPAT in all studied doses does not affect the motor activity of mice, which con-firms the specificity of the effect of 5-HT_{1A} agonist on the sexual motivation in males. Similar results were obtained with other 5-HT_{1A} agonists, flesinoxan and ipsapirone (Table 1). Flesinoxan (0.05 mg/kg) and ipsapirone (1 mg/kg) did not affect the number of approaches to the wall, but markedly shortened the duration of stay near the wall. Only the maximum dose of flesinoxan (0.125 mg/kg) sharply decreased both these parameters. The appearance of a female behind the wall induced, as was demonstrated previously [1,3,4], an increase in blood TS level in the male: the concentration of TS increased 2.5 times in 30 min (Fig. 1). Injection of 5-HT_{1A} agonists blocked the activation of the hypothalamo-pituitary-gonadal complex caused by a receptive female. All three agonists of 5-HT_{1A} receptors prevented the increase in the plasma TS level in the presence of a female. Moreover, injection of 8-OH-DPAT in doses of 0.25 and 0.5 mg/kg decreased the hormone level in comparison with the control. The results indicate that 5-HT_{1A} receptors are involved in the regulation of sexual motivation and blood TS level as an inhibitory mechanism preventing sexual activation. The inhibitory effect of serotonin on sexual behavior of males [5]

TABLE 1. Effect of 5-HT_{1A} Receptor Agonists on Behavioral Response of Males to Appearance of Females ($M\pm m$)

Agent, mg/kg	*n*	Behavior near the wall	
		duration of stay	number of approaches
Physiological saline	10	359.2±21.0	30.2±2.5
8-OH-DPAT, 0.25	10	202.3±36.9**	27.1±4.0
0.5	12	181.7±27.8**	19.1±2.5*
2	9	89.2±16.2***	19.1±3.3*
Physiological saline	10	385.9±17.2	23.7±1.6
Flesinoxan, 0.05	9	235.9±49.3*	19.5±2.8
0.125	4	89.1±64.1*	7.8±4.7*
Physiological saline	10	331.7±30.8	24.4±3.2
Ipsapirone, 1	9	137.6±25.8***	18.6±2.7

Note. *$p<0.05$; **$p<0.01$; ***$p<0.001$ *vs.* respective controls.

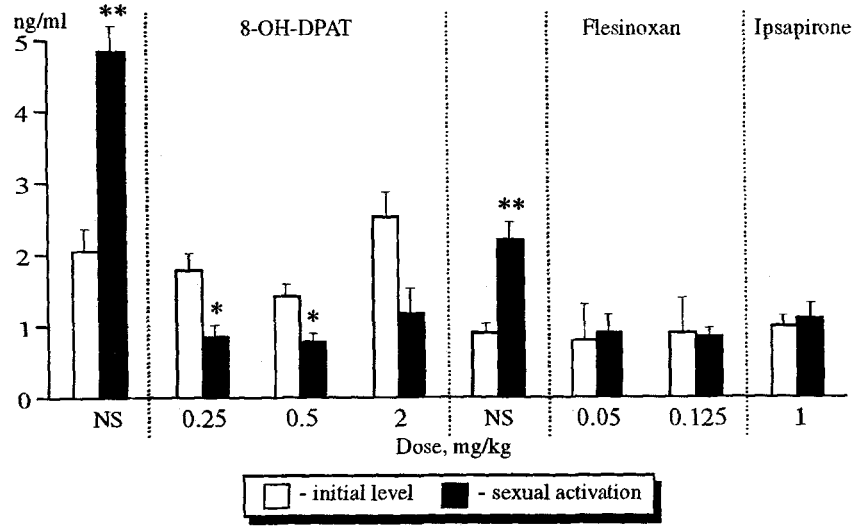

Fig. 1. Changes in blood testosterone level in the males in response to appearance of a receptive female after injection of selective 5-HT_{1A} receptor agonists: 8-OH-DPAT, flesinoxan, and ipsapirone. NS: physiological saline. *$p<0.05$; **$p<0.001$ *vs.* the initial level.

may be mediated, at least partially, by 5-HT_{1A} receptors.

The 5-HT_{1A} receptors agonists exerted similar inhibitory effects on the behavioral and hormonal components of sexual activation. This indicates that the behavioral and hormonal components of sexual activation are regulated by the serotoninergic mechanisms.

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