PHYSIOLOGY

Effects of 8-OH-DPAT and NAN-190 on Anxious-Depressive-Like Behavior of Female Rats during the Estrous Cycle

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We studied the effect of chronic administration of 5-HT_{1A}-receptor agonist 8-OH-DPAT (0.05 mg/kg subcutaneously) or antagonist NAN-190 (0.1 mg/kg intraperitoneally) for 14 days on anxious-depressive-like behavior of female rats during the key phases of the estrous cycle. Chronic administration of NAN-190 during the estrus phase produced an anxiogenic effect, while its administration during proestrus phase induced an anxiolytic effect. Administration of 8-OH-DPAT had no effect on anxiety level, but produced a pronounced antidepressive effect irrespective of the phase of the estrous cycle.

Key Words: *8-OH-DPAT; NAN-190; depression; anxiety; estrogens*

It is commonly accepted that the leading role in neurochemical mechanisms of anxious-depressive disorders is played by reduced norepinephrinergic and serotoninergic neurotransmission in the brain, which manifests in low norepinephrine and serotonin concentration in the synaptic cleft and impaired sensitivity, binding capacity, and number of β-adrenoceptors and subtype 1A and 1B serotonin receptors [2,3,9].

On the other hand, normal menstrual cycle can change the severity of symptoms of primary mental disorders [4,5,8]. Symptoms observed in women with premenstrual dysphoric disorders are similar and manifest in anxiety, sleep disturbances, depression, fatigue, irritability, and somatic symptoms characteristic of luteal phase [6,7,10].

Taking into account close interactions between the ovarian hormonal and serotoninergic neurotransmitter systems, it was interesting to evaluate the role of serotoninergic 1A receptors (5-HT_{1A}) in affective behavior of female rats during the key phases of the estrous cycle under conditions of natural fluctuation of estrogen level.

Here we evaluated the effect of chronic (for 14 days) administration of 5-HT_{1A}-receptor agonist 8-OH-DPAT or antagonist NAN-190 on anxious and depressive-like behavior of female rats during the estrous cycle.

MATERIALS AND METHODS

Experiments were carried out on female Wistar rats weighing 200-220 g (n=120, Rappolovo nursery). The animals were kept in a vivarium at natural illumination and maximum standardization of the temperature and feeding regimens with free access to food and water. The studies were performed during the first half of day (9.00-12.00). Pharmacological ligands were purchased from Sigma.

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For behavioral experiments the rats were divided into groups (8-10 rats per group) depending on the phase of the estrous cycle (diestrus, estrus, proestrus) and administered ligands: control, 8-OH-DPAT (0.05 mg/kg subcutaneously), and NAN-190 (0.1 mg/kg intraperitoneally).

Vaginal smears were taken for 8 days before the experiment to determine the phase of the estrous cycle. Only females with stable 4-day estrous cycle were used in the experiments.

Depression was modeled in the Porsolt test. Animal anxiety was evaluated using elevated plus-maze test [1].

The data were processed statistically using two-way ANOVA followed by Newman–Keuls post-hoc test. The differences were significant at $p<0.05$.

RESULTS

Testing in the elevated plus maze revealed significant differences in the effect of the phase of the estrous cycle on the time spent in open and closed arms of the maze and the number of entries in them (Table 1). Anxiety level in female rats was higher during estrus and proestrus, compared to that during diestrus. Two-way ANOVA also revealed significant differences in the effects of chronic treatment with serotoninotropic substances on the time spent in open and closed arms of the maze and number of entries in them. Chronic administration of NAN-190 during estrus produced an anxiogenic effect, while its administration during proestrus had an anxiolytic effect. Administration of 8-OH-DPAT had no effect on anxiety level irrespective of the phase of the estrous cycle.

Significant differences in immobility time in the Porsolt test in females depending on the phase of the estrous cycle were detected by ANOVA (Fig. 1). Anxiety level in rats was higher during estrus and proestrus, compared to that during diestrus. Two-way analysis of the data obtained in Porsolt test revealed significant differences in the effect of serotoninotropic substances on immobility time in female rats (Fig. 1). Administration of NAN-190 during the key phases of the estrous cycle aggravated depressive-like behavior compared to the control. On the contrary, administration of 8-OH-DPAT during both proestrus and estrus produced an antidepressive effect.

Thus, chronic administration of serotoninergic substances interacting with 5-HT_{1A} subtype receptors had opposite effects on manifestations of anxious-depressive state during the key phases of the estrous cycle. Administration of 8-OH-DPAT produced antidepressive effects irrespective of the level of endogenous estrogens in the organism, but had no effect on anxious behavior. On the contrary, administration of NAN-190 aggravated depressive state during estrus and proestrus. A clear-cut modulation of the anxious behavior depending on the phase of the estrous cycle was observed against the background of NAN-190 treatment: anxiolytic effect was observed against the background of high level of endogenous estrogens, while in animals with low level of endogenous estrogens it produced an anxiogenic effect.

TABLE 1. Effects of NAN-190 and 8-OH-DPAT on Anxious Behavior of Female Rats ($M\pm m$; $n=10$)

Phase of estrous cycle	Time spent in open arms, sec	Time spent in closed arms, sec	Number of entries into open arms	Number of entries into closed arms
Control				
Diestrus	86.4±6.2	213.6±2.4	1.8±0.2	2.1±0.4
Proestrus	36.4±3.4*	263.6±8.6*	0.4±0.1*	4.5±0.2*
Estrus	42.6±4.2*	257.4±2.2*	0.3±0.1*	4.0±0.6*
NAN-190				
Diestrus	81.2±3.4	218.8±8.6	1.2±0.2	2.2±0.2
Proestrus	90.3±3.4+	209.7±6.2+	0.4±0.2	4.0±0.4
Estrus	23.7±2.2+	276.3±3.8+	0.3±0.1	4.1±0.6
8-OH-DPAT				
Diestrus	80.5±3.2	219.5±2.4	1.8±0.2	2.4±0.2
Proestrus	33.7±3.2*	266.3±4.4*	0.4±0.1*	4.0±0.2*
Estrus	41.2±4.1*	258.8±2.2*	0.4±0.2*	4.0±0.2*

Note. $p<0.05$ compared to: *diestrus, +control.

Interesting, the effects of NAN-190 on anxious behavior of female rats during the estrous cycle are strongly determined by the phase of the estrous cycle, while its prodepressive effect did not depend on the level of endogenous estrogens in the organism. We can conclude that NAN-190 on the whole produces a negative effect on the severity of anxious-depressive behavior in female rats, except its anxiolytic effect against the background of high level of endogenous estrogens in the organism. On the other hand, the positive effects of 8-OH-DPAT on depressive-like behavior and the absence of its effect on anxious behavior manifested irrespectively of the hormonal status of females, which attested to the absence of determination of these effects on the phase of the estrous cycle. Pharmacotherapy with antidepressants and tranquilizers under conditions of adequate hormone balance is aimed at restoration of neurotransmission, accumulation of biogenic amines, and stimulation of 5-HT_{1A} receptor function [5,9,10]. For correction of affective state under conditions of estrogen imbalance, balanced state and coordination between functional activity of the hormone system and activity of neurotransmitter system should be restored. It can be hypothesized that the pronounced antidepressive effect of 8-OH-DPAT during the key phases of the estrous cycle is determined by its effect on not only hormone level, but also 5-HT_{1A} receptors and by adequate normalization of monoamine metabolism in the hippocampus and limbic system.

Our findings attest to an important role of 5-HT_{1A} serotonin receptors in affective behavior of female rats during different phases of the estrous cycle and substantiate the necessity of further studies of serotoninergic compounds as means for correction of anxious-depressive behavior during the estrous cycle.

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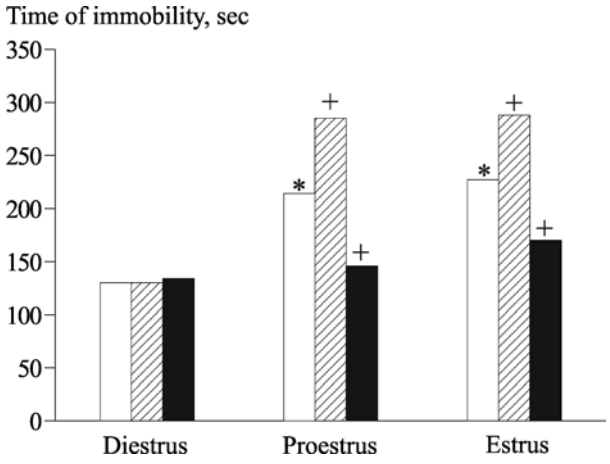

Fig. 1. Effects of NAN-190 and 8-OH-DPAT on depressive-like behavior of female rats during different phases of estrous cycle. Open bars: control; hatched bars: NAN-190; dark bars: 8-OH-DPAT. $p<0.05$ compared to: *diestrus, +control.

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