Numerous clinical observations have provided evidence that thyroid dysfunctions can be risk factors for the development of depressive episodes [11, 18, 22]. However, experimental studies of the mechanisms of this effect are difficult, largely because of the lack of the required models. We have recently demonstrated that catalepsy may provide a suitable model for investigations of the effects of thyroid abnormalities on behavior: a significant role for thyroid hormones was shown in controlling the extent of catalepsy in rats [1, 4, 26].

Catalepsy, or the freezing reaction, is a reversible involuntary immobilization with plastic muscle tone. Animals and humans in the state of catalepsy are, for prolonged periods, unable to correct an artificially imposed posture. In natural conditions, catalepsy-like freezing is a passive defensive reaction and its appearance is often associated with fear [13]. In humans, catalepsy has lost its original defensive sense, but persists in a very marked form as a symptom of various mental and nervous diseases, such as schizophrenia and depression [24].

Many years of breeding for high levels of predisposition to freezing reactions lead to changes in thyroid status: GC (Genetic Catalepsy) rats are characterized by a reduced blood total thyroxin level as compared with rats of the starting Wistar strain [1]. At the same time, thyroidectomy in rats of the non-cataleptic Wistar strain produced increases in their predisposition to catalepsy [1]. Furthermore, we recently demonstrated that prolonged administration of the thyroxine synthesis inhibitors mercaptozol and propylthiouracil also have cataleptogenic effects in Wistar rats [4, 26].

It should be noted that the hypothyroid state has been linked not only with increased predisposition to catalepsy, but also with other changes in behavior in rats. Thus, GC rats showed depression-like behavioral features [2], while...
Wistar rats given the thyroxine synthesis inhibitor propylthiouracil for prolonged periods were characterized by a reduction in the amplitude of the acoustic startle reflex and decreased sexual motivation [26].

An important aspect of verifying models of depressive states is demonstrating sensitivity to agents which are clinically effective in depression [29]. We have previously demonstrated that chronic administration of the tricyclic antidepressant imipramine decreases the signs of catalepsy in GC rats [5], this effect being accompanied by an increase in 5-HT_{2A} serotonin receptor mRNA in the cerebral cortex [3]. It should be noted that investigators have paid special attention to the brain serotonergic system as the probable link between impairments to thyroid function and depression [18]; this includes brain 5-HT_{2A} serotonin receptors, as changes in their functional activity are seen in hypothyroid-associated depression [11]. An answer to the question of whether the increased expression of the 5-HT_{2A} serotonin receptor gene seen in the cerebral cortex in the model of genetic predisposition to catalepsy is the universal mechanism normalizing behavior in response to imipramine requires comparative studies of the effects of this agent on this measure in other models.

The aims of the present work were to determine the sensitivity of behavioral changes induced by chronic administration of propylthiouracil to the action of the antidepressant imipramine and to study the role of 5-HT_{2A} serotonin receptors in this process. The following tasks were addressed: 1) to study the effects of imipramine and propylthiouracil on the extent of catalepsy, the amplitude of the acoustic startle reaction, and sexual motivation and 2) to study the effects of these agents on 5-HT_{2A} receptor mRNA levels in the frontal cortex of Wistar rats.

**METHODS**

Experiments were performed using 83 male Wistar rats. Animals were one month old at the beginning of the experiment and weighed 72 ± 2 g; they were kept in groups of 5–6 individuals throughout the study period. Rats were kept in cages of size 60 × 40 × 20 cm with natural illumination and standard animal-house conditions at the Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences. Standard feed was provided ad libitum. The animals were divided into four groups. Rats of group 1 received water throughout the experiment and served as controls (Control group, n = 26). Animals of group 2 received water during the first week of the experiment, followed by imipramine (Sigma, USA) for the next 21 days, dissolved in the drinking water to a concentration of 50 mg/liter (0.005%, PTU group, n = 27). Previous studies have demonstrated that this propylthiouracil administration protocol produces moderate reductions (by 30–35%) in total blood thyroxine levels in rats [14, 26]. Animals of group 4 received propylthiouracil solution (0.005%) during the first week of the experiment, followed by solution containing propylthiouracil at a concentration of 50 mg/liter and imipramine at a concentration giving a mean daily dose of 15 mg/kg for the next 21 days (the PTU + imipramine group, n = 15). The imipramine concentration was corrected for body weight (measured weekly) and the quantity of liquid consumed per day. Imipramine-containing solutions were changed daily and other solutions were changed every two days. After treatment ended, rats were isolated in cages of the same size for two days before testing for release of the effects of zoosocial stress resulting from keeping the animals in groups. Increases in body weight were identified by weighing the rats before and after treatment.

**Catalepsy test.** Tests for the extent of catalepsy were performed on the second day of isolation and were repeated on the third day. Rats were placed in a vertical position in the corner of the cage, the forepaws were lifted carefully with a rod, and the time they remained in this imposed vertical posture was measured. The procedure was repeated three times with each animal. The extent of catalepsy was assessed in terms of the mean during of freezing (sec) in two test sessions and the proportion of cataleptic animals (the ratio of the number of animals showing catalepsy to the total number of animals tested, %) were determined. Rats were regarded as cataleptic if they maintained the imposed vertical posture for 10 sec or longer [4].

**Open field test.** With the aim of excluding the possibility that the effects of agents seen in other tests were associated with changes in overall movement activity, an open field test was performed in an open chamber (140 × 70 × 45 cm) made of Plexiglas and painted white. The floor was divided into 98 squares (each 10 × 10 cm) and brightly illuminated with a 300-W lamp. The animal was placed close to the chamber wall at equal distances from the corners and tested for 6 min. Measures of horizontal (number of squares crossed) and vertical (number of rearings) movement activity were evaluated.

**The acoustic startle reflex** was measured using an SR-Pilot (San Diego Instruments, San Diego, CA, USA) instrument. The system consisted of a sound- and light-proofed chamber (14 × 21 × 23 cm) containing a platform with a sensitive probe. The chamber contained a peephole allowing the animal to be observed constantly. The animal’s twitches were converted into an analog signal by the piezoelectric probes attached to the platform. Signals were recorded using the in-built microcomputer, in arbitrary units. Constant white noise (65 dB) was generated within the chamber. The rat was placed within the chamber for 3 min for adaptation before the test started. Five wideband...