Chronic Administration of Imipramine Decreases Freezing Time in Rats Genetically Predisposed to Catalepsy

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 138, No. 10, pp. 450-453, October, 2004
Original article submitted November 20, 2003

The effects of acute and chronic imipramine treatment on the degree of catalepsy were compared in GC rats genetically predisposed to catalepsy. We recorded the time over which the rats remained in a vertical position they were placed. As differentiated from acute treatment, chronic administration of imipramine dose-dependently decreased the time of freezing in GC rats.

Key Words: *imipramine; genetic catalepsy; rat*

Catalepsy, or freezing reaction, is a state of immobility and muscular rigidity. Cataleptic animals and humans cannot correct abnormal position they are placed. Catalepsy in humans occurs in severe nervous and mental disorders [12,13]. In rats and mice catalepsy serves as a marker of serious nervous disorders and can be modeled by administration of dopamine D_2 receptor antagonist haloperidol [6,12]. Haloperidol-induced catalepsy is an animal model for testing antidepressant activity of drugs. The severity of this disorder decreases after acute administration of various tricyclic antidepressants, including imipramine [2,5].

Nonpharmacologic catalepsy is a rare disease developed only in a low number of Wistar rats [3]. Long-term selection of Wistar rats predisposed to catalepsy (GC rats) was performed at the Institute of Cytology and Genetics. Published data show that 60% GC rats not receiving pharmacological agents can retain a vertical position for more than 15 sec [3]. Nonpharmacological catalepsy in GC rats is a more severe disorder than haloperidol-produced catalepsy. Therefore, it can be considered as a pathological state.

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Here we studied the effect of acute and chronic treatment with imipramine on the degree of cataleptic freezing in GC rats.

MATERIALS AND METHODS

Experiments were performed on 49 male GC rats. This strain was maintained in a vivarium of the Institute of Cytology and Genetics over 50 generations. The study was conducted on 2-month-old rats weighing 180±12 g. The initial time of cataleptic freezing was 73.2±2.9 sec. The animals were housed in cages (60×40×20 cm) under standard illumination and temperature regimen. The effect of acute treatment with imipramine on freezing time was studied on 27 rats with a similar degree of catalepsy divided into 3 groups (8, 9, and 10 rats, respectively). The rats received intraperitoneal injections of physiological saline or imipramine in physiological saline (single doses 7.5 and 15 mg/kg, Sigma). The degree of catalepsy was estimated before and 1 h after administration of preparations. The effect of acute treatment was determined as the ratio between the time of freezing 1 h after and before imipramine administration (%).

The remaining 22 rats with similar degree of catalepsy were divided into 3 groups. Control animals

0007-4888/04/1384-0401

(*n*=7) received water for 27 days. Other rats received aqueous solution of imipramine in daily doses of 7.5 (*n*=8) and 15 mg/kg (*n*=7) for 26 and 24 days, respectively. The concentration of imipramine was adjusted to body weight (weekly measurements) and daily amount of consumed fluid. The solution of imipramine was replaced daily. This treatment regimen was selected to avoid stress and corresponded to the use of imipramine in clinical practice [8]. The rats were tested for catalepsy 2 times a week during treatment and 2 days after withdrawal. The time of freezing was expressed in percents of the baseline level (before imipramine administration).

The forelimbs were raised with a rod to place the animal in a vertical position in the corner of a cage. The degree of catalepsy was determined by the time over which the rats remained vertical pasture [3].

The degree of catalepsy was estimated before and after imipramine administration. The data on cataleptic freezing were expressed in percents of the baseline level (*M*±*m*). The results were analyzed by Student's *t* test (initial values were taken as 100%). The effect of chronic treatment was evaluated by multiple

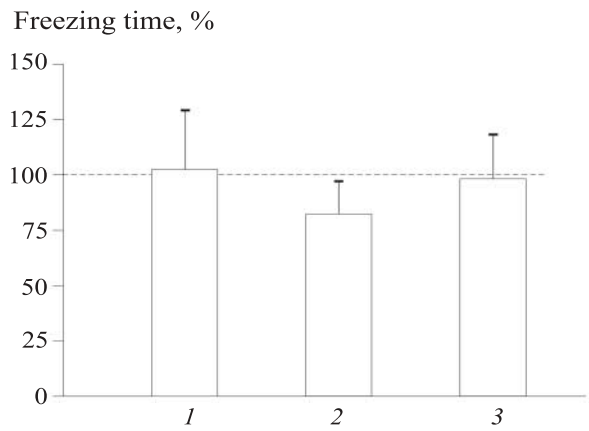

Fig. 1. Effect of acute intraperitoneal injection of physiological saline (*1*) or imipramine in doses of 7.5 (*2*) and 15.0 mg/kg (*3*) on the time of freezing in GC rats.

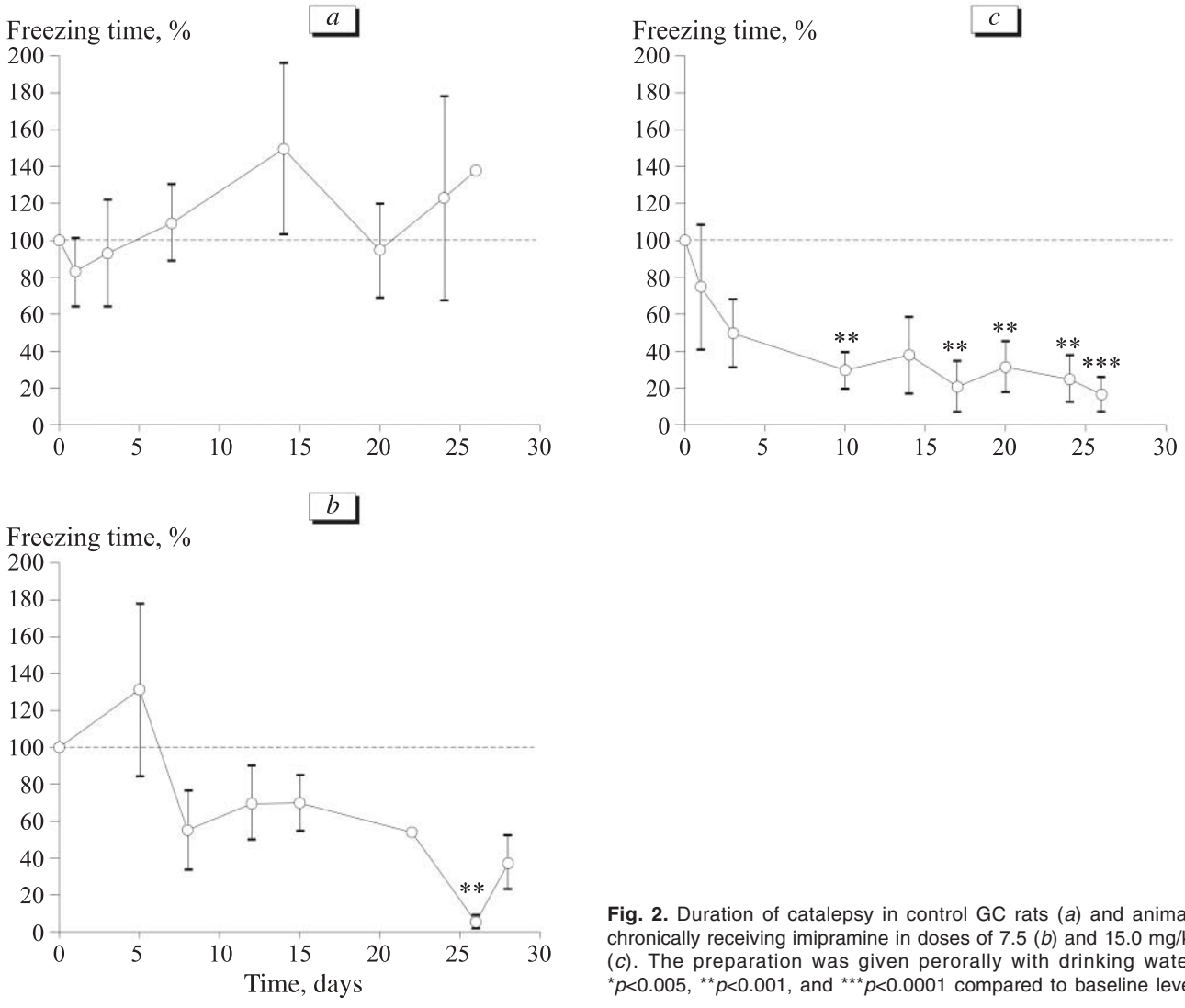

Fig. 2. Duration of catalepsy in control GC rats (*a*) and animals chronically receiving imipramine in doses of 7.5 (*b*) and 15.0 mg/kg (*c*). The preparation was given perorally with drinking water. **p*<0.005, ***p*<0.001, and ****p*<0.0001 compared to baseline level.

comparison method. The critical level of significance (0.05) was corrected by the number of comparisons (Bonferroni correction).

RESULTS

Single administration of physiological saline had no effect on the duration of catalepsy in GC rats. No changes were revealed in the time of freezing after acute intraperitoneal injection of imipramine in doses of 7.5 and 15.0 mg/kg (Fig. 1).

Chronic administration of imipramine had no effect on the time of freezing in control rats over 26 days of observations (Fig. 2, *a*). The time of freezing in animals receiving imipramine in a daily dose of 7.5 mg/kg progressively decreased over 25 days. This parameter decreased most significantly by the 26th day of treatment (5.3±1.6%, t_5=59.1, p<0.0001) and remained unchanged at least 48 h after withdrawal (37.1±14.2%, t_5=4.43, p<0.005, Fig. 2, *b*). In animals receiving imipramine in a daily dose of 15.0 mg/kg, the time of freezing decreased more rapidly. The difference became significant by the 10th day (29.7±9.2%, t_5=7.65, p<0.0001) and grew until the end of treatment. The effect persisted for at least 48 h after withdrawal of the preparation (16.5±8.8%, t_5=9.55, p<0.0001, Fig. 2, *c*).

Acute administration of imipramine had no effect on the degree of genetically determined catalepsy in GC rats, which contradicts published data on the anticataleptic effect of this preparation during haloperidol-induced catalepsy [2,5]. These data indicate that haloperidol-induced and genetically determined catalepsy are realized via different mechanisms. Haloperidol-induced catalepsy involves dopamine D_2 receptors [9, 11,15], while genetic catalepsy in GC rats is mediated via serotonin 5-HT_{2A} receptors [1,7,10]. Chronic administration of imipramine had a dose-dependent inhibitory effect on catalepsy in GC rats. The anticataleptic effect of imipramine progressively increased over observations. After administration of imipramine in high dose the inhibitory effect developed more rapidly and persisted for at least 2 days after withdrawal. It can be hypothesized that anticataleptic activity of imipramine is related to long-term neuronal changes, but not to the direct effect on transporters and/or receptors of biogenic amines.

Animal model of catalepsy serves is used in the studies of antidepressant activity of drugs [2,5]. Genetically determined catalepsy in GC rats sensitive to chronic administration of imipramine (but not to acute treatment) is more suitable for studying the behavioral effect of antidepressants compared to haloperidol-induced catalepsy. The clinical effect of antidepressants develops only after long-term treatment [4,14].

GC rats hold much promise for the studies of the mechanisms of antidepressant activity.

This work was supported by the Russian Foundation for Basic Research (grants No. 03-04-48170, 02-04-49265).

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