ISSN 2079-0597, Russian Journal of Genetics: Applied Research, 2017, Vol. 7, No. 1, pp. 93–99. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © R.V. Kozhemyakina, S.G. Shikhevich, A. Cagan, R.G. Gulevich, 2016, published in Vavilovskii Zhurnal Genetiki i Selektsii, 2016, Vol. 20, No. 2, pp. 165–171.

Effect of Single Ethanol Administration on the Behavior, Consumption, and Preference of Ethanol in Tame and Aggressive Rats

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Received October 2, 2015; in final form, November 30, 2015

Abstract—According to the stress relief hypothesis, a high level of anxiety or stress may cause greater alcohol consumption and alcohol addiction. However, the data obtained with experimental animals do not always confirm this statement. Strains of Norway rats selected for tame and aggressive attitude to humans can serve as a model for investigating relationships between anxiety, the function of the hypothalamic–pituitary–adrenal (HPA) system, and predisposition to alcohol addiction. Former studies of tame rats, based on the blood levels of the corticosterone and adrenocorticotropic hormone (ACTH) at rest and under stress, revealed a decrease in the manifestation of anxiety-like behavior and in the HPA function compared to aggressive and unselected rats. This work assesses the preferred consumption of ethanol at various concentrations with free access to ethanol and water (two-bottle choice test) and the effect of acute ethanol administration on the behavior of aggressive and tame male rats in an elevated plus maze (EPM). After intraperitoneal alcohol administration, tame and aggressive males show a reduced number of rearings in the center of the EPM, but the reduction is statistically significant only in the former. It points not only to the absence of the anxiolytic action of 12% ethanol but also to an enhancement of anxiety-like behavior in tame rats. After the withdrawal of alcohol for seven days, tame rats show signs of deprivation, because the alcohol consumption becomes greater than before the withdrawal. Thus, the difference between tame and aggressive rats during alcohol consumption varies with the alcohol concentration. Aggressive males drink more alcohol than water only at the 2% concentration. Hence, the hypothesis of stress relief is confirmed only for this concentration.

Keywords: ethanol, selection for behavior, tame and aggressive rats, anxiety-like behavior, elevated plus maze, deprivation effect

DOI: 10.1134/S2079059717010075

INTRODUCTION

Social stress caused by family or workplace conflicts provokes alcohol consumption more frequently than other stresses. Its influence on addictive behavior is often permanent (de Wit et al., 2003; Kudryavtseva et al., 2006; Thomas et al., 2011). Being the main stress-related hormones, glucocorticoids interact with the mesolimbic pathway and mediate stress-induced alcohol consumption (Spanagel et al., 2014). According to the stress relief hypothesis, highly anxious individuals may be more sensitive to the anxiolytic effect of alcohol and, consequently, be more predisposed to its consumption (Conger, 1956). However, not all experiments confirm this hypothesis. In has been shown that Wistar rats selected for elevated anxiety (High Anxiety Behavior, HAB) consume and prefer alcohol less frequently than rats selected of the opposite line (Low Anxiety Behavior, LAB) (Henniger et al., 2002).

Some authors believe that the alcohol-induced increase in the dopamine level in the nucleus accumbens (NAcc), a brain division involved in the mesolimbic pathway, is crucial for the development of addictive behavior (Comings and Blum, 2000; Blum and Oskar-Berman, 2014). As dopamine influences the sense of pleasure and suppresses stress, self-treatment with alcohol palliates discomfort and brings about a false sense of well-being. However, chronic abuse of alcohol or other psychoactivators suppresses dopamine production and causes a malfunction of the receptor (Comings and Blum, 2000).

Several laboratory-raised model rat strains, differing in their preference for ethanol, were created for studies of genetic and neurobiological mechanisms underlying alcohol addiction (Stewart et al., 1993;

Colombo et al., 1995; Möller et al., 1997). Nevertheless, there are practically no data on alcohol consumption by the strains selected for socially significant behavioral traits, in particular, the response to social stress. In this regard, the unique Norway rat strains selected at the Institute of Cytology and Genetics, Novosibirsk, Russia (hereinafter, ICG), for their aggressive and tolerant attitude to humans for 80 generations provide a convenient model for investigating hereditary traits concerning alcohol consumption and addictive behavior. It has been shown that the selection of rats for their attitude to humans is accompanied by changes in a broad range of physiological and behavioral parameters (Plyusnina and Oskina, 1997; Albert et al., 2008). In particular, rats with a positive attitude to humans (tame) demonstrate a lower activity of the hypothalamic–pituitary–adrenal (HPA) axis, a weakening of anxiety-like behavior, mitigation of intraspecies aggression in the resident–intruder test, and a longer latency of aggressive contacts in the social interaction test in comparison to aggressive or unselected animals (Naumenko et al., 1989; Plyusnina et al., 2011; Gulevich et al., 2015). In selecting rats for tame behavior, changes in the dopamine level and density and in the binding ability of dopamine receptors in the mesolimbic system of the brain in comparison to the unselected animals were noted (Nikulina et al., 1992). As shown by Albert et al. (2008), the dopamine level in the NAcc of tame rats is higher than in aggressive ones. Recent studies indicate that the expression of mRNA of the gene for dopamine receptors (DRD2) in the amygdalae of tame rats is higher than in aggressive or unselected animals.

As the selection of rats based on their attitude to humans touches the HPA axis and the dopaminergic system in the mesolimbic areas of the brain—systems that also mediate stress-induced alcohol consumption—it was reasonable to expect tame and aggressive rats to differ in terms of the influence of ethanol on their behavior and ethanol consumption.

The goal of the present work is to study the consumption and preference of ethanol and its influence on the behavior of male rats of the strains selected for tame and aggressive attitudes to humans.

MATERIALS AND METHODS

Animals

The experiments were performed with mature outbred Norway male rats (*Rattus norvegicus*) of the 83rd generation of selection for the absence (tame rats) and enhancement (aggressive rats) of the aggressive–fearful response to humans. Each group included 10 to 12 individuals. The animals were kept in groups of four in metal cages 50 × 33 × 20 cm in size under natural insolation. Food and water were given ad libitum. Prior to the experiment, the males were weighed and placed into cages singly. The study followed the conventional protocol for Wistar rats selected for anxiety (Henniger et al., 2002) modified with regard to the cages in which the rats were kept at the ICG vivarium.

The work was carried out in accordance with the regulations on studies with laboratory animals (Supplement to Ministry of Health and Medicine Order 267 of June 19, 2003).

Elevated Plus Maze Test

Behavior testing was conducted within 14:00–18:00 local time. Ten minutes before the test, the experimental males were intraperitoneally injected with 15% ethanol, 1 g/kg body weight. Control males received a normal saline solution.

The effect of alcohol on behavior was studied in the elevated plus maze (EPM) test, commonly used in testing anxiolytic and anxiogenic substances (Rodgers and Cole, 1994). The maze was a plus-shaped apparatus with two open and two enclosed arms 50 cm long and 10 cm wide, elevated 50 cm above the floor. The enclosed arms had three 40-cm high opaque walls each. A 10 × 10 cm central platform was located at the intersection of the arms. At the beginning of the test, a rat was placed at the center, with its nose facing an enclosed arm. Behavior parameters were being recorded for 5 min: latencies of entry to enclosed and open arms, number of entries to open arms and time of staying there; number of entries to enclosed arms and time of staying there; number of entries to the center and time of staying there; and number and time of partial entries (with two paws) to the center and open arms. After testing each rat, the maze was carefully washed and dried with paper towels.

The behavior was camcorded, and the record was processed with a home-made program to assess the share of each behavior pattern (Plyusnina et al., 2003).

Test of Consumption and Preference of Freely Accessible Ethanol (Two-Bottle Test)

Five days after the behavior test, two bottles were hung in each cage: with water and ethanol solution. The cages were too small to hang four bottles at a time (one with water and three with different ethanol concentrations, as in the study of Wistar rats (Henniger et al., 2002)). The bottles were weighed and swapped at one- or two-day intervals. The alcohol bottle contained 2% ethanol for the first 5 days, 5% for the next 5 days, and 10% for the last 5 days. Then the alcohol bottles were removed for 7 days and further they were returned with 10% ethanol, to assess the effect of withdrawal. The bottles were weighed again for 2 days. Alcohol consumption was assessed in g/kg, and preference as a percentage of the total amount of consumed liquid.

The results were evaluated by two-way ANOVA. The first factor was the rat strain, and the second, the

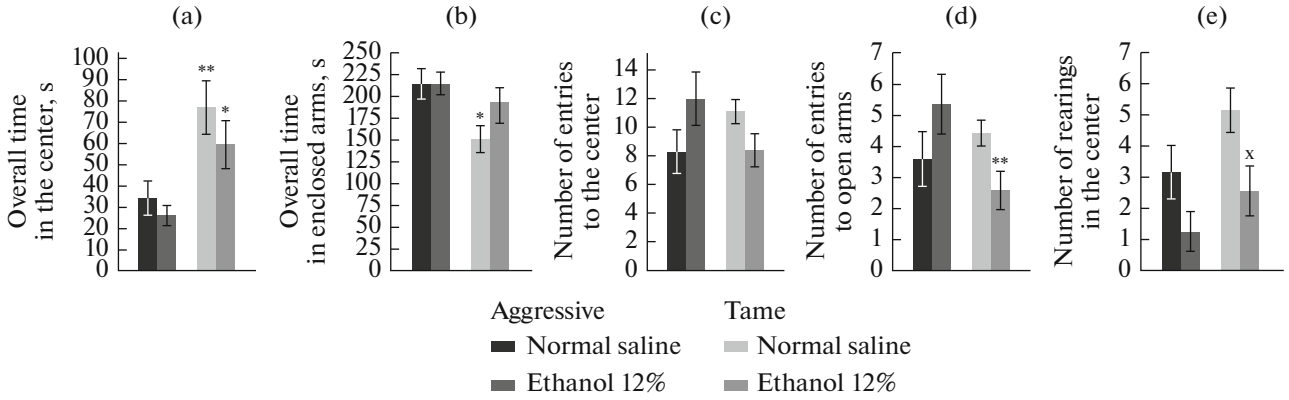

Fig. 1. Influence of ethanol on the behavior in the elevated plus maze. *$p < 0.05$, **$p < 0.01$ compared to aggressive males of the corresponding group; $^{x}p < 0.05$ compared to control animals having received a normal saline solution.

effect of the intraperitoneal alcohol injection in the behavior test or its concentration, days of presentation, and withdrawal in the experiment with freely accessible water and ethanol. The difference between groups was assessed by the Fisher post-hoc test.

RESULTS

The effect of a single ethanol administration on anxiety-like behavior is illustrated in Fig. 1. Two-way ANOVA revealed a significant influence of the genotype on the overall time spent by animals in the center ($F_{1.38} = 15.65$, $p < 0.001$) and in the enclosed arms ($F_{1.38} = 6.43$, $p < 0.05$). Ethanol administration did not affect these parameters ($F_{1.38} = 1.74$, $p > 0.05$ and $F_{1.38} = 1.60$, $p > 0.05$, respectively), as shown in Figs. 1a and 1b. The interaction of these factors was insignificant for the overall time in either center ($F_{1.38} = 0.22$, $p > 0.05$) or the enclosed arms ($F_{1.38} = 1.52$, $p > 0.05$). Males of the control tame group spent less time in the enclosed arms than the aggressive males ($p < 0.05$); however, this difference faded after intraperitoneal ethanol administration (Fig. 1b).

The genotype and ethanol administration factors did not influence the number of entries to the center ($F_{1.38} = 0.07$, $p > 0.05$ and $F_{1.38} = 0.12$, $p > 0.05$), respectively, but the interaction of these factors was significant ($F_{1.38} = 5.53$, $p < 0.05$). The numbers of entries to the open arms in the control animals did not differ between aggressive and tame ones; however, after ethanol administration, tame rats entered the open arms less often than aggressive ones ($p < 0.05$) (Fig. 1d).

The genotype and ethanol administration factors influenced the number of rearings in the center: $F_{1.38} = 4.64$, $p < 0.05$ and $F_{1.38} = 8.70$, $p < 0.01$, respectively (Fig. 1e). The interaction of these factors was insignificant ($F_{1.38} = 0.21$, $p > 0.05$). This parameter decreased in males of both genotypes after ethanol administration compared to the control. The decrease was significant in tame rats ($p < 0.05$) and on the brink of significance in aggressive ones ($p = 0.08$).

The mean daily amounts of various alcohol concentrations consumed, with ethanol and water being freely accessible, are shown in Fig. 2. Two-way ANOVA revealed no significant effect of genotype on this parameter ($F_{1.66} = 0.27$, $p > 0.05$), whereas the ethanol concentration factor affected ethanol consumption significantly ($F_{2.66} = 31.11$, $p < 0.001$). The interaction of these factors was insignificant ($F_{2.66} = 2.51$, $p > 0.05$). Rats with different behavior genotypes did not differ in the consumption of 2% as opposed to 5% ethanol solutions, whereas tame rats consumed 10% more ethanol than aggressive ones.

Figure 3 illustrates the data on the consumption of various ethanol concentrations on days 1 and 2 of the

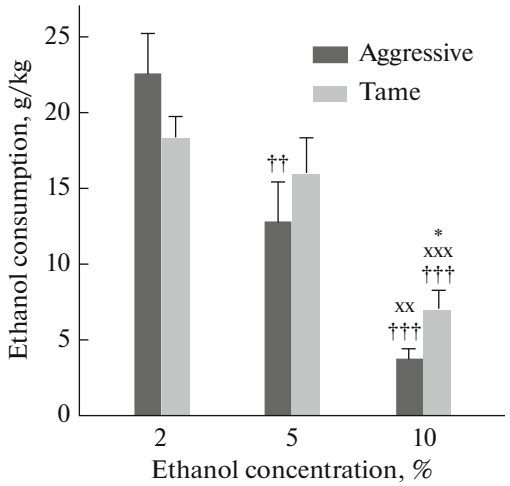

Fig. 2. Consumption of various ethanol concentrations within five days of presentation, daily average. *$p < 0.05$ compared to aggressive animals; $^{†††}p < 0.001$, $^{††}p < 0.01$ compared to 2% ethanol in the corresponding group; $^{xxx}p < 0.001$, $^{xx}p < 0.01$ compared to 5% ethanol in the corresponding group.

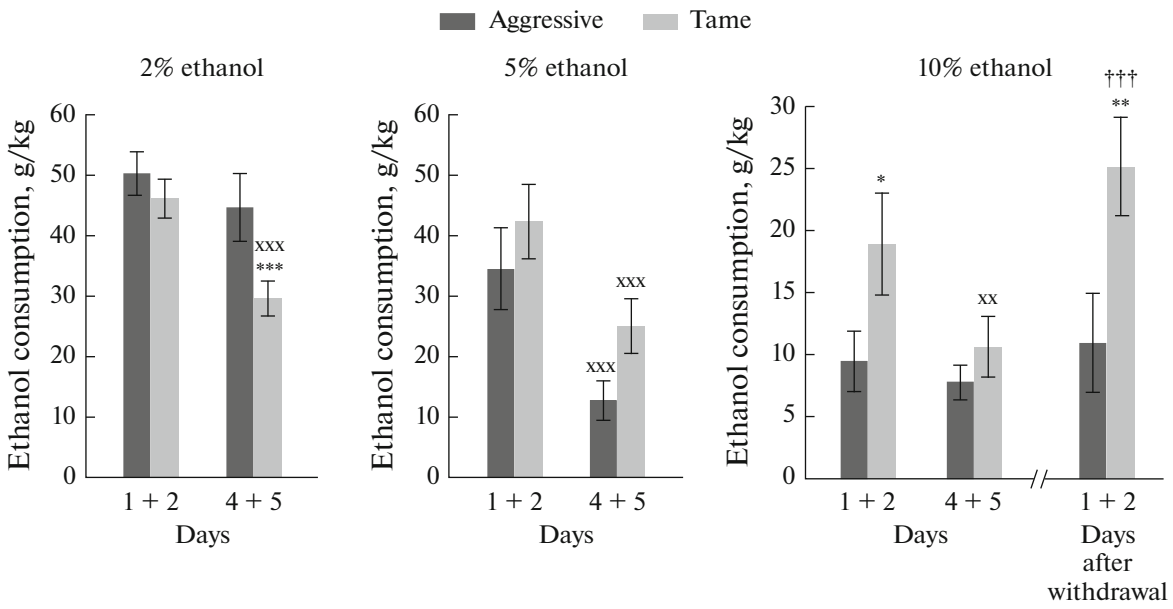

Fig. 3. Dynamics of ethanol consumption on days 1–2 and 4–5 of presentation and within the first two days after a 7-day withdrawal. ***$p < 0.001$, *$p < 0.05$ compared to aggressive animals on the corresponding days; $^{xxx}p < 0.001$, $^{xx}p < 0.01$ compared to the first two days in the corresponding group; $^{\dagger\dagger\dagger}p < 0.001$ compared to days 4–5 in the corresponding group.

presentation, on days 4 and 5, and within two days after the 7-day withdrawal. The consumption of 2% ethanol was affected by both the genotype ($F_{1.20} = 11.53$, $p < 0.01$) and days of presentation ($F_{1.20} = 10.12$, $p < 0.01$). The interaction of these factors was significant: $F_{1.20} = 15.46$, $p < 0.001$. The consumption of 5% ethanol was not affected by genotype ($F_{1.22} = 1.93$, $p > 0.05$) but was affected by the day of presentation ($F_{1.22} = 37.74$, $p < 0.001$), and the interaction of these factors was insignificant ($F_{1.22} = 0.53$, $p > 0.05$). Similarly, the genotype did not affect the consumption of 10% ethanol ($F_{1.21} = 3.93$, $p > 0.05$) but the days of presentation did ($F_{1.22} = 37.74$, $p < 0.001$). The interaction of these factors was also insignificant ($F_{1.22} = 0.53$, $p > 0.05$).

The factors of genotype and withdrawal affected the consumption of 10% ethanol ($F_{1.44} = 7.40$, $p < 0.01$ and $F_{1.44} = 7.96$, $p < 0.01$, respectively). The interaction of these factors was insignificant ($F_{1.44} = 3.30$, $p > 0.05$).

In tame rats, the consumption of 2% ethanol on days 4 and 5 decreased in comparison to the earlier days and became less than in aggressive ones (Fig. 3). The consumption of 5% ethanol on days 4 and 5 decreased in both tame and aggressive rats in comparison to the earlier days. The tame rats significantly surpassed the aggressive ones in the consumption of 10% ethanol on the first days of presentation ($p < 0.05$). On days 4 and 5, they reduced their ethanol consumption ($p < 0.01$), whereas aggressive animals did not change their consumption significantly. In the first two days after the 7-day withdrawal, the consumption of 10% ethanol by tame rats increased in comparison to days 4 and 5 of the initial presentation ($p < 0.001$), but the consumption by aggressive rats did not change significantly. In tame rats, the consumption of 10% ethanol after withdrawal, as in the first days of presentation, was higher than in aggressive ones ($p < 0.01$).

Two-way ANOVA revealed significant effects of genotype ($F_{1.66} = 12.48$, $p < 0.001$) and ethanol concentration ($F_{2.66} = 35.51$, $p < 0.001$) on ethanol preference (Fig. 4). The interaction of these factors was insignificant ($F_{2.66} = 1.22$, $p > 0.05$). With an increase in the ethanol concentration, its preference in aggressive rats decreased significantly, whereas in tame rats the preference did not differ for 2 and 5% solutions, but decreased only for 10% ethanol. The preference for the 2% solution did not differ between tame and aggressive rats, whereas the preference for 5% ethanol in tame rats was higher than in aggressive ones ($p > 0.01$). The same trend was observed with the 10% solution ($p = 0.06$).

DISCUSSION

Analysis of the preference for various ethanol concentrations by tame and aggressive rats shows that the maximum difference is observed in the case of the 2% solution (Fig. 4). This result is consistent with the data on the preference for alcohol at concentrations < 6% (Meisch and Lemaire, 1993) or 5% over 10% and 20% (Henniger et al., 2002). The preferences for 2% ethanol in tame and aggressive rats do not differ, whereas the preference for 5% solution in tame rats is higher

than in aggressive ones. The preference for ethanol in aggressive rats is inversely proportional to its concentration, and in tame rats, it significantly decreases at the 10% concentration.

The daily average ethanol consumption by aggressive rats, like the preference, significantly decreases with an increase in the concentration (Figs. 2, 4). In tame rats, the preferences for the 2 and 5% solutions do not differ significantly, and the preference for 10% solutions is less than for the lower concentrations. Thus, it is conceivable that aggressive rats are more sensitive to a variation in the ethanol concentration from 2 to 5% than tame rats.

Our results point to a higher consumption of 2% ethanol by aggressive rats on days 4 and 5 of its presentation in comparison to tame animals (Fig. 3). In earlier studies, aggressive rats showed elevated anxiety in the dark–light and startle response tests (Albert et al., 2008). According to the stress relief hypothesis, highly anxious individuals might be more sensitive to the anxiolytic effect of alcohol and, probably, be more predisposed to its consumption just for this reason (Conger, 1956). Consequently, it was reasonable to suggest that the anxiolytic effect of alcohol would be more pronounced in aggressive rats and, therefore, they would consume more alcohol than tame ones. However, this suggestion holds true only in the case of 2% ethanol but not for higher concentrations. Aggressive rats demonstrated low preference for 5% ethanol and for 10% solution in the first two days of presentation and during the average day, as well as after a 7-day withdrawal, in comparison to tame males. The latter also showed a deprivation effect, because the consumption of 10% ethanol after withdrawal was higher than before.

This result agrees with the greater alcohol consumption observed in rats selected for LAB in the EPM test than in rats of the strain selected in the opposite direction, HAB (Henniger et al., 2002). We have mentioned that tame rats show a lower anxiety level than aggressive ones (Albert et al., 2008). However, in contrast to tame rats, low-anxiety males show larger intermale aggression in the resident–intruder test than males of the contrasting strain (Veenema, Neumann et al., 2007). Also, the design of our experiment differed from the study on the HAB and LAB rats. In our experiment, the rats had access to two bottles: with water and ethanol of a certain concentration (2, 5, or 10%). In the experiment with HAB and LAB rats, they had access to four bottles simultaneously: water and ethanol in concentrations of 5, 10, and 20% (Henniger et al., 2002). In spite of the difference between the rat models (selected for anxiety and for their attitude to humans) and the experimental design, the results point to greater alcohol consumption by males with low anxiety than by animals of the corresponding contrasting strains. Our results confirm the opinion of other authors that a positive correlation between anxiety and alcohol consumption under home cage conditions is observed only with lower concentrations (2–4%), and the conditions themselves do not encourage anxiety-like behavior (Henniger et al., 2002).

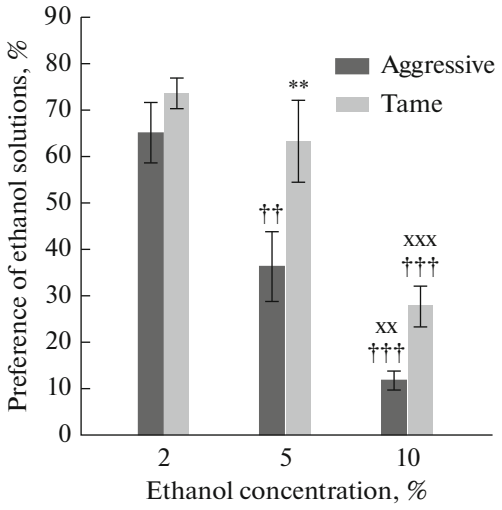

Fig. 4. Preference of ethanol solutions of different concentrations presented for 5 days each (% of the total volume of liquid consumed). $^{**}p < 0.01$ compared to the corresponding aggressive animals; $^{\dagger\dagger\dagger}p < 0.001$, $^{\dagger\dagger}p < 0.01$ compared to 2% ethanol in the corresponding group; $^{xxx}p < 0.001$, $^{xx}p < 0.01$ compared to 5% ethanol in the corresponding group.

The response of the HPA axis to nonsocial stress in LAB and tame rats was lower than in the corresponding contrasting strains (Veenema et al., 2007; Oskina et al., 2008). Basal dopamine levels in the NAcc did not differ between the LAB and unselected rats, whereas after the resident–intruder test the dopamine level in LAB rats became higher than in unselected ones (Beiderbeck et al., 2012). Nine brain areas were studied with regard to the dopamine levels in rats selected for the response to humans, and a difference was found only in the NAcc, where this index in tame rats was higher than in aggressive ones (Albert et al., 2008). This fact suggests that rat selection for tame behavior establishes certain interrelationships between the HPA axis and the dopaminergic system of the brain's mesolimbic areas. They favor elevated ethanol consumption and a preference for concentrations exceeding 5% in comparison to aggressive animals.

In the EPM test, control tame males spend less time in the enclosed arms than aggressive males. This difference fades after intraperitoneal ethanol administration. No significant difference is observed in the number of entries to the open arms, but after ethanol administration, tame rats enter open arms less often than aggressive ones. By putting together these results in rats differing in behavior, one may make an indirect conclusion on elevated anxiety in tame rats induced by ethanol administration, whereas the significant

decrease in the number of rearings in the center in tame rats having received ethanol in comparison to the control rates provides direct evidence. Hence, 12% ethanol not only does not exerts an anxiolytic effect but even enhances anxiety-like behavior. In this regard, tame Norway rats can serve as a model for the study of alcohol-induced anxiety elevation. Presumably, this response to alcohol in tame rats promotes its further consumption.

Our German colleagues pointed to the *ANKK1* gene for the ankyrin repeat and kinase domain containing 1 as one of the genes differing in structure between the Norway rats selected for tame and aggressive behavior. Mutations in this gene were found only in tame rats but not in the aggressive or unselected rats. This gene is tightly linked to the *DRD2* gene with the dopamine receptor. It is expressed in astrocytes, and the protein is classified with the family of kinases involved in signal transduction (Neville et al., 2004). Apomorphine, which acts as a dopamine agonist, strengthens the *ANKK1* gene expression in cultivated murine astrocytes; thus, it may be related to the dopaminergic system (Hoenicka et al., 2010). The Taq1A polymorphism in the human *ANKK1* gene (formerly believed to occur in *DRD2*) is being extensively studied in connection with addictive asocial behavior (Hoenicka et al., 2010; Lu et al., 2012). It is thought to be associated with behavior features such as novelty seeking and harm avoidance (Berman et al., 2002). In addition, it has been shown that Taq1A modulates the density and binding capability of the DRD2 receptors (Ariza et al., 2012). As mentioned above, the selection of rats for their tame behavior alters the dopamine level, as well as the density and binding ability of the dopamine receptors in the mesolimbic pathway in comparison to the unselected animals (Nikulina et al., 1992). As reported in (Albert et al., 2008), the dopamine level in the NAcc of tame rats is higher than in aggressive rats. Probably, the structural modifications in *ANKK1* found in tame rats affect the expression of the DRD2 dopamine receptor gene, and this change results in the increased preference for and consumption of ethanol solutions with concentrations >5%.

To summarize, the difference between tame and aggressive rats in alcohol consumption varies depending on the concentration. Aggressive males prefer ethanol only at the 2% concentration; thus, the stress relief hypothesis is confirmed only for this concentration.

ACKNOWLEDGMENTS

This work was performed in cooperation with the Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany. It was supported by State Budgeted Project 0324-2015-0004.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Translated by V. Gulevich