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EXPERIMENTAL PAPERS

Intermale Interactions on Neutral Territory and Subsequent Dynamics of Blood Corticosterone and Testosterone Levels in Tame and Aggressive Norway Rats (*Rattus norvegicus*)

R. G. Gulevich[a,*], S. G. Shikhevich[a], M. Y. Konoshenko[b], and R. V. Kozhemyakina[a]

[a] *Institute of Cytology and Genetics, Russian Academy of Sciences, Novosibirsk, Russia*

[b] *Institute of Chemical Biology and Fundamental Medicine, Russian Academy of Sciences, Novosibirsk, Russia*

**e-mail: gulevich@bionet.nsc.ru*

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Abstract—Previously, stress responses in gray Norway rats (*Rattus norvegicus*) selected for the absence or enhancement of aggressive and defensive behaviors toward humans (tame and aggressive behaviors, respectively) were studied mainly to nonsocial factors, whereas data on the consequences of social stress induced, specifically, by interactions with conspecifics are scarce. As has already been shown, the above selection of Norway rats causes attenuation or enhancement of intraspecific intermale aggression. To find out whether the differences in aggressiveness are accompanied by hormonal alterations, we addressed the dynamics of corticosterone and testosterone blood levels after intermale aggression testing in tame and aggressive rats, and unselected rats bred in a vivarium for 7–8 generations as a reference. The goal of this work was to investigate the effect of selection toward humans on agonistic interactions under conditions of an unfamiliar cage or neutral territory and on the subsequent dynamics of blood corticosterone and testosterone levels in tame, aggressive, and unselected rats. In our experiments, tame males, as compared to their aggressive or unselected conspecifics, demonstrated a longer attack latency, as well as a shorter duration and smaller number of patterns of aggressive behavior, approximating zero values. When tested on neutral territory, aggressive male rats were inferior to their unselected conspecifics in the total time of confrontations. More pronounced manifestations of aggression in unselected males compared to aggressive or tame animals arose against the background of elevated basal corticosterone levels and enhanced stress responsiveness to interacting with an unfamiliar male. At the same time, reduced aggressiveness of tame rats in the neutral territory test, as compared to unselected or aggressive animals, correlated with the lower testosterone level.

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Keywords: selection, Norway rats, behavior, aggressiveness, corticosterone, testosterone

INTRODUCTION

Aggressive behavior is a common symptom of many psychological disorders and psychic diseases, such as schizophrenia, bipolar disorders, increased anxiety, and autism [1–4]. Multiple

factors that contribute to the development of aggression include genetic, environmental (aggression training at childhood, parental care impairment), ontogenetic (i.e. disturbing the development of the central nervous system), hormonal and neurotransmitter dysfunctions. Compelling evidence for the hereditary component in the manifestation of aggression has been obtained during selection of animals for the specific parameters of aggressiveness [5–7].

The involvement of the hypothalamic–pituitary–adrenal (HPA) axis in the regulation of aggressive behavior is being widely discussed in the relevant literature [8–11]. In experiments on rats, it was shown that corticosterone administration enhances the manifestation of aggressive behavior, while the inhibitor of its synthesis, metyrapon, quite the contrary, attenuates it [8]. By the Haller's data (2014), when animals encounter with unfamiliar subjects and have to mobilize their resources to gain control over the situation, the HPA axis is already activated at early stages of social interaction, yet before the onset of fights, and glucocorticoids secreted in response to an encounter quickly stimulate aggressiveness [11]. In males of the rat strain selected for low anxiety-related behavior (LAB), in contrast to males of the rat strain selected for high anxiety-related behavior (HAB), intermale aggression was noted to be enhanced and the basal corticosterone blood level, as well as that of adrenocorticotropic hormone (ACTH), were found to rise 15 min after the onset of the resident–intruder test [6, 10]. In contrast, stress responses to non-social interaction induced by open-arm conditions of the elevated plus maze proved to be lower in LAB rats than in their HAB counterparts [12]. Meanwhile, in contrast to rats of these strains, the mice of the behaviorally opposite strains selected in different labs for enhanced (SAL, TA, NC900) and attenuated (LAL, TNA, NC100) aggressiveness did not differ substantially by their basal corticosterone level [13].

Testosterone, which is synthesized in testicular Leydig cells, is known to have a stimulatory effect on aggressive behavior, as evidenced, specifically, by the effects of castration of male rodents followed by testosterone administration [14, 15]. At the same time, according to the challenge hypothesis, cause-and-effect relationships between testosterone and aggressiveness are transient and arise only in polygamous competitive species, when males have to contest for the status and/or resources needed for reproduction [16]. However, in the above-mentioned HAB and LAB male rats differing by the degree of aggressiveness, testosterone blood levels differ neither in the quiescence nor one hour after the onset of the resident–intruder test [10]. In this case, only in more aggressive LAB males vs. less aggressive HAB males, one hour since the onset of the resident–intruder test, the authors observed an increase in the number of c-Fos-positive cells in the parvocellular region of the hypothalamic paraventricular nucleus (PVN), indicating neuronal activation of this region.

Gray Norway rats selected for a long period of time (80 generations) at the Institute of Cytology and Genetics (Novosibirsk) for the absence and enhancement of aggressive defensive responses toward humans (tame and aggressive behaviors) allow investigating the genetically determined features of intermale interactions and hormonal alterations caused thereupon, which can provide better insight into the mechanisms behind aggressive behavior which forms during selection. Previously, it was demonstrated that in tame male rats aggressive behavior toward conspecifics abates in the resident–intruder and neutral territory (or unfamiliar cage) tests, and that the anxiety level declines as judged by rat behavior in a light–dark chamber and the startle–response test [17–19]. In contrast to the resident–intruder test, when male rats defend their own territory, in the neutral territory test male aggressiveness manifests itself weaker [17, 20]. In a previously published work on rat intermale interactions on neutral territory, there were no data on the results of this test in unselected male rats. In one of the recent publications, there were reported data on the corticosterone blood level dynamics in tame, aggressive and unselected rats after restrictive stress [21]. However, it still remained unknown what features of the dynamics of this hormone are in tested rats after their interaction with an unfamiliar conspecific. In a study of intermale interactions in the resident–intruder test, data on the corticosterone blood level were presented only for a single point

after the test [18]. In this case, unselected rats were superior to aggressive and tame conspecifics in the hormone level both before and after the test. Furthermore, regardless of the behavior, the corticosterone blood level in male rats increased after the resident–intruder test vs. the basal level. In a number of previous studies carried out both on adult male rats and during ontogeny, tame, aggressive and unselected males were almost indistinguishable by the basal testosterone blood level [21, 22], but it was unclear how behavioral selection of rats influences the testosterone level after intermale interactions.

It was hypothesized that agonistic interactions among unselected male rats on neutral territory may have characteristic features in contrast to rats selected for tame and aggressive behavior, and that the vector of behavioral selection may influence the dynamics of corticosterone and testosterone levels after intermale interactions.

The goal of this work was to study the influence of selection toward humans on the parameters of intermale interactions under conditions of an unfamiliar cage (neutral territory), as well as the subsequent dynamics of corticosterone and testosterone blood levels in tame, aggressive and unselected male rats.

MATERIALS AND METHODS

Experimental animals

This study was carried out in compliance with the principles of the Basel Declaration and recommendations of the Bioethics Committee at the Institute of Cytology and Genetics of the Russian Academy of Sciences (ICG SB RAS), protocol no. 8 of March 19, 2012. Experiments were conducted in the Center for Collective Use "Vivarium of Conventional Animals" at ICG SB RAS on 2-month-old male gray Norway rats (*Rattus norvegicus*) weighing 270–300 g obtained due to an 80-generation selection for the absence and enhancement of aggressive defensive responses toward humans, hereinafter referred to as tame and aggressive, respectively. Rat responses were assessed in arbitrary units or so-called scores of the behavioral response to a human gloved hand under home-cage conditions in the interval from +4 to –4 scores [5, 23]. While testing, the frontal wall of the cage was reclined, and the experimenter extended his/her gloved hand into the open cage. Population mean scores of behavior reached (+)3.45 ± 0.05 in tame and (–)3.05 ± 0.07 in aggressive males. As a control, unselected males bred for 7–8 generations in a vivarium were used. The mean score of behavior in these animals, (–)2.26 ± 0.07, was significantly different from those in tame and aggressive males ($p < 0.001$ in both cases). Animals were kept in metal cages (50 × 33 × 20 cm), by 4 males per cage, under natural photoperiod with free access to food and water. A week before testing, male rats were separated by one individual per cage. All tests were carried out from 2 to 6 p.m.

Intermale aggression testing on neutral territory

The test was carried out in a cage made of transparent plastic (40 × 40 × 60 cm) separated by a partition into two identical compartments [23]. Two unfamiliar males of the same weight from the each test strain were simultaneously placed into these compartments, one at a time, and then the partition was taken away. Totally, 18 tests were carried out: 6—between wild (unselected) pairs, 6—between aggressive pairs, and 6—between tame pairs. Male behavior was recorded for 5 min on a video camera Panasonic SDR-H280EE-S (Japan). Eventually, video records were processed using a software developed in our laboratory, enabling the assessment of the number and duration of behavioral patterns, namely the latency of the first aggressive interaction, the number and duration of attacks, chases, hindlimb kicks, rearing, pinning, aggressive grooming, lateral threats [24]. Additionally, the duration of such social behavior patterns as approaching and sniffing a partner, as well as stretched attend (but not approach) postures toward a partner, was recorded.

Blood sampling and plasma hormone level determination

Immediately after a 5-min neutral territory test, blood was sampled from the tail tip, and then males were returned to their home cages. After that, blood was sampled after 30 min, 1 and 2 h after the end of testing. To assay the basal hormone level, blood was sampled 6 days after test-

ing. Blood was centrifuged, and the resultant plasma was frozen to –20°C until hormone assay. Corticosterone and testosterone plasma levels were assayed by the immunoenzyme technique using special EIA kits (IDS Ltd., UK). Sample staining intensity was recorded on a plate spectrophotometer Perkin Elmer 1420 Multilabel Counter. Each group comprised 9–12 animals, as indicated in figure captions. A part of samples dropped out either during the determination process or from the calibration curve.

Statistics

All values of the tested parameters were presented as $M \pm SEM$. The influence of the genotype factor on behavioral parameters of male rats were determined using a one-way ANOVA, while that of the genotype factor and intermale confrontations on the hormone dynamics before and after confrontations was assessed by a two-way repeated measures ANOVA. Statistical significance of intergroup differences was assessed using Kruskal–Wallis and Fisher LSD post hoc tests.

RESULTS

Testing of intermale interactions in male rats on neutral territory revealed a statistically significant influence of the genotype factor on the total aggression time $F_{2, 36} = 26.74$ ($p < 0.001$), attack latency $F_{2, 36} = 15.09$ ($p < 0.001$), attack number $F_{2, 36} = 15.61$ ($p < 0.001$), rearing number $F_{2, 36} = 18.18$ ($p < 0.001$), lateral threat number $F_{2, 36} = 12.72$ ($p < 0.001$), pinning number $F_{2, 36} = 7.02$ ($p < 0.05$), and wrestling number $F_{2, 36} = 25.09$ ($p < 0.001$).

The attack latency was significantly longer while the duration and number of all aggressive behavior patterns significantly less in tame vs. aggressive and unselected males (Fig. 1). By the total aggression time, aggressive males were inferior to unselected ones ($p < 0.05$).

A two-way repeated measures ANOVA showed the influence of the genotype and confrontation factors ($F_{2, 25} = 34.28$, $p < 0.001$ and $F_{4, 100} = 63.38$, $p < 0.001$, respectively) on the blood corticosterone dynamics in unselected, aggressive and tame males, while the interaction of these factors was statistically non-significant ($F_{8, 100} = 1.98$, $p > 0.05$). In all tested rat groups, the blood corticosterone level significantly increased vs. its basal level ($p < 0.001$ in all cases) immediately after interactions with an unfamiliar male, reching maximum values in wild and tame males 30 min and in aggressive males 1 h after the end of testing (Fig. 2). Two hours after testing, corticosterone levels in all tested rat groups became lower than the corresponding levels measured after 1 h ($p < 0.001$ – for unselected, $p < 0.01$ – for tame, $p < 0.05$ – for aggressive) but did not reach the basal values.

In unselected males, the blood corticosterone level, both in a quiescent state and at all test points after testing, was higher vs. aggressive and tame animals. Differences in the corticosterone level between aggressive and tame males were only detected 30 min after testing, with tame males being superior to aggressive ones ($p < 0.05$).

A two-way repeated measures ANOVA revealed that the influence of the genotype and confrontation factors ($F_{2, 27} = 3.41$, $p < 0.05$ and $F_{4, 108} = 5.67$, $p < 0.001$, respectively) on the blood testosterone level in unselected, aggressive, and tame rat males, while the interaction of these factors was non-significant ($F_{8, 108} = 1.65$, $p > 0.05$). By the basal testosterone level, rat males of all three genotypes did not differ significantly, and only in tame males there was observed a tendency toward a lower level of this hormone vs. unselected animals ($p = 0.06$). Immediately after intermale interactions, the testosterone level became significantly lower in tame vs. unselected and aggressive males ($p < 0.01$ in both cases) and 30 min after the end of testing remained lower than in aggressive rats ($p < 0.05$). Although in an hour after testing the testosterone level in tame males exceeded the basal level ($p < 0.05$), it was indistinguishable from the corresponding hormone levels in aggressive and unselected rats (Fig. 3). Two hours after testing, only in unselected males the hormone level fell below the basal one ($p < 0.05$).

DISCUSSION

Data on the corticosterone blood level dynamics in tame, aggressive and unselected rats after intermale interactions do not differ significantly

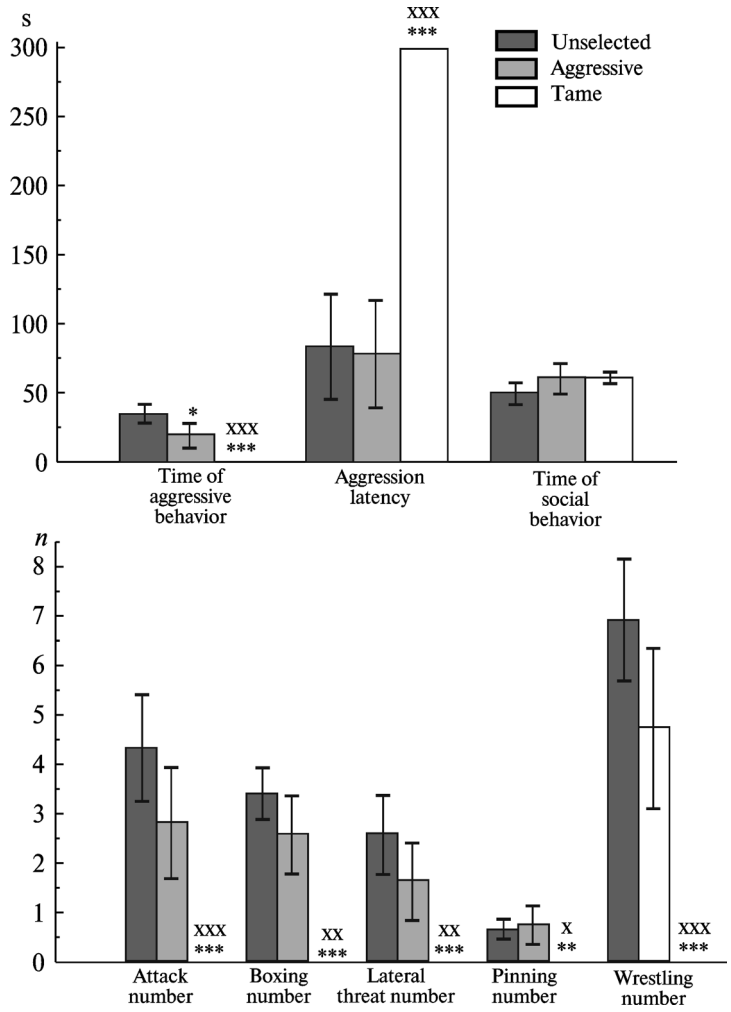

Fig. 1. Parameters of intermale aggression in unselected, aggressive, and tame rats on neutral territory. The top panel shows the duration of aggressive social behavior and its latency before the first aggressive interaction event. The bottom panel shows the number of specific aggressive behavior patterns. *** $p < 0.001$, ** $p < 0.01$,* $p < 0.05$ vs. unselected rats, ^{xxx} $p < 0.001$, ^{xx} $p < 0.01$, ^{x} $p < 0.05$ vs. aggressive rats. Values presented as $M \pm SEM$, $n = 12$.

from those obtained previously on these animals after restrictive stress [21], although on the other selection model it was demonstrated that differences in stress reactivity in rats contrasting by the anxiety and aggressiveness levels (LAB and HAB) depend on the social or nonsocial nature of stress exposure [10, 12]. For instance, stress reactivity toward a competitor male in LAB rats with increased aggressiveness is higher than in HAB rats with reduced aggressiveness [10], while stress reactivity toward nonsocial stressors, on the contrary, in LAB males is lower than in HAB conspecifics [12]. From the results obtained in this study, it follows that during rat selection toward humans stress reactivity of tame and aggressive males does not depend on the nature of stress exposures.

Parameters of aggressive rat behavior on neutral territory indicate an enhanced aggressiveness in unselected male rats compared not only tame but also aggressive rats. The tendencies we observe toward a larger number of attacks and rearings in unselected rats vs. aggressive ones was previously noted also in the resident–intruder test [18]. Moreover, in the present study it was shown that confrontations on neutral territory between unselected males take place over a longer time period than between aggressive animals (Fig. 1), while in the resident–intruder test such differences were not observed. Probably, a less pronounced manifestation of aggressiveness on neutral territory than while defending one's own territory in the resident–intruder test, as already mentioned

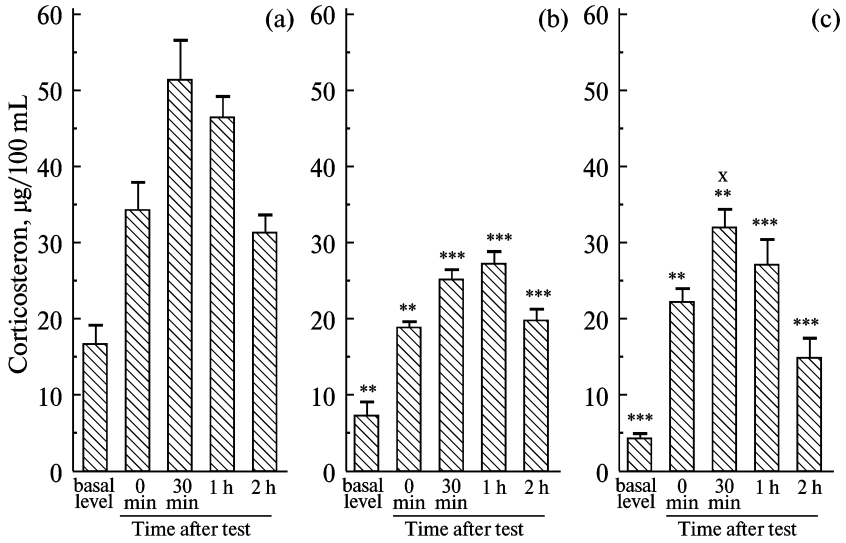

Fig. 2. Blood corticosterone levels in unselected (a), aggressive (b), and tame (c) rats before and after intermale interactions on neutral territory. *** $p < 0.001$, ** $p < 0.01$ vs. unselected rats; $^{x}p < 0.05$ vs. aggressive rats. Values presented as $M \pm SEM$, $n = 9–12$.

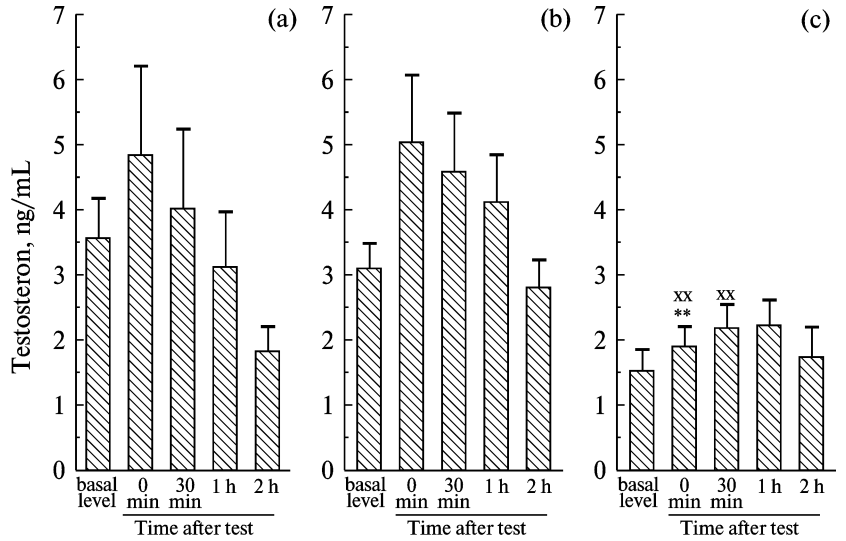

Fig. 3. Blood testosterone levels in unselected (a), aggressive (b), and tame (c) rats before and after intermale interactions on neutral territory. ** $p < 0.01$ vs. unselected rats; $^{xx}p < 0.01$ vs. aggressive rats. Values presented as $M \pm SEM$, $n = 10–12$.

above, makes it possible to reveal the differences in the duration of aggressive interactions between unselected and aggressive rats. These differences may also be determined by such a selection criterion as the reaction to a glove, which is related rather to the latent period of aggressive behavior than its duration.

From our results it follows that more pronounced manifestations of aggression in unselected vs. aggressive and tame males occur at the background of a higher basal corticosterone level and increased stress reactivity, since during 2 h after testing the blood corticosterone level in unselected rats remains higher than in two other strains (Fig. 2). These results are consistent with the data that corticosterone administration in rats enhances agonistic confrontations, while a corticosterone synthesis inhibitor metyrapon, by contrast, attenuates them [8]. More aggressive LAB males, compared to their HAB conspecifics, also exhibit elevated corticosterone levels before and after the resident–intruder test [10], although, in contrast to the LAB strain, unselected rats are characterized not only by increased aggressiveness

but also anxiety, as judged from a pronounced tendency toward a shorter time of being in the open field center compared to aggressive and tame rats [22].

The observed differences between unselected and aggressive rats in the total confrontation time and blood corticosterone level allows us to point out that selection for aggressive bahavior toward humans does not compensate the process of laboratorization which ensues from prolonged breeding and maintenance of rats under vivarium conditions.

In contrast to unselected rats, in which a more pronounced aggressiveness is accompanied by a higher basal corticosterone level and increased stress reactivity toward tame and aggressive rats, in the latter, the corticosterone level before testing is nearly the same as in tame rats and becomes even lower 30 min after testing. Previously, it was noticed that tame and aggressive rats exhibit no differences in the basal corticosterone level and stress reactivity after the resident–intruder test [18]. It is noteworthy that at early stages of selection the corticosterone level, both basal and after stress, was significantly higher in aggressive males than in tame ones [5, 23], whereas at leater stages the differences in the corticosterone level between aggressive and tame rats became more smoothed [21, 26]. It can be assumed that during selection for aggressive behavior the other mechanisms join in or become more significant, causing aggressiveness against the background of smoothed or even reduced functioning of the HPA axis compared to tame rats. A lack of differences in the basal corticosterone level was also reported for mouse strains selected both for the duration of the attack latency (SAL and LAL) and the frequency of attacks toward a social partner (NC900 and NC100) [12]. In this case, more aggressive NC900 mice demonstrated an increased anxiety, as well as a reduced level of the $GABA_A$ receptor α(2)-subunit in the frontal cortex and amygdala [27]. It is worth noting that aggressive rats are also characterized by increased anxiety compared to tame rats [19, 28]. Furthermore, magnetic resonance spectroscopy revealed in the dorsal hippocampus of aggressive rats a reduced, compared to tame rats, percentage of GABA in the total amount of neurometabolites [29]. Probably, selection of rodents for the reactivity both toward a social partner and human hand influences the GABA system in those brain regions that are associated with aggressiveness and anxiety.

In males of all three rat strains, the blood corticosterone level, immediately after 5-min interactions with a conspecific on neutral territory, rises compared to the basal level, which was also observed previously after the resident–intruder test [18]. Such an increase in the corticosterone level indicates that the nearby presence of an unfamiliar conspecific partner exerts a stressful influence on all males, irrespective of their behavior, and causes confrontations in unselected and aggressive rats but not in tame ones in which the latent period of aggression continues throughout the entrie 5-min test and all other parameters of aggressive behavior are close to zero values. Since it was shown previously that there is a fast positive feedback between the stress response and central mechanisms involved in the regulation of aggressiveness [9], it can be assumed that during selection for tame behavior such a feedback is impaired.

By the basal blood testosterone level, males of all three strains were significantly indiftinguishable, which supports the previous data [21, 22] and agrees with the results obtained on LAB and HAB males differing by the degree of aggressiveness [10]. The testosterone level in tame rats becomes significantly lower than in aggressive and unselected animals only after interactions with competitor males. These findings are consistent with the challenge hypothesis according to which the link between aggressiveness and testosterone level shows up in the period when males get into a fight for status or resources needed for reproduction [16]. In an hour after testing, all differences in the testosterone level in males of the three testes strains become leveled off. In LAB and HAB male rats, which exhibit different degree of aggressiveness, testosterone levels 1 h after the onset of the resident–intruder test are also statistically indistinguishable, but no data were reported therewith on the level of this hormone immediately upon cessation of testing [10].

It was shown immunohistochemically that in tame and aggressive male rats, after the resident–intruder test, the number of cells expressing the

transcription factor c-Fos, a neuronal activity marker, increases in the bed nucleus of the stria terminalis, medial amygdala and hypothalamic attack area compared to control aminals [30]. In this case, tame males were inferior to aggressive ones in the number of these cells in the hypothalamic attack area. The cells in this area, which refers to ventrolateral regions of the ventromedial hypothalamus [31, 32], send axons to other hypothalamic areas and, specifically, to the preoptic area [33] playing an important role both in aggressive and sexual behaviors [34]. Moreover, the preoptic area is the residence of GnRH neurons [35] which secrete the gonadotropin-releasing hormone (GnRH) stimulating the production of pituitary gonadotropins which, in turn, boost testosterone synthesis in the testes. In this regard, it can be assumed that the increased number of c-Fos-positive cells in the hypothalamic attack area of aggressive male rats after intermale interactions contributes to the activation of GnRH neurons in the hypothalamic preoptic area, which leads to a higher testosterone level in these animals compared to tame males.

Thus, in unselected rats and those selected for the enhancement of aggressive defensive responses toward humans, aggressiveness is accompanied by different functional levels of the HPA axis before and after the interaction with a competitor male on neutral territory, while tame males are distinguished from aggressive and unselected animlas by a lower blood testosterone level after the interaction with a competitor male.

AUTHORS' CONTRIBUTION

Konoshenko M.Yu., Gulevich R.G.: experimental design and planning; Kozhemyakina R.V., Shikhevich S.G.: data collection; Konoshenko M.Yu., Kozhemyakina R.V. and Shikhevich S.G.: data processing; Gulevich R.G. and Kozhemyakina R.V.: writing a manuscript.

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COMPLIANCE WITH ETHICAL STANDARDS

This study was carried out in compliance with the principles of the Basel Declaration and recommendations of the Bioethics Committee at the Institute of Cytology and Genetics of the Russian Academy of Sciences (ICG SB RAS), protocol no. 8 of March 19, 2012.

This study did not involve human subjects as research objects.

CONFLICT OF INTEREST

The authors declare that they no conflict of interests.

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