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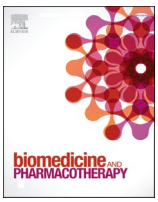

On an association between fear-induced aggression and striatal-enriched protein tyrosine phosphatase (STEP) in the brain of Norway rats

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ABSTRACT

Striatal-enriched protein tyrosine phosphatase (STEP) is a signal transduction protein involved in the pathogenesis of neuropathologies. A STEP inhibitor (TC-2153) has antipsychotic and antidepressant effects. Here, we evaluated the role of STEP in fear-induced aggression using Norway rats selectively bred for 90 generations for either high aggression toward humans (aggressive rats) or its absence (tame rats). We studied the effects of acute administration of TC-2153 on behavior and STEP expression in the brain of these animals and the influence of chronic treatment with TC-2153 on the behavior and STEP expression in aggressive rats in comparison with classic antidepressant fluoxetine, which is known to exert antiaggressive action. Acute TC-2153 administration decreased the aggressive reaction to humans in aggressive rats, while having no impact on the friendly behavior of tame rats. Moreover, in the elevated plus-maze test, the drug had an anxiolytic effect on both aggressive and tame rats. Aggressive rats demonstrated elevated levels of a STEP isoform (STEP46) as compared to tame animals, whereas acute TC-2153 administration significantly reduced STEP46 protein concentration in the brain of aggressive rats. Chronic treatment of aggressive rats with either TC-2153 or fluoxetine attenuated fear-induced aggression. Chronic administration of fluoxetine enhanced the exploratory activity in the elevated plus-maze test and decreased the STEP46 protein level in aggressive rats' hippocampus, whereas chronic TC-2153 administration did not affect these parameters. Thus, STEP46 can play an important role in the mechanisms of aggression and may mediate antiaggressive effects of TC-2153 and fluoxetine.

1. Introduction

Aggressive behavior (including overt fighting) plays an important role in the life of animal populations and their evolution [45]. In the wild, aggression is important for protection, reproduction, and survival. The molecular mechanisms underlying this complicated type of behavior are still unknown. Suitable models for studying the mechanism of aggression are two strains of wild Norway rats selectively bred for 90 generations at the Institute of Cytology and Genetics (Novosibirsk, Russia) for enhancement (aggressive rats) or absence (tame rats) of aggression toward humans. In addition to pronounced fear-induced aggression, the aggressive rats manifest high anxiety [1] and demonstrate deficits of learning and memory in the Morris water maze test [59] as compared to the tame rats. It is worth noting that aggression toward humans is a distinct type of aggression and differs from other types in ethological expression and molecular mechanisms [47,70]. The tame rats show friendly behavior and trust and express interest in humans. Furthermore, the aggressive and tame rats differ in brain 5-HT and

Abbreviations: 5-HT, serotonergic system; ANOVA, analysis of variance; BDNF, brain-derived neurotrophic factor; DMSO, dimethyl sulfoxide; EPM, elevated plus-maze; PTPN5, protein tyrosine phosphatase nonreceptor type 5; SD, standard deviation; SDS, sodium dodecyl sulfate; STEP, striatal-enriched tyrosine protein phosphatase; TC-2153, 8-(trifluoromethyl)-1,2,3,4,5-benzopentathiepin-6-amine hydrochloride.

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BDNF systems [25,30,51,66,68,69,86], indicating a potential alteration of neuroplasticity in the brain of these two strains.

Moreover, it has been shown that aggression is often associated with neurodegenerative disorders [16,43,46,55,87]. Therefore, the proteins involved in the regulation of neuronal plasticity may be implicated in the mechanism of aggression.

Striatal-enriched protein tyrosine phosphatase (STEP, also known as protein tyrosine phosphatase nonreceptor type 5 [PTPN5]) is encoded by the *Ptpn5* gene, and its transcript undergoes alternative splicing resulting in two active isoforms: STEP61 and STEP46 [44]. Both STEP61 and STEP46 contain a kinase-interacting motif and a protein tyrosine phosphatase domain [44]. In contrast to the cytosolic isoform (STEP46), membrane-associated STEP61 is well studied and has additional 172 amino acid residues at the N terminus including two transmembrane domains and two polyproline domains for specific substrate binding [5]. STEP61 is highly expressed throughout the central nervous system [26], whereas STEP46 has so far been found only in the striatum, amygdala, optic nerve, and retina [19,78]. STEP regulates synaptic plasticity by dephosphorylating and inactivating neuronal substrates, including kinases ERK1/2 and p38 [48], FYN [57], PYK2 [89], and subunits of NMDA receptor [42] and AMPA receptor [90]. STEP dysregulation is associated with several neurodegenerative and psychiatric disorders, in particular Alzheimer's disease, Huntington's disease, schizophrenia, Martin–Bell syndrome, ischemia, and stress-related disorders [17,27].

STEP selective inhibitor TC-2153 [8-(trifluoromethyl)− 1,2,3,4,5-benzopentathiepin-6-amine hydrochloride], first synthesized at Novosibirsk Institute of Organic Chemistry (Novosibirsk, Russia) [29], has strong psychotropic effects. TC-2153 possesses anxiolytic [29], anticataleptic [37] and antidepressant properties [36,38–40]. Furthermore, administration of TC-2153 increases the level of brain-derived neurotrophic factor (BDNF) [37] and significantly affects the serotonergic (5-HT) system [35,39,40]. Accordingly, TC-2153 has been proposed as a promising new-generation antidepressant [38,41]. Classic antidepressant fluoxetine raises the BDNF level and—just as other antidepressants—diminishes aggression [2,4,9,18,24,64,80]. Taking into account the close interactions among STEP, neurodegenerative disorders, BDNF, and 5-HT, we hypothesized STEP involvement in the mechanism of fear-induced aggression and the potential antiaggressive activity of a promising new-generation antidepressant, TC-2153.

Thus, the aim of this study was to evaluate the role of STEP isoforms in fear-induced aggression and a potential antiaggressive activity of TC-2153. For this purpose, we investigated the association between the expression of two isoforms of STEP in the brain and fear-induced aggression in the rats selectively bred for aggressive and tame behavior toward humans as well as the effects of acute TC-2153 administration on the behavior and expression of STEP in the brain of the aggressive and tame rats. Furthermore, we tested whether these effects would persist during chronic TC-2153 administration to aggressive rats and compared its action with the classic antidepressant fluoxetine.

2. Materials and methods

2.1. Animals

The experiments were performed on adult outbred male rats (*Rattus norvegicus*) (4–5 months old, weighing 300–350 g) selectively bred from wild rats for 90 generations at the Institute of Cytology and Genetics (Novosibirsk) for the absence (tame rats, n = 30) or enhancement (aggressive rats, n = 59) of an aggressive reaction to humans [49,61]. In this study, we used male rats to avoid potential effects of the estrous cycle of female rats on behavior and on gene expression in the brain.

The animals were housed in metal cages (50 × 33 × 20 cm) under standard laboratory conditions on a natural light–dark cycle with free access to water and food in groups of four individuals. All experimental procedures were carried out in compliance with the Guide for the Care and Use of Laboratory Animals approved by the Ministry of Public Health of Russia (Supplement to decree No. 267, June 19, 2003) and with National Institutes of Health "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 8023, revised in 1978) and were approved by the ethical committee of the Institute of Cytology and Genetics.

Every effort was made to minimize the number of animals used and their suffering. The study was conducted at the Centre for Genetic Resources of Laboratory Animals at the federal research center Institute of Cytology and Genetics, the Siberian Branch of the Russian Academy of Sciences (RFMEFI62119×0023). The animals' maintenance was funded by the Basic Research Project for a Young Researcher, grant number FWNR-2022-0010.

2.2. Experimental procedures and drugs

Experiment 1. First of all, we evaluated the impact of acute administration of the STEP inhibitor (TC-2153) on the behavior and STEP expression in the brain of the aggressive and tame rats. To this end, 60 rats (30 aggressive and 30 tame) were used. Two days before the drug administration, the animals were evaluated in the glove test to determine the basic scores of their aggressive or tame behavior. The STEP selective inhibitor TC-2153 [8-(trifluoromethyl)− 1,2,3,4,5-benzopentathiepin-6-amine hydrochloride, NIOCh, Novosibirsk, Russia] was diluted in a solution of 0.05% Tween 20 and 0.05% DMSO as described earlier [40]. Three groups of 10 rats of both strains were treated intraperitoneally (100 μL/100 g of body weight) with 10 or 20 mg/kg TC-2153 or vehicle (a 0.05% solution of Tween 20 and DMSO) as a control. Three hours after single TC-2153 or vehicle injection, the glove test and, immediately after, the elevated plus-maze (EPM) test were performed. Two hours after the behavioral tests, the rats were decapitated; their brains were rapidly removed on ice; the whole hypothalamus, hippocampus, and midbrain were dissected, frozen in liquid nitrogen, and stored at − 80 °C.

Experiment 2. We studied the influence of chronic TC-2153 or fluoxetine administration on behavior and STEP expression in the brain of aggressive rats. In this experiment, 29 aggressive male rats were subdivided into three groups and were treated with a drug dissolved in drinking water for 30 days. The administration of drugs via drinking water was chosen to avoid handling effects and minimize the stress of animals. Nine animals received an aqueous solution of 0.04% DMSO and 0.08% Tween 20 (control group); 12 rats were treated with 80 mg/L TC-2153 in an aqueous solution of 0.04% DMSO and 0.08% Tween 20; and eight rats received 80 mg/L fluoxetine hydrochloride, i.e., (±)-*N*-methyl-γ-[4-(trifluoromethyl)phenoxy]benzenepropanamine hydrochloride (Merck, USA), in the same solution of vehicle. The approximate amount of drinking solutions was 35–45 mL per rat per day. The drugs and vehicle were refreshed every 2 days. The concentration of 80 mg/L in water corresponds to a daily dose of approximately 10 mg/kg [20,28,71,82]. Before the drug administration, the animals were assessed by the glove test to determine their basic aggression scores. Subsequently, aggression scores were obtained on the 4th, 11th, 18th, 25th, and 29th days of treatment. On the 25th day of drug administration, the animals were isolated in individual cages to remove the group effect. On the 29th day of treatment, the EPM test was performed, and on the 30th day, the rats were decapitated. The brains were rapidly excised on ice; the whole hypothalamus, hippocampus, and midbrain were dissected, frozen in liquid nitrogen, and stored at − 80 °C.

2.3. The EPM test

The EPM device consisted of two crosswise arms (closed and open, 50 × 10 cm each) with a central area (10 × 10 cm). The closed arms bordered 40-cm-high walls. This device was elevated by 50 cm above the floor. A Panasonic camera on a tripod was placed at 50 cm from the end of the open arm. A rat was placed in the center of the maze facing a

closed arm, and the experimenter was able to watch the behavior of the rat on a computer from an adjacent room [32,60]. The duration of the test was 5 min. The behavior of rats was videotaped, and the time spent (%) in the center and closed and open arms as well as time points and numbers of peeks and head dips were analyzed by an experienced rater blinded to the group assignment of the rats. The arena was cleaned with wet and dry napkins after each test.

2.4. The glove (handling) test

The behavior of rats was assessed judging by the expression of a positive or negative emotional response to a gloved hand, depending on the distance between the hand and the rat in the glove test. The gloved hand was placed into a cage in which a rat was kept, and behavior toward the human being was evaluated on a scale ranging from − 4 (as aggressive as possible) to − 1 (slightly aggressive) in aggressive rats and from + 4 (maximally tame) to + 1 (somewhat tame) in tame rats [22,51,62]. Negative behavior or aggressiveness was scored as follows: − 4: as the hand approached a closed cage door, the rat emits threatening vocalization and attacks the hand; − 3.5: as the cage door opens, the rat attacks the hand as soon as it is placed on the open door; − 3: as the cage door opens, the rat retreats to the back wall, emits threatening vocalization, and attacks the approaching hand; − 2.5: the rat stays at the back wall, actively resists handling, and attempts to bite the hand; − 2: the rat stays at the back wall, resists handling, and when handled, tries to escape and vocalizes; − 1.5: the rat stays at the back wall, turns away from the approaching hand, hides in the corner, resists handling to some extent, and vocalizes; − 1: the rat flees to the back wall, avoids human touch and handling, and does not vocalize. Tameness was scored as follows: 4: the rat freely explores the hand, as the door opens, is completely relaxed when handled, displays interest in the researcher; 3.5: the rat freely explores the hand, as the door opens, is completely relaxed when handled; 3: the rat freely explores the hand, as the door opens, does not attempt to escape when handled but is somewhat tense; 2.5: the rat approaches the hand as the door opens and makes a weak attempt to escape when handled; 2: the rat does not approach the hand as the door opens, and when handled, makes a weak attempt to escape; 1.5: the rat stays at the back wall, approaches the extended hand, and avoids handling; 1: the rat stays at the back wall, does not explore the hand, and avoids the human touch and handling.

The whole structures of the brain (hippocampus, hypothalamus, and midbrain) were homogenized in 300 μL of Tris-HCl buffer (50 mM, pH 7.6) at 4 °C by means of a motor-driven grinder (Z359971, Sigma-Aldrich, USA), and aliquots of the homogenate were used for total-RNA and protein extraction.

2.5. Real-time quantitative PCR

Total RNA was extracted from 60 μL of a homogenate in Tris-HCl buffer (50 mM, pH 7.6) mixed with 300 μL of the TRIzol Reagent (Ambion, USA) according to the manufacturer's instructions. The extracted RNA was treated with RNA-free DNase (Promega, USA) and diluted to 0.125 μg/μL with diethyl pyrocarbonate–treated water. The obtained total RNA was subjected to cDNA synthesis with a random hexanucleotide mixture (BioLab Mix, Novosibirsk, Russia). To estimate the number of *Ptpn5* cDNA copies, we employed two pairs of primers: the first one was selected in the 8th exon encoding a part of the STEP61 isoform, and the second pair in the 16th exon encoding a part of both the STEP46 and STEP61 isoform (Table 1). SYBR Green I fluorescence detection (R-402 Master mix, Syntol, Moscow, Russia) was performed. As external standards, we used genomic DNA (0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, and 64 ng/μL) extracted from the rat liver [34,52,53]. Gene expression was evaluated as the number of cDNA copies per 100 copies of a housekeeping gene: DNA-dependent RNA polymerase II (*Polr2a*). To control amplification specificity, we performed melting curve analysis at the end of each run for each pair of primers.

Table 1
The primer sequences, annealing temperatures, and amplicon lengths.

Gene	Sequence	Annealing temperature, °C	Product length, bp
Polr2a	F: 5′-TTGTCGGGCAGCAGAACGTG-3′ R: 5′-CAATGAGACCTTCTCGTCCTCCC-3′	63	186
Ptpn5_ex8 (exon 8)	F: 5′-GACAGACGACAATCAGTGAGC-3′ R: 5′-AGTCAACGAGGTGGGATCAG-3′	63	162
Ptpn5_ex16 (exon 16)	F: 5′-CGTGTTTTTATCGCTGACTTTAA-3′ R: 5′-GACACCAAATGTCTCTGTATG-3′	61	59

2.6. Western blot analysis

For assessment of the STEP protein level, 100 μL of the homogenate in Tris-HCl buffer (50 mM, pH 7.6) was added to 100 μL of homogenization buffer (300 mM NaCl, 100 mM Tris-HCl pH 8, 4 mM EDTA, 0.2% of Triton X-100) with protease inhibitors (Pierce Protease Inhibitor tablets [Thermo Scientific], 1 mM sodium orthovanadate, and 2 mM PMSF) and rested for 1 h on ice. Then, the homogenate was centrifuged for 15 min at 12000 × *g* (4 °C), and the supernatant was transferred to a fresh 1.5 mL tube and kept at − 80 °C.

The concentration of total protein was evaluated by a bicinchoninic acid assay (Pierce BCA Protein Assay Kit) according to the manufacturer's instructions with the help of an Eppendorf spectrophotometer (BioPhotometer plus, Eppendorf, USA) followed by adjustment of the samples to equal total-protein concentrations with 2 × Laemmli sample buffer (4% of SDS, 20% of glycerol, 120 mM Tris-HCl pH 6.8, 10% of mercaptoethanol, 0.02% of bromophenol blue) and denaturing by boiling for 5 min at 95 °C. The extracts (20 μg per lane) were resolved on an SDS 10% polyacrylamide gel and blotted onto a nitrocellulose membrane (Thermo Fisher Scientific Inc., USA) with a TE77 PWR Semidry Blotter (GE Healthcare Bio-Sciences AB, Sweden) at a 50 mA current and room temperature overnight. The membranes were blocked in Tris-buffered saline supplemented with 0.1% of Tween 20 (TBST) and 5% of BSA for 1 h, rinsed, and next incubated with a polyclonal mouse anti-STEP antibody (dilution 1:1000 in 5% BSA, cat. # sc-23892, lot # KO314, Santa Cruz Biotechnology, USA) at 4 °C overnight and then with a goat anti-mouse IgG antibody conjugated with horseradish peroxidase (secondary antibody; dilution 1:10000, cat. # 31430, lot # TL272497, Invitrogen, USA) for 1 h at room temperature. Between the incubation steps, the membranes were washed in TBST five times for 5 min each time. The blots were treated with the SuperSignal West Femto Maximum Sensitivity Substrate (Thermo Fisher Scientific Inc., USA) according to the manufacturer's instructions. Protein bands were detected using a Fusion FX7–820 system (Vilber Lourmat, France). Quantification of protein bands was performed by volume densitometry in the ImageJ software (NIH, USA). As a reference, we probed the blots with an anti-GAPDH antibody (dilution 1:2000 in 5% BSA, cat. # ab9485, lot # GR192141–5, Abcam, UK) at 4 °C overnight and a goat anti-rabbit IgG antibody conjugated with horseradish peroxidase (secondary antibody; dilution 1:10000, cat. # 31460, lot # SH253595, Invitrogen, USA) for 1 h at room temperature to detect the signal. STEP61 and STEP46 protein levels were evaluated as a percentage ratio of fluorescence intensity of STEP to the fluorescence intensity of the GAPDH band. STEP61 and STEP46 were detected at 61 and 46 kDa, respectively. GAPDH migrated at the 37 kDa level.

2.7. Statistical analysis

The results of the glove test after acute administration of a drug are presented as block plots with whiskers, where blocks indicate mean ± SD, and whiskers min and max values. The data were analyzed by a nonparametric test for two dependent samples (the Sign test) followed by the Bonferroni correction. The data of the glove test in the chronic-treatment experiment are presented as means of scores ± SD received on each testing day. To evaluate the effect of timing (experiment day) on the aggression scores in each group, we carried out a nonparametric test for multiple dependent samples: the Friedman test. The Mann–Whitney test is performed to assess the difference between the control and TC-2153 as well as between the control and fluoxetine groups on each day. The data from the Friedman and Mann–Whitney tests were subjected to the Bonferroni correction. The data from the EPM test and assays of *Ptpn5* mRNA and STEP protein expression were checked for normality and equality of dispersion by Lilliefors and Barlett's test, respectively. These results are presented as mean ± standard error of the mean and were analyzed in the first experiment by two-way ANOVA with "Genotype" (strain) and "Treatment" as two independent factors that can interact, and in the second experiment, by one-way ANOVA. If any effect was significant, the difference between groups was assessed by Fischer's LSD post hoc multiple pair-wise comparisons. Statistical significance was set to $p < 0.05$. The Dixon criteria were applied to identify outliers.

3. Results

3.1. Effects of acute TC-2153 treatment on the aggressive and tame behavior in the glove test

We found that acute TC-2153 treatment had an antiaggressive effect on aggressive rats (Fig. 1a), without affecting tame animals (Fig. 1b). Vehicle administration to the aggressive control group ($Z = 0.48$, $p > 0.05$) did not alter the behavior of aggressive animals in the handling test. TC-2153 at 10 mg/kg ($Z = 2.27$, $p > 0.05$) exerted a slight anti-aggressive action, whereas 20 mg/kg TC-2153 significantly reduced aggression ($Z = 2.67$, $p < 0.05$) in these rats. TC-2153 in the dose of 10 mg/kg ($Z = 1.22$, $p > 0.05$) and 20 mg/kg ($Z = 1.15$, $p > 0.05$) as well as vehicle administration had no effect on the glove reaction of tame rats ($Z = 1.15$, $p > 0.05$) (Fig. 1b).

3.2. Effects of acute TC-2153 treatment on the behavior of aggressive and tame rats in the EPM test

We noticed a strong influence of the genotype on all parameters evaluated in the EPM test. Tame rats demonstrated longer time spent in the center ($F_{1,42} = 44.04$, $p < 0.001$) (Fig. 2b), open arms ($F_{1,42} = 11.14$, $p < 0.01$) (Fig. 2a), and longer rearings ($F_{1,42} = 41.94$, $p < 0.001$) (Fig. 2e) and head dips ($F_{1,42} = 18.75$, $p < 0.001$) (Fig. 2d), whereas time spent in the closed arms ($F_{1,42} = 72.02$, $p < 0.001$) (Fig. 2c) was significantly shorter for tame rats than for aggressive ones. These results revealed a higher exploratory activity and lower anxiety in tame rats than in the aggressive animals. Moreover, we registered a significant impact of TC-2153 on the time spent in the open ($F_{2,42} = 4.65$, $p < 0.05$) and closed ($F_{2,42} = 6.42$, $p < 0.01$) arms, but there were no effects on the time spent in the center ($F_{2,42} < 1$), and duration of rearings ($F_{2,42} < 1$) and head dips ($F_{2,42} = 1.56$, $p > 0.05$). TC-2153 in the dose of 20 mg/kg significantly prolonged the time spent in open arms for tame rats ($p < 0.05$), shortened the time spent in the closed arms for both tame ($p < 0.01$) and aggressive rats ($p < 0.05$), and increased the duration of head dips in aggressive rats ($p < 0.05$). At the same time, there were no effects of genotype × drug interaction on any investigated EPM test parameters [time spent in the center ($F_{2,42} < 1$), open arms ($F_{2,42} = 1.26$, $p > 0.05$), and closed arms ($F_{2,42} < 1$) and duration of rearings ($F_{2,42} < 1$) and head dips ($F_{2,42} < 1$)].

3.3. Effects of acute TC-2153 treatment on Ptpn5 mRNA expression in aggressive and tame rats

We detected no effects of a drug (midbrain $F_{2,35} < 1$; hippocampus $F_{2,32} < 1$; hypothalamus $F_{2,33} < 1$), genotype (midbrain $F_{1,35} = 1.71$, $p > 0.05$; hippocampus $F_{1,32} < 1$; hypothalamus $F_{1,33} = 1.30$, $p > 0.05$), or genotype × drug interaction (midbrain $F_{2,35} < 1$; hippocampus $F_{2,32} < 1$, hypothalamus $F_{2,33} < 1$) on the mRNA level of the STEP61 isoform as measured by the Ptpn5_ex8 pair of primers (binding to exon 8 specific to the STEP61 isoform) (Fig. 3a–c) in the assayed brain structures. Moreover, with the Ptpn5_ex16 pair of primers (binding to exon 16 and detecting both STEP61 and STEP46 expression), no influence of a drug (midbrain $F_{2,35} = 1.49$, $p > 0.05$; hippocampus $F_{2,32} < 1$; hypothalamus $F_{2,34} < 1$), genotype (midbrain $F_{1,35} < 1$; hippocampus $F_{1,32} < 1$; hypothalamus $F_{1,34} < 1$), or genotype × drug interaction (midbrain $F_{2,35} < 1$; hippocampus $F_{2,32} < 1$, hypothalamus $F_{2,34} = 2.11$, $p > 0.05$) in the studied brain structures was detected either (Fig. 3d–f).

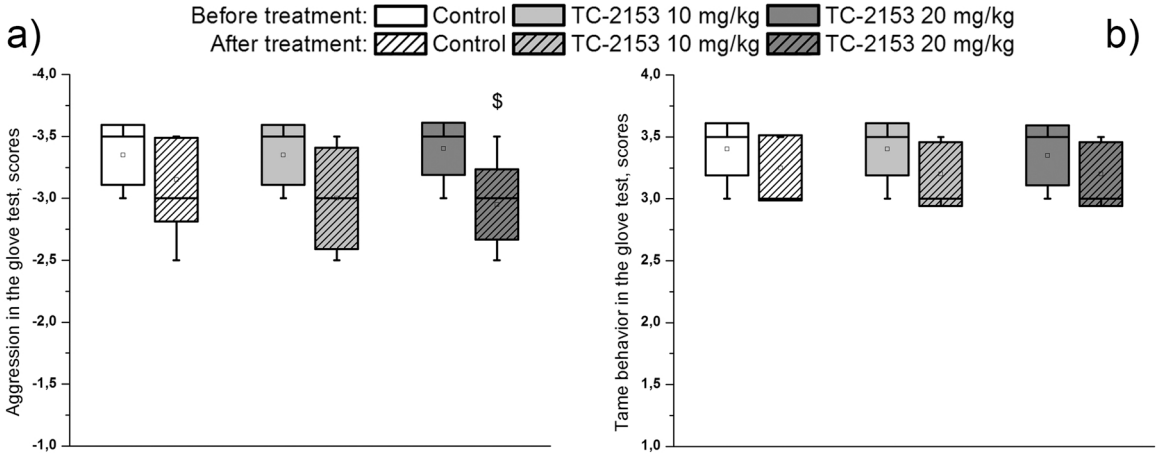

Fig. 1. Effects of acute treatment with vehicle (control) or TC-2153 at 10 or 20 mg/kg on the behavior of aggressive (a) and tame (b) rats in the glove test. Data are presented as block plots with whiskers, where blocks indicate mean ± SD, and whiskers min and max values. $^{\$}p < 0.05$ in comparison with the data point before treatment; 10 animals per group.

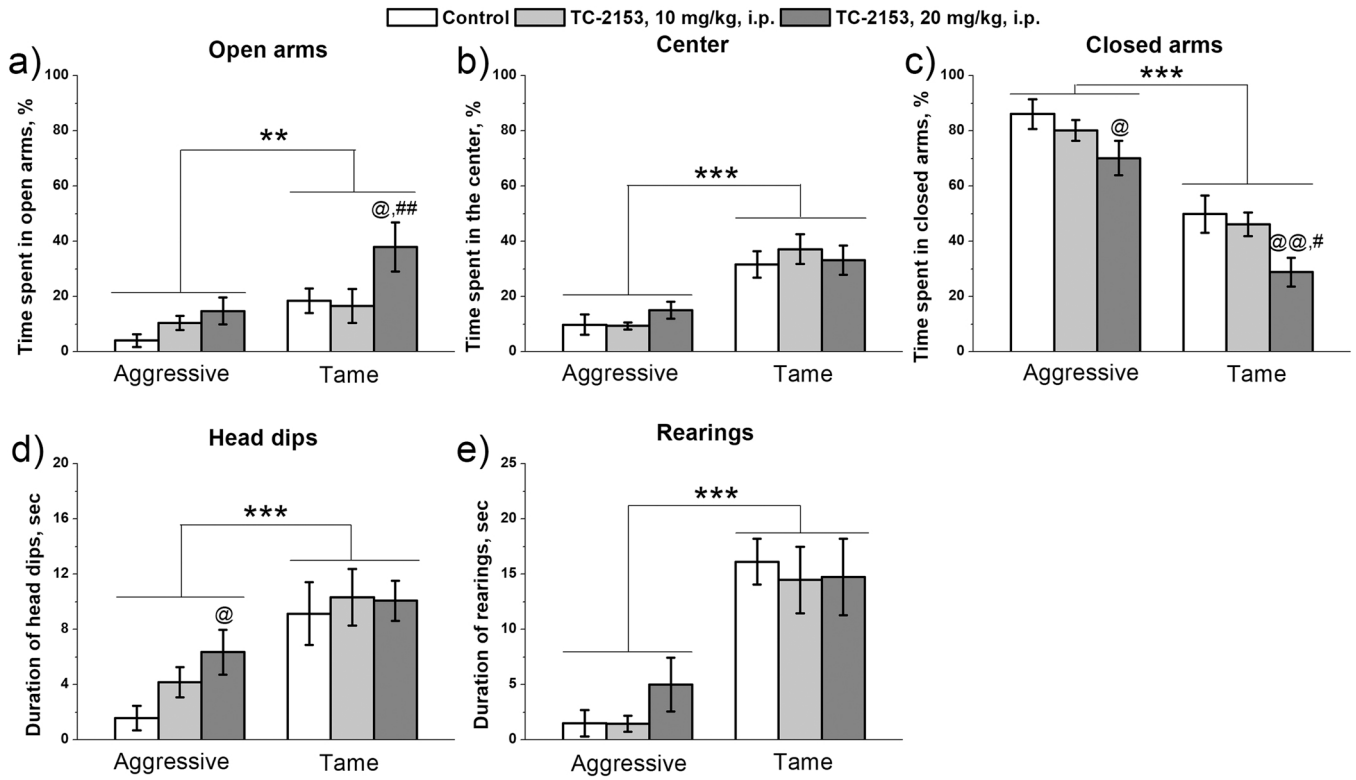

Fig. 2. Effects of acute treatment with either vehicle (control) or TC-2153 at 10 or 20 mg/kg on anxious behavior of aggressive and tame rats. * *$p < 0.01$, * **$p < 0.001$ for the genotype effect; $^{@}p < 0.05$, $^{@@}p < 0.01$ in comparison with the control group. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ in comparison with the TC-2153 10 mg/kg group (8 animals per group).

3.4. The impact of acute TC-2153 treatment on STEP61 and STEP46 protein levels in aggressive and tame rats

We documented a significant effect of the genotype on the STEP61 level in the hippocampus ($F_{1,37} = 5.59$, $p < 0.05$) (Fig. 4b), while there was no difference between the rat strains in this protein level in the midbrain ($F_{1,41} = 2.45$, $p > 0.05$) (Fig. 4a) and hypothalamus ($F_{1,37} < 1$) (Fig. 4c). No influence of a drug (midbrain $F_{2,41} < 1$, hippocampus $F_{2,37} < 1$; hypothalamus $F_{2,37} < 1$) or genotype × drug interaction (midbrain $F_{2,41} < 1$, hippocampus $F_{2,37} = 1.26$, $p > 0.05$, hypothalamus $F_{2,37} = 1.06$, $p > 0.05$) was found in all the analyzed brain structures in terms of the STEP61 level.

A significant effect of the genotype on the STEP46 protein level was observed. Aggressive animals had an elevated concentration of the STEP46 protein in the midbrain ($F_{1,41} = 53.04$, $p < 0.001$) (Fig. 5a), hippocampus ($F_{1,40} = 36.67$, $p < 0.001$) (Fig. 5b), and hypothalamus ($F_{1,40} = 31.86$, $p < 0.001$) (Fig. 5c) in comparison with tame rats. An influence of TC-2153 administration was also detectable in all the investigated brain structures (midbrain $F_{2,41} = 4.89$, $p < 0.05$; hippocampus $F_{2,40} = 4.16$, $p < 0.05$; hypothalamus $F_{2,40} = 5.24$, $p < 0.01$). TC-2153 in the dose of 20 mg/kg reduced the STEP46 protein level in the midbrain ($p < 0.01$), hippocampus ($p < 0.01$), and hypothalamus ($p < 0.001$) of aggressive rats, without affecting the STEP46 protein level in tame rats. The genotype × drug interaction was not significant in the studied brain regions (midbrain $F_{2,41} = 2.09$, $p > 0.05$; hippocampus $F_{2,40} = 2.44$, $p > 0.05$, hypothalamus $F_{2,40} = 2.73$, $p > 0.05$).

3.5. The influence of chronic TC-2153 or fluoxetine treatment on fear-induced aggression in the glove test

We noticed a significant antiaggressive effect of chronic administration of TC-2153 or fluoxetine (Fig. 6). Before the treatment was started, all animals were subjected to the glove test, and no differences in the aggression scores between the groups were detectable [$H(2) = 0.62$, $p > 0.05$].

We found a sequential decrease of aggression in the TC-2153 group [$X^2(5) = 38.22$, $p < 0.000001$] and fluoxetine group [$X^2(5) = 29.37$, $p < 0.0002$] but not in the control group [$X^2(5) = 9.88$, $p = 0.079$] in all these experiments. Fluoxetine reduced the aggression on the 4th day ($p < 0.05$) in comparison to the control group, whereas on the 11th day ($p > 0.05$), this difference disappeared and returned only on the 18th day ($p < 0.05$) and lasted until the end of the experiment. Meanwhile, TC-2153 lowered aggression on the 11th day ($p < 0.05$) until the 25th day ($p < 0.05$). On the 29th day, 4 days after the separation of the animals into individual cages, all the rats demonstrated elevation of aggression scores [TC-2153 (-2.75 ± 0.26); fluoxetine (-2.375 ± 0.35); control (-3.11 ± 0.22)]. There aggression scores diminished in the fluoxetine group ($p < 0.05$) but not in the TC-2153 group ($p > 0.05$) in comparison to the control animals. This phenomenon can be explained by the separation of the animals 4 days before the test.

3.6. Effects of chronic TC-2153 or fluoxetine treatment on the behavior of aggressive rats in the EPM test

Here we registered an effect of the drugs on the number of head peeks from the closed arms ($F_{2,26} = 4.32$, $p < 0.05$). The group that received fluoxetine ($p < 0.01$) demonstrated an increased number of head peeks in comparison to the control group, while TC-2153 ($p > 0.05$) did not affect this parameter. Additionally, we failed to detect an influence of the drugs on the time spent in the closed arms ($F_{2,24} < 1$), in the center ($F_{2,25} < 1$), and in the open arms ($F_{2,24} < 1$) and on the numbers of head dips ($F_{2,26} < 1$) and rearings ($F_{2,26} = 1.13$, $p > 0.05$) (Table 2).

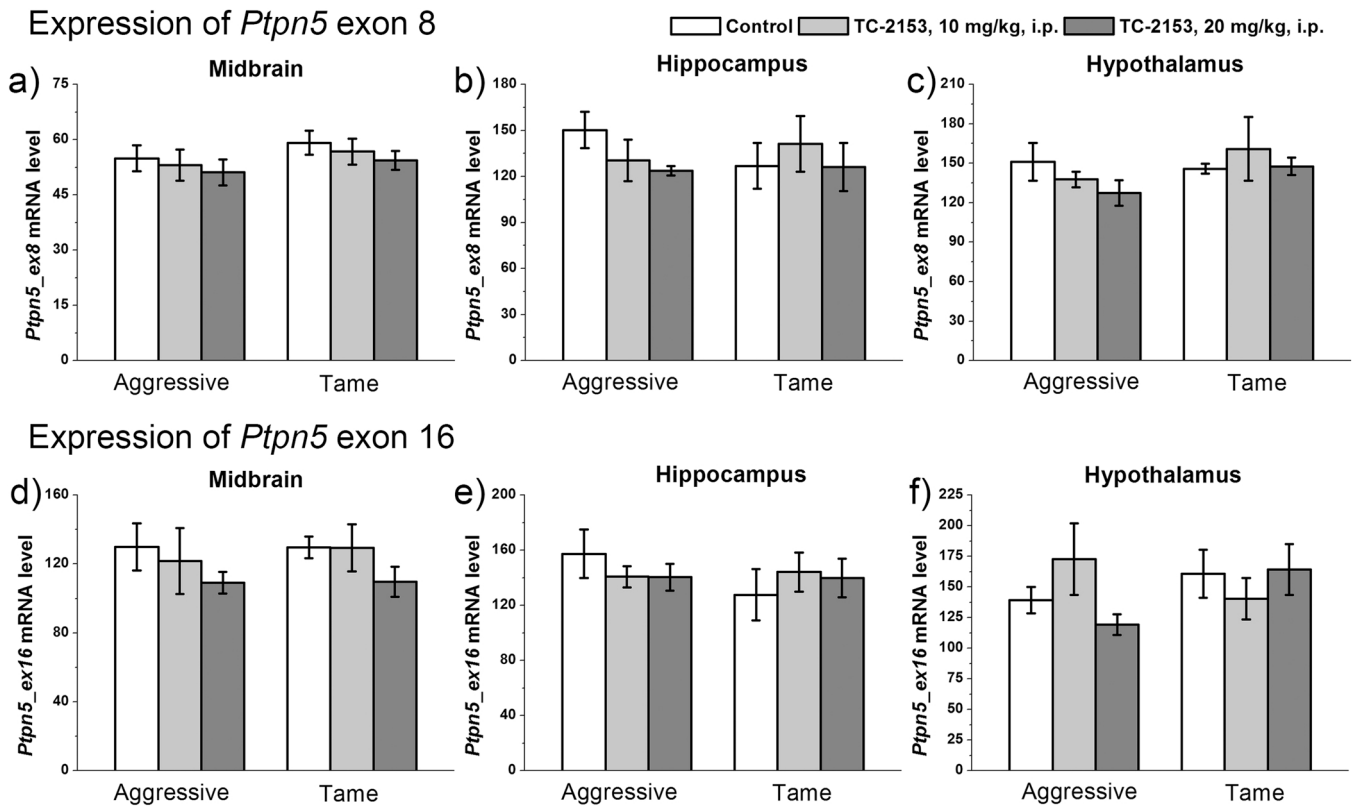

Fig. 3. Effects of acute administration of vehicle (control) or TC-2153 at 10 or 20 mg/kg on *Ptpn5* mRNA expression in the midbrain, hippocampus, and hypothalamus of aggressive and tame rats. The expression levels were measured using primers Ptpn5_ex8 (binding to the beginning of the 8th exon and detecting only STEP61 expression) and Ptpn5_ex16 (binding to the 16th exon and detecting the expression of both isoforms, STEP61 and STEP46). The expression levels were evaluated as the number of transcript copies per 100 copies of *Polr2a* mRNA (5–7 animals per group).

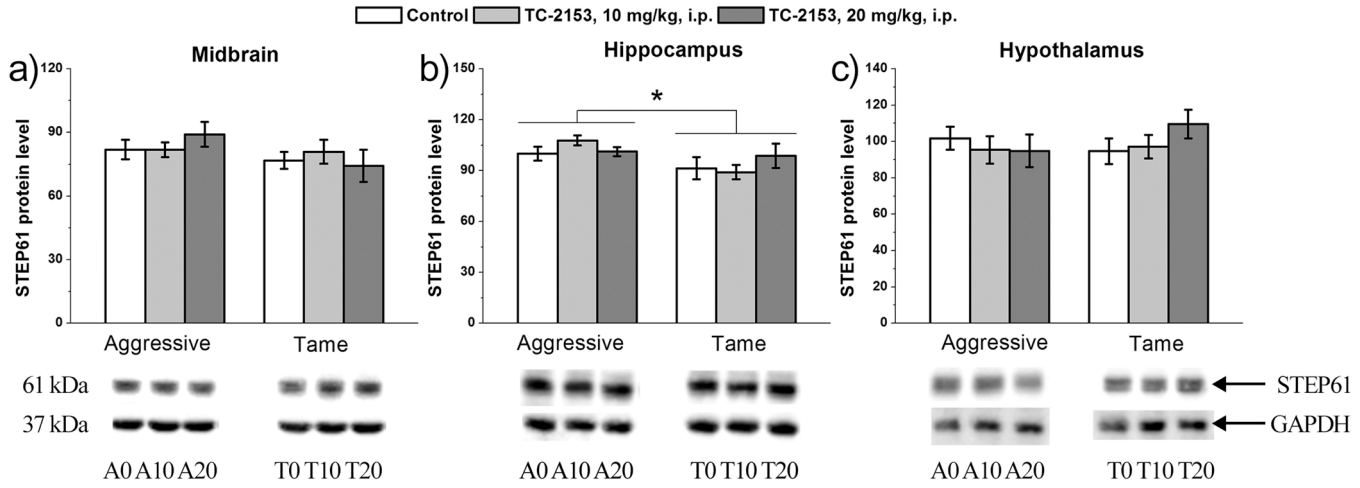

Fig. 4. Effects of acute administration of either vehicle (control) or TC-2153 at 10 or 20 mg/kg on the STEP61 protein level in the midbrain, hippocampus, and hypothalamus of aggressive and tame rats. The protein levels are presented as a percentage of the GAPDH protein level (6–8 animals per group). An example of a western blot for the quantification of the STEP61 protein. *$p < 0.05$: for the genotype effect. Groups: A0, aggressive rats, control; A10, aggressive rats TC-2153 at 10 mg/kg; A20, aggressive rats TC-2153 at 20 mg/kg; T0, tame rats, control; T10, tame rats TC-2153 at 10 mg/kg; and T20, tame rats TC-2153 at 20 mg/kg.

3.7. Effects of chronic treatment with TC-2153 or fluoxetine on Ptpn5 mRNA expression in aggressive rats

With the Ptpn5_ex8 pair of primers (binding to exon 8 and specific to the STEP61 isoform), no effect of drugs on the STEP61 mRNA level were found in the midbrain ($F_{2,26} < 1$), hippocampus ($F_{2,26} < 1$), and hypothalamus ($F_{2,25} = 1.14$, $p > 0.05$; Fig. 7a–c). Furthermore, chronic administration of TC-2153 or fluoxetine did not change the signals of Ptpn5_ex16 pair of primers (binding to exon 16 and detecting the expression of both STEP61 and STEP46) in the midbrain ($F_{2,25} < 1$), hippocampus ($F_{2,24} = 1.20$, $p > 0.05$), and hypothalamus ($F_{2,25} = 2.94$, $p > 0.05$; Fig. 7d–f).

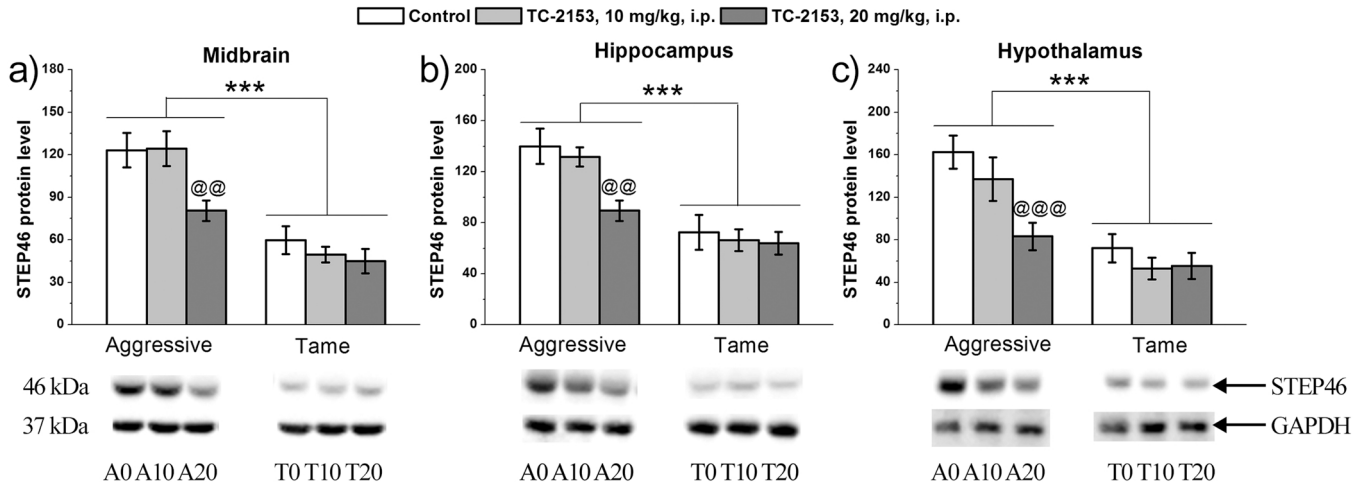

Fig. 5. Effects of acute administration of either vehicle (control) or TC-2153 at 10 or 20 mg/kg on STEP46 protein concentration in the midbrain, hippocampus, and hypothalamus of aggressive and tame rats. The protein levels are presented as a percentage of the GAPDH protein level. * **$p < 0.001$: for the genotype effect, $^{@@}p < 0.01$, $^{@@@}p < 0.001$ in comparison with the control group (7–8 animals per group). An example of a western blot for the measurement of STEP46 protein concentration. Groups: A0, aggressive rats, control; A10, aggressive rats TC-2153 10 mg/kg; A20, aggressive rats TC-2153 20 mg/kg; T0, tame rats, control; T10, tame rats TC-2153 10 mg/kg; and T20, tame rats TC-2153 20 mg/kg.

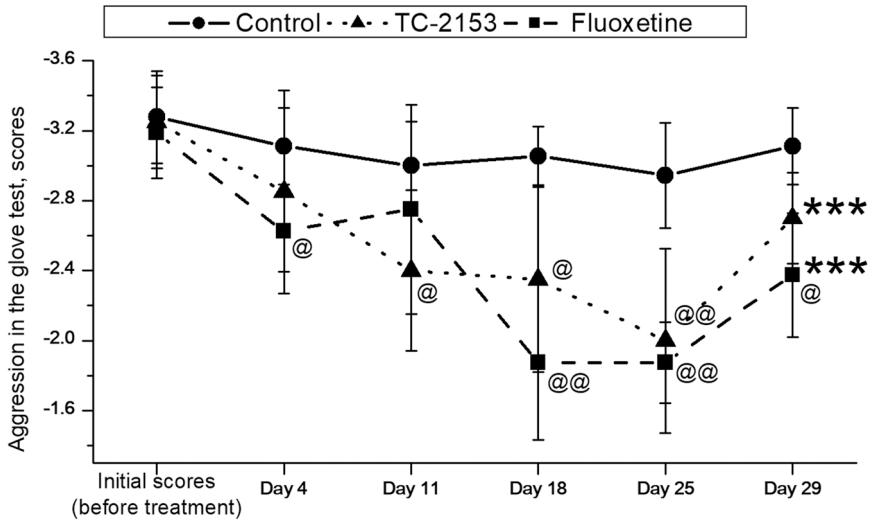

Fig. 6. Effects of chronic treatment with vehicle (control), TC-2153, or fluoxetine on fear-induced aggressive behavior of aggressive rats in the glove test. * **$p < 0.001$: for the effect of the chronic treatment, $^{@}p < 0.05$, $^{@@}p < 0.01$ in comparison to the control group on the same day (8–12 animals per group).

Table 2
Effects of chronic treatment with vehicle (control), TC-2153, or fluoxetine on anxious behavior of aggressive rats.

Behavioral parameter	Control	TC-2153	Fluoxetine	F	p
Number of head peeks	4.00 ± 1.12	9.50 ± 1.79	11.38 ± 2.19	$F_{2,26} = 4.32$	$p < 0.05$
Time spent in open arms, %	5.25 ± 2.67	3.90 ± 1.89	7.64 ± 2.77	$F_{2,24} < 1$	
Time spent in closed arms, %	87.04 ± 6.71	82.73 ± 5.78	80.17 ± 4.61	$F_{2,24} < 1$	
Time spent in center, %	10.68 ± 4.68	15.42 ± 4.26	9.45 ± 2.63	$F_{2,25} < 1$	
Duration of head dips, s	3.36 ± 1.48	3.11 ± 1.14	4.38 ± 1.80	$F_{2,26} < 1$	
Duration of rearings, s	1.76 ± 0.90	1.83 ± 0.82	0.31 ± 0.23	$F_{2,26} = 1.13$	$p > 0.05$

3.8. Effects of chronic TC-2153 or fluoxetine treatment on STEP61 and STEP46 protein levels in aggressive rats

Western blot assays of the STEP61 protein in the midbrain, hippocampus, and hypothalamus of aggressive rats did not show any impact of either TC-2153 or fluoxetine (midbrain: $F_{2,23} < 1$, hippocampus $F_{2,22} = 2.23$, $p > 0.05$; hypothalamus $F_{2,23} = 1.71$, $p > 0.05$) (Fig. 8a–c).

We found a significant effect of drug administration on the STEP46 content of the hippocampus ($F_{2,21} = 4.01$, $p < 0.05$). The protein concentration of STEP46 was lowered by the chronic treatment with fluoxetine ($p < 0.05$) (Fig. 9b), whereas TC-2153 failed to alter this protein's expression. In the midbrain and hypothalamus, no drug effect was detectable (midbrain: $F_{2,22} < 1$, hypothalamus $F_{2,23} < 1$; Fig. 9a,c).

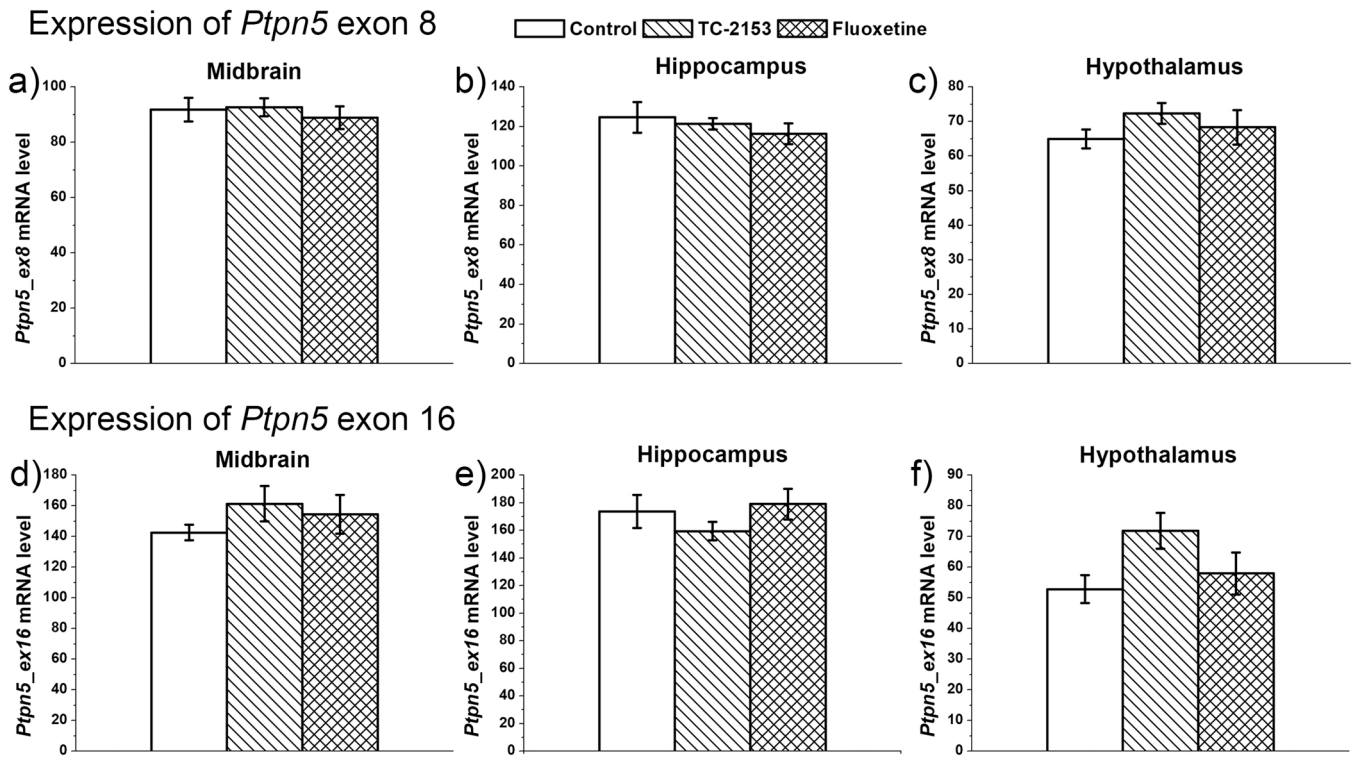

Fig. 7. Effects of chronic treatment with vehicle (control), TC-2153, or fluoxetine on *Ptpn5* mRNA expression in the midbrain, hippocampus, and hypothalamus of aggressive rats. The expression levels were measured with primers Ptpn5_ex8 located in the beginning of the 8th exon (detecting only STEP61 expression) and primers Ptpn5_ex16 located in the 16th exon (detecting the expression of both isoforms, STEP61 and STEP46). The expression level was evaluated as the number of transcript copies per 100 copies of *Polr2a* mRNA (8–12 animals per group).

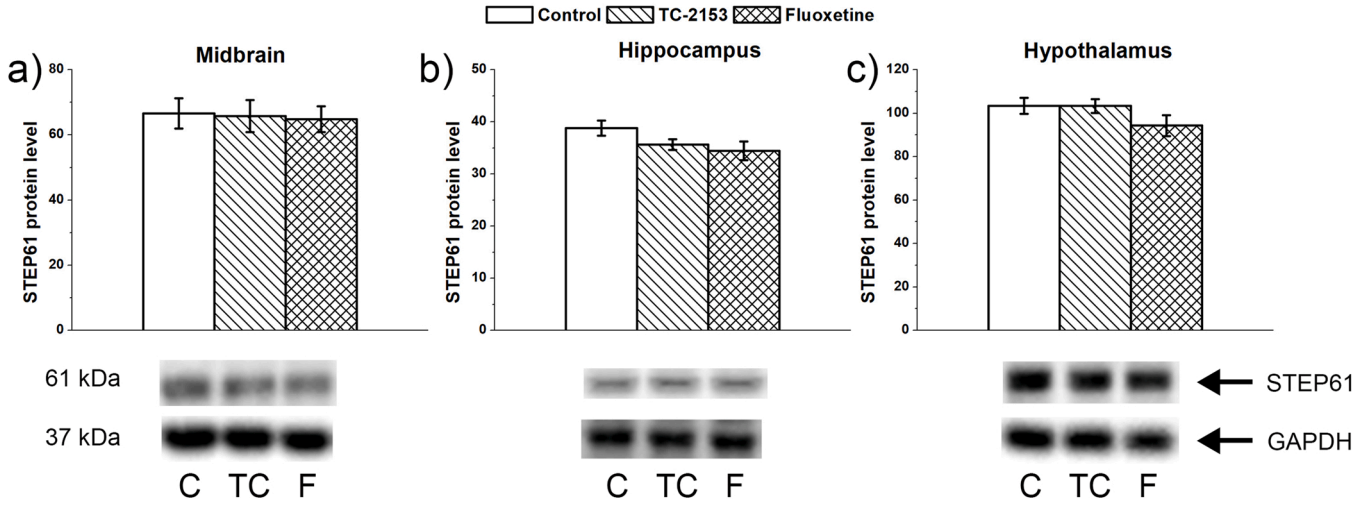

Fig. 8. Effects of chronic treatment with vehicle (control), TC-2153, or fluoxetine on the STEP61 protein content of the midbrain, hippocampus, and hypothalamus in aggressive rats. The protein amounts are presented as a percentage of the GAPDH protein level (7–10 animals per group). An example of a western blot for the quantification of the STEP61 protein in aggressive rats. Groups: C, Control; TC, TC-2153; and F, fluoxetine.

4. Discussion

In this study, we researched the association between STEP isoforms and fear-induced aggression using a unique model based on Norway rats selected for more than 90 generations for enhancement of aggression toward humans. The tame rats selected for the elimination of an aggressive reaction to humans have been suggested as a model of domestication [49] and were chosen in this project as an opposite phenotype relative to the aggressive rats. Although these rat strains have been extensively used to investigate the role of the brain 5-HT system in the mechanisms of fear-induced aggression and domestication [30,50,65–68,85], here we were the first to employ this model to elucidate the involvement of two STEP isoforms in these types of behavior.

The main approach in this work was the evaluation of the effects of acute and chronic treatment with a STEP inhibitor, benzopentathiepine TC-2153, on the behavior as well as on *Ptpn5* mRNA expression and amounts of STEP protein isoforms in the brain of aggressive rats.

We showed that acute TC-2153 administration attenuates fear-induced aggressive behavior in aggressive rats, while exerting no effect on the friendly behavior of tame rats as assessed by the glove test.

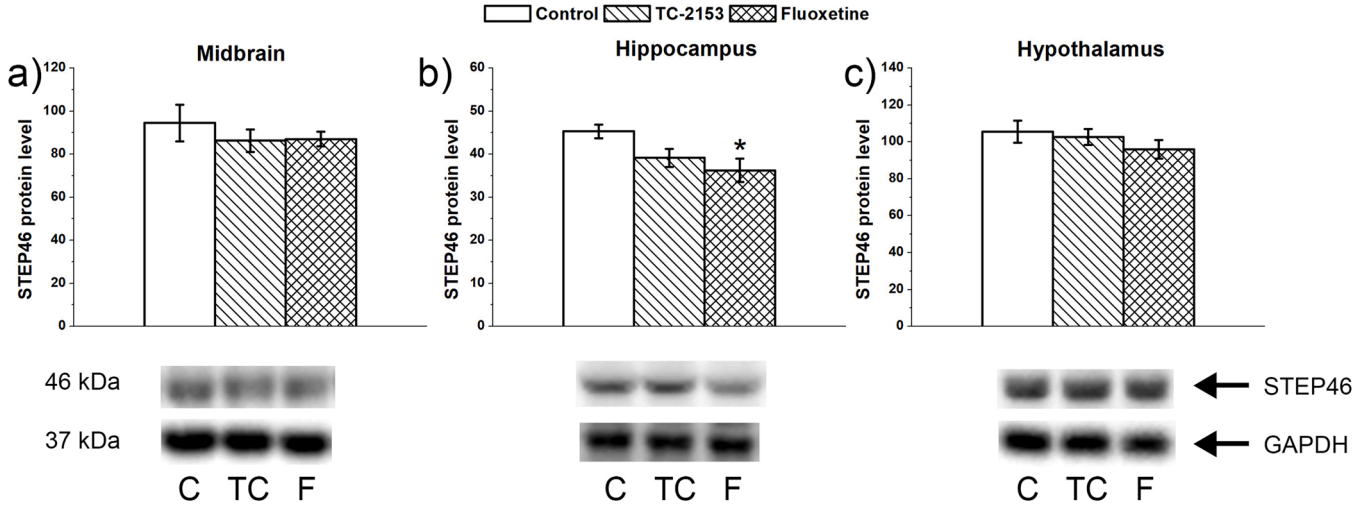

Fig. 9. Effects of chronic treatment with vehicle (control), TC-2153, or fluoxetine on the STEP46 protein level in the midbrain, hippocampus, and hypothalamus of aggressive rats. The protein amounts are presented as a percentage of the GAPDH protein level. *$p < 0.05$ as compared to the control group (7–10 animals per group). An example of a western blot for the measurement of STEP46 protein concentration in aggressive rats. Groups: C, Control; TC, TC-2153; and F, fluoxetine.

Based on the report that TC-2153 selectively inhibits STEP [88], it is fair to assume that STEP can participate in the mechanisms underlying fear-induced aggression. Notably, STEP knockout mice do not demonstrate changes in the aggressive behavior in comparison to the wild-type mice in the resident-intruder test [27]. Nevertheless, this finding can be explained by differences in the mechanisms of fear-induced and inter-male aggression types [70] and/or species-specific factors.

Numerous studies have proven the association between aggression and anxiety. Nevertheless, this link is inconsistent and depends on animal models and types of aggressive behavior [3,11,31,54,55,83,84]. Earlier, it was demonstrated that the aggression toward humans of the rat strains analyzed here is associated with increased fear [50]. Accordingly, in the present study, we decided to evaluate the effects of TC-2153 on anxiety-like behavior and exploratory activity by the EPM test. Earlier, an anxiolytic effect of TC-2153 has been reported for mice [29] in a hole-board test and for the fish *Danio rerio* in a novel tank test [33,75]. Here, for the first time, we demonstrated that acute TC-2153 administration produces a strong anxiolytic effect on both strains of rats in the EPM test. For example, the aggressive and tame rats treated with TC-2153 spent more time in the open arms and less time in the closed arms. It is known that classic anxiolytic drugs prolong the time spent in the open arms [15]. Moreover, TC-2153 increased the duration of head dips and rearings, indicating elevated exploratory activity. Furthermore, in this test, we demonstrated an effect of the genotype on anxiety-related behavior of these strains of rats. Consequently, aggressive rats showed more pronounced anxious behavior as compared to the tame ones. This observation is in good agreement with the data obtained by Albert and colleagues, who concluded that there is a difference in anxiety between the strains in the open-field test and dark-light box test [1]. It has been reported that the aggressive rats manifest an enhanced response in an acoustic startle reflex test as compared to the tame ones [50], indicating greater fear in this strain of rats. It should be noted that STEP knockout mice demonstrate deficits in pre-pulse inhibition in this test in comparison to the wild type [77].

In the hope to completely eliminate aggression in aggressive rats, we investigated the effect of chronic administration of TC-2153 on this type of behavior. Moreover, we compared the effect of chronic TC-2153 administration on the behavior of aggressive rats with that of a typical selective serotonin reuptake inhibitor: fluoxetine. The activity of fluoxetine has not previously been studied in this model of fear-induced aggression; however, this antidepressant is known to decrease aggression [13,18]. First of all, we showed that the basal level of aggression in control rats did not alter throughout the treatment period, thereby ruling out the handling effect in this behavioral test. Here for the first time, we revealed that chronic treatment with TC-2153 or fluoxetine significantly reduces fear-induced aggression. At the same time, the timelines of effects of these drugs differed: fluoxetine reduced aggressive behavior on the 4th day of treatment, whereas TC-2153 only on the 11th day of administration, and there was an increase in the aggressive score on the 29th day of TC-2153 treatment but not fluoxetine treatment. These results may be explained by possible stress induced by the separation of the animals on the 29th day. The animals that received TC-2153 were more vulnerable to this stress than those in the fluoxetine group. Besides, in the present study, we unexpectedly did not see any anxiolytic effect of chronic TC-2153 or fluoxetine administration in the EPM test, which was also performed on the 29th day of treatment. Earlier, anxiolytic effects of TC-2153 [29,33,75] and fluoxetine [72] have been reported. Moreover, it has been shown that prolonged administration (more than 30 days) of TC-2153 has adverse effects on the behavior of rats [73]. Therefore, TC-2153 is more effective during acute administration. In addition, during chronic treatment, TC-2153 is less effective than fluoxetine. This difference in the timeline of effects of TC-2153 and fluoxetine may result from dissimilarity of the pharmacokinetics of these drugs.

It is well known that fluoxetine is a selective serotonin reuptake inhibitor and increases the 5-HT level in the synaptic cleft thereby stimulating 5-HT receptors coupled with G_s proteins (5-HT4, 5-HT6, or 5-HT7), increases cAMP concentration in the neuron, activates protein kinase A, and increases BDNF synthesis. The synthesized BDNF in turn interacts with receptor TrkB and activates kinases ERK1/2, thus stimulating neurogenesis and neuronal survival [14]. Notably, recently, it was demonstrated that fluoxetine directly binds to TrkB and facilitates its activation by BDNF [7]. On the other hand, TC-2153 selectively inhibits STEP and in this way can facilitate ERK1/2 activation [48]. Additionally, TC-2153 upregulates BDNF in the brain [37] and elevates the level and metabolism of serotonin [39] as well as influences serotonergic receptors [35,40]. In the current study, we evaluated the impact of drugs on male rats, whereas the influence of sex on the response to antidepressants was examined earlier [79]; the effects of TC-2153 and fluoxetine on aggressive female rats are a good subject for future investigation. Nevertheless, our results indicate that TC-2153 and fluoxetine affect the regulation of fear-induced aggression.

According to the significant changes of aggressive behavior after the administration of the STEP inhibitor (TC-2153), we hypothesized the involvement of the STEP protein in this mechanism; the second aim of the present study was to elucidate the association of STEP with fear-

induced aggression. For this purpose, we intended to measure the levels of two transcripts, which code for isoforms STEP61 and STEP46, as well as the levels of these proteins in the whole hippocampus, hypothalamus, and midbrain. It is well known that all the brain structures under study are involved in the regulation of aggressive behavior and anxiety [6,10,21,23,55,76,81]. Isoforms STEP61 and STEP46 are located on the plasma membrane and in the cytosol, respectively [5]. To investigate the *Ptpn5* mRNA expression, we utilized two sets of primers. The first one, Ptpn5_ex8, anneals to exon 8, which is specific to the STEP61 isoform. The second set of primers, Ptpn5_ex16, binds to exon 16 and detects the expression of both isoforms, STEP61 and STEP46.

We did not notice any difference in Ptpn5_ex8- and Ptpn5_ex16-measured mRNA levels in all the studied brain structures between aggressive and tame rats. Moreover, neither acute nor chronic TC-2153 treatment affected the levels of these transcripts in these brain regions.

The TC-2153 treatment did not influence the STEP61 level in the hippocampus, midbrain, and hypothalamus either. STEP61 is a membrane-associated STEP isoform with two transmembrane domains [5] and can dephosphorylate and inactivate neuronal substrates, including kinases ERK1/2 and p38 [48], FYN [57], PYK2 [89], and subunits of NMDA receptor [42] and AMPA receptor [90].

Unlike STEP61, the STEP46 isoform is still poorly studied. STEP46 is a cytosolic isoform and can dephosphorylate kinases ERK1/2 and p38 [48]. Until now, it has been found only in the striatum, amygdala, optic nerve, and retina [19,78]. We are the first to find the STEP46 protein in the midbrain, hippocampus, and hypothalamus. Control aggressive rats feature higher concentration of this isoform in all studied brain structures than do the control tame animals. Furthermore, acute treatment with TC-2153 in the dose of 20 mg/kg downregulated the STEP46 protein in the midbrain, hippocampus, and hypothalamus of aggressive rats but not tame rats. Such an evident difference in STEP46 protein expression means that the selection for high and low aggression toward humans strongly affected this protein's expression. The influence on the protein level and not on the mRNA may indicate the effect of the drugs on a translation mechanism rather than on transcription. Moreover, it is known that TC-2153 can block the activity of recombinant STEP by forming a trisulfide bond with cysteine residues in the catalytic domain [88]. Perhaps, the complex of TC-2153 and STEP46 could be eliminated by some yet unknown molecular mechanism. Moreover, it is possible that TC-2153 more easily affects the cytosolic isoform STEP46 than the membrane joint isoform. This hypothesis requires additional studies.

Nonetheless, chronic treatment with TC-2153 did not affect STEP46 concentration in all the assayed brain structures in aggressive rats. Nowadays, the only known direct target of the drug TC-2153 is STEP [88], whereas it has been shown that acute as well as chronic administration of TC-2153 also affects the serotoninergic system [35,39,40]. The observed unexpected absence of the effect of chronic TC-2153 treatment on the STEP protein with the significant antiaggressive effect of acute and chronic administration of this drug could be explained by some compensatory mechanisms or, perhaps, the effect on behavior could be affected by a direct or indirect influence of TC-2153 on another system, for instance, the serotonergic one. At the same time, we found that chronic fluoxetine treatment downregulated STEP46 in the hippocampus. The impact of fluoxetine on STEP46 expression can be attributed to the recent discovery that fluoxetine directly influences receptor TrkB [7] and through this receptor can reduce the STEP46 level [63,74].

Furthermore, the hippocampus is responsible for learning, memory, and neuroplasticity [10,56]. Earlier, it was found that in the Morris water maze test, the aggressive rats exhibit a reduction in learning abilities and memory as compared to the tame animals [59]. The aggressive rats are characterized by an elevated level of proapoptotic proBDNF in the hippocampus and midbrain [25] and changes in the serotoninergic system [30,51,66,68,69,86]. Moreover, in the present study, we demonstrated that STEP46 expression is significantly increased in aggressive animals in the hippocampus, midbrain, and hypothalamus. It can be hypothesized that STEP via dephosphorylation of kinases ERK1/2 can diminish 5-HT and BDNF signaling [38], thereby enhancing anxiety and fear-induced aggression [8,12,55,58,70,76]. It is well known that the elevation of STEP amounts is associated with neurodegeneration [17,27]. Consequently, these data may indicate an impairment of neuronal plasticity in these two strains of rats.

Thus, in this study, we for the first time demonstrated that striatal-enriched protein tyrosine phosphatase is involved in fear-induced aggression. The acute and chronic administration of the STEP inhibitor TC-2153 significantly diminished the aggression of aggressive rats. Moreover, the acute TC-2153 treatment produced a strong anxiolytic effect. Chronic administration of the classic antidepressant fluoxetine decreased the aggression and influenced the STEP46 expression in aggressive rats. This finding implies an interesting similarity between the mechanisms of action of TC-2153 and fluoxetine. This research brings us one step closer to the understanding of the mechanisms of fear-induced aggression as well as to the development of new strategies for aggressiveness correction.

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CRediT authorship contribution statement

Vitalii S. Moskaliuk: Conceptualization, Investigation, Formal analysis, Visualization, Writing – original draft preparation, Writing – review & editing. **Rimma V. Kozhemyakina:** Investigation, Resources. **Elena Terenina:** Investigation. **Darya V. Bazovkina:** Investigation. **Tatyana M. Khomenko:** Resources. **Konstantin P. Volcho:** Resources. **Nariman F. Salakhutdinov:** Resources. **Alexander V. Kulikov:** Conceptualization, Formal analysis, Software, Writing – review & editing. **Vladimir S. Naumenko:** Conceptualization, Investigation, Writing – review & editing. **Elizabeth A. Kulikova:** Conceptualization, Investigation, Formal analysis, Writing – original draft preparation, Writing – review & editing, Supervision.

Conflict of interest statement

None.

Data Availability

Data will be made available on request.

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The English language was corrected and certified by shevchuk-editing.com.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2022.112667.

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