Medicinska istaživanja 2022; 55(3):29-41 | DOI: 10.5937/medi55-40877

OPEN ACCESS

Medical Research | Published by Faculty of Medicine University of Belgrade

ORIGINAL ARTICLE

Physical activity decreases anxiety-related behavior in chronic prostatitis/chronic pelvic pain syndrome: functional behavioral study on the crossroad of experimental exercise physiology and andrology

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Recived: 29 September 2022

Revised: 15 October 2022

Accepted: 07 November 2022

Check for updates

Funding information:
Ministry of Education, Science and Technological Development of the Republic of Serbia (MNTR), grant number 200110, international grant FA4Lin by MNTR and TUBITAK. The corresponding author is MC member in EU COST Actions 20135 (TEATIME) and 20119 (ANDRONET).

Competing interests:
The authors have declared that no competing interests exist

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Summary

Introduction: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a inflammatory syndrome, manifested by pain, voiding symptoms, sexual dysfunction, and mental health issues including anxiety. Beneficial effects of exercise are known, but its influence on CP/CPPS has not been investigated. This study aimed to determine the effects of chronic aerobic physical activity on anxiety-related behavior and pain in rats with experimental CP/CPPS.

Material and Methods: Adult male *Wistar albino* rats (n=32) were randomly assigned to 4 groups (n=8 in each): **Sham-SED** (30-days sedentary-SED protocol on treadmill and intraprostatic injection of 0.9% NaCl); **Sham-PA** (30-days physically active-PA protocol on treadmill and intraprostatic injection of 0.9% NaCl); **CP/CPPS-SED** (30-days SED protocol on treadmill and intraprostatic injection of 3% λ-carrageenan); **CP/CPPS-PA** (30-days PA protocol on treadmill and intraprostatic injection of 3% λ-carrageenan). To establish pain dynamics, scrotal skin pain thresholds were measured by electronic von Frey aesthesiometer (evF) preoperatively: 2 and 1 day, and also postoperatively: 2nd, 3rd, and 7th day. Anxiety-like behavior was estimated by subjectiong the animals to the open field (OF), elevated plus maze (EPM) and light/dark (L/D) tests at the same postoperative days as evF.

Results: Rats that developed experimental CP/CPPS showed decreased mechanical pain threshold in the scrotal skin in all postoperative time points, in comparison to the Sham group. Also, in rats with prostatitis increased anxiety-like behavior was observed in OF, EMP and L/D test, compared to corresponding controls. Protocol of 30-day long exercise in rats with CP/CPPS led to reversion of anxiety-like behavior and increased scrotal pain threshold.

Conclusion: Results of the present study showed that exercise pretreatment on the treadmill for 30 consecutive days led to the amelioration of anxiety-related and pain-related behavior in rats with CP/CPPS.

Keywords: CP/CPPS, pain, anxiety, exercise, treadmill, rat

Cite this article as: Šutulović N, Zubelić A, Macut Đ, Vesković M, Mladenović D, Rašić-Marković A, Grubač Ž, Stanojlović O, Hrnčić D. Physical activity decreases anxiety- related behavior in chronic prostatitis/chronic pelvic pain syndrome: functional behavioral study on the crossroad of experimental exercise physiology and andrology
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INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) presents a urological entity with a growing prevalence of 35-50% among men of all ages. It is the most common type of non-infective prostatitis (1) manifested as a chronic painful condition in which a prominent symptom is spontaneous or provoked perineal pain in the absence of positive bacterial cultures in the prostate exprimate (2). This syndrome is followed by different urological signs and symptoms (erectile dysfunction, difficult and/or frequent urination, painful ejaculation), but it is also accompanied with plenty of psychiatric comorbidities (3). These comorbidities additionally lower the patient's quality of life (4). The CP/CPPS etiopathogenesis is complex and has been unelucidated by now. The most prevalent opinion is the one that chronic genitourinary pain is triggered by a neuropathic cause (5), which in addition induces pathological changes in various brain structures (6) followed by increased pro-inflammatory cytokines synthesis (7). A disbalance in the cytokine milieu ultimately results in the lowering of primary nociceptive neuronal activation threshold, peripheral sensitization, and development of neuropathic pain and prostatodynia(8).

Having in mind such a lack of understanding of the underlying mechanisms, therapeutic options are limited and success rates in these patients vary, especially when it comes to mental health-related comorbidities (9). Various studies indicated that chronic pain is associated with poorer quality of life, worse sleep quality, reduced physical activity, mood alterations and the development of anxiety disorder (10). Anxiety is defined as a psychobiological emotional state or reaction, consisting of an unpleasant feeling of tension, nervousness and worry followed by activation of the autonomic nervous system (11). The results of the research by Gureja et al. (12) suggest that the presence of chronic painful condition originating from different anatomical localization dramatically increases the likelihood of the development of psychiatric disorders. Therefore, there is an urgent need to find additional, preferably non-pharmacological, modes of treatment of CP/CPPS-related mental health issues including anxiety. Regular physical activity could be an option, but we still don't have direct evidence for its beneficial effects on CP/CPPS.

A sedentary lifestyle is a well-known risk factor for health impairment, and it is associated with a higher possibility for cardiovascular diseases, diabetes mellitus type 2, hypertension and osteoporosis, but also the development of different behavioral alterations (13). On the other hand, dosed and planned physical activity represents a proven mode of prevention of psychiatric diseases, such as anxiety disorders, and it is strongly associated with health improvement in general population (14). Epidemiological data suggest that more active people are less likely to develop a stress-related disorder, and also that exercise can reduce symptoms of anxiety (15). Also, it is well known that sedentary people have a higher risk of developing chronic pain (16). Other studies showed that exercise was an effective and potent non-pharmacological treatment for a variety of pain conditions and that it led to pain relief (17). Although positive effects of physical activity in patients with anxiety are known (18), the exact mechanisms of its influence on pain sensitivity and psychological comorbidities in patients with CP/CPPS have not been investigated yet. Animal exploratory behavior can be partially or completely inhibited by pain or anxiety, therefore reduced exploratory behavior may represent an indirect measure of anxiety (19). Chronic aerobic physical activity on a treadmill for small experimental animals enables appropriate modeling and dosing of physical activity in experimental conditions on animal subjects *in vivo*. These facts prompted us to consider physical activity as a suitable amelioration strategy for anxiety provoked by CP/CPPS.

The aim of this study was to investigate the effects of chronic aerobic physical activity on anxiety-related behavior and pain sensitivity in rats with experimentally induced CP/CPPS.

MATERIALS AND METHODS

Ethical statement

All experimental procedures were in full compliance with the Directive of the European Parliament and the Council (2010/63/EU) and approved by The Ethical Committee of the University of Belgrade (Permission No. 323-07-01339/2017-05/3).

Animals and housing

In our experiment, we used 32 adult male *Wistar albino* rats, obtained from the Military Medical Academy breeding laboratory (Belgrade, Serbia), which were three-month-old, and weighed 250–350g at the beginning of the experiment. Animals were kept under the controlled laboratory ambient conditions (22-24°C, 50±5% air humidity, 12/12h light: dark cycle with the light turned on from 08:00 a.m. to 08:00 p.m.) during the seven-day acclimation period, as well as, during the entire experiment. Animals were use in the experiment only once. During the experiment, animals were allowed to consume food and water *ad libitum*.

Experimental design and protocol

To examine the effects of chronic aerobic physical activity on experimental CP/CPPS development, we performed experiments **(Fig. 1.)** in accordance with our previous research (6,20) and literature data (21).

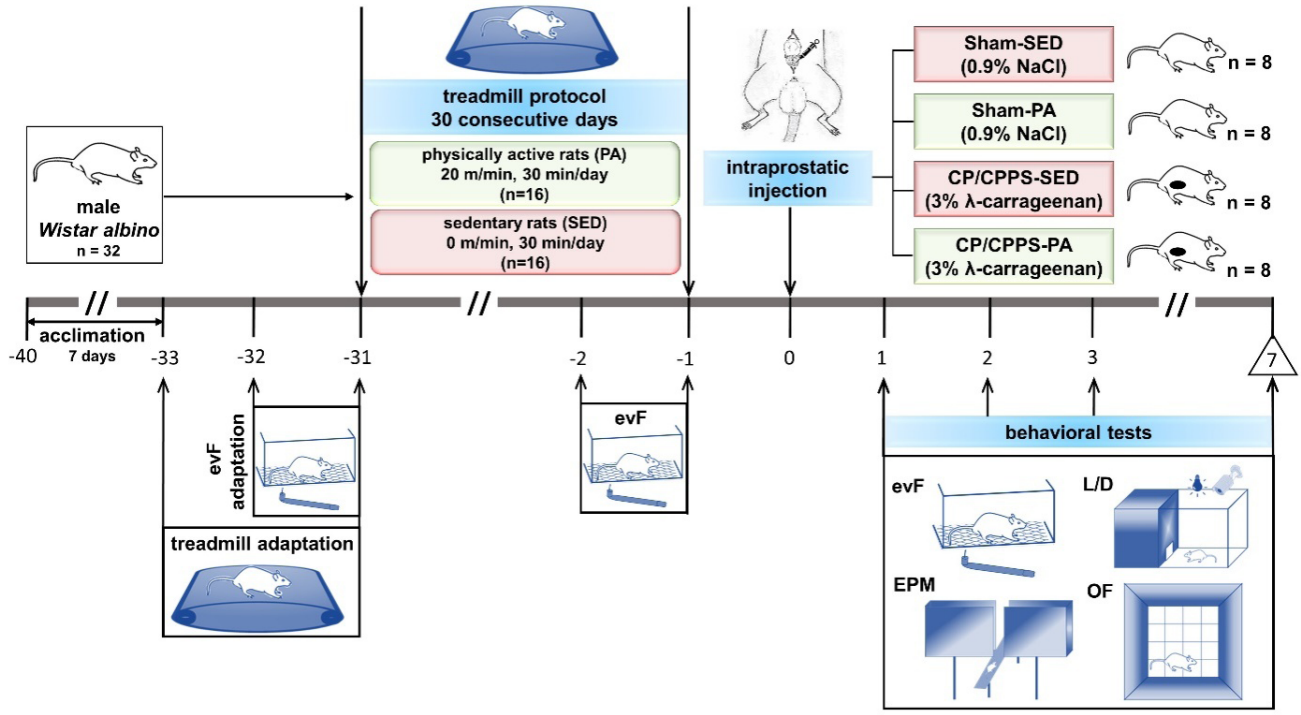

Figure 1. Experimental design. From the fortieth (-40) to the thirty-third (-33) preoperative day, male Wistar albino rats (n=32) acclimated within seven days to standard laboratory conditions. Afterward, from the thirty-third (-33) to the thirty-first (-31) preoperative day, the rats underwent three consecutive days of treadmill adaptation (10 min/day, belt speed: 10 m/min), as well as within the two consecutive days to scrotal pain threshold measurement adaptation by an electronic von Fray (evF) esthesiometer. In accordance with our previous research (22) and depending on the thirty consecutive days treadmill protocol which lasted from the thirty-first (-31) to the first (-1) preoperative day, the animals were divided into two groups. The animals that ran on a treadmill (30 min/day, belt speed: 20 m/min; n=16) were considered physically active (PA) rats, while the animals which spent the same amount of time on the treadmill off (30 min/day, belt speed: 0 m/min; n=16) were considered as sedentary (SED) rats. Further treatment which involved an intraprostatic injection during surgery (considered as day 0 of the experiment) led to an additional division of the rats into four groups: Sham-SED (intraprostatic injection of 0.9% NaCl and preoperative sedentary treadmill protocol; n=8); Sham-PA (intraprostatic injection of 0.9% NaCl and preoperative physically active treadmill protocol; n=8); CP/CPPS-SED (intraprostatic injection of 3% λ-carrageenan and preoperative sedentary treadmill protocol; n=8); CP/CPPS-PA (intraprostatic injection of 3% λ-carrageenan and preoperative physically active treadmill protocol; n=8).
To assess and monitor the development of experimental CP/CPPS, mechanical pain thresholds were measured in the scrotal skin by evF aesthesiometer in the pre-surgery period: 2 days and 1 day before intraprostatic injection, as well as, in post-surgery period: 2, 3, and 7 days upon intraprostatic injection. To assess anxiety-like behavior, the animals from all groups were subjected to a standard battery of three ethological tests (consisting of OF, EPM, and L/D tests in the order listed) at different post-surgery time points: 2, 3, and 7 days upon intraprostatic injection.

Forty days before surgery (-40), male *Wistar albino* rats (n=32) started a seven-day acclimation to laboratory conditions. Treadmill adaptation (3 consecutive days, 10 min/day, speed: 10 m/min), and scrotal pain threshold measurement using evF aesthesiometer (two consecutive days), were performed from the thirty-third (-33) to the thirty-first (-31) preoperative day. Depending on the treadmill protocol, which lasted from the thirty-first (-31) to the first (-1) preoperative day, the animals were divided into physically active rats (PA, 30 consecutive days, 30 min/day, speed: 20 m/min; n=16) and sedentary rats (SED, 30 consecutive days, 30 min/day, speed: 0 m/min; n=16). Further intraprostatic injection during surgery (0) has additionally divided the rats into four groups: Sham-SED (intraprostatic injection of 0.9% NaCl and preoperative sedentary treadmill protocol; n=8); Sham-PA (intraprostatic injection of 0.9% NaCl and preoperative physically active treadmill protocol; n=8); CP/CPPS-SED (intraprostatic injection of 3% λ-carrageenan and preoperative sedentary treadmill protocol; n=8); CP/CPPS-PA (intraprostatic injection of 3% λ-carrageenan and preoperative physically active treadmill protocol; n=8). Scrotal pain threshold measurement was performed on 2 (-2) and 1 (-1) days before, as well as 2, 3, and 7 days upon intraprostatic injection (0). Also, to determine anxiety-like behavior, 2, 3, and 7 days upon surgery (0), rats underwent the standard battery of three behavioral tests (EPM = elevated plus maze test, LD = light/dark test, OF = open field test). On the seventh (7) postoperative day, after the completion of behavioral tests, the rats were sacrificed, and prostates were sampled for histology hematoxylin-eosin (H&E) examination.

Chronic aerobic physical activity using treadmill apparatus

The treadmill apparatus for small experimental animals (NeuroSciLaBG-Treadmill, Elunit, Belgrade, Serbia), which was used in this study, consisted of one moving belt and four plexiglass-separated running compartments. For the purpose of stimulating the rats to run, each running compartment possessed an electrified metal grid with

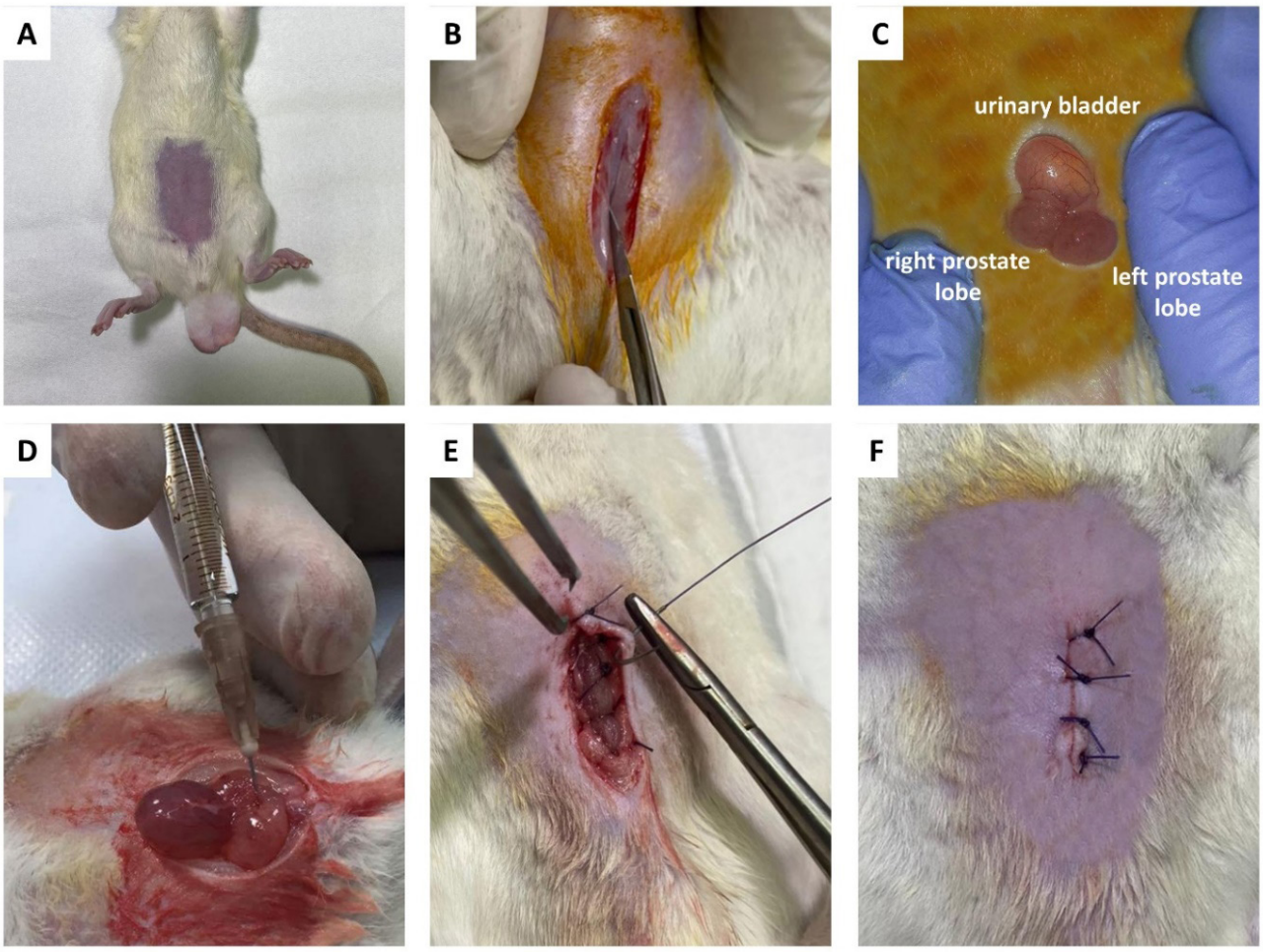

Figure 2. Experimental CP/CPPS induction by surgery and intraprostatic injection. Surgery was performed on a previously shaved and disinfected surgery field (A). A small midline incision of the lower front abdominal wall was done (B) and the urinary bladder with both(left and right) ventral prostate lobes were exposed (C). After the intraprostatic injection (D), the wound was closed in layers (E) using an absorbable suture (F).

the electric shock of low intensity (0.2 mA), as a negative stimulation on the starting edge, as well as a dark area as a positive stimulation on the ending edge. Rats were placed on the moving belt and ran in the direction opposite from the belt movement towards the positive stimulation and escaping the negative stimulation. Additionally, using the accompanied software, the protocol of belt moving (duration and speed), as well as the belt inclination were previously given. During the entire treadmill protocol, the belt was 0 ° incline.

Before starting the training protocol, the animals were adapted and familiarized with the treadmill apparatus over 3 consecutive days (10 min/day, belt speed: 10 m/min).

Physically active animals were made to run on the treadmill for 30 consecutive days (30 min/day, speed: 20 m/min). Exercise training using this protocol at this belt speed for treadmill running rats is considered aerobic in accordance with literature data which indicated that maximal lactate steady state (MLSS, i.e., the highest running intensity with constant exercise load at which blood lactate level does not reach up beyond the initial transient increase) was established (22-24). Corresponding sedentary animals were also kept in the treadmill off the apparatus for the same amount of time over 30 consecutive days (30 min/day, belt speed: 0 m/min).

Induction of experimental CP/CPPS by surgery and intraprostatic injection

Experimental CP/CPPS was induced in rats by surgical application of intraprostatic injection through a standard protocol described in detail in our previous papers (6,20). Briefly, in anesthetized rats **(Fig. 2A)** middle incision in the lower abdominal area **(Fig. 2B)** was done and left and right ventral prostate lobes with urinary bladder were exposed **(Fig. 2C)**. After this, the intraprostatic injection was applied **(Fig. 2D)**. Sterile suspension of 3% λ-carrageenan (Sigma Aldrich, St. Louis, MO, USA) in a total volume of 50 µl was injected in both ventral prostate lobes of the CP/CPPS group, while Sham animals were treated in the same way with intraprostatic injection of the equal volume of sterile 0.9% saline. The wound was closed in layers **(Fig. 2E)** using an absorbable suture **(Fig. 2F)**.

Scrotal pain threshold to mechanical stimuli

To assess scrotal skin pain thresholds to mechanical stimuli, we used an electronic von Frey aesthesiometer (IITC Life Sciences, CA) with polypropylene rigid filaments. The rats were situated in plexiglass-separated boxes with metal grid floors to adapt to the conditions in the measurement platform for 30 min. Perpendicular application of stimulus started on the restful rat when the rat remained quiet with the scrotum brought down on the platform bottom. A gradual increase of the pressure lasted until a reflex response (moving of the rat from resting position) was observed. An average value of three consecutively repeated measurements was used as the scrotal pain threshold. The rats were returned to their home cages immediately after the measurement was over.

Open field test

In the assessment of anxiety-like behavior, we used an automated and infrared sensor-equipped apparatus (Experimetria Ltd., Budapest, Hungary) with its accompanying software package (Conducta 1.0), as we previously described (20,25). At the beginning of the testing, to freely explore the new environment for 15 minutes, rats were placed individually in the central part of the sound-isolated, red-illuminated arena surrounded by black-colored walls. The system automatically registered, through infrared sensors, the parameters of horizontal locomotor activity, the total distance and time of ambulatory movements, as well as the number of rearings, as a parameter of vertical locomotor activity. Additionally, using an accompanying software, the open field area was divided into16 squares of which 4 middles were marked as the central zone, while the remaining 12 were marked as a peripheral zone. The time that the animal spent in the central zone was calculated and used as the reliable parameter of the anxiety-related behavior. In addition, to express the ratio between the rat's ambulation in the peripheral zone and the total ambulatory distance, we calculated thigmotaxis index which was expressed in percentages (%).

Elevated plus maze test

The elevated plus maze platform (Elunit, Belgrade, Serbia), 0.5 m-raised from the ground, consisted of two pairs of identical open arms and identical enclosed arms, merging on the central platform at an angle of 90 degrees. The rats were placed individually on a central platform and allowed to explore the maze for 5 min, while their behavior was recorded with the computer-attached infrared camera (HikVision Bullet 2612, China) placed above the platform. To reduce olfactory stimuli, after each rat finished testing, the maze was carefully cleaned with alcohol solution. This test is based on the animal's conflict between the innate need to explore and the innate fear of a new, unfamiliar environment, represented by raised, bright and unprotected open arms. Avoiding such an environment and sticking to a closed, sheltered environment, represented by closed arms, is a characteristic of anxiety-related behavior (26). The output parameters of this test included the total number of transitions between closed and open arms and the time spent in the open arms, as a trustworthy measure of the anxiety level. These variables inversely reflect the anxiety level. Video records are analyzed offline by an investigator blinded to the treatment.

Light/dark test

For this test, the light-dark test arena (Elunit, Belgrade, Serbia) consisted of a bigger, white-colored opened light compartment which is connected by a small squared aperture with a smaller one, black-colored closed dark compartment. The rats were individually placed in the center of the light compartment and allowed to explore the test area, while their behavior was monitored with camera (Logitech C210, Switzerland) mounted above the light compartment. The output parameters of this test were: the time that an animal spent in the light compartment of the light-dark test, as well as the number of transitions from the light to the dark compartment. Captured video sequences were analyzed after test completion by an investigator blinded to the experimental protocol.

Statistical analysis

To assess the normality of variables distribution, *Kolmogorov-Smirnov* test was used. The output data of pain and anxiety-like behavioral tests showed normal distribution. Hence, the results were expressed as means ± standard deviation (SD) for all variables. The statistical significance of the differences between the groups, as well as in-group differences were estimated by One-way ANOVA with *Tukey-Kramer LSD post hoc* test. The values of $p<0.05$, $p<0.01$, or $p<0.001$ were considered to be significant.

RESULTS

Chronic aerobic physical activity increased scrotal pain thresholds in rats with experimentally induced CP/CPPS

There were no significant differences between control and experimental animals in scrotal pain thresholds for mechanical stimuli in basal conditions, i.e. 2 days and 1 day before the surgery (Sham-SED vs. CP/CPPS-SED, $p>0.05$; Sham-PA vs. CP/CPPS-PA, $p>0.05$, **Fig. 3**). Also, there were no differences within the Sham-SED and Sham-PA groups in all postoperative measurements in

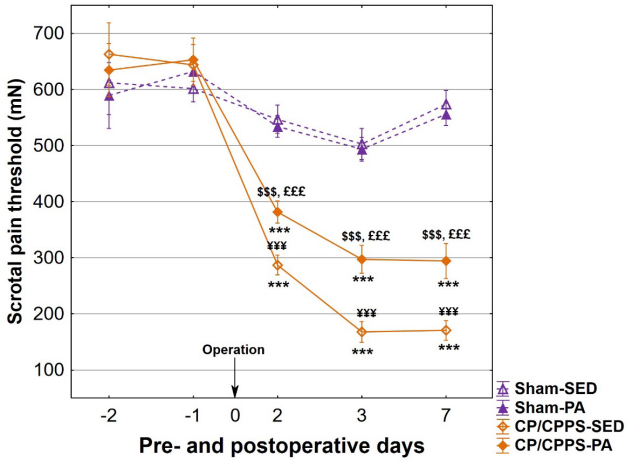

Figure 3. Scrotal pain thresholds in control (Sham-SED, Sham-PA) and experimental (CP/CPPS-SED, CP/CPPS-PA) rats.
Scrotal pain threshold measurements were performed by evF 2 and 1 day before, as well as 2, 3, and 7 days upon the operation (0). Values are mean± SD. Statistical significances of between-group differences in the scrotal pain threshold (¥¥¥p<0,001 vs. Sham-SED; £££p<0.001 vs. Sham-PA; $$$p<0.001 vs. CP/CPPS-SED), as well as within-group differences (***p<0.001 vs. -1) were estimated by one-way ANOVA with Tukey-Kramer LSD post hoc test. For details see the caption to **Fig. 1**.

comparison with the basal values (p>0.05, **Fig. 3**). Scrotal pain thresholds in rats with CP/CPPS (groups CP/CPPS-SED and CP/CPPS-PA) were highly significantly reduced (p<0.001), when compared to the thresholds in Sham operated rats (groups Sham-SED and Sham-PA) on the 2nd, 3rd, as well as 7th day upon surgery (**Fig. 3**). Also, pain thresholds were highly significantly reduced within the CP/CPPS-SED and CP/CPPS-PA rats in all postoperative days, compared to their basal pain thresholds (p<0.001, **Fig. 3**).

On the other hand, 30-day lasting chronic aerobic exercise on a treadmill led to a high statistically significant increase of postoperative scrotal pain thresholds in CP/CPPS-PA rats, in comparison to the corresponding sedentary rats from CP/CPPS-SED group (CP/CPPS-PA vs. CP/CPPS-SED, p<0.001, **Fig. 3**).

Chronic aerobic physical activity beneficially modified anxiety-like behavior in rats with experimentally induced CP/CPPS

Open field test

Analysis of the exploratory locomotor activity of control, Sham operated rats (Sham-SED and Sham-PA groups), and experimental rats with CP/CPPS(CP/CPPS-SED and CP/CPPS-PA groups) in the OF showed different behavioral patterns, which indicated the occurrence of anxiety-like behavior in rats with CP/CPPS (CP/CPPS-SED and CP/CPPS-PA rats), as shown in representative traces of ambulatory movements in the OF arena **(Fig. 4A-D)**.

Quantitative analysis of output variables of OF test showed that physically active Sham-PA rats had statistically significant higher ambulatory distance **(Fig. 5A)** on the 2nd (p<0.001), 3rd (p<0.05), and 7th postoperative day (p<0.05), in comparison with the Sham-SED rats. The same holds for the time of the ambulatory movements **(Fig. 5B)** on2nd (p<0.001), 3rd (p<0.01), and 7th postoperative day (p<0.05). Also, Sham-PA animals, in comparison to the Sham-SED animals, spent statistically significantly more time in the center of the OF **(Fig. 6A)** in 2nd (p<0.01), 3rd (p<0.001), and 7th postoperative day (p<0.001). A similar observation was made regarding the number of rearings **(Fig. 6B)** on the 2nd (p<0.001), 3rd (p<0.001), and 7th postoperative day (p<0.01). Index of thigmotaxis **(Fig. 7)** was statistically significantly lower in Sham-PA rats on the 2nd (p<0.001), 3rd (p<0.05), and 7th postoperative day (p<0.05), in comparison with the Sham-SED rats. Within-group differences of all OF the test parameters among the Sham-SE D and Sham-PA rats were not significantly changed in the 3rd and 7th, in comparison with the 2nd postoperative day.

Further analysis showed that the total ambulatory distance **(Fig. 5A)** and time **(Fig. 5B)** were significantly decreased in CP/CPPS-SED and CP/CPPS-PA rats, compared to the corresponding control Sham-SED and Sham-PA rats in 3rd (p<0.001) and 7th postoperative day (p<0.001). On the 2nd postoperative day, a statistically significant difference (p<0.001) in mentioned parameters was observed only between CP/CPPS-PA and Sham-PA rats, while the difference between CP/CPPS-SED and Sham-SED rats was not statistically significant (p>0.05). Also, CP/CPPS-PA animals, in comparison to the Sham-PA animals, spent statistically significantly less time in the center of the OF **(Fig. 6A)** in 2nd (p<0.01), 3rd (p<0.001), and 7th postoperative day (p<0.01), also had a statistically significant lower number of rearings **(Fig. 6B)** in 2nd (p<0.001), 3rd (p<0.001), and 7th postoperative day (p<0.01), and additionally revealed a higher index of thigmotaxis **(Fig. 7)** in 3rd (p<0.001), and 7th postoperative day (p<0.001). A similar observation was in the comparison of CP/CPPS-SED and Sham-SED rats onthe 3rd and 7th postoperative day in all test parameters **(Fig. 5-7)** in the 3rd (p<0.001), and 7th postoperative day (p<0.001). The difference between mentioned groups in all test parameters was not statistically significant onthe 2nd day ofthe surgery (p>0.05, **Fig. 5-7**). Within-group differences of all OF the test parameters among the CP/CPPS-SED rats were not significantly changed in the 3rd (p<0.001) and 7th (p<0.001), in comparison to the 2nd postoperative day. Physically active CP/CPPS-PA rats had statistically significant lower ambulatory distance **(Fig. 5A)** and time **(Fig. 5B)**, as well as a higher index of thigmotaxis **(Fig. 7)** in 3rd (p<0.05) and 7th (p<0.05), in comparison to the 2nd postoperative day. On the other hand, the difference was not statistically significant regarding time in the center of the open field **(Fig. 6A)** and

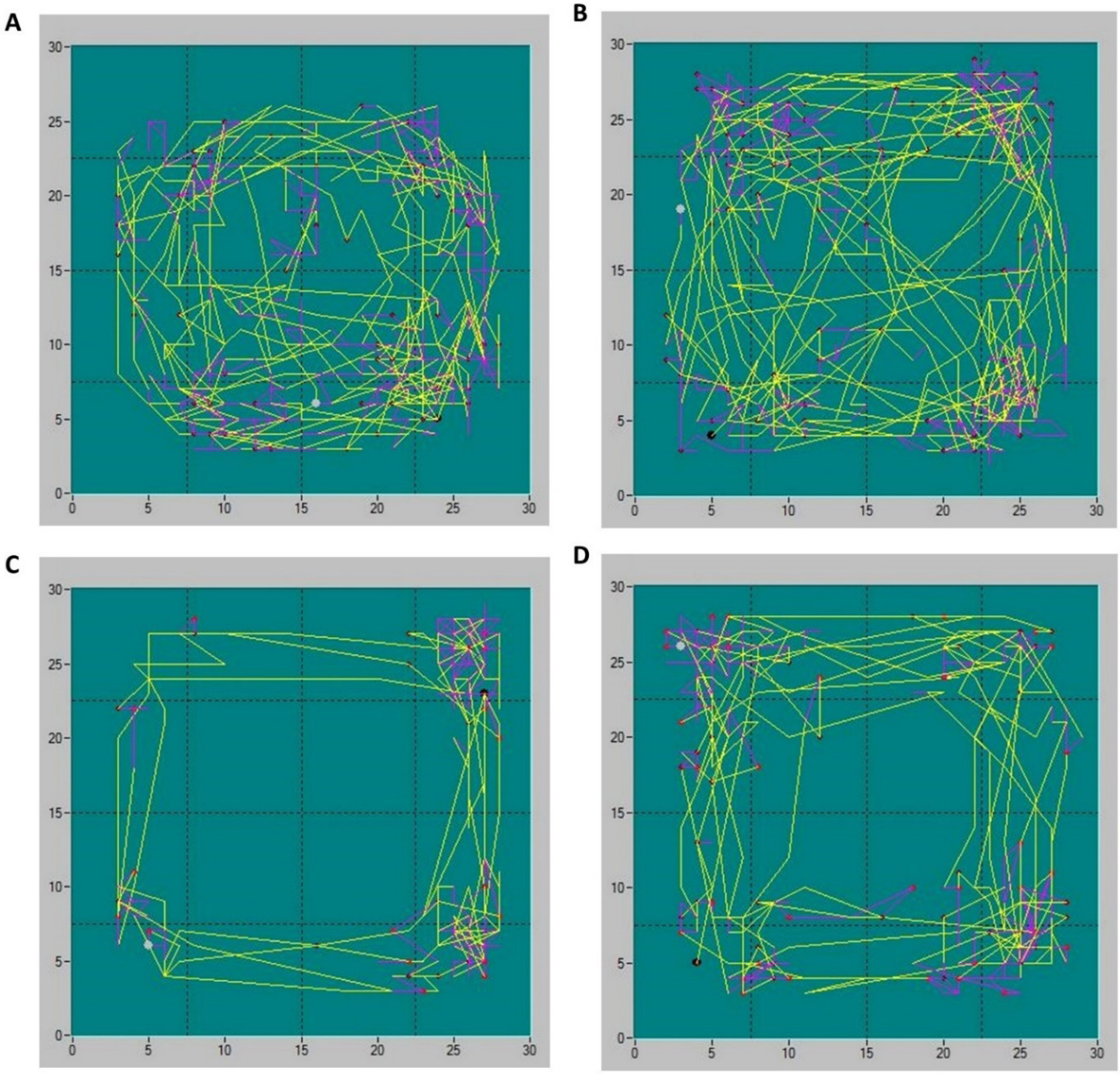

Figure 4. Representative open field traces of horizontal and vertical locomotor activity of control: Sham-SED (A), Sham-PA (B), and experimental: CP/CPPS-SED (C) and CP/CPPS-PA (D) animals.
Each animal was individually tested in the open field for 15 minutes. Horizontal and vertical spontaneous locomotor activity was automatically recorded by an infrared sensor system, and then additionally analyzed using the accompanying software package (Conducta 1.0). For details see the caption in **Fig. 1**.

a number of transitions **(Fig. 6B)** on3rd (vs. 2, p>0.05) and 7th postoperative day (vs. 2, p>0.05).

The partial anxiolytic effect of the exercise pretreatment was observed through a comparison of physically active CP/CPPS-PA and sedentary CP/CPPS-SED animals with prostatitis. There were no statistically significant differences in all OF the test parameters **(Fig. 5-7)** on the 2nd postoperative day between the mentioned groups (CP/CPPS-PA vs. CP/CPPS-SED, p>0.05). On the 3rd postoperative day, the differences between CP/CPPS-SED and CP/CPPS-PA rats were highly statistically significant (p<0.001) in all parameters, except the ambulatory time (p>0.05, **Fig. 5A**). Physically active CP/CPPS-PA rats, compared to the sedentary CP/CPPS-SED rats on the 7th day upon surgery had statistically significant higher ambulatory distance (p<0.001, **Fig. 5A**) and time (p<0.01, **Fig. 5B**), they spent more time in the center of the open field (p<0.01, **Fig. 6A**) and made more rearings (p<0.05, **Fig. 6B**), and also had a lower index of thigmotaxis (p< 0.05, **Fig. 7**).

Elevated plus maze test

Quantitative analysis of the output data derived from the EPM test showed that exercise treatment in Sham-PA rats lead to a statistically significant increase in a number of open/closed arms transitions **(Fig. 8A)** in the 2nd (p<0.001), 3rd (p<0.01), and 7th postoperative day (p<0.001), in comparison with the Sham-SED rats. The same holds true for the time that animal spent in the open

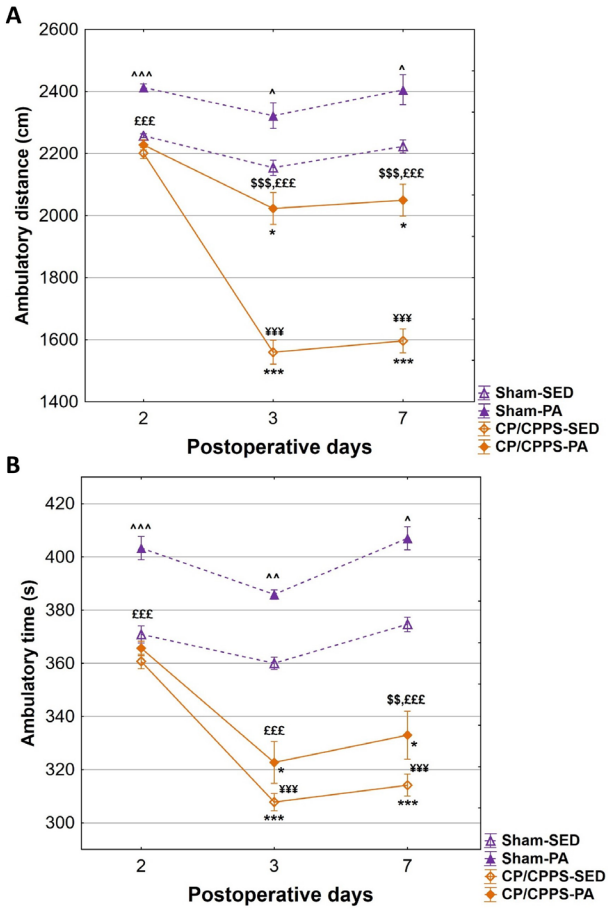

Figure 5. Ambulatory distance (A) and time (B) during open field testing in control: Sham-SED, Sham-PA, and experimental: CP/CPPS-SED, CP/CPPS-PA animals.
Values are mean±SD. Statistical significances of between-group differences in the ambulatory distance and time (^p<0.05, ^^p<0.01, ^^^p<0.001 vs. Sham-SED; ¥¥¥p<0.001 vs. Sham-SED; £££p<0.001 vs. Sham-PA; $$p<0.01, $$$p<0.001 vs. CP/CPPS-SED), as well as, within-group differences (*p<0.05, **p<0.01, ***p<0.001 vs. 2) were estimated by one-way ANOVA with Tukey-Kramer LSD post hoc test. For details see the caption in **Fig. 1**.

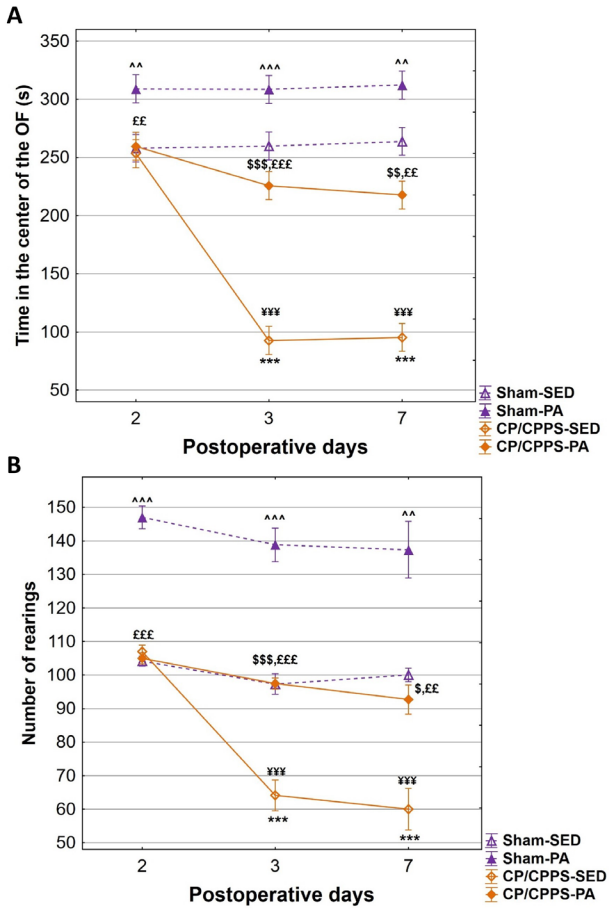

Figure 6. Time spent in the center of the open field (A) and a number of rearing (B) in control: Sham-SED, Sham-PA, and experimental: CP/CPPS-SED, CP/CPPS-PA animals.
The number of rearings was presented as the number of the rat's hind legs propping up. Values are mean±SD. Statistical significances of between-group differences in time spent in the center of the open field and number of rearings (^^p<0.01, ^^^p<0.001 vs. Sham-SED; ¥p<0.05, ¥¥¥p<0.001 vs. Sham-SED; ££p<0,01, £££p<0.001 vs. Sham-PA; $p<0.05, $$p<0.01, $$$p<0.001 vs. CP/CPPS-SED), as well as, within-group differences (*p<0.05, ***p<0.001 vs. 2) were estimated by one-way ANOVA with Tukey-Kramer LSD post hoc test. For details see the caption in **Fig 1**.

arms **(Fig. 8B)** on the 2nd (p<0.05), 3rd (p<0.01), and 7th postoperative day (p<0.01). Within-group differences of all EPM test parameters among the Sham-SED and Sham-PA rats were not significantly changed on the 3rd and 7th, in comparison with the 2nd postoperative day.

No differences in EPM test variables were detected between the rats with prostatitis and the control rats on the 2nd postoperative day (Sham-SED vs. CP/CPPS-SED, p>0.05; Sham-PA vs. CP/CPPS-PA, p>0.05, **Fig. 8A, B**). On the other hand, sedentary CP/CPPS-SED, and physically active CP/CPPS-PA rats with prostatitis, compared to the corresponding Sham-SED and Sham-PA controls had a lower number of open/closed arms transitions **(Fig. 8A)** and spent less time in the open arms **(Fig. 8B)** in 3rd (p<0.001) and 7th postoperative day (p<0.001). Also, there was a highly significant reduction of the number of open/closed arms transitions **(Fig. 8A)**, as well as the time spent in the open arms **(Fig. 8B)** within the CP/CPPS-SED and CP/CPPS-PA rats on the 3rd (p<0.001) and 7th postoperative day (p<0.001).

However, exercise (CP/CPPS-PA group) significantly increased the number of open/closed arms transitions **(Fig. 8A)** on the 3rd (p<0.05), as well as 7th day upon the surgery (p<0.05), in comparison to the sedentary CP/CPPS-PA animals. Also, there is a highly significant increase in the time animals spent in the open arms **(Fig. 8B)** in CP/CPPS-PA rats on the 3rd (p<0.01) and 7th day (p<0.001) upon surgery, in comparison with the CP/CPPS-SED rats.

Light/dark test

Sham-PA animals spent statistically significantly more time in the light compartment on all postoperative days (p<0.05, **Fig. 9A**), in comparison with the Sham-SED rats. The same observation concerning the number of L/D transitions **(Fig. 9B)** on the 2nd (p<0.05), 3rd (p<0.01), and 7th postoperative day (p<0.01). Within-group differ-

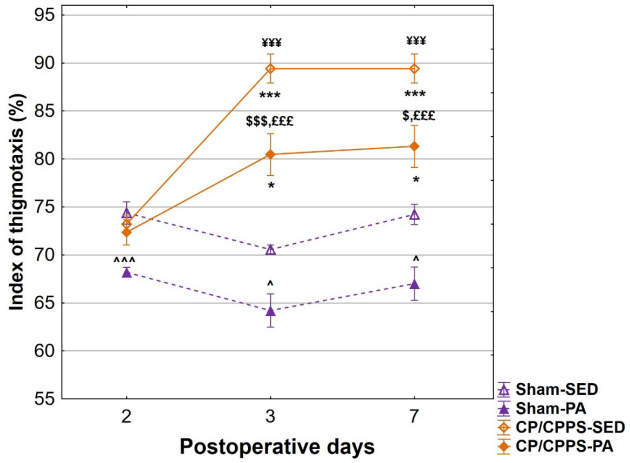

Figure 7. Index of thigmotaxis in control: Sham-SED, Sham-PA, and experimental: CP/CPPS-SED, CP/CPPS-PA animals.
The index of thigmotaxis was calculated as a ratio between the distance of rat ambulatory distance in the peripheral zones and the total ambulatory distance and expressed in percentages (%). Values are mean±SD. Statistical significances of between-group differences in the index of thigmotaxis (^p<0.05, ^^^p<0.001 vs. Sham-SED; ¥¥¥p<0.001 vs. Sham-SED; £££p<0.001 vs. Sham-PA; $p<0.05, $$p<0.01 vs. CP/CPPS-SED), as well as within-group differences (*p<0.05, ***p<0.001 vs. 2) were estimated by one-way ANOVA with Tukey-Kramer LSD post hoc test. For details see the caption to **Fig. 1.**

ences of L/D test parameters among the Sham-SED and Sham-PA rats were not significantly changed on the 3rd (vs. 2, p>0.05), and 7th postoperative day (vs. 2, p>0.05).

The time that CP/CPPS-SED and CP/CPPS-PA animals spent in the light compartment **(Fig. 9A)** was significantly shorter, compared to Sham-SED and Sham-PA groups on the 3rd (p<0.001), as well as the 7th day upon the surgery (p<0.001). The same holds for the number of L/D compartment transitions **(Fig. 9B)** on the 3rd(p<0.001), as well as, on the 7th day upon surgery (p<0.001). Within-group differences among the CP/CPPS-SED rats were statistically significant regarding the time in the light compartment of the L/D test **(Fig. 9A)**, as well as the number of L/D transitions **(Fig. 9B)** on the 3rd (vs. 2, p<0.001) and 7th postoperative day (vs. 2, p<0.001). A similar observation was made in CP/CPPS-PA group on the 3rd (vs. 2), and the 7th (vs. 2) postoperative day, regarding the time that the animal spent in the light compartment of the L/D test (p<0.001, **Fig. 9A**), as well as the number of L/D transitions (p<0.05, **Fig. 9B**). There was no statistically significant difference in these parameters in 2nd day between the mentioned groups (p>0.05, **Fig. 9A, B**).

Additionally, chronic aerobic exercise in CP/CPPS-PA rats, compared to the sedentary CP/CPPS-SED rats, on the 3rd (p<0.05), as well as on the 7th day upon intraprostatic injection (p<0.05), led to a statistically significant increase in the time spent in the light compartment of the L/D test **(Fig. 9A)**, and also in the number of the L/D transitions **(Fig. 9B)**. There was no statistically significant difference in the parameters derived from the L/D test on the 2nd day between these groups (CP/CPPS-PA vs. CP/CPPS-SED, p>0.05, **Fig. 9A, B**).

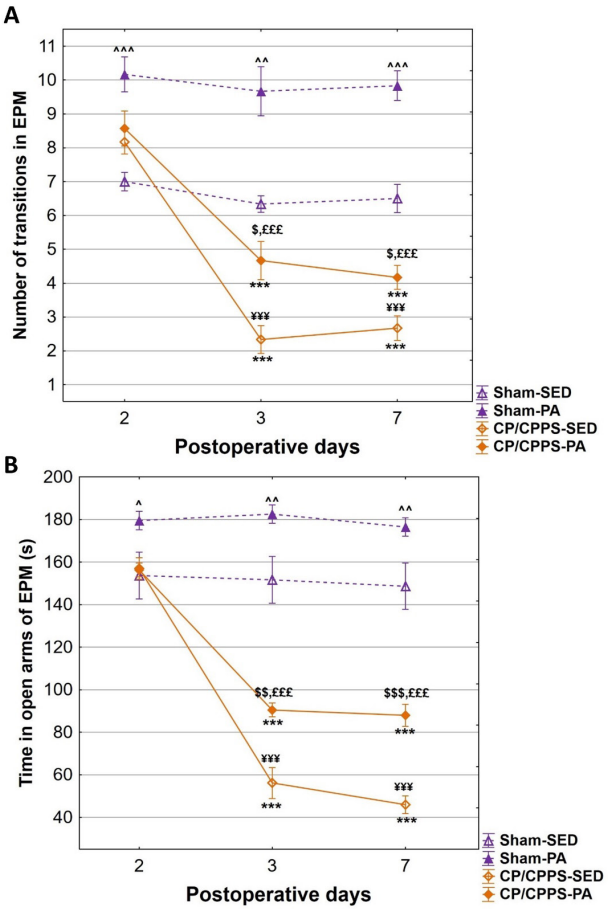

Figure 8. A number of transitions between the opened and closed arm (A) and the time spent in the open arms (B) of elevated plus maze test (EPM) in control: Sham-SED, Sham-PA, and experimental: CP/CPPS-SED, CP/CPPS-PA animals.
Values are mean±SD.Statistical significances of between-group differences in time spent in the light compartment and the number of transitions between the light and dark compartment of the L/D test (^p<0.05, ^^p<0.01 vs. Sham-SED; ¥¥¥p<0.001 vs. Sham-SED; £££p<0.001 vs. Sham-PA; $p<0.05 vs. CP/CPPS-SED), as well as, within-group differences (*p<0.05, ***p<0.001 vs. 2) were estimated by one-way ANOVA with Tukey-Kramer LSD post hoc test. For details see the caption in **Fig. 1**.

DISCUSSION

Considering that chronic pelvic pain and discomfort are the most prominent symptoms among the patients suffering from CP/CPPS (Krieger et al., 1999), the occurrence and dynamics of experimental CP/CPPS development in our study are confirmed by functional test, i.e. pain threshold measurement. Namely, intraprostatic injection of 3% λ-carrageenan significantly reduced scrotal mechanical pain thresholds in rats with CP/CPPS (both SED and PA group) on the 3rd and the 7th day upon surgery, in comparison with the respective control Sham operated rats (receiving 0.9% saline). The rats with developed experimental CP/CPPS showed increased anxiety-like behavior, compared to the corresponding sham operated controls.

Results of the present study showed that 30-day long exercise on the treadmill led to amelioration of anxiety-re-

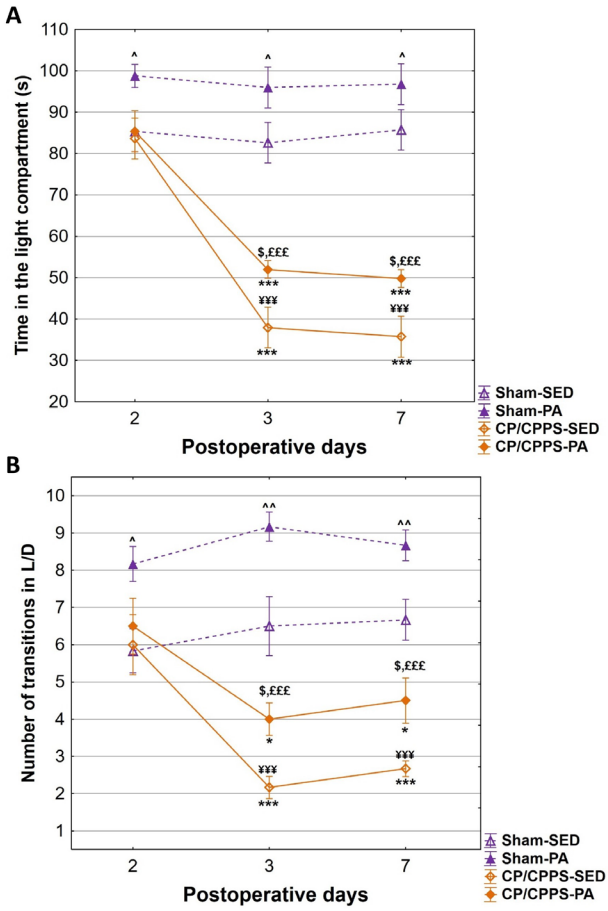

Figure 9. The time spent in the light compartment (A) and the number of transitions between the light and the dark compartment (B) of light/dark (L/D) test in control: Sham-SED, Sham-PA, and experimental: CP/CPPS-SED, CP/CPPS-PA animals.
Values are mean±SD. Statistical significances of between-group differences in number of transitions and time spent in the opens arms of EPM (^p<0.05, ^^p<0.01, ^^^p<0.001 vs. Sham-SED; ¥¥¥p<0.001 vs. Sham-SED; £££p<0.001 vs. Sham-PA; $p<0.05, $$p<0.01, $$$p<0.001 vs. CP/CPPS-SED), as well as, within-group differences (***p<0.001 vs. 2) were estimated by one-way ANOVA with Tukey-Kramer LSD post hoc test. For details see the caption in **Fig. 1**.

lated and pain-related behavior in rats with CP/CPPS, as it was evident by favorable modulation of all parameters in the applied battery of ethological tests for the assessment of anxiety-like behavior. Thus, chronic aerobic physical activity on the treadmill is a potent non-pharmacological therapeutic option for anxiety in CP/CPPS.

Results obtained in our study by the functional behavioral testing could be explained by several potential mechanisms. The heterogeneous group of symptoms that characterize CP/CPPS is the reason for the still unknown and unclear etiopathogenesis, although numerous risk factors are identified, including intraprostatic urinary reflux, endocrine disbalance, inflammation through the CNS, psychological and hereditary factors, immunological disbalance and muscle-skeletal dysfunctions (27). Statistically significant changes in serum cortisol levels have been found in patients with CP/CPPS (28), while the hypothalamic-pituitary-adrenal (HPA) axis dysfunction is hypothesized to be one of the main mechanisms that links CP/CPPS with anxiety (29). We also previously found that elevated levels of corticosterone in the rat's serum have a positive correlation with lipid peroxidation and oxidative stress in the cortex, thalamus and hippocampus (20). Therefore, corticosterone, by increasing the level of available glucose in the brain, and via the impaired signaling pathways on the other hand, promotes the spontaneous generation of free oxygen radicals, increases pro-oxidant genes transcription and reduces antioxidant defense mechanisms. Impaired redox balance, on the other hand, could mediate the development of anxiety–related behavior, as it has been previously linked in basic and clinical studies (30).

Antinociceptive effect of physical activity observed in our study by mechanical pain threshold tests, could be explained by the increased concentration of endogenous cannabinoids in the serum, which has been observed in humans and animals after running and cycling (31). Cannabinoids are known for their analgesic effects (32). Physical activity reduces pain sensitivity through changes in neuroendocrine and autonomic nervous functions, especially through increasing levels of endogenous endorphins and modifying neurotransmitter systems including dopaminergic, noradrenergic and serotonergic systems (33). Additionally, there is an increase in the plasma nitrogen oxide (NO) concentration instantly after physical activity (34) and the antinociceptive effect of NO has been demonstrated (35).

In a study performed by Dybowski et al. (36), it has been shown that the symptoms of anxiety can worsen the pain severity, the degree of voiding problems, as well as quality of life in patients with prostatodynia. These data explain the potential mechanisms of pelvic pain development, but also indicate that anxiety is not only a consequence of chronic pain in CP/CPPS, but that it can also be one of the etiological factors for CP/CPPS. Although the effects of physical activity on numerous different physiological and psychological factors are proven, the precise mechanism of the anxiolytic effect is still unclear. This effect can be partially explained by the favorable influence of physical activity in the regulation of stress response, through the HPA axis stabilization (37) or glucocorticoid concentration reduction, but also through the stimulation of neurogenesis and angiogenesis by upregulated brain-derived neurotrophic factors (BDNF) synthesis, which is important for proper brain functioning and anxiety reduction (15). Given that CP/CPPS is characterized by an increased ROS generation and intense oxidative stress damage of neurons which negatively affect behavioral performances (20), physical activity with proven antioxidant effect can lower the lipid peroxidation level, reduce ROS generation, and ameliorate behavioral performances (38).

There is a wide range of therapeutic modalities for treating CP/CPPS, acting on the different pathophysio-

logical mechanism or directly on the manifested symptom, which reflects the complexity of this syndrome. Giubilei et al. (39) performed a randomized prospective trial to investigate the effects of physical activity on patients with CP/CPPS, and participants in the aerobic exercise group showed reduced pain and anxiety levels in comparison to subjects in the placebo/stretching group. These results are by our findings derived in an experimental setting. Planned and dosed physical activity is often recommended to reduce the harmful effect of chronic inflammation and chronic painful conditions in the body (40).

Conclusions

The results of the present study showed that regular exercise on the treadmill for 30 consecutive days led to the amelioration of anxiety-related and pain-related behavior in rats with CP/CPPS. Thus, chronic aerobic physical activity should be considered a non-pharmacological therapeutic option for treating anxiety in CP/CPPS patients. These experimental findings should be confirmed in further clinical studies in the field of sports medicine and andrology.

Acknowledgments

None.

Conflict of interest

The authors declare that they have no conflict of interest.

Author Contributions

NŠ, AZ, MV, DM, ARM and DH designed the experiment, performed the experiments and drafted the manuscript. DjM and OS contributed to the experimental studies and drafted the manuscript. All authors reviewed and approved the final manuscript.

Funding Statement

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (MNTR), grant number 200110, international grant FA4Lin by MNTR and TUBITAK. The corresponding author is MC member in EU COST Actions 20135 (TEATIME) and 20119 (ANDRONET).

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FIZIČKA AKTIVNOST MENJA PONAŠANJE POVEZANO SA ANKSIOZNOŠĆU U HRONIČNOM PROSTATITISU/SINDROMU HRONIČNOG PELVIČNOG BOLA: FUNKCIONALNA I BIHEJVIORALNA STUDIJA NA RASKRSNICI EKSPERIMENTALNE FIZIOLOGIJE VEŽBANJA I ANDROLOGIJE

Nikola Šutulović[1], Aleksa Zubelić[1], Djuro Macut[2], Milena Vesković[3], Dušan Mladenović[3], Aleksandra Rašić-Marković[1], Željko Grubač[1], Olivera Stanojlović[1], Dragan Hrnčić[1*]

Sažetak

Uvod: Hronični prostatitis/sindrom hroničnog pelvičnog bola (eng. *Chronic prostatitis/chronicpelvicpainsyndrome*, CP/CPPS) je neinfektivni inflamatorni sindrom, manifestovan brojnim urološkim simptomima, ali često praćen seksualnom disfunkcijom i problemima sa mentalnim zdravljem, uključujući i anksioznost. Studije su pokazale povoljne efekte hroničnog vežbanja u tretmanu anksioznosti i hroničnog bola, ali njen uticaj na bol i anksioznost u CP/CPPS još uvek nije ispitan. Cilj ovog istraživanja je bio da se utvrde efekti hronične aerobne fizičke aktivnosti na ponašanje povezano sa anksioznošću kod pacova sa eksperimentalno izazvanim CP/CPPS.

Materijali i metode: Odrasli mužjaci pacova soja *Wistar albino* (n=32) su nasumično podeljeni u grupu fizički aktivnih koji su trčali na tredmilu 30 uzastopnih dana (PA, 30 min/dn, brzina: 20 m/min; n=16) i grupu sedentarnih koji su proveli isto vreme u isključenom tredmilu (SED, 30 min/dn, brzina: 0 m/min; n=16). Nakon protokola na tredmilu, u zavisnosti od intraprostatične injekcije tokom operacije (0.9% NaClili 3% λ-karagenin), pacovi su nasumično podeljeni u sledeće grupe (n=8 u svakoj): **Sham-SED** (sedentarni protokol i 0,9% NaCl); **Sham-PA** (protokol vežbanja i 0,9% NaCl); CP/CPPS-SED (sedentarni protokoli 3% λ-karagenin); **CP/CPPS-PA** (protokol vežbanja i 3% λ-karagenin). U cilju praćenja razvoja CP/CPPS i dinamike bola, skrotalni prag bola na mehaničku draž je meren upotrebom elektronskog von Freyestezi-ometra(evF), i to: 2. i 1. preoperativnog dana, kao i 2., 3., i 7. postoperativnog dana. Kako bi se ispitalo postojanje ponašanja povezanog sa anksioznošću, životinje iz svih grupa su podvrgnute bateriji tri etološka testa (test otvorenog polja, test uzdignutog krstastog lavirinta i test svetlo/tama) u 2., 3. i 7. postoperativnom danu.

Rezultati: Pacovi koji su razvili eksperimentalni CP/CPPS, u poređenju sa Sham pacovima, su imali snižen skrotalni prag bola na mehaničku draž u svim ispitivanim postoperativnim danima, a takođe su ispoljavali i ponašanje povezano sa anksioznošću u sva tri etološka testa. Protokol vežbanja na tredmilu, u trajanju od 30 uzastopnih dana je kod pacova sa CP/CPPS doveo do smanjenja ponašanja povezanog sa anksioznošću i do povećanja skrotalnog praga bola.

Zaključak: Rezultati ovog istraživanja su pokazali da je dozirano i planirano vežbanje na tredmilu u trajanju od 30 uzastopnih dana dovelo do smanjenja anksioznosti i bola kod pacova sa eksperimentalnim CP/CPPS.

Ključne reči: CP/CPPS, bol, anksioznost, trening, tredmil, pacov.

Primljen: 29.09.2022. I **Revizija:** 15.10.2022. I **Objavljen:** 07.11. 2022

Medicinska istaživanja 2022; 55(3):29-41