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Vanadium shows no effect in stress-induced hyperthermia and the tail suspension test in healthy mice

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ABSTRACT

Vanadium (V) is a trace element in the environment; it is detected in soil, water, air, dust, and food products. V-containing compounds have shown therapeutic potential in the treatment of diabetes. However, studies on the effects of V on animal behavior remain limited and sporadic. This study investigates the impact of acute (0.2, 2, 5 mg/kg, and 20 mg/kg) or repeated V administration (2 mg/kg/day; 7 days) in mice, employing stress-induced hyperthermia (SIH) as the primary behavioral assay. Additionally, its influence was assessed through single-dose administration in the tail suspension test (TST) and the Rota-rod test. The findings indicate no significant effects of V on the studied parameters, although motor coordination was notably impaired. Electrophysiological experiments were conducted to further elucidate vanadium's influence on neuronal function to assess its effects on long-term potentiation (LTP), a key process in synaptic plasticity, revealing no discernible impact. Moreover, the expression levels of gamma-aminobutyric acid (GABA) receptors, specifically GABAA1, GABAB1, and GABAB2, as well as glutamic acid decarboxylase (GAD67), were analyzed in the frontal cortex (FCx) using western blotting. Collectively, the results indicate a negligible influence of V on glutamatergic transmission and GABAergic receptor activity, after a single administration to healthy mice.

1. Introduction

Vanadium (V) is a transition metal of the fourth period, with an atomic number of 23, and its concentration has been increasing in the environment (in water, soil, air, food and biological organisms) due to its wide range of applications in industry [1,2]. V has a wide range (+ 2, + 3, + 4 and + 5) of oxidative states [2]; in body fluids, the pentavalent form predominates (VO^{3-}), while intracellularly - mainly the tetravalent form (VO^{2+}), [2]. V concentration in drinking water is in the amount of 10 nM, in the human body it is about 0.3 μM, daily doses consumed with food are at a range of 0.01–0.03 mg [3]. According to Toxical profile of Vanadium (ATSDR, 1990) a 14 days LD50 for mice is about 31 mg/kg. In medicine V has been proposed mainly as an antidiabetic compound [1, 2]. Moreover, its anticancer, cardioprotective, neuroprotective, anti-cholesterolemic potential has also been described [2]. V is controversial due to its potential to be toxic to living organisms [1,2]. It was documented, that V is essential in trace amounts of 0.05 μM, and toxic above 10 μM, which indicates its duality [2]. In men exposed to V, visuospatial and attention deficits were described [4]. In rats, on the other hand, reduction in two-way shock avoidance learning, and motor activity were found [5]. It is known that V inhibits several ATP-ases and phosphatases [3]. Its potential to induce cyclooxygenase-2 (COX-2) expression [6,7] pointed out its potential involvement in mechanisms related to the onset of depression or anxiety. Even more so, as reduced levels of V in the prefrontal cortex have been shown in patients with bipolar disorder (BP) [8].

Stress induced hyperthermia (SIH) is a protocol widely used for the searching of potential of tested compounds in anxiety [9]. According to the van der Heyden et al. [9] SIH is a paradigm "*putatively reflecting anticipatory anxiety*". Its potential was documented in a wide range of data [10,11]. SIH is observed especially in CD-1 mice [9]. The increase in temperature measured in the rectum of mice, which is observed after the mice in the group are removed from their home cage, is a reproducible and very strong phenomenon [9]. Temperature differences

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reach up to 1.5 °C [9,10]. Compounds possessing anti-anxiety potential have been shown to lower the temperature measured as SIH (T2-T1) without interfering with the basal temperature of mice [9,10]. On the other hand, the Tail Suspension Test (TST) is a screening test used to test the antidepressant-like potential of compounds and is also widely used in the science [12]. A strain of mice particularly sensitive to TST is C57Bl/6J [12–14].

In consideration of the above information, the main idea was to test whether V properties in depression or anxiety. Two different mouse strains (CD-1 and C57Bl/6J) were used, depending on their suitability for the protocols. To this end, a dose-dependent study was conducted using the SIH protocol, TST, LA and Rotarod. To test the effects of V on mouse brain and glutamatergic (Glu) transmission, electrophysiological recordings of frontal cortex (FCx) mouse brain activity were conducted. Furthermore, GAD67, GABAA1, GABAB1 and GABAB2 receptors were assessed in FCx using Western blot.

2. Materials and methods

2.1. Animals and housing

The experiments were performed on group-housed male CD-1 and C57BL/6J mice (8–10 weeks old) and were carried out in accordance with the European Communities Council Directive of September 22, 2010 (2010/63/UE) on the protection of animals used for scientific purposes and national law. All procedures were approved by the Ethics Committee of the Maj Institute of Pharmacology, Polish Academy of Sciences in Krakow, Poland (Approval Number: 1267 and 106/2023). The mice were kept on a 12/12 h light-dark cycle with light on at 6:00 a.m. and off at 6:00 p.m. Standard food was available ad libitum and had free access to tap water.

2.2. Drug treatment

Sodium orthovanadate, Na_3O_4V (Tocris Cookson, Bristol, UK; Cat. No. 2821) was dissolved according to the manufacturer's instructions. Control group injections involved administering H_2O. V was injected *i.p.* once (0.2, 2, 5 mg/kg, and 20 mg/kg), or for 7 consecutive days (2 mg/kg) before 11:00 a.m.

2.3. Modified stress-induced hyperthermia (SIH) in singly housed mice

The procedure was described in detail by Stachowicz [10]. For the SIH test, CD-1 mice were single housed for 24 h before the experiment. Then body temperature was measured in each mouse at t = 0 min (T1) and t = + 15 min (T2). Mice were placed in a new cage immediately after the T1 measurement. The temperature difference (T2 - T1) was considered a measure of stress-induced hyperthermia. A comparison of T1 in control mice and those receiving V was used to determine whether the agent affected body temperature. Rectal temperature was measured to the nearest 0.1 °C using highly sensitive and accurate thermometer (Ellab, Denmark). A lubricated thermistor probe (2 mm in diameter) was inserted 20 mm into the rectum. During this determination, the mouse was held by the base of the tail, and the thermistor probe remained in place until a constant reading was obtained (± 15 s).

2.4. Tail suspension test (TST)

C57BL/6J mice were suspended individually by their tails to the tabletop, 75 cm above the ground. using adhesive tape placed 1 cm from the tip of the tail. Total duration of immobility was measured over a period of 6 min. Mice were considered immobile only when they hanged down passively and completely motionless.

2.5. Locomotor activity (LA)

The locomotor activity of mice was measured in Plexiglas locomotor activity chambers (40 × 20 × 15 cm) in a 20-station photobeam activity system (Opto-M3 Activity Meter; Columbus Instruments, OH, USA). The animals were placed there individually, and the total number of ambulations was recorded for the next 6 min.

2.6. Rota-rod test

The Rota-rod test was performed with a Mouse Rota-Rod NG apparatus (UGO BASILE SRL, Gemonio, Italy). C57Bl/6J mice were trained at a speed of 18 rpm for 3 min for one session per day for 3 consecutive days. If a mouse fell off during the habituation period, it was placed back on the apparatus. On the following day (4th day), the test trial was performed. After the mice were placed on the apparatus moving at a speed of 12 rpm, the accelerating mode was started (maximum speed – 24 rpm). The latency to fall was measured during a 3-min test session.

2.7. Measurement of body weight of mice

Body weight was measured approximately one hour prior to behavioral testing using a calibrated electronic scale. Each mouse was weighed individually.

2.8. Electrophysiological studies – slice preparation

Mice were anesthetized with isoflurane (Aerrane, Baxter, UK) and decapitated. Cortical slices (380 μm) were cut using a vibrating microtome (Leica VT1000s, Germany) in N-methyl-D-glucamine (NMDG)-based artificial cerebrospinal fluid (ACSF) containing (in mM): NMDG (92), KCl (2.5), CaCl2 (0.5), MgSO4 (10), NaH2PO4 (1.2), NaHCO3 (30), HEPES (20), glucose (25), sodium ascorbate (5), thiourea (2), sodium pyruvate (3), pH= 7.35. Slices were then incubated at 32 °C for 25 min while gradually introducing NaCl . When Na spike-in protocol was finished, slices were transferred to ACSF containing (in mM): NaCl (132), $NaHCO_3$ (26), KCl (2), $CaCl_2$ (2.5), $MgSO_4$ (1.3), KH_2PO_4 (1.25) and D-glucose (10), bubbled with 95 % O_2 + 5 % CO_2 at 2.5 ml/min (32 ± 0.5 °C) incubation chamber for 60 min. After the incubation, a single slice was transferred to the interface recording chamber.

2.9. Extracellular recording and LTP induction

Individual slices were placed in the recording chamber of an interface type which was superfused (2.5 ml/min) with ACSF containing (in mM) NaCl (132), KCl (2), CaCl2 (2.5), MgSO4 (1.3), KH2PO4 (1.25), NaHCO3 (26), and D-glucose (10), bubbled with 95 % O2 and 5 % CO2 (temperature 32.0 ± 0.5 °C). Cortical field potentials (FPs) were evoked by stimulation (0.033 Hz, duration 200 μs) using a constant-current stimulus isolation unit (WPI) and a bipolar Pt-Ir electrode (FHC) placed in layer V. FPs were recorded using ACSF-filled glass micropipettes (~ 1 MΩ) placed in layer II/III. The responses were amplified (EXT 10-2F amplifier, NPI), filtered (1 Hz to 1 kHz), A/D converted (10-kHz sampling rate, Axon Instruments), and stored on PC using the Micro1401 interface, and Signal 4 software (CED). A stimulus–response (input–output) curve was made for each slice. To obtain the curve, stimulation intensity was gradually increased stepwise (16 steps; 0–100 μA). One response was recorded at each stimulation intensity. Then, stimulation intensity was adjusted to evoke responses of 30 % of the maximum amplitude. Cortical LTP was induced by theta burst stimulation (TBS). TBS consisted of 10 trains of stimuli at 5 Hz, repeated 5 times every 15 s. Each train was composed of five pulses at 100 Hz. During TBS, pulse duration was increased to 0.3 ms. Amplitude was measured in FCx.

2.10. Tissues collection

Decapitation was performed 45 min after drug injection. Animal brains were removed at once. The frontal cortex (FCx) was obtained following the coordinates included in the Mouse Brain Atlas [15] by cutting the anterior part of the forebrain at Bregma 2.20 mm. Olfactory bulbs and the anterior striatum were cut off. Therefore, the tissue taken for analysis contained most of the FCx. Before biochemical analysis, the tissues were frozen on dry ice and stored at − 80 °C.

2.11. Western blot analysis

Protein levels in the FCx was determined using the Western blot method. The tissues were homogenized in 2 % SDS, denaturated (10 min at 95 °C), and centrifugated (5 min at 9000 × *g*; 4 °C). The BCA method (Thermo Fisher Scientific; Rockford, IL, USA) was used to establish the total protein concentration in the resulting supernatants. Then the samples containing 40 µg of total protein were prepared and loaded on gels. The following steps involved SDS-PAGE fractionation and transferring the proteins from the gel to nitrocellulose membrane (Bio-Rad; Frankfurt, Germany). 1 % blocking solution (11921681001; Western Blocking Reagen, Roche; Basel, Switzerland) was used to prevent non-specific binding (60 min at RT). Next, the membranes underwent overnight incubation at 4 °C with primary antibodies: Rabbit Recombinant Monoclonal GABA A Receptor alpha 1 antibody (diluted 1:1000; Abcam, Cambridge, UK, ab252430; 50 kDa); GABAB1 - Anti-GABA B Receptor 1 antibody (ab55051; Abcam; 1:300; 108 kDa); GABAB2 - Anti-GABA B Receptor 2 antibody (ab52248; Abcam; 1:800; 106 kDa); GAD67 (ab26116; Abcam; 1:5000; 65 kDa). The successive stage involved washing membranes in Tris-buffered saline with 1 % Tween 20 (TBS-T) and incubating for 60 min at room temperature with a goat HRP-conjugated anti-rabbit/mouse IgG (diluted 1:5000; #170-5046, #170-5047; Bio-Rad, Frankfurt, Germany). TBS-T was used for subsequent washing. The luminescent signal was detected employing an enhanced chemiluminescence reaction (Clarity Western ECL Substrate, #1705061, Bio-Rad, Frankfurt, Germany) and analyzed using Syngene G:BOX Chemi XT 4 with GeneSys software version 1.8.10. GAPDH was monitored on each membrane to verify the amount of total proteins in each sample. To this end, a mouse monoclonal anti-GAPDH antibody (diluted 1:150; sc-365062; Santa Cruz Biotechnology; Dallas, TX, USA) was used. The final results for each sample are expressed as the ratio of the optical density of a particular protein to the optical density of GAPDH.

2.12. Statistical analysis

The obtained data were evaluated with one-way ANOVA, using Mann Whitney test, GraphPad Prism software, ver. 8.0 (ver. 10.4 in electrophysiology) (San Diego, CA, USA). Furthermore unpaired t test was used when two groups were compared. The obtained data are presented as the mean ± S.E.M, and $P < 0.05$ was considered significant.

3. Results

3.1. Changes in T1 but not in SIH in mice treated with V. dose-dependence study

A dose-dependent study of V (0.2, 2, and 20 mg/kg) given singly, showed no effect of treatment on SIH [a one-way ANOVA: $F(3,28) = 0.590$; $P = 0.627$], (Fig. 1A). A single injection of V at 20 mg/kg resulted in a significant reduction in T1 [a one-way ANOVA: $F(3,28) = 32.60$; $P < 0.001$], (Fig. 1B). Since visually "sedative" behavior was observed in mice after administration of V at a dose of 20 mg/kg, it was decided to test a lower dose, 5 mg/kg. The 5 mg/kg dose did not change the mice's SIH behavior [*t*-test: ns], (Fig. 1C), while it caused a decrease in T1 similarly to the 20 mg/kg dose [*t*-test: $P = 0.01$], (Fig. 1D).

3.2. Lack of effects in SIH in mice treated for seven days with V

Because the V at a dose of 2 mg/kg did not changed T1 after single injection, furthermore did not changed visually observed behavior of mice (see Fig. 1), the dose was selected for repeated treatment. Seven days of V administration at a dose of 2 mg/kg resulted with no changes in SIH [*t*-test: $P = 0.552$, ns], (Fig. 2A). Similarly, there was no effects of seven days of treatment with V at a dose of 2 mg/kg on T1 [*t*-test: $P = 0.059$, ns], (Fig. 2B).

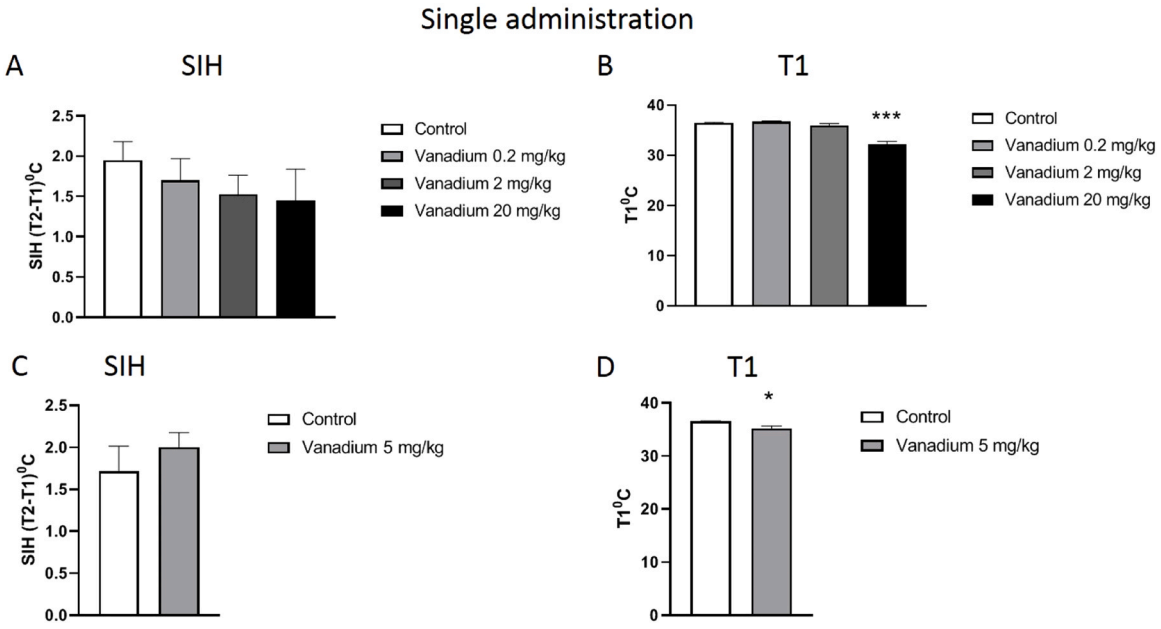

Fig. 1. The effect of treatment with V (0.2, 2, 5, 20 mg/kg *i.p.*) on behavior of CD-1 mice in SIH. (A, C) shows SIH, (B, D) shows T1. Compound was injected 45 min. before the test, $^{*}P < 0.05$, $^{***}P < 0.001$ vs control group; n = 8.

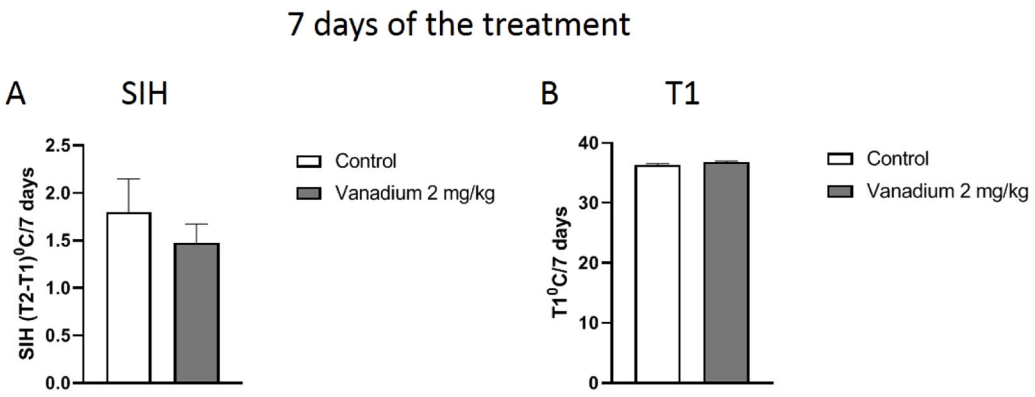

Fig. 2. The effect of treatment with V (2 mg/kg *i.p.*) for seven days on behavior of CD-1 mice in SIH. (A) shows SIH, (B) shows T1. Compound was injected 45 min. before the test; n = 8.

3.3. No changes in body weight in mice treated with V

The repeated treatment of V (2 mg/kg) for seven days did not changed body weight of mice [*t*-test: $P = 0.573$], (Fig. 3).

3.4. Increase in immobility and decrease in locomotor activity of mice treated with V. Dose-dependence study

In an trial experiment on a small cohort of mice (n = 4) increase in immobility time in TST was found [nonparametric Kruskal-Wallis: F (4,15) = 7.388; P = 0.042], (Fig. 4A). At the same time, the highest dose of V was examined (20 mg/kg) in LA, and significantly reduced locomotion of mice [*t*-test: P = 0.0012], (Fig. 4B). The result indicates the absence of a V effect on the TST, and the increase in immobility observed in the test is due to a disruption of the animal's locomotion.

Since the test was performed on a small cohort of mice, it was repeated on a separate cohort of mice to confirm the observed results (Fig. 5). Our results strongly suggests that increased immobility induced by V 20 mg/kg *i.p.* in TST is an effect of decreased LA in mice. T-test revealed significant effect of V 20 mg/kg in TST [*t*-test: t = 3.707; df= 10; $P = 0.0041$] (Fig. 5A), and significant decrease in LA [*t*-test: t = 6.960; df= 10; $P < 0.0001$] (Fig. 5B).

3.5. Disruptive effect of single injections of V on rota-rod performance in mice

A dose-dependence study using Rota-rod showed no effect of V (2 mg/kg) on latency to fall, while negative effects were found using the dose of 20 mg/kg of V [$F(2,12) = 23.89$; $P < 0.0001$] (Fig. 6).

3.6. Lack of changes in LTP in cortical slices from mice treated acutely with V

Analyses of FPs recorded in brain slices obtained from mice receiving V (20 mg/kg) injections showed no changes in the relationship between stimulus intensity and FP amplitude (input–output curve) compared with the slices obtained from control animals (Fig. 7A). Paired-pulse ratio (1.108 ± 0.026 and 1.034 ± 0.01) and LTP (138.8 ± 8.97 and 137.8 ± 7.43) recorded in PFC was unaltered as well (Figs. 7B and 7C/C_1).

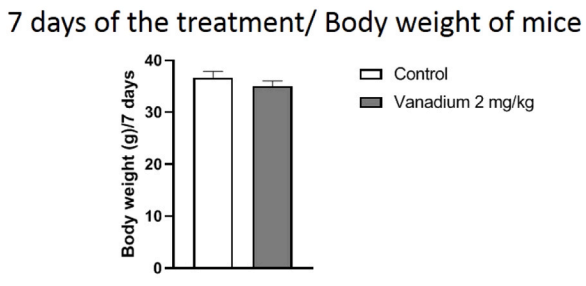

Fig. 3. The effect of treatment with V 2 mg/kg for seven days on body weight; n = 8.

3.7. The effects of V injections on GABAA1, GABAB1 and GABAB2 receptors and GAD67 levels in FCx of C57Bl/6J mice

Single injection with V 20 mg/kg was without any effects on the levels of GAD67 (t = 1.164, df = 10, ns) (Fig. 8A), GABAA1 (t = 0.2292, df = 10, ns) (Fig. 8B), GABAB1 (t = 0.2673, df = 10, ns) (Fig. 8C), GABAB2 (t = 0.1756, df = 10, ns) (Fig. 8D).

4. Discussion

Here, a dose-dependent study of V in SIH and TST protocols in mice was applied for the first time. Dose-dependent treatment with V at doses of 0.2, 2, 5 and 20 mg/kg showed no effect on SIH in single housed mice. Subsequently, no effect of V was observed when repeated treatment for seven days was applied. Our results are consistent with those of Dyer and Butte [16], on Sprague-Dawley rats treated with V powder showed no altered behavior in the open field test. However, there are also contradictory results documenting both positive and negative effects on stress parameters detected in mice exposed to V [17–20]. Franklin et al. [20] used V as an anxiety inducer in the elevated open space test. Cho et al. [17] using Jeju ground water (containing high V concentration, obtained from volcanic bedrock) documented decreased serum cortisol level in chronically stressed mice, among other positive changes. Conversely, exposure to V-peroxide for 21 days was associated with severe hematological, oxidative, and histopathological alterations [19]. Since there are no results in the literature indicating the effect of V-acting in an emotional stress like the SIH procedure, our study is pioneering, so we can't compare them. However, the authors emphasize the different effects of V depending on the dose, exposure time, and the chemical carrying the element [16–19]. What is interesting in the results we obtained is the lowering of the T_1 parameter in the SIH test. It is interpreted that the lowered T_1 indicates the involvement of the GABAergic component in the observed mechanisms [21], which may suggest involvement in emotional behavior [22]. However our results are just a dose-dependent study in healthy mice, what should be included in speculation.

Our investigation did not detected changes in the body weight of mice treated repeatedly for seven days with V, which is in line with the literature [16,23]. It was documented, that changes in body weight linked with V toxicity are observed in prolonged treatment that was 22 and 62 days of the treatment [23].

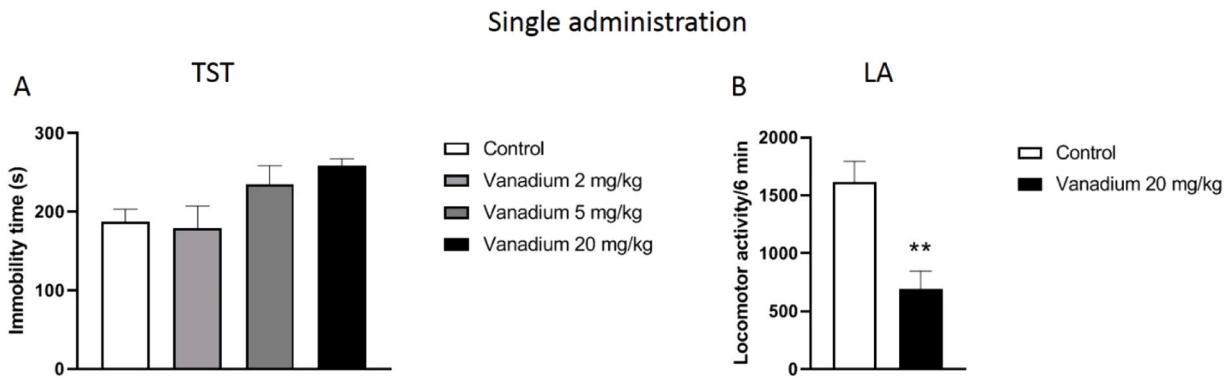

Fig. 4. The effect of treatment with V (2, 5, 20 mg/kg *i.p.*) on behavior of C57Bl/6J mice in the TST (A; n = 4) and LA (B; n = 6). Compound was injected 45 min. before the test, $^{**}P < 0.01$ vs control group.

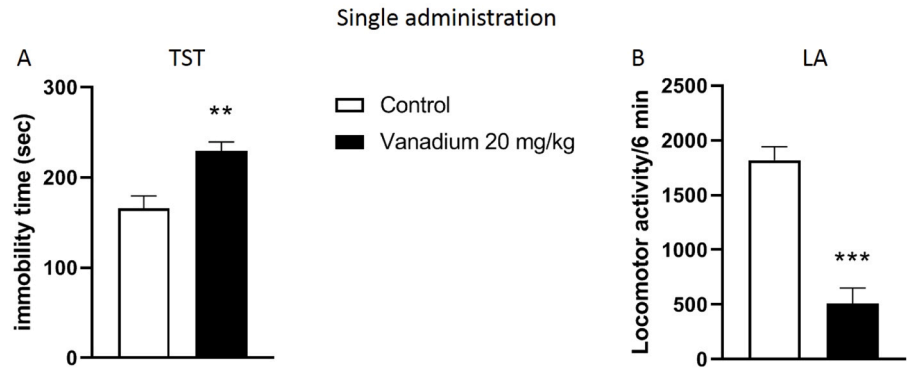

Fig. 5. The effect of treatment with V (20 mg/kg *i.p.*) on behavior of C57Bl/6J mice in the TST (A) and in LA (B). Compound was injected 45 min. before the test, $^{**}P < 0.01$, $^{***}P < 0.001$ vs control group; n = 6.

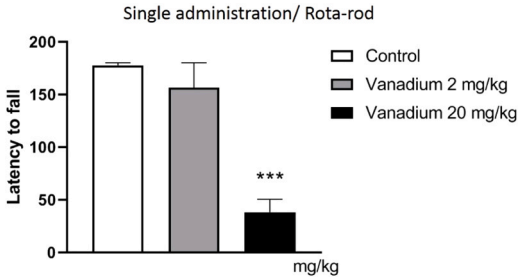

Fig. 6. The effect of treatment with V (2 and 20 mg/kg *i.p.*) on behavior of C57Bl/6 J mice in the Rota-rod. Compound was injected 45 min. before the test, $^{***}P < 0.001$ vs control group; n = 5.

TST is a screening test for searching depressive-like potential of tested substances [24]. Here, a dose-dependent increase in immobility was detected and decreased LA of mice, which all together suggests no effect of V on depressive behavior of healthy mice. However, in the literature, there are discrepancies in the topic [8]. The discrepancies in the topic do not relate to the results of tests examining the effect of V on depressive parameters, in the TST or forced swim test (FST), these results coincide. The differences are due to the interpretation of the results based on locomotor activity (LA). In our study, we observed a decrease in locomotor activity, which skews the positive result in the TST. LA lowering by V is commonly observed [5]. However, in the study of Sampath et al. [8], the activity measured by the open field showed no change. The world literature considers different results of this parameter depending on the route of administration, the number of doses or the chemical form of V [5,8,16,25]. In Sampath et al. [8], V was administered in the form of intracerebroventricular (*i.c.v.*) injection of 3 μl of sodium metavanadate ($NaVO_3$) in artificial cerebrospinal fluid (*aCSF*, 10 mM) into the lateral ventricle. Our study is based on intraperitoneal (*i.p.*) injections with sodium orthovanadate (Na_3O_4V). In addition, from our behavioral observations and pretesting, it appears that V has its strongest effect around 45 min after administration, we then observe "sedation-like behavior", which is why we focused on this time of administration. Sampath's et al. tests were performed 15 min after V administration, and 24 h later [8]. However, to get rid of any doubts we repeated the experiment using a separate cohort of mice and the highest dose of V. Indeed significant decrease in LA brings the conclusion of a lack of effects of V in TST. Furthermore Rota-rod test [26] we performed, confirmed disruptive effects of V in a dose of 20 mg/kg on locomotion of mice.

In order to study the mechanisms of V's action and check its potential to change parameters related to Glu release at the synapse, we performed an electrophysiological study of LTP. The state of knowledge indicating the involvement of Glu-induced excitotoxicity in depression is accepted [27]. However, our results showed no effect of acute injections of V on LTP in cortical slices. Some delay in amplitude was observed which in line with T1 in a SIH test, were enough suggestive to bring our attention to check GABA involvement in a V action. However, the WB results showed no effect of V on GABA metabolism or receptors; therefore, other mechanisms must be involved in the changes observed in the LA, and the Rota-rot, or other brain structures may be susceptible to V after a single exposure rather than FCx. Such suggestions are provided by studies on the effect of vanadium on the state of mitochondria [28,29].

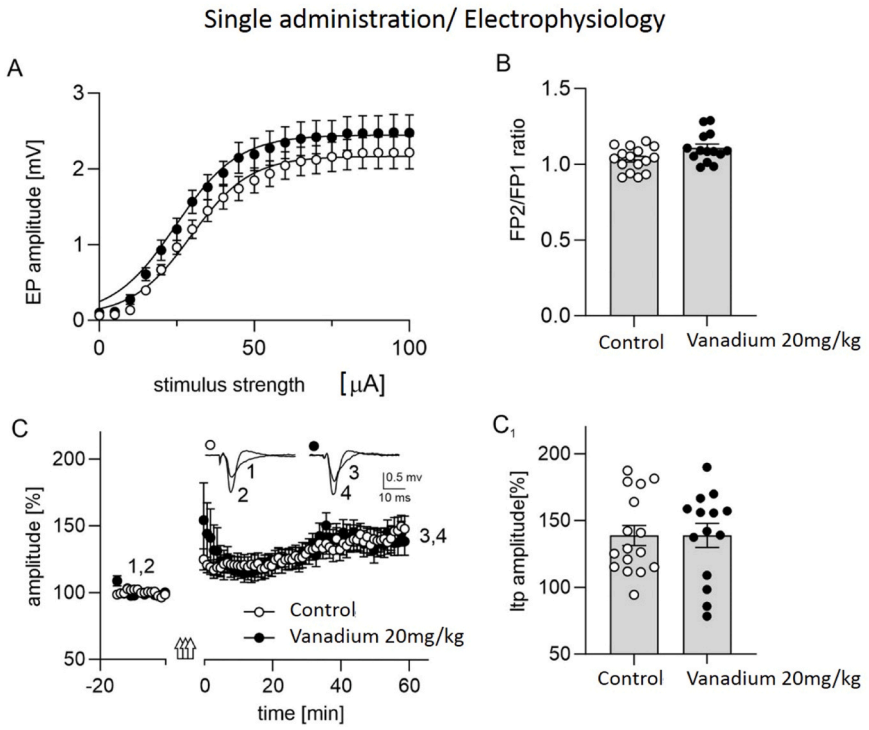

Fig. 7. The effect of V (20 mg/kg) administration on FP recording, paired-pulse stimulation, and LTP induction. (A) Effects of control and V 20 mg/kg treatment on the relationship between stimulus intensity and the amplitude of FPs (B) Summary quantification of the average paired pulse ratio of control and V 20 mg/kg. (C/C_1) Comparisons of LTP analysis on slices received from control and V 20 mg/kg animals. Arrows denote the theta burst, insets show the superposition of averaged FPs recorded in representative experiments at the times indicated by numbers. Control (white circles) n = 16, V 20 mg/kg (black circles) n = 14.

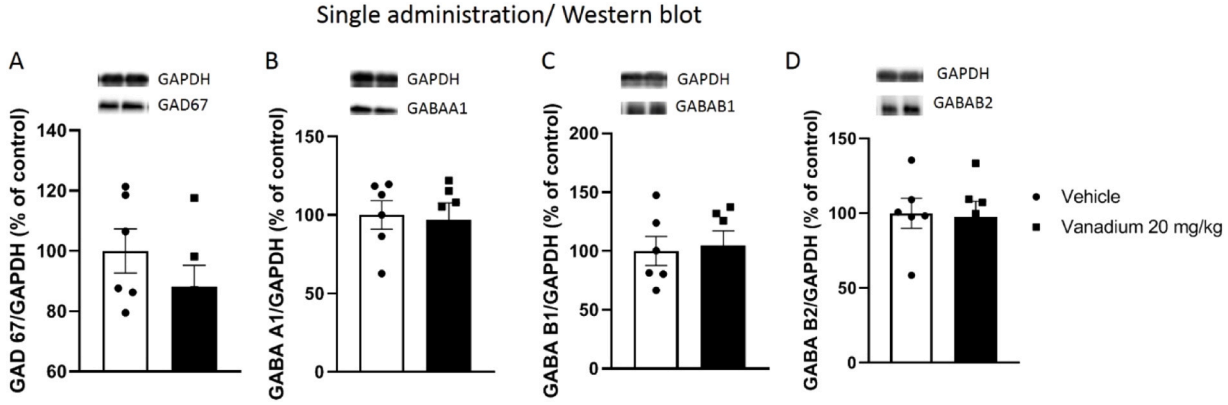

Fig. 8. The effect of single injection with V (20 mg/kg) on the level of GAD67 (A), GABAA1 (B), GABAB1 (C), and GABAB2 (D) in FCx of mice, using Western blot; n = 6.

5. Conclusions

Our study showed no effect of V in the SIH and TST tests, but a significant effect on LA following acute administration in mice. Electrophysiological recordings revealed no changes in cortical LTP after acute V injection. Although results across studies are often contradictory, V appears to play a role in the mechanisms of anxiety and depression. Discrepancies may be due to methodological differences, such as the schedule of administration (acute, repeated or chronic) and dosage form. In addition, V may act differently in healthy vs diseased organisms. This fact highlights the need for further research.

CRediT authorship contribution statement

Patrycja Pańczyszyn-Trzewik: Methodology, Investigation, Formal analysis. **Magdalena Sowa-Kućma:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Bartosz Bobula:** Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Natalia Gałka:** Methodology, Formal analysis. **Katarzyna Stachowicz:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors state no conflict of interest.

Acknowledgments

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