EVALUATION OF ANTI-MANIC ACTIVITY OF PREGABALIN IN A MOUSE MODEL OF METHYLPHENIDATE-INDUCED MANIA

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Abstract:
Mania is a psychiatric disorder which may occur alternately with depression as a bipolar disorder, or much less often as an individual disease. It might be accompanied by other disorders, i.e. schizophrenia, dementia or withdrawal syndrome. Only a few effective drugs are used for the treatment of mania. Patients suffering from bipolar disorder are treated with mood-stabilizing drugs, administered during the course of the disease, and drugs that are implemented when mania or depression episodes occur. Some studies report effectiveness of anticonvulsant drugs in the cessation of mania, thus in our study we assessed the effectiveness of pregabalin in a mouse model of mania induced by administration of metylphenidate (5 mg/kg; s.c). Pregabalin was tested in the forced swim test (75 mg/kg, 100 mg/kg; i.p.) and the elevated plus maze test (75 mg/kg; i.p.) to assess its antidepressant-like and anxiolytic-like properties, respectively. In the elevated plus maze in MPH-treated mice pregabalin significantly reduced time spent in open arms ($p<0.001$ vs. MPH-treated control). In the forced swim test MPH compared to vehicle significantly ($p<0.001$) reduced duration of immobility. In MPH-treated mice pregabalin partially reversed this effect of MPH. This effect was significant only for the dose of 75 mg/kg ($p<0.05$). In the rotarod test neither MPH, nor its combination with pregabalin (75 mg/kg; 100 mg/kg) influenced motor coordination of mice at any speed tested. To conclude our study revealed that pregabalin might reverse manic-like action of MPH related to hyperlocomotion, which may indicate for its possible effectiveness in mania episodes.

Key words: bipolar disorder; mania; anxiety; depression; metylphenidate; pregabalin

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Mania is a psychiatric disorder characterized by occurring alternately with episodes of depression forming a bipolar disorder (BPD). Mania is manifested by elevated and irritable mood, increased activity and restlessness, racing thoughts, increased talkativeness and faster talking, reduced need for sleep, distractibility and self-destructive behavior. In BPD, the episodes of mania and depression usually occur one after another, although their duration is different. Of note, mania can also accompany other diseases, such as schizophrenia, psychotic episodes, dementia, and syndromes due to psychoactive substance abuse. FDA-approved therapy of mania comprises mainly mood stabilizers, i.e. lithium, valproate, carbamazepine, lamotrigine and atypical antipsychotics (aripiprazole, asenapine maleate, clozapine, and olanzapine) [**1**] but other drugs, such as clonazepam [**2**] or verapamil [**3**] are also useful. In addition, the therapy of BPD comprises antidepressant drugs during depressive phase occurring between mania episodes but noteworthy their use is often limited because these medications may increase the risk of mania episodes by converting depression into mania.

The effectiveness of anti-manic drugs correlates with dopaminergic hypothesis of mania [**4**] which assumes that the enhanced dopaminergic neurotransmission results in mania. Unfortunately, the most popular treatment with the use of lithium is often limited because of adverse effects, starting with less dangerous excessive urination, nausea, and diarrhea, also including life-threatening symptoms within the cardiovascular system and kidneys [**5**]. Moreover, with the increasing age of patients, a decreased effectiveness of lithium is observed [**6**]. There are also episodes of dysphoric or mixed mania permanently resistant to lithium therapy [**1**]. In such patients satisfying effects of BPD treatment may

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be achieved using second-generation antiepileptic drugs, such as topiramate [**7**] and lamotrigine [**8**]. Of note, the therapy utilizing these medicines is safer and produces lower incidence of adverse effects. Since there is also less contraindication for these drugs, this type of pharmacotherapy could be more widely available.

The effectiveness of other antiepileptic drugs in mania is much less recognized as compared to classical BPD pharmacotherapy based on mood normalizers. Hence, in our present study we assessed the activity of one of the second-generation antiepileptic drugs – pregabalin (PGB) in a mouse model of mania. Apart from its use in the treatment of seizures, PGB is also effective in numerous non-epileptic conditions, including chronic, neuropathic pain [**9, 10, 11, 12**, **13**, **14**] and anxiety [**11**, **15**]. Of note, anxiolytic properties of PGB may attenuate some symptoms of mania.

To assess potential antimanic-like properties of PGB we used a mouse model of mania induced by the acute treatment with methylphenidate (MPH) [**16**]. This model enables to assess the efficacy of PGB in mania due to abuse of psychoactive substances. Two behavioral tests were utilized to evaluate the effectiveness of PGB under these conditions, namely the forced swim test (FST) to assess potential antidepressant-like activity of PGB in MPH-treated mice, and the elevated plus maze (EPM) test to evaluate its anxiolytic-like properties. Additionally, the influence of PGB on animals' motor coordination was studied to exclude possible motor-impairing properties of this drug.

Materials and methods

Animals and housing conditions

All in vivo procedures were approved by the Local Ethics Committee of the Jagiellonian University in Krakow and the treatment of animals was in full accordance with ethical standards laid down in respective Polish and EU regulations (Directive No. 86/609/EEC). Behavioral experiments were carried out at the Department of Pharmacodynamics, Faculty of Pharmacy, Jagiellonian University Medical College in Krakow. Adult male Albino Swiss (CD-1) mice weighing 18-22 g were purchased from the Animal Breeding Farm of the Jagiellonian University Faculty of Pharmacy. Before behavioral tests the animals were kept in groups of 10 mice in standard plastic cages, and housed under controlled conditions (room temperature of 22±2° C, light/dark (12:12) cycle, lights on at 8 AM, humidity 50-60% and free access to food and water). Experimental groups consisted of 8-10 animals/dose. For the tests the animals were selected randomly. The experiments were performed in a sound-attenuated room under dim light and continuous white noise of 65 dB. After the assay the mice were immediately euthanized by cervical dislocation. All experiments were performed between 9 AM and 3 PM.

Chemicals used in behavioral assays

For in vivo tests MPH (Tocris Bioscience, Germany) was suspended in 1% methylcellulose (Loba Chemie, Germany) solution. PGB (Tocris Bioscience, Germany) was dissolved in 0.9% saline solution. In behavioral assays it was tested at doses 75 mg/kg and 100 mg/kg 60 min after intraperitoneal injection, except for the EPM paradigm, in which only the dose of 75 mg/kg was used. These doses were selected on the basis of available literature data and our previous studies (**19** Zohar et al., 2008). Control mice received saline or methylcellulose.

Behavioral assays

Induction of mania-like symptoms

To induce model of mania, a single, subcutaneous injection of MPH (5 mg/kg) was used 30 min before each behavioral test and 30 min after PGB administration. This fast and effective model was described by Barbosa et al. [**16**]. Modifications of this method have been widely used [**17, 18**]. Animals treated with MPH exhibit features characteristic for mania, i.e. increased locomotor activity and arousal. These symptoms might be also related to other diseases, so acute treatment with MPH is a useful tool for modeling schizophrenia, too [**19**] and the treatment with mood stabilizers results in the remission of these features [**17, 18**].

Elevated plus maze test

EPM enables the assessment of potential anxiolytic-like properties in rodents. This paradigm was performed according to method previously used in our laboratory [**20**]. The apparatus for EPM test (Panlab, Spain) consists of two opposing open (30 cm x 5 cm), and two enclosed arms (30 cm x 5 cm x 25 cm) connected by a central platform (5 cm x 5 cm) whole construction forming the shape of a plus sign. In this test each mouse was individually placed at the central field of the apparatus with the head turned toward one of the closed arms. Animals' behavior was observed and recorded during 5 min-test by a video camera

(Sony Digital, Japan), which was fixed to the wall above the EPM. In this test absolute time spent in open arms was recorded. To exclude the impact of excrements or smell left by a previous mouse on behavior of the next one, the device was cautiously cleaned after each session.

Forced swim test

FST was performed according to a method described by Porsolt et al. [**21**] with some minor modifications [**22**]. This test enabled evaluation of antidepressant-like properties. Mice were dropped individually into glass cylinders (height: 25 cm, diameter: 10 cm) filled with water to a height of 10 cm (23-25°C) and remained there for 6 min. In this assay after an initial 2-min period of vigorous activity, the mice become immobile and the duration of immobility is measured during the final 4 min of the whole 6-min testing period.

The rotarod test

The test was performed according to the method recently described [**23**]. Briefly, the mice were trained daily for three days on the rotarod apparatus (Rotarod apparatus, May Commat RR0711, Turkey; rod diameter: 2 cm) rotating at a constant speed of 18 rotations per minute (rpm). During each training session, the animals were placed on a rotating rod for 3 min with an unlimited number of trials. The proper experimentation was conducted 24 h after the final training trial. Motor coordination of mice was assessed at 6, 18 and 24 rpm. Motor impairments, defined as the inability to remain on the rotating rod for 1 min, were measured at each speed and the mean time spent on the rotarod apparatus was counted in each experimental group.

Statistical analysis

Data analysis of the results was carried out using GraphPad Prism software (ver. 5, CA, USA). Numerical results from the tests are expressed as means ± standard error of the mean (SEM). For the statistical analysis one-way analysis of variance (ANOVA) was used, followed by Dunnett's or Tukey's post-hoc comparisons. $P < 0.05$ was considered significant.

Results

Anxiolytic-like activity (elevated plus maze test)

In EPM the treatment using MPH and PGB compared to non-treated controls significantly influenced time spent in open arms ($F[3,30]=10.39$; $p<0.0001$). MPH compared to vehicle significantly ($p<0.05$) increased time spent in open arms. In contrast to this, MPH combined with PGB significantly reduced time spent in open arms ($p<0.001$ vs. MPH-treated control). In this assay PGB administered alone did not demonstrate significant activity, although a trend towards the prolongation of time spent in open arms was observed (Fig. 1).

Antidepressant-like activity (forced swim test)

In this test a potential antidepressant-like activity of MPH and combined MPH and PGB at doses 75 and 100 mg/kg was assessed (Fig. 2). A significant effect of treatment was observed ($F[3,32]=10.08$; $p<0.0001$). MPH compared to vehicle significantly ($p<0.001$) reduced duration of immobility. In MPH-treated mice PGB partially reversed this effect of MPH. This effect was significant only for the dose of 75 mg/kg ($p<0.05$).

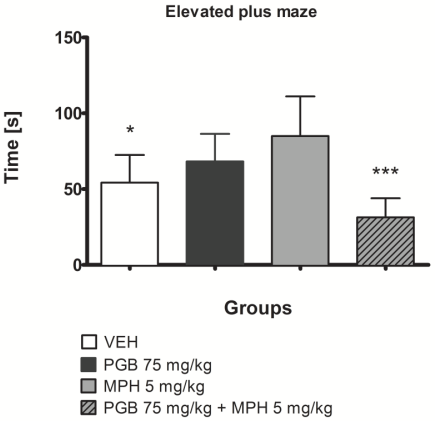

Fig. 1. Effects of MPH (5 mg/kg, s.c.) and combined MPH (5 mg/kg, s.c.) and PGB (75 mg/kg, i.p.) administrations on time spent in open arms in EPM test in mice. Statistical analysis: one-way analysis of variance (ANOVA) followed by Tukey's post hoc analysis. Significance vs. MPH-treated group: * $p<0.05$, *** $p<0.001$; n=8-10.

Rotarod test

In the rotarod test neither MPH, nor its combination with PGB (75 mg/kg; 100 mg/kg) influenced motor coordination of mice at each speed of the rotating rod (6 rpm: $F[3,34]=0.9279$, $p>0.05$; 18 rpm: $F[3,36]=2.471$, $p>0.05$; 24 rpm: $F[3,36]=0.6306$, $p>0.05$).

Discussion

The results of this study confirmed the usefulness of MPH as a simple mouse model of mania

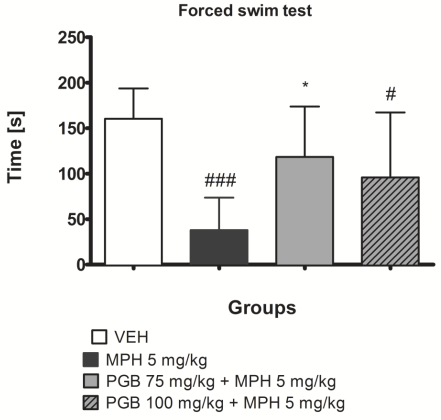

Fig. 2. Effect of MPH (5 mg/kg, s.c.) and combined MPH (5 mg/kg, s.c.) and PGB (75 mg/kg; 100 mg/kg, i.p.) administrations on the duration of immobility measured using FST in mice. Results are shown as duration of immobility (±SEM). Statistical analysis: one-way analysis of variance (ANOVA) followed by Tukey's post hoc analysis. Significance vs. vehicle-treated group: # $p<0.05$, ### $p<0.001$, and vs. MPH-treated group: * $p<0.05$; n=8-12.

that could be applied to test anti-manic activity of drugs for BPD. The role of dopaminergic neurotransmission in mania is still not fully understood. Several dopaminergic agents are known to produce mania-like symptoms, which correlates well to the dopaminergic hypothesis of mania and BPD [**4**]. On the other hand, although bupropion – an inhibitor of dopamine – and norepinephrine transporters increases dopamine level in the central nervous system, it does not trigger off mania in a such a great extent [**24**]. There are also studies showing that dopaminergic agents, e.g. pramipexole [**25**], or even chronic MPH effectively attenuate episodes of mania in BPD [**26**].

In rodents a single injection of MPH mimics the main symptoms observed in humans suffering from mania. In our study we observed that MPH-treated mice spent significantly more time in open arms of the EPM as compared to control mice, which might indicate that MPH induces anxiolytic-like behavior. Of note, in mice not treated with MPH, PGB slightly prolonged the time spent in open arms, which might also confirm its anxiolytic-like properties observed in previous studies [15, 27, 28, 29]. In contrast, mice treated with combined PGB and MPH showed anxiogenic behavior as they spent less time in open arms of the EPM as compared to vehicle-treated mice, as well as to MPH-treated mice and PGB-treated mice. Possible explanation for this effect might be that in EPM anxiolytic-like properties of PGB are observed in naïve mice but not in mice showing features of mania. On the other hand, PGB might also reduce MPH-induced hyperlocomotion and this activity might be also an explanation for the observed reduced time spent in open arms in those mice.

In the FST MPH demonstrated a highly significant activity. However, this effect seems to be a false positive one and is typical for psychostimulant drugs [**30**]. MPH-induced hyperlocomotion observed previously in the locomotor activity test (data not shown) might be responsible for the decreased immobility observed in FST. In FST, in MPH-treated mice PGB (75 mg/kg) was able to reverse the effect of MPH on the duration of immobility.

According to available literature, the development of BPD and mania is related to the imbalance between cholinergic and dopaminergic systems [**4**]. Stronger activity of the latter is associated with the appearance of manic episodes [31].

Although some newer anticonvulsant drugs are used in therapy of BPD, by influencing not only main BPD features but also other co-existing symptoms, such as anxiety, pain etc., they are preferred for chronic, stabilizing therapy rather than interruption of mania [**1**]. The involvement of GABAergic neurotransmission in BPD and mania is still unclear [**32**]. Untreated patients present decreased level of GABA [**33**]. Interestingly, the involvement of drugs modulating GABA-ergic transmission led to GABA reduction [**34**]. In our study PGB was used. It should be noted that the mechanism of its action involves interaction with $\alpha_2\delta$ subunit-containing voltage-dependent calcium channels. Furthermore, PGB increases the density of GABA transport proteins and the rate of functional GABA transport [**35**]. Drugs interacting with L-type calcium channels reveal high anti-manic activity and are becoming a new trend in the therapy of BPD [**3**]. Thus gabapentanoids, including PGB, are of interest not as clear GABAergic agents, but rather as inhibitors of voltage-dependent calcium channels. Available data indicate that in contrast to lamotrigine which is an antiepileptic drug effective mainly in stabilizing therapy in patient with tendency to depressive episodes [**36**], PGB was active both in mania and depressive episodes, in patient resistant to other therapies [**37**]. Other anticonvulsant drug

– levetiracetam was inactive in BPD [**36**].

Presented results demonstrated that PGB possessed weak antimanic-like properties in a mouse model of mania induced by MPH. This effect was observed in FST but not EPM, which indicates that PGB interferes more with symptoms of depressive phase of BPD than other symptoms that accompany BPD, e.g. anxiety. However, to clearly specify a possible role of PGB in the treatment of BPD patients further investigation is needed.

Resumo

Manio estas psikiatra perturbo, kiu povas okazi alterne kun depresio kiel bipolara perturbo aŭ multe pli malofte kiel memstara malsano. Ĝi povos esti akompanita de aliaj perturboj, nome skizofrenio, demenco aŭ retirsindromo. Nur kelkaj efikaj drogoj estas uzataj por la kuracado de manio. La pacientoj suferantaj pro bipolara perturbo estas kuracataj per animstatstabiligantaj drogoj aplikataj dum la kuro de la malsano kaj drogoj, kiuj estas efikaj kiam estas epizodoj de manio aŭ depresio. En certaj esploroj oni konstatis efikecon de antikonvulsiaj drogoj por la ĉesigo de manio, tial en nia studo ni taksis la efikecon de pregabalino en musmodelo de manio induktita per administrado de metilfenidato (5 mg / kg; s.c). Pregabalino estis provita en la devigita naĝtesto (75 mg / kg, 100 mg / kg; ip) kaj la levita pluslabirinto-testo (75 mg/kg; ip) por pritaksi ĝiajn antidepresivo-similajn kaj anksiolitiko-similajn ecojn. In la levita pluslabirinto en MPH-traktita musoj pregabalino signife reduktis la tempon pasigitan en malfermitaj brakoj ($p < 0.001$ kontraŭ MPH-traktita kontrolo).

En la devigita naĝtesto MPH kompare al kontrolo ($p < 0.001$) estis reduktita la daŭro de senmoveco. En/ĉe musoj traktitaj per MPH pregabalino parte inversigis la efikon de MPH. Tiu efiko estis signifa nur por la dozo de 75 mg / kg ($p < 0.05$). En la rotacia testo nek MPH, nek lia kombino kun pregabalino (75 mg / kg; 100 mg / kg) influis la movkapablon de musoj en iu ajn ekzamenita rapideco. Konklude nia studo malkaŝis, ke pregabalino povus inversigi maniosimila efiko de MPH rilate al troa moviĝemo, kiu povas indiki eblan efikecon en maniaj epizodoj.

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