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Original research article

Reboxetine and its influence on the action of classical antiepileptic drugs in the mouse maximal electroshock model

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ABSTRACT

Background: Our previous studies revealed that different classes of antidepressant drugs differently affect seizure phenomena. Continuing our research in this field, in the present study we wanted to investigate the influence of acute and chronic treatment with reboxetine, a selective norepinephrine reuptake inhibitor, on the anticonvulsant action of classical antiepileptic drugs.
Methods: Experiments were conducted in the model of electroconvulsive threshold and maximal electroshock in mice. Motor coordination was evaluated in the chimney test and long term memory in the step-through passive avoidance task. Brain concentrations of antiepileptic drugs were detected by fluorescence polarization immunoassay.
Results: Acute treatment with reboxetine (8–16 mg/kg) significantly raised the electroconvulsive threshold. In contrast, chronic reboxetine (2–16 mg/kg) did not affect this parameter. Single administration of the antidepressant applied at its subthreshold doses enhanced the action of valproate, carbamazepine and phenobarbital. The antielectroshock effect of phenytoin was also potentiated by acute reboxetine, but only at doses increasing the threshold. Repeated administration of reboxetine (8–12 mg/kg) enhanced the anticonvulsant action of carbamazepine, but not that of three remaining antiepileptic drugs. Neither acute nor chronic reboxetine changed the brain concentrations of valproate, carbamazepine, phenytoin or phenobarbital. Therefore, all revealed interactions seem to be pharmacodynamic. In terms of undesired effects, acute/chronic reboxetine and its combinations with classical antiepileptic drugs did not significantly impair motor performance or long-term memory in mice.
Conclusions: As far as the obtained data can be extrapolated into clinical conditions, it seems that reboxetine may be safely used in the treatment of depressive disorders in epileptic patients.

Introduction

Many antidepressant drugs, applied at their therapeutic doses, have exhibited anticonvulsant action in many models of experimental seizures [1]. For the first time, the antielectroshock effect of some tricyclic antidepressants was reported 45 years ago [2]. This observation encouraged many clinicians to treat depression co-existing with epilepsy. As a result, several studies demonstrated that most antidepressants of first and second generation did not affect seizure frequency in epileptic patients over one year of administration [3]. Fluoxetine has been even found to improve the course of seizures [4]. Growing body of evidence suggests that the proper antidepressant therapy may improve the outcome of both disorders [5].

For depression, the exact mechanism of action of antidepressant drugs remains unclear. The most documented hypothesis refers to the enhancement of monoamine neurotransmission [6]. Similarly, the exact mechanism of anticonvulsant action of antidepressants has not been established so far. However, available data indicate that it may also be related to increased monoaminergic activity in the brain. For instance, the negative correlation between brain serotonin/norepinephrine levels and seizure severity has been proved in several electrical, chemical and genetic seizure models. Increased brain concentrations of serotonin and/or norepinephrine attenuated seizures in most animal models with the exception of tottering mice [7–12]. In line with these observations, almost all selective serotonin reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake

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inhibitors (SNRIs) were reported to raise the convulsive threshold and enhance the protective effect of several antiepileptic drugs [5,13–16]. Similar action was shown by mianserin. This antidepressant blocks α_2-adrenergic autoreceptors and heteroreceptors, thus enhancing both noradrenergic and serotonergic neurotransmission [17]. Therefore, the question arose as to whether the next generation of antidepressant drugs, norepinephrine reuptake inhibitors (NRIs), could affect experimental seizures in a comparable manner.

The first drug described as a selective NRI was reboxetine. It has been shown to have negligible affinity for serotonin and dopamine uptake sites. Moreover, reboxetine has only weak affinity for muscarinic, histaminergic H_1, adrenergic alpha$_1$, and dopaminergic D_2 receptors. Reboxetine has proved an antidepressant action in three animal models of depression: the tail-suspension test, forced swimming, and the DRL72 operant responding test [18]. This drug has been approved for the treatment of major depression in many European countries, but the application for approval was rejected in the United States. Reboxetine has been also found useful in narcolepsy, ADHD, panic attack disorder and depression in patients with Parkinson's disease [19]. Although many previous reports have documented that effectiveness of reboxetine in major depressive illness [20] is equal to other antidepressants, the recent meta-analysis suggests that this antidepressant is ineffective and potentially harmful for the treatment of acute depression [21]. However, regardless of the future of reboxetine in clinical practice, the drug still remains a very valuable tool for psychopharmacological research.

In previous studies we investigated the effect of different classes of antidepressants on the antielectroshock action of some antiepileptic drugs. Obtained results prompted us to examine the influence of enhanced noradrenergic neurotransmission on the anticonvulsant action of valproate, carbamazepine, phenytoin and phenobarbital against the maximal electroshock-induced seizures in mice. Results of the present study can also help to assess the usefulness of reboxetine in the treatment of depression in patients with co-existing epilepsy.

Materials and methods

Animals

Experiments were carried out on male Swiss mice weighing 20–25 g. The animals were housed in colony cages with free access to food (chow pellets) and tap water. The experiments started after 7-day acclimatization to standardized laboratory conditions (temperature 21 ± 1 °C, a natural light–dark cycle). The tested groups, consisting of eight animals, were randomly assigned. All experiments were performed in spring months (from March to June) between 9:00 a.m. and 2:00 p.m. Each mouse was used only once. The Local Ethical Committee of Lublin Medical University approved all experimental procedures of this study.

Drugs

The following drugs were used in the study: reboxetine (Edronax, Pharmacia & Upjohn, NJ, USA), carbamazepine, phenytoin, valproate magnesium (all three drugs from Sigma–Aldrich, St. Louis, MO, USA), and phenobarbital (Polfa, Kraków, Poland). Valproate was dissolved in distilled water, while reboxetine, carbamazepine, phenytoin, and phenobarbital were suspended in a 1% solution of Tween 80 (Sigma–Aldrich, St. Louis, MO, USA). All drugs were prepared each day as fresh solutions or suspensions and administered intraperitoneally (*ip*) in a volume of 0.01 ml/g body weight. Reboxetine was applied in a single injection 30 min before tests (acute protocol), or it was given for 14 days every 24 h, on the last day – 30 min before tests (chronic protocol). Antiepileptic drugs were injected only once, phenytoin – 120 min, phenobarbital – 60 min, while valproate and carbamazepine – 30 min before electroconvulsions and behavioral tests.

Electroconvulsive threshold and maximal electroshock seizure test

Electrically induced seizures in rodents are a well-known animal model of tonic-clonic convulsions [22].

Electroconvulsions were produced by a Hugo Sachs generator (Rodent Shocker, type 221, Freiburg, Germany). An alternating current (50 Hz, fixed current intensity of 25 mA, maximum stimulation voltage of 500 V, 0.2 s stimulus duration) was delivered via ear-clip electrodes. The generator is equipped with an internal stabilization system providing self adjustable constant current stimulation, i.e. changes in impedance did not alter current intensity. Tonic hindlimb extension (the hindlimbs of animals outstretched 180° to the plane of the body axis) was considered as the endpoint.

The electroconvulsive threshold was evaluated as (CS_{50}), which is a current strength (expressed in mA) necessary to induce tonic convulsions in 50% of animals. To estimate the electroconvulsive threshold, at least four groups of mice (eight animals per group) were challenged with currents of various intensities (4–12 mA). Subsequently, an intensity–response curve was calculated on the basis of the percentage of convulsing animals.

The protective efficacy of antiepileptic drugs was determined as ability to protect 50% of animals against the maximal electroshock-induced tonic hindlimb extension and expressed as respective values of the median effective dose (ED_{50}). To evaluate each ED_{50} value (in mg/kg), at least four groups of mice received progressive doses of an antiepileptic drug and were challenged with the maximal electroshock test. A dose–response curve was constructed based on the percentage of mice protected [23].

Chimney test

The effect of antiepileptic drugs, reboxetine, and combinations of reboxetine with antiepileptics on motor coordination was quantified in the chimney test [24]. In this test, animals had to climb backward up the plastic tube (25 cm length, 3 cm inner diameter). Motor impairment was indicated by the inability of mice to perform this test within 60 s.

Step-through passive-avoidance task

The effect of antiepileptic drugs, reboxetine and reboxetine/antiepileptics combinations on time of retention was assessed in the step-through passive-avoidance that may be recognized as a measure of long-term memory [25]. The drug-treated mice were placed in an illuminated box (10 cm × 13 cm × 15 cm) connected to a large dark box (25 cm × 20 cm × 15 cm), which was equipped with an electric grid floor. Entrance of the animals to the dark box was punished by an electric foot shock (0.6 mA for 2 s; facilitation of acquisition). The mice that did not enter the dark compartment within 60 s were excluded from the experiment. On the next day (24 h later), the same animals, without any treatment, were put into the illuminated box and observed up to 180 s. The median time to enter the dark box was subsequently calculated. The control (vehicle-treated animals) did not enter the dark box within the observation time limit. The results were shown as medians with 25th and 75th percentiles.

Measurement of brain concentrations of antiepileptic drugs

Mice were administered one of the conventional antiepileptic drugs + vehicle or the respective antiepileptic drug + reboxetine.

The antidepressant was applied in a single injection or chronically for 14 days. Animals were killed by decapitation at times respective to those scheduled for the maximal electroshock test. Brains were removed from skulls, weighed, and homogenized using Abbott buffer (Abbott Laboratories, North Chicago, IL, USA – 2:1 vol/weight) in an Ultra-Turrax T8 homogenizer (IKA-WERKE, Stauffen, Germany). The homogenates were centrifuged at 10,000 × *g* for 10 min. The supernatant samples (75 μl) were analyzed by fluorescence polarization immunoassay for phenytoin, carbamazepine, valproate, or phenobarbital content using a TDx analyzer and reagents exactly as described by the manufacturer (Abbott Laboratories, North Chicago, IL, USA). All concentrations of antiepileptic drugs are expressed in micrograms per milliliter of brain supernatants as means ± standard deviation (SD) of at least eight determinations.

Statistics

ED_{50} values with their respective 95% confidence limits were estimated using computer log-probit analysis according to Litchfield and Wilcoxon [23]. Subsequently, standard error (SEM) of the mean values were calculated on the basis of confidence limits and ED_{50} values were compared with the Student's *t*-test [26].

Qualitative variables from the chimney test were compared by the Fisher's exact probability test, whereas the results obtained in the step-through passive-avoidance task were statistically evaluated using the Kruskal–Wallis nonparametric analysis of variance (ANOVA) followed by *post hoc* Dunn's test.

Total brain concentrations of antiepileptic drugs were evaluated by the use of the unpaired Student's *t*-test. The significance level was set at $p \leq 0.05$.

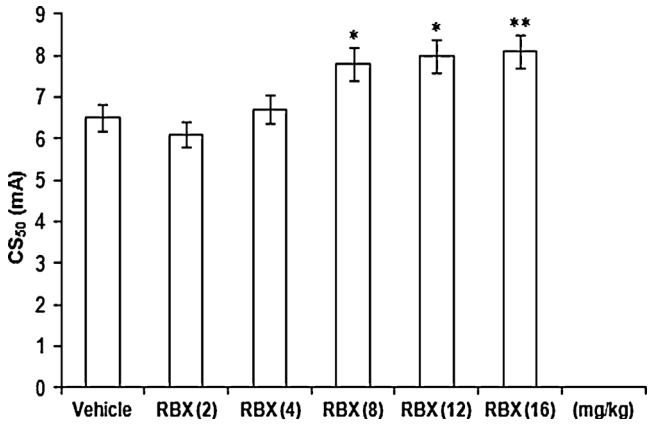

Fig. 1. Effect of the acute treatment with reboxetine (RBX) on the electroconvulsive threshold in mice. Data are presented as median current strength (CS_{50} with SEM) producing tonic convulsions in 50% of animals. RBX was injected *ip* 30 min before the test. $^{*}p < 0.05$, $^{**}p < 0.01$ vs. control.

Results

Electroconvulsive threshold test

Acute reboxetine applied at doses of 8–16 mg/kg significantly increased threshold for electroconvulsions from 6.5 ± 0.35 mA to 7.8 ± 0.41, 8.0 ± 0.43 and 8.1 ± 0.32 mA, respectively (Fig. 1). However, chronic reboxetine administered at the dose range of 2–16 mg kg did not affect the threshold (Table 1).

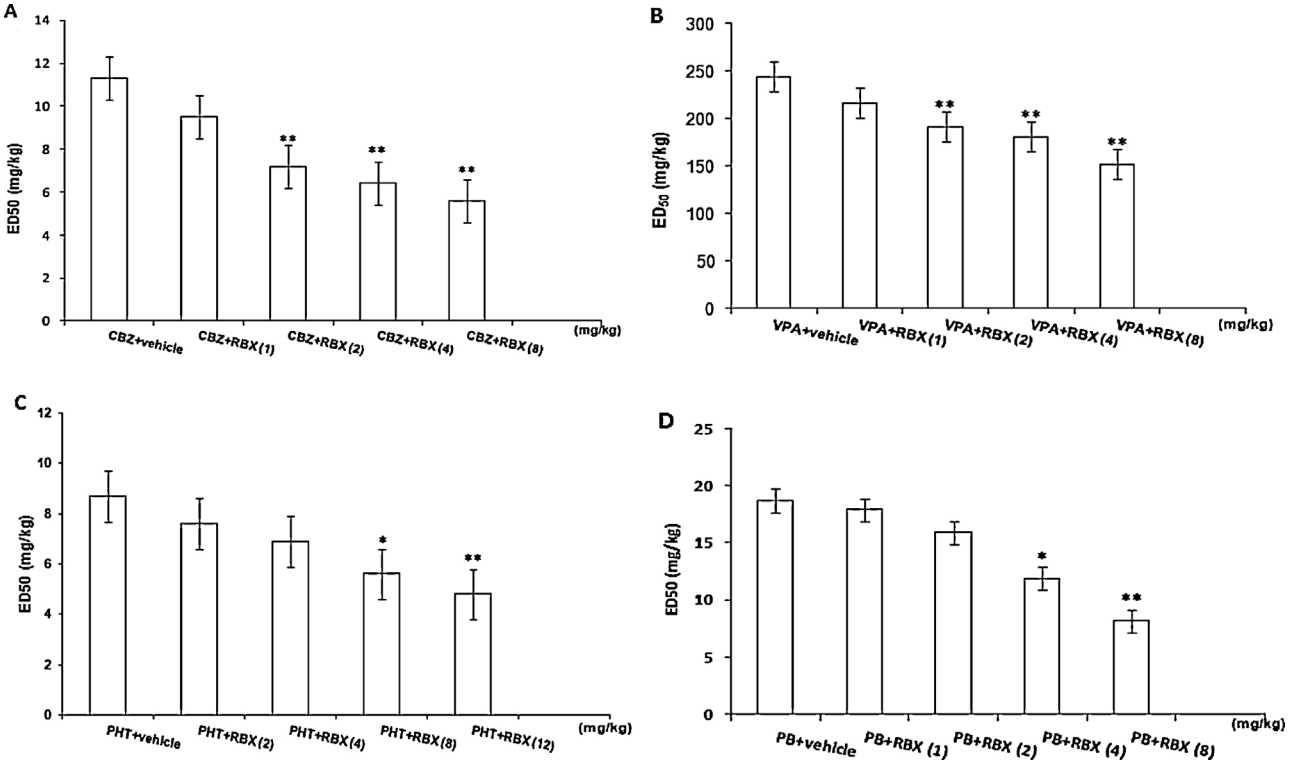

Fig. 2. Effect of the acute treatment with reboxetine (RBX) on the anticonvulsant action of carbamazepine – CBZ (A), valproate – VPA (B), phenytoin – PHT (C), and phenobarbital – PB (D) against maximal electroshock-induced seizures in mice. Data are presented as median effective doses (ED_{50} doses with SEM values), at which antiepileptic drugs alone and in combinations with RBX protected 50% of animals against seizures. All drugs were administered *ip*: RBX, VPA and CBZ – 30 min, PB – 60 min, and PHT – 120 min before electroconvulsions. $^{*}p < 0.05$, $^{**}p < 0.01$ vs. control (animals treated with an antiepileptic plus saline).

Maximal electroshock test

Both acute and chronic reboxetine administered alone were ineffective in the maximal electroshock test in mice. Single administration of the antidepressant at its subprotective doses in the electroconvulsive threshold (2 and 4 mg/kg) significantly enhanced the anticonvulsant action of valproate, decreasing its ED_{50} from 244.3 ± 11.22 mg/kg to 191.5 ± 7.62 and 181.0 ± 8.28 mg/kg, respectively. Acute reboxetine applied at the same doses diminished the ED_{50} value of carbamazepine from 11.3 ± 0.59 mg/kg to 7.2 ± 0.57 and 6.4 ± 0.71 mg/kg. Single administration of reboxetine given at the dose of 4 mg/kg enhanced the action of phenobarbital, reducing its ED_{50} from 18.7 ± 1.51 mg/kg to 11.9 ± 1.62 mg/kg. In contrast, the antidepressant applied at subprotective doses failed to affect the action of phenytoin. However, the antielectroshock action of phenytoin was enhanced by reboxetine applied at higher (protective) doses of 8 and 12 mg/kg (Fig. 2).

Repeated treatment with reboxetine, applied at the dose range 2–16 mg/kg, did not change ED_{50} values of valproate (240.2 ± 14.47 mg/kg), phenobarbital (24.6 ± 2.13 mg/kg) or phenytoin (9.9 ± 0.86 mg/kg) (Table 2). However, chronic reboxetine (at 8 and 12 mg/kg) potentiated the antielectroshock action of carbamazepine, decreasing its ED_{50} from 11.9 ± 0.85 mg/kg to 9.3 ± 0.59 and 8.7 ± 0.66 mg/kg, respectively (Fig. 3).

Chimney test and step-through passive-avoidance task

Reboxetine alone (in single or repeated administration) and classical antiepileptic drugs administered alone (at doses equal to their ED_{50} values) or in combinations with acute or chronic reboxetine did not cause any significant motor impairment or long-term memory in mice. In acute study protocol, the greatest motor impairment was observed in 20% of mice after the combined treatment of reboxetine (4 mg/kg) with valproate (181 mg/kg) or carbamazepine (6.4 mg/kg). Combined treatment of chronic reboxetine (8 mg/kg) and valproate (202.7 mg/kg) or phenytoin (10.2 mg/kg) led to an insignificant motor deficit in 30% of mice. As regards long-term memory, the median retention time was slightly lower than the control value of 180 s only after the combined treatment of acute reboxetine (4 mg/kg) with valproate (181 mg/kg) or phenytoin (5.6 mg/kg) and chronic reboxetine (8 mg/kg) with phenytoin (10.2 mg/kg). The respective medians with 25th, 75th percentiles were calculated as 158 (137, 180), 174 (148, 180), and 171 (142, 180). The differences between these values and the control value did not reach the level of significance (data not shown).

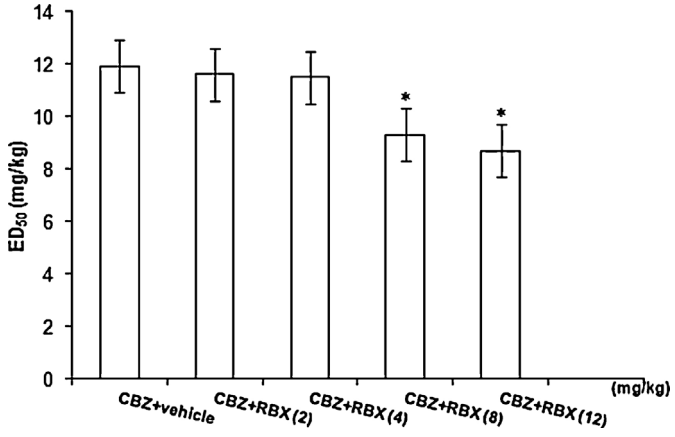

Fig. 3. Effect of the chronic treatment with reboxetine (RBX) on the anticonvulsant action of carbamazepine (CBZ) against maximal electroshock-induced seizures in mice. Data are presented as median effective doses (ED_{50} doses with SEM values), at which CBZ alone and in combinations with RBX protected 50% of animals against seizures. All drugs were administered *ip*, RBX for 14 days and CBZ in a single injection 30 min before electroconvulsions. $^{*}p < 0.05$ vs. control (animals treated with CBZ plus saline).

Table 1
The effect of chronic treatment with reboxetine on the electroconvulsive threshold in mice.

Treatment (mg/kg)	CS_{50} (mA)
Vehicle	6.8 ± 0.31
RBX (2)	7.1 ± 0.32
RBX (4)	6.9 ± 0.42
RBX (8)	6.8 ± 0.41
RBX (12)	7.2 ± 0.33
RBX (16)	7.3 ± 0.28

Results are expressed a current strength inducing tonic-clonic convulsions in 50% of tested mice (CS_{50}) ± SEM RBX, reboxetine.

Table 2
Effect of chronic reboxetine on the anticonvulsant action of conventional antiepileptic drugs in the maximal electroshock-induced seizures in mice.

Treatment (mg/kg)	ED_{50} (mg/kg)
VPA + vehicle	240.2 ± 12.67
VPA + RBX (2)	244.6 ± 7.68
VPA + RBX (4)	231.2 ± 10.05
VPA + RBX (8)	202.7 ± 10.95
VPA + RBX (12)	203.1 ± 8.08
VPA + RBX (16)	210.3 ± 11.42
PHT + vehicle	9.9 ± 0.86
PHT + RBX (2)	9.7 ± 0.69
PHT + RBX (4)	9.9 ± 0.86
PHT + RBX (8)	10.2 ± 0.90
PHT + RBX (12)	9.4 ± 0.94
PHT + RBX (16)	9.6 ± 0.48
PB + vehicle	24.6 ± 2.13
PB + RBX (2)	25.5 ± 1.63
PB + RBX (4)	24.3 ± 1.56
PB + RBX (8)	23.7 ± 1.51
PB + RBX (12)	22.7 ± 2.13
PB + RBX (16)	23.3 ± 1.48

Results are expressed as median effective doses with SEM values. VPA, valproate; PHT, phenytoin; PB, phenobarbital; RBX, reboxetine.

Influence of reboxetine on total brain concentrations of antiepileptic drugs

Neither acute nor chronic reboxetine affected the brain concentrations of valproate, carbamazepine, phenobarbital and phenytoin (Table 3).

Discussion

Results presented herein demonstrated that single application of reboxetine dose-dependently increased the threshold for electroconvulsions, while repeated treatment did not affect this parameter. Acute reboxetine administered at its subprotective doses enhanced the antielectroshock action of valproate, carbamazepine and phenobarbital. On the other hand, the antidepressant given chronically potentiated the action of carbamazepine only. It is worth stressing that all interactions between reboxetine and antiepileptic drugs seem to have a pharmacodynamic nature. Reboxetine did not significantly alter brain levels of antiepileptic drugs tested in the study. Although we cannot exclude that some or all classical antiepileptic drugs increase the brain level of reboxetine, it is not very probable that such an increase could enhance the antielectroshock action of these antiepileptics. Reboxetine did not present its own anticonvulsant effect in the

Table 3
Effect of acute and chronic reboxetine on the brain concentrations of conventional antiepileptics in mice.

Acute treatment (mg/kg)	Brain concentration (μg/ml)	Chronic treatment (mg/kg)	Brain concentration (μg/ml)
VPA (181.0) + vehicle	228.10 ± 38.64	VPA (202.7) + vehicle	267.60 ± 31.31
VPA (181.0) + RBX (4)	257.30 ± 35.11	VPA (202.7) + RBX (8)	274.80 ± 34.68
CBZ (6.4) + vehicle	3.05 ± 0.61	CBZ (9.3) + vehicle	3.75 ± 0.67
CBZ (6.4) + RBX (4)	3.13 ± 0.58	CBZ (9.3) + RBX (8)	3.96 ± 0.42
PB (11.9) + vehicle	18.25 ± 2.38	PB (23.7) + vehicle	33.25 ± 1.38
PB (11.9) + RBX (4)	18.47 ± 2.84	PB (23.7) + RBX (8)	34.47 ± 1.84
PHT (5.6) + vehicle	1.85 ± 0.13	PHT (10.2) + vehicle	2.35 ± 0.19
PHT (5.6) + RBX (8)	1.96 ± 0.21	PHT (10.2) + RBX (8)	2.56 ± 0.38

Data are presented as means ± S.D. of at least eight determinations. Statistical analysis of the brain concentrations of antiepileptic drugs was performed using the unpaired Student's *t* test. RBX, reboxetine; CBZ, carbamazepine; PB, phenobarbital; PHT, phenytoin; VPA, valproate.

maximal electroshock, whereas being given at the dose used in combinations with antiepileptics (8 mg/kg) was slightly protective only after single administration.

The anticonvulsant action of most antidepressant drugs is usually explained by an increase of serotonergic and/or noradrenergic neurotransmission. Furthermore, serotonergic and/or noradrenergic deficits are likely to lead to both affective and epileptic disorders [1,27,10]. However, an interesting observation was that the effect of a given antidepressant drug on the electroconvulsive threshold depends on whether this drug was administered only once or repeatedly. Some representatives of SSRIs, SNRIs, and NRIs increased the electroconvulsive threshold only after single administration. This phenomenon applies, for example, to fluoxetine [13,16], milnacipran [14], and reboxetine. Venlafaxine, an SNRIs, was a kind of exception because it increased the threshold also after repeated administration [15]. On the other hand, trazodone, a representative of serotonin antagonist and reuptake inhibitors (SARIs), showed an inverse property – it increased the threshold after chronic but not acute administration [28]. Such inconsistent results suggest that not only increased monoaminergic neurotransmission but also other unrecognized mechanisms contribute to this effect. One of them may be up-regulation of allopregnanolone biosynthesis at the time of therapy with SSRIs [29].

The question arises why the protective effect of some antidepressant drugs disappeared after chronic treatment. A quite probable hypothesis refers to the net effect of adaptive changes in serotonergic and noradrenergic receptors. As a result, the development of antidepressant action is accompanied by loss of anticonvulsant properties. According to literature, receptor adaptive changes primarily include decreased responsiveness of β_1 and 5-HT_2 receptors and increased sensitivity of 5-HT_1 receptors [30,31]. Nevertheless, adaptation may be specific for each antidepressant. In the case of fluoxetine neural remodeling is associated with desensitization of inhibitory 5-HT_{1A} receptors [32] and a regional up-regulation of β_1-adrenergic receptors [33]. On the other hand, repeated administration of milnacipran leads to desensitization of the presynaptic α_2-heteroreceptors located on serotonergic terminals. Thus, milnacipran enhances serotonergic but reduces noradrenergic neurotransmission [34]. All mentioned adaptive changes may contribute to the loss of anticonvulsant action observed after chronic treatment with the two antidepressants. According to this line of reasoning, repeated administration of venlafaxine fails to attenuate $5HT_{1A}$ receptor [35], which may, in turn, result in persistent anticonvulsant activity of this drug. Finally, one of the plausible explanations as to why chronic reboxetine did not affect the electroconvulsive threshold may be gradual desensitization of β-adrenoceptors observed during long-term therapy with this drug [36]. It cannot be, of course, excluded that the brain concentration of antidepressant drugs decreased during the chronic treatment, thus contributing to the loss of their anticonvulsant properties. But if so, the same drugs applied at higher doses should increase the electroconvulsive threshold. However, such effect was not observed.

Antidepressant drugs, whether given once or repeatedly, can potentiate the anticonvulsant action of classical antiepileptic drugs. Such action was demonstrated in the case of acute and chronic fluoxetine [13,16], milnacipran and venlafaxine [14,15]. Some of these interactions had a pharmacokinetic nature, others had a pharmacodynamic background. Surprisingly, chronic mianserin as well as acute and chronic trazodone showed quite different effect. Both drugs attenuated the action of some conventional antiepileptics [17]. This strongly suggests that the combined treatment with antidepressant and antiepileptic drugs can affect seizures in a different way than antiepileptic alone. The final effect of a given combination cannot be predicted on the basis of the theoretical considerations about component drug mechanisms of action.

Results of experimental studies often serve as a basis for the formulation of clinical theses. Our results could suggest that reboxetine, as a drug with positive pharmacological profile in a mouse model of seizures, may be also a good drug candidate for the treatment of depression in epileptic patients. Nevertheless, in light of recent studies, we cannot draw such a conclusion. Initially, reboxetine has been claimed to show superior efficacy to placebo and at least similar efficacy to other antidepressant drugs [37]. However, the recent German meta-analysis [21], analyzing not only published, but also unpublished data from the manufacturer of reboxetine, revealed that the former evidence overestimated benefits of this antidepressant. In fact, reboxetine was proved to be inferior to SSRIs for remission and response rates, and to SSRIs and placebo for withdrawals and adverse effects [21]. However, it does not diminish the scientific value of obtained results – reboxetine, most probably due to enhanced noradrenergic neurotransmission, exhibited its own anticonvulsant properties and increased the antielectroshock activity of some classical antiepileptic drugs.

Conflict of interest

None of the authors has any conflict of interest.

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