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Concomitant use of carbamazepine and olanzapine and the effect on some behavioral functions in rats

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Abstract:
As shown in clinical studies, combinations of first generation normothymics (carbamazepine – CBZ) with atypical neuroleptics (olanzapine – OLA) lead to improvements in approximately half of patients treated for relapses of bipolar affective disease. Our previous studies have shown OLA to have an antidepressant effect when administered at a dose of 0.5 mg/kg only upon single administration; the effect did not last throughout chronic administration, whereas CBZ administered at a dose of 30 mg/kg showed an antidepressant effect only after 7 days of administration. As shown in our previous studies, both OLA and CBZ improve memory in rats but only after chronic administration. The improved antidepressant effect of many drugs, including OLA and CBZ used in combined therapy – as observed in our clinic – as well as confirmed evidence of OLA's and CBZ's positive effects on cognitive functions in humans and animals substantiated commencement of research on defining the effect of combined administration of OLA and CBZ on sedation (tested in a locomotor activity test), antidepressant effect (Porsolt test) and spatial memory (Morris test) in animals. The tests were performed on male Wistar rats. It was found that in combined administration of CBZ and OLA for 7 and 14 days, OLA would completely prevent the CBZ's sedative effect. With combined administration of CBZ and OLA, both as a single dose and after prolonged treatment for 7 days, a significant reduction in immobility time was observed. Combined administration of CBZ and OLA did not improve memory in rats that received these drugs in a single dose, whereas statistically significant differences were observed in the chronic experiments. It can be assumed that the observed effects of combined administration of CBZ and OLA may be due to the pharmacokinetic interactions, but further studies are necessary to confirm these assumptions.

Key words:
carbamazepine, olanzapine, concomitant use, memory function, antidepressant activity, motor coordination, rats

Introduction

Previous experience treating bipolar affective disease indicates that, in some patients, monotherapy with a normothymic drug alone does not yield optimal results, and improvement is achieved only with combined therapy. This applies in particular to treating mania and preventing its relapses [34]. In mania therapy, usually combinations of first generation normothymics (lithium and valproate) or combined therapy (lithium or valproate with a neuroleptic, e.g., olanzapine OLA) are used, which leads to clinical improvement [35, 44].

As shown in clinical studies, combinations of two first generation normothymics (lithium, carbamazepine (CBZ) or valproate) or combining first generation normothymics with atypical neuroleptics (OLA) or lamotrigine leads to improvement in approximately half of the patients treated for relapses of the bipolar affective disease [34]. It has also been found that the addition of OLA to first generation normothymics gives higher effectiveness in preventing relapses compared to monotherapy with these drugs [44]. In grave forms of bipolar affective disease, for example, those with frequent phase changes, the use of combined therapy is already recommended at the beginning of the treatment [33].

At the same time, in patients treated for bipolar affective disease or schizophrenia a deterioration of cognitive functions, in particular memory, is observed, which adversely affects quality of life of these patients as well as their functioning in the society and at work [6]. It has been found that cognitive function deficits in bipolar affective disease may be mitigated with pharmacotherapy, although it should be noted that some drugs (typical neuroleptics) do not improve cognitive skills and even deteriorate them due to their antimuscarinic and antidopaminergic actions [20, 38].

As shown in clinical studies and meta analyses, atypical drugs improve cognitive functions mainly in the areas of memory and learning, verbal fluency or motor skills [20, 50]. Improvement of cognitive functions also entails treatment with normothymic drugs mainly because of their effect on processes related to transmission of intracellular signals [10]. As shown in our previous studies, both OLA and CBZ improve memory in rats but only with chronic administration (7 and 14 days) [26].

The present study was conducted to investigate the efficacy of the combined use of OLA (atypical antipsychotic) with CBZ (classified as normothymic drug) on spatial memory functions in the Morris test. The Morris water maze test is a challenging task for rodents that is used to study learning behavior that comprises acquisition, consolidation and retrieval [21].

Keeping in mind that combining CBZ and OLA brings measurable clinical benefits in the therapy of bipolar affective disease, the antidepressant activity of these substances as well as the effect of their combined administration on antidepressant activity still needs to be confirmed in clinical as well as experimental trials. Considering the fact that the new normothymic drugs, unlike typical neuroleptics, induce side effects less frequently, it was important to examine any adverse effects resulting from combined administration of OLA and CBZ, measured with the chimney test (motor coordination).

Materials and Methods

Animals

Male Wistar rats (200 ± 20 g), 10–12 weeks of age, purchased from a licensed breeder (license of the Ministry of Agriculture, Warszawa, Poland) were used in the study. The animals were housed under standard laboratory conditions and 12 h light/dark cycle with the lights on at 6 a.m. in a temperature controlled room at 21 ± 2°C, humidity of 70%, with free access to water and standard granulated food (if not stated otherwise in the text). The rats were kept four to a cage (30 × 30 × 20 cm). Each experimental and control group consisted of 10 animals.

The experimental part of our research took into consideration the welfare of the experimental animals.

Drugs

Sodium carboxymethylcellulose (CMC) PURE bpc was purchased from Koch-Light Laboratories Ltd. (London, England); OLA (Zyprexa) was synthesized by Lilly Research Laboratories, and CBZ was obtained from a local pharmacy (Polpharma, Stargard Szczeciński Pharmaceutical Factory, Poland). OLA (0.5 mg/kg) was suspended in a 0.5% solution of CMC and administered *ip* 30 min before the test. CBZ (30 mg/kg) was suspended in the CMC solution and administered *ip* 60 min before the test. OLA and CBZ were used at effective doses in tests described in the reports by Nowakowska et al. [24, 26].

In the chronic experiments, OLA was administered once a day, and CBZ twice a day for a period of 2 weeks. Each week, after one drug-free day to wash out the remnants of the last dose, the test was performed after administering the usual dose of the drug. Both single and chronic administration experiments were conducted on the same animals. The controls were given only CMC (2 ml/kg *ip*) according to same schedule.

The animal experiments were performed in accordance with the Ministry of High Education Report of 1959 as well as the UNECO Declaration of Animals'

Rights of 1978 (Paris). All procedures related to the use of animals in these experiments were conducted in line with ethical standards regarding experiments on animals. The study protocol was approved by the Local Ethical Commission for Research on Animals in Poznań.

Behavioral tests

Locomotor activity

Locomotor activity was measured in the study and control groups using eight 20.5 × 28 × 21 cm wire grid cages, each with two horizontal infrared photocell beams along the long axis, 3 cm above the floor. Photocell interruptions were recorded by electromechanical counters in an adjacent room. After 30 min of habituation to the novel cage, rats were treated with CBZ and OLA, and then photocell activity was recorded at 10-min intervals for 1 h. This test provided an index of basal locomotor activity of animals in a familiar environment, necessary to indicate the presence of a central stimulant or sedating effects of the drug used in the novelty test.

Forced swimming test – measurement of immobility according to Porsolt et al. [27]

a) Pretest: 24 h before the experiments, the rats were placed individually in Plexiglas cylinders (40 cm high, 18 cm in diameter) containing water at 25°C up to 17 cm height of the cylinder, and 15 min later they were removed to a 30°C drying room for 30 min.

b) Test: The drugs were administered 24 h after the pretest, and 30 min later the animals were placed once again in the cylinders and immobility was measured for 5 min. A rat was judged to be immobile when it remained floating in the water, in an upright position, making only very small movements necessary to keep its head above water. The total duration of immobility during 5 min was recorded by an observer who did not know which treatment the rats had received.

c) After prolonged administration (7 or 14 days) the drug action was tested as under b).

The water was changed after the observation of each rat.

Morris water maze test [21]

The apparatus was a circular basin (diameter = 180 cm, height = 50 cm) filled with water (approximately 22–24°C) to the depth of 24 cm, with pieces of Styrofoam hiding an escape platform (diameter = 8 cm) placed 1 cm below the water surface (learning place, invisible condition). Many extra-maze visual cues surrounding the maze were available, and the observer remained in the same location for each trial.

The rats were placed in the water close to and facing the midpoint section of the wall at one of four equally spaced locations: North (N), East (E), South (S) and West (W). The pool was divided into 4 quadrants: NW, NE, SE and SW. The rats were allowed to swim freely until they found the platform on top of which they could climb. If a rat failed to locate the platform within 60 s it was placed on the platform where it remained for 5 s. Each rat was submitted to 6 trials per day, and at each trial the starting position was changed (starting on the N side, followed by E, S, and W sides in that order). The inter-trial interval was 5 min between trials 1–3 and 4–6, and 10 min between trails 3 and 4. For the first 3 days of maze testing, the submerged platform was placed in the NW quadrant and then in the SE quadrant for the following 2 days. After these 5 testing days, there was a period of 7 days without any testing. On day 6, the rats were retested with the platform located as on day 5. On day 7 (one day later), the platform was lifted above the water level and placed in the SW quadrant. On the test day, each rat was subjected to a single probe trial swim (6 trials). The total number of times each rat crossed the probe target area and the time of probe trial swim were recorded by the observer. The time of each of the 6 trials was noted, and a mean value for each rat was calculated. The same procedures were followed in the chronic experiments (7 and 14 days).

Statistical analysis

The data are shown as the mean values ± SEM. The data distribution pattern was not normal (unlike a Gaussian function). Statistical analyses for the memory test and antidepressant test were carried out using a nonparametric ANOVA Kruskal-Wallis test for unpaired data and ANOVA Friedman test for paired data. Statistical significance was then tested in the *post-hoc* Dunn test. Statistical analysis for locomotor activity was carried out using the ANOVA Kruskall–Wallis test for unpaired data and ANOVA Friedman test for paired data, followed by the Mann–Whitney U-test.

Results

Locomotor activity effects of CBZ and OLA

Locomotor activity results are shown in Table 1. Single administration of CBZ at a dose of 30 mg/kg did not modify the locomotor activity in rats, but after 7 and 14 days of treatment with CBZ, we observed a statistically significant decrease in locomotor activity. OLA at a dose of 0.5 mg/kg in single administration and administered for 7 and 14 days did not lead to locomotor activity impairments compared to the control group. Combined administration of both drugs did not decrease locomotor activity neither in single nor repeated administration compared to the control group (Tab. 1). In combined administration of CBZ + OLA (7 and 14 days), however, OLA would completely prevent CBZ's sedative effect (Tab. 1).

Immobility time

OLA at 0.5 mg/kg *ip* decreased the immobility time, as shown in Table 2, after a single administration, whereas CBZ at 30 mg/kg *ip* decreased the immobility time after 7 days of treatment; this effect did not last through the following (14) days of CBZ administration. In the case of combined administration of CBZ and OLA, both as a single dose and after a prolonged treatment for 7 days, a significant shortening of immobility time was observed (Tab. 2).

Effects of CBZ and OLA on memory

Effect of acute and chronic treatment with CBZ and OLA on spatial memory (the Morris water maze test) in rats. Values of escape latencies

As shown in Table 3, after CBZ administration (30 mg/kg) as a single dose, or OLA also as a single dose (0.5 mg/kg *ip*) no changes of escape latencies compared to the control group could be observed, but after chronic treatment with CBZ or OLA (7 and 14 days) we observed a decrease in escape latencies, which is a sign of memory improvement in the rats. Combined administration of CBZ and OLA did not improve memory in rats that received these drugs as a single dose (*vs.* control group), whereas statistically significant differences were be observed in the chronic experiment (*vs.* control group) (Tab. 3).

Effect of acute and chronic treatment with CBZ and OLA on the spatial memory (Morris water maze test) in rats. Number of crossed quadrants

Single administration of CBZ and OLA, just like their combined administration, did not change the parameter of crossed quadrants (Tab. 4) but after 7 and 14 days of administration of CBZ, OLA or their combined administration significantly decreased the number of crossed quadrants compared to the control group, indicating improved performance (Tab. 4).

Tab. 1. Effect of CBZ and OLA on locomotor activity of rats in photocell activity cages

Group	Activity counts/mean			Friedman H [3.37]
	Single administration (x ± SEM)	Chronic treatment		
		7 days (x ± SEM)	14 days (x ± SEM)	
Control 0.5% CMC 0.5 ml/rat *ip*	104.4 ± 7.8	105.8 ± 3.2	116.9 ± 5.1	2.1
CBZ 30 mg/kg, *ip* 60 min before the test	95.4 ± 5.9	51.1 ± 4.3*	30.4 ± 5.4*	12.3
OLA 0,5 mg/kg, *ip* 30 min before the test	97.0 ± 4.5	101.2 ± 4.0	109.1 ± 5.8	2.6
CBZ 30 mg/kg, *ip* 60 min before the test + OLA 0.5 mg/kg, *ip* 30 min before the test	90.3 ± 4.8	112.3 ± 3.1^{+}	132.60 ± 11.8^{+}	5.6
Kruskal-Wallis H [3.37]	1.7	8.1	11.4	

Number of housed animals = 10, * – significant difference $p < 0.05$ *vs.* control group, $^{+}$ – significant difference $p < 0.05$ *vs.* CBZ group

Tab. 2. Effect of CBZ and OLA on immobility time in rats

Group	IT – time (s)			Friedman H [3.37]
	Single administration (x ± SEM)	Chronic treatment		
		7 days (x ± SEM)	14 days (x ± SEM)	
Control 0.5% CMC 0.5 ml/rat *ip*	243.2 ± 3.4	260.9 ± 4.8	249.8 ± 6.8	3.1
CBZ 30 mg/kg, *ip* 60 min before the test	245.2 ± 4.1	228.9 ± 4.2*	245.9 ± 5.9	3.9
OLA 0.5 mg/kg, *ip* 30 min before the test	213.4 ± 9.6*	267.9 ± 6.3	270.8 ± 2.4	6.1
CBZ 30 mg/kg, *ip* 60 min before the test + OLA 0.5 mg/kg, *ip* 30 min before the test	216.0 ± 2.5*+	237.8 ± 9.6*°	251.6 ± 5.3°	6.8
Kruskal-Wallis H [3.37]	1.8	8.2	6.9	

Number of housed animals = 10, * – significant difference $p < 0.05$ *vs.* control group, + – significantdifference $p < 0.05$ *vs.* CBZ group, ° – significant difference $p < 0.05$ *vs.* OLA group

Tab. 3. Effect of CBZ and OLA on spatial memory in rats (Morris water maze test). Values of escape latencies

Group	Escape latencies (s)			Friedman H [3.37]
	Single administration (x ± SEM)	Chronic treatment		
		7 days (x ± SEM)	14 days (x ± SEM)	
Control 0.5% CMC 0.5 ml/rat *ip*	10.5 ± 0.9	9.3 ± 0.6	8.3 ± 0.6	3.0
CBZ 30 mg/kg, *ip* 60 min before the test	10.3 ± 1.1	7.1 ± 0.7*	6.7 ± 0.8*	3.9
OLA 0,5 mg/kg, *ip* 30 min before the test	11.9 ± 1.2	6.6 ± 0.7*	6.8 ± 0.5*	6.1
CBZ 30 mg/kg, *ip* 60 min before the test + OLA 0.5 mg/kg, *ip* 30 min before the test	10.1 ± 1.0	5.8 ± 0.4*+	5.6 ± 0.4*+°	6.7
Kruskal-Wallis H [3.37]	1.4	10.9	9.2	

Number of housed animals = 10, * – significant difference $p < 0.05$ *vs.* control group, + – significant difference $p < 0.05$ *vs.* CBZ group, ° – significant difference $p < 0.05$ *vs.* OLA group

Tab. 4. Effect of CBZ and OLA on spatial memory in rats (Morris water maze test). Number of crossed quadrants

Group	Quadrants			Friedman H [3.37]
	Single administration (x ± SEM)	Chronic treatment		
		7 days (x ± SEM)	14 days (x ± SEM)	
Control 0.5% CMC 0.5 ml/rat *ip*	2.1 ± 0.4	1.6 ± 0.2	1.4 ± 0.2	1.7
CBZ 30 mg/kg, *ip* 60 min before the test	2.1 ± 0.3	1.1 ± 0.2*	0.8 ± 0.2*	6.3
OLA 0,5 mg/kg, *ip* 30 min before the test	2.4 ± 0.3	0.7 ± 0.1*	0.7 ± 0.2*	7.9
CBZ 30 mg/kg, *ip* 60 min before the test + OLA 0.5 mg/kg, *ip* 30 min before the test	1.9 ± 0.4	0.9 ± 0.2*°	0.9 ± 0.1*	7.6
Kruskal-Wallis H [3.37]	1.3	12.4	8.7	

Number of housed animals = 10, * – significant difference $p < 0.05$ *vs.* control group, ° – significant difference $p < 0.05$ *vs.* OLA group

Discussion

Recent years have witnessed a real revolution in terms of pharmacotherapy used to treat mental illnesses, including bipolar disease. Bipolar affective disorders have many forms, indicating that individual disease stages feature various psychopathological states requiring different therapeutic approaches [36]. In addition, many patients cannot tolerate the side effects associated with available medications [12]. One should also bear in mind that monotherapy is often inadequate, thus polytherapy has become common [22].

Many clinical studies indicate that combined treatment with a first generation normothymic drug (CBZ) and second generation normothymic drug (OLA) yields greater therapeutic efficacy in treating bipolar affective disease than monotherapy with these drugs [35]. The combination of CBZ and OLA is often used in clinical practice in the management of mania [43].

Efficacy of antidepressant activity of OLA and CBZ combination was the subject of many studies. Nearly all reports confirm antidepressant effect of OLA [24, 37] and CBZ [4, 26, 53, 54] both in humans and animals. Among second generation neuroleptics, the largest amount of data on effective preventive action in bipolar affective disease available concerns OLA [52]. For instance, it has been shown that OLA added to lithium and valproate in combined therapy shows a much better preventive effect compared to each of these two drugs administered in monotherapy [45]. It is worth emphasizing that OLA is currently approved for long-term administration in bipolar affective disease both in the United States and in Europe [36].

Efficacy of the antidepressant activity in combined administration of CBZ and OLA was also found in this study. Combined single administration of CBZ and OLA shows an antidepressant effect similar to that of OLA alone; upon 7 days of combined administration of the two drugs the antidepressant effect found was similar as with CBZ alone. Upon 14 days of administration of the study drugs (CBZ or OLA) or their combined administration, however, no antidepressant effect was observed.

It is very important that the combined administration of CBZ and OLA leads to an antidepressant effect, and mutual interactions between the study drugs may be pharmacokinetic. It seems that the interactions observed show no signs of synergy, or even additivity. From the literature, it is possible that OLA metabolism may be induced by CBZ [18], which may lead to a reduced OLA concentration. CBZ is also a substrate and inducer for some P450 cytochrome isoenzymes [13, 16, 19] through which it affects transformation of many drugs metabolized in the liver, and at the same time, its metabolism depends on the action of other substances. CBZ may, therefore, catalyze metabolism and weaken the action of many drugs administered simultaneously.

Immobility time of rats in the Porsolt test was lower upon single combined administration of CBZ and OLA and after 7 days of chronic administration. This effect did not continue through the prolonged (14-day) combined administration of the two drugs.

Our previous studies have shown OLA to have an antidepressant effect administered at the same dose (0.5 mg/kg) only upon single administration, as the effect did not continue throughout the chronic administration [24], whereas CBZ administered at the dose of 30 mg/kg would show an antidepressant effect only upon 7 days of administration [26]. Our studies clearly indicate that the use of CBZ and OLA in combined administration lead to an antidepressant effect, which substantiates concomitant use of these drugs in the treatment of manic psychotic disorders [34–36].

The theory of using polytherapy in the treatment of mental illnesses is confirmed by clinical studies on long-term use of another atypical antipsychotic agent (clozapine) combined with CBZ in particularly severe cases of bipolar affective disease [8], although it needs to be emphasized that the combination of CBZ and clozapine is generally contraindicated because CBZ and clozapine each produce hematologic side effects, and CBZ probably lowers the level of clozapine, possibly more than it lowers the levels of traditional neuroleptics [12]. Thus, the combination of CBZ and clozapine should not be considered safe [8]. On the other hand, our studies have shown no adverse effects of combined administration of CBZ and OLA on motor coordination in animals (results not shown) or a sedative effect upon combined, single and repeated administration of the two drugs The lack of adverse effects with combined administration of CBZ and OLA is an additional advantage advocating the use of this combination in clinical practice, even more so that a sedative effect was observed with CBZ monotherapy [26]. It is worth emphasizing that in the chronic experience OLA would completely prevent CBZ's sedative effect, which may be related to auto-

induction of microsomal enzymes of the P450 cytochrome. $T_{1/2}$ for CBZ is 36 h in humans and approximately 8–9 h in animals and, with chronic administration, was reduced to 16–24 h in humans [14, 39, 49]. It should be remembered that simultaneous application of microsomal enzymes inducers additionally reduces $t_{1/2}$ of the drug used [14, 49].

Cognitive processes play a vital role in our daily life; therefore, an analysis of irregularities occurring in the course of diseases and during the pharmacotherapy used is an important issue. Perception or memory impairments resulting from a disease or a poorly chosen pharmacotherapy may entirely exclude the patient from social and professional life; hence, there has been a continuous search for drugs which would not only relieve the disease symptoms but also have potentially minimal adverse effects on cognitive functions [5, 6]. A number of studies have shown that impairments of cognitive processes are an inherent characteristic of mental illnesses [5, 6, 51]. In schizophrenia, attention and operating memory processes are impaired [32] and the condition persists in the acute stage of the disease but also once the psychotic symptoms subside [30]. These deficits are one of the key symptoms of schizophrenia, which is why the medications used should not impair cognitive functions [23]. Cognitive function disorders in CHAD affect memory and learning and impair intelligence or verbal fluency [3, 11]. Impairments of cognitive processes may result from a depressed mood and low self-esteem [23] of the treated patients.

There are a number of studies reporting a positive effect of CBZ [1, 15, 26, 28, 41, 42, 48] and OLA [9, 25] on memory both in humans and animals. Our studies [24, 26] have also shown repeated administration of CBZ or OLA alone to lead to memory improvements in animals in two distinct experiments. The available references fail, however, to document the effect of CBZ and OLA polytherapy on cognitive functions in humans and animals.

Our studies have shown that repeated combined administration of CBZ and OLA, similar to CBZ and OLA alone, lead to a similar effect – memory improvement in animals. This effect may be strictly related to pharmacokinetic parameters, because, as Sudha [41] reports, doses of 20 and 40 mg/kg CBZ *ip* (plasma levels of 2.5 and 4.5 μg/ml, respectively) improved the rats' performances in the T-maze and passive avoidance tests, but the CBZ dose of 80 mg/kg, *ip* (plasma level of 9 μg/ml) caused no change in memory and learning, and made the rats drowsy instead [41]. It is believed that central nervous system side effects are frequent with CBZ concentrations > 9 μg/ml [29] and may have an important role in learning and memory. The same effect can most likely be attributed to OLA.

Brain serotoninergic neurons are also involved in learning and memory in rodents [10]. Cognitive function improvement in the course of treatment with atypical drugs (including OLA), which distinguishes them from traditional drugs, may result, for instance, from this drug's antagonistic effect on 5-HT_{2A}, 5-HT_{2C} and 5-HT_6 receptors and the simultaneous stimulation of 5-HT_{1A} receptors or increased dopamine and acetylcholine release in the prefrontal cortex and the hippocampus [50]. On the other hand, spatial memory improvement observed in rats upon chronic CBZ administration is probably related to a reduced AChE activity, which results in an increased acetylcholine concentration in the central nervous system and thus can lead to cognitive improvement [41]. Sudha [41] also believes that an increased turnover of 5-HT and dopamine in the hippocampus (the structure responsible for the memory function) may play a role in memory improvement. For certain, the memory improvement effect observed in combined CBZ and OLA administration may also correspond to the reduced incidence of EPS in humans [46, 47] or catalepsy in animals [24, 26].

Our studies confirm the reports of other authors that the addition of CBZ to different types of antidepressants produces significant therapeutic effects in the treatment of mood disorders [17, 40]. Similar effects are also observed in animal studies [2, 7, 31]. Thus, it can be assumed that co-administration of OLA and CBZ can be useful for treating mental and psychiatric diseases with memory function disorders.

Conflict of interest

The authors declare that there are no conflicts of interest with respect to the rules of the International Committee of Medical Journal Editors.

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