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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'