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Coadministration of tramadol with aripiprazole and venlafaxine—The effect on spatial memory functions in male rats

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ABSTRACT

Background: The impairment of memory functions is very common in patients with chronic pain, particularly in patients with existing cognitive disorders. Results of some studies confirmed that tramadol (TRM), a frequently prescribed analgesic drug, improves memory functions in humans. However, there are no studies on the effect of co-administration of TRM with antidepressants or antipsychotics on memory; therefore, the aim of this study was to evaluate the effect of concomitant use of TRM with a second generation antipsychotic–aripiprazole (ARI) and an antidepressant–venlafaxine (VEN) on memory using an animal model.

Methods: The effect of TRM (5 mg/kg) + ARI (1.5 mg/kg) and TRM (5 mg/kg) + VEN (20 mg/kg) on memory in Wistar rats was examined using the Morris water maze test after single and chronic administration (7 and 14 days).

Results: It was observed that a single and chronic administration of TRM, VEN or ARI alone, but not a combination of TRM + VEN or TRM + ARI (except for 14 days of treatment) can improve memory in rats compared to the control group. After 14 days of administration, both combinations achieved improvement similar to each drug individually and improved spatial memory in rats compared to the control animals.

Conclusion: It can be assumed that chronic treatment with combinations of TRM + VEN or TRM + ARI is unlikely to cause memory impairment and interfere with either any antidepressant effect of VEN or any antipsychotic effect of ARI in patients suffering from chronic pain using TRM.

Introduction

Tramadol (TRM) is a centrally acting analgesic often used in the treatment of post-operative pain, and chronic non-malignant and cancer pain. The analgesic effect is caused by agonistic action on the opioid receptors and by inhibition of serotonin and norepinephrine reuptake [1]. TRM has been also shown to have an antidepressant effect, both in tests on animals, *e.g.* [2–8] and in clinical observations [9].

Chronic pain can be associated with the appearance of depressive states in patients, which often involves negative effects on cognition and memory, particularly in patients with pre-existing cognitive impairment [10]. It has been demonstrated that chronic pain may contribute to memory impairment, regardless of the age of the patients [11]. The effect of drugs on memory is, however, particularly evident in older people, mainly due to polytherapy. Memory problems are associated with aging, but can also be of iatrogenic origin, especially when changes in memory occur suddenly, without prior symptoms of dementia [12].

Literature data confirm the positive effect of TRM on memory functions in humans [12–19]. Also, a 2nd generation antipsychotic–aripiprazole (ARI) [20–23] and an antidepressant–venlafaxine (VEN) [24], often used in patients with cognitive impairement, have proven to be effective in improving memory in the animal model.

However, it has been demonstrated that the effect of antidepressants, including VEN, on memory can be phase-dependent; it is inhibitory during acquisition/consolidation (pre-training administration) and facilitatory during consolidation and retrieval (post-training administration) [25]. In the case of pre-training administration of VEN, it has been demonstrated, *e.g.*, that memory improved in rats after single and repeated administration

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of this drug [24,26]. However, in studies performed by Ulak et al. [27] memory impairement was observed in rats after repeated administration of VEN; on the other hand, in studies of Yan et al. [28] no effect on memory in rats was observed after subacute administration of the drug [25]. In the case of post-training administration of VEN it was proved that after single, subacute, and repeated administration in rats, the drug always improved memory in the studied animals [25,29,30].

All above drugs have a similar mechanism of action on the noradrenergic, serotoninergic and dopaminergic systems which play a significant role in memory processes. Unfortunately, there are no literature data on the effect of co-administration of these drugs on memory functions. Therefore, the aim of this study was to evaluate the effect of concomitant use of TRM, ARI and VEN on spatial memory functions in rats. In view of the fact that TRM is often used in the treatment of chronic pain [1,9] also in patients with depression or schizophrenia who experience cognitive disorders, it is advisable to determine the effect of TRM administered in conjunction with antidepressants or antipsychotics on memory processes.

Materials and methods

Animals

Male Wistar rats (body weight 200–250 g, age 3 months) provided by a licensed breeder (Sadowski, Poznan University of Medical Sciences, Poland, licensed by Ministry of Agriculture in Warszawa, Poland) were used in the study. The rats were acclimated to local conditions for 2 weeks before the experiments. Animals were placed in standard laboratory conditions in a temperature-controlled room at 20 ± 2 °C, humidity of 60%, with 12 h light/dark cycle (lights on at 6 a.m.). They had free access to water and standard granulated food (Labofeed pellet, Warsaw, Poland). The rats were housed four per cage ($30 \times 30 \times 20$ cm). A total of 60 healthy animals were used (control and each experimental groups consisted of 10 rats). Rats were assigned randomly to a Morris water maze (MWM) test. The control group was given oral and intraperitoneal carboxymethylcellulose solution (0.5% CMC, 0.5 ml/rat, 30 and 60 min before the test). The five experimental groups were given:

1. TRM (5 mg/kg *ip*, 60 min before the test),
2. ARI (1.5 mg/kg *ip*, 30 min before the test),
3. VEN (20 mg/kg *po*, 30 min before the test),
4. TRM (5 mg/kg *ip*, 60 min before the test) + ARI (1.5 mg/kg *ip*, 30 min before the test),
5. TRM (5 mg/kg *ip*, 60 min before the test) + VEN (20 mg/kg *po*, 30 min before the test).

Different times of drug administration (ARI and VEN 30 min, and TRM 60 min before the test) were used to harmonize timepoints of the highest concentration in blood for each of the drugs, so that tests can be started at the time of the maximum effect of each drug. TRM (5 mg/kg) and VEN (20 mg/kg) were used at the effective dose in the forced swimming test described in our earlier report [6]. The dose of ARI (1.5 mg/kg) was also chosen on the basis of our previous studies [21–23]. The tests were performed on day 1, day 7 and day 14. The same animals were used both in single and chronic (once daily up to 14 days) administration experiments.

All the tests were took place between 7.00 a.m. and 1.00 p.m. All procedures related to the use of rats 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 Poznan (Consent No. 2/2014).

Drugs

Pure CMC was obtained from Koch-Light Laboratories Ltd. (London, England); TRM (CAS: 27203-92-5, Tramal® 100 mg/ml, solution for injections)—Grünenthal, Germany; VEN (CAS: 93413-69-5)—Wyeth–Ayerts Laboratories, Princeton, NJ (USA), ARI (CAS: 129722-12-9)—Otsuka Pharmaceutical Europe, Bristol-Myers Squibb Poland.

TRM was dissolved in the 0.9% NaCl solution and administered *ip* at the dose of 5 mg/kg 60 min before the tests. ARI and VEN were suspended in a 0.5% CMC solution and administered 30 min before the tests (ARI 1.5 mg/kg *ip*, VEN 20 mg/kg *po*).

Morris water maze test (MWM) [31]

The water maze apparatus was a round bath (height = 50 cm, diameter = 180 cm) filled with water at 22–24 °C to a depth of 24 cm, and pieces of Styrofoam hid 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.

MWM test was initiated with a pretest consisting in placing each rat in the pool in which it was to find the platform and climb it. The next day, a 6-day-long training period of animals selected in the pretest began, and the test was performed on the 7th day.

During the 6-day training, the rats from all groups (control, TRM, ARI, VEN, TRM + ARI and TRM + VEN) were placed in the water 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 four quadrants: NW, NE, SE and SW. The rats were allowed to swim freely until they found the platform and climbed onto it. If a rat failed to locate the platform within 60 s, it would be placed on the platform for 5 s. Each rat was submitted to six trials per day and the starting position was changed in each trial (starting on the N side, followed by E, S, and W sides, in that order). The intertrial interval was 5 min between trials 1–3 and 4–6, and 10 min between trials 3 and 4. For the first 3 days, the submerged platform was located in the NW quadrant. Then, the platform was placed in the SE quadrant for the following 3 days (as reversal trials enhance the detection of spatial impairments).

After the completion of the 6-day training, on day 7 (the test day), the platform was lifted above the water surface, and rats were given: oral and intraperitoneal 0.5% CMC, 0.5 ml/rat, 30 and 60 min before the test (control group), TRM (5 mg/kg *ip*) 60 min before the test, ARI (1.5 mg/kg *ip*) 30 min before the test, VEN (20 mg/kg *po*) 30 min before the test, and jointly TRM with ARI, and TRM with VEN, as described above. On the test day, each rat was submitted to one experiment consisting of six individual trials. The time of each of the six trials was noted, and a mean value was calculated for each rat. The observer recorded the total number of times each rat crossed the probe (crossed quadrants—space exploration) target area and the time of the probe trial (escape latencies—space navigation) swim. The observer who counted the probe trial performance was blind to the treatment of the animals.

This way, results for escape latencies and the number of crossed quadrants for single administration for all groups of animals were obtained.

Next, animals were administered the studied drugs, *i.e.* TRM, ARI, VEN, TRM + ARI and TRM + VEN or 0.5% solution of CMC (in the control group) once a day for 14 days. The test procedure described above, which was performed on day 7 of the study, was repeated twice (on the 7th and 14th day of drug administration), so that