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NS-3, a TRH Analog, Reverses Repeated ECS-Induced Deficits in Water Maze Performance in the Rat

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KHAN, A., H. LAI, Y. UKAI AND M. H. MIROLO. *NS-3, a TRH analog, reverses repeated ECS-induced deficits in water maze performance in the rat.* PHARMACOL BIOCHEM BEHAV **47**(3) 477–481, 1994.—Rats given five consecutive daily electroconvulsive shock (ECS) treatments and trained to run in the Morris water maze, starting three days posttreatment, showed deficits in learning and memory functions. Treatment before each training session with the thyrotropin-releasing hormone (TRH) analog NS-3 [(CG-3703), (3R),(6R)-6-methyl-5-oxo-3-thiomorphorinyl-l-histidyl-l-prolinamide tetrahydrate] reversed these behavioral deficits. The possible use of TRH and its analogs as therapeutic treatment for the cognitive dysfunctions resulting from electroconvulsive shock treatment for depression and the possible involvement of central cholinergic systems in the cognitive dysfunctions are discussed.

Electroconvulsive shock NS-3 TRH Morris water maze Learning Memory

DESPITE more than 50 years of controversy, electroconvulsive therapy (ECT) still remains as a principal treatment for the severely mentally ill (6). A significant therapeutic response is seen in about 80% of depressed patients who have not received adequate antidepressant pharmacotherapy (19). It consists of the induction of a series of grand mal seizures using an electric stimulus. Compared with clinical responses to antidepressants, ECT has a dramatic effect on depressive symptoms after three to four treatment sessions, which are usually administered within 7 to 10 days. On the average, eight sessions are used as a therapeutic course in approximately 100 persons per million of the population per year in the United States (its utilization is two- to fivefold higher in Western Europe). Currently, electroconvulsive therapy is increasing as a treatment option since there are more patients referred to psychiatrists who are either unresponsive to pharmacotherapy or cannot tolerate the required doses of antidepressants. Due to these factors, ECT is being used more frequently in older patients.

The major controversy regarding ECT is its effect on cognition. Although no evidence exists that structural damages occur to the nervous system after ECT (1), multiple cognitive deficits occur after increasing number of treatment sessions. After the first few treatment sessions, patients experience anterograde amnesia. After six or more treatment sessions, other cognitive deficits occur that include disturbances in language, verbal fluency, naming abilities, and perceptual learning. The magnitude of these deficits has been suggested to be linked to both the amount and waveform of electrical energy used, as well as the location of electrodes through which electricity is passed into the brain (43). Attempts have been made to lessen the cognitive effects by varying these stimulus parameters.

Other investigators have attempted to use pharmacological agents to mitigate ECT-induced cognitive deficits (20). To achieve this, it is necessary to better understand the nature of the ECT-induced cognitive deficits and the neural mechanisms involved. One of the early suggestions as to the mechanisms involved in the ECT-induced cognitive deficits was that there was a deficiency in cholinergic functions in the central nervous system (5). Several investigators have noted changes in the

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central cholinergic systems following a series of electroconvulsive shocks (ECSs) in animals (2,10,25-27). These findings led us to hypothesize that a major cause of ECT-induced cognitive deficits is a deficiency of cholinergic transmission in the brain, and factors that can reverse this neurotransmitter deficiency will counteract the cognitive deficits. To verify our hypothesis, we conducted the present research.

To further understand the cognitive dysfunctions associated with ECT, in the present experiment we investigated the effects of repeated ECS treatment on learning and memory in the rat. Performance in the Morris water maze was used in our investigation of these effects, inasmuch as it is a behavioral task for measuring spatial learning and memory functions. The study of spatial memory functions in rodents has been suggested as a model to investigate the cognitive and memory functions in humans (8,49). We also investigated whether treatment with the thyrotropin-releasing hormone (TRH) analog NS-3 [(CG-3703), (3R),(6R)-6-methyl-5-oxo-3-thiomorphorinyl-l-histidyl-l-prolinamide tetrahydrate] could reverse the behavioral deficits caused by the repeated ECS treatment. It has been suggested that TRH can be used to treat the cognitive dysfunctions in certain neurological diseases, especially those due to a decrease in cholinergic functions in the brain (54). For example, it has been reported that TRH improves learning and memory in patients with Alzheimer's disease (24,36) and that it attenuates scopolamine-induced memory deficits in humans (37). In an animal experiment (14) it has been shown that MK-771, a TRH analog, can reverse the learning deficit in medial septal-lesioned rats performing in the radial-arm maze, a task involving spatial learning and memory functions. Since then, we have reported that TRH can improve the performance in a T-maze of rats subjected to ECS (21).

The TRH analog NS-3 was used in the present experiment because it has a longer plasma half-life and better penetration into the central nervous system than TRH (7,52). Furthermore, it has been shown in animal experiments to improve performance in various behavioral tasks. For example, NS-3 improves the learning and memory deficits in passive avoidance task in the rat caused by scopolamine and cycloheximide (Ogasawara et al., Nippon Shinyaku Co., Ltd., unpublished results). It enhances the long-term potentiation in guinea pig hippocampal slices, a phenomenon related to memory (16). Furthermore, NS-3 has been shown to affect consciousness, which may be essential in learning and memory functions (48).

METHODS AND PROCEDURES

Animals

Male Sprague-Dawley rats (250-300 g) purchased from Tyler Laboratory (Bellevue, WA) were used in this study. The rats were housed three in a cage in a temperature-controlled (23°C) vivarium maintained on a 12-h light-dark cycle (light on 0700-1900) and provided with food and water ad lib.

Electroconvulsive Shock Treatment

Animals were anesthetized with pentobarbital sodium (25 mg base/kg, IP) and ECS was administered by two electrodes clipped to the ears. The electrodes were lubricated with Aquasonic gel (Parker Lab., Inc., Orange, NJ). The electric shock (40 mA, 60 Hz, 2 s) was generated by a GSC-700 shock generator (Greson-Stadler Co., W. Concord, MA). The shock produced a tonic/clonic muscular movement in the rats for approximately 10 s. Control (sham treatment) rats were similarly anesthetized with pentobarbital and the electrodes were clipped to their ears for 10 s without the passage of electricity. This treatment (ECS or sham) procedure was repeated for five consecutive days between 0800 and 0900 each day.

Drug Treatment

Water maze training sessions were started three days after the last ECS/sham treatment. At 15 min before each maze training session rats were injected with either NS-3 (0.3 mg/kg, IP; dissolved shortly before injection in pyrogen-free, physiological saline and injected in a volume of 1 ml/kg) or physiological saline (1 ml/kg, IP). Thus, the experiment included four treatment groups of animals: ECS/saline, ECS/NS-3, sham/saline, and sham/NS-3. The dosage and treatment time of NS-3 were used because previous studies have shown that the 0.3-mg/kg dose is effective in affecting operant behavior and the drug reaches a peak effect at 15 min after IP injection (Ogasawara et al., unpublished results). NS-3 was kindly provided by Gruenthol GmbH (Germany).

Water Maze Running Procedure

The water maze was a plastic circular pool (246 cm in diameter) filled with water (23°C) to a depth of 27 cm. The water was made opaque by addition of powdered milk. A Plexiglas platform (15 × 20 cm) was placed at the center of one of the quadrants of the maze and submerged 5 cm below the surface of the water. Each animal was given two training sessions daily on three consecutive days starting at three days after the ECS or sham treatment. The two daily sessions were seperated by 1 h. During each session an animal was released into the water from the wall of the maze at points separating the quadrants. Therefore, there were four trials per animal per training session. The sequence of points of release into the water followed a random order. The animal was allowed to swim to the platform, and if it could not locate the platform within 1 min it was picked up and placed on the platform. It remained there for 30 s before another trial or was removed from the maze after four trials. Performance in the maze was videotaped using a closed-circuit television system for detailed analysis later. In addition, at 1 h after the last (sixth) training session each animal was given a probe trial in which the animal was allowed to swim in the maze for 1 min with the platform removed.

Data Analysis

From the video recording, the escape time (i.e., the time from release into the water to landing on the platform) was scored for each training trial. Trials with no successful escapes were given a score of 60 s. The average escape time of the four trials in each training session for each rat was used in data analysis. In the probe trial, the time spent in the quadrant of the maze where the platform was previously located was scored.

Escape time data were analyzed by the repeated measurement analysis of variance (ANOVA), and data from the probe trial were analyzed by the two-way ANOVA. Differences between two data points were compared by the Newman-Keuls test. A difference at $p < .05$ was considered statistically significant.

RESULTS

Average escape times in the six training sessions of the different treatment groups are shown in Fig. 1. In all four

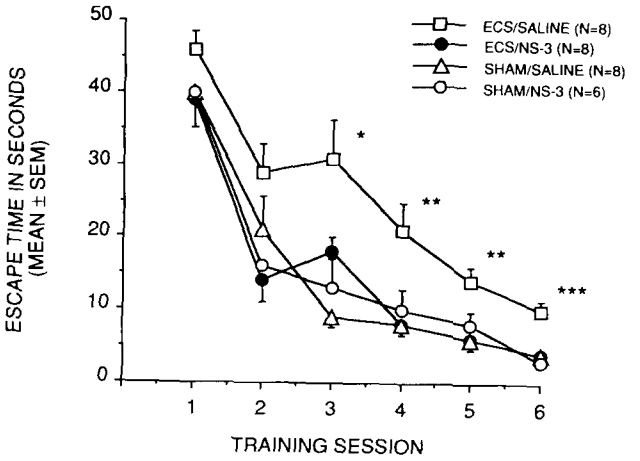

FIG. 1. Average escape times of the different treatment groups in the six training sessions. $*p < .02$, $**p < .01$, and $***p < .001$ (Newman-Keuls test) between the sham/saline and ECS/saline groups at the various training sessions.

treatment groups a decrease in escape time was observed with training. Repeated measurement ANOVA of the data showed a significant treatment (ECS and drug) effect, $F(3, 26) = 8.254$, $p < .005$, and significant changes in performance over the learning sessions, $F(5, 130) = 108.85$, $p < .0001$, whereas no significant interaction between treatment and learning sessions was found, $F(15, 130) = 1.730$, $p = .0524$.

When the learning curves of the ECS/saline and sham/saline animals were compared, no significant difference in escape time was observed between the two groups in the first two learning sessions (Newman-Keuls test). However, a significant difference was seen in training sessions 3-6, with the ECS/saline animals taking significantly longer time to escape onto the platform. However, no significant difference was found between the learning curves of the ECS/NS-3 and the sham/saline group. These data indicate that learning was delayed by ECS treatment and the effect was reversed by NS-3 treatment. Furthermore, NS-3 treatment did not significantly affect the performance of the sham-treated animals (i.e., no significant difference was found between the learning curves of the sham/saline and sham/NS-3 rats).

Data on the time spent in the previously platformed quadrant during the 1-min probe trial of the different treatment groups are shown in Fig. 2. Two-way ANOVA showed no significant ECS effect, $F(1, 26) = 2.804$, NS, but there was a significant NS-3 treatment effect, $F(1, 26) = 5.295$, $p < .05$, and a significant ECS × NS-3 interaction effect, $F(1, 26) = 9.312$, $p < .01$. The Newman-Keuls test comparing results between two treatment groups showed that the ECS/saline animals spent significantly less time in the previously platformed qradrant of the maze (ECS/saline vs. sham/saline, $p < .01$). Treatment with NS-3 reversed this effect (ECS/NS-3 vs. sham/saline, nonsignificant). In addition, treatment with NS-3 had no significant effect on the performance of the sham-treated animals during the probe trial, since there was no significant difference between the sham/saline and sham/NS-3 rats.

To explore whether the changes in escape time after ECS treatement and reversal by NS-3 are due to differences in motor activity between the treatment groups, we also calculated the swim speed of the animals. The swim speed of the different treatment groups during the first trial in the first training session was obtained by measuring the length of the path of swim and then dividing by time. Average swim speeds (mean ± SE) of the sham/saline, ECS/saline, sham/NS-3, and ECS/NS-3 animals were 27.1 ± 1.9 ($n = 8$), 26.8 ± 1.7 ($n = 8$), 31.5 ± 1.7 ($n = 6$), and 30.2 ± 1.2 ($n = 8$) cm/s, respectively. One-way ANOVA showed no significant treatment effect among the treatment groups, $F(3, 26) = 1.879$, nonsignificant, and no significant difference was found between pairs of the treatment groups (Newman-Keuls test). Thus, both ECS and NS-3 did not significantly change the swim speed of the animals in the maze.

DISCUSSION

Data from the present experiment showed that repeated ECS treatment caused both spatial learning and memory deficits in the rat while performing in the Morris water maze. Treatment with the TRH analog NS-3, before each maze training session, reversed these effects of repeated ECS, whereas NS-3 had no significant effect on the performance of sham-treated controls. The data also indicate that the effects on learning and memory functions can last approximately one week after the termination of treatment. These findings parallel those seen after the termination of ECT treatment in humans who receive approximately eight sessions in a period of two to three weeks and where the cognitive deficits could last for weeks after treatment.

The neural mechanisms involved in the repeated ECS-induced learning and memory deficits are not known. A likely possibility is that the deficits are due to a decrease in cholinergic functions in the brain. Central cholinergic systems are well known to be involved in learning and memory functions (42,44), and disturbances in cholinergic systems have been reported after repeated ECS. Two groups of researchers (2,26,27) have reported a decrease in the concentration of muscarinic cholinergic receptors in the hippocampus and cerebral cortex in the rat after repeated ECS treatment (seven daily ECSs of 0.75 s at 130 V). Such neurochemical changes have been suggested to be related to the anterograde amnesia seen in the ECS-treated rats (25,27). Interestingly, another group of researchers (10) found an increase in muscarinic re-

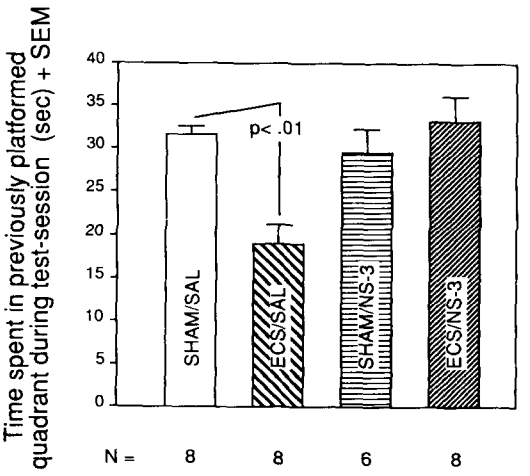

FIG. 2. Average time spent in the previously platformed quadrant in the maze during the probe trial by the different treatment groups.

ceptor concentration in the frontal cortex of the rat after repeated ECS (seven daily ECS shocks of 0.2 s at 90 mA). These data suggest that ECS may have a complex interactive effect on the functions of the central cholinergic systems, which can depend on the parameters of the electric shock.

Further indirect support for the hypothesis that the ECS-induced behavioral deficits are due to disturbances in central cholinergic functions comes from our findings that repeated ECS disturbs water maze performance and the effects are reversible by treatment with a TRH analog. Studies of the neurochemical basis of water maze performance have implicated the cholinergic systems in the brain as playing a major role, especially the septo-hippocampal and basalis-cortical cholinergic pathways. For example, training in the water maze increased high-affinity choline uptake, an index of cholinergic activity, in the hippocampus (3). Performance deficits were seen after lesioning of the septo-hippocampal or the basalis-cortical cholinergic pathways (11,29–31,33,34,38,39,45,51) or treatment with cholinergic antagonists (50,51). Furthermore, performance deficits in the water maze seen in brain-lesioned animals were reversed by treatment with cholinergic agonists (4,29,32,35,46), and transplantation of septal cholinergic neurons to the hippocampus reversed the deficits of septal-lesioned animals (47).

On the other hand, one of the most well-documented neurochemical effects of TRH is to enhance cholinergic transmission in the brain (13). It enhances cholinergic activity in the hippocampus (15,18,23) and the cerebral cortex (12,41,53) of rats. An interesting finding is that TRH is particularly efficient in increasing the cholinergic activity of animals with a decrease in cholinergic functions [e.g., after pentobarbital treatment or partial lesioning of the cholinergic pathways (12,14,40)]. This may explain our finding that NS-3, the TRH-analog, reverses the learning and memory deficits in the ECS-treated animals but exerts no significant effect on the performance of the sham-treated animals. Furthermore, the ability of NS-3 to improve learning and memory functions has been suggested to be mainly due to the enhancement of neuronal activity in the septo-hippocampal and basalis-cortical cholinergic pathways (17).

Even though the mechanism is not well understood, the fact that TRH can affect learning and memory in animals is well known (13). It may be significant to point out here that repeated ECS has been shown to decrease TRH activity in the brain. A decrease in TRH release from nucleus accumbens slices (28) and an increase in the concentration of TRH in the limbic areas of the brain (22) were reported in rats subjected to repeated ECS. Perhaps the decrease in TRH activity is responsible for the water maze performance deficits seen in the ECS-treated rats, and injection of NS-3 can reverse the deficits. This is also consistent with the hypothesis that repeated ECS decreases cholinergic activity in the brain, since release of TRH is under the control of cholinergic innervations. For example, an increase in the concentration of TRH in the septum, perhaps a result of decreased release, was found in rats treated with the cholinergic antagonist atropine (9).

Thus, our results suggest that TRH or its analogs can possibly be used for the treatment of ECT-induced cognitive deficits in humans. In further studies we plan to investigate neurochemical changes of the central cholinergic systems of the rat after repeated ECS treatment. This may provide direct proof for the role of the cholinergic functions in repeated ECS-induced learning and memory deficits.

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