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Differentiations of the effect of NMDA on the spatial learning of rats with 4 and 12 week diabetes mellitus

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This study examines possible interactions between behavioral effects and influence of N-methyl-D-aspartate acid (NMDA) receptors in 4 and 12-week streptozotocin (STZ) induced diabetic rats. Effects of NMDA receptor agonist on spatial learning were tested in control groups of rats and in rats with 4 and 12 weeks diabetes mellitus (DM). Experimental diabetes was induced by a single intravenous injection of streptozotocin at a dose of 65 mg/kg, dissolved in citrate buffer. We used the water maze task and examined the acquisition and the retrieval of spatial memory in rats. In our present experiments, we observed that DM had no significant influence on acquisition and retrieval in 4 week diabetic rats on Morris water maze, but impaired examined parameters in 12 week diabetic rats in this test. The NMDA receptor agonist did not influence acquisition but increased recall on water maze in 12 week streptozotocin diabetic rats.

Key words: N-methyl-D-aspartate acid, ionotropic glutamate receptor, spatial learning, memory, rats

INTRODUCTION

Diabetes mellitus (DM) is a common metabolic disorder characterized by hyperglycemia due to an absolute or relative insulin deficiency. DM is a chronic disease characterized by widespread complications, among which are the peripheral and central neuropathies (Gispen and Biessels 2000). Neurobehavioral studies have reported a learning decline in subjects with diabetes, and neurophysiologic investigations have revealed conduction abnormalities in the central auditory, somatosensory, and visual pathways in diabetic individuals (Biessels and Gispen 2005, Cukierman et al. 2005, Biessels et al. 2006). On the other hand, people with diabetes (especially older adults) apparently face a greater risk of vascular dementia, with large population studies detecting an association between diabetes mellitus, dementia and Alzheimer's disease (Balenger et al. 2004). Moderate disturbances of learning and memory and complex information processes have been reported in both type 1 and 2 diabetic patients (Biessels and Gispen 2005, Cukierman et al. 2005, Biessels et al. 2006). Animal models of diabetes can make an important contribution to the understanding of the pathophysiology of the effects of diabetes on the brain (Biessels et al. 1998). As in diabetic humans, a variety of neurophysiologic parameters are impaired in diabetic rats and mice (Collingride 1987, Popovic 2001).

The changes in learning that occur in STZ-diabetic rats have been reviewed previously. The performance of diabetic rats on same-behavioral tasks, such as a passive avoidance (Wiśniewski et al. 2000, Grzęda et al. 2007), object learning, and radial maze is disturbed (Biessels et al. 1998, Kamal et al. 2000).

The disturbed hippocampal long-term potentiation (LTP) and long-term depression (LTD) in STZ–induced rats after 10 weeks duration of DM correlated well with the learning disturbance (Kamal et al. 2000). LTP and LTD are activity-dependent modifications of synaptic strength, which have attracted considerable attention in the search for cellular mechanisms of

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learning and memory (Shors 2004, Snyder et al. 2005).

Glutamate receptors, which are the major excitatory receptors within the central nervous system, are objects of particular attention since their regulation appears to be crucial for controlling synaptic operation during learning and memory (Trudeau et al. 2004). NMDA and non-NMDA (kainite and AMPA) receptors are two families of ionotropic receptors activated by glutamate (Antzoulatos and Byrne 2004). In this study, the role of the glutaminergic NMDA receptors was of special interest. NMDA receptors are heteromeric glutamate-gated ion channels in the CNS, formed by monomers of two families of homologous subunits NR1 and NR2 A-D that are differentially expressed in the CNS (Di Luca et al. 1999, Antzoulatos and Byrne 2004).

Several observations indicate that diabetes mellitus might be accompanied by a certain erosion of brain function (Schulingkamp et al. 2000, Nitta et al. 2002). Learning deficits in streptozotocin-diabetic rats were earlier shown to be paralleled by alternations in hippocampal synaptic plasticity (Popovic et al. 2001). NMDA receptor expression and phosphorylation have also been reported to be down-regulated in postsynaptic densities from the brains of chronic streptozotocin-induced diabetic rats (Di Luca et al. 1999, Gardoni et al. 2002).

The Morris water maze is a convenient and standard test of cognitive function in rodents. This test allows the researcher to study spatial and working memory processes. In the Morris water maze the latency to reach the platform is measured with the help of a video system, while simultaneously directly observing the rats. During these tests, we did not ascertain any abnormal and repetitive behaviors in rats.

It cannot be excluded that the NMDA treatment may prove to be useful for modulating behavior and causing repetitive stereotypic behavior. It is known that NMDA receptors have been implicated in the appearance of long-term potentiation in several brain regions, and this receptor type seems to be very important for learning and memory (frontal cortex and hippocampus) (Di Luca et al. 1999, Gispen and Biessels 2000, Riedel et al. 2003). The long-term effect of NMDA receptor activation causes modulation of function of other neurotransmitter systems. Drugs which activate NMDA receptors have shown anti-dopaminergic activity (D_1, D_2 receptors) and inhibit dopamine-mediated behavior in rats (Savelli et al. 1995). The existence of interaction between the NMDA receptors and the AMPA, dopamine, metabotropic and opioid systems is also important (Northoff et al. 2005).

Also, NMDA receptor antagonists and channel blockers have a number of side effects: learning impairments, ataxia, sedation, as well as psychomimetic side effects (Qi et al. 2008).

This observation indicates that the impairment of synaptic plasticity in streptozotocin-rats can be linked to an inappropriate level of NMDA receptor stimulation required for the induction phase of long term potentiation.

The aim of our study was to investigate the influence of NMDA as an agonist of glutamate receptors of certain behaviors, such as spatial learning acquisition and retrieval in rats 4 and 12 weeks after STZ administration.

METHODS

Animals

The study was conducted on male Wistar rats weighing 250–300 g. They were housed in cages (55 × 40 × 20 cm), six animals per cage, in an air-conditioned (humidity 50–60%) and temperature-controlled (22°C) room under 12 h light/12 h dark cycle beginning at 7:00 AM. The animals were fed standard diet; food and water were freely available. The experiments were carried out between 8:00 AM and 12:00 PM. Each animal was used only once and the same rat was not used in a different test. We have used 106 rats for these experiments (14–18 weeks old).

The experimental procedures applied in this study were in compliance with the Board for Ethical Affairs and Supervisions over Research on Animals and Individuals, Medical Academy of Białystok. Every effort was made to minimize the number of animals used and their suffering. All experiments were in accordance with the EU Directive 86/609/EEC and International Guidelines on the Ethical Use of Animals.

Diabetic-rats model

Type I diabetes mellitus was induced by a single intravenous injection of streptozotocin at 65 mg/kg (SIGMA, Germany). The streptozotocin was dissolved

in 0.1 M citrate buffer (pH adjusted to 4.5), and then was injected to rat *via* the tail vein. In this work, 5 days after the streptozotocin injection, urine glucose level was measured by Tetra Phan Dia test (Pliva Lachema). Urine glucose level was determined in all STZ-injected animals. Four and twelve weeks after streptozotocin administration blood glucose concentration was measured using blood glucose test meter "super glucocard II" (Arkay, Japan).

Glucosuria and hyperglycemia (600 mg/dl) was observed in all STZ-injected animals. All experiments were carried out 4 and 12 weeks after streptozotocin treatment.

Drugs

NMDA (Tocris, UK) at the dose of 15 mg/kg per rat was injected i.p. The injections, as a freshly prepared NMDA solution, were given 30 min before the acquisition tests (once, before first session on 1st day) or 30 min before the trial on the third day in retrieval spatial memory. The control rats received 0.9 % NaCl (Polfa, Poznań). After the experiments, rats were anesthetized with vetbutal at the dose of 20 mg/kg per rat (i.p.) and then they were killed by decapitation.

Behavioral testing

All experiments were carried out in a quiet, dimly lit room with each group equally represented at the times of testing. Rats were randomly allocated to experimental groups and used only once. Each group comprised 8–12 rats.

Morris Water Maze apparatus

The water maze was a gray, metal circular pool (210 cm in diameter, 40 cm in height) was filled to a height of 24 cm with lukewarm (22ºC) water that was changed after each session. The pool was divided into four quadrants: NW (Northwest), NE (Northeast), SE (Southeast), SW (Southwest). A gray cylindrical platform (9 cm in diameter, 22 cm high) was located on a fixed location in the center of the target quadrant, 2 cm below the water surface. The water maze was located in a room that was full of distal cues (i.e. window, doors, lamp, the investigator) that were in fixed locations. Data were collected by the camera signal that was digitized and fed to a computerized tracking system (VideoMot TSE-System, Germany) that monitored and stored the position of the rats, real time spent in any designated area of the pool, the swim path and estimated escape latency.

Experimental procedure

The procedure was based on that described by Morris (1984). For adaptation rats were placed into the room where we performed the experiment for two hours and then returned to their cages. This was done in the day preceding water maze assessment. In our modification of MWM (Morris water maze) rats are trained in a short period of time. The water maze task was conducted during two consecutive days. In MWM rats learn and do not forget the position of the submerged platform, as confirmed by shortened time of finding of the platform on the next sessions. Rats were placed into the water at one of the three equally spaced locations: East (E), South (S), and West (W). A trial began by placing the rat in water facing the wall of the pool at one of the starting points. Rats were allowed to swim freely until they found the platform on top of which they could climb. A trial ended when a rat finds the platform or when 120 s had passed. When the rat did not find the escape platform within 120 s, it was placed on it by the experimenter for 15 s. Rats received six trials per day (two sessions of three trials). The sessions were separated by a 120 min interval resting period during which the rat was returned into its cage for two consecutive days. After the final daily trial the rat was returned to the home cage.

The experiment aimed to examine the acquisition of spatial memory. Rats received i.p. administration of NMDA (15 mg/kg) or saline before swimming trials only on the first day. The latency to reach the escape platform was measured. The average distance and swim speed required for all groups to reach the platform was equivalent during the acquisition test.

A free-swim trial was carried out 24 h after the 2-day training period. To examine the retrieval of previously learned spatial information, groups of trained rats were injected with the treatment 30 min before sessions on the third day. The percentage of quadrant time (the time spent by the rat in target quadrant where the platform was formerly placed) was recorded and calculated. In this design the effect of NMDA on retrieval of spatial information on well-trained rats was evaluated.

Statistical analysis

Data were presented as means ± standard error of mean (SEM). Two-way analysis of variance (ANOVA II) with repeated measures followed by the *post-hoc* Newman-Keuls test was used for results obtained in the acquisition in MWM. A two-way analysis of variance (ANOVA II), followed by Newman-Keuls test for chosen group comparisons, was used for the recall test in Morris water maze. *F*-ratios and *P* values are presented only for significant differences. For all comparisons, differences between particular groups with *P* equal to or lower than 0.05 were considered as significant. Statistical analyses were carried out using Statistica 6 software.

RESULTS

The effect of NMDA on acquisition on Morris water maze in control and diabetic rats

Two-way Anova of the latencies to reach platform in the Morris water maze revealed significant session effect in rats with 4-weeks DM (4DM) $F_{3,128}$=46.9 (P<0.001), but no significant treatment and no significant treatments × session interaction. In our present experiments we observed that 4-weeks DM had no significant influence on time latency in rats. There was no significant interaction between diabetes and session. The tested dose NMDA caused no change in time latency on water maze acquisition in control and 4 weeks diabetic rats (Fig. 1A).

Computerized path measures of distance swam to platform showed no significant interaction of 4-weeks diabetes and session as well as treatment and session. The average distance required for all groups to reach the platform was equivalent during the acquisition test (Fig. 1B).

The analysis of swim speed (Table I) revealed significant treatments and diabetic interaction ($F_{3,128}$=5.72, P<0.05). Rats with 4-weeks DM showed decreases *versus* controls in swim speed on Session 3 (P<0.05) and 4 (P<0.05). Rats with 12-weeks DM (12 DM) showed an impairment in the time reaching the platform compared with control rats, as indicated by increased time to find the hidden platform on Sessions 3 (P<0.05) and 4 (P<0.01), diabetes effect $F_{1,62}$=79.9 (P<0.001). There was also a significant interaction between diabetes and session $F_{3,124}$=10.25 (P<0.001). The treatment with NMDA caused no change in time latency in rats with 12 weeks DM. ANOVA II of the latencies to reach the platform in the MWM revealed no significant treatment effect in this group (Fig. 2A).

Table I

Effect of motor abilities on the maze performance of control and diabetic rats treated with NMDA or NaCl 30 min before the 1 daily session in the hidden platform version of the water maze shown by the swim speed

Session of training	Control rats		Rats with 4-week DM (4 DM)		Rats with 12-week DM (12 DM)	
	0.9% NaCl	NMDA (15 mg/kg)	0.9% NaCl	NMDA (15 mg/kg)	0.9% NaCl	NMDA (15 mg/kg)
	Morris water maze: swimming speed (cm/s)					
Session 1	27.29 ± 2.04	29.51 ± 2.89	27.78 ± 3.01	26.21 ± 3.45	20.41 ± 2.73***, xx	20.01 ± 3.93
Session 2	28.97 ± 2.96	29.03 ± 2.57	25.9 ± 3.07	27.1 ± 3.39	17.82 ± 4.25***, x	23.10 ± 4.18#
Session 3	29.80 ± 2.71	29.3 ± 2.5	25.2 ± 2.79*	26.01 ± 2.76	19.03 ± 3.38***, x	24.27 ± 2.56#
Session 4	29.66 ± 4.28	29.52 ± 1.75	25.72 ± 3.04*	27.43 ± 5.75	18.11 ± 3.84***, xx	26.63 ± 3.1##

*P<0.05; ***P<0.001 vs. control, x P<0.05; xx P<0.01 vs. DM 4, # P<0.05; ## P<0.01 vs. DM 12. Data analyzed with two-way ANOVA with measures followed by the Newman-Keuls test. Data are presented as mean ± SEM.

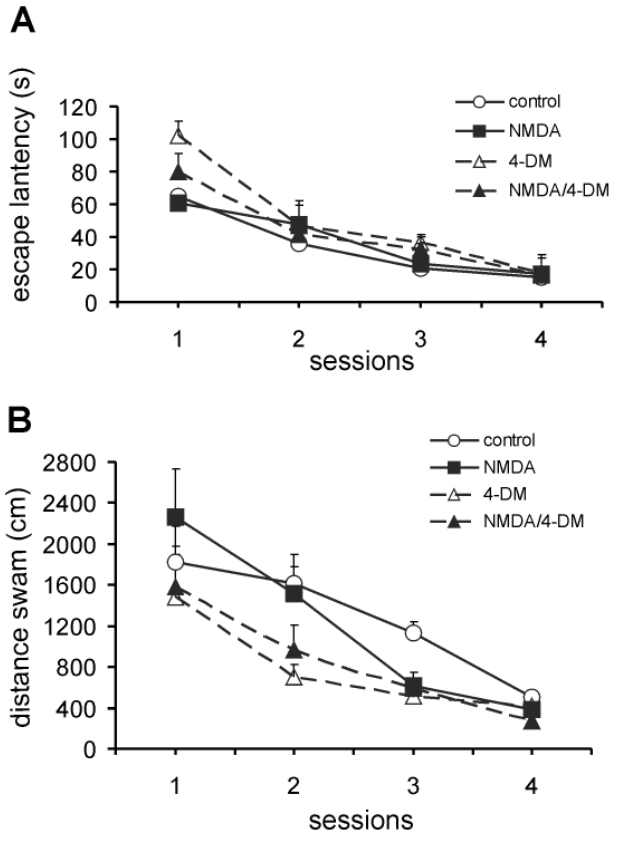

Fig. 1. The effect of NMDA on the acquisition of spatial learning in rats with 4 DM. (A) escape latency, in seconds, to reach the platform during each session (2 sessions per day, 2 days of training), (B) the distance taken to reach the platform over the 2 days of training. Rats received NMDA at the dose of 15 mg/kg i.p. Control rats received 0.9% NaCl. Columns represent means ± SEM of the values obtained from 8–10 rats. (ANOVA II, Newman-Keuls test).

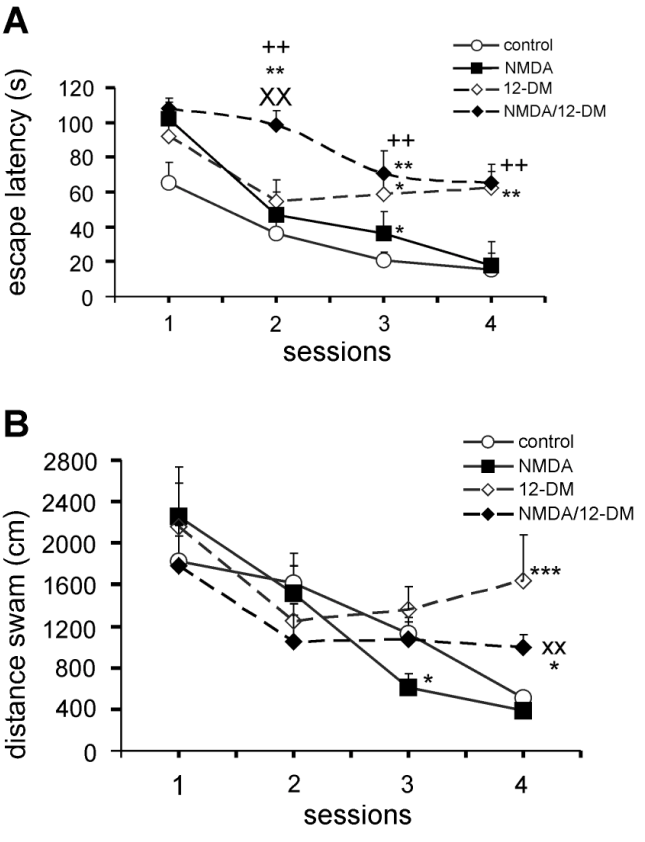

Fig. 2. The effect of NMDA on the acquisition of spatial learning in rats with 12 DM. (A) escape latency, in seconds, to reach the platform during each session (2 sessions per day, 2 days of training), (B) the distance taken to reach the platform over the 2 days of training. Rats received NMDA at the dose of 15 mg/kg i.p. Control rats received 0.9% NaCl. Columns represent means ± SEM of the values obtained from 8–10 rats. **P*<0.05,***P*<0.01, ****P*<0.001 vs. control; ^{xx}P<0.01 vs. 12-DM; ^{++}P<0.01 vs. NMDA (ANOVA II, Newman-Keuls test).

Path measures of distance swam to platform (Fig. 2B) showed significant interaction of 12-weeks diabetes and session $F_{3,124}$=7.07 (P<0.001). Rats with 12 weeks DM showed increases versus controls in swim distance to platform on Session 4 (P<0.001). Diabetic rats treated with NMDA showed a shorter distance swam than 12 DM rats on this session (P<0.01).

The analysis of swim speed (Table I) revealed a significant main effect of treatment ($F_{3,124}$=11.8, P<0.001), significant diabetes effect ($F_{1,62}$=6.35, P<0.05) and significant treatment × diabetes interaction ($F_{3,124}$=5.72, P<0.05). Rats with 12 DM were significantly slower than control in all sessions. Treatment with NMDA exerted positive effect on swim speed on Session 2 (P<0.05), 3 (P<0.05) and 4 (P<0.01).

The effect of NMDA on retrieval on Morris water maze in control and diabetic rats

ANOVA II of the percentage of time in target quadrant in the recall test in 12 DM showed significant diabetes effect ($F_{3,28}$=11.33, P<0.001) and treatment effect ($F_{3,28}$=8.7 P<0.01). In present experiments we observed that DM did not significantly affect 4 week diabetic rats on retrieval of spatial memory in Morris water test. NMDA at the dose 15 mg/kg caused no change in target quadrant time in control and 4 week diabetic rats (Fig. 3A).

The time spent in target quadrant by rats with 12 week diabetes mellitus was significantly shorter

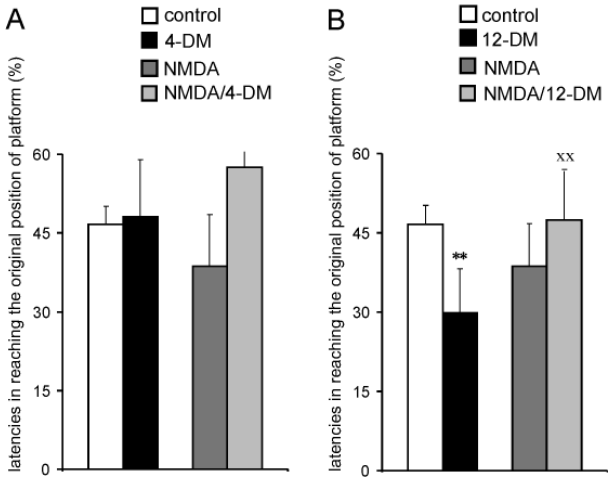

Fig. 3. The effect of NMDA on the retrieval of spatial learning in rats with (A) 4 DM and (B) 12 DM. Rats received NMDA at the dose of 15 mg/kg i.p. Control rats received 0.9% NaCl. Columns represent means ± SEM of the values obtained from 8–10 rats. ***P<0.001 vs. control; ^{xx}P<0.01 vs. 12-DM (ANOVA II, Newman-Keuls test).

than the time spent by control animals (P<0.01). NMDA showed a significant effect on increasing the time in the target quadrant in rats with 12 week DM (P<0.01) (Fig. 3B).

DISCUSSION

In the present study, on acquisition of the water maze the control and pre-4-week diabetic rats showed a reduced latency to escape into the hidden platform with increasing number of training sessions. This suggests that animals, despite the STZ treatment 4 weeks earlier, were able to learn in the MWM. However, the effect of treatment after 12 weeks in the STZ study implies that there was a significant impairment in latency to find the hidden platform when compared to control rats.

In our present experiments, we observed that NMDA, the agonist of glutamate receptor administered i.p. with a dosage of 15 mg/kg did not change the acquisition in any tested groups.

In this study, we have compared the effects of the NMDA agonist using a hippocampal-dependent acquisition and retrieval in the Morris water test to determine spatial memory in rats with 4- and 12-week DM. Twelve-week DM significantly impaired retrieval processes in the Morris water maze, but 4-week DM did not have any influence in this test. Rats with 12-week DM spent significantly less time searching for the location of the hidden platform than control rats.

NMDA attenuated retrieval deficits induced by 12 weeks diabetes, in addition, deficits in diabetes impairment psychomotor activity in rats (especially in rats with 12-week DM), were attenuated by NMDA in diabetic rats (distance and speed swim).

Animal models of diabetes can contribute to the understanding of the pathophysiology of the effects of diabetes on the brain. STZ–induced diabetic rats are a model that has been used extensively in studies into the pathogenesis and treatment of peripheral and central diabetic neuropathy (Biessels and Gispen 2005).

Our data show that diabetes mellitus had no significant influence in 4-week STZ-diabetic rats on spatial memory, but impaired spatial memory in 12-week diabetic rats in the Morris test. In animal models of diabetic pathology, such as 3–4 month STZ-diabetic rats, spatial learning impairments have been reported (Biessels et al. 1998). In more complex learning tasks, such as active and passive avoidance on radial maze, rats with longer duration experimental diabetes consistently showed performance deficits (Biessels et al. 1998, Kamal et al. 2000, Grzęda et al. 2007). Cognitive dysfunction should therefore be added to the list of chronic complications of diabetes (Cukierman et al. 2005, Biessels et al. 2006).

The intensity and variety of electrophysiological abnormalities, structural changes and cognitive deficits may change in the course of diabetes and with an intensification of pathological processes: that is, with increasing disease duration as well as with increasing age, diabetic adults might show acceleration in the rate and magnitude of cognitive decline as compared to their healthy peers (Ryan 2005).

Deficits in water maze learning in 12-week diabetic rats were possibly associated with the change in hippocampal long-term potentiation (LTP) (Di Luca 1999, Riedel et al. 2003).

Impaired performance in rats with diabetes lasting 3 months are characteristic of the impaired expression AMPA (Kamal et al. 1999), sigma (Mardon 1999), 5-HT and metabotropic receptors (Tomiyama et al. 2005). The diabetic state was accompanied by the change in adenosine, acetylocholine and catecholamine secretion (Mardon 1999, Ramakrishan et al. 2005). This fact seems to contribute to different memory deficits in 4- and 12-week diabetic rats on the spatial memory.

It is known that expression of NMDA receptor subunits is decreased in the brains of streptozotocin-diabetic

rats (Di Luca et al. 1999, Riedel et al. 2003). In 2002, Gardoni and his coworkers showed that one month of STZ-diabetes in rats did not affect the NMDA receptor complex. In contrast, 3–4 months after induction, diabetes in rats' immunoreactivity NR2B subunit was reduced (Gardoni et al. 2002).

Glutamate is the primary neurotransmitter mediating neurotransmission in the central nervous system (CNS) *via* ligand-gated channels (Riedel et al. 2003). Among the ionotropic glutamate receptor subtypes, the N-methyl-D-aspartate (NMDA) receptor plays an important role in brain function and neurotoxicity (Magleby 2004). NMDA receptors are found in high concentrations in those brain regions involved in learning and memory, including hippocampus and cortex (Riedel et al. 2003). Induction of long-term potentiation requires NMDA receptors that are concentrated in the hippocampus (Sonntag et al. 2000, Riedel et al. 2003).

In our experiments NMDA did not have an influence on acquisition in any tested groups, but increased retrieval in rats with 12-week DM. At a cellular level there is evidence that the NMDA receptor is critical for memory acquisition. Some authors have described that treatment of nonselective NMDA receptors antagonist exhibited memory acquisition in the water Morris maze (Castellano et al. 2001, Newcomer and Krystal 2001). However, Guscott and others (2003) did not observe a significant effect of treatment with CP 101,606 (NMDA receptor NR2B subunit selective antagonist) in rats in an acquisition in the Morris water maze. This result implies that the NMDA receptors may not play an important role in cognitive function, however mice over-expressing the NR2B subunit-containing receptor were found to have increased long-term potentiation and enhanced performance in several behavioral tasks, including novel object recognition and spatial navigation, suggestive of improved cognitive ability (Tang et al. 1999). It is therefore surprising that the NMDA receptor agonist does not appear to change performance in acquisition in the water maze.

Some research has shown the existence of an interaction between the glutaminergic system and other systems. More recently, interest has developed in the interaction between the NMDA receptors and the AMPA, dopamine, metabotropic and opioid systems (Northoff et al. 2005). Emerging evidence suggests that their systems' signaling plays a role in cognitive functions (Wu et al. 2004). Long-term diabetes can change neurophysiological function, receptors' signaling and disturb the interaction between the glutaminergic system and other systems (especially the metabotropic system) (Biessels and Gispen 2005).

NMDA attenuated the retrieval deficit of spatial memory in rats with 12-week DM in the Morris maze. There is evidence that the NMDA receptor is not involved in retrieval of memories. Steel and Morris (1999) have found that blocking NMDA receptors in the hippocampus did not exert an effect on the retrieval of a spatial memory. However, some authors have found that calcineurin and CaMK are involved in retrieval (Abel and Lattal 2001). The NMDA receptor interferes with the activation of calcineurin and CaMK (Alagarsamy et al. 2005). These data indicate that the NMDA receptor may play a role in the retrieval of spatial memory.

NMDA receptor antagonists like ketamine impair episodic memory retrieval (Newcomer and Krystal 2001). This fact shows the possible role of NMDA receptors in retrieval of memory. In this study, NMDA attenuated retrieval deficits induced by long-term diabetes.

The variation in the results of these behavioral studies may be partially explained by differences in task complexity, animal models and duration of the diabetes.

In summary, diabetes profoundly impaired the acquisition and recall in the Morris water maze. In this study, NMDA attenuated retrieval deficits induced by long-term diabetes. NMDA caused no change in control and 4-week diabetic rats in the water maze.

On the other hand, many studies have indicated that the overactivation of ionotropic receptors such as NMDA receptors may mediate acute excitotoxic events (Haberny et al. 2002). However, in our data we have not noticed any negative impact of NMDA given at a dose 15 mg/kg of learning and memory in both groups of rats. Long-term diabetes is characterized by hypofunction of the NMDA receptor so activation of this receptor may have a positive effect. More neuropathological, behavioral and neurophysiological data are required to understand the role of the NMDA receptor in learning and memory.

CONCLUSIONS

This study seems to justify the conclusion that the agonist of NMDA receptor attenuated retrieval deficits induced by long-term diabetes. Our data demonstrate that DM had no significant influence on examined parameters in 4 week diabetic rats on water maze, but impaired acquisition and retrieval in 12 weeks diabetic

rats in this test. NMDA did not influence acquisition but increased recall on water maze in 12 week streptozotocin diabetic rats.

The present data suggest that NMDA receptor agonist may have therapeutic potential in disturbances of learning and memory in patients with diabetes mellitus.

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