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Role of Hippocampal Nitric Oxide in Memory Retention in Rats

A-MIN HUANG* AND EMINY H. Y. LEE†[1]

*Institute of Life Sciences, National Defense Medical Center and †Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, The Republic of China

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HUANG, A.-M. AND E. H. Y. LEE. *Role of hippocampal nitric oxide in memory retention in rats.* PHARMACOL BIOCHEM BEHAV **50**(3) 327-332, 1995.—The present study investigated the role of hippocampal nitric oxide (NO) in memory retention of an inhibitory avoidance learning task in rats. The anatomical locus was aimed at the dentate gyrus (DG). Results indicated that intra-DG administration of a NO generator, sodium nitroprusside (SNP), at moderate doses enhanced retention performance in a dose-response fashion in rats. SNP at higher doses, on the other hand, impaired memory retention. Intra-DG injection of a NO inhibitor, L-N^G-monomethylarginine (L-MeArg), impaired retention performance at moderate doses. Coadministration of a NO precursor L-arginine (2.9 and 7.2 μg) reversed the memory-impairing effect of L-MeArg. An in vitro ADP-ribosylation experiment showed five protein bands with molecular weights around 118, 94, 54, 43, and 39 kDa that were labeled. The labeling intensity of these proteins decreased as the concentration of in vivo SNP increased. These results suggest that hippocampal NO plays a facilitatory role in the memory process of an inhibitory avoidance learning task in rats.

Nitric oxide (NO) Sodium nitroprusside (SNP) L-N^G-Monomethylarginine (L-MeArg) L-Arginine ADP-ribosylation Dentate gyrus Rat

NITRIC oxide (NO) recently has been widely accepted as a novel neuronal messenger in the brain (5,9,14,19). Particularly, it was proposed to act as a retrograde messenger in *N*-methyl-D-aspartate (NMDA) receptor-mediated long-term potentiation (LTP) (20), which is considered to be a synaptic model of certain forms of memory (1). Nitric oxide is synthesized from L-arginine by the enzyme NO synthase (NOS). Endogenous synthesis of NO can be readily inhibited by competitive NOS inhibitors, the analogues of L-arginine, and exogenous administration of NO generators, such as sodium nitroprusside (SNP), which mimics the actions of NO (19). Several laboratories have shown that induction of hippocampal LTP is blocked by competitive NOS inhibitors, including L-N^G-nitroarginine (L-NoArg), L-N^G-monomethylarginine (L-MeArg or L-NMMA), and L-N^G-nitroarginine methylester (L-NAME) [for review see (18,24)]. Studies also showed that SNP produces long-lasting enhancement in synaptic efficacy similar to LTP (2,4).

Recently, the effects of systemic administration of NOS inhibitors on learning and memory have been studied in rats (12), rabbits (8), and chicks (15). In general, these results suggest that NO participates in the acquisition of learning and the execution of memory tasks. However, all these studies used systemic injection paradigm, and systemic administration of NOS inhibitors may have differential effects, or these effects may antagonize each other at different brain regions. On the other hand, the relationship between NO and LTP has been studied to a certain extent, whereas relatively less attention has been paid to the role of NO in memory consolidation.

In this study, we examined the role of NO in memory retention by directly injecting SNP, L-MeArg, and arginine into the dentate gyrus (DG) of the hippocampus using the paradigm of inhibitory avoidance learning task. One of the molecular targets of NO is adenosine diphosphate (ADP)-ribosyltransferase, which is independent from the known NO-cGMP pathway (7). ADP-ribosyltransferases occur with high concentrations in most mammalian tissues, including the brain. These enzymes catalyze the transfer of ADP-ribose from nicotinamide adenine dinucleotide (NAD) to particular amino acid residues of specific substrate proteins. A recent preliminary study has reported that alteration in NO-stimulated endogenous ADP-ribosylation is associated with LTP (11). Whether the NO-ADP-ribosylation signaling is also involved in the memory process is unknown. In this study, we

[1] To whom requests for reprints should be addressed.

also examined the effects of NO on endogenous ADP-ribosylation during memory consolidation.

METHOD

Animals

The subjects were male albino Sprague-Dawley rats bred in the Institute of Biomedical Sciences, Academia Sinica of Taiwan. The rats weighed 220–300 g. They were housed individually in hanging cages (30 × 23 × 20 cm) after surgery, and were maintained at a room temperature of 23 ± 2°C with a 12L : 12D cycle (light on at 1800 h). Food and water were continuously available. Behavioral experiments were conducted during the light phase of the diurnal rhythm.

Drugs

The drugs used were L-MeArg (Calbiochem), L-arginine, and SNP (Sigma Chemical Co.). [^{32}P]NAD was purchased from Amershan. All other chemical reagents were obtained from Merck of the highest grade. Doses refer to the salt form. Drugs were dissolved in 0.9% isotonic saline immediately before use.

Surgery

The rats were subjected to stereotaxic surgery under sodium pentobarbital (50 mg/kg, IP) anesthesia. Stainless steel (23 ga) thin-wall guide cannulae (10 mm long) were implanted bilaterally into the dorsal dentate gyrus of the hippocampus (3.6 mm posterior to bregma, 2.5 mm lateral to the midline, and 3.0 mm ventral to the skull surface). The tooth bar was set at −2.4 mm according to the atlas by Paxinos and Watson (22). The guide cannulae were fixed to the skull with three stainless screws and dental acrylic cement. A stainless steel stylet was inserted into each cannula to maintain patency. The rats were allowed 7–10 days to recover from the surgery.

Inhibitory Avoidance Task

One-trial step-through avoidance task was used to measure memory retention of rats. The apparatus consisted of a trough-shaped alley divided by a sliding door into an illuminated compartment and a dark compartment. A shock generator was connected to the floor of the dark compartment. The rat was placed in the illuminated compartment facing away from the door. As the rat turned around, the door was opened. After the rat entered the dark compartment, the door was closed and a 1 mA/1 s foot shock was given. The rat was then removed from the alley immediately after receiving the shock and returned to its home cage. The retention test was given 24 h later. The rat was again placed into the illuminated compartment and the latency to step into the dark compartment was recorded as a measure of the retention performance. Rats that did not enter the dark compartment within 600 s were removed from the alley and assigned a ceiling score of 600.

Intra-DG Drug Administration

Animals received bilateral intra-DG injections of saline, L-MeArg, L-arginine, or SNP immediately after the training procedure. The animal was awake and gently held by the experimenter when receiving injections. The injection was administered through a 30-ga injection needle connected to a 10-μl Hamilton microsyringe by 0.5-m polyethylene tubing (PE-20). The injection needle was bent at a length such that, when inserted into the cannula, the needle tip would protrude 1.5 mm beyond the tip of the cannula. Drug solutions were introduced into the PE tubing and the microsyringe and were delivered into the DG manually at a rate of 0.2 μl/min. A volume of 0.8 μl was injected into each DG throughout all experiments.

In Vitro ADP-Ribosylation

ADP-ribosylation reactions were carried out under conditions that have been optimal for pertussis toxin labeling of G_i/G_o-proteins because alterations in endogenous ADP-ribosylation have been shown to associate with LTP under those conditions (11). Brains were removed from decapitated rats, placed in ice-cold saline for 5 min, and then sliced on an ice-cold platform. The dentate gyrus was dissected out using a 2-mm punch and was frozen on dry ice immediately. Frozen tissues were sonicated (Sonifier/Cell Disruptor, Branson Sonic Power Co.) for three times at 15 s each time in homogenization buffer containing 50 mM Tris (pH 8.0), 6 mM $MgCl_2$, 1 mM EDTA, 3 mM benzamidine, 1 mM dithiothreitol, 5% (w/v) sucrose, 1 μg/ml soybean trypsin inhibitor at a concentration of 30 mg/ml. Homogenates were centrifuged at 1000 × *g*, 4°C, for 10 min to remove unbroken cells and cell debris. Aliquotes of homogenates were used to determine the concentration of protein. Proteins (100 μg) were then subjected to ADP-ribosylation study in vitro in a buffer containing the following chemicals: 100 mM Tris (pH 8.0), 10 mM thymidine, 10 mM isoniazid, 5 mM $MgCl_2$, 2.8 mM dithiothreitol, 2.4 mM benzamidine, 0.8 mM EDTA, 2.5 mM ATP, 2 mM GTP, 4% (w/v) sucrose, 0.8 μg/ml soybean trypsin inhibitor, 0.5% (v/v) Triton X-100, and 25 μM [^{32}P]NAD (final specific activity 40 Ci/mmol). The final volume was 100 μl. The reactions were carried out at 37°C for 1 h and were terminated by the addition of 10 μl of 100% trichloroacetic acid (TCA). The samples were then centrifuged at 10,000 × *g*, 4°C, for 10 min. The supernatant was removed and the pellet was washed with 1.25 ml of water saturated with ethyl ester. After the ethyl ester evaporated, the samples were resolved in the sample loading buffer [10% (v/v) glycerol, 2% (w/v) 2-mercaptoethanol], boiled for 2 min, and subjected to SDS-polyacrylamide gel electrophoresis with 9% (w/v) acrylamide, 0.25% (w/v) bis-acrylamide in the resolving gel. After electrophoresis, the gels were dried and autoradiographed at −80°C for 3 days.

Histology

After the memory test, animals were sacrificed by decapitation and the brains were removed. For histological examination of cannula and needle placement in the DG, the brains were frozen-sectioned in a cryostat and checked individually. Tissue sections (20 μm) taken at 40-μm intervals through the hippocampus were mounted on slides and stained with thionine blue. Animals were accepted for data analysis if both needle placements were located within the DG according to the atlas of Paxinos and Watson (22). Animals that the needle placement was not at the correct position were deleted from the study. Figure 1 illustrates the placement of needle position in the DG under microscopic examination.

Statistics

Because the distribution of retention scores was uneven and was truncated at 600, nonparametric Kruskal–Wallis analyses followed by Mann–Whitney one-tailed *U*-tests were used

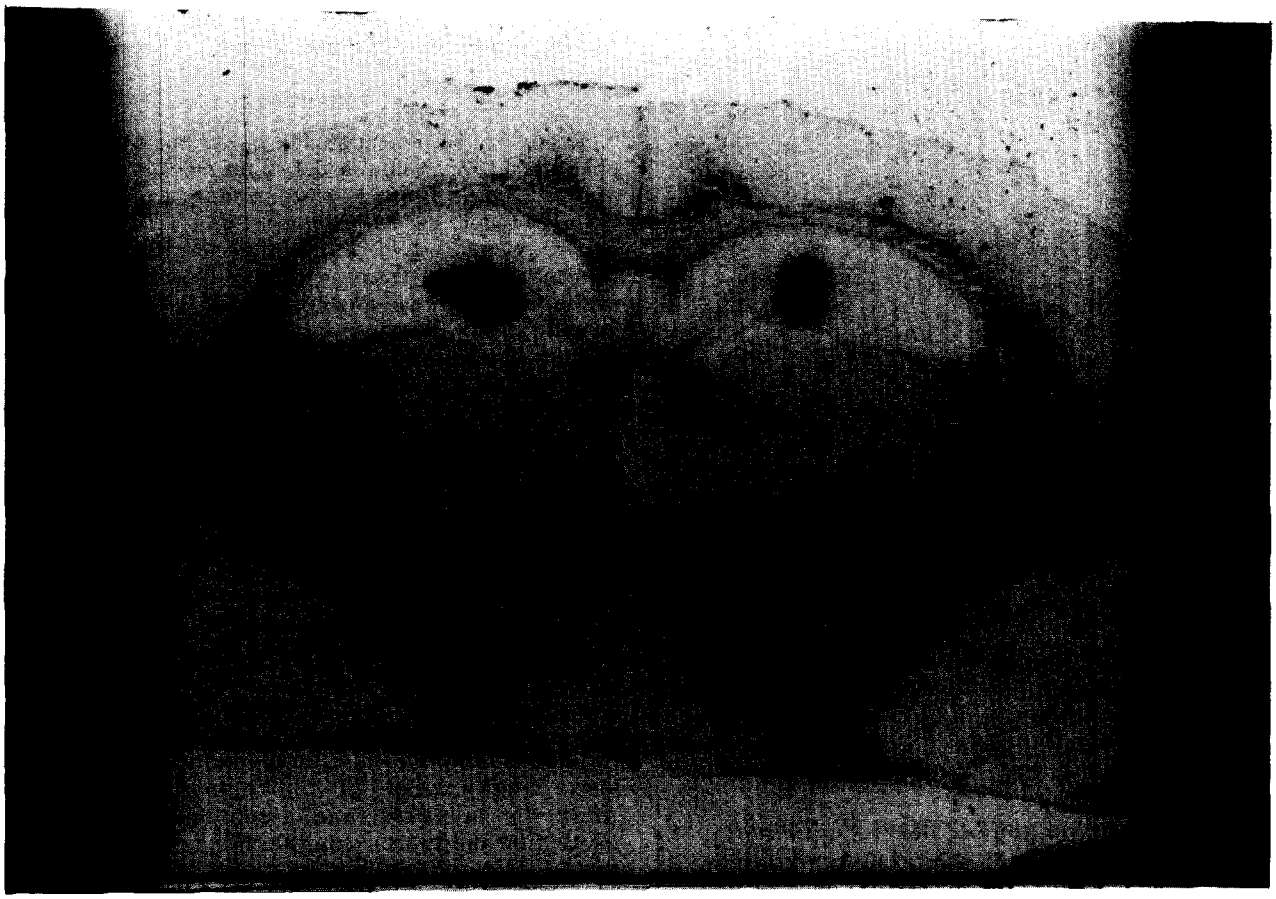

FIG. 1. Typical placement of injection needles and dye distribution in the DG of hippocampus of a representative rat. Methylene blue dye (0.8 μl, 3 mg/ml) was infused into each DG. A 20-μm-thick section through the DG is shown.

to analyze the data for the inhibitory avoidance task (23). The *U*-value was then translated into a *Z*-value.

Experiment 1

According to the findings reported in the literature, we hypothesized that NO should also play a facilitatory role in our current paradigm. The first study was designed to examine the dose-response effects of SNP on retention performance in rats. Animals were divided into six groups. Group I (n = 20) received intra-DG saline infusions; group II (n = 9) received 0.024 intra-DG SNP infusions; group III (n = 10) received 0.03 μg intra-DG SNP infusions; group IV (n = 16) received 0.06 μg intra-DG SNP infusions; group V (n = 14) received 0.24 μg intra-DG SNP infusions; and group VI (n = 16) received 2.4 μg intra-DG SNP infusions. Infusions were given immediately after the training procedure and animals were subjected to the memory test 24 h later. The hippocampus from three animals in each group was subjected to the in vitro ribosylation study later. Other animals were subject to histological examination.

Experiment 2

If NO plays a facilitatory role in memory retention, then blockade of NO production should impair retention. This experiment was designed to test this hypothesis. Animals were divided into four groups. Group I (n = 20) received intra-DG saline infusions; group II (n = 9) received 0.02 μg intra-DG L-MeArg infusions; group III (n = 19) received 0.2 μg intra-DG L-MeArg infusions; and group IV (n = 9) received 2.0 μg intra-DG L-MeArg infusions. Other experimental procedures were the same as described in Experiment 1.

Experiment 3

If prevention of NO production impairs retention performance, then administration of a NO precursor should reverse this effect. Animals were also divided into four groups. Group I (n = 14) received intra-DG saline + saline infusions; group II (n = 12) received intra-DG saline + 0.2 μg L-MeArg infusions; group III (n = 8) received 2.9 μg Arg and 0.2 μg L-MeArg infusions at the DG; and group IV (n = 6) received 7.2 μg Arg and 0.2 μg L-MeArg infusions at the DG. Both administrations were given together immediately after training. All other procedures were the same as in Experiment 1.

RESULTS

Experiment 1. Effects of Intra-DG SNP on Retention Performance in Rats

The dose-response effects of intra-DG SNP administration on retention performance of the inhibitory avoidance task in rats are shown in Fig. 2. Kruskal-Wallis one-way ANOVA revealed a significant main effect of SNP on retention (H =

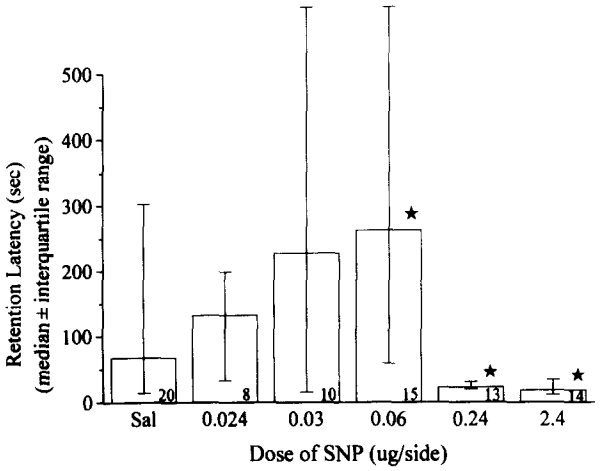

FIG. 2. Dose-response effects of intra-DG SNP on retention performance in rats. Data are expressed as median ± interquartile range. *$p < 0.05$ when compared with the control group.

16.71, $p < 0.01$). Further Mann-Whitney U-tests indicated that SNP at 0.06 μg significantly enhanced memory retention ($Z = 1.70, p < 0.05$). On the contrary, at higher doses (0.24 and 2.4 μg), SNP markedly impaired memory retention ($Z = 1.86, p < 0.05$ and $Z = 2.5, p < 0.01$, respectively).

Experiment 2. Effects of Intra-DG L-*MeArg on Retention Performance in Rats*

The dose-response effects of intra-DG L-MeArg on retention performance of the inhibitory avoidance task in rats are shown in Fig. 3. There was no overall significant effect of L-MeArg on memory retention ($H = 5.26, p > 0.05$). Further analyses indicated that L-MeArg at 0.02 μg did not significantly affect memory retention ($Z = 1.06, p > 0.05$), whereas at 0.2 μg it markedly impaired retention performance ($Z = 1.78, p < 0.05$). Although high dose of L-MeArg (2.0 μg) did not markedly decrease the retention score when compared with the control group ($Z = 0.53, p > 0.05$), it is significantly different from that of the low-dose L-MeArg group ($Z = 1.83, p < 0.05$).

Experiment 3. Interactive Effects of L-*Arginine and* L-*MeArg on Retention Performance in Rats*

Interactions between L-arginine and L-MeArg on memory retention are shown in Fig. 4. Consistent with the results in Experiment 2, L-MeArg at 0.2 μg also markedly impaired retention ($Z = 1.88, p < 0.05$). Coadministration of L-arginine at 2.9 and 7.2 μg prevented the memory-impairing effect of L-MeArg ($Z = 1.19$ and 0.47, both $p > 0.05$ when compared with the L-MeArg group).

In Vitro ADP-Ribosylation

To examine the dose-response effects of SNP on endogenous ADP-ribosylation during the memory consolidation process, tissue of DG from Experiment 1 was subject to ADP-ribosylation study in vitro in the presence of [^{32}P]NAD. The pattern of ADP-ribosylated proteins is illustrated in Fig. 5. As shown in this figure, five major proteins with molecular weight around 118, 94, 54, 43, and 39 kDa were labeled. Further, the labeling intensity of these proteins decreased as the concentration of in vivo SNP increased.

DISCUSSION

Results in the present study support our hypothesis that NO plays an important role during the memory consolidation process in rats as assessed by the inhibitory avoidance learning task. We found that intra-DG injection of SNP, a spontaneous NO generator, at moderate doses, enhanced retention performance in a dose-response fashion. This is the first in vivo evidence to show that administration of a NO generator enhanced memory retention in a behavioral learning task. This memory-enhancing effect of SNP was supported by another finding that SNP produces a long-lasting enhancement of synaptic efficacy that mimics LTP in hippocampal slices (2). These results together suggest that NO is involved in both memory processing and synaptic plasticity. In the present study, high doses of SNP were shown to impair memory retention. This is probably due to the neurotoxicity produced by the high concentration of NO, and consequently, high level of free radicals in the brain [see (16) for review]. Through histochemical examination, we have found that SNP at 2.4 and 24 μg indeed produced tissue damage in the DG of the hippocampus (data not shown). At the concentration of 24 μg, SNP increased the death rate of animals within a week, and at an even higher concentration (240 μg), none of the animals survived (unpublished observations).

Nitric oxide was also proposed to act as a retrograde messenger in hippocampal LTP (20). To act as a retrograde messenger, NO has been suggested to potentiate neurotransmitter release from presynaptic terminals. NO has been suggested to potentiate neurotransmitter release from hippocampal neurons in the dissociated cell culture (20). In the hippocampal cross-chopped slices, SNP was reported to stimulate the release of norepinephrine (17). These data suggest that NO may enhance retention performance by increasing the amount of transmitter release. Norepinephrine has been implicated in the memory process of higher vertebrates. Current studies are ongoing to investigate the effect of NO upon in vivo NE release.

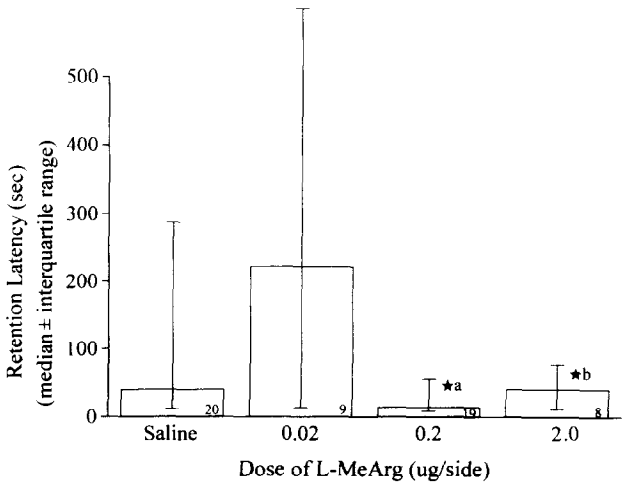

FIG. 3. Dose-response effects of intra-DG L-MeArg on retention performance in rats. Data are expressed as in Fig. 2. a, When compared with the control group; b, when compared with 0.02 μg L-MeArg group.

These results should help to further clarify the role of NO in memory processing.

The involvement of NO in the memory process of the inhibitory avoidance task was further supported by the finding that intra-DG injections of L-MeArg, a NO synthase inhibitor, impaired retention performance. Moreover, administration of the NO precursor L-arginine reversed this effect. Recently, inhibition of NO synthase has been shown to preferentially impair different forms of learning and/or memory. For example, systemic administration of L-NAME, another inhibitor of NO synthase, impaired place navigation learning but not visual discrimination learning in a water maze task (8,12). Intrahippocampal injection of L-NAME was reported to impair working memory but not reference memory in a three-panel runway task (21). Bohme et al. have reported that systemic injection of another NO synthase inhibitor, L-NoArg, impairs spatial learning in a radial arm maze and olfactory memory in a social recognition test, but not shock-avoidance learning in rats (3). The discrepancy of the effect of NO synthase inhibitor between our study and Bohme's study may be due to the following reasons. First, we used intra-DG injection paradigm instead of systemic injections. NO may yield different or even opposite effects in different brain areas. Secondly, the foot shock intensity we adopted is 1 mA for 1 s whereas Bohme et al. used 0.8 mA for 20 s. Habituation may have developed during this relatively long interval.

Our results have also demonstrated that the higher the dose of intra-DG SNP, the less in vitro ADP-ribosylation (Fig. 5). These results indicated that in vivo SNP administration resulted in endogenous ADP-ribosylation dose dependently; therefore, less in vitro ADP-ribosylation was observed. In another study, Duman et al. similarly reported that in hippocampal slices in which LTP has been induced, there is a significant reduction of in vitro ADP-ribosylation produced by SNP (11). Furthermore, we found two phosphoprotein bands with molecular weight around 39 and 54 kDa, which showed ADP-ribosylation. These proteins are similar to the proteins named GAPDH and GAP-43, respectively (10), and they are also the substrate proteins for ADP-ribosylation.

The present results suggest that hippocampal NO plays an important role in the memory consolidation process of an inhibitory avoidance task in rats. However, several issues still remain to be resolved. For example, immunohistochemical studies have indicated that the hippocampus exhibits a relatively low NOS level (13). Further, the CA1 layer of the hippocampus, an area strongly implicated in LTP and learning/memory, also lacks NOS activity (5,6). Moreover, SNP at high doses seem to produce a neurotoxicity, whereas at low and moderate doses (which presumably also produce free radicals) it facilitates memory formation. The mechanisms for these effects are yet unknown. Clarification of these points should help to further understand the role of NO in the central nervous system.

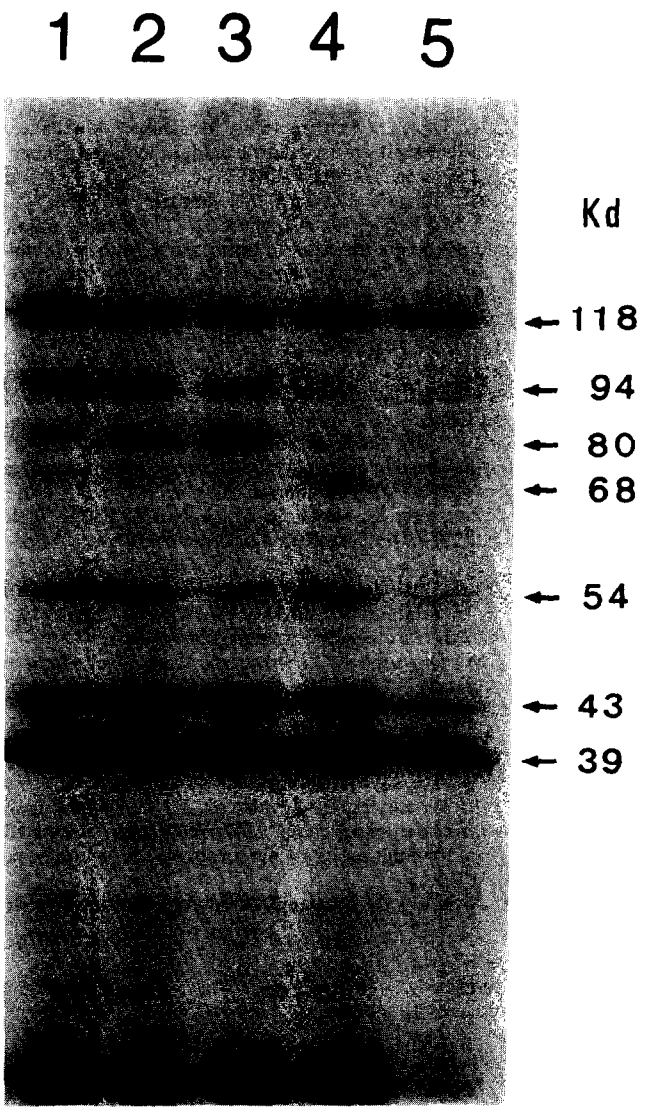

FIG. 5. Effects of intra-DG SNP administration on in vitro ADP-ribosylation of proteins in this area. Lane 1: saline group (with a retention score around 100 s); lane 2: 0.03 μg SNP group; lane 3: 0.06 μg SNP group; lane 4: 0.24 μg SNP group; lane 5: 2.4 μg SNP group.

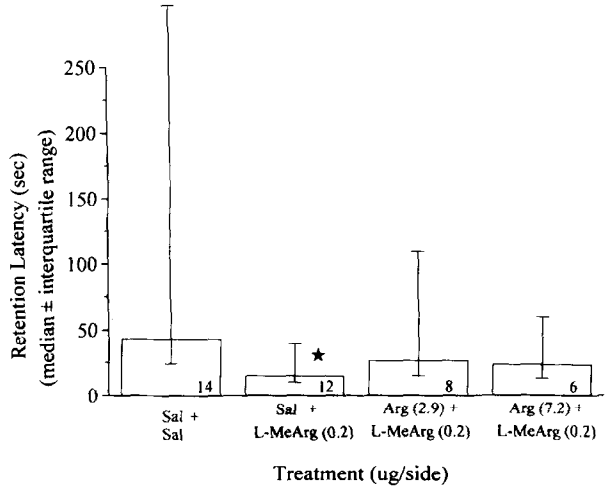

FIG. 4. Interactive effects of intra-DG arginine and L-MeArg on retention performance in rats. Data are expressed as in Fig. 2.

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