Available online at www.sciencedirect.com

SCIENCE DIRECT

European Journal of Pharmacology 511 (2005) 159–166

www.elsevier.com/locate/ejphar

Post-training intrahippocampal infusion of the COX-2 inhibitor celecoxib impaired spatial memory retention in rats

Mohammad Sharifzadeh[a], Nasser Naghdi[b], Sara Khosrovani[a], Seyed Nasser Ostad[a], Kurdistan Sharifzadeh[a], Ali Roghani[c,d,*]

[a]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[b]Department of Pharmacology, Iran Pasteur Institute, Tehran, Iran
[c]Department of Pharmacology and Neuroscience, Texas Tech University Health Sciences Center, Lubbock, TX, USA
[d]Texas Institute of Environmental and Human Health, Texas Tech University, Lubbock, TX, USA

Received 27 September 2004; received in revised form 10 January 2005; accepted 28 January 2005
Available online 17 March 2005

Abstract

In this study, we investigated the effects of intrahippocampal infusion of indomethacin as a non-selective cyclooxygenase inhibitor and celecoxib as a selective cyclooxygenase-2 inhibitor on spatial memory in the Morris water maze. Rats were trained for 3 days; each day included two blocks, and each block contained 4 trials. Tests were performed 48 h after surgery. Bilateral intrahippocampal infusion of indomethacin (0.01, 0.1, or 1 M) did not show any significant effect on spatial memory retention at these concentrations in rats. We also examined effects of infusion of celecoxib (0.02, 0.06, or 0.1 M) on memory retention. Bilateral infusion of 0.1 M celecoxib significantly altered escape latency and traveled distance in rats. These results strongly suggest that cyclooxygenase-2 is involved in spatial memory retention.

Keywords: Stereotaxic surgery; Cyclooxygenase; Hippocampus; Morris water maze

1. Introduction

Cyclooxygenase is the first enzyme in the prostaglandin/prostacyclin/thromboxane pathway. It converts arachidonic acid to prostaglandins and thromboxanes, which are collectively known as prostanoid metabolites (Needleman et al., 1986; Teather et al., 2002; Turini and Dubois, 2002). These metabolites have important roles in various physiologic and pathologic conditions (Turini and Dubois, 2002). Cyclooxygenase enzymes catalyze both the biooxygenation of arachidonic acid to form prostaglandin G_2 and the peroxidative reduction of prostaglandin G_2 to form prostaglandin H_2 in the biosynthesis of prostanoids (Vane et al., 1998). Three cyclooxygenase isoforms, cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), and cyclooxygenase-3 (COX-3), have been identified (Kujubu et al., 1991; Shaftel et al., 2003; Xie et al., 1991). COX-1 is the constitutive form of cyclooxygenase and performs a housekeeping function to synthesize prostaglandins, which are involved in regulating normal cellular activities (Herschman, 1996; Smith et al., 1991). In contrast, COX-2 is the inducible form of cyclooxygenase, as its expression can be induced by inflammatory stimuli or mitogens (Dubois et al., 1998), tumor necrosis factor-alpha (Chen et al., 2000, 2001), and the transcription factor CCAAT enhancer binding protein (c/EBP) beta (Gorgoni et al., 2001). The brain possesses both COX-1 and COX-2 isoforms (Breder et al., 1992; Teather, 1998). COX-2 appears to be expressed in dendrites and cell bodies of neurons in several areas of the brain, such as the temporal cortex, amygdala, dentate gyrus,

* Corresponding author. Texas Tech University Health Sciences Center, Department of Pharmacology and Neuroscience, 3601 4th Street, Lubbock, TX 79430, United States. Tel.: +1 806 743 2425x258; fax: +1 806 743 2744.
E-mail address: Ali.Roghani@ttuhsc.edu (A. Roghani).

0014-2999/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2005.01.041

and CA1 of hippocampus (Yamagata et al., 1993; Breder et al., 1995; Kaufmann et al., 1996; Teather, 1998; Murray and O'Connor, 2003; Hoozemans et al., 2004). Moreover, the neuronal expression of COX-2 is dynamically regulated by physiological synaptic activity (Yamagata et al., 1993). These observations suggest a role for COX-2 in activity-dependent neuronal plasticity, indicating an important function for COX-2 in cell signaling and neurotransmission (Kaufmann et al., 1996).

Memory formation is a complex process that requires the occurrence of different pre- and post-synaptic events. Numerous studies have been conducted to identify molecular mechanisms underlying activity-dependant synaptic changes during memory formation, and many proteins, including transcription factors, that play a role in different aspects of memory formation have been identified (Dou et al., 2003; Hebert and Dash, 2002; Li et al., 2003; Runyan et al., 2004; Woolf et al., 2001).

Previous studies showed a high level of expression of COX-2 in the hippocampal CA1 region where COX-2 has an important role in spatial memory processing (Kaufmann et al., 1996; Kunz and Oliw, 2001; Geinisman et al., 2004). A body of evidence indicates that COX-2 is probably involved in the physiological mechanisms underlying memory formation. First, intrahippocampal infusion of a COX-2 inhibitor attenuated memory acquisition in rats (Rall et al., 2003). Second, intraperitoneal administration of a COX-2 inhibitor immediately post-training impaired memory consolidation when tested 24 h after training. In the latter study, the retention test escape latencies of rats that received injections of selective and non-selective cyclooxygenase inhibitors 2 h post-training were not significantly different from those of vehicle-treated rats (Teather et al., 2002). The involvement of COX-2 and its metabolites in passive avoidance memory in chicks has also been reported previously by other investigators (Holscher, 1995).

Acquisition of the hidden platform in the water maze task is mediated by the hippocampus (Mishkin and Petri, 1984; Packard and McGaugh, 1992; Packard, 2001; Teather et al., 2002). In the present study, to examine the role and the significance of COX-1 and COX-2 in spatial memory retention, we infused either indomethacin or celecoxib into the CA1 region of the hippocampus after the rats were trained in the hidden platform Morris water maze. In these studies, celecoxib was used as a selective COX-2 inhibitor and indomethacin as a non-selective COX (i.e., COX-1 and COX-2) inhibitor. Spatial memory retention was tested and measured 48 h later.

2. Materials and methods

2.1. Drugs

Indomethacin, celecoxib, ketamine, and xylazine were purchased from Sigma (St. Louis, MO, USA). Indomethacin and celecoxib were dissolved in dimethyl sulfoxide (DMSO), and ketamine and xylazine were dissolved in distilled water.

2.2. Animals

Seventy-two male albino Wistar rats (200–250 g) were subjects in the present study. The animals were purchased from Pasteur Institute of Iran and housed in groups of five in stainless steel cages, handled daily, and provided food and water ad libitum. A 12-h light/12-h dark cycle was maintained, and the animals were trained and tested during the light cycle. These animal experiments were carried out in accordance with recommendations from the declaration of Helsinki and the internationally accepted principles in the use of experimental animals.

2.3. Behavioral training and testing

We performed two sets of experiments in this study. In the first series of the experiments, we randomly assigned rats (n=24) to three groups. One group received saline (n=8), the second received DMSO (n=8) and the third, called the intact group (n=8), did not receive any drugs. In the second series of experiments, the animals (n=48) were randomly assigned to receive indomethacin (0.01, 0.1, or 1 M) and celecoxib (0.02, 0.06, or 0.1 M). Concentrated DMSO (100%) was used as vehicle or control as well as a solvent for indomethacin and celecoxib. All animals were subjected to surgical bilateral infusions of either control (saline or DMSO) or a COX inhibitor into the CA1 region of the hippocampus immediately after training. The volume of injection in all groups was 0.5 μl, each injected during a 1-min period.

Training consisted of placing the animals in the Morris water maze, which included a circular, black-painted pool (136 cm in diameter, 60 cm in height) filled to a depth of 25 cm with water 22±1 °C. The pool was divided into four quadrants with four starting locations called north (N), east (E), south (S), and west (W) at equal distances on the rim. An invisible platform (10 cm diameter) made of Plexiglas was submerged 1 cm below the water and placed in the center of northern quadrant. The animals were trained for 3 days at approximately the same time (9–11 a.m.) each day. Each training day included two blocks, and each block consisted of four trials. Each trial was initiated by placing the animals in one of the four quadrants randomly. Animals were allowed to find the hidden platform during a period of 90 s. The rats rested 5 min between two consecutive blocks, and the inter-trial interval time was 30 s in each block. A video camera was mounted directly above the water maze pool. This camera was linked to a computer and used to record the rats' swim paths. More specifically, the escape latency (the time to reach the hidden platform), the traveled distance (the length of swim path), and swimming speed for each rat were all recorded automatically by a video tracking system. The data were used to prepare the graphs shown in Figs. 2–5. Spatial memory retention tests were performed 48 h after surgery,

similar to other studies, which assessed retention with a different kind of task in this type of time-frame (Woolf et al., 2001). All the experimental groups were tested at approximately the same time of the day in a given morning.

2.4. Infusion of COX inhibitors

The drug infusions were performed after the completion of all training trials. Each rat was anesthetized separately by injecting 75 mg/kg ketamine combined with 8.6 mg/kg xylazine intraperitoneally. We then prepared rats for surgery and placed them in the stereotaxic instrument. The CA1 region of the hippocampus was targeted. Stereotaxic coordinates for the CA1 region were set at 5 mm posterior and 3.0 mm lateral to bregma and 3.0 mm ventral to the surface of the skull according to the atlas of Paxinos and Watson (1997).

At each brain site, we infused indomethacin (0.01, 0.1, or 1 M), using a 10-μl Hamilton syringe, immediately after the last training trial. Celecoxib (0.02, 0.06, or 0.1 M) also was infused at each brain site immediately after the last training trial. No guide cannulae were implanted before the training trials because each animal received only one bilateral injection. For all the drug-infusions, as well as vehicle infusions (i.e., DMSO only), undiluted or 100%, DMSO was used. 48 h following drug infusion, the rats were tested for spatial memory retention by measuring escape latency, traveled distance and swimming speed. Following the testing trials, each animal was decapitated, and the brain was removed. Randomly selected brains were cut on a cryostat as 50-μm-thick coronal sections, mounted on glass slides, and stained with cresyl violet. The sections were then examined under a light-microscope to find the bilateral sites of infusion and to ascertain whether the sites were in the dorsal hippocampus. For those animals whose sites of infusion were shown not to be in the dorsal hippocampus, any collected data were discarded.

2.5. Statistics

We used a one-way analysis of variance (ANOVA) in most cases and a two-way ANOVA when specified. A Tukey–Kramer test was performed to assess differences in behavioral scores. A P value of 0.05 or less was considered statistically significant.

3. Results

3.1. Evaluation of escape latency, traveled distance, and swimming speed during the training days in the Morris water maze

After 3 days of training in the Morris water maze for all of our experiments, intact animals, as well as all treated groups (i.e., animals selected to receive bilateral infusion of either saline, DMSO, indomethacin or celecoxib), learned how to find the hidden platform as indicated by decreasing escape latencies and traveled distance (Fig. 1A and B). There was a significant difference (*P<0.01) between the third and the first day

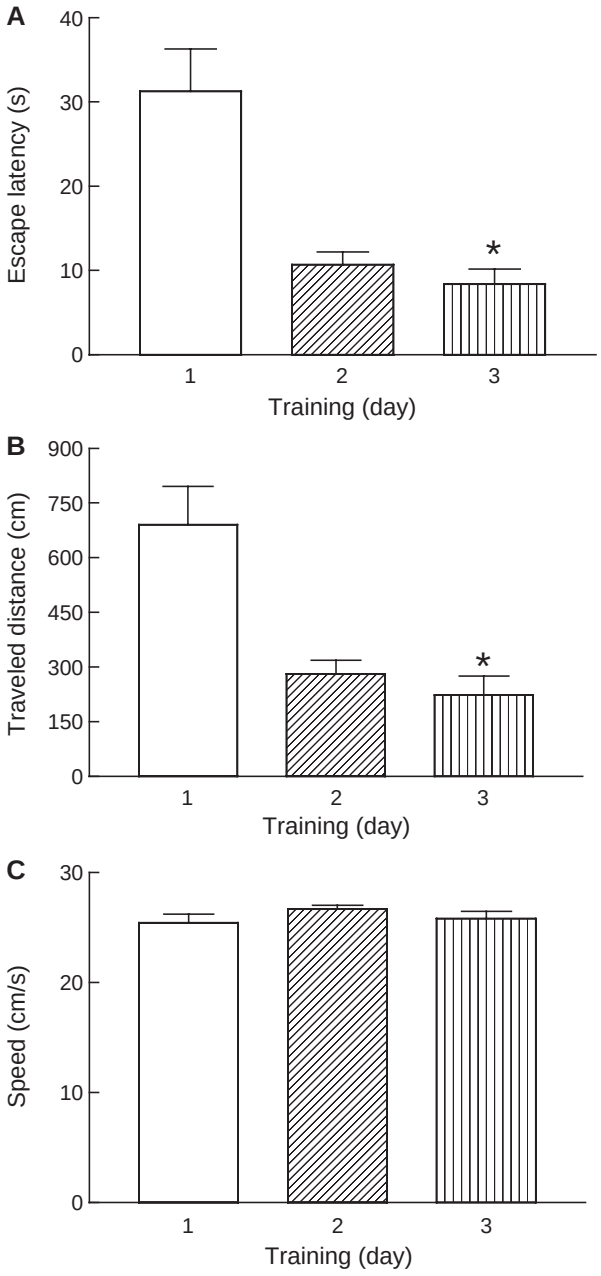

Fig. 1. Spatial navigation in the Morris water maze for experiment 1. The figure shows that all groups of the animals (intact or treated as well as those infused with saline, DMSO, indomethacin, and celecoxib) learned how to find the hidden platform. There was a significant difference (*P<0.01) in escape latency (A) and traveled distance (B) between the first and third day of training. No significant difference was observed for speed of swimming among first, second, and third day of training. Error bars in panels A–C show the S.E.M.

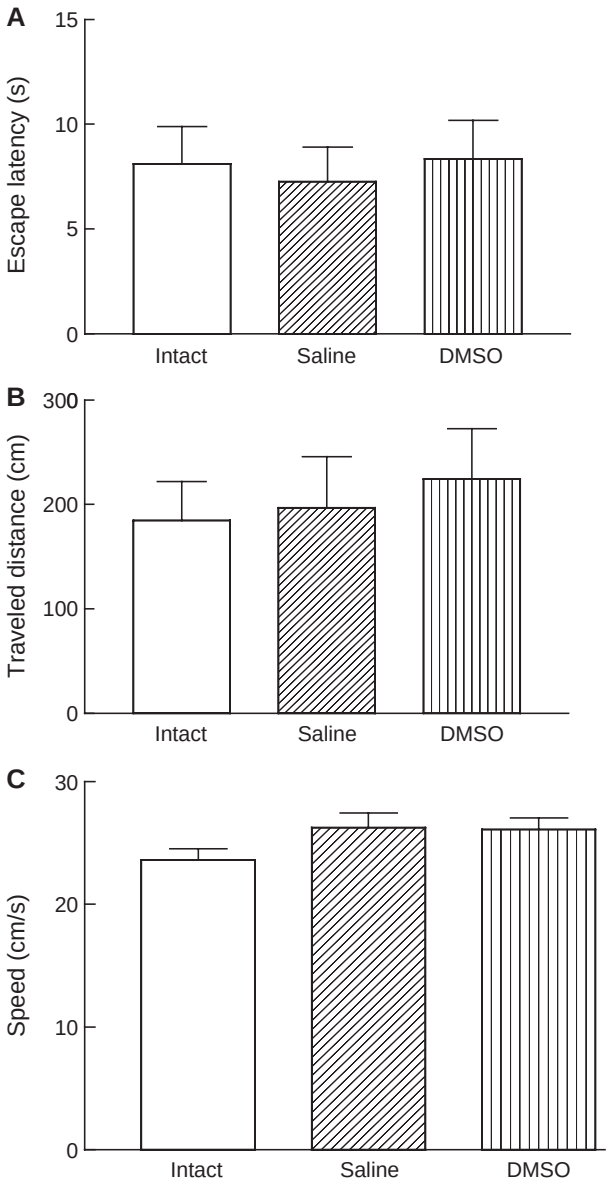

Fig. 2. Effect of DMSO infusion on memory retention test. In all experiments, the testing trials were performed 48 h after any infusion. DMSO caused no significant alteration in escape latency (A), traveled distance (B), and swimming speed (C) during testing compared with those of intact and animals infused with saline. Each bar graph shows Mean±S.E.M. for 8 animals.

of training in terms of escape latency and traveled distance for finding the hidden platform. The swimming speed was not significantly affected by training days in any of the animal groups (Fig. 1C).

3.2. Effects of DMSO on time and distance of finding hidden platform during the test trials

We dissolved indomethacin and celecoxib in DMSO, and DMSO was used as a vehicle. Post-training bilateral infusion of DMSO (0.5 μl per infusion site) into the CA1 region of the hippocampus did not cause any significant behavioral differences (i.e., in escape latency, travel distance, or swimming speed) in rats compared to intact and saline-infused groups (Fig. 2A, B, C).

3.3. Effects of indomethacin and celecoxib on escape latency, traveled distance, and swimming speed during the test trials

We performed the spatial memory retention test 48 h after the drug infusions. Post-training bilateral infusion of indomethacin (0.01, 0.1, or 1 M) into the CA1 of the hippocampus did not produce any statistically significant changes ($P>0.05$) in escape latency and traveled distance

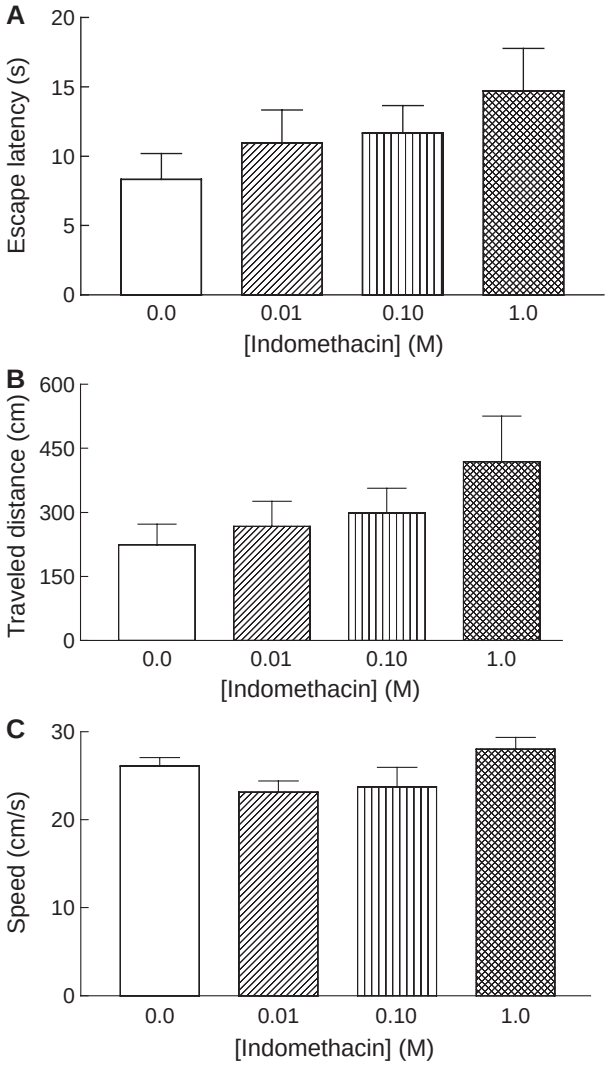

Fig. 3. The indomethacin-infused rats did not show spatial deficit during the testing trials. The escape latency (A) and traveled distance (B) were not significantly increased by indomethacin infusions ($P>0.05$) compared with control group. The swimming speed in the indomethacin-infused animals (C) did not show any significant changes. Each bar graph shows Mean±S.E.M. for 8 animals.

compared to the control group (Fig. 3A and B). Also, the swimming speed was very similar in control and indomethacin-infused groups, reflecting no motor disturbances (Fig. 3C). We also examined the effects of intrahippocampal infusion of celecoxib (0.02, 0.06, or 0.1 M) on spatial memory retention. Bilateral infusion of celecoxib (0.06 or 0.1 M) into the CA1 of the hippocampus caused spatial memory deficits as shown in Fig. 4A and B. Compared to the control group, significant differences (**P<0.05) in escape latency and traveled distance were observed only with 0.1 M celecoxib. However, the swimming speed was very similar in control and celecoxib-infused groups (Fig. 4C). An increase in travel path following infusion of celecoxib (0.1 M) was also shown in Fig. 5A and B. Compared to control group (A), the travel path substantially increased by celecoxib infusion (B).

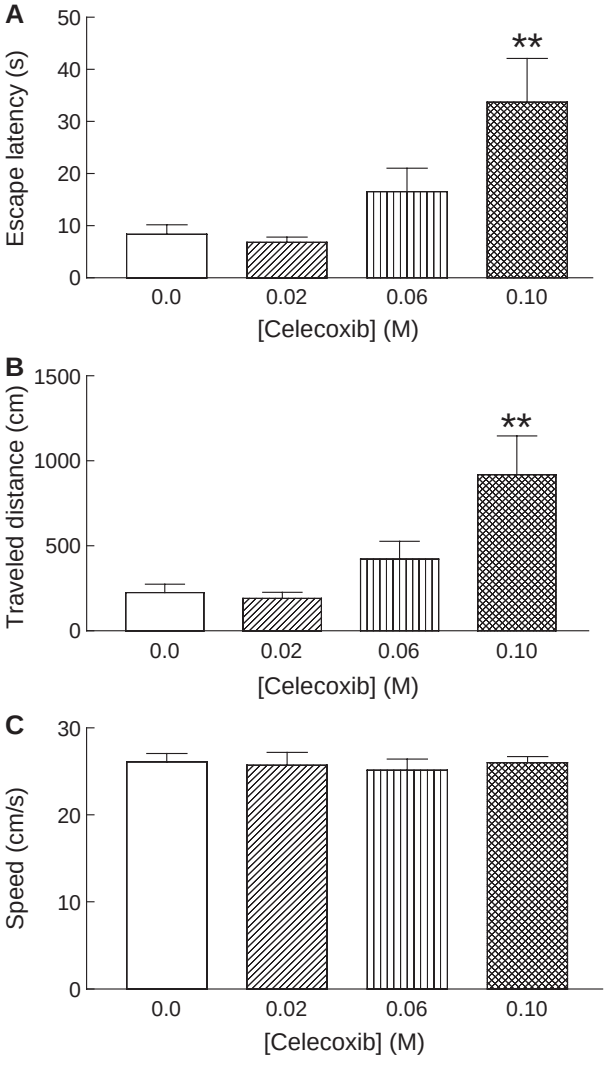

Fig. 4. The celecoxib-infused rats showed spatial memory deficit during the testing trials. The escape latency (A) and traveled distance (B) were significantly increased by celecoxib (0.1 M) infusions (**P<0.01) compared with the control group. The swimming speed in the celecoxib-infused animals did not show any significant changes (C). Each bar graph shows Mean±S.E.M. for 8 animals.

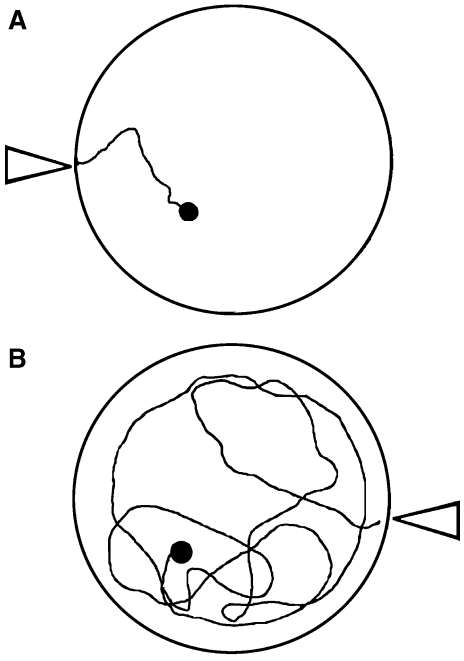

Fig. 5. Infusion of celecoxib increased travel path in the test day. Diagrams A–B show representative traces of travel path following infusion of DMSO (A) and 0.1 M celecoxib (B). The arrowheads designate swim starting points and the solid circles designate the position of the hidden platforms. Compared to DMSO, the travel path substantially increased with the celecoxib infusion.

4. Discussion

In our present work, we employed the Morris water maze to study spatial memory since performing the related tasks in this maze depends on the hippocampus (Brandeis et al., 1989). We found that a post-training intrahippocampal infusion of the COX-2-specific inhibitor celecoxib, but not the non-selective COX inhibitor indomethacin (Gierse et al., 1999), significantly impaired spatial memory in the Morris water maze with a hidden platform when tested 48 h after training. Previous findings from a somewhat similar study indicated that peripheral injection of both the COX-2-specific inhibitor NS-398 and the non-selective COX inhibitor indomethacin, but not the COX-1-specific inhibitor piroxicam, impaired memory consolidation in a hidden platform water maze task when tested 24 h after completion of training trials (Teather et al., 2002). Their results suggested that COX-2, but not COX-1, was important in memory consolidation. In comparison, Teather et al. obtained their findings by an intraperitoneal injection of the COX inhibitors administered after training trials, whereas in our study, we investigated the effects of COX-2 inhibition by testing a selective COX-2 inhibitor (celecoxib) compared to a non-selective COX inhibitor

(indomethacin) infused directly into the CA1 of the hippocampus. Interestingly, our results with indomethacin contradict findings of Teather et al. This could be in part due to the fact that in our study, we used approximately one-tenth the amount of indomethacin. It may also be important to note that our test trials were performed 48 h after training. Results from a separate study also indicated that intrahippocampal infusion of celecoxib attenuated memory acquisition in rats (Rall et al., 2003), suggesting that COX-2 has a dual role in memory acquisition and consolidation.

In our work, indomethacin and celecoxib were dissolved in DMSO (100%) for all infusions. We found that DMSO was a suitable and effective solvent for these drugs. In fact, DMSO-infused animals showed no significant differences in escape latencies, traveled distance and swimming speed when compared with intact or saline-infused rats during testing trials. Therefore, it appeared that DMSO infusions did not cause motor disturbances or have significant effects on spatial memory parameters. The effective use of DMSO as a vehicle has also been reported by others (Naghdi et al., 2001; Packard et al., 1996).

We also observed no significant differences for swimming speed among the first, second and third day of training. In addition, the animals receiving indomethacin or celecoxib infusions did not show any significant differences in swimming speed compared with the speed of animals receiving saline or DMSO infusions (control groups). These observations demonstrate that the infusions caused no undesirable motor disturbances and give credence to our conclusion that celecoxib infusions impaired spatial memory retention in rats. Although swim speeds were not affected, our results cannot rule out the possibility, given that the hippocampus is probably not mediating the swim behavior very much.

Understanding the cellular and molecular mechanism(s) by which COX-2 inhibition impairs memory retention is rather significant. Recent investigations showed a role for prostaglandin E_2 (an arachidonic metabolite) in neural plasticity (Andreasson et al., 2001; Chen et al., 2002; Li et al., 2003; Teather et al., 2002). For instance, it has been shown that administration of exogenous prostaglandin E_2 overcomes the negative effects of the COX-2 inhibitor NS-398 on spatial memory retention in a water maze task (Chen et al., 2002; Teather et al., 2002). It is worthwhile to mention that prostaglandins have modulatory effects on adrenergic, noradrenergic, and glutaminergic transmission (Partington et al., 1980; Kimura et al., 1985; Robinson et al., 1989; Packard and Teather, 1997; Bezzi and Volterra, 2001; Amateau and McCarthy, 2002). These observations, our data, and those of others (Rall et al., 2003; Teather et al., 2002) point to a neuromodulatory role for COX-2-mediated prostaglandin production in neural plasticity. It is conceivable that our observed COX-2 inhibition and memory retention deficit may be due to a reduction in prostaglandin E_2 production, also suggested by previous findings in a memory acquisition study (Rall et al., 2003).

In addition to modulating neurotransmission, prostaglandins are involved in the regulation of acetylcholine receptor sensitivity (Buccafusco et al., 1993). It is of interest to note that acetylcholine has a regulatory effect on COX-2 activity (Reichman et al., 1987), indicating a possible interaction between the cholinergic system and prostaglandin pathways in memory. Moreover, previously published reports suggest an interactive role for the COX-2-mediated prostaglandin pathway and the cholinergic system in neuronal plasticity (Bugajski et al., 2002). Therefore, it is reasonable to assume that the observed deficit in spatial memory retention (induced by COX-2 inhibition) found in this and other selected studies may be in part due to a reduction in expression of cholinergic markers, such as choline acetyltransferase and vesicular acetylcholine transporter. To test this possibility in the future, expression of choline acetyltransferase and vesicular acetylcholine transporter proteins in the hippocampus should be determined by immunohistochemistry and/or by Western blot analysis, and should be quantified following the infusion of celecoxib.

In contrast to our findings, some investigators recently showed that COX-2 up-regulation during stressful conditions such as cerebral ischemia caused learning deficits (Li et al., 2003). Their findings indicated that intermittent hypoxia-induced COX-2 up-regulation was associated with increased prostaglandin E_2 tissue levels, neuronal apoptosis and neurobehavioral deficit. Furthermore, NS-398 treatment attenuated intermittent hypoxia-induced deficit in the acquisition and retention of a spatial task in the Morris water maze (Li et al., 2003). This controversy could be related to different physiological functions of COX-2 in the mammalian central nervous system, particularly in pathological conditions.

In our study, the effects of indomethacin as a non-selective COX inhibitor on escape latency and traveled distance were not significant. Different behavioral results obtained by various COX inhibitors indicate that COX-1 and COX-2 enzymes may not act similarly (Breder et al., 1995), and it is possible that the function of COX-1 in spatial memory retention in the brain is different from that of COX-2 or that COX-1 has a role in spatial memory retention at the early steps of memory formation. Also, it is possible that the concentrations of indomethacin we chose in our study were not high enough to impair memory retention.

It is worth mentioning that, in our study, the main objective was to evaluate the effects of drug infusion on memory retention. Drug infusions were performed only after all training trials were completed. It is possible that a lower dose of the drug, infused after each day of training would have been more effective in impairing spatial memory retention, but this would complicate the investigation by introducing possible effects on memory acquisition. It is also worth reiterating that, in our work, spatial

memory retention was tested 48 h after the infusion of COX inhibitors. However, the duration of training, number of trials, type of learning tasks, and testing time may all be important in the assessment of physiological function of COX isozymes in memory formation processes. Effects of changing these parameters will be addressed in our future studies.

In conclusion, our data demonstrate that endogenous COX-2 activity in the dorsal hippocampus is necessary for spatial memory retention. Further research is needed to reveal the cellular and molecular mechanism(s) mediating the role of COX-2 in spatial memory retention.

Acknowledgments

We thank Mr. Brent Weiser for preparation of the manuscript and Dr. Charles C. Bittle for his critical reading. This study was supported in part by funds from Tehran University of Medical Sciences to MS and grant NS35356 from NIH to AR.

References

Amateau, S.K., McCarthy, M.M., 2002. A novel mechanism of dendritic spine plasticity involving estradiol induction of prostaglandin-E2. J. Neurosci. 22, 8586–8596.

Andreasson, K.I., Savonenko, A., Vidensky, S., Goellner, J.J., Zhang, Y., Shaffer, A., Kaufmann, W.E., Worley, P.F., Isakson, P., Markowska, A.L., 2001. Age-dependent cognitive deficits and neuronal apoptosis in cyclooxygenase-2 transgenic mice. J. Neurosci. 21, 8198–8209.

Bezzi, P., Volterra, A., 2001. A neuron-glia signalling network in the active brain. Curr. Opin. Neurobiol. 11, 387–394.

Brandeis, R., Brandys, Y., Yehuda, S., 1989. The use of the Morris water maze in the study of memory and learning. Int. J. Neurosci. 48, 29–69.

Breder, C.D., Smith, W.L., Raz, A., Masferrer, J., Seilbert, K., Needleman, P., Saper, C.B., 1992. Distribution and characterization of cyclo-oxygenase immunoreactivity in the ovine brain. J. Comp. Neurol. 322, 409–438.

Breder, C.D., Dewitt, D., Kraig, R.P., 1995. Characterization of inducible cyclooxygenase in rat brain. J. Comp. Neurol. 355, 296–315.

Buccafusco, J.J., Lapp, C.A., Aronstam, R.S., Hays, A.C., Shuster, L.C., 1993. Role of prostanoids in the regulation of central cholinergic receptor sensitivity. J. Pharmacol. Exp. Ther. 266, 314–322.

Bugajski, J., Gadek-Michalska, A., Bugajski, A.J., 2002. Effect of constitutive- and inducible-cyclooxygenase in the carbachol-induced pituitary–adrenocortical response during social stress. J. Physiol. Pharmacol. 53 (3), 453–462.

Chen, C.C., Sun, Y.T., Chen, J.J., Chiu, K.T., 2000. TNF-alpha-induced cyclooxygenase-2 expression in human lung epithelial cells: involvement of the phospholipase C-gamma 2, protein kinase C-alpha, tyrosine kinase, NF-kappa B-inducing kinase, and I- kappa B kinase 1/2 pathway. J. Immunol. 1, 2719–2728.

Chen, C.C., Sun, T., Chen, J.J., Chang, Y.J., 2001. Tumor necrosis factor-alpha-induced cyclooxygenase-2 expression via sequential activation of ceramide-dependent mitogen-activated protein kinases, and IkappaB kinase 1/2 in human alveolar epithelial cells. Mol. Pharmacol. 59, 493–500.

Chen, C., Magee, J.C., Bazan, N.G., 2002. Cyclooxygenase-2 regulates prostaglandin E2 signaling in hippocampal long-term synaptic plasticity. J. Neurophysiol. 87, 2851–2857.

Dou, J., Cui, C., Dufour, F., Alkon, D.L., Zhao, W.Q., 2003. Gene expression of alpha-endosulfine in the rat brain: correlative changes with aging, learning and stress. J. Neurochem. 87, 1086–1100.

Dubois, R.N., Abramson, S.B., Crofford, L., Gupta, R.A., Simon, L.S., Van De Putte, L.B., Lipsky, P.E., 1998. Cyclooxygenase in biology and disease. FASEB J. 12 (12), 1063–1073.

Geinisman, Y., Ganeshina, O., Yoshida, R., Berry, R.W., Disterhoft, J.F., Gallagher, M., 2004. Aging, spatial learning, and total synapse number in the rat CA1 stratum radiatum. Neurobiol. Aging 25, 407–416.

Gierse, J.K., Koboldt, C.M., Walker, M.C., Seibert, K., Isakson, P.C., 1999. Kinetic basis for selective inhibition of cyclo-oxygenases. Biochem. J. 339, 607–614.

Gorgoni, B., Caivano, M., Arizmendi, C., Poli, V., 2001. The transcription factor C/EBPbeta is essential for inducible expression of the COX-2 gene in macrophages but not in fibroblasts. J. Biol. Chem. 276 (44), 40769–40777.

Hebert, A.E., Dash, P.K., 2002. Extracellular signal-regulated kinase activity in the entorhinal cortex is necessary for long-term spatial memory. Learn. Mem. 9, 156–166.

Herschman, H.R., 1996. Prostaglandin synthase 2. Biochim. Biophys. Acta 1299, 125–140.

Holscher, C., 1995. Inhibitors of cyclooxygenases produce amnesia for a passive avoidance task in the chick. Eur. J. Neurosci. 7, 1360–1365.

Hoozemans, J.J., Veerhuis, R., Rozemuller, A.J., Arendt, T., Eikelenboom, P., 2004. Neuronal COX-2 expression and phosphorylation of pRb precede p38 MAPK activation and neurofibrillary changes in AD temporal cortex. Neurobiol. Dis. 15, 492–499.

Kaufmann, W.E., Worley, P.F., Pegg, J., Bremer, M., Isakson, P., 1996. COX-2, a synaptically induced enzyme, is expressed by excitatory neurons at postsynaptic sites in rat cerebral cortex. Proc. Natl. Acad. Sci. U. S. A. 93, 2317–2321.

Kimura, H., Okamoto, K., Sakai, Y., 1985. Modulatory effects of prostaglandin D2, E2, and F2 alpha on the postsynaptic actions of inhibitory and excitatory amino acids in cerebellar Purkinje cell dendrites in vitro. Brain Res. 330, 235–244.

Kujubu, D.A., Fletcher, B.S., Varnum, B.C., Lim, R.W., Herschman, H.R., 1991. TIS10, a phorbol ester tumor promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase/cyclooxygenase homologue. J. Biol. Chem. 266, 12866–12872.

Kunz, T., Oliw, E.H., 2001. The selective cyclooxygenase-2 inhibitor rofecoxib reduces kainate-induced cell death in the rat hippocampus. Eur. J. Neurosci. 13, 569–575.

Li, R.C., Row, B.W., Gozal, E., Kheirandish, L., Fan, Q., Brittian, K.R., Guo, S.Z., Sachleben Jr., L.R., Gozal, D., 2003. Cyclooxygenase 2 and intermittent hypoxia-induced spatial deficits in the rat. Am. J. Respir. Crit. Care Med. 168, 469–475.

Mishkin, M., Petri, H.L., 1984. Memories and habits: some implications for the analysis of learning and retention. In: Squire, R., Butters, N. (Eds.), Neurophysiology of Memory. Guilford, New York, pp. 287–296.

Murray, H.J., O'Connor, J.J., 2003. A role for COX-2 and p38 mitogen activated protein kinase in long-term depression in the rat dentate gyrus in vitro. Neuropharmacology 44, 374–380.

Naghdi, N., Nafisy, N., Majlessi, N., 2001. The effects of intrahippocampal testosterone and flutamide on spatial localization in the Morris water maze. Brain Res. 897, 44–51.

Needleman, P., Turk, J., Jakschik, B.A., Morrison, A.R., Lefkowith, J.B., 1986. Arachidonic acid metabolism. Annu. Rev. Biochem. 55, 69–102.

Packard, M.G., 2001. On the neurobiology of multiple memory systems: Tolamn versus Hull, system interactions, and the emotion–memory link. Cogn. Process. 1, 1–22.

Packard, M.G., McGaugh, J.L., 1992. Double dissociation of fornix and caudate nucleus lesions on acquisition of two water maze tasks: further evidence for multiple memory systems. Behav. Neurosci. 106, 439–446.

Packard, M.G., Teather, L.A., 1997. Double dissociation of hippocampal and dorsal–striatal memory systems by posttraining intracerebral injections of 2-amino-5-phosphonopentanoic acid. Behav. Neurosci. 111, 543–551.

Packard, M.G., Teather, L.A., Bazan, N.G., 1996. Effects of intrastriatal injections of platelet-activating factor and the PAF antagonist BN 52021 on memory. Neurobiol. Learn. Mem. 66, 176–182.

Partington, C.R., Edwards, M.W., Daly, J.W., 1980. Regulation of cyclic AMP formation in brain tissue by alpha-adrenergic receptors: requisite intermediacy of prostaglandins of the E series. Proc. Natl. Acad. Sci. U. S. A. 77, 3024–3028.

Paxinos, G., Watson, C., 1997. The Rat Brain in Stereotaxic Coordinates. Academic Press, San Diego.

Rall, J.M., Mach, S.A., Dash, P.K., 2003. Intrahippocampal infusion of a cyclooxygenase-2 inhibitor attenuates memory acquisition in rats. Brain Res. 968, 273–276.

Reichman, M., Nen, W., Hokin, L.E., 1987. Acetylcholine releases prostaglandins from brain slices incubated in vitro. J. Neurochem. 49, 1216–1221.

Robinson, G.S., Crooks, G.B., Shinkman, P.G., Gallagher, M., 1989. Behavioral effects of MK-801 mimic deficits associated with hippocampal damage. Psychobiology 17, 156–164.

Runyan, J.D., Moore, A.N., Dash, P.K., 2004. A role for prefrontal cortex in memory storage for trace fear conditioning. J. Neurosci. 24, 1288–1295.

Shaftel, S.S., Olschowka, J.A., Hurley, S.D., Moore, A.H., O'Banion, M.K., 2003. COX-3: a splice variant of cyclooxygenase-1 in mouse neural tissue and cells. Brain Res. Mol. Brain Res. 119, 213–215.

Smith, W.L., Marnett, L.J., Dewitt, D.L., 1991. Prostaglandin and thromboxane biosynthesis. Pharmacol. Ther. 49, 153–179.

Teather, L.A., 1998. "Neurobiological mechanisms of anatomically and functionally distinct mammalian memory systems". PhD thesis Louisiana State university medical center, New Orleans.

Teather, L.A., Packard, M.G., Bazan, N.G., 2002. Post-training cyclooxygenase-2 (COX-2) inhibition impairs memory consolidation. Learn. Mem. 9, 41–47.

Turini, M.E., Dubois, R.N., 2002. Cyclooxygenase-2: a therapeutic target. Annu. Rev. Med. 53, 35–57.

Vane, J.R., Bakhle, Y.S., Botting, R.M., 1998. Cyclooxygenases 1 and 2. Annu. Rev. Pharmacol. Toxicol. 38, 97–120.

Woolf, N.J., Milov, A.M., Schweitzer, E.S., Roghani, A., 2001. Elevation of nerve growth factor and antisense knockdown of TrkA receptor during contextual memory consolidation. J. Neurosci. 21, 1047–1055.

Xie, W.L., Chipman, J.G., Robertson, D.L., Erikson, R.L., Simmons, D.L., 1991. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. Proc. Natl. Acad. Sci. U. S. A. 88, 2692–2696.

Yamagata, K., Andreasson, K.I., Kaufmann, W.E., Barnes, C.A., Worley, P.F., 1993. Expression of a mitogen-inducible cyclooxygenase in brain neurons: regulation by synaptic activity and glucocorticoids. Neuron 11, 371–386.