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Requirement of hippocampal phospholipase A_2 activity for long-term memory retrieval in rats

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Summary In rats, the inhibition of phospholipase A_2 (PLA_2) in hippocampus was reported to impair memory acquisition. In the present study we investigated in rats whether PLA_2 inhibition in hippocampus is also related to impairment of memory retrieval. Rats were bilaterally implanted with cannulae in hippocampal CA1 region. After recovery, animals were submitted to one-trial step-down inhibitory avoidance task and tested for long-term memory (LTM) 24 h later. Before test session, animals received infusions of vehicle or the PLA_2 inhibitor $PACOCF_3$. Inhibition of PLA_2 activity impaired LTM retrieval. Memory impairment was fully reversed once PLA_2 activity was recovered. Moreover, LTM retrieval *per se* increased PLA_2 activity. To our knowledge, we demonstrated for the first time that PLA_2 activity is required for memory retrieval. Because reduced PLA_2 activity has been found in Alzheimer's disease brains, the present results may be relevant to clarify at least part of the biology of this disorder.

Keywords: Phospholipase A_2, rats, hippocampus, memory, inhibitory avoidance, Alzheimer's disease

Introduction

Phospholipase A_2 (PLA_2) refers to a family of hydrolytic enzymes that catalyse the cleavage of fatty acids from the *sn*-2 position of membrane phospholipids to release free fatty acids and lysophospholipids. The family of PLA_2 enzymes is classified into three main groups: extracellular or secreted Ca^{2+}-dependent PLA_2 ($sPLA_2$); cytosolic Ca^{2+}-dependent PLA_2 ($cPLA_2$); and intracellular Ca^{2+}-independent PLA_2 ($iPLA_2$) (Dennis, 1994). The mRNA and/or the activity of the three PLA_2 groups were detected in rat and human brains (Yoshihara and Watanabe, 1990; Owada et al., 1994; Larsson et al., 1998; Molloy et al., 1998; Kishimoto et al., 1999; Pickard et al., 1999; Yang et al., 1999; Mancuso et al., 2000). PLA_2 preferentially cleaves membrane phosphatidylcholine to release free arachidonic acid and lysophosphatidylcholine, which are important mediators in neuronal functions necessary for memory processing (Farooqui et al., 1997).

In fact, several studies have suggested an involvement of PLA_2 in memory function. Hence, infusions of PLA_2 inhibitors into the chick intermediate medial hyperstriatum ventrale impaired learning of a passive avoidance task (Hölscher and Rose, 1994). In addition, intraperitoneal injections of a non-selective PLA_2 inhibitor in rats impaired spatial learning tested in the Morris water maze (Hölscher et al., 1995), and intracerebroventricular infusions of a selective $iPLA_2$ inhibitor in mice also impaired spatial learning tested in the Y-maze (Fujita et al., 2000). Finally, recent studies from our laboratory showed that infusions of dual $cPLA_2$ and $iPLA_2$ inhibitors and a selective $iPLA_2$ inhibitor directly into rat hippocampus impaired memory acquisition of step-down inhibitory avoidance (IA) task (Schaeffer and Gattaz, 2005).

The biochemical cascade of memory has been extensively studied in the CA1 region of the dorsal hippocampus of rats in connection with one-trial step-down IA task, which involves learning not to step down from a platform in order to avoid a mild foot shock (Izquierdo and Medina, 1997). In this paradigm, the retrieval of long-term memory (LTM) involves activation of glutamatergic and cholinergic receptors in CA1 (Barros et al., 2003). Several *in vitro* studies have shown that PLA_2 activation (an the resulting release of arachidonic acid) causes increased binding of ligands to glutamatergic receptors in rat hippocampus (Massicotte and Baudry, 1990; Tocco et al., 1992; Catania

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et al., 1993; Chabot et al., 1998). Moreover, membrane phosphatidylcholine is a precursor of choline for the synthesis of acetylcholine (Blusztajn et al., 1987a, b). In rat hippocampal slices, PLA_2 inhibition blocked the release of lysophosphatidylcholine and, consequently, of choline (Weichel et al., 1999). Together, these data suggest that PLA_2 may be involved in memory retrieval for IA task.

In the present study, using the step-down IA task, we investigated the effect of PLA_2 inhibition in the CA1 region of rat hippocampus on the retrieval of LTM, as well as the effect of recovery of the enzyme activity on memory retrieval. We determined further the involvement of PLA_2 activation in rat hippocampus during LTM retrieval.

Material and methods

One hundred and sixty-four adult male Wistar rats (2.5–3.0 months old; 270–330 g) from the Central Animal Laboratory House of Federal University of São Paulo were used in the present study. All the procedures described were in accordance with the FELASA (Federation of the European Laboratory Animal Science Associations) recommendations to minimise the number of animals used and their suffering, and were approved by the institutional animal ethics committee.

Stereotaxic surgery

A total of one hundred and forty rats were submitted to stereotaxic surgery. The rats were anaesthetised with an intraperitoneal injection of $15\,mg \cdot kg^{-1}$ ketamine and $1.6\,mg \cdot kg^{-1}$ diazepam, placed in a stereotaxic frame (David Kopf, Tujunga, CA), and bilaterally implanted with 22-gauge guide cannulae aimed 1.0 mm above the CA1 region of the dorsal hippocampus at stereotaxic coordinates anterior −4.3 mm from *bregma*, lateral ± 4.0 mm from midline, and ventral 3.4 mm from dura (Paxinos and Watson, 1998). The cannulae were fixed to the skull with dental glass ionomer cement.

Drug infusion procedures

After recovery from surgery, 30-gauge infusion cannulae were fitted into the guide cannulae, and the rats received an acute bilateral 0.5 µl infusion into the CA1 region of a vehicle (0.3% DMSO in saline) or of palmitoyl trifluoromethylketone ($PACOCF_3$; Biomol, Plymouth Meeting, PA), a reversible dual $cPLA_2$ and $iPLA_2$ inhibitor (Ackermann et al., 1995; Balsinde and Dennis, 1997), dissolved in the vehicle to a concentration previously described to prevent induction of long-term potentiation in rat CA1 region *in vitro* (Fujita et al., 2001) and to impair memory acquisition when given into rat CA1 *in vivo* (Schaeffer and Gattaz, 2005). The infusions were performed manually using a µl syringe (Hamilton, Reno, NV) connected to the infusion cannula by a polyethylene tube; the tip of the infusion cannula protruded 1.0 mm beyond that of the guide cannula. The infusions were carried out for about 90 s, first on one side and then on the other; the infusion cannula was left in place for an additional 30 s.

Behavioral procedures

a) Inhibitory avoidance task

Two different experiments were carried out.

1. *Effect of $PACOCF_3$ on memory retrieval*. This experiment assessed the effect of vehicle or 100 µM $PACOCF_3$ ($n = 11$ per group) infused into the CA1 region on memory retrieval. Once recovered from surgery, rats were submitted to one-trial step-down IA task, as previously described (Barros et al., 2002). The animals were placed on an 8.0 cm wide, 5.0 cm high platform at the left of a 50 cm wide, 25 cm deep, 25 cm high IA box (Albarsch, Brazil), whose floor was an electrified grid made of a series of parallel 1.0 mm caliber stainless steel bars spaced 1.0 cm apart. In training sessions, immediately after stepping down from the platform, placing the four paws on the grid, the rats received a 0.4 mA, 4.0 s scrambled foot shock. Latencies to step down were measured. Rats were tested for retention 24 h after training (for LTM). In test sessions, latencies to step down from the platform were measured up to a ceiling of 180 s, and no foot shock was given. Drugs were infused 30 min prior to test session performance.

2. *Effect of recovery of PLA_2 activity on memory retrieval.* This experiment assessed the effect of spontaneous recovery of PLA_2 activity after infusion of 100 µM $PACOCF_3$ ($n = 11$) into the CA1 region on memory retrieval in relation to vehicle ($n = 12$). Once recovered from surgery, rats were submitted to step-down IA task as follows. The animals were placed on the platform at the left of the IA box. Training sessions were performed as above. Three test sessions were carried out: the first, 1.5 h after training (for short-term memory; STM); the second, 24 h after training (for LTM); and the third, 25.5 h after training (for LTM after recovery of PLA_2 activity). Drugs were infused 30 min prior to the test session performance measured 24 h after training.

b) Control for changes in locomotor and exploratory activities

At 30 min after infusion of vehicle or 100 µM $PACOCF_3$ ($n = 8$ per group) into the CA1 region, rats were submitted to free exploration of IA apparatus, as previously described (Quillfeldt et al., 1996; Izquierdo et al., 1997). The animals were allowed to explore the training apparatus freely for 3 min, during which crossings of three imaginary lines that divided its floor into four equal 12.5 cm wide and 25 cm deep segments were counted.

c) Control for anxiety

At 30 min after infusion of vehicle or 100 µM $PACOCF_3$ ($n = 9$ per group) into the CA1 region, rats were submitted to the elevated plus maze test of anxiety, as previously described (Pellow et al., 1985). The elevated plus maze was made of wood and had two open arms (50 cm long, 10 cm wide) and two enclosed arms of the same size with walls 40 cm high, elevated 50 cm above the ground. The animals were placed in the central square (10×10 cm) facing an open arm and allowed to explore the apparatus freely for 5 min. The behavioral parameters were the frequencies of open and closed arms entries (one arm entry means all four paws into an arm) and the percentage of time spent in the open arms.

Control of cannula placements

At the end of behavioral procedures, sixty rats received a bilateral 0.5 µl infusion of a solution of 5% Evans blue in the vehicle into the brain sites implanted with cannulae. After 30 min, the animals were killed by decapitation and the brains were withdrawn, fixed in a solution of 10% formaldehyde in bidistilled water for 48 h, and then cut manually for histological localisation of infusion sites. We found that infusions spread with a radius of 1.0–1.5 m^3 in each cannula-implanted site, as previously described (Izquierdo et al., 1997). Infusions were found to be correct in 95% of the rats analysed. Only data from these animals were included in the statistical analysis. A total of eighty rats submitted to stereotaxic surgery had the brain dissected and prepared for determination of PLA_2 activity.

Determination of PLA_2 activity

Three different experiments were carried out.

1. *Effect of $PACOCF_3$ on PLA_2 activity.* The animals from the experiment which assessed the effect of vehicle or 100 µM $PACOCF_3$ ($n = 11$ per

group) on LTM retrieval of IA were killed by decapitation immediately after retention performance in order to dissect the CA1 region for PLA_2 activity determination around the time of retrieval. The brains were rapidly withdrawn, and about 2.0 m^3 of the CA1 region corresponding to the infusion sites were bilaterally dissected and immediately stored at −70°C until use. The CA1 tissue was homogenised in 20 vol. of 5 mM Tris–HCl buffer (pH 7.4, 4°C) and stored at −70°C. Prior to PLA_2 assay, total protein levels were determined for each aliquot by the Bio-Rad DC Protein Assay (Bio-Rad, Hercules, CA) modified from the Lowry assay (Lowry et al., 1951). PLA_2 activity was determined by a radioenzymatic assay, as previously described (Schaeffer and Gattaz, 2005). Briefly, as enzyme substrate, we used L-α-1-palmitoyl-2-arachidonyl-phosphatidylcholine labelled with [1-^{14}C] in the arachidonyl tail at the *sn*-2 position (arachidonyl-1-^{14}C-PC) (PerkinElmer, Boston, MA). The assay samples (500 µl), containing 100 mM Tris–HCl (pH 8.5), 1 µM $CaCl_2$, 300 µg of protein from homogenates, and 0.06 µCi arachidonyl-1-^{14}C-PC, were incubated for 30 min at 37°C. The radioactivity of the liberated [1-^{14}C]AA was measured in a liquid scintillation counter (Tri-Carb 2100TR; Packard, Meriden, CT) and used for calculating the PLA_2 activity, which is expressed in pmol · mg protein · min^{-1}. All determinations of PLA_2 activity were performed in triplicate.

2. *Recovery of PLA_2 activity following $PACOCF_3$ infusion.* This experiment examined the degree of PLA_2 inhibition in *post-mortem* CA1 region from rats infused with vehicle or 100 µM $PACOCF_3$ and killed by decapitation at different times after infusion, *i.e.*, at 30 min, 1 h (vehicle, $n = 8$; $PACOCF_3$, $n = 7$), 2 h, or 3 h (vehicle and $PACOCF_3$, $n = 7$) after infusion. Brain tissue preparation and PLA_2 assay were carried out as described above.

3. *Effect of memory retrieval on PLA_2 activity.* This experiment examined the effect of memory retrieval of IA on PLA_2 activity. Twenty-seven non-implanted adult male Wistar rats were divided into three groups: (*a*) naïve animals: killed by decapitation immediately after withdrawal from their home cages ($n = 9$); (*b*) trained animals: trained in the IA task and killed by decapitation 24 h later ($n = 9$); and (*c*) trained/tested animals: trained in the IA task, tested for retention 24 h later, and killed by decapitation immediately after retention test session ($n = 9$). Brain tissue preparation and PLA_2 assay were carried out as described above.

Statistical analysis

Due to the 180 s ceiling used for step-down latencies in test sessions, data from the IA task were analysed by non-parametric procedures and are expressed as median (interquartile interval). Comparisons of training session latencies between the groups were done by Kruskal-Wallis analyses of variance. Increments in latencies within the groups were evaluated by Wilcoxon tests. For statistical analysis, increments in latencies in different groups were calculated as percentages of the latencies in training sessions, and intergroup comparisons were done by Mann-Whitney *U*-tests. Data from the free exploration of IA apparatus, elevated plus maze and PLA_2 activity determination were analysed by Student's *t*-tests and are expressed as mean (± SEM). Two-tailed probabilities <0.05 were considered significant. The data were analysed using a statistical software package (SPSS 10.0 for Windows).

Results

Effect of $PACOCF_3$ on memory retrieval of IA task

Training session latencies were similar in animals which would receive vehicle or $PACOCF_3$ ($H = 13.05$, $df = 12$, $p > 0.3$). At 30 min after infusion (*i.e.*, 24 h after training), latencies for LTM increased by 10-fold in animals infused with vehicle ($z = -2.97$, $p = 0.003$). Infusions of $PACOCF_3$ prevented the increments of latencies for LTM as compared to vehicle ($U = 28$, $p = 0.03$) (Fig. 1A).

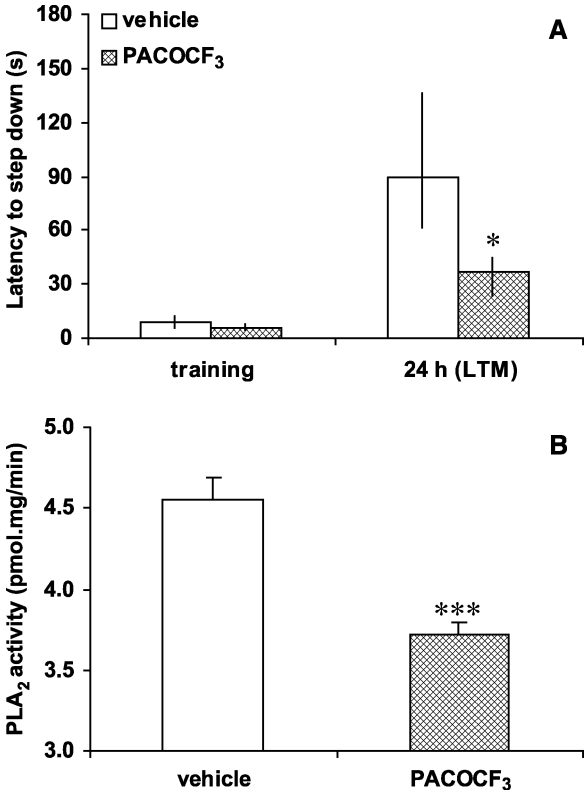

Fig. 1. Effect of $PACOCF_3$ on memory retrieval and on PLA_2 activity. (A) Step-down latencies (in s) are given as median (interquartile interval). Infusion of $PACOCF_3$ ($n = 11$) prevented the increments of latencies for long-term memory (LTM) as compared to vehicle ($n = 11$) ($^{*}p < 0.05$); (B) PLA_2 activity (pmol · mg protein · min^{-1}) is given as mean (± SEM). Infusion of $PACOCF_3$ ($n = 11$) reduced PLA_2 activity as compared to vehicle ($n = 11$) ($^{***}p < 0.001$)

Effect of $PACOCF_3$ on PLA_2 activity around the time of retrieval

The activity of PLA_2 in *post-mortem* CA1 region from rats killed immediately after retention performance was significantly inhibited by 18% after infusion of $PACOCF_3$ as compared to vehicle ($t = 5.28$, $df = 20$, $p < 0.001$) (Fig. 1B).

Effect of $PACOCF_3$ on locomotor and exploratory activities

In these experiments, we investigated whether the amnesic effect of $PACOCF_3$ in IA task was due to the action of this drug on general activity (locomotor and exploratory activities) during retention performance. We found that the number of crossings of three imaginary lines on the floor of IA apparatus was similar in animals infused with vehicle

(46.4 ± 2.78) or $PACOCF_3$ (41 ± 2.4) ($t = 1.46$, $df = 14$, $p > 0.1$), indicating that the impairing effect on memory of the pre-test infusion of $PACOCF_3$ was not caused by gross behavioral alterations on testing.

Effect of $PACOCF_3$ on anxiety

In these experiments, we investigated whether the amnesic effect of $PACOCF_3$ in IA task was due to the action of this drug on the anxiety state of the animals during retention performance. For all behavioral parameters measured in the elevated plus maze no difference was found between animals infused with vehicle or $PACOCF_3$: (*a*) number of entries into open arms (vehicle: 7.7 ± 0.44; $PACOCF_3$: 7.9 ± 0.42; $t = -0.36$, $df = 16$, $p > 0.5$); (*b*) number of entries into closed arms (vehicle: 8.1 ± 0.54; $PACOCF_3$: 7.2 ± 0.22; $t = 1.53$, $df = 16$, $p > 0.1$); and (*c*) percentage of time in open arms (vehicle: 24.4 ± 1.52; $PACOCF_3$: 23.6 ± 2.28; $t = 0.28$, $df = 16$, $p > 0.5$). These findings indicate that the impairing effect on memory of the pre-test infusion of $PACOCF_3$ was not caused by alterations in the anxiety levels on testing.

Recovery of PLA_2 activity following $PACOCF_3$ infusion

Compared to vehicle, the activity of PLA_2 in *post-mortem* CA1 region was significantly inhibited by 21% at 30 min and by 23% at 1 h after infusion of $PACOCF_3$ ($t = 3.31$, $df = 13$, $p < 0.01$; $t = 2.7$, $df = 13$, $p < 0.02$, respectively). This inhibition disappeared and the enzyme activity was recovered at 2 and 3 h after infusion ($t = 1.83$, $df = 12$, $p > 0.05$; $t = 1.42$, $df = 12$, $p > 0.1$, respectively) (Fig. 2A).

Effect of recovery of PLA_2 activity on memory retrieval of IA task

Training session latencies were similar in animals which would receive vehicle or $PACOCF_3$ ($H = 8.9$, $df = 13$, $p > 0.5$). After training, latencies for STM were similar in animals which would receive vehicle or $PACOCF_3$ ($U = 64$, $p > 0.5$), and were increased by 8 and 10-fold, respectively (vehicle: $z = -3.06$; $PACOCF_3$: $z = -2.94$, $p < 0.01$). In the first test session for LTM (24 h after training; 30 min after infusion), latencies were decreased in animals infused with $PACOCF_3$ as compared to vehicle ($U = 25.5$, $p < 0.02$). This difference disappeared in the second test session for LTM (25.5 h after training; 2 h after infusion), and latencies were similar in animals infused with vehicle and $PACOCF_3$ ($U = 61.5$, $p > 0.5$) (Fig. 2B).

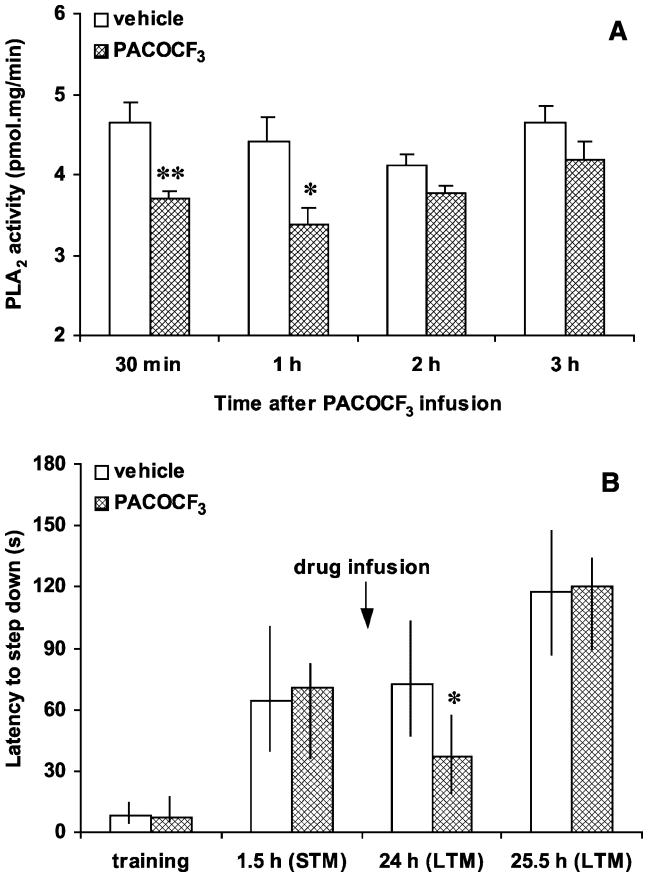

Fig. 2. Effect of recovery of PLA_2 activity on memory retrieval. (A) PLA_2 activity (pmol · mg protein · min^{-1}) is given as mean (± SEM). PLA_2 activity was reduced at 30 min ($^{**}p < 0.01$) and 1 h ($^{*}p < 0.02$) after infusion of $PACOCF_3$ ($n = 7$ per group) as compared to vehicle ($n = 8$ per group), and was recovered at 2 and 3 h after infusion of $PACOCF_3$ as compared to vehicle ($n = 7$ per group); (B) Step-down latencies (in s) are given as median (interquartile interval). Latencies for short-term memory (STM) were significantly increased after training in the absence of drugs. Infusion of $PACOCF_3$ ($n = 11$) decreased the latencies for long-term memory (LTM) measured 24 h after training (30 min after infusion) ($^{*}p < 0.02$) as compared to vehicle ($n = 12$). Latencies for LTM measured 25.5 h after training were similar in animals infused with vehicle and $PACOCF_3$, once PLA_2 activity was recovered in $PACOCF_3$-infused animals

Effect of memory retrieval of IA task on PLA_2 activity

As inhibition of hippocampal PLA_2 activity impaired memory retrieval of IA task, we carried out biochemical assays to evaluate directly whether memory retrieval *per se* changes hippocampal PLA_2 activity. We therefore measured the activity of PLA_2 in *post-mortem* CA1 region of three groups of animals: (*a*) naïve; (*b*) trained (killed 24 h after training); and (*c*) trained/tested (killed immediately after retrieval measured 24 h after training). We found that PLA_2 activity significantly increased by 9% in trained/tested animals as compared to naïve animals ($t = -3.0$, $df = 16$, $p < 0.01$). Additionally, PLA_2 activity significantly increased by 8%

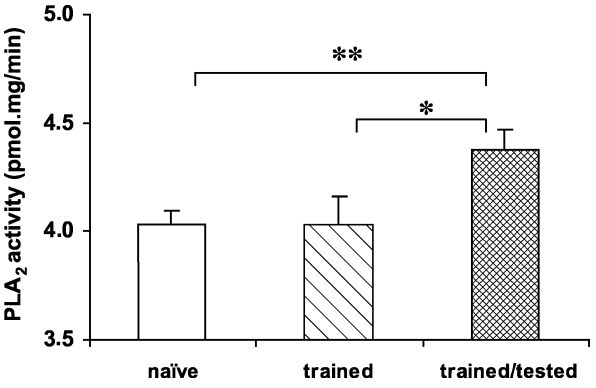

Fig. 3. Effect of memory retrieval on PLA_2 activity. PLA_2 activity (pmol · mg protein · min^{-1}) is given as mean (± SEM). PLA_2 activity was significantly increased in trained/tested animals in inhibitory avoidance task as compared to naïve ($^{**}p<0.01$) and trained animals ($^{*}p<0.05$) ($n=9$ per group). Trained animals had similar values of PLA_2 activity as naïve animals

in trained/tested animals as compared to trained animals ($t=-2.15$, $df=16$, $p<0.05$), indicating that increments in PLA_2 activity were specifically caused by the IA retrieval. Trained animals had similar values of PLA_2 activity as naïve animals ($t=-0.3$, $df=16$, $p>0.5$) (Fig. 3).

Discussion

The present study showed that the inhibition of PLA_2 activity in the CA1 region of the dorsal hippocampus of rats impaired the retrieval of LTM. It should be noticed that PLA_2 activity was significantly inhibited in *post-mortem* CA1 region from rats that showed impairment of memory retrieval. Memory impairment was not due to effects of PLA_2 inhibition on locomotor and exploratory activities or anxiety during retention performance, since $PACOCF_3$ treatment did not affect general activity in the IA apparatus or anxiety levels measured in the plus maze. Previous studies from our and other laboratories showed that intracerebral or intracerebroventricular infusions of PLA_2 inhibitors impaired memory acquisition in chicks (Hölscher and Rose, 1994), mice (Fujita et al., 2000), and rats (Schaeffer and Gattaz, 2005), and that intraperitoneal injections of PLA_2 inhibitors also impaired learning in rats (Hölscher et al., 1995). The present study extended the effect of PLA_2 inhibition to the mechanisms of memory retrieval.

Measurement of the degree of PLA_2 inhibition in *post-mortem* CA1 region from rats killed by decapitation at different times after infusion of $PACOCF_3$ showed significant reduction of PLA_2 activity at 30 min and 1 h, and a recovery of the enzyme activity at 2 and 3 h after infusion. Based on these time points, we investigated the effect of spontaneous recovery of PLA_2 activity on memory retrieval. The impairment of memory observed at 30 min after infusion of $PACOCF_3$ was fully reversed 2 h after infusion, a time in which PLA_2 activity was found to be recovered. In the present experiments, the recovery of the enzyme activity 2 h after $PACOCF_3$ infusion evidences the integrity of the PLA_2 metabolic pathway, confirming our previous finding on the absence of neuronal death after acute infusion of $PACOCF_3$ into rat CA1 region *in vivo* (Schaeffer and Gattaz, 2005). These results suggest thus a functional effect of hippocampal PLA_2 on the neurochemistry of LTM retrieval.

In our previous study (Schaeffer and Gattaz, 2005) we found that PLA_2 activity was increased in the CA1 region of rat hippocampus immediately after acquisition (training) of the IA task. In the present study we observed that this training effect on PLA_2 disappeared after 24 h. However, the retrieval of the trained behavior in the IA task increased again the enzyme activity in the CA1 region of rat hippocampus. Together, the experimental evidences strongly suggest a relationship between hippocampal PLA_2 activity and both acquisition and retrieval of memory.

In the present study, the effect of reduced PLA_2 activity on memory impairment may be mediated by decreased glutamate binding to AMPA (Bernard et al., 1994) and metabotropic receptors (Collins et al., 1995), as well as by decreased production of choline (precursor of acetylcholine) (Weichel et al., 1999). In addition, we recently demonstrated that *in vivo* PLA_2 inhibition reduced the fluidity of hippocampal CA1 membranes from rats (Schaeffer et al., 2005). Reduced membrane fluidity in rat hippocampus has been related to memory impairment (Hong, 1995; Clarke et al., 1999), likely by decreasing the density of muscarinic cholinergic receptors (Muccioli et al., 1996; Scheuer et al., 1999). All these biochemical mechanisms (AMPA and metabotropic glutamate receptors, and muscarinic receptors) in CA1 region are known to participate in LTM retrieval of IA task in rats (Barros et al., 2003).

The results of the present study showing that PLA_2 inhibition in rat hippocampus impaired memory retrieval, and that recovery of the enzyme activity caused recovery of memory, are of interest in face of previous reports showing reduced PLA_2 activity in *post-mortem* brains of patients with Alzheimer's disease (AD) (Gattaz et al., 1995; Ross et al., 1998; Talbot et al., 2000). It is worth noticing that reduced PLA_2 activity may affect the processing of the amyloid precursor protein contributing to the production of the β-amyloid peptide (Emmerling et al., 1993, 1996; Nitsch et al., 1997), the major component of neuritic plaques in AD. This assumption is in line with our previous

finding in *post-mortem* brains of AD patients showing a correlation between the reduction of PLA_2 activity and the density of neuritic plaques (Gattaz et al., 1995).

In summary, in the present study, using the step-down IA task, we showed that significant inhibition of PLA_2 activity in hippocampal CA1 region of rats impaired LTM retrieval. Memory impairment was fully reversed once PLA_2 activity was recovered. We showed further that LTM retrieval of IA *per se* significantly increased PLA_2 activity in rat CA1. To our knowledge, we demonstrated for the first time that PLA_2 activity is required for memory retrieval. In face of these data, it is tempting to speculate that the modulation of PLA_2 activity may offer new strategies for the treatment of AD.

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