

Brief Communication

PKM ζ inactivation induces spatial familiarityDiego Moncada¹ and Haydée Viola^{1–3}¹Instituto de Biología Celular y Neurociencias, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires 1121, Argentina;²Departamento de Fisiología, Biología Molecular y Celular, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Buenos Aires 1428, Argentina

Spatial familiarization consists of a decrease in the exploratory activity over time after exposure to a place. Here, we show that a 30-min exposure to an open field led to a pronounced decrease in the exploratory behavior of rats, generating context familiarity. This behavioral output is associated with a selective decrease in hippocampal PKM ζ levels. A short 5-min exposure did not induce spatial familiarity or a decrease in PKM ζ , while inactivation of hippocampal PKM ζ by the specific inhibitor ZIP was sufficient to induce spatial familiarity, suggesting that the decrease in PKM ζ is involved in setting a given context as a familiar place.

Rodents have an innate and spontaneous exploratory behavior. When rats face a novel environment, they actively explore it in order to gather information about the place, and then, in subsequent exposures, their exploratory behavior begins to decrease. With persistent exposure, not accompanied by any biologically relevant consequence, the environment becomes familiar, and exploration wanes.

When animals go over a place, they realize whether that place is novel or was previously explored by comparing it with stored memories. In parallel, rats recollect information about specific environmental details such as remembering particular characteristics about the place, when it was visited, or what happened there. The efficiency and speed of novelty detection confer an evolutionary advantage that provide a reason for the existence of a familiarity discrimination network in addition to those networks used for recollection (Brown and Aggleton 2001; Bogacz and Brown 2003). In a recent review, it was emphasized that recollection and familiarity signals are evident in both perirhinal cortex and the hippocampus, suggesting that these two components of memory could be interpreted in terms of strong and weak memories (Squire et al. 2007).

The hippocampal region is critically involved in the processing of spatial and associative learning tasks. Particularly, surgical or pharmacological interventions in the dorsal hippocampus prevent the formation of these memories (Broadbent et al. 2004; Izquierdo et al. 2006). However, a recent study reported that, in rats with a selective damage to the hippocampus involving its dorsal region, an increased familiarity of an odor paradigm was found (Sauvage et al. 2008). This result suggests that the inactivation of the hippocampus improves familiarity processes.

We have previously studied the molecular changes in the hippocampus of rats submitted to a novel or familiar environment. We found that a short exposure to a novel arena, in this case a 5-min open field (OF) session, led to an active exploration associated with a sequential rise in protein kinase A (PKA) activity and activation of the extracellular regulated kinases (ERKs) 1/2 and the α -subunit of calcium calmodulin-dependent protein kinase (CAMKII α) in the hippocampus of rats (Vianna et al. 2000). Indeed, we reported an increment in phosphorylated cAMP response element-binding protein (pCREB) levels, specifically associated with the detection of a novel environment (Winograd and Viola 2004). On the other hand, when animals explored the environment for 30 min and became familiarized to it, a marked

decrease in the exploration scores occurred, leading to a decrease in hippocampal pCREB levels that is not related to memory retrieval or the formation of a better long-term memory of habituation (Moncada and Viola 2006). Unfortunately, little is known about the intracellular signaling pathways leading to spatial familiarity.

Therefore, this study explores the hippocampal biochemical changes associated with spatial familiarity. All experiments were performed using male Wistar rats (age, 2 mo; weight, 180–210 g), with a handling period of 3 d at 3 min/d previous to the experiments. Here, we used three different behavioral protocols: (1) a single session familiarization (SSF) training consisting of a 30-min-long exposure to the OF; (2) a multiple session familiarization (MSF) protocol, in which rats were exposed to an OF for 5 min followed by two other sessions of 20 and 5 min, respectively, all separated by a 3-h intertrial interval; and (3) a novelty exposure training (novelty) consisting of a single 5-min OF exploration. In both the SSF and MSF protocols, rats explored the arena for 30 min, which was the period of time previously found to be needed to induce spatial familiarity (Moncada and Viola 2006). Naïve groups never explored the OF. Finally, spatial familiarity was tested in an OF for 5 min, 3 h after training. For all protocols, a square open field was used, consisting in a 50-cm-high, 50-cm-wide, and 40-cm-deep arena with black plywood walls and a brown floor divided into nine squares by black lines. Exploratory activity was measured as the number of crossings (number of times that rats cross a line with the four paws) and the number of rearings (number of times that the rats stand up on two back paws to perform aerial exploration of the environment) minute by minute, and pooled in 5-min blocks to perform statistical analysis (Moncada and Viola 2006).

To investigate the molecular mechanisms involved in spatial familiarity, we trained rats in SSF or MSF protocols and sacrificed them 1 h later to measure hippocampal kinases levels by immunoblot assays, as described previously (Cammarota et al. 2000; Moncada and Viola 2006). The behavioral output of spatial familiarity is a marked decrement of the exploratory activity in a subsequent exposure to the arena. As shown in Figure 1, while no differences were observed in the first 5 min of the training session in any of the three experimental groups (SSF, MSF, and novelty group), a clear decrease of the exploratory activity was observed in the 5-min test session for the SSF and MSF groups (familiarized animals) with respect to the novelty group (non-familiarized animals) ($P < 0.001$).

Immunoblot analysis of hippocampal homogenates (obtained as in Moncada and Viola 2006) showed specific decrease

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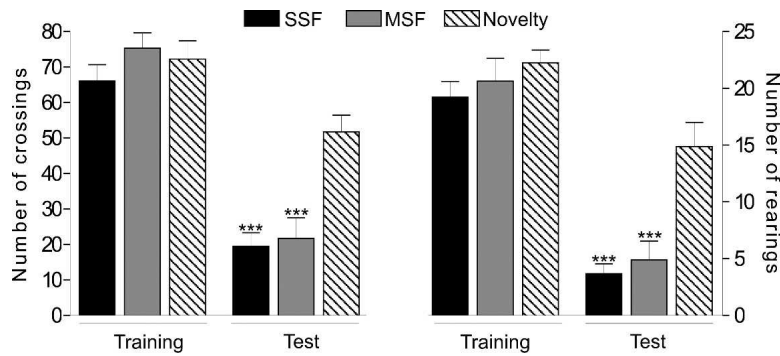


Figure 1. A prolonged 30-min OF exploration induces spatial familiarity. Rats were exposed to a 30-min OF training session (single session familiarization group, SSF), to a multiple OF session protocol (multiple session familiarization group, MSF), or to a 5-min OF session (novelty group) and tested 3 h later. The figure depicts exploratory activities, expressed as mean \pm SEM of the number of crossings and rearings, performed by rats in the initial 5 min of the OF training and in a 5-min test session. (***) $P < 0.001$, with respect to the novelty group test session performance; Newman-Keuls multiple comparison test after one-way repeated measures ANOVA; $n = 8$.

of PKM ζ levels in rats familiarized using the SSF protocol, in comparison with the naïve group, while no changes were found in the phosphorylated levels of ERK1, ERK2, or CAMKII α proteins (Fig. 2A). Furthermore, hippocampal subcellular fractionation (performed as in Medina et al. 1989) revealed that this PKM ζ decrement was observed in the crude fraction containing the synaptic terminals (P2) (naïve, 100 ± 10.7 ; SSF, 67.8 ± 3.6 ; $n = 5-7$, $P < 0.01$, percent integrated optical density [IOD] levels, Student's t -test), but not in the nuclear fraction (naïve, 100 ± 9.0 ; SSF, 105 ± 8.7 ; $n = 6-8$, $P > 0.05$, percent IOD levels, Student's t -test). The changes in PKM ζ levels were corroborated by using the PKM ζ /actin ratio to perform the analysis for the homogenates (naïve, 100 ± 14.4 ; SSF, 61.6 ± 10.6 ; $n = 9-10$, $P < 0.05$, Student's t -test) and P2 fraction (naïve, 100 ± 11.6 ; SSF, 60.8 ± 5.2 ; $n = 5-7$, $P < 0.01$, Student's t -test).

In order to confirm these findings, we trained animals with an MSF protocol, extensively used in our laboratory to familiarize rats to the environment (Moncada and Viola 2006). Here again, the levels of PKM ζ in hippocampal homogenates also decreased 1 h after animals became familiarized (Fig. 2B, $P < 0.05$). This decrease was also present in P2 (naïve, 100 ± 10.9 ; MSF, 62.8 ± 6.6 ; $n = 6-7$, $P < 0.05$, percent IOD levels, Student's t -test) but not in the nuclear fraction (naïve, 100 ± 9.5 ; MSF,

108.9 ± 13.2 ; $n = 12$, $P > 0.05$, percent IOD levels, Student's t -test). Likewise, no changes in pERK1, pERK2, or pCAMKII α proteins were observed in hippocampal homogenates of familiarized animals with respect to naïve rats (Fig. 2B, $P > 0.05$). Here again, the differences in PKM ζ levels were corroborated by using PKM ζ /actin normalization to perform the analysis for homogenates (naïve, 100 ± 7.2 ; MSF, 74.3 ± 5.4 ; $n = 10-12$; $P < 0.05$, Student's t -test) and P2 fraction (naïve, 100 ± 4.4 ; SSF, 67.8 ± 8.15 ; $n = 6-7$, $P < 0.05$, Student's t -test). Therefore, two different spatial familiarization protocols resulted in a selective decrease of hippocampal PKM ζ levels. In contrast, a 5-min exploration of a novel OF, which does not induce spatial familiarity (Fig. 1), was unable to induce such changes in PKM ζ levels (Fig. 2C). Even more, its levels were significantly higher than in familiarized animals (naïve, 100 ± 5.8 ; novel, 101.9 ± 9.7 ; SSF, 73.7 ± 5.8 ; MSF, 75.5 ± 5.8 , percent IOD with respect to naïve group, $P < 0.05$; novel vs. SSF and MSF, Newman-Keuls analysis after one-way ANOVA, $n = 8-12$). The levels of another PKC isoform (PKC ζ), also detected by the antibody used, were similar in all experimental groups (naïve, 100 ± 8.6 ; novel, 97.2 ± 10.7 ; SSF, 102.5 ± 11.9 ; MSF, 90.1 ± 8.1 ; percent IOD with respect to naïve group, $P > 0.05$, one-way ANOVA, $n = 8-12$), showing the specificity of PKM ζ level changes.

Based on these findings, we asked whether this decrement in PKM ζ levels is involved in the mechanisms underlying spatial familiarity. To test this hypothesis, we trained animals in a 5-min novel OF session that does not produce spatial familiarity and is not associated with a decrease in PKM ζ (Figs. 1, 2C). One hour later, at the time at which the SSF and MSF protocols induce the decrease in PKM ζ , we infused the PKM ζ inhibitor ZIP (peptide sequence myr-SIYRRGARRWRKL-OH; Biosource; 1 nmol in 1 μ L of saline per side) in the dorsal hippocampus of cannulated rats (as described in Moncada and Viola 2007). A test session to analyze whether or not the animals became familiarized to the OF was carried out 2 h later. Assuming a volume of 100 μ L for the dorsal hippocampus (Dash et al. 2006), this dose was reported to

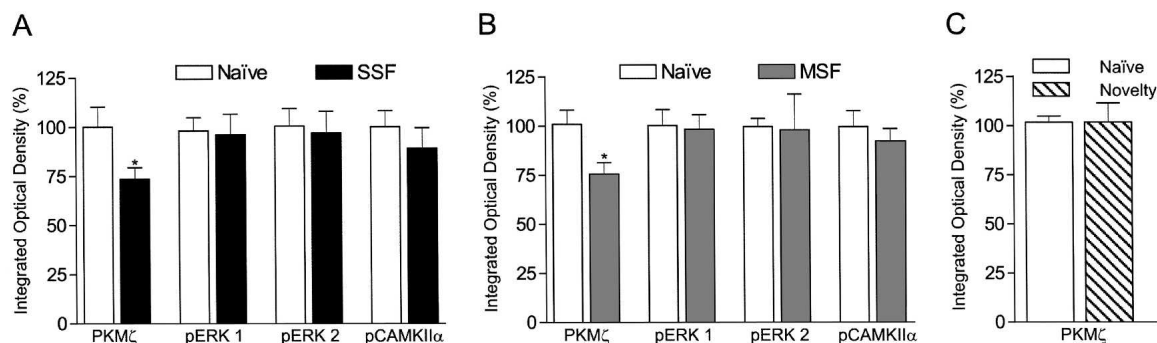


Figure 2. Selective reductions in hippocampal PKM ζ protein levels are observed after spatial familiarization to an open field. Rats were exposed to a 30-min OF training session (single session familiarization group, SSF), to a multiple OF session protocol (multiple session familiarization group, MSF), or to a 5-min OF session (novelty group), and sacrificed 1 h later to obtain hippocampal homogenates. Protein levels for PKM ζ (1:5000; Santa Cruz Biotechnologies), pERKs 1/2 (1:4000; Cell Signaling), and pCAMKII α (1:1500; SCBT) were evaluated by Western blot technique. The figure depicts densitometric analysis of immunoblots, as mean \pm SEM of integrated optical density expressed as the percentage with respect to the naïve group (% IOD) of animals trained in: (A) SSF, (*) $P < 0.05$, Student's t -test, $n = 9-12$; (B) MSF, (*) $P < 0.05$, Student's t -test, $n = 9-12$; or (C) novel exposure training protocols, $P > 0.05$, Student's t -test, $n = 7$. Western blots were developed within the linearity range used for densitometry. Densitometric analyses of the films were performed using Gel-pro Analyzer 4 (Media Cybernetics).

totally and selectively inhibit the phosphotransferase activity of PKM ζ protein (Ling et al. 2002). After the end of the behavioral procedures, 1 μ L of 4% Methylene-Blue solution was infused into the implanted site. Animals were killed by decapitation 15 min later, and the brains were analyzed for histological localization of the infusion sites. Only data from animals with correct cannula implants (95% of the rats) were included in statistical analyses.

As can be seen in Figure 3, animals submitted to novelty and SSF protocols depicted the same exploratory activity during the first 5 min of the training session. In the test session, the novelty group infused with ZIP exhibited significantly less exploratory activity than the novelty groups infused with vehicle solution or with SCR-ZIP, an inactive version of ZIP peptide with a scrambled amino acid sequence (myr-RLYRKRIWRSAGR-OH; Genebiotech; 1 nmol in 1 μ L of saline per side; $P < 0.001$). Moreover, this marked decrease in the exploratory behavior of animals injected with ZIP was comparable to the performance of rats trained with the SSF protocol and infused with vehicle solution (Fig. 3).

Finally, to rule out nonspecific effects of ZIP on exploratory activity and exploration, an untrained group of rats was infused with ZIP or vehicle 2 h before a 5-min OF test session. Both groups of animals actively explored the arena to the same extent (Crossings: Veh, 76.8 ± 5.9 ; ZIP, 75.4 ± 5.7 ; Rearings: Veh, 17.9 ± 1.4 ; ZIP, 16.3 ± 1.1 ; $n = 7$, $P > 0.05$; Student's *t*-test), indicating that neither the pharmacological treatment nor the manipulation of the animals alters their behavior. These findings demonstrated that, in contrast to what was observed in trained animals, the inhibition of hippocampal PKM ζ in untrained rats produced no effects on locomotor activity and exploration. In conclusion, PKM ζ inactivation 1 h after the exploration of a novel OF is sufficient to induce spatial familiarity to the arena.

In sum, the main finding of the present study is that inactivation of hippocampal PKM ζ promotes spatial familiarity. Thus, the blockade of PKM ζ activity in rats submitted to a novel context induced a marked decrease in exploratory activity similar to that observed in animals familiarized with the context. Moreover, the spatial familiarity attained by a 30-min OF exposure is associated with a selective decrease in PKM ζ levels in the hippocampus.

When animals became familiarized to the environment, a marked decrease in their locomotor activity was observed, a phenomenon that persisted in a subsequent exposure to the arena 3 h, but not 24 h, later (Moncada and Viola 2006). Thus, the familiarity to the arena could be alternatively interpreted as a strong short-term memory of habituation.

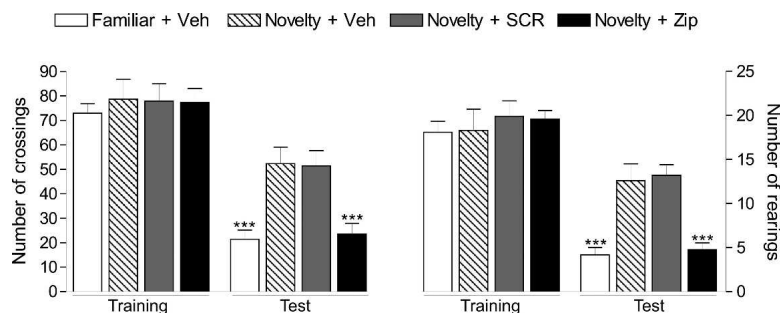


Figure 3. The blockade of PKM ζ induces spatial familiarity. Rats were trained in a 5-min novel OF exploration session and 1 h later received an infusion of vehicle (Novelty + Veh), the PKM ζ inhibitor myr-ZIP (Novelty + ZIP), or the scrambled version of myr-ZIP (Novelty + SCR) in the CA1 region of dorsal hippocampus. A fourth group of rats were trained in a 30-min OF session and 1 h later received a local infusion of a vehicle solution (SSF + Veh). The figure shows the exploratory activity, expressed as mean \pm SEM of the number of crossings and rearings, during the 5-min OF training session (for the SSF group, it was considered the initial 5 min) and in the 5-min test session performed 3 h later. (***) $P < 0.001$, with respect to the Novelty + Veh and Novelty + SCR groups in test session performance; Newman-Keuls multiple comparison test after one-way repeated measures ANOVA, $n = 10-11$.

Recently, Shema et al. (2007) suggested that the persistence of a taste aversion memory is dependent on the ongoing activity of PKM ζ . The administration of an inhibitor of this kinase in the insular cortex, 3 d after training or after retrieval, erased the long-term memory of the taste aversion. However, the infusion of ZIP had no effect on the acquisition of the taste aversion task. Moreover, the PKM ζ inhibitor did not disrupt taste familiarity (Shema et al. 2007). Consistent with these results, our data show that far from disrupting spatial familiarity, ZIP, in fact, induces it; moreover, a decrement in hippocampal levels of PKM ζ accompanied the process of spatial familiarization. Thus, the decrease in PKM ζ could erase the novelty of the spatial stimuli and set the hippocampus in a biochemical state compatible with a familiar experience.

Different forms of hippocampus-dependent synaptic plasticity and learning tasks involve the activation of different kinases (Izquierdo et al. 2006; Reymann and Frey 2007). Consistent with their findings, a short exposure to a novel environment induced activation of several kinases and an increase in the phosphorylation state of CREB (Vianna et al. 2000; Winograd and Viola 2004). Conversely, our results show that after a prolonged exposure to an OF, several hippocampal kinases were not activated. In fact, the levels of PKM ζ (Fig. 2) and pCREB (Moncada and Viola 2006) decreased, suggesting an hippocampal switch-off when the spatial stimuli lacks novelty. In this context, electrophysiological analysis of place cells in the CA1 region of the hippocampus shows that hippocampal spatial representations are not fully expressed at the beginning of an animal's exposure to a novel arena and improve with experience (time spent in the arena) by a mechanism that seems to imply the silencing of several neurons (Wilson and McNaughton 1993). Therefore, taking into account that PKM ζ is able to regulate cell excitability, its decrease after spatial familiarization might reflect the "sharpening" of the place fields involved in the OF recognition.

What is the intracellular signaling leading to the decrease in PKM ζ protein level? Kelly et al. (2007) found that PI3-kinase, pCAMKII α , ERKs, PKA, and mTOR, as well as preexisting PKM ζ , regulate the synthesis of PKM ζ during long-term potentiation (LTP). They showed that the blockade of any of these kinases impaired both LTP and PKM ζ synthesis. Given that in our work the decrease in PKM ζ levels was not associated with a decrease in pERK1/2 or pCAMKII α , other signaling cascades should be considered.

We have recently demonstrated that both SSF and MSF protocols induce a consistent decrease in hippocampal levels of active CREB (phosphorylated at Ser 133) (Moncada and Viola 2006). A wide number of kinases can phosphorylate CREB at this residue (see Johannessen et al. 2004). Among the most studied are PKA, ERKs, and CAMKs (Xing et al. 1996; Shaywitz and Greenberg 1999; Lee et al. 2005). Our results show that none of these kinases decreased in the hippocampus after spatial familiarization, at the time of the decline in pCREB levels (Moncada and Viola 2006; this study).

Alternatively, CREB deactivation could be attained by an increase in phosphatases activity (Shaywitz and Greenberg 1999). Previous experiments revealed that total phosphatase activity was not altered in hippocampal nuclear samples of familiarized rats (Moncada and Viola 2006), and preliminary experi-

ments showed that neither PP1 nor PP2B phosphatase activities were changed (data not shown).

Thus, we did not find any decrease in the levels of PKA, pERKs 1/2, and pCAMKII α , nor an increment in phosphatase activity, that could explain the fall of pCREB observed after spatial familiarization (Moncada and Viola 2006; this study). In contrast, a selective decrease in PKM ζ protein level occurs simultaneously and consistently with the decreased level of pCREB, both in SSF- and MSF-trained rats. Even though there is no evidence linking PKM ζ with CREB phosphorylation, we decided to infuse ZIP into the dorsal hippocampal region to study pCREB levels. The infusion of ZIP (400 μ M; 0.5 μ L/side) did not change pCREB levels with respect to vehicle-infused rats, 30 min after drug administration (Veh, 100 ± 13.7 ; ZIP, 106.8 ± 11.7 ; percent IOD; $P > 0.05$, Student's *t*-test, $n = 7$). Thus, hippocampal PKM ζ inactivation did not affect the phosphorylation state of CREB. Conversely, it is possible that the transcription factor CREB regulates the expression of PKM ζ mRNA. In that sense, it was reported that the promoter region of the PKM ζ gene presents a conserved canonical CRE region in both rodents and humans (Hernandez et al. 2003). Alternatively, the decrease in PKM ζ levels after SSF or MSF could be due to its proteolytic degradation by calpain (Hrabetova and Sacktor 1996).

In sum, spatial familiarization processing results in a marked decrease in exploratory activity and in PKM ζ and pCREB levels in the hippocampus. Previous results have showed that both molecules have a well-established role in synaptic plasticity and memory processing. A bidirectional regulation of PKM ζ has been shown for the maintenance of LTP and long-term depression (LTD). Hrabetova and Sacktor (1996) showed that during the maintenance phase of LTD, a reduction of hippocampal pCREB level occurs. In the same way, *in vivo* LTD induction selectively promotes a decrease of pCREB in dorsal hippocampus (Thiels et al. 2002). Therefore, synaptic depression shows a good correlation with PKM ζ and pCREB decreases. Interestingly, Castellucci et al. (1978) analyzed the habituation behavior in *Aplysia* and showed that both, short- and long-term habituation produce a profound depression in the efficacy of synaptic transmission. More recently, Simons-Weidenmaier et al. (2006) proposed that the habituation of the startle response in rats is mediated by synaptic depression of the sensory pathway. In sum, it is widely accepted that habituation is mediated by a synaptic depression of the neuronal circuitry. Therefore, as spatial familiarity can be visualized by a marked decrease in the exploratory activity, the possibility exists that spatial familiarity could be induced throughout a PKM ζ decrease by a mechanism of synaptic depression like LTD.

In conclusion, our results show that familiarization to an environment induces a selective decrease in hippocampal PKM ζ levels and that dorsal hippocampal PKM ζ inactivation is sufficient to induce a spatial familiarity behavior, suggesting that the decline in PKM ζ plays a predominant role at the moment of coding an environment as a familiar place.

Acknowledgments

We thank Jorge H. Medina, Pedro Bekinschtein, and Maria C. Martinez for their helpful comments and discussion of the manuscript. This work was supported by grants from the UBACyT, ANPCyT, and Antorchas Foundation.

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Received July 3, 2008; accepted in revised form August 28, 2008.



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Learn. Mem. 2008 15: 810-814

Access the most recent version at doi:[10.1101/lm.1139508](https://doi.org/10.1101/lm.1139508)

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