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Short communication

Distinct effects of estrogen receptor antagonism on object recognition and spatial memory consolidation in ovariectomized mice

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ABSTRACT

Exogenous treatment with the potent estrogen 17β-estradiol (E_2) or selective estrogen receptor α/β (ERα/β) agonists enhances the consolidation of hippocampal-dependent object recognition (OR) and object placement (OP) memories in ovariectomized rodents. Although such data suggest that individual ERs are sufficient for memory consolidation, the necessity of a given ER for memory consolidation can only be demonstrated by blocking receptor function, for example with an ER antagonist. However, the effects on memory of antagonizing ERα or ERβ function are not well understood. Moreover, ER antagonism in ovariectomized subjects also provides indirect information about the role of individual ERs in the memory-enhancing effects of local hippocampal E_2 synthesis. Therefore, this study used pharmacological inhibition of ERα and ERβ to elucidate the importance of each ER to memory consolidation. Specifically, we examined effects on OR and OP memory consolidation of immediate post-training dorsal hippocampal (DH) infusion of MPP and PHTPP, selective antagonists for ERα and ERβ, respectively. Each drug exhibited a distinct effect on OR and OP. DH infusion of MPP (0.28 or 2.78 ng/hemisphere) impaired memory in OP, but not OR. However, DH infusion of PHTPP (0.21 or 2.12 ng/hemisphere) impaired memory in both OR and OP. Neither drug affected the elapsed time to accumulate object exploration in either task, suggesting a specific effect on memory. These results indicate that activation of either classical ER within the dorsal hippocampus is important for hippocampal memory consolidation in ovariectomized mice, but suggest that specific ER involvement is memory- or task-specific. The findings also indirectly support a role for ERα and ERβ in mediating the memory-enhancing effects of hippocampally-synthesized E_2.

1. Introduction

17β-Estradiol (E_2) is a key modulator of memory consolidation. The rapid effects of E_2 on consolidation have been revealed using two-trial object recognition (OR) and object placement (OP) tasks (Rothblat and Kromer, 1991; Tuscher et al., 2015) that permit evaluation of E_2's effects on object recognition and spatial memory formation without the confounds associated with appetitive or aversive reinforcement (Ervin et al., 2013; Tuscher et al., 2015). Immediate post-training systemic injection or dorsal hippocampal (DH) infusion of E_2 enhances long-term memory in the OR and OP tasks among ovariectomized rodents, demonstrating a vital role for the rapid effects of DH E_2 in object recognition and spatial memory consolidation (Walf et al., 2008; Boulware et al., 2013; Kim et al., 2016).

One mechanism through which hippocampal E_2 might mediate memory formation is *via* binding to estrogen receptors alpha and beta (ERα and ERβ), which are abundant at both nuclear and extranuclear sites within hippocampal pyramidal neurons in the mouse (Milner et al., 2005; Mitterling et al., 2010). In rodents, ERα and ERβ are found in glia, as well as within nuclei, dendrites, dendritic spines, axons, and axon terminals of pyramidal neurons (Milner et al., 2001; Mitterling et al., 2010; Waters et al., 2011). Both ERs are also located within GABAergic interneurons in hippocampal neurons (Murphy et al., 1998; Blurton-Jones and Tuszynski, 2002). Both ERs physically interact with metabotropic glutamate receptors at the cell membrane in the hippocampus of ovariectomized rodents, triggering cell-signaling events that lead to gene transcription (Boulware et al., 2005; Boulware et al., 2013). Of particular relevance, rapid ER/mGluR1a signaling is essential for the beneficial effects of E_2 on long-term OR and OP memory consolidation in ovariectomized mice (Boulware et al., 2013). In general, post-training systemic or DH administration of the ERα agonist PPT or ERβ agonist DPN enhances memory consolidation in the OR and OP tasks in ovariectomized rats and mice (Frye et al., 2007; Walf et al., 2008; Frick et al., 2010; Boulware et al., 2013; Pereira et al., 2014).

*Abbreviation:*ER, antagonism and memory

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Collectively, these gain-of-function studies suggest that ERα and ERβ in the DH are sufficient for object recognition and spatial memory consolidation.

However, ER agonist studies cannot reveal whether a given ER is *necessary* for memory consolidation. This information can be gleaned only from loss-of-function approaches, the most common of which are administration of ER antagonists or use of ER knockout mice. In knockout mouse models, post-training systemic E_2 enhances OR and OP memory consolidation in ERα knockouts, but not ERβ knockouts (Walf et al., 2008), suggesting a role for ERβ, rather than ERα. However, knockout studies are complicated by the loss of ER throughout development, which may result in unintended compensatory changes. ER antagonists provide a more acute functional loss, allowing the necessity of individual ERs to be assessed in a normally developed brain. Yet the effects of ER antagonists on hippocampal memory consolidation have not been tested.

When administered to ovariectomized subjects, the inhibition of a single ER by an ER antagonist also provides indirect information about the role of the ER in the memory-enhancing effects of local hippocampal E_2 synthesis. E_2 is synthesized within the hippocampus, where levels are higher than in plasma in both sexes (Kato et al., 2013). Bilateral ovariectomy removes the primary endogenous source of E_2, yet ovariectomy produces hippocampal E_2 levels comparable to diestrus (Kato et al., 2013), suggesting that the hippocampus may produce sufficient E_2 to mediate memory formation. Indeed, object training produces a transient increase in hippocampal E_2, and post-training DH infusion of the aromatase inhibitor letrozole impairs OR and OP memory consolidation in ovariectomized mice (Tuscher et al., 2016). Because any hippocampal E_2 in ovariectomized females would presumably be derived from local synthesis rather the gonads, these data indicate an important role for hippocampal E_2 synthesis in memory consolidation. Relevant to the present study, because learning-induced local E_2 would presumably enhance memory *via* binding to ERs, impairing effects of ER antagonists in ovariectomized females could provide insights into the underlying role of individual ERs in mediating the learning-induced effects of local hippocampal E_2.

Therefore, this study examined the effects of selective ERα and ERβ antagonists on object recognition and spatial memory consolidation in ovariectomized mice. ER antagonists were infused directly into the DH immediately after training in OR and OP to examine rapid effects of ER antagonism on long-term memory consolidation. ERα antagonism impaired OP, but not OR, memory consolidation. ERβ antagonism impaired both OP and OR memory consolidation. These data suggest that ERα and ERβ are necessary for rapid hippocampal memory consolidation, although their involvement depends on the type of memory tested. Moreover, the findings support a key contribution of local E_2 synthesis to hippocampal memory consolidation.

2. Materials and methods

2.1. Subjects

Ten week-old female C57BL/6 mice (Taconic Biosciences) were group-housed (Ancare 75 cages, 300 × 190 × 130 mm) until surgery, after which they were singly housed without any enrichment. Mice were maintained in a 12 h light/dark cycle and provided with *ad libitum* access to food (Invigo Teklad Rodent Diet 8604) and water. Behavioral testing was conducted in a quiet room under dim lighting. All procedures were approved by the University of Wisconsin-Milwaukee Institutional Animal Care and Use Committee and followed policies of the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Surgery

Mice were bilaterally ovariectomized and then implanted bilaterally with cannuale (22 gauge; C232G, Plastics One) aimed at the DH (-1.7 mm AP, ± 1.5 mm ML, −2.3 mm DV) as described and characterized previously (Fernandez et al., 2008; Boulware et al., 2013; Kim et al., 2016). Cannula tips were implanted in the CA1 region, with the infuser extending down towards CA3 and the dentate gyrus, as illustrated in Orr et al. (2009) and Fortress et al. (2015). Mice were allowed to recover for six days prior to the start of handling and habituation to the behavioral testing apparatus.

2.3. Drugs and infusions

All infusions were conducted immediately post-training as described previously (Kim et al., 2016). Dummy cannulae were replaced by an infusion cannula (C3131, 28-gauge, extending 0.8 mm beyond the 1.5 mm guide). Drugs were infused bilaterally into the DH at a rate of 0.5 µl/minute for 1 min. Previous studies demonstrated that this infusion protocol results approximately 1 mm^3 of drug diffusion, suggesting that drug effects were likely restricted to the dorsal hippocampus (Lewis and Gould, 2007; Lewis et al., 2008). Doses selected for infusion were based on *in vitro* and *in vivo* specificity of MPP (1,3-Bis(4-hydroxyphenyl)-4methyl-5-[4-(2-piperidinylethoxy) phenol]-1H-pyrazole dihydrochloride, Tocris Bioscience) and PHTPP (4-[2-Phenyl-5,7-bis(trifluoromethyl)pyrazolo [1,5-a]pyrimidin-3-yl]phenol, Tocris Bioscience) for ERα and ERβ, respectively (Lopez-Gonzalez et al., 2011; Al-Nakkash, 2012). MPP is > 200-fold more selective for ERα over ERβ, with K_i values of 2.7 and 1800 nM for ERα and ERβ, respectively (Sun et al., 2002; Harrington et al., 2003). PHTPP is 36-fold more selective for ERβ over ERα (Compton et al., 2004). MPP and PHTPP were dissolved in 1% DMSO in saline. Vehicle groups for all experiments were infused with 1% DMSO in saline.

2.4. Behavioral testing

OR and OP were performed as described previously (Boulware et al., 2013; Kim et al., 2016). Behavioral testing began 11 days after recovery from surgery. Six days after surgery, mice underwent three days of handling by experimenters. Handling was followed by two consecutive days (5 min/day) of habituation to the behavioral testing arena. For training, two identical objects were placed near the upper adjacent corners of a square arena, and mice were allowed to investigate the objects until they accumulated a total of 30 s of object exploration (or until 20 min had elapsed). Immediately after this training, mice were removed, infused, and returned to their home cage. OR memory was tested 24 h later, a point at which vehicle-infused mice remember the identity of the training objects (Boulware et al., 2013), thus permitting observation of potential impairing effects on object recognition. OR memory was tested by allowing mice to accumulate 30 s exploring a novel object and an object identical to that explored during training. Fifteen seconds represented chance, a point at which mice spend equal time with both objects.

OP training occurred two weeks after OR to allow effects of the first infusion to dissipate prior to the second infusion. OP used the same apparatus and procedure as OR, except that OP memory was tested by moving one training object to the lower left or right corner. Memory was tested 4 h after training, a delay at which vehicle-infused mice remember the location of the training objects (Boulware et al., 2013; Kim et al., 2016), thus permitting observation of potential impairing effects on spatial memory.

For both tasks, time spent exploring the objects and elapsed time to accumulate 30 s of exploration were recorded using ANYmaze tracking software (San Diego Instruments).

2.5. Data analysis

Analyses were conducted using GraphPad Prism 6 (La Jolla, CA). One-sample *t*-tests were performed to determine if the time spent with

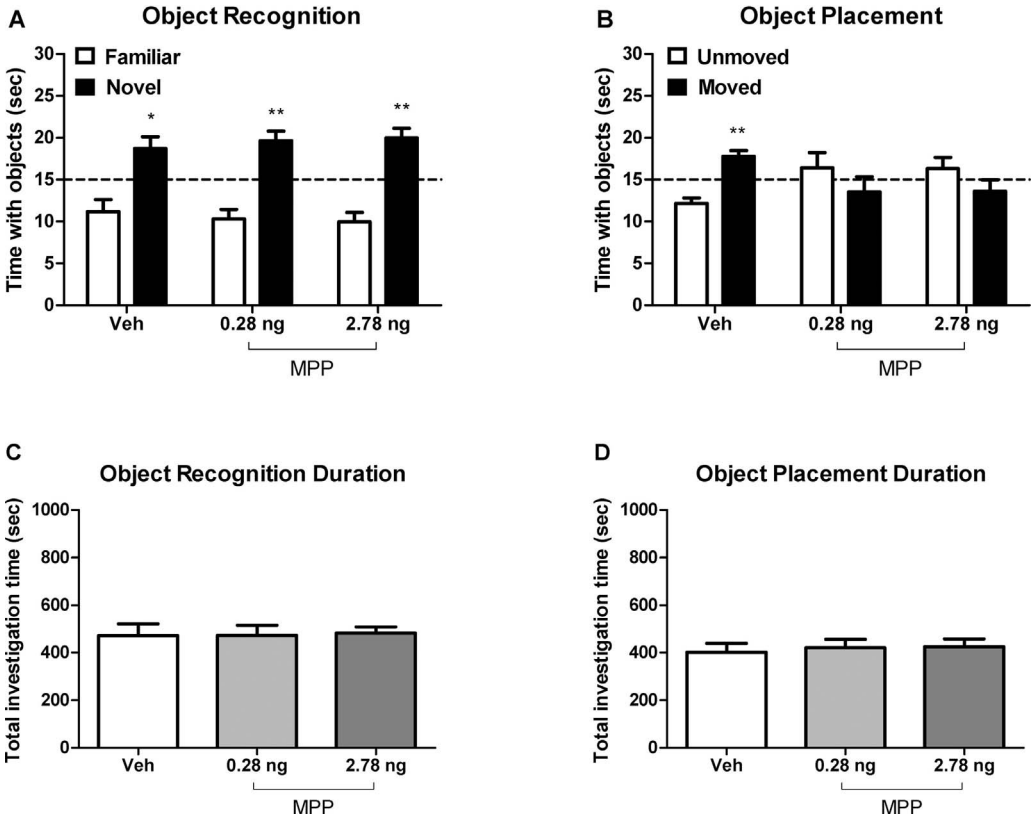

Fig. 1. The ERα antagonist MPP impaired OP memory but not OR memory. (A) Mice receiving DH infusion of vehicle or either dose of the ERα antagonist MPP (0.28 ng or 2.78 ng) spent significantly more time than chance (dashed line at 15 s) with the novel object 24 h later, suggesting that neither dose impaired OR memory (Vehicle, n = 12; 0.28 ng MPP, n = 10; 2.78 ng MPP, n = 10). (B) Four hours after OP training, only mice infused with vehicle showed a significant preference for the moved object, indicating that both doses of MPP impaired spatial memory consolidation (Vehicle, n = 8; 0.28 ng MPP, n = 9; 2.78 ng MPP, n = 9). For panels A and B, each bar represents the mean ± SEM time spent with the objects (*$p < 0.05$, **$p < 0.01$ relative to the chance level of 15 s). (C, D) Elapsed time to accumulate 30 s of exploration in OR and OP was not affected by MPP infusion. Each bar in panels C and D represents the mean ± SEM time spent in the testing arena.

each object differed significantly from chance (15 s). Elapsed time to accumulate 30 s of exploration was analyzed using one-way ANOVA. Significance was determined at $p < 0.05$ and data were expressed as the mean ± standard error of the mean (SEM).

3. Results

3.1. ERα antagonism impaired spatial, but not object recognition, memory consolidation

Mice first received bilateral DH infusion of vehicle or one of two doses of the ERα antagonist MPP (0.28 or 2.78 ng/hemisphere) immediately after OR training. Mice receiving vehicle ($t(11) = 2.627$, $p = 0.024$), 0.28 ng/hemisphere MPP ($t(9) = 4.130$, $p = 0.003$), or 2.78 ng/hemisphere MPP ($t(9) = 4.361$, $p = 0.002$) spent significantly more time than chance (15 s) with the novel object 24 h after OR training, suggesting intact object recognition memory (Fig. 1A). In contrast, MPP impaired spatial memory in OP. Although mice receiving DH infusion of vehicle ($t(7) = 4.359$, $p = 0.004$) spent more time than chance with the moved object, mice infused with 0.28 ng/hemisphere MPP ($t(8) = 0.797$, $p = 0.449$) or 2.78 ng/hemisphere MPP ($t(8) = 1.029$, $p = 0.334$) did not (Fig. 1B), suggesting that ERα antagonism impaired spatial memory consolidation. These data suggest that spatial memory is more sensitive to ERα antagonism than object recognition memory, at least at the doses tested. Elapsed time to accumulate 30 s of exploration did not differ among the groups for either OR ($F(2,29) = 0.019$, $p = 0.982$; Fig. 1C) or OP ($F(2,23) = 0.126$, $p = 0.882$; Fig. 1D).

3.2. ERβ antagonism impaired both object recognition and spatial memory consolidation

We next examined effects of ERβ antagonism on hippocampal memory consolidation. Immediately after OR training, mice received bilateral DH infusion of vehicle or one of two doses of PHTPP (0.21, 2.12 ng/hemisphere). Mice receiving vehicle ($t(7) = 2.477$, $p = 0.042$) spent significantly more time than chance with the novel object, whereas mice infused with PHTPP did not (0.21 ng/hemisphere, $t(8) = 1.104$, $p = 0.302$; 2.12 ng/hemisphere, $t(8) = 0.49$, $p = 0.637$), suggesting impaired object recognition memory after ERβ antagonism (Fig. 2A). In OP, mice receiving DH infusion of vehicle ($t(7) = 5.548$, $p = 0.001$) spent significantly more time than chance with the moved object. In contrast, mice receiving either dose of PHTPP did not prefer the moved object (0.21 ng/hemisphere, $t(9) = 0.441$, $p = 0.669$; 2.12 ng/hemisphere, $t(8) = 1.072$, $p = 0.315$), indicating that ERβ antagonism impaired spatial memory (Fig. 2B). Elapsed time to accumulate 30 s of exploration did not differ among the groups for either OR ($F(2,23) = 0.326$, $p = 0.725$; Fig. 2C) or OP ($F(2,24) = 0.678$, $p = 0.517$; Fig. 2D).

4. Discussion

The present findings indicate that ERα antagonism impairs spatial, but not object recognition, memory consolidation in ovariectomized mice, whereas ERβ antagonism impairs both types of memory at the doses tested. These data suggest that ERα and ERβ are necessary for OP memory consolidation, but that only ERβ is necessary for OR memory consolidation, in ovariectomized mice.

DH infusion of the ERβ antagonist PHTPP impaired both OR and OP, suggesting that ERβ is necessary for both object recognition and spatial memory consolidation. These results are consistent with post-training findings that DH-infused DPN enhances OR memory consolidation in ovariectomized mice (Boulware et al., 2013) and systemic E_2 does not enhance OR memory consolidation in ERβ knockouts (Walf et al., 2008). That PHTPP also blocked consolidation in the OP task is consistent with reports that post-training DPN enhances OP in ovariectomized rodents (Walf et al., 2008; Frick et al., 2010; Boulware et al., 2013) and support the necessity of ERβ in object recognition and spatial memory formation.

The impairment in OP induced by the ERα antagonist MPP is

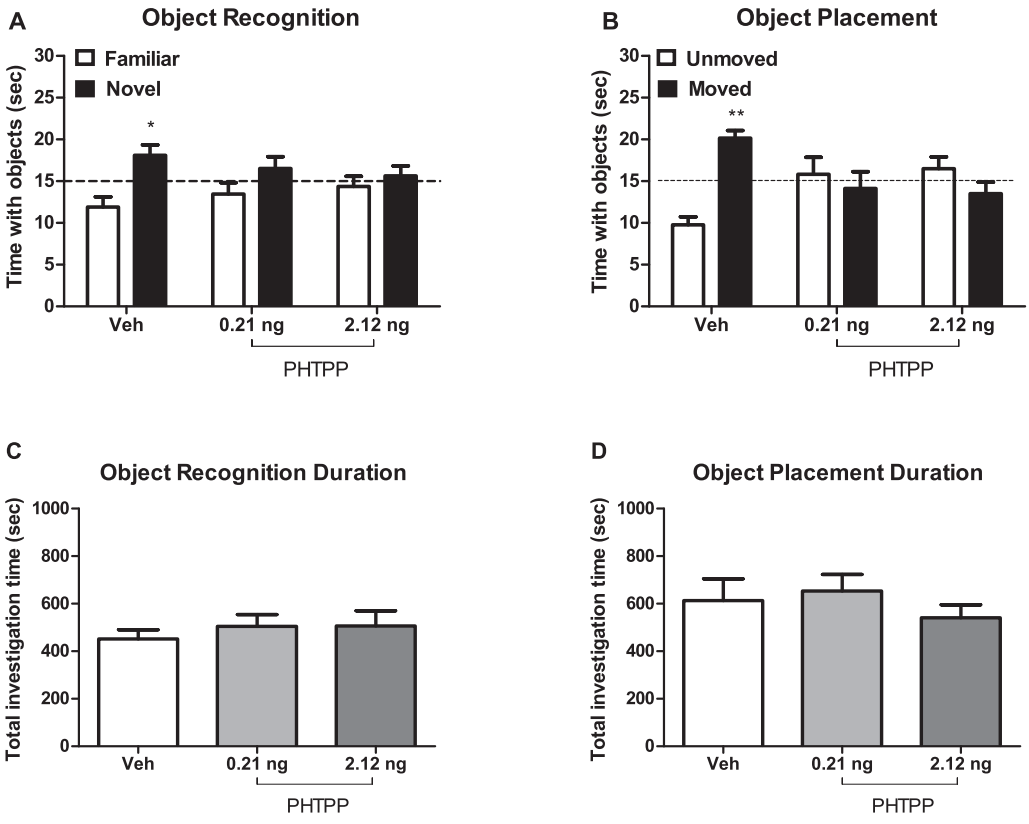

Fig. 2. The ERβ antagonist PHTPP impaired memory in both OR and OP. (A) Mice receiving vehicle, but not 0.21 or 2.12 ng PHTPP, spent more time than chance with the novel object 24 h after OR training, indicating that DH infusion of both doses of PHTPP impaired object recognition memory consolidation (Vehicle, n = 8; 0.21 ng PHTPP, n = 9; 2.12 ng PHTPP, n = 9). (B) Mice receiving 0.21 or 2.12 ng PHTPP were also impaired in the OP task, suggesting that ERβ antagonism impaired spatial memory consolidation (Vehicle, n = 8; 0.21 ng PHTPP, n = 10; 2.12 ng PHTPP, n = 9). Each bar in panels A and B represents the mean ± SEM time spent with the objects (*$p < 0.05$, **$p < 0.01$ relative to chance level of 15 s). (C, D) In both the OR and OP tasks, elapsed time to accumulate 30 s of exploration was not affected by PHTPP infusion. Each bar represents the mean ± SEM time spent in the testing arena.

consistent with studies showing that post-training treatment with PPT enhances memory consolidation in OP among ovariectomized rodents (Frye et al., 2007; Boulware et al., 2013). In contrast, MPP had no detrimental effect on OR, which is curious because post-training DH-infused PPT enhances OR in ovariectomized mice (Boulware et al., 2013). This discrepancy could be a methodological issue, in that MPP doses may have been too low to observe an effect. Alternatively, this discrepancy could suggest that OR is more sensitive to the stimulatory effects of ERα than to antagonism of ERα. Perhaps stimulating ERα is sufficient to enhance memory, but blocking ERα function is not sufficient to impair memory. In other words, ERα is sufficient, but not necessary, to facilitate memory consolidation in OR. Why ERα is necessary for OP, but not OR, is unclear. This difference could be due to the nature of hippocampal ERα itself (*e.g.*, its function or cellular distribution) or to the role of the hippocampus in OR. The dependence of OR on the hippocampus has been long debated, and several other regions (*e.g.*, perirhinal cortex, entorhinal cortex) are also involved in OR memory (Squire et al., 2007). Thus, distinct effects of ERα on OR and OP may be related to the involvement of other brain regions in OR, thereby blunting the effects of hippocampal ERα antagonism.

That ER antagonism blocks memory consolidation in ovariectomized females may suggest an important role for local hippocampal E_2 in memory formation. Object training transiently increases dorsal hippocampal E_2 levels in ovariectomized mice, and both this increase and memory consolidation in OR and OP are blocked by DH infusion of letrozole (Tuscher et al., 2016), suggesting that preventing learning-induced E_2 synthesis impairs memory formation. Because this newly synthesized E_2 presumably binds to ERα and/or ERβ, the present results indicate that preventing learning-induced ER activation in the DH impairs memory formation. Although we should note that E_2 can be made in other non-gonadal tissues (*e.g.*, adrenals, fat), the fact that aromatase inhibition in the DH blocks OR and OP memory consolidation strongly suggests that the learning-induced E_2 that influences memory consolidation is hippocampally derived. Interestingly, antagonism of one ER was generally sufficient to disrupt memory consolidation, suggesting that binding of E_2 to the other ER could not compensate for its loss of function. In addition to ERα and ERβ, E_2 may bind to the membrane ER G-protein-coupled estrogen receptor (GPER), and it is notable that DH infusion of a GPER antagonist also impairs OR and OP memory consolidation in ovariectomized mice (Kim et al., 2016). However, GPER antagonism does not prevent exogenously infused E_2 from enhancing memory in OR and OP (Kim et al., 2016), so it is unlikely that GPER plays a role in the effects observed here. That antagonism of a single ER can disrupt memory formation may indicate unique functions of these ERs to be examined in future work.

Collectively, the present study supports the importance of dorsal hippocampal ERs in regulating memory consolidation, and are consistent with previous studies demonstrating the necessity of local hippocampal E_2 synthesis for memory consolidation in the DH (Rensel et al., 2013; Tuscher et al., 2016). These results imply that classical ERs are necessary for some forms of hippocampal memory consolidation, but that their involvement depends on the task or type of memory tested.

Conflict of interest

The authors declare no competing financial interests.

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