Differential roles for Nr4a1 and Nr4a2 in object location vs. object recognition long-term memory

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Nr4a1 and Nr4a2 are transcription factors and immediate early genes belonging to the nuclear receptor Nr4a family. In this study, we examine their role in long-term memory formation for object location and object recognition. Using siRNA to block expression of either Nr4a1 or Nr4a2, we found that Nr4a2 is necessary for both long-term memory for object location and object recognition. In contrast, Nr4a1 appears to be necessary only for object location. Indeed, their roles in these different types of long-term memory may be dependent on their expression in the brain, as NR4A2 was found to be expressed in hippocampal neurons (associated with object location memory) as well as in the insular and perirhinal cortex (associated with object recognition memory), whereas NR4A1 showed minimal neuronal expression in these cortical areas. These results begin to elucidate how NR4A1 and NR4A2 differentially contribute to object location versus object recognition memory.

[Supplemental material is available for this article.]

It is well established that long-term memory (LTM) formation requires transcription (for review, see Alberini 2009). Transcription regulated specifically by cAMP response element binding protein (CREB) has been shown to be essential for long-term memory (Bourtchuladze et al. 1994; Yin et al. 1994; Guzowski and McGaugh 1997; Pittenger et al. 2002; Sekeres et al. 2010; but see Balschun et al. 2003). Two CREB-dependent immediate early genes that have been implicated in LTM are Nr4a1 and Nr4a2 (Pena de Ortiz et al. 2000; von Hertzen and Giese 2005a,b; Colon-Cesario et al. 2006). Nr4a1 (Nurr77) and Nr4a2 (Nurr1) are members of the nuclear steroid/thyroid hormone receptor superfAMILY that bind in an apparently ligand-independent manner to nerve growth factor-related (NGF-R) response elements (Baker et al. 2003; Wang et al. 2003).

Expression of both Nr4a1 and Nr4a2 has been shown to increase in the hippocampus following learning. Nr4a1 expression increased in the CA1 region of the hippocampus during context shock memory consolidation, and Nr4a2 increased in CA1 and CA3 pyramidal cell layers of the rat hippocampus following a spatial discrimination task (Pena de Ortiz et al. 2000; von Hertzen and Giese 2005a,b; Colon-Cesario et al. 2006). Nr4a1 (Nurr77) and Nr4a2 (Nurr1) are members of the nuclear steroid/thyroid hormone receptor superfamily that bind in an apparently ligand-independent manner to nerve growth factor-related (NGF-R) response elements (Baker et al. 2003; Wang et al. 2003).

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Transcription of both Nr4a1 and Nr4a2 appear to be regulated by chromatin modification via histone acetylation and deacetylation. Histone deacetylase (HDAC) activity was shown to interfere with formation of the pre-initiation complex at the Nr4a1 promoter, suggesting that acetylation is necessary for its transcription (Fass et al. 2003). In addition, during memory consolidation, the HDAC inhibitor Trichostatin A (TSA) maintained the expression of both Nr4a1 and Nr4a2 during memory consolidation, without maintaining the expression of several other CREB-dependent genes (Vescey et al. 2007).

We recently showed that HDAC3 may modulate long-term memory formation in an Nr4a2-dependent manner (McQuown et al. 2011). Deletion of HDAC3 in the dorsal hippocampus transformed a subthreshold training event that normally does not result in LTM into an event that led to robust LTM. Deletion of HDAC3 also facilitated Nr4a2 expression following subthreshold training. In contrast, the HDAC3 deletion had no effect on Nr4a2 expression in naive-handled mice, suggesting that the increase in Nr4a2 required an activity-dependent event. Notably, siRNA knockdown of Nr4a2 in animals with HDAC3 deletions prevented the enhanced LTM that occurred following the subthreshold training (McQuown et al. 2011). Together, these studies suggest that Nr4a1 and Nr4a2 are key target genes regulated by acetylation during long-term memory formation.

The studies discussed above have demonstrated an important role for Nr4a1 and Nr4a2 in long-term memory formation. They also indicate that expression of these genes during consolidation is regulated by chromatin modification through histone acetylation and deacetylation. The current study aimed to further understand the role of these genes in long-term memory formation.

To investigate the role of Nr4a1 and Nr4a2 in learning and memory processes, we examined the basal and activity-dependent levels of NR4A1 and NR4A2 proteins in brain regions involved in learning and memory. We chose to examine regions involved in object location memory and object recognition memory, as the...
training for these tasks is the same, but the testing depends on different brain regions. (Bermudez-Rattoni et al. 2005; Balderas et al. 2008; Roozendaal et al. 2010; Haettig et al. 2011). We performed immunohistochemistry on 20-μm coronal sections of formaldehyde-fixed brain tissue from adult male mice to examine expression of NR4A1 and NR4A2 in the hippocampus as well as the insular, perirhinal, and entorhinal cortices. We also used transient siRNA knockdown to specifically examine the roles of Nr4a1 and Nr4a2 in learning and memory as measured by object location and novel object recognition memory tasks. The findings presented here provide new insight into how Nr4a1 and Nr4a2 regulate memory formation in different tasks utilizing different brain regions.

We found that NR4A1 protein was strongly expressed throughout the hippocampus, including the CA1–CA3 regions (Fig. 1B–D). Notably, in addition to hippocampal expression (Fig. 1H–J), NR4A2 showed strong expression in discrete foci within cortical layer VI (Allen Brain Atlas coordinates: −2.25 to −5.25 ventral to bregma) (Fig. 1K,L). Double labeling for NR4A2 and NeuN showed that cortical NR4A2 is expressed in neurons (Fig. 1L). These findings demonstrate that both NR4A1 and NR4A2 were expressed in the hippocampus, whereas NR4A2 also exhibited strong expression in cortical layer VI.

Next we examined changes in expression of NR4A1 and NR4A2 following training for an object memory task that activates these brain regions (Bermudez-Rattoni et al. 2005; Balderas et al. 2008; Roozendaal et al. 2010; Haettig et al. 2011). Adult male C57Bl/6J mice were habituated to the context for 4 d and then on the fifth day were returned to the same context and either exposed to two identical objects for 10 min (trained) or without objects (habituated). Preliminary time-course studies showed that Nr4a2 mRNA levels increased for 60 min following a learning event, and Jo et al. (2009) demonstrated that NR4A2 protein is stable for >2 h. Therefore, 2 h after training animals were perfused and formaldehyde-fixed brains were collected for immunohistochemistry. The NR4A1 and NR4A2 antibodies we used for immunohistochemistry are directed against the variable N-terminal region of the two proteins, and the specificity of the antibodies was verified by Western blot analysis (Supplemental Fig. 1).

We quantified NR4A1 and NR4A2 expression in area CA1 of the hippocampus and cortical layer VI of the insular, perirhinal, and entorhinal cortices. Following training, there were significant 40% increases in both NR4A1 (habituated: 1.03 ± 0.07 N = 23 vs. trained: 1.43 ± 0.07 N = 31, P = 0.0003) (Fig. 2B) and NR4A2-immune-positive cells in area CA1 (habituated: 1.00 ± 0.19 N = 12 vs. trained: 1.39 ± 0.11 N = 16, P = 0.04) (Fig. 2C). There was no significant change in cortical NR4A1-immune-positive cells (habituated: 1.00 ± 0.36 N = 23 vs. trained: 0.72 ± 0.15 N = 26, P = 0.24) (Fig. 2D). In addition, we found a significant twofold increase in cortical NR4A2-immune-positive cells in mice that received a 10-min training compared with habituated animals (habituated: 1.00 ± 0.12 N = 21 vs. trained: 1.96 ± 0.19 N = 27 P = 0.0002) (Fig. 2E). Representative images of hippocampal NR4A1 (Fig. 2F,G) and hippocampal (Fig. 2H,I) and cortical NR4A2 (Fig. 2J,K) are shown.

To further investigate the role of Nr4a1 and Nr4a2 in learning and memory, we used small interfering (si) RNAs to transiently knock down expression of Nr4a1 and Nr4a2. Targeted SMART pool siRNAs (Dharmacon) were prepared with jetSi (Polyplus Transfection) at a final concentration of 4 μM before injection. A nontargeting control siRNA with an RNA-induced silencing complex (RISC)-free modification was used as a control (siRISC). Mice received intrahippocampal infusions of RISC-free control, Nr4a1, or Nr4a2 siRNA directly into the dorsal CA1 area of the hippocampus (AP, −2.0 mm; DV, −1.5 mm; ML, ±1.5 mm). To assess specific knockdown of each transcript, RNA was isolated from 1-mm hippocampal punches and quantitative real-time RT-PCR was performed as previously described (McQuown et al. 2011) using a Roche LightCycler:

\[
\text{Nr4a1 probe 93: 5'-tctgtgctc-3', forward primer: 5'-agctggtgtgtgtagttc-3', reverse primer: 5'-aatgcgattctg-3'}.
\]

\[
\text{Nr4a2 probe 2: 5'-ctctttcg-3', forward primer: 5'-tgcagataatgacctgca-3', reverse primer: 5'-tgcagataatgacctgg-3'}.
\]

\[
\text{Gapdh probe: 5'-tggcgcatttgg-3', forward primer: 5'-atggatgctgctgtagt-3', reverse primer: 5'-aatcccattttcagc-3'}.
\]

Hippocampal infusion with siRNA against Nr4a1 significantly and specifically decreased expression of Nr4a1 by more than twofold as compared with the RISC-free control (siRISC = 1.58 ± 0.43, siNr4a1 = 0.70 ± 0.18; P = 0.04). There was no significant difference in expression of Nr4a2 following infusion with siNr4a1 (1.99 ± 0.37; P = 0.25) (Fig. 3A). Infusion with siNr4a2 also significantly

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**Figure 1.** NR4A1 and NR4A2 are expressed in the hippocampus and NR4A2 is also expressed in cortical layer VI extending through the insular, perirhinal, and entorhinal cortices. Representative images showing (A) Nuclear DAPI staining 4× magnification. (B) NR4A1-immune-positive cells, 4× magnification. (C) NR4A1-immune-positive cells in CA1 of the hippocampus, 20× magnification. (D) NR4A1-immune-positive cells in CA2 and CA3 of the hippocampus, 20× magnification. (E) NR4A1-immunoreactivity in cortical layer VI, showing diffuse staining. (F) Minimal colocalization of NeuN- and NR4A1-immunopositive cells. (G) Nuclear DAPI staining, 4× magnification. (H) NR4A2-immune-positive cells, 4× magnification. (I) NR4A2-immune-positive cells in the CA1 area of the hippocampus, 20× magnification. (J) NR4A2-immune-positive cells in CA2 and CA3 of the hippocampus, 20× magnification. (K) NR4A2-immune-positive cells in cortical layer VI, showing strong focal expression. (L) Colocalization of NeuN- with NR4A2-immunopositive cells. The primary antibodies were directed against NR4A1 (sc-5569, Santa Cruz), NR4A2 (sc-5568, Santa Cruz), and NeuN (MAB377, Millipore Corporation). Images were acquired with an Olympus (BX51) microscope using 4× (A,B,G,J) or 20× (C–F,L–I) objectives and a CCD camera (QImaging) using QCapture Pro 6.0 software (QImaging).
and specifically knocked down Nr4a2 expression more than two-fold when compared with RISC-free control (siRISC = 0.97 ± 0.23, siNr4a2 = 0.46 ± 0.07; P = 0.02). No significant difference was found in expression of Nr4a1 following infusion with siNr4a2 (0.72 ± 0.11; P = 0.17) (Fig. 3B). Each primer–probe set produced a single real-time RT-PCR product. In addition, there were no significant differences in Gapdh mRNA expression following siRNA knockdown (Supplemental Fig. 2).

We then used the object location memory (OLM) task to investigate the roles of Nr4a1 and Nr4a2 in the hippocampus. Two days prior to training, mice received hippocampal siRNA infusions and 48 h after infusion were trained with two identical objects for 10 min (Fig. 3C). The percentage of time spent exploring the objects during training did not differ significantly between the groups (statistics calculated using ANOVA). Twenty-four hours after training, the animals were placed in the identical context with one object moved to a novel location (OLM) (Fig. 3C). Animals that spent more time with the object in the novel location are considered to demonstrate memory for the object in the familiar location. Animals that received infusions of the control RISC-free siRNA exhibited memory for the familiar object and spent more time with the object in the novel location (% discrimination index [DI] = 27.7 ± 8.4 N = 8) (Fig. 3D). In contrast, animals infused with siRNA against either Nr4a1 or Nr4a2 had significantly impaired memory for the familiar object (% DI for Nr4a1 = 4.8 ± 5.5 N = 9, % DI for Nr4a2 = −6.9 ± 4.7 N = 10, P = 0.002). These results suggest that both Nr4a1 and Nr4a2 are required for hippocampus-dependent long-term memory for object location.

We next examined the role of Nr4a1 and Nr4a2 in long-term memory in a standard novel object recognition task (ORM) (Fig. 3E). Two days prior to training, mice received intracerebroventricular (ICV) infusions (AP, −0.34 mm; DV, −2.1 mm; ML, ± 1.0 mm) of small interfering (si) RNAs to transiently knockdown expression of Nr4a1 and Nr4a2. In the ORM task, 48 h after siRNA infusion, animals previously habituated to the context were trained with two identical objects for 10 min (Fig. 3E). There were no significant differences in total exploration times between groups during training or testing (statistics calculated using ANOVA).

Twenty-four hours after training, animals were given a retention test in which one familiar object was replaced with a novel object (Fig. 3E). At testing, animals infused with siRNA targeted against Nr4a2 had a significantly lower discrimination index (% DI) for the novel object (% DI = 10.1 ± 4.5 N = 6; P = 0.03) than mice infused with either control siRISC (% DI = 27.88 ± 5.7 N = 9) or siRNA directed against Nr4a1 (% DI = 29.1 ± 2.6 N = 7). There was no difference between control animals and animals infused with siNr4a1 (Fig. 3F). The siRNAs targeted to Nr4a2 resulted in a significant knockdown of Nr4a2 protein in layer VI of the ipsilateral, perirhinal, and entorhinal cortices 2 h after training with objects, (siRISC = 1.00 ± 0.30 N = 13, siNr4a2 = 0.35 ± 0.05 N = 15, P = 0.02) (Fig. 3H). As predicted from the lack of neuronal Nr4a1 expression in cortical areas, no significant difference in cortical expression was observed following Nr4a1 knockdown (siRISC = 0.97 ± 0.38 N = 13, siNr4a1 = 0.83 ± 0.33 N = 15, P = 0.38) (Fig. 3G). These data show that cortical knockdown of Nr4a2 impaired long-term memory for the object itself.

Both Nr4a1 and Nr4a2 mRNAs are highly expressed in the CA1 and CA3 regions of the hippocampus (Honkanieni et al. 1995; Xiao et al. 1996; this study), an area critical for context and location-dependent memory formation (O’Keefe and Burgess 1999; Fanselow 2000; Maren and Holt 2000). Through a number of recent studies, it has been found that mRNA expression of Nr4a1 and Nr4a2 increases during memory acquisition and consolidation, suggesting that induction of these genes is integral to the formation of long-term memory (Pena de Ortiz et al. 2000; von Hertzen and Giese 2005a,b; Colon-Cesario et al. 2006). Acquisition and LTM for a spatial discrimination task in rats is disrupted...
Intracerebroventricular infusions of cortex, as measured by immunohistochemistry (Nr4a2) and parietal expression of objects. Another 24 h later they were given a retention test in which one object was moved to a different location while the other object was replaced with a novel object. Twenty-four hours later they were given a retention test where one identical object was removed and a novel object was added. siRNA against Nr4a1 or Nr4a2 displayed no preference for the novel object in the OLM task in contrast to animals that received control RISC-free siRNA. Forty-eight hours later they received 10 min of training with two identical objects. During a 24-h retention test, mice that received hippocampal infusions of either siRNA against Nr4a1 or Nr4a2 displayed no preference for the novel object in the OLM task in contrast to animals that received control RISC-free siRNA (P = 0.002) and no preference in the OLM task in contrast to animals that received control RISC-free siRNA targeted to Nr4a2 in the cortex led to a significant reduction in NR4A2 and impaired a cortex-dependent memory task. Together these findings suggest a critical role for NR4A2, but not NR4A1 in cortex-dependent memory formation.

While the perirhinal cortex is considered essential for multi-modal object recognition (Albasser et al. 2011), the hippocampus is believed to be necessary for object location. However, a functional interaction between the hippocampus and the perirhinal cortex is important for multisensory processing and memory (Barker and Warburton 2011). The results presented here suggest that Nr4A1 is a critical signaling molecule involved in object location memory, while NR4A2 is critical for both object location and recognition memory. Previously, we showed that Nr4a2 was necessary for memory enhancement resulting from a focal hippocampal deletion of HDAC3 (McQuown et al. 2011). In the present study, we showed that in addition to Nr4a2, Nr4a1 is critical for hippocampal memory formation. Further studies have shown that HDAC activity interferes with transription of Nr4a1 and an HDAC inhibitor increases expression of both Nr4a1 and Nr4a2 in the hippocampus (Fass et al. 2003; Vecsey et al. 2007). Therefore, further studies will be needed to answer whether HDAC3 is also a critical regulator of Nr4a1 expression during LTM formation. We also found that cortical NR4A2 is specifically required for long-term memory for object recognition. These data suggest that Nr4a1 and Nr4a2 are critical for specific types of memory and represent different mechanisms required for consolidation of long-term memory in different brain regions.

**Figure 3.** Knockdown of Nr4a2, but not Nr4a1, in cortical regions including the insular, perirhinal, and entorhinal cortices reduces preference for the novel object in the object recognition (ORM) task, while hippocampal knockdown of both Nr4a1 and Nr4a2 affects performance in the object location (OLM) task. (A) siRNA directed against Nr4a1 significantly reduced hippocampal expression of Nr4a1 (P = 0.04) without affecting Nr4a2 (P = 0.25). (B) siRNA against Nr4a2 significantly reduced hippocampal expression of Nr4a2 (P = 0.02) without affecting Nr4a1 expression (P = 0.17). (C) Forty-eight hours after injection, habituated animals received 10 min of training with two identical objects. Another 24 h later they were given a retention test in which one object was moved to a novel location. (D) During a 24-h retention test, mice that received hippocampal infusions of either siRNA against Nr4a1 or Nr4a2 displayed no preference for the novel object in the OLM task in contrast to animals that received control RISC-free siRNA (P = 0.002). (E) Habituatized mice received intracerebroventricular (ICV) infusions of control RISC-free, Nr4a1, or Nr4a2 siRNA. Forty-eight hours later they received 10 min of training with two identical objects. Twenty-four hours later they were given a retention test where one object was replaced with a novel object. (F) During a 24-h retention test, mice that received ICV infusions of siRNA targeted to Nr4a1 or Nr4a2 displayed no preference for the novel object in contrast to animals that received control RISC-free siRNA or siRNA targeted to Nr4a1 (P = 0.03). (G) Intracerebroventricular infusions of Nr4a1 siRNA did not change expression of NR4A1 in the cortex, as measured by immunohistochemistry (P = 0.4). (H) Intracerebroventricular infusions of Nr4a2 siRNA significantly decreased expression of NR4A2 in the cortex, as measured by immunohistochemistry (P = 0.02).
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