

Differential Role for CBP and p300 CREB-Binding Domain in Motor Skill Learning

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Cyclic adenosine monophosphate response element binding protein (CREB) binding protein (CBP) and E1A binding protein (p300) are highly homologous transcriptional coactivators with histone acetyltransferase activity. Although CBP and p300 have unique functions *in vivo* during embryogenesis and hematopoiesis, their functions within the nervous system remain poorly understood. The authors demonstrate that these coactivators have differential roles in motor skill learning. Mice with a mutation in the CREB-binding (KIX) domain of CBP exhibited motor learning deficits. However, mice with the analogous mutation in the KIX domain of p300 showed normal motor learning. Further, CREB knock-out mice exhibited a motor learning deficit similar to that of CBP-KIX mutant mice. These results suggest that the CREB–CBP interaction is more limiting or critical than the CREB–p300 interaction for motor skill learning. Thus, CBP and p300 are genetically distinct at the behavioral level.

Keywords: cAMP response element binding protein, CREB binding protein, p300, KIX domain, motor skill learning

Cyclic adenosine monophosphate response element binding protein (CREB) binding protein (CBP) and E1A binding protein (p300) are transcriptional coactivators with intrinsic histone acetyltransferase activity. CBP was originally identified as a protein that binds to phosphorylated CREB (Chrivia et al., 1993), and p300 was first described as an adenovirus E1A-associated protein (Eckner et al., 1994), but these coactivators share several conserved protein–protein interaction domains, such as the CREB-binding (KIX) domain and the enzymatic histone acetyltransferase (HAT) domain. The HAT domain mediates acetylation of lysine residues on the N-terminal tails of histone proteins (Kalkhoven, 2004). Acetylation neutralizes the positively charged lysine residues in histones and disrupts the interaction between histones and DNA, increasing DNA accessibility for transcription factors to activate gene expression. Although CBP and p300 are highly homologous and share many functional properties (reviewed in Vo & Goodman, 2001), there has been recent genetic evidence that these coactivators are not interchangeable in blood cells (Kasper et al., 2002, 2006).

In many early studies, CBP and p300 were thought to have redundant functions as determined by protein–protein interaction experiments. For example, following their initial identifications,

CBP and p300 were shown to interact with both CREB and E1A (Arany, Newsome, Oldread, Livingston, & Eckner, 1995; Lee, Zhang, & Shi, 1996). Furthermore, transfection-based assays demonstrated that both CBP and p300 interact with many common transcription factors, which can use either coactivator for gene expression (reviewed in Vo & Goodman, 2001). However, recent *in vivo* genetic studies have demonstrated that CBP and p300 have unique functions during embryogenesis and hematopoiesis. Homozygous CBP and p300 knock-out mice have different developmental phenotypes, suggesting nonredundant functions during embryogenesis (Kung et al., 2000; Yao et al., 1998). Kasper et al. (2002) showed that mice homozygous for point mutations in the KIX domain of p300 have multilineage defects in hematopoiesis. In contrast, mice homozygous for identical mutations in the KIX domain of CBP were essentially normal. This was the first *in vivo* study suggesting that a conserved domain (KIX) in these two highly related coactivators has a unique function. However, the functions of CBP and p300 within the nervous system remain poorly understood, especially at the behavioral level.

In the present study, we investigated whether CBP and p300 have similar or distinct functions during motor skill learning. Mice carrying a triple-point mutation in the KIX domain of CBP and/or p300 (Kasper et al., 2002) were examined on the accelerating rotarod task. We found that mice carrying the KIX mutation in CBP, but not p300, exhibited impaired motor skill learning. One of the transcription factors known to recruit these coactivators during gene activation, through the KIX domain, is the cyclic adenosine monophosphate- and calcium-responsive transcription factor, CREB, which is believed to play a central role in learning and memory. Thus, we also examined mice with a targeted disruption of the alpha and delta isoforms of CREB (CREB $\alpha\Delta$ knock-out

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mice; Hummler et al., 1994) in the accelerating rotarod task. We found that these mice exhibited impaired motor skill learning similar to CBP-KIX mutant mice. These results suggest that the CREB–CBP interaction, but not CREB–p300, is involved in motor skill learning, even though both CBP and p300 are expressed in the brain. Moreover, our results are the first to suggest that CBP and p300 have genetically nonredundant roles in the central nervous system at the behavioral level.

Method

Animals

All mice were 8–16 weeks old and had free access to food and water in their home cages. Lights were maintained on a 12-hr light–dark cycle, with all behavioral testing carried out during the light portion of the cycle. The CBP^{KIX/+} and p300^{KIX/+} mice were generated as previously described (Kasper et al., 2002). Briefly, CBP^{KIX/+} and p300^{KIX/+} mice contained a triple-point mutation—Tyr650Ala, Ala654Gln, and Tyr658Ala or Tyr630Ala, Ala634Gln, and Tyr638Ala, respectively—in their CREB-binding (KIX) domain. The CBP^{KIX/+} and p300^{KIX/+} mice were backcrossed to C57BL/6J. The CBP^{KIX/KIX} homozygous knock-in mice were generated from CBP^{KIX/+} heterozygous matings. CBP^{+/+/p300^{+/+}}, CBP^{+/+/p300^{KIX/+}}, CBP^{KIX/+/p300^{+/+}}, and CBP^{KIX/+/p300^{KIX/+}} mice were generated from the mating of CBP^{KIX/+} heterozygous mice with p300^{KIX/+} heterozygous mice. Genotyping was performed as previously described (Kasper et al., 2002). For experiments with CREB $\alpha\Delta$ knock-out mice, male and female wild-type and homozygous mutant mice were a product of an F1 cross of C57BL/6J and 129/SvEvTac mice. The CREB $\alpha\Delta$ mutation (Hummler et al., 1994) was backcrossed in a heterozygous state in each parental strain for 9–11 generations. Genotyping was performed as previously described (Graves, Dalvi, Lucki, Blendy, & Abel, 2002). All experiments were conducted according to the National Institutes of Health's (1986) *Guide for the Care and Use of Laboratory Animals* and were approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania. The investigator was blind to the genotype of the mice during behavioral testing.

Accelerating Rotarod

The rotarod experiments were performed as previously described (Wood, Kaplan, Brensinger, Guo, & Abel, 2005). Briefly, the rotarod apparatus (Ugo Basile, Stoelting Co., Wood Dale, IL) had a 3-cm diameter rotating rod raised 16 cm above a platform and divided into five sections for testing multiple mice simultaneously. The rotarod gradually increased its rotation speed from 4 to 40 rpm over the course of 5 min. Latency to fall was recorded. Three trials were given per day during 3 consecutive days with an intertrial interval of 1 hr. Each trial started at the same time every day and ended when mice fell off the rod or when mice ran for 300 s.

Data Analysis

Two-way repeated-measures analyses of variance (ANOVAs) were performed in all experiments by use of SigmaStat (Version 2.03, Systat Software, Point Richmond, CA). In all experiments, we observed a main effect of day and a main effect of genotype. To isolate which group(s) differed from the others, we used the Student–Newman–Keuls multiple comparisons method. Data were analyzed by trial as well as by day, as shown in the figures. Genotype was confirmed by PCR analysis following behavioral tests.

Results

Homozygous CBP^{KIX/KIX} and p300^{KIX/KIX} mice carried mutations in three highly conserved residues within the KIX domain of

the endogenous alleles (Kasper et al., 2002). These residues are critical for the binding surface between the KIX domain and the phosphorylated CREB-kinase inducible domain (KID; Radhakrishnan, Perez-Alvarado, Dyson, & Wright, 1998). CBP^{KIX/KIX} mice were essentially normal, apart from a modest decrease in thymus size (Koo et al., 2005). However, p300^{KIX/KIX} mice had a marked reduction in thymocyte numbers and severe anemia and thrombocytosis (Kasper et al., 2002). Heterozygous CBP^{KIX/+} and p300^{KIX/+} mice were essentially normal. It is important that there did not appear to be compensation by the increased expression of p300 in CBP^{KIX/KIX} cells, and the expression of the CBP^{KIX} allele appeared similar to that of the wild-type CBP allele. Similarly, CBP expression in p300^{KIX/KIX} cells did not increase, and expression of the p300^{KIX} allele was comparable to the wild-type p300 allele (Kasper et al., 2002).

To study whether the transcriptional coactivators, CBP and p300, play a role in motor skill learning, we tested mice carrying a triple-point mutation in the CREB-binding (KIX) domain of the CBP and/or p300 gene (Kasper et al., 2002) on the accelerating rotarod task. In the first experiment, we tested CBP^{KIX/KIX} homozygous knock-in mice. These mice exhibited significantly decreased time on the rotarod, $F(1, 225) = 21.87$, $p < .0001$, as compared with wild-type littermates (Figures 1A and 1B). Note that CBP^{KIX/KIX} homozygous mice showed normal anxiety and locomotor activity as determined by performance on the elevated zero maze (data not shown). There were no statistically significant differences (as determined by a 2-way repeated-measures ANOVA and multiple comparisons Student–Newman–Keuls method post hoc analysis) between genotypes during the first two trials of each experiment (shown in Figure 1A and 1C and in Figure 2A). This suggests that balance, coordination, and muscle fatigue were not factors in the differences we observed during subsequent trials. In addition, CBP^{KIX/KIX} homozygous mice had similar swim speed in the Morris water maze (data not shown) as compared with wild-type littermates, which also suggests that they have no coordination or muscle fatigue impairments. These results suggest that the KIX domain of CBP is required for the function of CBP in motor skill learning.

Because most studies show that CBP and p300 are functionally equivalent with regard to CREB function, we examined whether the KIX domain of p300 also contributes to motor skill learning. p300^{KIX/KIX} homozygous mice on a mixed genetic background often die before they reach 3 weeks of age, and those that live longer are usually 50%–70% of the size of wild-type littermates (Kasper et al., 2002). Thus, we chose to address the role of the KIX domain of p300 in motor skill learning using p300^{KIX/+} heterozygous mice, CBP^{KIX/+} heterozygous mice, and CBP^{KIX/+}/p300^{KIX/+} double heterozygous mice. Use of these three different genotypes and their wild-type counterparts allowed us to determine whether the KIX domain of p300 has a role in motor skill learning similar to that of the KIX domain of CBP, and whether the combined dosage of CBP and p300 KIX domains is important.

As shown in Figures 1C and 1D, CBP^{KIX/+} heterozygous mice (CBP^{KIX/+}/p300^{+/+}) exhibited significantly decreased time on the rotarod, $F(3, 261) = 16.31$, $p < .0001$, as compared with wild-type (CBP^{+/+/p300^{+/+}}) littermates (post hoc analysis: CBP^{KIX/+} vs. wild-type, $q = 8.34$, $p < .0001$, Student–Newman–Keuls). This result agrees with data shown in Figures 1A and 1B demonstrating that CBP^{KIX/KIX} homozygous mice have impaired motor skill

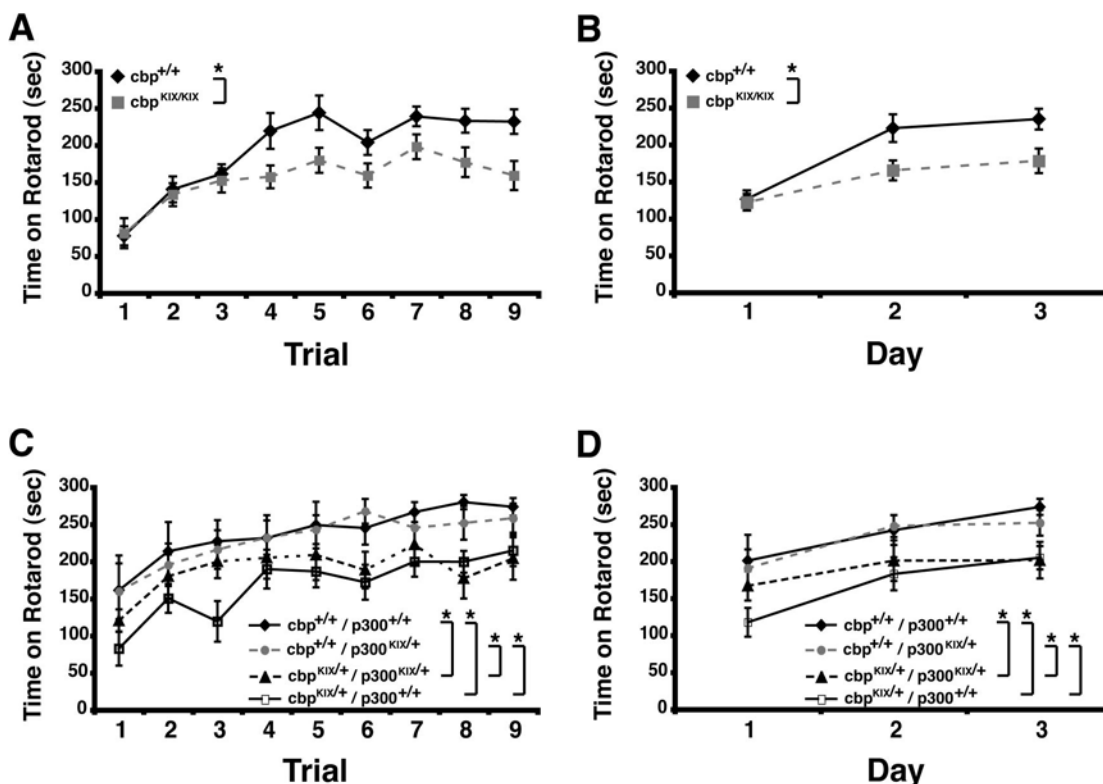


Figure 1. Mice carrying the cAMP response element binding protein (CREB)-binding domain (KIX) mutation in CREB binding protein (CBP), but not E1A binding protein (p300), exhibited impaired motor skill learning. Latency to fall from the rotarod is shown across training trials (A, C) and across days (three trials per day; B, D). A, B: Motor skill learning of CBP^{KIX/KIX} mice ($n = 12$) was significantly impaired as compared with wild-type littermates ($n = 15$). C, D: CBP^{KIX/+}/p300^{+/+} ($n = 10$) and CBP^{KIX/+}/p300^{KIX/+} ($n = 7$) mice showed significantly impaired motor skill learning as compared with CBP^{+/+}/p300^{+/+} ($n = 7$) and CBP^{+/+}/p300^{KIX/+} ($n = 9$) littermates. It is important to note that CBP^{KIX/+}/p300^{+/+} and CBP^{KIX/+}/p300^{KIX/+} mice did not differ from each other. Similarly, CBP^{+/+}/p300^{+/+} and CBP^{+/+}/p300^{KIX/+} mice did not differ from each other. Values are means (\pm SEM). * $p < .05$, as determined by two-way repeated-measures analysis of variance. Pairwise multiple comparisons were performed by use of the Student–Newman–Keuls method.

learning. These results further demonstrate that it requires only a single allele of CBP to carry a mutation in the KIX domain for mice to exhibit this phenotype. In contrast, p300^{KIX/+} heterozygous mice (CBP^{+/+}/p300^{KIX/+}) exhibited similar time on the rotarod as compared with wild-type littermates (post hoc analysis: p300^{KIX/+} vs. wild-type, $q = 1.01$, *ns*, Student–Newman–Keuls). It is interesting that CBP^{KIX/+}/p300^{KIX/+} double heterozygous mice exhibited significantly decreased time on the rotarod as compared with wild-type littermates (post hoc analysis: CBP^{KIX/+}/p300^{KIX/+} vs. wild-type, $q = 5.37$, $p < .001$, Student–Newman–Keuls). The CBP^{KIX/+}/p300^{KIX/+} double heterozygous mice were not different from CBP^{KIX/+} heterozygous mice (CBP^{KIX/+}/p300^{+/+}, post hoc analysis: CBP^{KIX/+}/p300^{KIX/+} vs. CBP^{KIX/+}, $q = 2.52$, *ns*, Student–Newman–Keuls). These results demonstrate that either the KIX domain of CBP or p300 have unique functions or they are not together limiting, with respect to motor skill learning.

Both CBP and p300 function as coactivators for the transcription factor CREB. Upon activity-dependent stimulation, CREB is

phosphorylated by numerous kinases at the KID, which is a recruitment signal for either CBP or p300 (Chrivia et al., 1993; Kwok et al., 1994; Lundblad, Kwok, Laurance, Harter, & Goodman, 1995; Parker et al., 1996). The phospho-KID domain interacts with the KIX domain of CBP and p300. Thus, we next examined whether CREB has a role in motor skill learning by testing CREB $\alpha\Delta$ knock-out mice on the accelerating rotarod. As shown in Figures 2A and 2B, CREB $\alpha\Delta$ knock-out mice exhibited significantly decreased time on the rotarod, $F(1, 315) = 114.30$, $p < .0001$, as compared with wild-type littermates. Note that CREB $\alpha\Delta$ knock-out mice showed no ataxia or motor disorders (Bourtchouladze et al., 1994) and no performance deficits with respect to swim speed in the Morris water maze (Graves et al., 2002), suggesting that the impairment in CREB $\alpha\Delta$ knock-out mice in the rotarod task does not reflect broad defects in motor activity but rather impaired motor skill learning. Together, our data suggest that the CREB–CBP, but not the CREB–p300, interaction is involved in motor skill learning.

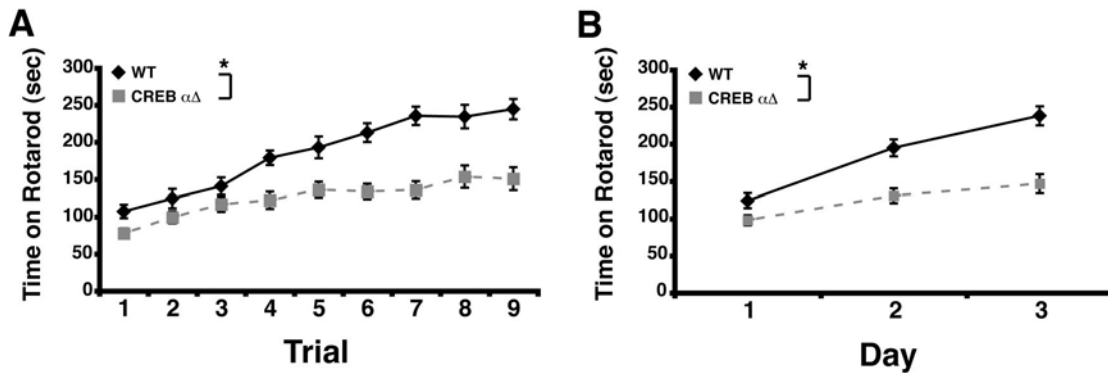


Figure 2. CREB $\alpha\Delta$ knock-out mice (i.e., mice with targeted disruption of the alpha and delta isoforms of cyclic adenosine monophosphate response element binding protein) exhibited impaired motor skill learning. Latency to fall from the rotarod is shown across training trials (A) and across days, with three trials per day (B). Motor skill learning of CREB $\alpha\Delta$ knock-out mice ($n = 19$) was significantly impaired as compared with wild-type (WT) littermates ($n = 18$). Values are means (\pm SEM). * $p < .05$, as determined by two-way repeated-measures analysis of variance.

Discussion

Our findings suggest that a highly homologous domain in the two transcriptional coactivators CBP and p300 is differentially required for motor skill learning. Genetically modified mice heterozygous for a triple-point mutation in the CREB-binding (KIX) domain of CBP exhibited significant impairments on the accelerating rotarod. In contrast, mice heterozygous for the analogous mutation in the KIX domain of p300 showed normal motor learning. One of the transcription factors known to recruit these coactivators during gene activation through the KIX domain is CREB. CREB mutant mice exhibited a motor learning deficit similar to that of CBP-KIX mutant mice. These results suggest that the CREB–CBP interaction is more critical than the CREB–p300 interaction in motor skill learning.

It is possible that there are other potential CBP and p300 targets that could be affected other than CREB. A very recent article described the CBP and p300 interactome, which consists of 312 viral and mammalian proteins that interact physically or functionally with CBP or p300 in vitro (Kasper et al., 2006). However, the triple-point mutation in the KIX domain of CBP and p300 likely affects only CREB (and related family members activating transcription factor 1 and cAMP responsive element modulator) and myeloblastosis proto-oncogene (c-Myb; and perhaps the related A-Myb [myeloblastosis viral oncogene homolog-1]; Kasper et al., 2002). First, the triple-point mutation was designed based upon the nuclear magnetic resonance solution structure between the CBP-KIX domain and the phosphorylated KID domain of CREB, which elucidated the pivotal KIX–phospho–KID interaction residues (Radhakrishnan et al., 1998). Second, even among KIX-interacting proteins, CREB and c-Myb are thought to have distinctly different binding sites within KIX as compared with JUN proto-oncogene, p53, human T-cell leukemia virus type 1 (HTLV-1) transcriptional activator, and sterol regulatory element binding protein (Campbell & Lumb, 2002; Kasper et al., 2002; Liu, Chang, & Chang, 2003). Thus, to date, we are only aware that the CBP and p300 KIX domain mutations affect CREB and c-Myb (Kasper et al., 2002), and the data we present here suggest that CREB is a KIX domain interacting factor involved in motor skill learning.

Similar to the different functions of CBP and p300 during embryogenesis and hematopoiesis (Kasper et al., 2002; Tanaka et al., 2000; Yao et al., 1998), our results provide evidence that these coactivators may also have different functions in the central nervous system at the behavioral level. This difference in brain function may be caused by unique biochemical properties of the KIX domain (or other domains) of CBP that are absent in p300, or it may be that CBP and p300 are differentially expressed in key target cells. Indeed, CBP protein is relatively more abundant compared with p300 in wild-type whole brain, when compared with a hematopoietic cell type that is sensitive to the p300 KIX mutation (i.e., megakaryocytes; Kasper et al., 2002). Thus the severity of the phenotype caused by the KIX mutation roughly correlates with the relative abundance of CBP and p300 in the affected organ.

In our experiments, we found that introducing the triple-point mutation into the KIX domain of a single CBP allele was sufficient to impair motor skill learning in mice. Because we did not examine CBP^{KIX/KIX} homozygous mice (Figures 1A and 1B) at the same time as CBP^{KIX/+} heterozygous mice (Figures 1C and 1D) in our experiments, we cannot quantitatively determine whether homozygous mice were more impaired. It would not be surprising to find that CBP^{KIX/KIX} homozygous mice exhibit greater impaired motor skill learning than CBP^{KIX/+} heterozygous mice. There is evidence in the literature demonstrating dose-dependent effects of CBP. For example, a homozygous CBP knock-out is embryonically lethal (Tanaka et al., 2000), whereas a heterozygous CBP knock-out mutation results in viable mice, albeit with skeletal and growth abnormalities (Tanaka et al., 1997), and these mice exhibit memory and synaptic plasticity deficits as well as impaired rotarod performance (Alarcon et al., 2004). It is difficult to distinguish performance from motor skill learning in these mice, but it further supports that a partial reduction in CBP activity is sufficient to observe a motor phenotype. In our CBP^{KIX/+} heterozygous point-mutation mice, there were no skeletal and growth abnormalities, but there was a significant motor skill learning deficit. Considering that cellular levels of CBP are tightly regulated and that CBP is limited (Kamei et al., 1996), it seems reasonable that even a more

subtle mutation like that of the CBP^{KIX/+} heterozygous mice is sufficient to disrupt processes requiring KIX-interacting factors.

Motor skill learning involves several brain regions, including the sensorimotor cortex, basal ganglia, and cerebellum, and a number of different mechanisms have been proposed to account for how motor skill learning occurs (reviewed in Hikosaka, Nakamura, Sakai, & Nakahara, 2002). A recent study suggests that motor skill learning requires protein synthesis (Luft, Buitrago, Kaelin-Lang, Dichgans, & Schulz, 2004). Using the accelerating rotarod, the authors demonstrated that protein synthesis inhibitors, at doses that do not impair motor function (see Davis & Squire, 1984), block motor learning but not performance (Luft et al., 2004). Our results show that transcriptional regulation may also be involved in motor skill learning, demonstrating that the KIX domain of CBP, and thus the interaction between CBP and CREB, and CREB–CBP-mediated transcription is required for motor skill learning.

Numerous studies in *Aplysia*, *Drosophila*, and mice have shown that CREB is involved in learning, memory, and synaptic plasticity (reviewed in Kaplan & Abel, 2003; Lonze & Ginty, 2002). Recently, we and others have demonstrated that CBP is critical for hippocampus-dependent long-term memory (Bourtchouladze et al., 2003; Korzus, Rosenfeld, & Mayford, 2004; Oike et al., 1999) and synaptic plasticity (Alarcon et al., 2004; Wood, Kaplan, Park et al., 2005; reviewed in Josselyn, 2005). The first hint of a role for CBP in motor skill learning came from a study in which heterozygous CBP mice (one endogenous allele of CBP has been deleted) showed impairments in the rotarod task (Alarcon et al., 2004). However, the mice used in this study had a 50% decrease in the amount of CBP protein, which caused various skeleton abnormalities and developmental impairments (Tanaka et al., 1997). Thus, it is not possible to rule out that the impaired motor skill learning was due to developmental defects. In contrast, homozygous CBP^{KIX/KIX} mice, heterozygous CBP^{KIX/+} mice, and homozygous CREB $\alpha\Delta$ knock-out mice were apparently normal with respect to anxiety, locomotor activity, and development (Bourtchouladze et al., 1994; Graves et al., 2002; Kasper et al., 2002; data not shown), and CBP^{KIX/KIX} homozygous mice exhibit swim speed in the Morris water maze (data not shown) similar to that of wild-type littermates, which also suggests that they have no coordination or muscle fatigue impairments. In addition, we found no statistically significant differences (as determined by a two-way repeated-measures ANOVA and multiple comparisons Student–Newman–Keuls Method post hoc analysis) between genotypes during the first two trials of each experiment (shown in Figures 1A and 1C and in Figure 2A). Together, our results demonstrate that CBP and CREB are involved in motor skill learning and not in coordination or locomotor capability.

Several studies have implicated loss of CREB and CBP function as a key cellular defect in polyglutamine diseases, including Huntington's Disease (HD; reviewed in McCampbell & Fischbeck, 2001). HD is a neurodegenerative disease caused by polyglutamine expansion in the Huntington protein (Htt). Currently, the molecular mechanism by which the expanded polyQ sequence in Htt causes selective neurodegeneration is unclear. One hypothesis suggests that polyQ–Htt has gain-of-function properties resulting in novel protein–protein interactions. One key protein that has been shown to interact with polyQ–Htt is CBP (Nucifora et al., 2001; Steffan et al., 2000). Studies show that decreased transcrip-

tion and histone acetylation may play a significant role in HD pathogenesis (Sugars, Brown, Cook, Swartz, & Rubinsztein, 2004; reviewed in Sugars & Rubinsztein, 2003). It is interesting that one of the characteristic phenotypes of mouse models of HD is impaired locomotor activity (reviewed in Hickey & Chesselet, 2003). Further, in a clinical study, patients with HD were found to have significant motor skill learning impairments despite motor coordination problems (Heindel, Salmon, Shults, Walicke, & Butters, 1989). In mice, the motor impairment was ameliorated by treating mice with the histone deacetylase (HDAC) inhibitor suberoyl-anilide hydroxamic acid in a mouse model of HD that has been extensively used for preclinical trials (Hockly et al., 2003). HDAC inhibitors induce a histone hyper-acetylation state, and presumably in the HD mouse model these HDAC inhibitors compensate for the decrease in histone acetylation activity caused by polyQ–Htt sequestration of CBP. Together, these results suggest that CBP and histone acetylation may be required for the transcriptional activation of genes involved in motor skill learning, impairments in which may underlie deficits in motor skills observed in certain neurodegenerative disorders.

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