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Research report

Spatial learning induces neurotrophin receptor and synapsin I in the hippocampus

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Abstract

We report that rats learning a spatial memory task in the Morris water maze show elevated expression of the signal transduction receptor for BDNF and the synaptic associated protein synapsin I in the hippocampus. Nuclease protection assays showed maximal levels of TrkB and synapsin I mRNAs in the hippocampus by the time that asymptotic learning performance had been reached (Day 6). Increases in synapsin I mRNA were matched by changes in synapsin I protein as revealed by western blot analysis. Synapsin I is a downstream effector for the BDNF tyrosine kinase cascade pathway which has important roles in synaptic remodeling and function. Therefore, parallel changes in TrkB and synapsin I mRNAs suggest a role of the BDNF system in synaptic function or adaptation. Levels of TrkB mRNA in the hippocampus were attenuated after learning acquisition (Day 20), but synapsin I mRNA was still elevated, suggesting that the BDNF system may participate in events secondary to learning, such as strengthening of neural circuits. TrkB and synapsin I mRNAs showed an increasing trend in the cerebellum of learning rats and no changes were observed in the caudal cerebral cortex. The selectivity of the changes in trkB and synapsin I, affecting the hippocampus, is in agreement with the role of this structure in processing of spatial information. Behavioral regulation of neurotrophins may provide a molecular basis for the enhanced cognitive function associated with active lifestyles, and guide development of strategies to promote neural healing after CNS injury or disease.

Theme: Development and regeneration

Topic: Neurotrophic factors: expression and regulation

Keywords: Rat; Neural activity; Exercise; Neurotrophin; Lifestyle; Synaptogenesis; Use-dependent plasticity

1. Introduction

Although is becoming well accepted that experience can produce profound changes in the structure and function of the CNS, the molecular mechanisms underlying these events remain poorly understood. Neurotrophins such as brain-derived neurotrophic factor (BDNF) are likely candidates for mediating molecular processes associated with experience. In particular, there is increasing evidence suggesting an involvement of BDNF on learning and memory events. Recent studies show that spatial learning [16] or contextual learning [11] induces the expression of BDNF mRNA in the hippocampus — a region highly involved with learning retention. The physiological significance of changes in neurotrophin expression is contingent on the availability of appropriate signal transduction receptors. The biological effects of neurotrophins are mediated by a family of specific transmembrane tyrosine kinase receptors (Trk), with TrkB as the primary signal transduction receptor for BDNF [3] Accordingly, we evaluate the possibility that spatial learning has an impact on the expression of the gene for TrkB.

Learning is associated with electrophysiological changes in neural circuits involved with the processing of information [7,8], particularly in the hippocampus. BDNF can critically facilitate synaptic transmission in the hippocampus under various experimental paradigms [9,10,14,19], and can also increase synaptic density [6]. Long-term potentiation (LTP), a postulated substrate for learning, evokes significant increases in BDNF in the CA1 region of hippocampal slices [26]. Animals with reduced

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expression of BDNF show deficits on a learning and memory task [20], and lose their capacity to generate LTP [17,25]. It has been shown that BDNF impacts the synthesis [27] and the phosphorylation [12,13] of synapsin I. Synapsin I is the best characterized member of a family of nerve terminal-specific phosphoproteins implicated in neurotransmitter release, axonal elongation, and formation and maintenance of synaptic contacts [1,5,13,21,27]. Thus, synapsin I appears as an excellent marker to evaluate the role of BDNF on synaptic adaptation or function associated with learning.

To evaluate a possible role of the BDNF system on synaptic structure and function associated with learning, we have assessed changes in synapsin I in conjunction with TrkB mRNA in response to spatial learning. The possibility that learning involves changes in the expression of BDNF and its receptor, leading to synaptic modification, is important to better understand the molecular mechanisms underlying behavioral plasticity.

2. Methods

2.1. Experimental design

Sprague Dawley male rats ($n=55$, approximately 3 months old) individually housed in a 12/12 light/dark vivarium with ad lib access to food and water were randomly assigned to: (i) the spatial learning group that received 8 trials per day for 1, 3, 6, or 20 consecutive days of training in the Morris water maze, (ii) the control-active group (yoked) that matched the swimming time of each learning rat in the maze without the platform, or (iii) the sedentary control group. All animal procedures were performed according to NIH guidelines and were approved by the UCI and UCLA animal Research Committees.

2.1.1. Morris water maze

In the Morris water maze task, the rat uses spatial clues while swimming to locate a submerged platform. Activation of relevant neuronal circuits likely has an impact on cellular and molecular changes in regions involved with the processing of the behaviors involved. For each water maze trial, the spatial learning rats were placed into tank facing the wall at one of four equally spaced designated entry point and were allowed to swim until they located the platform. There were four entry points (N, S, W, and E) located with a 90° of separation, and each rat was positioned following the sequence W, E, N, S, E, W, S, N, etc. If the platform was not located within 2 min the rat was guided by hand through the water and placed onto the platform. After the rat reached the platform they were allowed to rest for 30 s. At the completion of a swim, rats were dried and maintained in a dry cage. Animals were acclimated to swimming in the tank for two 1-min periods with no platform present the day before the first day of training. The apparatus was a galvanized steel water tank, 1.7 m in diameter and 1 m deep, filled with approximately 30 cm of clear water (25°C). A clear plexiglas platform was submerged 5 cm beneath the surface at a constant location. Salient cues in the environment were held constant so the rats could determine their spatial location and navigate in an effective manner.

Animals were given eight randomized trials each day with entry into the tank twice at each point and the latency to find the platform was recorded. Rats were sacrificed after 1, 3, 6, or 20 consecutive days of training. An active yoked rat with no access to a platform was matched with each learning rat to swim for the same time, to evaluate the effects of physical activity and minimize the spatial learning component of the task. Sedentary rats were not placed into the water maze and were used to determine the effect of no activity on the variables under study. All rats were sacrificed immediately after the last trial by 2 PM. Rats were rapidly decapitated and the whole cerebellum and hippocampi were removed and frozen. Cerebral hemispheres were separated at the longitudinal cerebral fissure, and the cerebral cortices were then divided into three sections by making coronal cuts at the posterior and anterior poles of the thalamus.

2.1.2. Nuclease protection assay

Total RNA was isolated by guanidine thiocyanate extraction and nuclease protection assays were performed as previously described [16,24]. Synapsin I riboprobe (provided by Dr. Richard Melloni [21]) corresponds to pSYN5 clone subcloned into pSPT18 and by cutting with Bgl II generates a 140 bp for nuclease protection assay experiments. A linearized pFRK29 vector containing a 290 bp insert of mouse TrkB gene (protected fragment, pFRK29 provided by Dr. M. Barbacid [4]) was used to prepare the TrkB sense and antisense that recognizes the extracellular domain of gp145 TrkB receptor. A separate hybridization was performed with a 376 bp glyceraldehyde 3-phosphate dehydrogenase (GAPDH, Ambion, TX) cRNA probe (protected fragment=316 bp) to ensure that samples contain an equivalent amount of RNA. cRNA probes were labelled with a-^{32}P-CTP (Amersham; 800 Ci/mmol), and quantitative changes were estimated by computer densitometry.

2.1.3. Western blot

Protein samples were separated by electrophoresis on an 8% polyacrilamide gel and electrotransfered to a Hybond-PVDF membrane (Amersham, Arlington Heights, IL). Non-specific binding sites were blocked with 2% BSA, 0.1% Tween-20 in TBS overnight at 4°C. Membranes were rinsed for 10 min in buffer (0.1% Tween-20 in TBS) and then incubated for 2 h at room temperature with an affinity purified goat polyclonal antibody against the carboxy terminal of synapsin I (1:500, Santa Cruz Biotechnology). After rinsing three times for 10 min each with buffer,

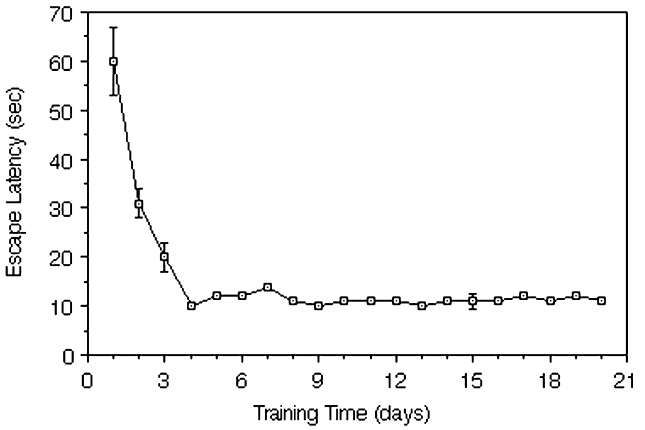

Fig. 1. (A) Performance in the water-maze task was assessed by the average latency taken for the rat to locate the submerged platform on each of the test days. Rats reached asymptotic levels of performance between 3 and 5 days of training. Analysis of variance for performance across days of testing indicated that rats improved significantly during the first few days of training, and there was no significant difference between rats at any given day. Each point represents mean±S.E.M.

membranes were incubated with peroxidase-conjugated secondary antibody (1:2000 dilution, anti-goat HRP, Santa Cruz) during 1 h at room temperature. After rinsing five times for 10 min each with buffer, bands were developed on autoradiographic film by chemiluminescence using an ECL kit (Amersham, Arlington Heights, IL). The film signals were digitally scanned and then quantified using NIH Image software.

2.1.4. Statistical analysis

Mean data from nuclease protection assays were computed for each group, and compared using ANOVA and matched-paired *t*-tests (learning vs. yoked) or *t*-tests adjusted for multiple measures (learning and yoked vs. sedentary controls). The results were corrected according to GAPDH values and were expressed as a percent of controls.

3. Results

3.1. Training performance

Performance on the water-maze task was assessed by the average latency, or time, it took the rat to locate the submerged platform on each of the test days. Rats quickly learned the task, reaching asymptotic levels of performance by approximately 3–5 days of training (Fig. 1). Analysis of variance for performance across days of testing indicated that rats improved significantly during the first few days of training ($P<0.01$), and there was no significant difference between groups at any given training day ($P>0.05$). Biochemical measures for TrkB mRNA and synapsin were performed for rats sacrificed immediately after training at days 1, 3, 6, and 20. In the initial assessment with a small group of rats ($n=3$/group), there were no detectable changes in any of the variables at Day 1; therefore, this timepoint was eliminated and the experiment replicated to increase the number of animals to 7 per group.

3.2. Hippocampus

3.2.1. TrkB mRNA (Fig. 2a)

In the learning group, levels of TrkB mRNA were elevated to approximately 210% of sedentary control values by training Day 6 ($P<0.01$) and decreased to 132% by Day 20 ($P<0.01$). The yoked group showed smaller

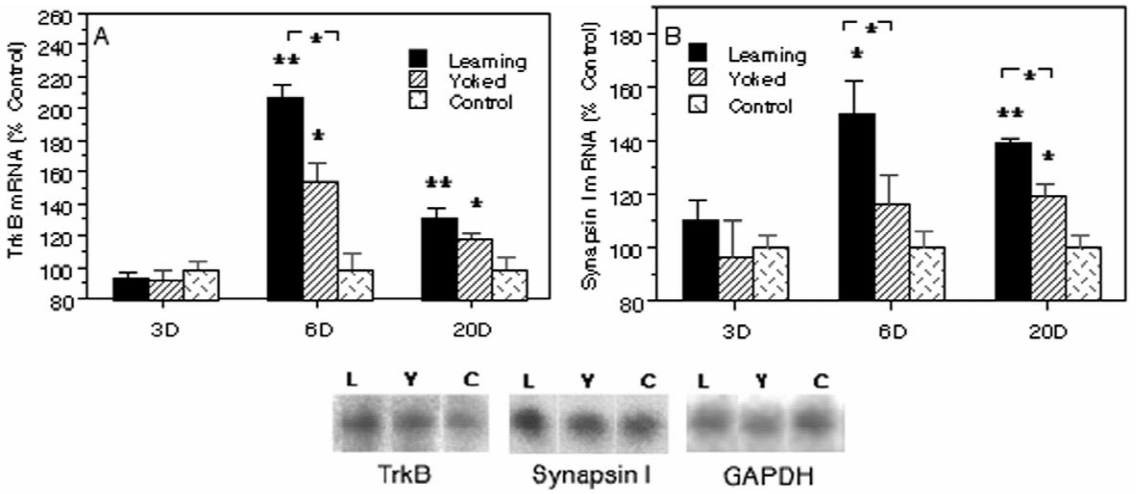

Fig. 2. Nuclease protection assays were performed with α^{32}P-labeled cRNA to determine levels of (A) TrkB mRNA or (B) synapsin I mRNA in the hippocampus, after 3, 6, or 20 days of training. Sample gels show protected fragments for TrkB, synapsin I or glyceraldehyde 3-phosphate dehydrogenase (GAPDH) for learning (L), yoked (Y), and sedentary controls (C). Values are mean±S.E.M. *$P<0.05$, **$P<0.01$, ANOVA and matched-paired *t*-tests (learning vs. yoked) or *t*-tests (learning and yoked vs. sedentary controls).

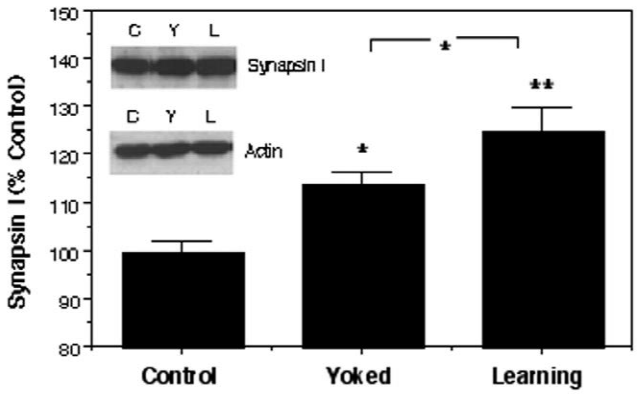

Fig. 3. Relative levels of synapsin I were assessed using western blot analysis in the hippocampus of rats trained in the water maze for 6 consecutive days. Sample gels are shown for synapsin I and actin (used as an internal control). Values are mean±S.E.M. *$P<0.05$, **$P<0.01$, ANOVA and matched-paired *t*-tests (learning vs. yoked) or *t*-tests (learning and yoked vs. sedentary controls).

increases in TrkB mRNA levels relative to sedentary controls, with values of 156% by Day 6 ($P<0.05$), and 124% Day 20 ($P<0.05$). Levels of TrkB mRNA in the spatial learning group were significantly higher than the yoked group by Day 6 only ($P<0.05$). TrkB mRNA contents were substantially attenuated in both groups by Day 20 and the learning group showed an increasing trend as compared to yoked values.

3.2.2. Synapsin I mRNA (Fig. 2B)

Synapsin I mRNA levels in the learning rats reached approximately 150% ($P<0.05$) by Day 6 and decreased to about 138% ($P<0.01$) by Day 20, relative to sedentary control values. An increasing trend in synapsin I mRNA by Day 6 in the yoked group reached significance ($P<0.05$) by Day 20, relative to sedentary controls. Levels of synapsin I mRNA in the spatial learning group were significantly higher than the yoked group at Days 6 and 20 ($P<0.05$). We used western blot analysis to determine whether changes in synapsin I mRNA were accompanied by changes in synapsin I protein. Relative levels of synapsin I protein were measured in hippocampal tissue from animals trained for 6 consecutive days (Fig. 3). Results showed an increase in levels of synapsin I in the learning group (125%, $P<0.01$) and yoked (114%, $P<0.05$) relative to sedentary controls. In turn, the learning group showed a significant increase in synapsin I levels relative to yoked rats ($P<0.05$).

3.3. Cerebellum

3.3.1. TrkB mRNA (Fig. 4A)

Levels of TrkB mRNA for the learning and yoked groups were elevated to approximately 120% (non-significant) by Day 3, increased to 134% ($P<0.05$) by Day 6, and decreased to about sedentary controls values by Day 20. TrkB mRNA values for the yoked rats were elevated to about 127% ($P<0.05$) of controls by Day 6 and decreased to about sedentary control levels by Day 20. Levels of TrkB mRNA in the learning group did not differ from the yoked group.

3.3.2. Synapsin I mRNA (Fig. 4B)

Synapsin I mRNA values in the learning group reached about 138% ($P<0.05$) by Day 3, 140% ($P<0.05$) by Day 6, and decreased to about sedentary control values by Day 20. The yoked group reached 140% ($P<0.05$) by Day 3, 125% ($P<0.05$) by Day 6, and continued decreasing to about sedentary control values by Day 20. Levels of

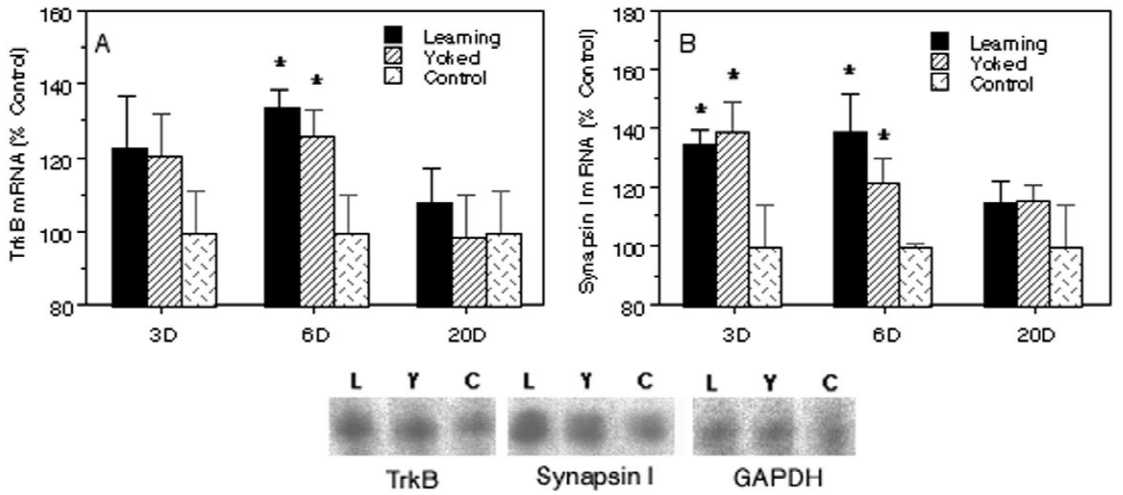

Fig. 4. Graph showing relative levels of (A) TrkB mRNA or (B) synapsin I mRNA in the cerebellum, after 3, 6, or 20 days of training. Sample gels of nuclease protection assays display protected fragments for TrkB, synapsin I, or glyceraldehyde 3-phosphate dehydrogenase (GAPDH) riboprobes for learning (L), yoked (Y), and sedentary controls (C). Values are mean±S.E.M. *$P<0.05$, **$P<0.01$, ANOVA and matched-paired *t*-tests (learning vs. yoked) or *t*-tests (learning and yoked vs. sedentary controls).

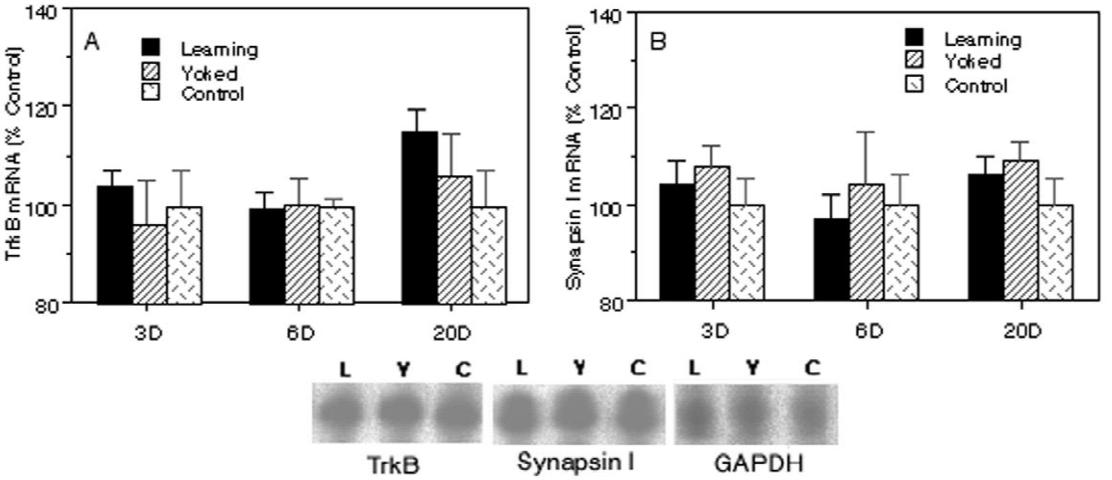

Fig. 5. Graph showing relative levels of (A) TrkB mRNA or (B) synapsin I mRNA in the caudal portion of the cerebral cortex, after 3, 6, or 20 days of training. Sample gels from nuclease protection assays with α^{32}P-labeled riboprobes for TrkB, synapsin I, or glyceraldehyde 3-phosphate dehydrogenase (GAPDH) are shown for learning (L), yoked (Y), and sedentary controls (C). Values are mean±S.E.M. *$P<0.05$, **$P<0.01$, ANOVA and matched-paired *t*-tests (learning vs. yoked) or *t*-tests (learning and yoked vs. sedentary controls).

synapsin I mRNA in the spatial learning group were never significantly higher than those in the yoked group.

The caudal portion of the cerebral cortex did not show statistically significant changes in TrkB mRNA (Fig. 5A) or synapsin I mRNA (Fig. 5B) for any of the two experimental groups, at any of the time points examined.

4. Discussion

We have previously shown that rats that learn a spatial task have elevated expression of BDNF in the hippocampus [16]. The present results show that the same behavioral paradigm elevates the expression of the TrkB, signal transduction receptor for BDNF. In addition, results show that increases in TrkB mRNA were accompanied by increases in the mRNA and protein for the synaptic associated molecule synapsin I. Synapsin I is under regulatory control of BDNF [6,12,13,27], suggesting that increases in BDNF and its receptor may have an impact on synaptic growth or function.

Levels of TrkB mRNA and synapsin I mRNA and protein in the learning group were significantly higher than active controls (yoked) in the hippocampus, but not in the cerebellum or caudal cerebral cortex. These results are in general agreement with abundant evidence indicating that performance in the Morris water maze task relies primarily on hippocampal function. The yoked group was included to determine how reduced spatial clues, while maintaining physical activity intensity, affect the response to water maze training. It can be inferred that the absence of the platform renders the task less reliant on hippocampal activity associated with spatial learning, while maintaining otherwise similar experimental conditions.

It is noteworthy that the yoked rats had higher levels of TrkB mRNA and synapsin I mRNA than sedentary controls in the hippocampus (Days 6 and 20) and cerebellum (Day 6). This suggests that the physical activity component of the task may also be an important factor for the induction of these genes in the hippocampus and cerebellum. We have previously shown that other types of physical activity such as voluntary wheel running, induce BDNF mRNA in the hippocampus and cerebellum of rodents [23,24]. We cannot discard the possibility, however, that other learning modalities may have some impact on elevated TrkB and synapsin I expressions in yoked rats. Changes in TrkB and synapsin I mRNAs were not detected in the caudal cerebral cortex under any experimental circumstance in the present study. These results are in general agreement with previous studies showing no changes in BDNF mRNA in the caudal cerebral cortex in response to water maze training [16], and suggest a region-specific effect of training. It is notable that rodents, which are nocturnal animals, were training and tested during the day when they are less active. It is possible that the magnitude of changes in expression for the molecules examined could have been higher if animal had been tested during the wake period of their circadian cycle.

The timing for the elevation in the expression of BDNF, followed by its receptor, and synaptic changes as an end product, may help to elucidate the putative role of BDNF in learning. Previous studies [16] have shown that water maze training induces the expression of BDNF mRNA in the hippocampus by training Days 3 and 6. The present results show that levels of TrkB mRNA are not increased until Day 6 of training. Hence, it appears that increases in TrkB and synapsin I mRNAs succeed changes in BDNF mRNA. The learning performance reached asymptote approximately by Day 3, preceding the peak of the TrkB mRNA and synapsin I mRNA responses (Day 6). There-

fore, it is possible that BDNF may support cellular events which are secondary to learning such as the maintenance or strengthening of neural circuitry.

The newly discovered roles of BDNF on synaptic function and reorganization may be important to understand the role of BDNF in learning mechanisms. Interestingly, there is much new evidence indicating that BDNF is a powerful modulator of synaptic transmission [9], acting on pre-synaptic terminals [10. Applications of BDNF into the hippocampus causes a long-lasting increase in excitatory postsynaptic potentials (EPSPs) in the Schaffer collateral-CA1 pathway in the rat [14]. Endogenous supply of BDNF seems necessary to support the capacity of cells to generate LTP [17,25]. It is intriguing that the effects of BDNF on synaptic facilitation and transmission in the hippocampus are dependent on local protein synthesis [15] — protein synthesis is a requirement for long-term memory [2,8]. A further involvement of the BDNF system in learning is supported by a study showing that deletion of the TrkB gene results in impaired learning behavior and hippocampal function [22].

According to our results, the timing and magnitude of the increase in synapsin I mRNA followed closely the changes in TrkB mRNA in the hippocampus. It is also remarkable that changes in synapsin I mRNA were paralleled by changes in synapsin I protein as measured by training Day 6. We used a cRNA probe that recognizes the extracellular domain of gp145 TrkB receptor which is expressed in neurons [4]. 'Previous in situ hybridization studies [4] using the same cRNA probe have shown that TrkB is expressed in pyramidal neurons of all the hippocampal subfields and in granule cells of the dentate gyrus. In turn, in situ hybridization studies [21] have shown that synapsin I mRNA has a similar cellular distribution to TrkB mRNA in the hippocampal formation. Synapsin I is a neuron-specific protein localized within the presynaptic terminals in the adult brain, and appears to regulate neurotransmitter release, and formation and maintenance of synaptic contacts [1,5,21,27]. It has been shown that BDNF upregulates synapsin I production [27], and that BDNF phosphorylates synapsin I via protein kinase signaling pathways [12,13]. Therefore, it is possible that the BDNF system is involved in the cascade of events that support synaptic reorganization or function in learning and other types of experiences.

The overall evidence indicates that physical activity and spatial learning can promote changes in the expression of BDNF, its receptor, and synapsin I in select brain regions. It is likely that select experiences may contribute to maintain neuronal function via a neurotrophin mediated mechanism. It has recently been reported that fitness and cognitive challenges can preserve cognitive function in aging individuals [18]. It is important to determine how specific behavioral paradigms can promote changes in neurotrophin production that can counteract the effects of brain insult or disease.

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