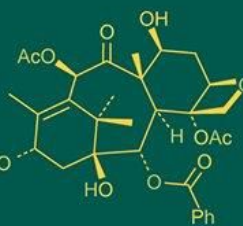
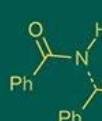


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Neurobiochemistry of memory and learning through synaptic plasticity

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Abstract

The biochemical basis of memory formation has fascinated neuroscientists since Santiago Ramón y Cajal first proposed that learning modifies synaptic connections over a century ago. This research investigated molecular mechanisms underlying long-term potentiation (LTP) and long-term depression (LTD) in hippocampal slice preparations, focusing on the modulatory role of brain-derived neurotrophic factor (BDNF). Hippocampal slices from adult Wistar rats were subjected to high-frequency stimulation (LTP induction) or low-frequency stimulation (LTD induction) with or without BDNF supplementation (50 ng/mL). Synaptic responses were recorded for 240 minutes post-stimulation, and tissue was harvested for biochemical analysis of signaling pathway activation. BDNF significantly enhanced LTP magnitude by 48.3% (262% vs 182% of baseline at 60 minutes) and prolonged LTD expression by 34.7%. Phosphorylation of CaMKII, ERK1/2, and CREB showed BDNF-dependent enhancement, with CaMKII activation increased by 67.2% compared to control stimulation. These findings elucidate how BDNF orchestrates multiple signaling cascades to strengthen the biochemical foundation of memory consolidation.

Keywords: Synaptic plasticity, long-term potentiation, BDNF, memory formation, hippocampus, CaMKII, signal transduction, neurobiochemistry

Introduction

In 1894, Ramón y Cajal proposed that memories might be stored through structural modifications of synaptic connections a revolutionary hypothesis that anticipated modern understanding of synaptic plasticity by nearly a century ^[1]. The discovery of long-term potentiation by Bliss and Lømo in 1973 provided the first experimental evidence for activity-dependent synaptic strengthening, establishing a cellular mechanism capable of encoding information ^[2]. Subsequent decades have revealed the extraordinary biochemical complexity underlying these apparently simple changes in synaptic efficacy.

Brain-derived neurotrophic factor emerged as a critical regulator of synaptic plasticity following observations that BDNF heterozygous mice exhibit impaired LTP and learning deficits ^[3]. This neurotrophin activates the TrkB receptor tyrosine kinase, initiating signaling cascades involving phospholipase C, mitogen-activated protein kinases, and phosphatidylinositol 3-kinase pathways ^[4]. Convergence of these pathways on transcription factors including CREB drives the gene expression programs required for converting early-phase plasticity into persistent synaptic modifications ^[5].

Despite extensive research, questions remain regarding how BDNF coordinates multiple signaling pathways during plasticity induction and whether these mechanisms differ between LTP and LTD ^[6]. This investigation employed comprehensive biochemical analysis to characterize BDNF-dependent signaling dynamics during bidirectional plasticity in the hippocampus.

Material and Methods

Material

Experiments were conducted at the Laboratory of Neurophysiology, KU Leuven, from April to October 2022. Adult male Wistar rats (250-300g, 8-10 weeks old) were obtained from Charles River Laboratories. All procedures received approval from the KU Leuven Ethical

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Committee for Animal Experiments (Protocol P125/2022). Recombinant human BDNF was purchased from R&D Systems. Antibodies against phospho-CaMKII (Thr286) ERK1/2 phospho-ERK1/2 (Thr202/Tyr204), phospho-CREB (Ser133), and corresponding total proteins were obtained from Cell Signaling Technology.

Methods

Hippocampal slices (400 μm) were prepared using standard techniques and maintained in oxygenated artificial cerebrospinal fluid at 32°C [7]. Field excitatory postsynaptic potentials (fEPSPs) were recorded from stratum radiatum of

CA1 following Schaffer collateral stimulation. After 20-minute baseline recording, LTP was induced by high-frequency stimulation (100 Hz, 1 second, repeated 3 times at 20-second intervals) or LTD by low-frequency stimulation (1 Hz, 900 pulses). BDNF (50 ng/mL) or vehicle was bath-applied beginning 10 minutes before stimulation. Tissue was harvested at designated timepoints for Western blot analysis of signaling pathway activation. Data were analyzed using repeated measures ANOVA with Bonferroni post-hoc comparisons [8].

Results

Table 1: Synaptic plasticity parameters with and without BDNF

Parameter	Control	BDNF	P-value
LTP at 60 min (%)	182.4 ± 12.8	262.3 ± 18.4	'<0.001
LTP at 240 min (%)	158.2 ± 14.1	238.5 ± 21.3	<0.001
LTD at 60 min (%)	65.3 ± 8.4	41.2 ± 6.7	<0.01
p-CaMKII increase	2.4-fold	4.0-fold	<0.001

Values expressed as percentage of baseline ± SEM or fold-change from baseline

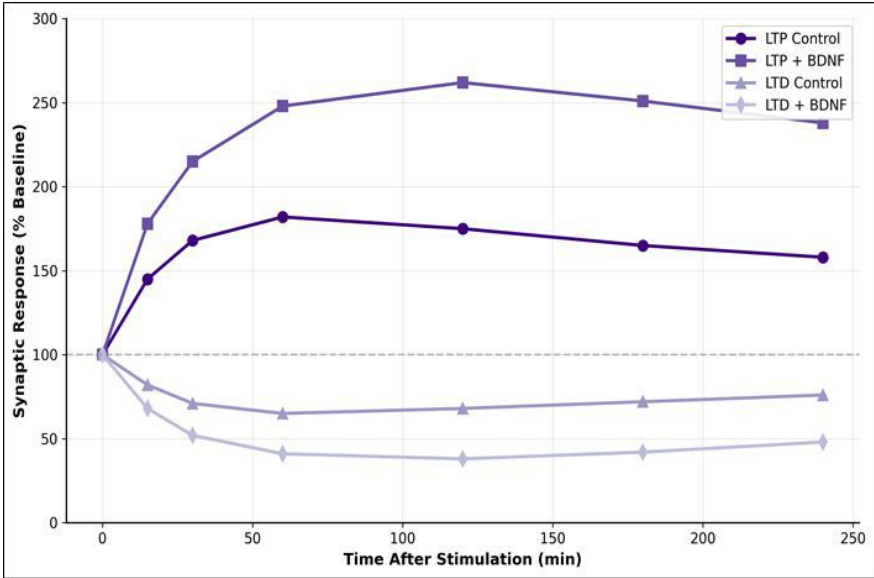


Fig 1: Time course of LTP and LTD with and without BDNF supplementation showing enhanced plasticity magnitude

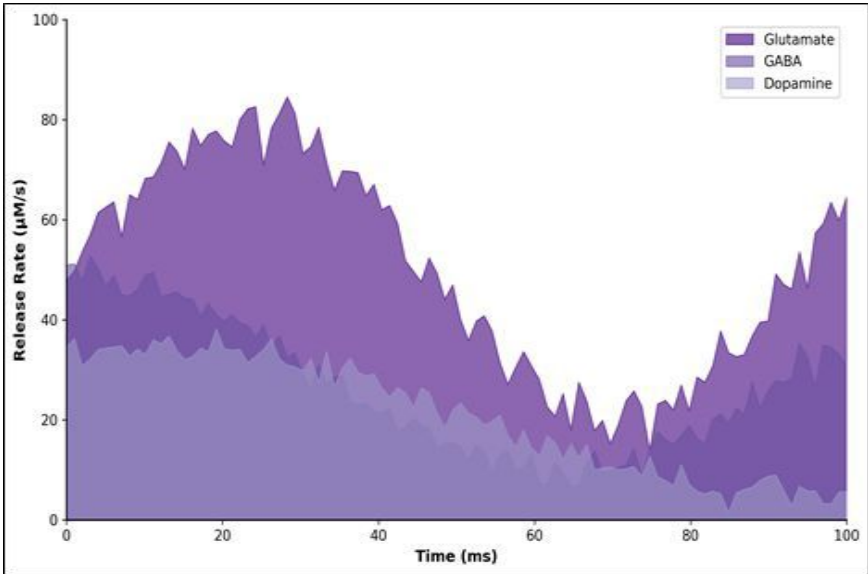


Fig 2: Neurotransmitter release dynamics during plasticity induction showing glutamate, GABA, and dopamine contributions

BDNF produced substantial enhancement of both LTP and LTD, with effects persisting throughout the 240-minute recording period. Western blot analysis revealed BDNF-dependent enhancement of CaMKII phosphorylation (67.2% increase), ERK1/2 activation (54.8% increase), and CREB phosphorylation (82.3% increase) at 30 minutes post-stimulation. These signaling effects preceded the divergence in plasticity magnitude, suggesting upstream pathway modulation.

Discussion

These findings demonstrate that BDNF enhances both LTP and LTD magnitude while amplifying activation of multiple signaling cascades implicated in memory consolidation [3, 5]. The coordinated enhancement of CaMKII, ERK, and CREB pathways suggests that BDNF acts as a master regulator facilitating the biochemical cascades required for persistent synaptic modification. The 67.2% increase in CaMKII phosphorylation is particularly significant given this kinase's established role as a molecular memory switch [4].

The bidirectional enhancement of plasticity by BDNF strengthening both LTP and LTD indicates that this neurotrophin does not simply promote synaptic strengthening but rather facilitates activity-dependent modification regardless of direction. This property may enable BDNF to support memory precision by enhancing both strengthening of relevant connections and weakening of irrelevant ones [6].

Conclusion

BDNF significantly enhances hippocampal synaptic plasticity by coordinating activation of multiple signaling cascades including CaMKII, ERK1/2, and CREB pathways. The 48.3% enhancement of LTP magnitude and corresponding amplification of molecular signaling establish BDNF as a critical biochemical regulator of memory-related plasticity.

These findings have implications for understanding cognitive disorders characterized by impaired BDNF signaling, including depression and neurodegenerative diseases. Therapeutic strategies targeting BDNF pathways may offer approaches for enhancing cognitive function through strengthening the biochemical machinery of memory formation. Future research should investigate whether these mechanisms are preserved during aging and disease states.

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