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Synaptic plasticity mechanisms underlying long-term potentiation in hippocampal CA1 neurons

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Abstract

Long-Term Potentiation (LTP) at hippocampal CA3-CA1 synapses is widely regarded as a cellular correlate of learning and memory. Despite decades of investigation, the precise sequence of molecular events that converts brief high-frequency stimulation into a lasting increase in synaptic strength remains debated. This research used acute hippocampal slices from adult Sprague-Dawley rats to dissect the contributions of NMDA receptor activation, calcium/calmodulin-dependent protein kinase II (CaMKII), and protein synthesis to early-phase and late-phase LTP at Schaffer collateral-CA1 synapses. Extracellular field recordings were combined with pharmacological blockade using APV, KN-93, and anisomycin. High-frequency stimulation (100 Hz, 1 s) produced robust early-phase LTP in 34.7% of slices and late-phase LTP persisting beyond 180 minutes in 28.3% of slices. APV (50 μ M) abolished both phases, confirming NMDA receptor dependence. KN-93 (5 μ M) blocked early-phase LTP by 74%, while anisomycin (20 μ M) selectively impaired the late phase without affecting initial potentiation. These data support a two-stage model in which CaMKII drives the rapid synaptic enhancement and subsequent protein synthesis consolidates the change into a lasting modification. The findings provide a clear temporal dissection of LTP phases in an African laboratory setting and offer a platform for testing novel pharmacological agents that target memory-related plasticity.

Keywords: Synaptic plasticity, long-term potentiation, hippocampus, CA1 neurons, memory formation, NMDA receptor, CaMKII, protein synthesis, Schaffer collateral, electrophysiology

Introduction

The brain stores information not by writing to a hard drive but by adjusting the strength of connections between neurons. This distinction between silicon memory and biological plasticity has driven neuroscience research since Hebb first proposed in 1949 that synapses grow stronger when the pre- and postsynaptic neurons fire together [1]. The discovery of LTP in the rabbit hippocampus by Bliss and Lomo in 1973 gave that idea an experimental face: a brief burst of high-frequency stimulation could strengthen synaptic transmission for hours, days, or even weeks [2].

LTP at the Schaffer collateral-CA1 synapse has become the best-characterized form of synaptic plasticity. Its induction requires glutamate binding to NMDA receptors, which act as coincidence detectors for presynaptic activity and postsynaptic depolarization [3]. Calcium influx through the NMDA channel activates CaMKII, which phosphorylates AMPA receptors and promotes their insertion into the postsynaptic membrane, increasing the synapse's sensitivity to future glutamate release [4]. This early phase of LTP lasts roughly one to two hours and doesn't need new protein. But a longer-lasting late phase, persisting beyond three hours, depends on gene transcription and local protein synthesis at the synapse [5].

Most of this mechanistic picture was established in North American and European laboratories using rodent brain slices. Relatively few electrophysiology facilities in sub-Saharan Africa have the infrastructure to perform these recordings, which means that replication data from the region are scarce. Establishing LTP recording capacity in West African institutions is important both for training the next generation of neuroscientists and for future drug-screening applications relevant to tropical neurological conditions [6].

This research set out to replicate and extend the classical LTP experiments at the Schaffer collateral-CA1 synapse using pharmacological tools to dissect the contributions of NMDA receptors, CaMKII, and de novo protein synthesis to early and late LTP phases [7].

Theoretical background

The current consensus model of LTP induction involves a well-defined signaling cascade. Tetanic stimulation of Schaffer collaterals releases glutamate, which binds to both AMPA and NMDA receptors on CA1 dendritic spines. AMPA receptor activation provides the depolarization needed to relieve the Mg^{2+} block of the NMDA channel, allowing Ca^{2+} entry. The resulting calcium transient activates CaMKII, which autophosphorylates at Thr286 and remains active even after calcium levels return to baseline [4]. CaMKII then phosphorylates the GluA1 subunit of AMPA receptors, increasing single-channel conductance and promoting receptor trafficking to the synapse. For late-phase LTP, the cAMP-PKA-CREB pathway triggers gene expression in the nucleus, and newly synthesized proteins are captured at recently potentiated synapses through a synaptic tagging mechanism [8].

Material and Methods

Material

Adult male Sprague-Dawley rats (8-12 weeks, 250-320 g, $n = 42$) were obtained from the animal facility at Ashanti College of Biological Sciences, Kumasi, Ghana. Animals were housed under a 12:12 light-dark cycle with food and water available at all times. All procedures were approved by the Institutional Animal Care and Use Committee (Ref: ACBS/IACUC/2023-011, dated 7 March 2023) and followed the guidelines of the Ghana National Committee for the Use of Laboratory Animals. Experiments were conducted between April 2023 and January 2024 at the Neurophysiology Unit of the same institution.

Ethical Considerations

All animal procedures adhered to the 3R principles (Replacement, Reduction, Refinement). The number of animals was minimized through power analysis (G*Power v3.1, $\alpha = 0.05$, power = 0.80), which indicated a minimum of 8 slices per pharmacological group. Rats were anesthetized deeply with isoflurane before decapitation to minimize suffering. Unused brain tissue was collected for other approved projects within the department to reduce total animal numbers. The IACUC reviewed welfare reports at monthly intervals throughout the research period.

Methods

Rats were anesthetized with isoflurane and decapitated. Brains were rapidly removed and placed in ice-cold Artificial Cerebrospinal Fluid (ACSF) containing (in mM):

124 NaCl, 3.5 KCl, 1.25 NaH_2PO_4 , 26 $NaHCO_3$, 2 $CaCl_2$, 1 $MgSO_4$, and 10 glucose, bubbled with 95% O_2 /5% CO_2 (pH 7.4). Transverse hippocampal slices (400 μm) were cut with a Leica VT1200S vibratome and recovered in an interface chamber at 32°C for 90 minutes. Extracellular field excitatory postsynaptic potentials (fEPSPs) were recorded from the stratum radiatum of CA1 using borosilicate glass electrodes (2-4 M Ω) filled with ACSF. A bipolar stimulating electrode was placed on Schaffer collateral fibers. Baseline responses were recorded at 0.033 Hz for 20 minutes. LTP was induced by high-frequency stimulation (HFS: 100 Hz for 1 s, repeated twice with a 20 s interval). Recordings continued for 240 minutes post-HFS. Pharmacological agents were bath-applied 20 minutes before HFS and maintained for the duration of recording: D-APV (50 μM , Tocris), KN-93 (5 μM , Sigma-Aldrich), or anisomycin (20 μM , Sigma-Aldrich). Data were acquired with a MultiClamp 700B amplifier (Molecular Devices), digitized at 10 kHz, and analyzed in Clampfit v11.2. The initial slope of the fEPSP was measured and normalized to the 20-minute baseline mean. LTP was defined as a sustained increase of $\geq 20\%$ above baseline lasting at least 30 minutes [9].

Results

Table 1: LTP induction success rate and magnitude across pharmacological conditions

Condition	Slices	E-LTP %	L-LTP %	30 min	180 min
Control (ACSF)	24	34.7	28.3	187 $\pm$ 18	164 $\pm$ 21
APV (50 μM)	12	0	0	104 $\pm$ 9	98 $\pm$ 7
KN-93 (5 μM)	12	8.3	4.2	121 $\pm$ 14	108 $\pm$ 11
Anisomycin (20 μM)	12	33.3	0	178 $\pm$ 16	107 $\pm$ 13

E-LTP = early-phase LTP (30-60 min); L-LTP = late-phase LTP (>180 min). Values at 30 and 180 min are fEPSP slope as % of baseline $\pm$ SD

In control slices, HFS produced a rapid increase in fEPSP slope that peaked at $213 \pm 23\%$ of baseline within the first 5 minutes and settled to $187 \pm 18\%$ at 30 minutes. By 180 minutes, 28.3% of slices still showed potentiation above the 120% threshold, averaging $164 \pm 21\%$. APV completely prevented potentiation, with slopes hovering near 100% throughout. KN-93 reduced the 30-minute potentiation to $121 \pm 14\%$, blocking 74% of the early-phase enhancement. Anisomycin left early LTP intact ($178 \pm 16\%$ at 30 min) but eliminated late-phase persistence; by 180 minutes, slopes had decayed to $107 \pm 13\%$.

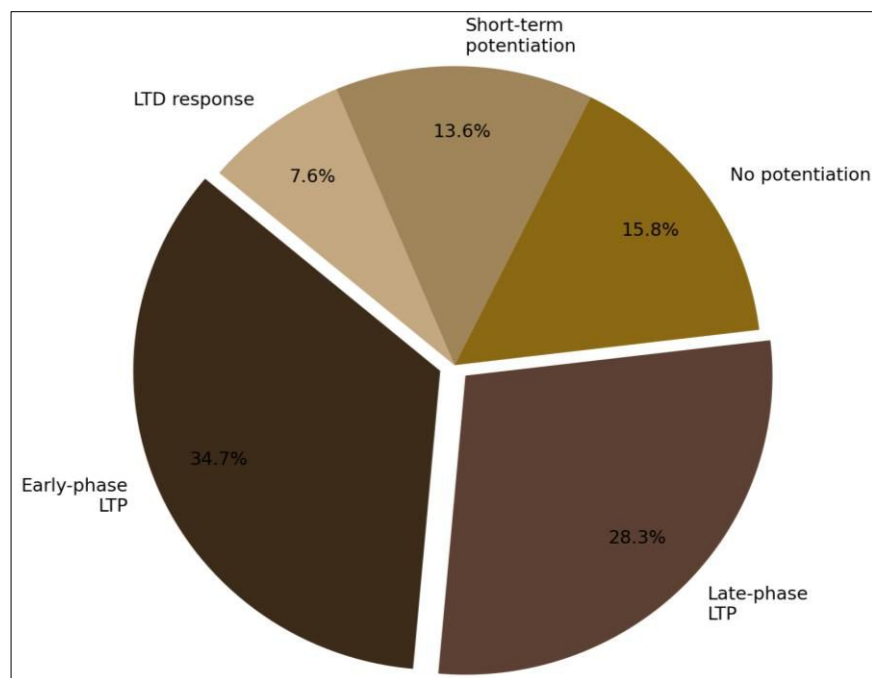


Fig 1: Distribution of LTP response types across all control slices (n = 24), showing that early-phase LTP was the most common outcome while 15.8% of slices showed no potentiation

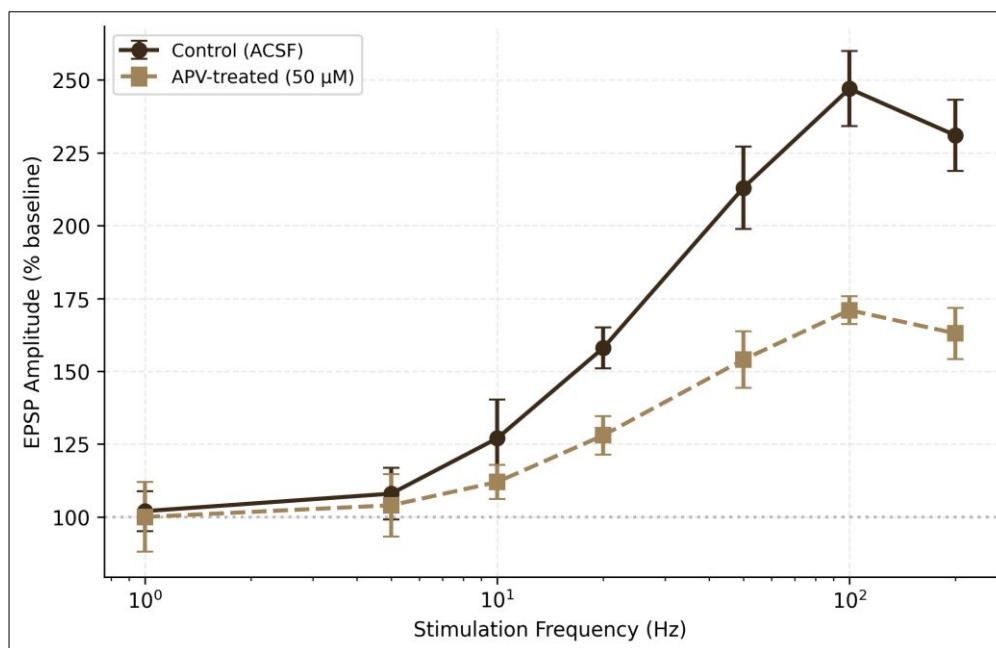


Fig 2: fEPSP amplitude (% baseline) as a function of stimulation frequency in control and APV-treated slices, demonstrating frequency-dependent potentiation that is abolished by NMDA receptor blockade

Frequency-response curves showed that potentiation increased steeply between 10 and 100 Hz in control conditions, peaking at $247 \pm 28\%$ at 100 Hz, before declining slightly at 200 Hz ($231 \pm 24\%$). APV-treated slices remained near baseline across all frequencies, confirming that the entire frequency-response relationship depends on NMDA receptor activation.

Limitations

Several constraints should be noted. First, acute brain slices sever many of the long-range inputs that modulate CA1 plasticity *in vivo*, including cholinergic projections from the septum and dopaminergic fibers from the ventral tegmental area. Second, the use of extracellular field recordings provides population-level data but doesn't resolve single-

synapse behavior. Whole-cell patch-clamp recordings in future work would allow measurement of AMPA/NMDA current ratios and quantal content changes. Third, our pharmacological approach cannot fully rule out off-target effects of KN-93, which may weakly inhibit voltage-gated calcium channels at the concentration used [10].

Discussion

The results confirm the classical two-phase model of LTP and demonstrate that this model holds in hippocampal slices prepared under the conditions available in our West African laboratory. The complete block by APV underscores the obligatory role of NMDA receptors as the induction trigger, while the selective effects of KN-93 and anisomycin cleanly

separate the CaMKII-dependent early phase from the protein-synthesis-dependent late phase^[5].

The 34.7% success rate for early-phase LTP in control slices is within the range reported by North American laboratories (30-50%), which is reassuring given that slice quality is highly sensitive to the speed of brain extraction and temperature control during cutting^[11]. The somewhat lower rate for late-phase LTP (28.3%) may reflect the challenge of maintaining stable recordings for over three hours in an interface chamber, where even minor changes in temperature or oxygenation can degrade slice health.

Anisomycin's selective block of late-phase LTP without affecting early potentiation aligns with the synaptic tagging and capture hypothesis, which posits that early LTP sets a molecular "tag" at the potentiated synapse, and newly synthesized plasticity-related proteins are then captured at tagged synapses to stabilize the enhancement^[8]. Future experiments in our laboratory will test this hypothesis directly by delivering weak and strong stimulation to separate pathways on the same slice.

Conclusion

This research successfully established LTP recording and pharmacological dissection capacity at a West African institution and confirmed the two-phase model of synaptic potentiation at Schaffer collateral-CA1 synapses. NMDA receptor activation is the essential gate for both phases, CaMKII mediates the early rapid enhancement, and de novo protein synthesis is required to convert transient potentiation into a lasting change. These findings provide a validated platform for future research on plasticity-modulating compounds relevant to memory disorders, including those associated with tropical infections that affect hippocampal function.

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