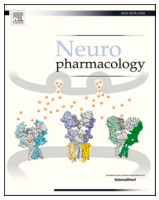
Neuropharmacology 238 (2023) 109668

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm



Impairments in hippocampal oscillations accompany the loss of LTP induced by GIRK activity blockade

Ana Contreras [a,1], Souhail Djebari [a,1], Sara Temprano-Carazo [a], Alejandro Múnera [a,b], Agnès Gruart [c], José M. Delgado-Garcia [c], Lydia Jiménez-Díaz [a,2,*], Juan D. Navarro-López [a,2,*]

[a] University of Castilla-La Mancha, NeuroPhysiology & Behavior Lab, School of Medicine of Ciudad Real, Spain
[b] Behavioral Neurophysiology Laboratory, Universidad Nacional de Colombia, 111321, Bogotá, Colombia
[c] Division of Neurosciences, University Pablo de Olavide, 41013, Seville, Spain

ARTICLE INFO

Keywords:
GIRK channel
Neuronal oscillations
Synaptic plasticity
Tertiapin-Q
In vivo
Dorsal hippocampus

ABSTRACT

Learning and memory occurrence requires of hippocampal long-term synaptic plasticity and precise neural activity orchestrated by brain network oscillations, both processes reciprocally influencing each other. As G-protein-gated inwardly rectifying potassium (GIRK) channels rule synaptic plasticity that supports hippocampal-dependent memory, here we assessed their unknown role in hippocampal oscillatory activity in relation to synaptic plasticity induction.

In alert male mice, pharmacological GIRK modulation did not alter neural oscillations before long-term potentiation (LTP) induction. However, after an LTP generating protocol, both *gain-* and *loss-of* basal GIRK activity transformed LTP into long-term depression, but only specific suppression of constitutive GIRK activity caused a disruption of network synchronization (δ, α, γ bands), even leading to long-lasting ripples and fast ripples pathological oscillations.

Together, our data showed that constitutive GIRK activity plays a key role in the tuning mechanism of hippocampal oscillatory activity during long-term synaptic plasticity processes that underlies hippocampal-dependent cognitive functions.

CRediT author statement

Conceptualization, LJD and JDNL; Investigation, STC; Formal analysis, AM, AC and SD; Resources, JMDG, AG, LJD and JDNL; Writing - original draft, AC and SD; Writing – review and editing, AC, SD, LJD and JDNL; Funding acquisition, LJD and JDNL.

1. Introduction

Neuronal oscillations are rhythmic fluctuations of the postsynaptic potentials of a neuronal group (local field potentials, LFP) or a cortical region (electroencephalography, EEG; magnetoencephalography, MEG) that are considered a basic mechanism of neural communication, therefore playing an important role in cognitive and motor processes (Buzsáki et al., 2012; Mysin and Shubina, 2022). The formation of hippocampal-dependent memory requires precise neural activity orchestrated by various brain oscillatory activities, classified based on their frequency (Kalweit et al., 2017). *Delta* oscillations (δ, 1–4 Hz) in the CA1 hippocampal area are associated with non-REM sleep states and sensory selection (Girardeau and Lopes-Dos-Santos, 2021; McCormick and Bal, 1997). *Theta* oscillations (Θ, 4–8 Hz) arise from areas such as CA3, CA1 or the medial septum (Colom, 2006; Dragoi et al., 1999) and are linked to cell temporal firing and synaptic plasticity, which are crucial for the encoding and consolidation of spatial memory (Girardeau and Lopes-Dos-Santos, 2021; Hyman et al., 2003). *Alpha* oscillations (α, 8–12 Hz) are relevant during working memory formation due to their association with attention (Kienitz et al., 2022), while *beta* oscillations (β, 12–30 Hz) are related to motor activity (Barone and Rossiter, 2021). *Gamma* oscillations (γ, 30–100 Hz) are involved in context-association during memory encoding and retrieval, particularly for spatial memory (Tort et al., 2009). Finally, *ripples* (100–250 Hz) and *fast ripples* (250–500 Hz) are high-frequency oscillations originating in the

* Corresponding authors. NeuroPhysiology and Behavior Lab, University of Castilla-La Mancha, 13071, Ciudad Real, Spain.
E-mail addresses: Lydia.Jimenez@uclm.es (L. Jiménez-Díaz), Juan.Navarro@uclm.es (J.D. Navarro-López).
[1] These authors share first authorship.
[2] These authors contributed equally to this work and share last authorship.

https://doi.org/10.1016/j.neuropharm.2023.109668
Received 25 April 2023; Received in revised form 6 July 2023; Accepted 13 July 2023
Available online 19 July 2023

hippocampus and contribute to memory consolidation (Girardeau and Zugaro, 2011). *Ripples* can occur during both physiological and pathological events, whereas *fast ripples* appear exclusively in pathological cases involving altered excitability and excitation/inhibition (E/I) imbalance (Gulyás and Freund, 2015). Additionally, oscillations at different frequency bands can interact with each other, a phenomenon known as cross-frequency coupling (Salimpour and Anderson, 2019). Among these, *Theta-Gamma* Coupling (TGC) is considered a neuronal correlate of learning processes, specifically for spatial learning and the processing of episodic memories (Brooks et al., 2020; Tamura et al., 2017). Furthermore, *theta* and *gamma* oscillations typically exhibit an inversely proportional pattern, with high *theta* power accompanied by low *gamma* power and *vice versa* (Kalweit et al., 2017).

Furthermore, *theta* oscillations are known as the "*online*" state of the hippocampus as they play a crucial role in the induction of long-term potentiation (LTP) and therefore memory formation (Buzsáki, 2002; Colom, 2006; Nuñez and Buño, 2021). It has been proposed that a precise pattern of hippocampal oscillations is necessary for the proper generation of long-term plasticity processes that underlie learning and memory capabilities. Simultaneously, LTP serves as a trigger for the reorganization of neural network activity (Bikbaev and Manahan-Vaughan, 2007, 2008; Buzsáki and Moser, 2013; Hyman et al., 2003). Thus, neural oscillations and synaptic plasticity are closely interlinked in the hippocampus.

On another note, G-protein-gated inwardly rectifying potassium (GIRK) channels, a family of K^+ channels activated by various G-protein-coupled receptors (Jeremic et al., 2021b; Lüscher and Slesinger, 2010), have been implicated in mediating neuronal synchronization in the firing of pyramidal cells in the hippocampus (Anderson et al., 2021; Dascal, 1997). Consequently, they have emerged as potential targets for regulating network oscillatory activity (Huang et al., 2005; Kamarajan et al., 2017; Mattis et al., 2014; Sun et al., 2002). The GIRK channel subunits (GIRK1-GIRK4) can form functional tetrameric channels with different combinations (Jeremic et al., 2021b). In the brain, GIRK1/GIRK2 heteromultimers are the neural prototypical GIRK channel although heterotetramers of GIRK1/GIRK3, or GIRK2/GIRK3 can also be found (Fernandez-Alacid et al., 2011). In the dorsal hippocampus, GIRK channel conductance is constitutively active (Kim and Johnston, 2015), hyperpolarizing neurons and thus controlling neural excitability (Malik and Johnston, 2017). Additionally, GIRK channels gate synaptic plasticity processes that support learning and memory formation (Djebari et al., 2021; Malik and Johnston, 2017). Moreover, GIRK activity has been implicated in alterations in *theta* (Kamarajan et al., 2017) and *gamma* (Johnston et al., 2014; Pietersen et al., 2009) oscillations during reward processing, and it may contribute to the neurogenetic basis of cognitive dysfunctions in addiction and other disorders (Kamarajan et al., 2017). Likewise, GIRK activity regulates *ripples* in the dorsal hippocampus, as blocking it increases *sharp wave-ripples* (*SPW-Rs*) (Trompoukis et al., 2020). However, the precise role of GIRK activity in hippocampal oscillations during long-term synaptic plasticity processes remains largely unknown.

Hence, there exists a finely tuned relationship between synaptic plasticity and oscillatory activity in the hippocampus for proper memory acquisition. GIRK channels play a crucial role in governing synaptic plasticity underlying memory formation and retrieval (Djebari et al., 2021). Therefore, the objective of the present study was to determine their role in dorsal hippocampal oscillatory activity before and after the induction of long-term synaptic plasticity in alert animals, aiming to gain further insights into the mechanisms by which GIRK channels may modulate hippocampal function.

2. Materials and methods

2.1. Animals

Male C57BL/6 adult mice (n = 57; 3-5-month-old; 28–35 g) were used (Charles River). Prior to surgery, the animals were group-housed, with 5 mice per cage. Following surgery, animals were housed individually. They were maintained under a 12 h light/dark cycle at a constant temperature (21 ± 1 °C) and humidity (50 ± 7%). Food and water were available *ad libitum*.

All experimental procedures were reviewed and approved by the Ethical Committee for Use of Laboratory Animals of the University of Castilla-La Mancha (PR-2015-01-01 and PR-2018-05-11) and conducted according to the European Union guidelines (2010/63/EU) and the Spanish regulations for the use of laboratory animals in chronic experiments (RD 53/2013 on the care of experimental animals: BOE February 08, 2013).

2.2. Drugs

All chemicals used in this study were purchased from Abcam (Cambridge, UK) and dissolved in phosphate-buffered saline (PBS). To pharmacologically modulate GIRK channels in the dorsal hippocampus both, a blocker and a selective activator were used. Tertiapin-Q (TQ) is one of most selective and potent compounds for blocking GIRK channels (Jeremic et al., 2021b; Jin and Lu, 1998). Conversely, ML297 is a selective activator of GIRK1-containing channels recently available (Jeremic et al., 2021b; Kaufmann et al., 2013). Therefore, as hippocampal GIRK channels are mainly GIRK1/GIRK2 heterotetramers, TQ (1.2 μg/μL) was used to block GIRK channels, while ML297 (0.5 μg/μL) selectively opened GIRK1-containing channels. TQ and ML297 concentrations for intracerebroventricular (*icv*.) administration were determined through preliminary tests and based on previous reports (Djebari et al., 2021; Sánchez-Rodríguez et al., 2017, 2019). The animals were randomly assigned to experimental groups, and they received a 3 μL *icv*. Injection of either TQ, ML297 or vehicle (PBS) through an injection cannula inserted in a chronically implanted guide cannula (see details below). The injections were administered in alert freely moving mice using a Hamilton syringe and a pump at a rate of 0.5 μL/min, as described elsewhere (Djebari et al., 2021; Sánchez-Rodríguez et al., 2020).

2.3. Surgery

For chronic recording and drug injection, mice underwent surgery to be implanted with recording and stimulating electrodes and a guide cannula (Fig. 1A). The mice were anesthetized with 4–1.5% isoflurane (induction and maintenance, respectively; ISOFLO, Proyma S.L.) delivered using a calibrated R580S vaporizer (RWD Life Science; flow rate: 0.5 L/min O2), as previously described (Djebari et al., 2021).

Two bipolar electrodes, made from 50 μm Teflon-coated tungsten wire (Advent Research Materials, UK), were implanted in each animal at the right hippocampus (Fig. 1C). The stimulating electrode was positioned at the Schaffer collateral-commissural pathway in the CA3 area (2 mm lateral and 1.5 mm posterior to bregma; depth from brain surface, 1.0–1.5 mm). The recording electrode was placed in the *stratum radiatum* beneath the CA1 area (1.2 mm lateral and 2.2 mm posterior to bregma; depth from brain surface, 1.0–1.5 mm) (Paxinos and Franklin, 2004). The final position of the hippocampal electrodes was verified by Nissl staining after the completion of the experiments (Fig. 1E). A silver wire (0.1 mm) was attached to the skull as ground reference. Both electrodes and the ground wire were connected to a 6-pin socket (Mouser Electronics, US), which was secured to the skull using dental cement.

For *icv*. administration of the studied drugs, the animals were also implanted with a blunted, stainless steel, 26-G guide cannula (Plastics One, US) in the left ventricle (Fig. 1B; 1 mm lateral and 0.5 mm posterior to bregma; depth from brain surface, 1.8 mm) (Paxinos and Franklin, 2004). The cannula was implanted contralateral to the bipolar electrodes to preserve the physiological properties of the CA3-CA1 synapse in the right hippocampus. The diffusion of *icv*. injections to both dorsal hippocampi has been demonstrated in previous studies (Djebari et al.,

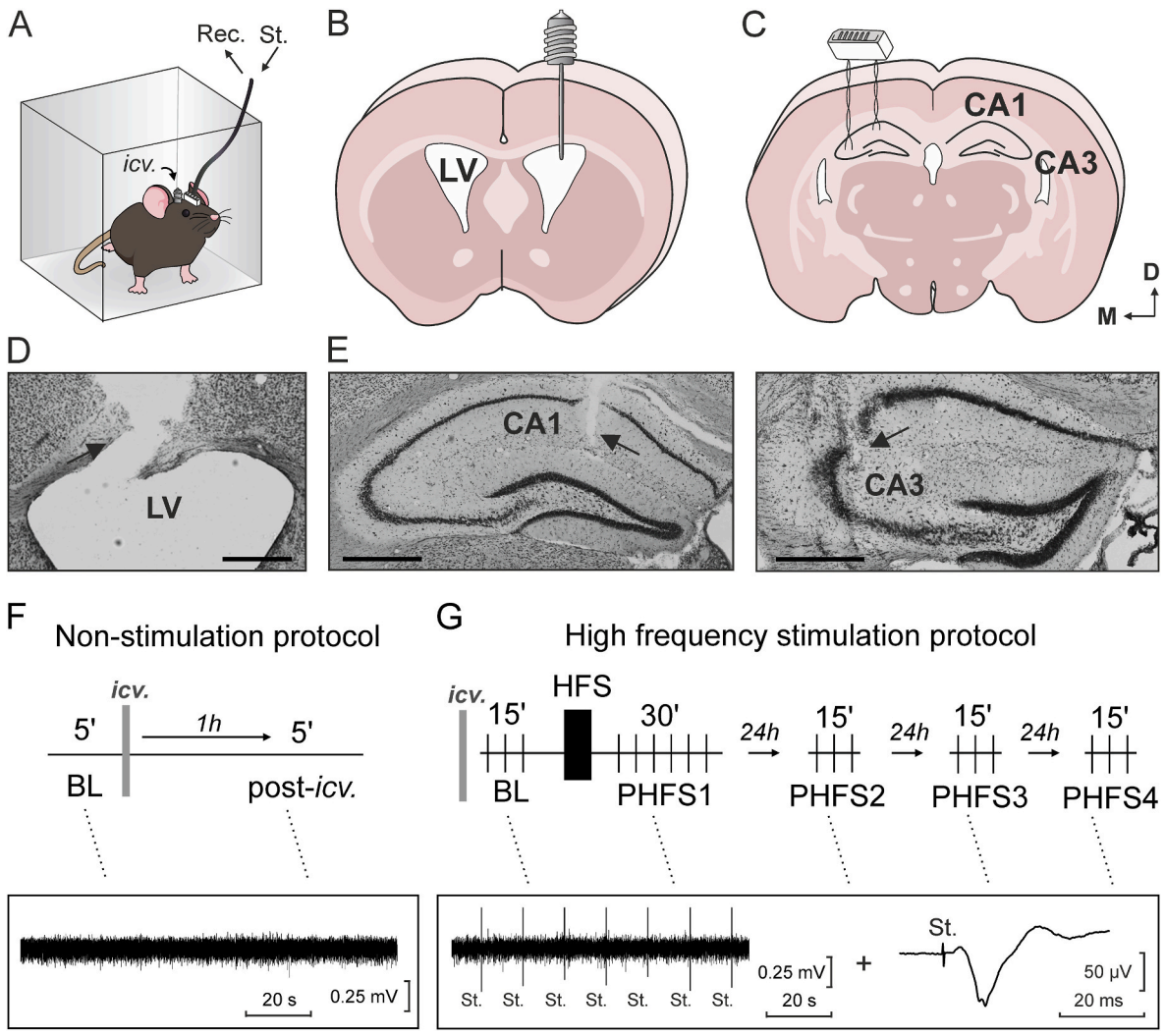


Fig. 1. Experimental design. (A) For all the experiments, mice were placed in a 9.5 × 9.5 × 7 cm small box allowing free movement during intracerebroventricular (*icv*.) injections, recording and/or stimulation procedures. **(B)** Location of the stainless-steel guide cannula implanted for *icv*. drug administration, on the left ventricle, contralaterally to recording/stimulation electrodes to preserve CA3–CA1 synapse functionality. **(C)** Location of electrodes surgically implanted in CA1 (recording) and CA3 (stimulating) for chronic fEPSPs and LFPs recordings. **(D)** Histologic verification of cannula position (black arrow). Scale bar: 500 µm. **(E)** Histologic verification of CA1 (left) and CA3 (right) electrodes position (black arrows). Scale bars: 500 µm. **(F)** Schematic diagram of the non-stimulation protocol, in which LFPs were recorded pre- (baseline, BL) and post-*icv*. treatment without external stimulation. **(G)** Schematic diagram of the high-frequency stimulation protocol (HFS) used, in which both fEPSPs (with single electrical pulses applied every 15 s) and LFPs were recorded pre- and post-HFS stimulation. LV, lateral ventricle; Rec. recording; St, stimulation; D, dorsal; M, medial.

2021; Sánchez-Rodríguez et al., 2020). The final position of the cannula was also confirmed through Nissl staining (Fig. 1D). Mice were given at least a week to recover before the experimental procedures.

2.4. *In vivo electrophysiological recordings*

LFP activity and field excitatory postsynaptic potentials (fEPSPs) were recorded from the hippocampal CA1 area of alert behaving mice using Grass P511 differential amplifiers and a high-impedance probe (2 × 1012 Ω, 10 pF).

In the first set of experiments, to evaluate GIRK modulation effect on hippocampal oscillatory activity, the animals were placed in a small box (9.5 × 9.5 × 7 cm; Fig. 1A) and LFPs were recorded, without applying any type of stimulation, during 5 min before (pre-treatment values) and 1 h after *icv*. injections (Fig. 1F). Up to 3 min of artifact-free recordings were selected for subsequent spectral analysis using the Spike2 software.

In the second set of experiments, to determine GIRK modulation effect on network function after high-frequency stimulation (HFS)-induced synaptic plasticity, both fEPSPs and LFPs were collected. Baseline (BL) measurements were obtained by stimulating with 100 µs, square, biphasic pulses at 0.05 Hz during 15 min prior to LTP induction, as described previously (Djebari et al., 2021). The stimulus intensity was selected based on two criteria: 1) ~35% of its asymptotic value, and 2) a second stimulus, presented 40 ms later, evoked a larger (≥150%) synaptic field potential compared to the first one (Bliss and Gardner-Medwin, 1973). Following the BL recordings, a HFS protocol was applied, consisting of five 100 Hz, 100 ms trains of pulses at a rate of 1/s repeated 6 times, with 1 min intervals, resulting in a total of 300 pulses in each HFS session (Sánchez-Rodríguez et al., 2017). The same stimulus intensity was used during BL, HFS and post-HFS (PHFS) sessions to avoid evoking large population spikes and/or cortical seizures. After HFS protocol application for LTP induction, fEPSPs and LFPs were recorded for 30 min on the same day (PHSF-1) and for 15 min on three consecutive days (PHFS-2, -3 and -4; Fig. 1G). The duration of recording sessions was chosen based on our previous research (Djebari et al., 2021; Mayordomo-Cava et al., 2015; Sánchez-Rodríguez et al., 2019) to obtain reliable and comparable data while minimizing potential stress to the mice. All fEPSP amplitude data obtained from the CA1 hippocampal

region during and after the HFS session were normalized using BL fEPSP values collected on the first day as 100%. The power spectrum of the hippocampal activity was computed using the Spike2 software, averaging all 15 s windows between pulses, starting 1 s after the stimulus (Fig. 4A).

The frequency bands analyzed in both sets of experiments were: *delta* (δ, 1–4 Hz), *theta* (θ, 4–8 Hz), *alpha* (α, 8–12 Hz), *beta* (β, 12–30 Hz), *gamma* (γ, 30–100 Hz), *ripples* (100–250 Hz) and *fast ripples* (250–500 Hz) (Kalweit et al., 2015).

2.5. Data collection

The recorded data were stored digitally on a computer using an analog/digital converter (CED 1401 Plus). Offline analysis was performed using the Spike2 (CED) program to quantify fEPSP amplitude and LFPs. Spectral analysis, a commonly used method for LFP quantification, was employed to examine the distribution of signal power across different frequencies. This analysis was achieved using the Fourier Transform (FT), a mathematic algorithm that transforms the signal into frequency-dependent functions. By applying the FT, the power spectrum was obtained, which provides information about the power at each frequency band. This allows for the study of different frequency bands and their relationships with various physiological processes.

2.6. Statistical analysis

Data were represented as the mean ± SEM (standard error of the mean) and analyzed by one-way or two-way ANOVA, with time and treatment as within- and between-subjects factors, respectively. For repeated measures two-way ANOVA, Greenhouse-Geiser correction was applied and indicated in the text when sphericity was not assumed. Specific information for each experiment can be found in the Results section. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using GraphPad Prism software (version 8.3.1). Final figures were created using CorelDrawX8 Software.

3. Results

3.1. GIRK modulation does not affect hippocampal network activity in basal conditions

GIRK channels dysfunction has been implicated in various central nervous system pathologies and cognitive deficits associated with imbalances in neuronal excitability (Jeremic et al., 2021b). These include epilepsy (Huang et al., 2018; Mazarati et al., 2006), Down syndrome (Cooper et al., 2012; Reeves et al., 1995; Sago et al., 1998) or Alzheimer's disease, which are characterized by multiple alterations in oscillatory network activity (Mayordomo-Cava et al., 2015, 2020; Nava-Mesa et al., 2013; Sánchez-Rodríguez et al., 2017). Therefore, we decided to study the role of these channels in the oscillatory activity of the dorsal hippocampal CA1 region by analyzing the LFPs recordings before and after *icv.* administration of GIRK channel modulators: the channel blocker TQ ($n = 11$), the selective activator ML297 ($n = 9$), or PBS as control vehicle ($n = 15$) (Fig. 1F; Fig. 2). To do so, the following frequency bands were analyzed: δ (1–4 Hz), Θ (4–8 Hz), α (8–12 Hz), β (12–30 Hz), γ (30–100 Hz), *ripples* (100–250 Hz) and *fast ripples* (250–500 Hz). The power of these frequency bands during the post-injection session was expressed as a percentage relative to the pre-injection session.

Results showed that there were no significant differences in any of the frequency bands analyzed following *icv*. Injection of either the GIRK channel opener or the blocker (Fig. 2A and B): δ ($F_{(2,32)} = 1.201$, $p = 0.345$), θ ($F_{(2,32)} = 0.847$, $p = 0.438$), α ($F_{(2,32)} = 0.664$, $p = 0.522$), β ($F_{(2,32)} = 0.187$, $p = 0.831$), γ ($F_{(2,32)} = 2.303$, $p = 0.116$), *ripples* ($F_{(2,32)} = 0.722$, $p = 0.493$) and *fast ripples* ($F_{(2,32)} = 0.235$, $p = 0.792$). These findings suggest that under basal conditions, i.e. in the absence of any artificial stimulation, pharmacological modulation of GIRK channels

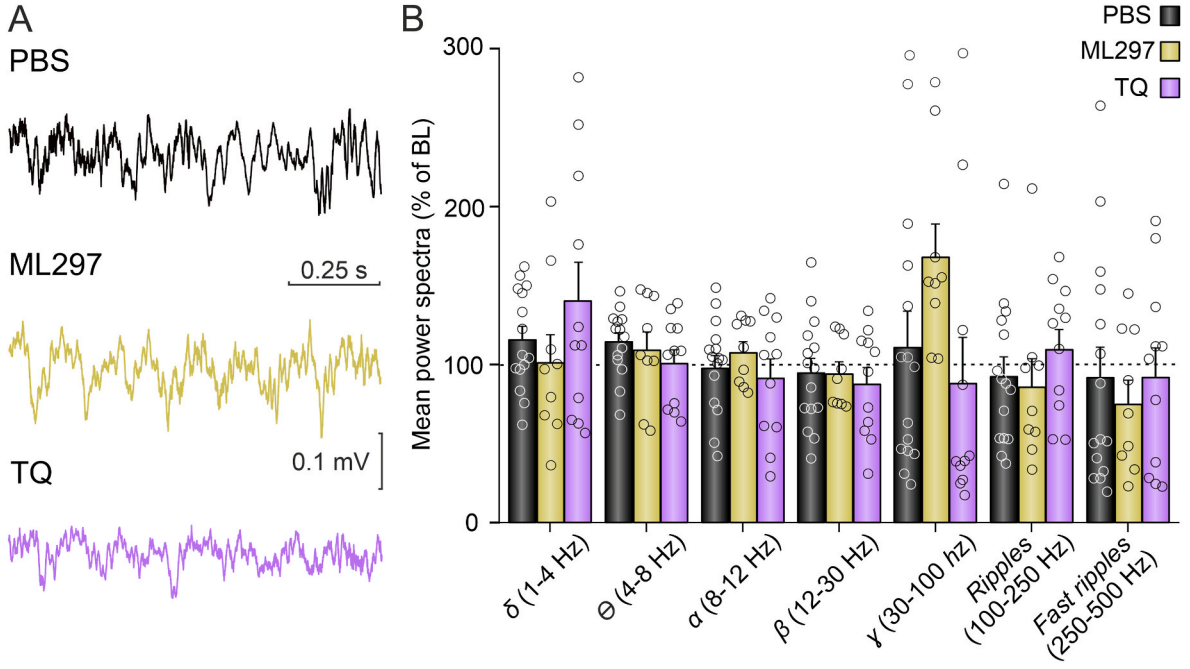


Fig. 2. Pharmacological modulation of GIRK function does not affect hippocampal oscillatory activity in non-stimulating conditions. (A) Representative examples of LFPs recorded from the CA1 region of the dorsal hippocampus in alert mice following treatment with GIRK modulators ML297 (channel opener) and TQ (channel blocker). **(B)** Histograms of the spectral power of LFP activities recorded in the CA1 region after PBS (control vehicle), ML297 or TQ injections. The dashed line represents the percentage of baseline (BL, 100%) recordings (pre-treatment). Note that pharmacological modulation of GIRK channel did not result in significant changes in the selected spectral bands, including δ, Θ, α, β, γ, *ripples* and *fast ripples* oscillations. Data is expressed as mean ± SEM and as a percentage of baseline recordings (BL, 100%).

does not alter CA1 hippocampal oscillatory activity.

3.2. Constitutive GIRK activity is needed for proper hippocampal synaptic plasticity

However, as aforementioned, LTP generation in the hippocampus is accompanied by changes in neuronal oscillations (Bikbaev and Manahan-Vaughan, 2007). In light of previous findings from our group demonstrating that GIRK channel pharmacological modulation inhibits LTP both *in vivo* and *in vitro* (Djebari et al., 2021; Sánchez-Rodríguez et al., 2017), we aimed to study the role of GIRK channels in the oscillatory activity of the dorsal hippocampus following a LTP induction protocol (see methods section for details). To do so, we first studied the effect of constitutive GIRK channel activity modulation on LTP induction in the CA1 region by applying HFS at the Schaffer collateral pathway. The evolution of fEPSPs was compared among different groups and at various timepoints (Fig. 1G). Briefly, fEPSPs were obtained by single pulse stimulation at 0.05 Hz (i.e., every 15 s) at pre- (baseline, BL) and at four post-HFS periods (immediately after HFS on day 1, PHFS-1; and 24, 48 and 72 h post-HFS on days 2, 3 or 4 respectively (PHFS-2, -3 or -4) (Fig. 3).

Here, our results showed a significant treatment effect (Fig. 3C; $F_{(2,19)} = 10.956$, $p > 0.01$) when comparing the control group and both the ML297-treated and TQ-treated groups. In the vehicle-injected control mice, the stimulation protocol induced a robust LTP in CA3-CA1 synapse (Fig. 3A–C; 194 ± 11% of BL; $n = 7$), with a significant increase in fEPSP amplitude observed during the 30 min following HFS ($F_{(8,48)} = 9.061$, $p < 0.001$), which was sustained until 24 h post-HFS (141 ± 11% of BL; $F_{(2.1,12,7)} = 7{,}052$, $p = 0{,}008$, Greenhouse-Geiser correction). However, the induction of LTP was not achieved after pharmacological GIRK channel activity increase nor reduction through *icv.* injections of ML297 ($F_{(8,48)} = 0.571$, $p = 0.791$; $n = 4$) or TQ ($F_{(1.73,17.27)} = 1.184$, p = 0.323, Greenhouse-Geiser correction; n = 11), respectively (Fig. 3A–C). Instead, 72 h after HFS, while the amplitude of CA1 fEPSPs recovered BL values in control animals (100 ± 11% of BL), both treatments led to a noticeable depression of the synaptic response (Fig. 3B; ML297: 68 ± 12% of BL; TQ: 68 ± 5% of BL), thus showing a HFS-induced long-term depression (LTD).

3.3. Constitutive GIRK activity supports network function after HFS-induced synaptic plasticity

Finally, to examine the potential changes in hippocampal oscillations accompanying the observed alterations in synaptic plasticity, LFPs were also recorded during BL and the same post-HFS periods described above (PHSF-1, -2, -3 and -4) in all the 15 s windows between single pulses (Figs. 1G and 4A).

In the low frequency bands, a significant treatment effect was found in the δ band (Fig. 4B; $F_{(2,20)} = 8.649$, $p = 0.002$). *Post-hoc* analysis revealed differences between mice injected with TQ and controls during PHFS-1, as control mice exhibited an increase in δ frequency following LTP induction, whereas TQ-treated mice did not show this increase, suggesting the involvement of GIRK channels in δ rhythm generation during HFS. Furthermore, a significant time effect was observed ($F_{(2.89,56.38)} = 4.473$, $p = 0.0075$, Greenhouse-Geiser correction), as the initial increment declined progressively during the following days (PHFS-2, -3 and -4).

In contrast, neither increasing nor decreasing GIRK-dependent signaling in the dorsal hippocampus significantly affected the Θ band after the HFS protocol for LTP induction (Fig. 4C; $F_{(2,19)} = 2.032$, $p = 0.1586$). Analysis of the α band revealed a significant treatment effect (Fig. 4D; $F_{(2,19)} = 7.140$, $p = 0.0049$), specifically during PHFS-1, where *alpha* frequency transiently decreased in control and ML297-injected mice, but remained close to BL levels in TQ-injected mice. The β band was also altered by treatment (Fig. 4E; $F_{(2,19)} = 6.665$, $p = 0.0064$), although no specific differences were observed in the *post-hoc* analysis. Similarly, the γ band showed a significant treatment effect (Fig. 4F; $F_{(2,19)} = 9.764$, $p = 0.0012$) during PHFS-3 and PHFS-4, with differences

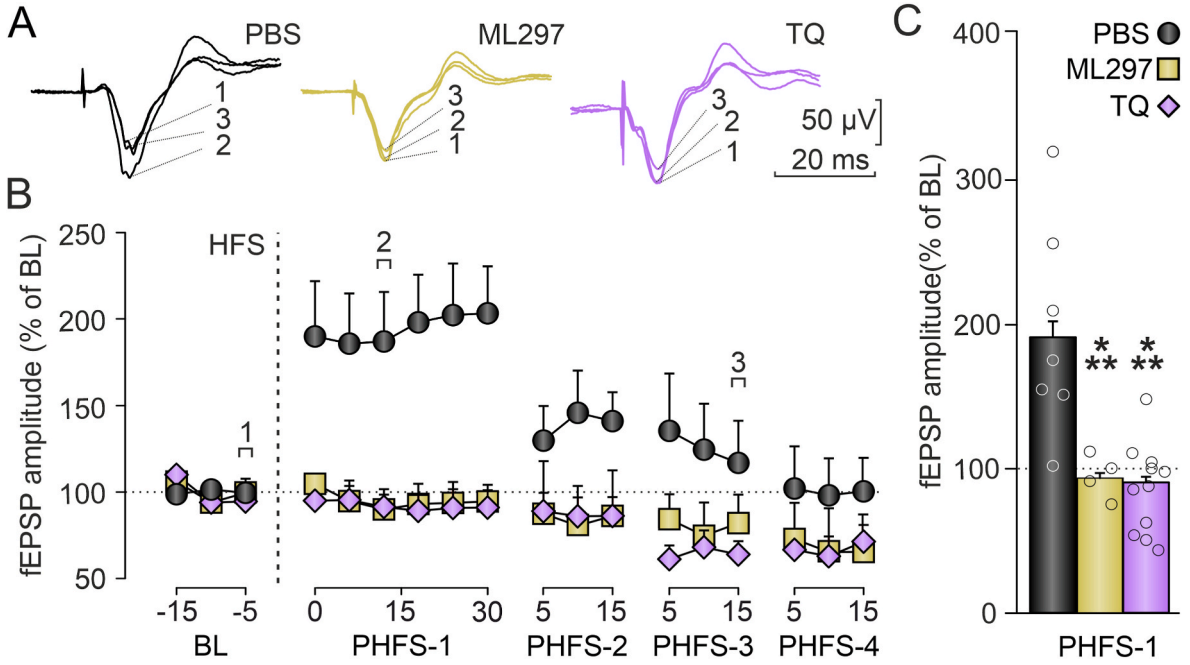


Fig. 3. Constitutive GIRK activity is needed for proper hippocampal synaptic plasticity *in vivo*. **(A)** Representative examples of fEPSPs (averaged 5 times) evoked at the CA3–CA1 synapse by single stimulation collected after *icv.* drug administration but prior to HFS (1, BL), following HFS (2) and 48 h after HFS (3) in mice injected with vehicle (PBS, control), GIRK channel opener ML297 or channel blocker TQ. **(B)** Evolution of fEPSPs recorded in alert mice of each experimental group during 15 min prior to HFS (BL), during 30 min after LTP induction that same day (PHFS-1) and during 15 min on three consecutive days (PHFS-2, -3 and -4). Data is expressed as the mean amplitude ± SEM and as a percentage of BL recordings (100%) **(C)** Bars illustrate fEPSPs amplitude to show potentiation level (mean ± SEM) after PHFS-1. ***$p < 0.001$ *vs.* PBS.

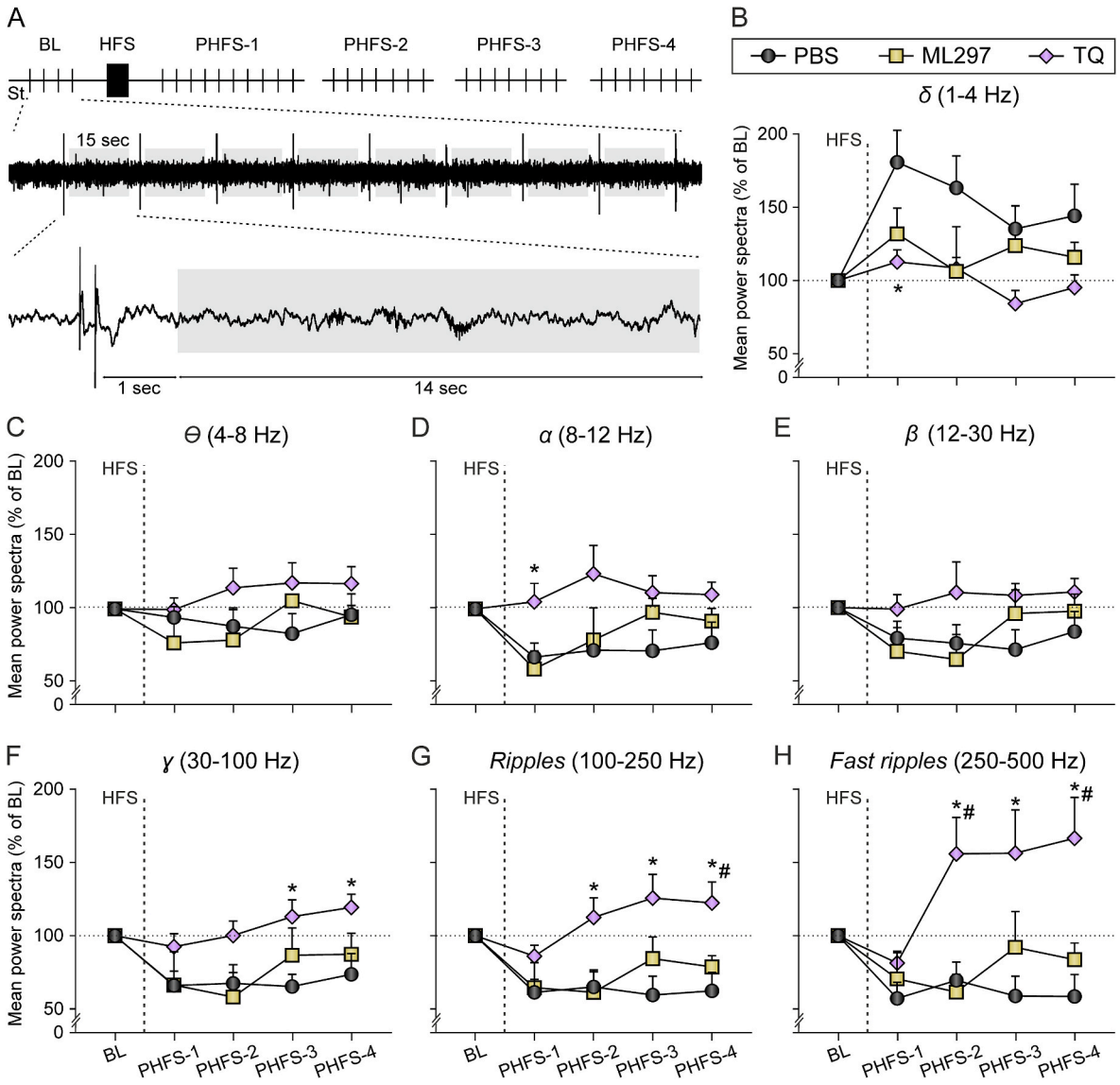


Fig. 4. Constitutive GIRK activity supports network function after HFS-induced synaptic plasticity. (A) Schematic representation of the protocol used to analyze LFPs in all the 15 s windows between pulses during BL and the different post-HFS sessions (PHFS-1, -2, -3 and -4). Average spectral power of frequency intervals corresponding to *delta* **(B)**, *theta* **(C)**, *alpha* **(D)**, *beta* **(E)**, *gamma* **(F)**, *ripples* **(G)** and *fast ripples* **(H)** bands. Data is expressed as mean ± SEM and as a percentage of baseline recordings (BL, 100%). *$p < 0.05$ *vs.* PBS (vehicle); #$p < 0.05$ *vs.* ML297.

between control animals and TQ treated mice.

Control mice exhibited a decrease in *gamma* frequency after LTP induction, whereas the TQ group showed a progressive enhancement, peaking at PHFS-4. As observed with the *delta* band, a significant time effect was also detected ($F_{(3.10,55.84)} = 2.951$, $p = 0.0388$, Greenhouse-Geiser correction).

In the high-frequency bands, a significant treatment effect was observed in the *ripples* band (Fig. 4G; $F_{(2,19)} = 10.411$, $p = 0.0009$). *Post-hoc* analysis revealed differences between TQ-treated animals and controls. Both controls and ML297-injected animals showed a reduction in *ripple* frequency after LTP induction, while TQ-treated mice displayed an increase, specifically during PHFS-2, -3 and -4. Furthermore, a significant treatment effect was detected in the *fast ripples* band (Fig. 4H; $F_{(2,19)} = 8.008$, $p = 0.003$). Once again, TQ-treated mice exhibited an increase in this band during PHFS-2, -3 and -4, whereas no such increase was observed in control or ML297-treated mice.

Hence, all these alterations in the power spectra induced by the lack of GIRK activity after a HFS protocol, but not under non-stimulation conditions, suggest a differential role for GIRK channels in neural oscillations and long-term synaptic plasticity processes that underlie learning and memory.

4. Discussion

During hippocampal-dependent memory processing, and the underlying long-term synaptic plasticity generation, significant changes occur in neuronal oscillation activity (Abubaker et al., 2021; Bikbaev and Manahan-Vaughan, 2008, 2017). Our findings demonstrate the relevant role of GIRK channel activity in these interconnected processes.

4.1. GIRK activity modulation does not alter basal network oscillations at dorsal hippocampal CA1 region

Given the link between oscillatory activity, LTP and GIRK channels, we started by pharmacologically modulating GIRK channel function in dorsal hippocampus of alert mice, without applying external stimulation, to study their contribution to oscillatory activity. However, our results did not show significant changes in any of the frequency bands

considered in this study. Nevertheless, it is important to note that different results have been reported by other authors. For instance, Tatard-Leitman et al. (2015) observed an increase in Θ (4–12 Hz), β (13–30 Hz) and γ (30–80 Hz) bands in a NMDA-R1 knocked-out mice model that exhibited decreased expression of the GIRK2 subunit in the synaptic membrane. However, since this manipulation affects several hippocampal synaptic pathways, it cannot be concluded that these changes are solely due to GIRK channel downregulation. Additionally, pharmacological blockade of GIRK channels by TQ was found to increase the occurrence rate of *SPW-Rs* (110–200 Hz) in dorsal hippocampal slices (Trompoukis et al., 2020). Similarly, constitutive knockout of GIRK2 in mice has been associated with increased susceptibility to seizures (Blednov et al., 2001; Pravetoni and Wickman, 2008; Victoria et al., 2016), which could be related to an enhancement in the amplitude of neural oscillations. However, in our approach, *icv.* application of a GIRK blocker did not induce any signs of epileptiform activity in the hippocampus (Djebari et al., 2021). Furthermore, previous work from our laboratory showed that while ML297 *icv.* administration had no effect on the Θ and γ spectral bands, this GIRK opener was able to restore control values when co-administered with Amyloid-β peptide (a toxic strongly associated with increased excitability neuropathology in Alzheimer's disease (Jeremic et al., 2021a)), since both Θ and γ are known to be dramatically altered by hyperexcitability in animal models of Alzheimer's disease (Sánchez-Rodríguez et al., 2017). Thus, the impact of GIRK modulation on dorsal hippocampal oscillatory activity *in vivo* appears to depend on hippocampal excitability levels and may be particularly relevant in pathological conditions involving an Excitatory/Inhibitory (E/I) imbalance (Jeremic et al., 2021b).

4.2. Constitutive GIRK activity supports synaptic plasticity and network function after HFS protocol

Mice lacking GIRK2 in forebrain pyramidal neurons (CaMKII-Cre(+): $GIRK2^{flox/flox}$) have been reported to exhibit a depletion of LTP, an enhanced LTD, and blunted LTP depotentiation (Victoria et al., 2016). GIRK channels are also critical for LTP of synaptic inhibition, a form of synaptic plasticity that prevents saturation of synaptic potentiation and increases the flexibility and storage capacity of neuronal circuits (Huang et al., 2005; Sánchez-Rodríguez et al., 2019). In addition, our recent results indicated that both enhancement and blockade of GIRK channel activity disrupt LTP induction (Djebari et al., 2021). GIRK opener ML297 may impair LTP by causing intense hyperpolarization of pyramidal neurons and insufficient activation of NMDA receptors (NMDARs) (Djebari et al., 2021), while TQ may increase GABA release, leading to pyramidal neurons inhibition (Davies et al., 1991). Both mechanisms could explain the observed effects in the dorsal hippocampus *in vivo*, highlighting the critical role for GIRK channel conductance in regulating LTP/LTD induction threshold and subsequent memory processes (Djebari et al., 2021). Furthermore, HFS-induced LTD could be explained, at least partially, by the Bienenstock, Cooper and Munro (BCM) theory, which proposes that changes in neuronal excitability, with GIRK channels playing a significant role in their control in the hippocampus, and thus influencing hippocampal activity levels, can alter the induction threshold of long-term plasticity processes (Keck et al., 2017). However, the exploration of neuronal oscillations during synaptic plasticity generation could provide an alternative explanation, as demonstrated in the present study.

Consequently, the next step was to analyze whether pharmacological GIRK channel activity modulation could influence hippocampal oscillations that pair with synaptic plasticity events. Our results indicated that, while GIRK activity enhancement by ML297 administration did not significantly modify any of the frequency bands analyzed, the reduction of GIRK function using TQ led to imbalances in almost all neuronal oscillations during synaptic plasticity induction and maintenance. In dorsal CA1, GIRK channels are constitutively active, contributing to a decrease in excitability and maintaining an E/I balance (Kim and Johnston, 2015). Increasing GIRK activity beyond physiological basal values with ML297 would raise the threshold for LTP induction, disrupting the plasticity process (Cummings et al., 1996; Djebari et al., 2021). According to our present results, this mechanism appears to be independent of hippocampal oscillations. Conversely, decreasing GIRK constitutive activity with TQ, which diminishes the necessary basal inhibitory transmission required for proper hippocampal function, seems to alter the oscillatory activity required for successful LTP induction (Bikbaev and Manahan-Vaughan, 2008). Thus, both function gain and loss of GIRK activity impair LTP through two different pathways.

To deepen the understanding of the involvement of GIRK channel conductance in hippocampal network activity following LTP induction, we will first focus on cross-frequency coupling, a fundamental feature of oscillatory activity that is a critical component of physiological cognitive function (Canolty and Knight, 2010; Lisman and Jensen, 2013). TGC is the most studied coupling, and several works have demonstrated its involvement in memory formation processes (Canolty and Knight, 2010; Lisman and Jensen, 2013), suggesting that *theta* and *gamma* oscillations could serve as an intrinsic mechanism for LTP to occur (Bikbaev and Manahan-Vaughan, 2008). In this regard, Bikbaev and Manahan-Vaughan (2008) demonstrated a specific pattern of changes in *theta* and *gamma* frequencies associated with LTP, including an increase in *theta* power and a transient increase (up to 100 s after high-frequency tetanisation) followed by a decrease in *gamma* power. Although the experimental procedure used in the current study, which involved averaging the spectral power over the entire session (30 or 15 min), did not capture these transient variations in different frequency bands, our results indicated a decrease in γ power after LTP induction in control and ML297-treated animals, lasting at least 4 days post-HFS. Interestingly, blockade of GIRK channels by TQ progressively increased this frequency, being significantly higher on the last 2 days, coinciding with the depression of fEPSP amplitude observed in these mice. This finding may partially underlie the HFS-induced LTD described here and elsewhere (Djebari et al., 2021). In this line, a link between GIRK channels decreased expression and an increased baseline hippocampal γ power (Tatard-Leitman et al., 2015) has been previously proposed. Surprisingly, we did not observe any significant changes in the amplitude of Θ power, neither in control mice nor after GIRK modulation. This may be attributed to the stimulating protocol used to induce LTP. The current study employed a HFS protocol (Gruart et al., 2006), due to its better performance during *in vivo* stimulating, while a *theta*-burst stimulation (TBS) protocol has been previously related to alterations in TGC after LTP induction (Radiske et al., 2020). These distinct protocols are known to activate distinct intracellular signaling cascades, resulting in divergent outcomes for LTP (Hegemann and Abraham, 2021; Liu et al., 2020; Mastrolia et al., 2021), which might also impact Θ power modulation.

Less is known about how other rhythms such as *delta*, *alpha* or *beta* are modulated after a plasticity mechanism is triggered. Our results showed an enhancement of δ power and a reduction of α power after *in vivo* HFS in control animals, which were reversed in TQ-treated mice. These findings align with previous research, demonstrating the suppression of δ frequency when LTP is hindered in a rat model of psychosis (Kalweit et al., 2017). Additionally, *delta-alpha* coupling has been implicated in TGC and serves as a gating mechanism for prioritizing relevant information in working memory tasks (Leszczyński et al., 2015). Thus, the alterations observed in these frequency bands may be related to the learning and memory deficits previously reported when GIRK channel activity is reduced (Djebari et al., 2021; Mett et al., 2021). Regarding β oscillations, no specific differences were observed in the current study. This lack of significant findings may be attributed to the restraint of the animals in a small box without engaging in any behavioral tasks, as β frequency is typically associated with motor activity (Barone and Rossiter, 2021).

Another aspect investigated in this study was the modulation of *SPW-Rs*, which are influenced by 5-HT_{1A} receptors in the hippocampus and

have been implicated in memory consolidation. HFS protocols that induce LTP can also trigger *SPW-Rs* (ul Haq et al., 2016). Given the known interaction between GIRK channels and 5-HT_{1A} receptors (Jeremic et al., 2021b) and their role in modulating hippocampal *gamma* oscillations (Johnston et al., 2014), the evaluation of *ripples* and *fast ripples* becomes particularly relevant. Here, we found that GIRK channels blockade increased the power of both *ripples* and *fast ripples* after HFS, even several days after the induction of synaptic plasticity. This is consistent with previous findings showing an increased occurrence of *ripples* in dorsal hippocampal slices with GIRK channel blockade with TQ (Trompoukis et al., 2020). *Ripples* have been shown to be critically involved in the process of memory consolidation during sleep and are generated by the disinhibition of pyramidal cells (Evangelista et al., 2020). Therefore, the low levels of *ripple* oscillations observed in control animals, consistent with their awake state, and the increased levels in TQ-treated mice suggest that blocking GIRK channel activity leads to hippocampal disinhibition. Furthermore, the loss of inhibition can transform *ripples* into *fast ripples*, as observed in our results. which are pathological oscillations associated with epileptic activity (Gulyás and Freund, 2015), where GIRK channels have been shown to play a critical role (Jeremic et al., 2021b).

5. Conclusions

In summary, neuronal oscillations are crucial for supporting normal information processing and storage in the hippocampus, and LTP and oscillatory activity are reciprocally interlinked to contribute to memory formation (Bikbaev and Manahan-Vaughan, 2007). Here, we found that the suppression of GIRK constitutive activity in the dorsal hippocampus disrupts the correct synchronization of neuronal networks, leading to pathological oscillations (*fast ripples)* during long-term synaptic plasticity events but not under basal conditions (without artificial stimulation). Consequently, all these alterations in spectral power may account for the impairment of LTP and memory function previously reported (Djebari et al., 2021; Sánchez-Rodríguez et al., 2017, 2019, 2020) and shed light on how GIRK channels contribute to synaptic and network processes that supports hippocampal-dependent cognitive capabilities.

Funding

This work was supported by grants BFU 2017-82494-P, PID 2020-115,823-GB100 funded by MCIN/AEI/10.13039/501100011033, SBPLY/21/180501/000150 funded by JCCM/ERDF - A way of making Europe, and UCLM intramural funding (2022-GRIN-34354) to LJ-D and JDN-L. AM held a Senior Visiting Researcher Fellow funded by "Plan Propio de Investigación" Programme of the University of Castilla-La Mancha. AC held a *Margarita Salas* Postdoctoral Research Fellow funded by European Union NextGenerationEU/PRTR.

Data statement

The data reported in this paper is available from the corresponding authors upon request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

We thank José M. Gonzalez Martín, María Sánchez Enciso, and José A. Santos for their excellent technical assistance.

References

Abubaker, M., Al Qasem, W., Kvašňák, E., 2021. Working memory and cross-frequency coupling of neuronal oscillations. Front. Psychol. 12, 756661.
Anderson, E.M., Demis, S., D'Acquisto, H., Engelhardt, A., Hearing, M., 2021. The role of parvalbumin interneuron GIRK signaling in the regulation of affect and cognition in male and female mice. Front. Behav. Neurosci. 15, 621751.
Barone, J., Rossiter, H.E., 2021. Understanding the role of sensorimotor beta oscillations. Front. Syst. Neurosci. 15, 655886.
Bikbaev, A., Manahan-Vaughan, D., 2007. Hippocampal network activity is transiently altered by induction of long-term potentiation in the dentate gyrus of freely behaving rats. Front. Behav. Neurosci. 1, 7.
Bikbaev, A., Manahan-Vaughan, D., 2008. Relationship of hippocampal theta and gamma oscillations to potentiation of synaptic transmission. Front. Neurosci. 2, 56–63.
Bikbaev, A., Manahan-Vaughan, D., 2017. Metabotropic glutamate receptor, mGlu5, regulates hippocampal synaptic plasticity and is required for tetanisation-triggered changes in theta and gamma oscillations. Neuropharmacology 115, 20–29.
Blednov, Y.A., Stoffel, M., Chang, S.R., Harris, R.A., 2001. Potassium channels as targets for ethanol: studies of G-protein-coupled inwardly rectifying potassium channel 2 (GIRK2) null mutant mice. J. Pharmacol. Exp. Therapeut. 298, 521–530.
Bliss, T.V., Gardner-Medwin, A.R., 1973. Long-lasting potentiation of synaptic transmission in the dentate area of the unanaestetized rabbit following stimulation of the perforant path. J. Physiol. 232, 357–374.
Brooks, H., Goodman, M.S., Bowie, C.R., Zomorrodi, R., Blumberger, D.M., Butters, M.A., Daskalakis, Z.J., Fischer, C.E., Flint, A., Herrmann, N., Kumar, S., Mah, L., Mulsant, B.H., Pollock, B.G., Voineskos, A.N., Rajji, T.K., Group, P.A.-M.S., 2020. Theta-gamma coupling and ordering information: a stable brain-behavior relationship across cognitive tasks and clinical conditions. Neuropsychopharmacology 45, 2038–2047.
Buzsáki, G., 2002. Theta oscillations in the hippocampus. Neuron 33, 325–340.
Buzsáki, G., Anastassiou, C.A., Koch, C., 2012. The origin of extracellular fields and currents–EEG, ECoG, LFP and spikes. Nat. Rev. Neurosci. 13, 407–420.
Buzsáki, G., Moser, E.I., 2013. Memory, navigation and theta rhythm in the hippocampal-entorhinal system. Nat. Neurosci. 16, 130–138.
Canolty, R.T., Knight, R.T., 2010. The functional role of cross-frequency coupling. Trends Cognit. Sci. 14, 506–515.
Colom, L.V., 2006. Septal networks: relevance to theta rhythm, epilepsy and Alzheimer's disease. J. Neurochem. 96, 609–623.
Cooper, A., Grigoryan, G., Guy-David, L., Tsoory, M.M., Chen, A., Reuveny, E., 2012. Trisomy of the G protein-coupled K+ channel gene, Kcnj6, affects reward mechanisms, cognitive functions, and synaptic plasticity in mice. Proc. Natl. Acad. Sci. U. S. A. 109, 2642–2647.
Cummings, J.A., Mulkey, R.M., Nicoll, R.A., Malenka, R.C., 1996. Ca2+ signaling requirements for long-term depression in the hippocampus. Neuron 16, 825–833.
Dascal, N., 1997. Signalling via the G protein-activated K+ channels. Cell. Signal. 9, 551–573.
Davies, C.H., Starkey, S.J., Pozza, M.F., Collingridge, G.L., 1991. GABA autoreceptors regulate the induction of LTP. Nature 349, 609–611.
Djebari, S., Iborra-Lázaro, G., Temprano-Carazo, S., Sánchez-Rodríguez, I., Nava-Mesa, M.O., Múnera, A., Gruart, A., Delgado-García, J.M., Jiménez-Díaz, L., Navarro-López, J.D., 2021. G-Protein-Gated inwardly rectifying potassium (Kir3/GIRK) channels govern synaptic plasticity that supports hippocampal-dependent cognitive functions in male mice. J. Neurosci. 41, 7086–7102.
Dragoi, G., Carpi, D., Recce, M., Csicsvari, J., Buzsáki, G., 1999. Interactions between hippocampus and medial septum during sharp waves and theta oscillation in the behaving rat. J. Neurosci. 19, 6191–6199.
Evangelista, R., Cano, G., Cooper, C., Schmitz, D., Maier, N., Kempter, R., 2020. Generation of sharp wave-ripple events by disinhibition. J. Neurosci. 40, 7811–7836.
Fernandez-Alacid, L., Watanabe, M., Molnar, E., Wickman, K., Lujan, R., 2011. Developmental regulation of G protein-gated inwardly-rectifying K+ (GIRK/Kir3) channel subunits in the brain. Eur. J. Neurosci. 34, 1724–1736.
Girardeau, G., Lopes-Dos-Santos, V., 2021. Brain neural patterns and the memory function of sleep. Science 374, 560–564.
Girardeau, G., Zugaro, M., 2011. Hippocampal ripples and memory consolidation. Curr. Opin. Neurobiol. 21, 452–459.
Gruart, A., Muñoz, M.D., Delgado-García, J.M., 2006. Involvement of the CA3-CA1 synapse in the acquisition of associative learning in behaving mice. J. Neurosci. 26, 1077–1087.
Gulyás, A.I., Freund, T.T., 2015. Generation of physiological and pathological high frequency oscillations: the role of perisomatic inhibition in sharp-wave ripple and interictal spike generation. Curr. Opin. Neurobiol. 31, 26–32.
Hegemann, R.U., Abraham, W.C., 2021. Postsynaptic cell firing triggers bidirectional metaplasticity depending on the LTP induction protocol. J. Neurophysiol. 125, 1624–1635.
Huang, C.S., Shi, S.H., Ule, J., Ruggiu, M., Barker, L.A., Darnell, R.B., Jan, Y.N., Jan, L.Y., 2005. Common molecular pathways mediate long-term potentiation of synaptic excitation and slow synaptic inhibition. Cell 123, 105–118.
Huang, Y., Zhang, Y., Kong, S., Zang, K., Jiang, S., Wan, L., Chen, L., Wang, G., Jiang, M., Wang, X., Hu, J., Wang, Y., 2018. GIRK1-mediated inwardly rectifying potassium

current suppresses the epileptiform burst activities and the potential antiepileptic effect of ML297. Biomed. Pharmacother. 101, 362–370.
Hyman, J.M., Wyble, B.P., Goyal, V., Rossi, C.A., Hasselmo, M.E., 2003. Stimulation in hippocampal region CA1 in behaving rats yields long-term potentiation when delivered to the peak of theta and long-term depression when delivered to the trough. J. Neurosci. 23, 11725–11731.
Jeremic, D., Jimenez-Diaz, L., Navarro-Lopez, J.D., 2021a. Past, present and future of therapeutic strategies against amyloid-beta peptides in Alzheimer's disease: a systematic review. Ageing Res. Rev. 72, 101496.
Jeremic, D., Sanchez-Rodriguez, I., Jimenez-Diaz, L., Navarro-Lopez, J.D., 2021b. Therapeutic potential of targeting G protein-gated inwardly rectifying potassium (GIRK) channels in the central nervous system. Pharmacol. Ther. 223, 107808.
Jin, W., Lu, Z., 1998. A novel high-affinity inhibitor for inward-rectifier K+ channels. Biochemistry 37, 13291–13299.
Johnston, A., McBain, C.J., Fisahn, A., 2014. 5-Hydroxytryptamine1A receptor-activation hyperpolarizes pyramidal cells and suppresses hippocampal gamma oscillations via Kir3 channel activation. J. Physiol. 592, 4187–4199.
Kalweit, A.N., Amanpour-Gharaei, B., Colitti-Klausnitzer, J., Manahan-Vaughan, D., 2017. Changes in neuronal oscillations accompany the loss of hippocampal LTP that occurs in an animal model of psychosis. Front. Behav. Neurosci. 11, 36.
Kalweit, A.N., Yang, H., Colitti-Klausnitzer, J., Fülöp, L., Bozsó, Z., Penke, B., Manahan-Vaughan, D., 2015. Acute intracerebral treatment with amyloid-beta (1-42) alters the profile of neuronal oscillations that accompany LTP induction and results in impaired LTP in freely behaving rats. Front. Behav. Neurosci. 9, 103.
Kamarajan, C., Pandey, A.K., Chorlian, D.B., Manz, N., Stimus, A.T., Edenberg, H.J., Wetherill, L., Schuckit, M., Wang, J.C., Kuperman, S., Kramer, J., Tischfield, J.A., Porjesz, B., 2017. A KCNJ6 gene polymorphism modulates theta oscillations during reward processing. Int. J. Psychophysiol. 115, 13–23.
Kaufmann, K., Romaine, I., Days, E., Pascual, C., Malik, A., Yang, L., Zou, B., Du, Y., Sliwoski, G., Morrison, R.D., Denton, J., Niswender, C.M., Daniels, J.S., Sulikowski, G.A., Xie, X.S., Lindsley, C.W., Weaver, C.D., 2013. ML297 (VU0456810), the first potent and selective activator of the GIRK potassium channel, displays antiepileptic properties in mice. ACS Chem. Neurosci. 4, 1278–1286.
Keck, T., Hubener, M., Bonhoeffer, T., 2017. Interactions between synaptic homeostatic mechanisms: an attempt to reconcile BCM theory, synaptic scaling, and changing excitation/inhibition balance. Curr. Opin. Neurobiol. 43, 87–93.
Kienitz, R., Schmid, M.C., Dugué, L., 2022. Rhythmic sampling revisited: experimental paradigms and neural mechanisms. Eur. J. Neurosci. 55, 3010–3024.
Kim, C.S., Johnston, D., 2015. A1 adenosine receptor-mediated GIRK channels contribute to the resting conductance of CA1 neurons in the dorsal hippocampus. J. Neurophysiol. 113, 2511–2523.
Leszczyński, M., Fell, J., Axmacher, N., 2015. Rhythmic working memory activation in the human Hippocampus. Cell Rep. 13, 1272–1282.
Lisman, J.E., Jensen, O., 2013. The θ-γ neural code. Neuron 77, 1002–1016.
Liu, A., Ji, H., Ren, Q., Meng, Y., Zhang, H., Collingride, G., Xie, W., Jia, Z., 2020. The requirement of the C-terminal domain of GluA1 in different forms of long-term potentiation in the Hippocampus is age-dependent. Front. Synaptic Neurosci. 12, 588785.
Lüscher, C., Slesinger, P.A., 2010. Emerging roles for G protein-gated inwardly rectifying potassium (GIRK) channels in health and disease. Nat. Rev. Neurosci. 11, 301–315.
Malik, R., Johnston, D., 2017. Dendritic GIRK channels gate the integration window, plateau potentials, and induction of synaptic plasticity in dorsal but not ventral CA1 neurons. J. Neurosci. 37, 3940–3955.
Mastrolia, V., Al Massadi, O., de Pins, B., Girault, J.A., 2021. Pyk2 in dorsal hippocampus plays a selective role in spatial memory and synaptic plasticity. Sci. Rep. 11, 16357.
Mattis, J., Brill, J., Evans, S., Lerner, T.N., Davidson, T.J., Hyun, M., Ramakrishnan, C., Deisseroth, K., Huguenard, J.R., 2014. Frequency-dependent, cell type-divergent signaling in the hippocamposeptal projection. J. Neurosci. 34, 11769–11780.
Mayordomo-Cava, J., Iborra-Lazaro, G., Djebari, S., Temprano-Carazo, S., Sanchez-Rodriguez, I., Jeremic, D., Gruart, A., Delgado-Garcia, J.M., Jimenez-Diaz, L., Navarro-Lopez, J.D., 2020. Impairments of synaptic plasticity induction threshold and network oscillatory activity in the Hippocampus underlie memory deficits in a non-transgenic mouse model of amyloidosis. Biology 9.
Mayordomo-Cava, J., Yajeya, J., Navarro-López, J.D., Jiménez-Díaz, L., 2015. Amyloid-β(25-35) modulates the expression of GirK and KCNQ channel genes in the Hippocampus. PLoS One 10, e0134385.
Mazarati, A., Lundström, L., Sollenberg, U., Shin, D., Langel, U., Sankar, R., 2006. Regulation of kindling epileptogenesis by hippocampal galanin type 1 and type 2 receptors: the effects of subtype-selective agonists and the role of G-protein-mediated signaling. J. Pharmacol. Exp. Therapeut. 318, 700–708.
McCormick, D.A., Bal, T., 1997. Sleep and arousal: thalamocortical mechanisms. Annu. Rev. Neurosci. 20, 185–215.
Mett, A., Karbat, I., Tsoory, M., Fine, S., Iwanir, S., Reuveny, E., 2021. Reduced activity of GIRK1-containing heterotetramers is sufficient to affect neuronal functions, including synaptic plasticity and spatial learning and memory. J. Physiol. 599, 521–545.
Mysin, I., Shubina, L., 2022. From mechanisms to functions: the role of theta and gamma coherence in the intrahippocampal circuits. Hippocampus 32, 342–358.
Nava-Mesa, M.O., Jiménez-Díaz, L., Yajeya, J., Navarro-Lopez, J.D., 2013. Amyloid-β induces synaptic dysfunction through G protein-gated inwardly rectifying potassium channels in the fimbria-CA3 hippocampal synapse. Front. Cell. Neurosci. 7, 117.
Nuñez, A., Buño, W., 2021. The theta rhythm of the Hippocampus: from neuronal and circuit mechanisms to behavior. Front. Cell. Neurosci. 15, 649262.
Paxinos, G., Franklin, K.B.J., 2004. The Mouse Brain in Stereotaxic Coordinates. Elsevier Academic Press.
Pietersen, A.N., Lancaster, D.M., Patel, N., Hamilton, J.B., Vreugdenhil, M., 2009. Modulation of gamma oscillations by endogenous adenosine through A1 and A2A receptors in the mouse hippocampus. Neuropharmacology 56, 481–492.
Pravetoni, M., Wickman, K., 2008. Behavioral characterization of mice lacking GIRK/Kir3 channel subunits. Gene Brain Behav. 7, 523–531.
Radiske, A., Gonzalez, M.C., Conde-Ocazionez, S., Rossato, J.I., Köhler, C.A., Cammarota, M., 2020. Cross-frequency phase-amplitude coupling between hippocampal theta and gamma oscillations during recall destabilizes memory and renders it susceptible to reconsolidation disruption. J. Neurosci. 40, 6398–6408.
Reeves, R.H., Irving, N.G., Moran, T.H., Wohn, A., Kitt, C., Sisodia, S.S., Schmidt, C., Bronson, R.T., Davisson, M.T., 1995. A mouse model for Down syndrome exhibits learning and behaviour deficits. Nat. Genet. 11, 177–184.
Sago, H., Carlson, E.J., Smith, D.J., Kilbridge, J., Rubin, E.M., Mobley, W.C., Epstein, C. J., Huang, T.T., 1998. Ts1Cje, a partial trisomy 16 mouse model for Down syndrome, exhibits learning and behavioral abnormalities. Proc. Natl. Acad. Sci. U. S. A. 95, 6256–6261.
Salimpour, Y., Anderson, W.S., 2019. Cross-frequency coupling based neuromodulation for treating neurological disorders. Front. Neurosci. 13.
Sánchez-Rodríguez, I., Djebari, S., Temprano-Carazo, S., Vega-Avelaira, D., Jiménez-Herrera, R., Iborra-Lázaro, G., Yajeya, J., Jiménez-Díaz, L., Navarro-López, J.D., 2020. Hippocampal long-term synaptic depression and memory deficits induced in early amyloidopathy are prevented by enhancing G-protein-gated inwardly rectifying potassium channel activity. J. Neurochem. 153, 362–376.
Sánchez-Rodríguez, I., Gruart, A., Delgado-García, J.M., Jiménez-Díaz, L., Navarro-López, J.D., 2019. Role of GirK channels in long-term potentiation of synaptic inhibition in an in vivo mouse model of early amyloid-β pathology. Int. J. Mol. Sci. 20.
Sánchez-Rodríguez, I., Temprano-Carazo, S., Nájera, A., Djebari, S., Yajeya, J., Gruart, A., Delgado-García, J.M., Jiménez-Díaz, L., Navarro-López, J.D., 2017. Activation of G-protein-gated inwardly rectifying potassium (Kir3/GirK) channels rescues hippocampal functions in a mouse model of early amyloid-β pathology. Sci. Rep. 7, 14658.
Sun, Q.Q., Huguenard, J.R., Prince, D.A., 2002. Somatostatin inhibits thalamic network oscillations in vitro: actions on the GABAergic neurons of the reticular nucleus. J. Neurosci. 22, 5374–5386.
Tamura, M., Spellman, T.J., Rosen, A.M., Gogos, J.A., Gordon, J.A., 2017. Hippocampal-prefrontal theta-gamma coupling during performance of a spatial working memory task. Nat. Commun. 8, 2182.
Tatard-Leitman, V.M., Jutzeler, C.R., Suh, J., Saunders, J.A., Billingslea, E.N., Morita, S., White, R., Featherstone, R.E., Ray, R., Ortinski, P.I., Banerjee, A., Gandal, M.J., Lin, R., Alexandrescu, A., Liang, Y., Gur, R.E., Borgmann-Winter, K.E., Carlson, G.C., Hahn, C.G., Siegel, S.J., 2015. Pyramidal cell selective ablation of N-methyl-D-aspartate receptor 1 causes increase in cellular and network excitability. Biol. Psychiatr. 77, 556–568.
Tort, A.B., Komorowski, R.W., Manns, J.R., Kopell, N.J., Eichenbaum, H., 2009. Theta-gamma coupling increases during the learning of item-context associations. Proc. Natl. Acad. Sci. U. S. A. 106, 20942–20947.
Trompoukis, G., Rigas, P., Leontiadis, L.J., Papatheodoropoulos, C., 2020. I(h), GIRK, and KCNQ/Kv7 channels differently modulate sharp wave - ripples in the dorsal and ventral hippocampus. Mol. Cell. Neurosci. 107, 103531.
ul Haq, R., Anderson, M.L., Hollnagel, J.O., Worschech, F., Sherkheli, M.A., Behrens, C. J., Heinemann, U., 2016. Serotonin dependent masking of hippocampal sharp wave ripples. Neuropharmacology 101, 188–203.
Victoria, N.C., Marron Fernandez de Velasco, E., Ostrovskaya, O., Metzger, S., Xia, Z., Kotecki, L., Benneyworth, M.A., Zink, A.N., Martemyanov, K.A., Wickman, K., 2016. G protein-gated K(+) channel ablation in forebrain pyramidal neurons selectively impairs fear learning. Biol. Psychiatr. 80, 796–806.