MULTI ELECTRODE ARRAY

Synaptic transmission and plasticity in hippocampus

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MAIN SUMMARY

- ❑ SC – CA1 SYNAPSES
- ❑ PERFORANT PATHWAY - DENTATE GYRUS
- ❑ MOSSY FIBERS – CA3
- ❑ TEMPORO AMMONIC PATHWAY

SC-CA1 SYNAPSES

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SUMMARY - SC-CA1 synapses

Main summary

SC-CA1 synapses

- Synaptic Transmission
- Short-term plasticity
- Long-term plasticity
- Paired-pulse inhibition

RESULTS

- AMPA receptors – Perampanel
- NMDA receptors – D-AP5 / MK-801 / Memantine / Magnesium / D-serine / DAAOi / Ketamine / Amantadine
- GABA receptors – Diazepam / Clonazepam / Picrotoxin / CGP 55845 / Gabazine / DMCM / L655,708
- mGluR I – DHPG / CHPG
- Muscarinic receptors – Oxotremorine / Pirenzepine / AF-DX-116 / Topicamide / VU10010
- Synaptic vesicle protein 2A – Levitiracetam
- Enzymes & cytokines – Rolipram / Interleukin 1β / VX-745 / DYRK1a inhibitor
- mTORC – NV-5138
- Opioids receptors – Fentanyl
- Somatostatin receptors – L-803,087
- L-glutamate uptake – 7-chlorokynurenic acid
- Amyloid-β peptides – Edonerpic / Amyloid-β
- Model of impaired plasticity – Memantine / D-serine

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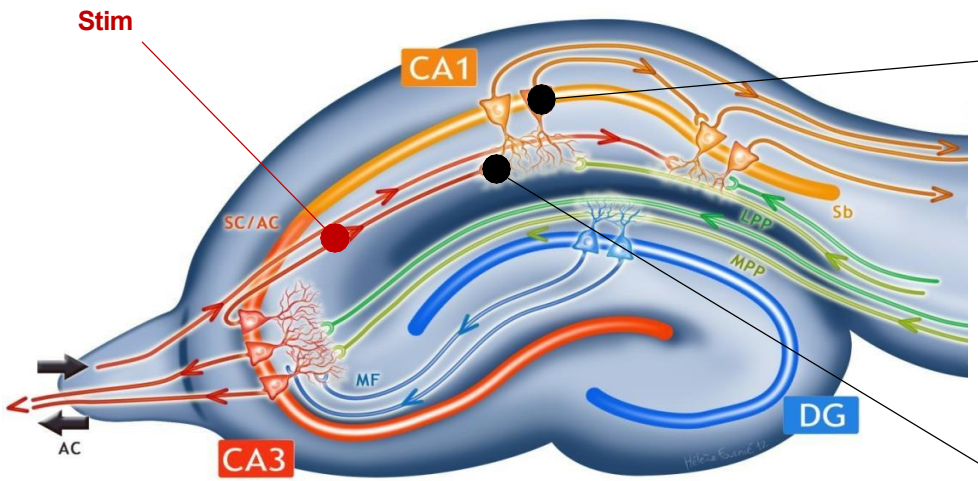
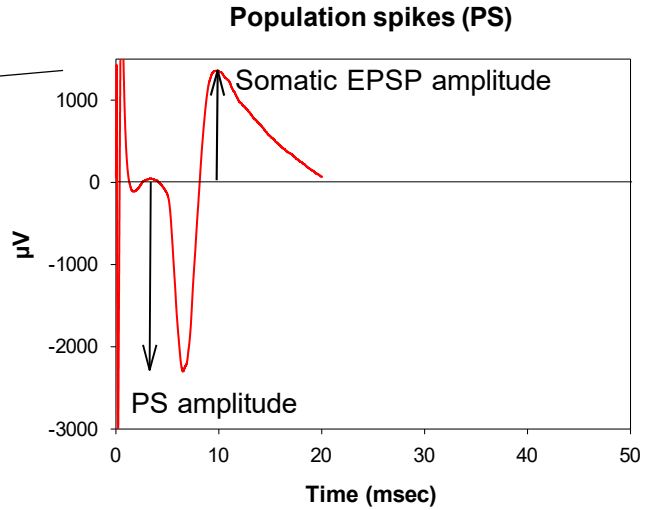
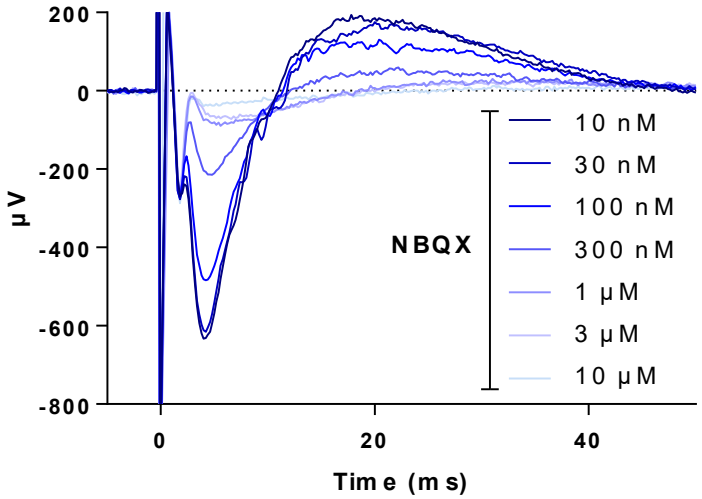
SC-CA1 SYNAPSES

Synaptic transmission

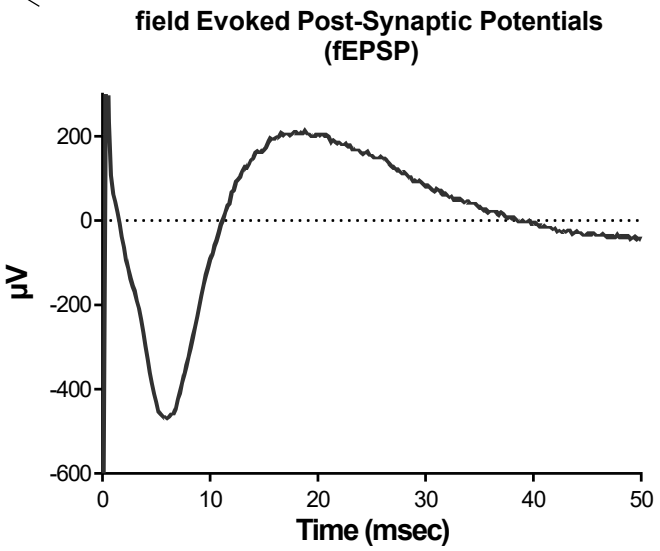
Main summary
SC-CA1 summary







- **Evoked-responses (excitatory post-synaptic potentials, EPSP) reflect the synaptic activity and population spikes (PS) reflects the firing induced by the synaptic activity. Both can be recorded in brain slices with Multi-Electrode Arrays (MEA).**
- **Long-Term Potentiation (LTP) or Long-Term Depression (LTD) can be recorded in the CA1 region of hippocampal slices, and these mechanisms are known to be NMDA-receptors dependent.**
- **Excitatory synaptic transmission and plasticity is continuously balanced by mechanisms of inhibitory synaptic transmission.**



The synaptic transmission is related to the AMPA-kainate ions channels. NBQX dose-dependently decreased the amplitude of fEPSP.

Glutamatergic synaptic transmission within the hippocampus is modulated by a wide panel of enzymes, ions channels and receptors (Ca2+ channels, 5-HT, opioid, $GABA_A$ receptors,, etc – non exhaustive list).

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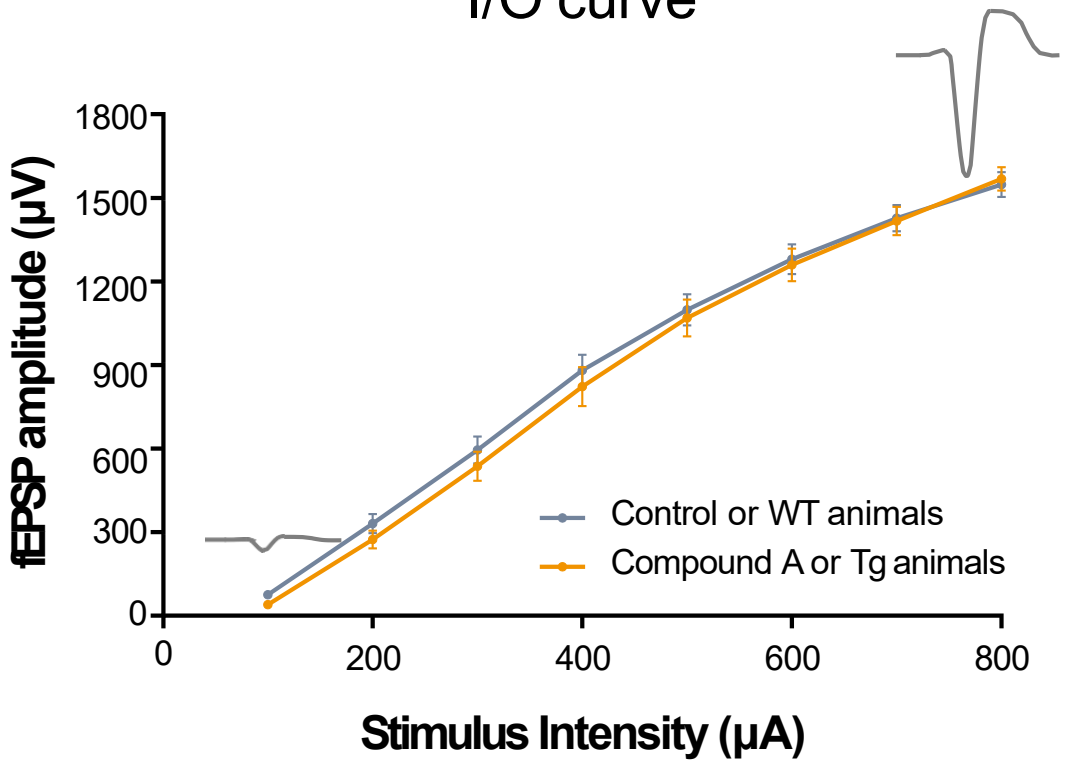
SC-CA1 SYNAPSES

Synaptic transmission

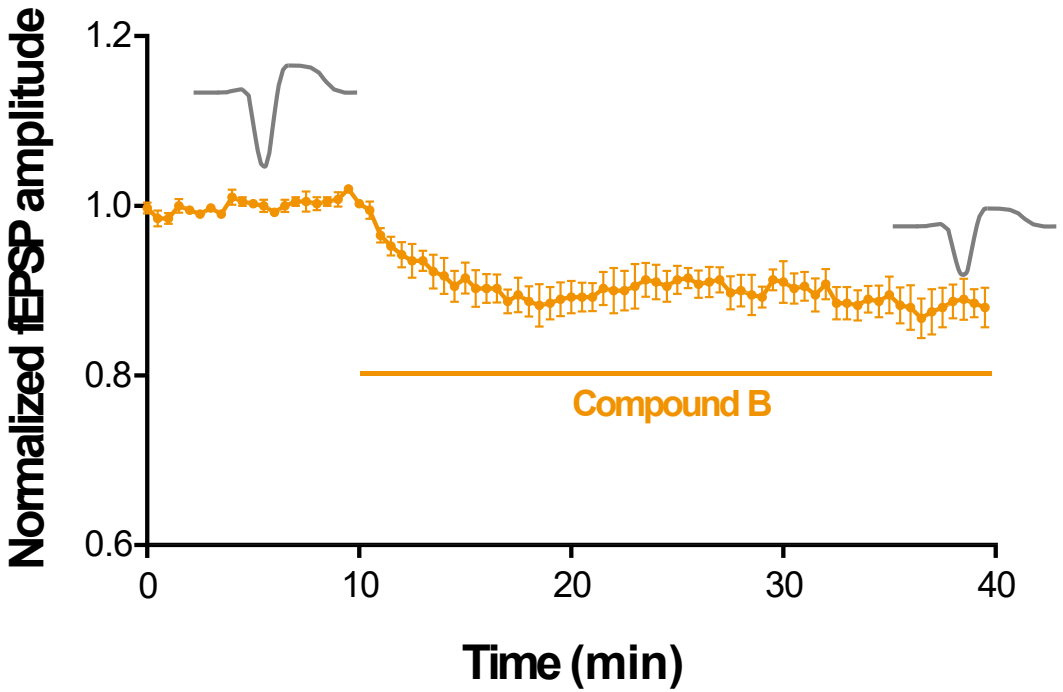
Main summary
SC-CA1 summary

I/O curve



Input/Output (I/O) curve (unpaired comparisons): stimulation intensities between 100 and 800 µA, by 100 µA steps.

Basal synaptic transmission



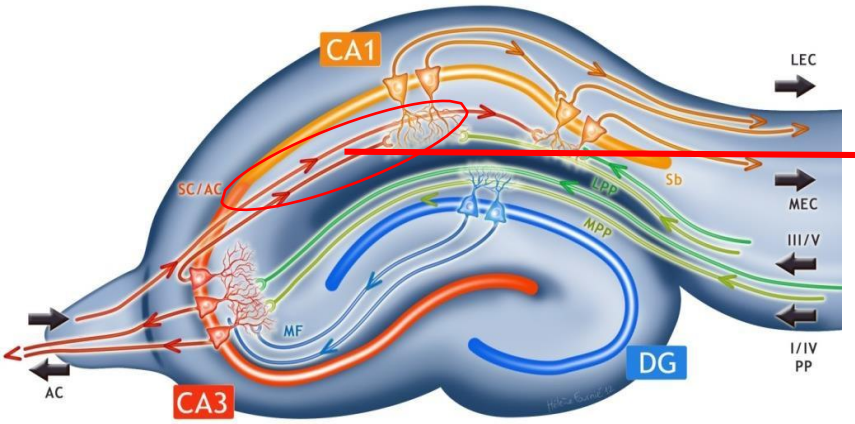
Basal synaptic transmission (paired comparisons): The stimulus intensity is set to 40% I_{max} at 0.033Hz. NBQX is applied systematically at the en dof experiment to subtract the Background noise.

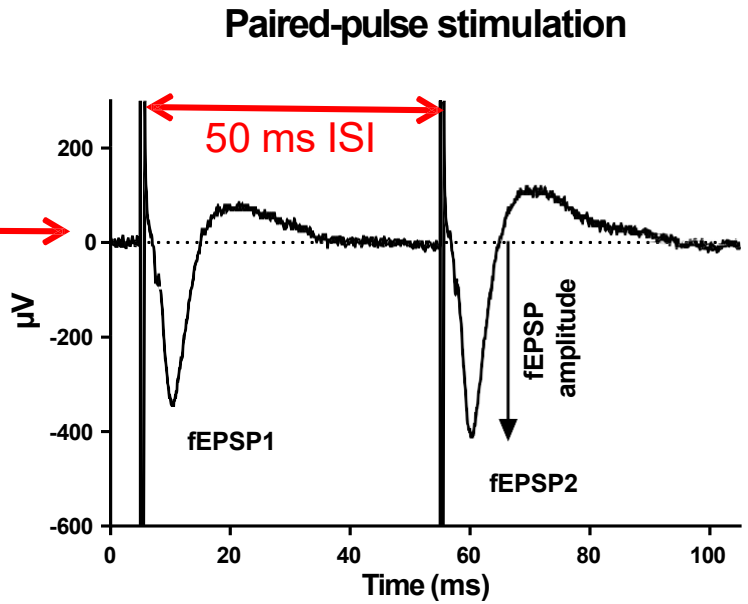
SC-CA1 SYNAPSES

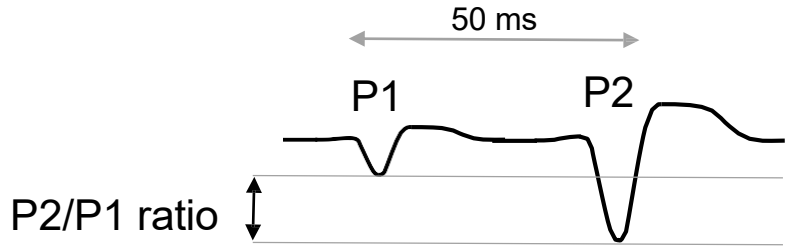
Short-term plasticity

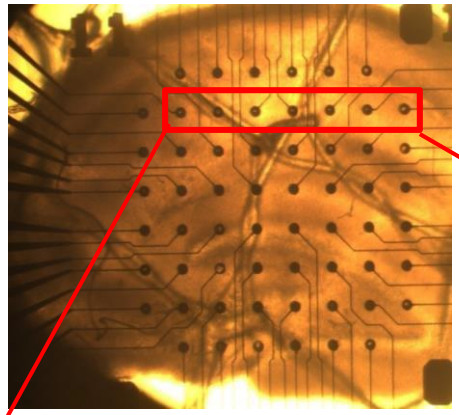
Main summary

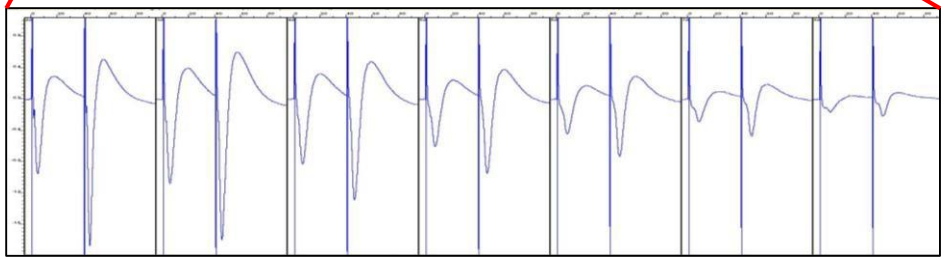
SC-CA1 summary











- Paired-Pulse Facilitation (PPF), is a protocol in which postsynaptic potentials (fEPSP) evoked by a rapid double stimulation are increased in magnitude (second vs. first fEPSP). In this context, PPF is a well known form of short-term synaptic plasticity.
- When an action potential arrives at the presynaptic terminal, it triggers calcium entry. An elevated concentration of calcium enables synaptic vesicles to fuse to the presynaptic membrane and release their contents. The amount of neurotransmitter released is a function of the amount of calcium influx. PPF results from a build-up of calcium within the presynaptic terminal when the two action potentials are triggered rapidly in succession. The second fEPSP is of a higher amplitude since more calcium is present at the presynaptic terminal when the second action potential arrives.
- Importantly, the mechanisms underlying PPF are exclusively pre-synaptic. Thus, when a compound modifies the paired-pulse ratio, it is a clear sign that it acts at the pre-synaptic level.

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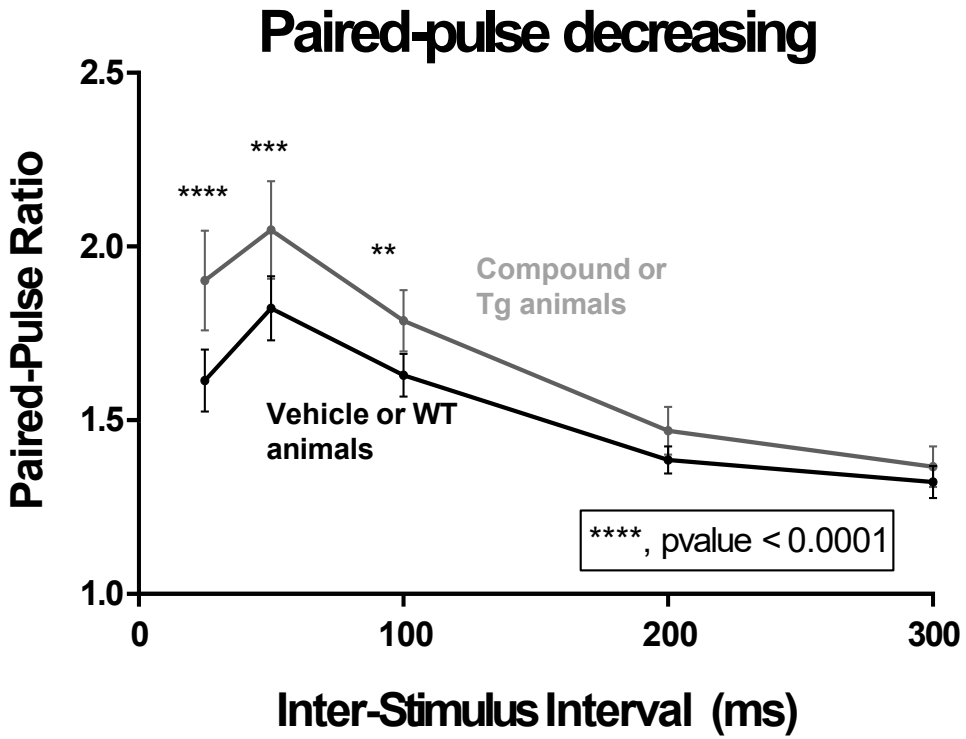
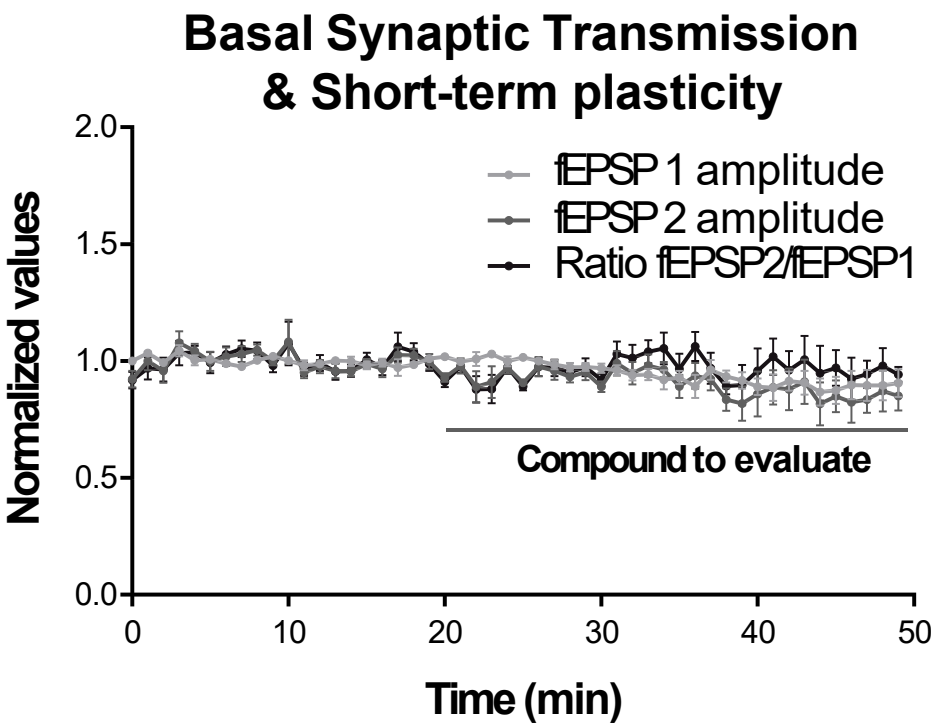
SC-CA1 SYNAPSES

Short-term plasticity

Main summary
SC-CA1 summary





Paired-Pulse Facilitation (PPF) (unpaired comparisons): Two pulses with a decreasing inter-stimulus interval (e.g. 300 ms, 200 ms, 100 ms, 50 ms, 25 ms) are applied at Schaeffer collaterals. Both stimuli are of equal intensity and settled at 40 % of the maximal amplitude responses.

Paired stimulation (50 ms interval) applied every minute at the CA3 border of the Schaffer collateral (paired comparisons). Allow a Dynamic monitoring of the **basal synaptic transmission (fEPSP1 as a function of time)** and the **short-term plasticity (fEPSP2 amplitude and fEPSP2/1 ratio as a function of time).**

SC-CA1 SYNAPSES

Long-term plasticity

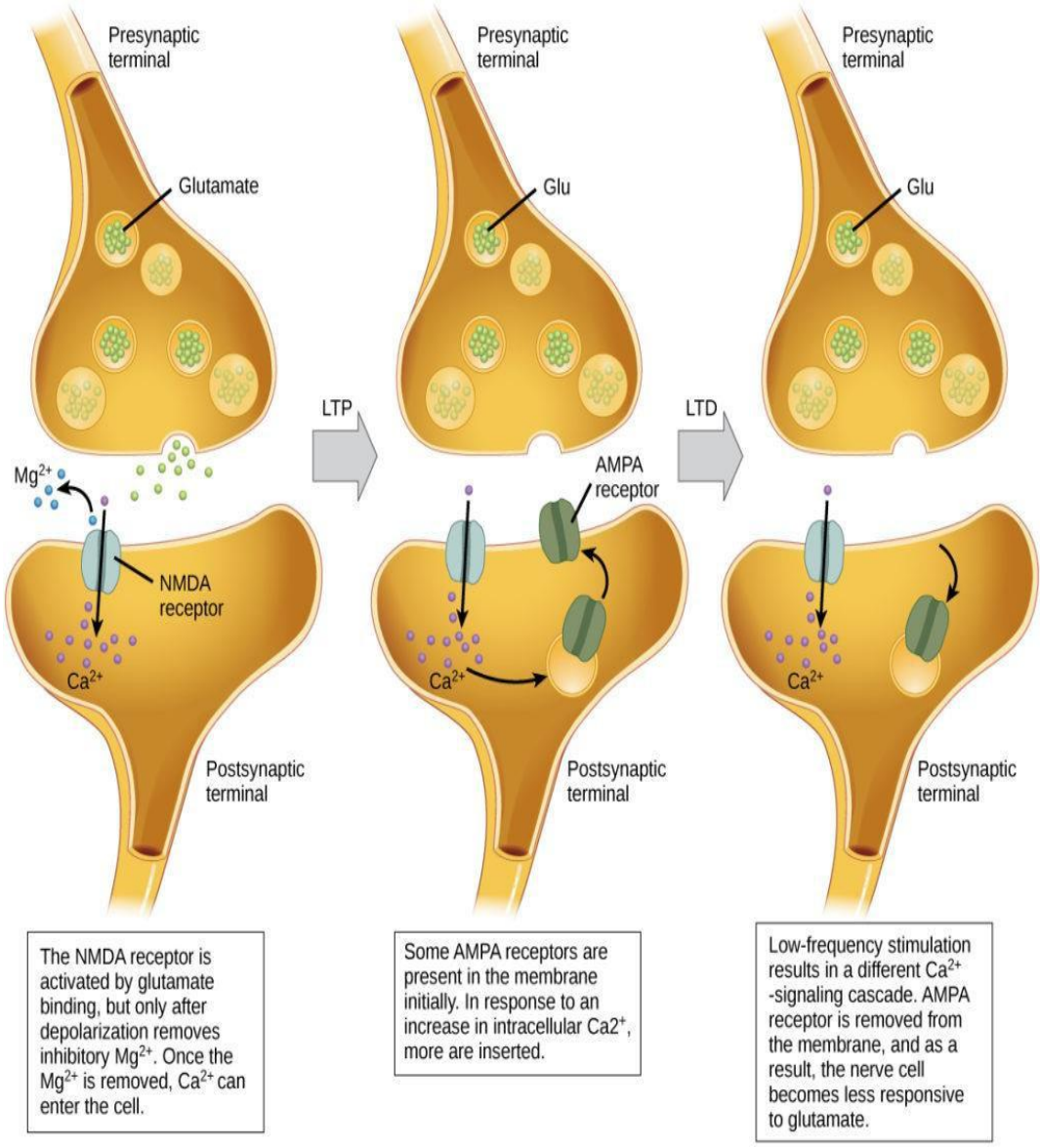
Main summary

SC-CA1 summary

Mechanisms of synaptic plasticity are fundamental for basic learning tasks and higher cognitive functions. Indeed, molecular, cellular and physiological investigations have provided compelling evidence that synaptic plasticity is mandatory for learning and memory storage processes, from primary invertebrate organisms up to humans. Synaptic plasticity is the ability of synapses to strengthen or weaken their “weight” over time, in response to neuronal input that encodes signals in frequency modulation.

Two main synaptic plasticity mechanisms have been described: Long-Term Potentiation (LTP) and Long-Term Depression (LTD). Briefly, LTP is triggered by a high-frequency stimulation protocol whereas LTD is induced by a low-frequency stimulation protocol. In mammals the hippocampus plays a central role in memory tasks (notably declarative memory and spatio-temporal memory). The hippocampus is often used as a “native network” substrate for studying synaptic plasticity mechanisms either *in vitro* or *in vivo*.

- **Both LTP and LTD depend on NMDA receptor activation and intracellular calcium mobilization. Compounds that are able to modulate NMDA receptor function may interfere with memory/cognition processes.**
- **The role of LTP/LTD in learning/cognitive tasks has been amply illustrated. Animals treated with NMDA receptors antagonists display severely impaired performance in behavioral assays for learning/spatial recognition (Morris water maze, for instance).**
- **Pharmacological or genetic manipulations that interfere with LTP in vitro often affect learning or memory in vivo (ex: Scopolamine or MK-801 treated animals). In addition, LTP is impaired in rodents genetic model of neurodegenerative diseases (Alzheimer, Huntington, ….) and in aged animals.**
- **Conversely, manipulations that enhance LTP *in vitro* may be pro-cognitive *in vivo*.**

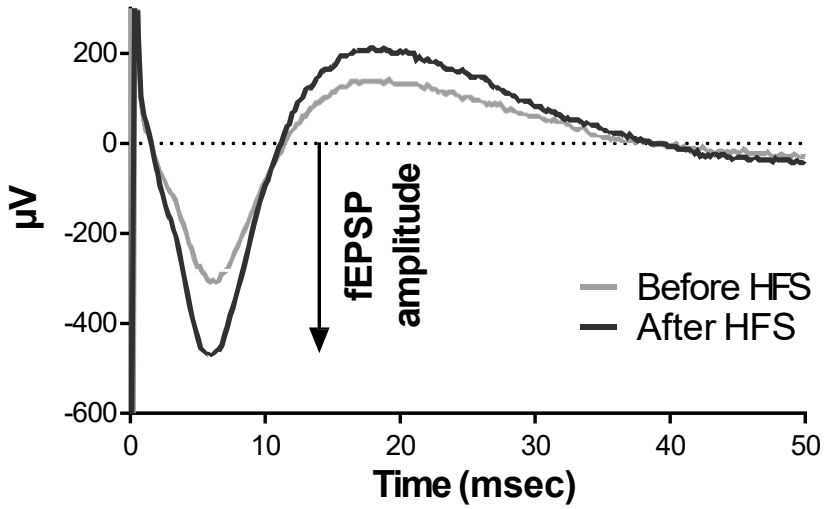


SC-CA1 SYNAPSES

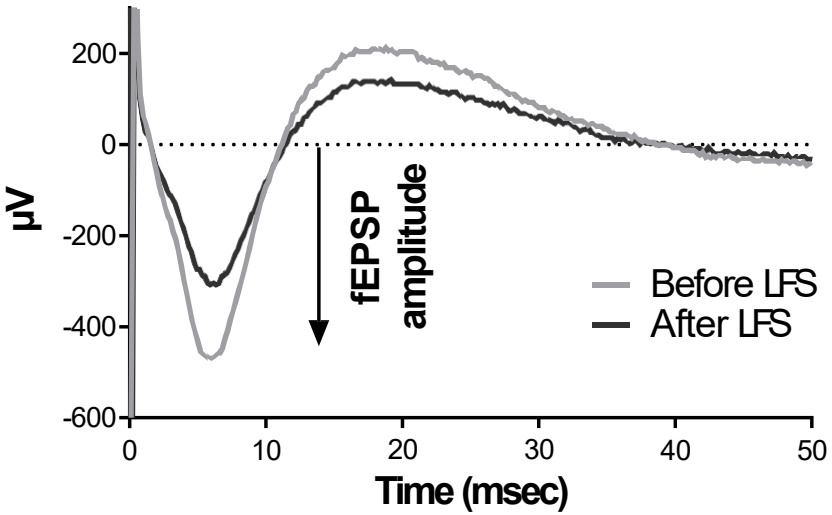
Long-term plasticity

Main summary
SC-CA1 summary

Long-term potentiation



Long-term depression

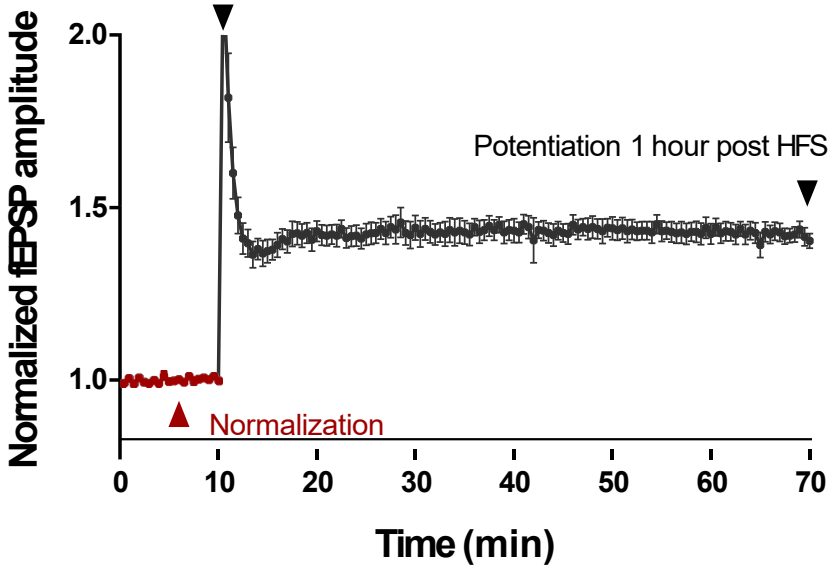


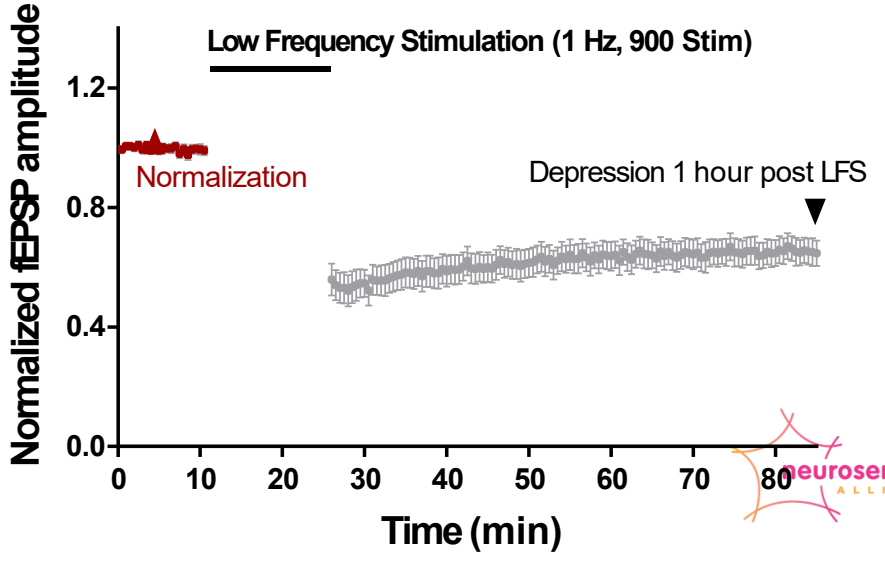
30 seconds bins

Normalization
(to the baseline before HFS / LFS)

Background noise suppression
(subtraction of the fEPSP amplitude recorded during the NBQX period)

High Frequency Stimulation



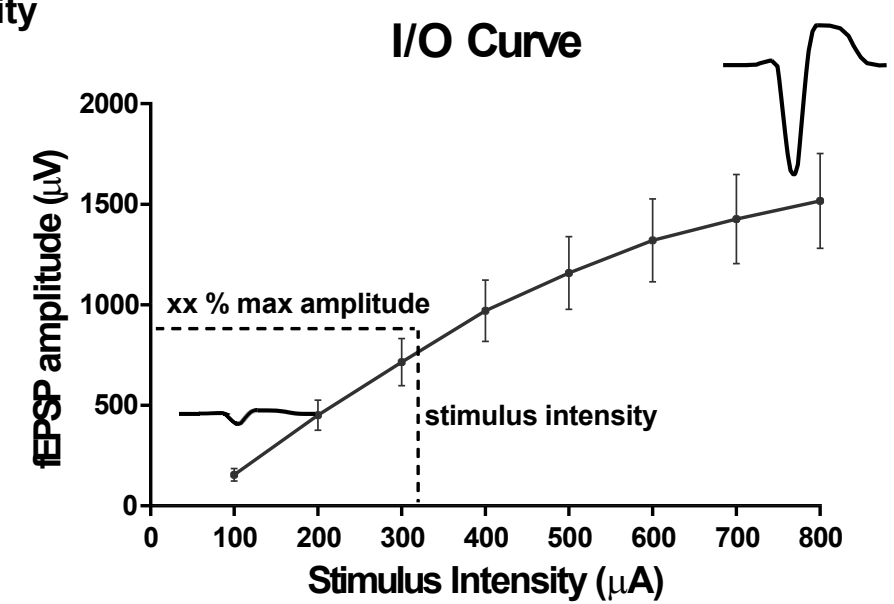


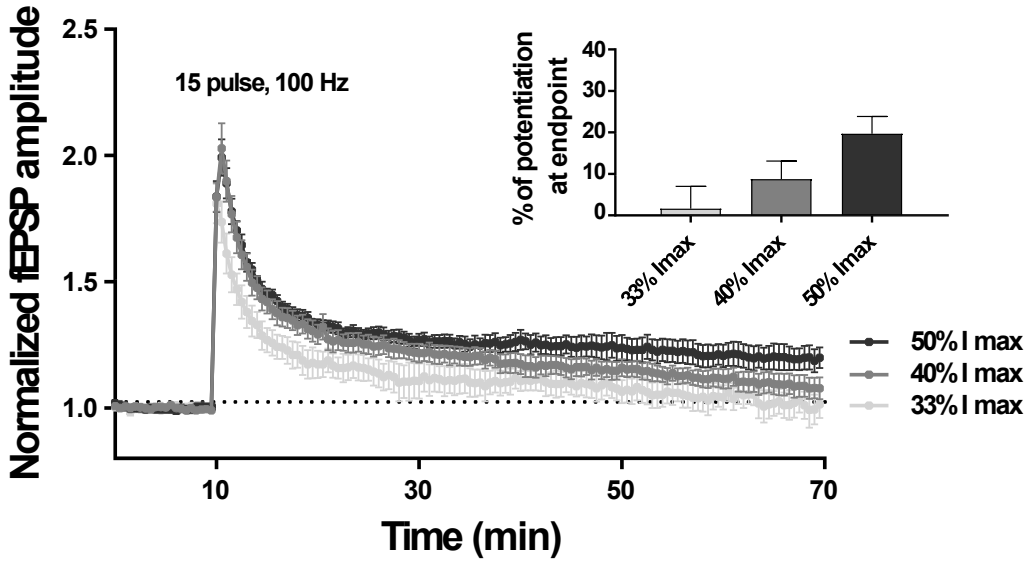
SC-CA1 SYNAPSES

Long-term plasticity- Stimulation paradigms

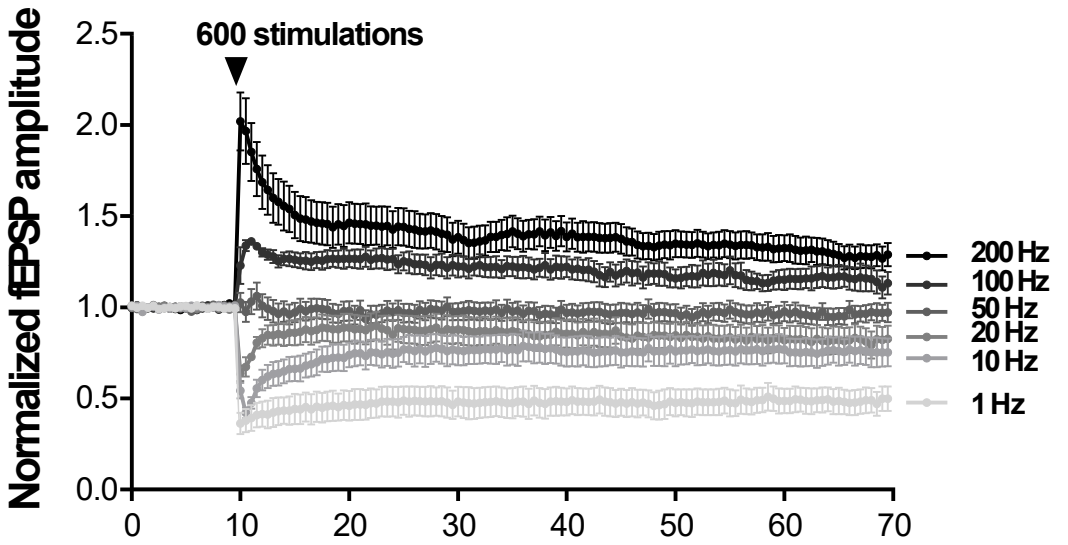
Main summary
SC-CA1 summary

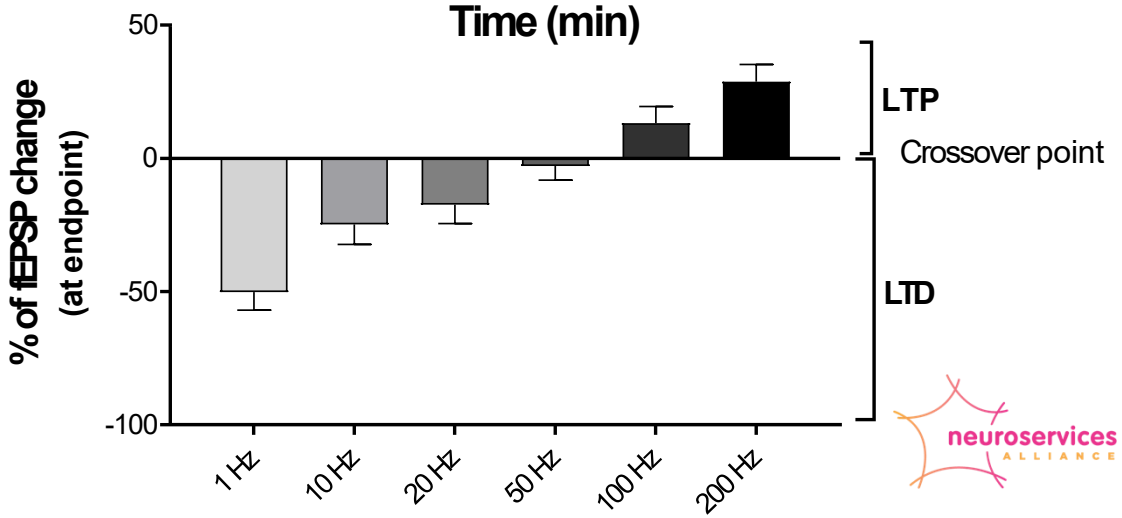
Intensity





Frequency





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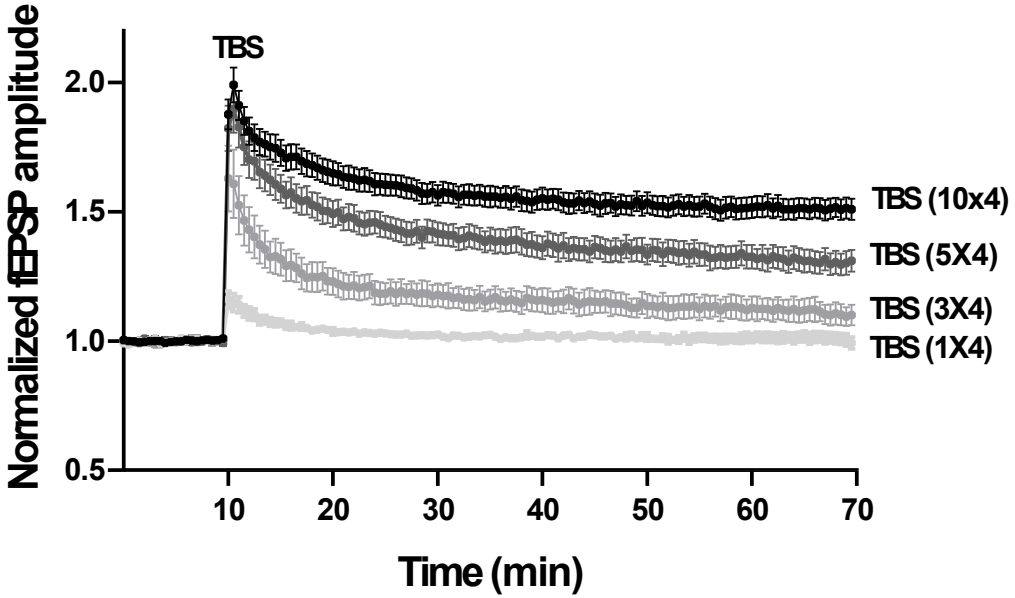
SC-CA1 SYNAPSES

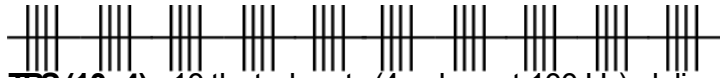
Long-term plasticity- Stimulation paradigms

Main summary
SC-CA1 summary

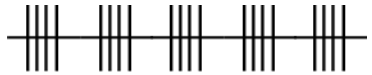
Pattern

Theta Burst Stimulation (TBS)

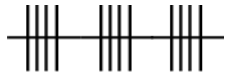




TBS (10x4) : 10 theta-bursts (4 pulses at 100 Hz), delivered at 5 Hz (200 ms interval)



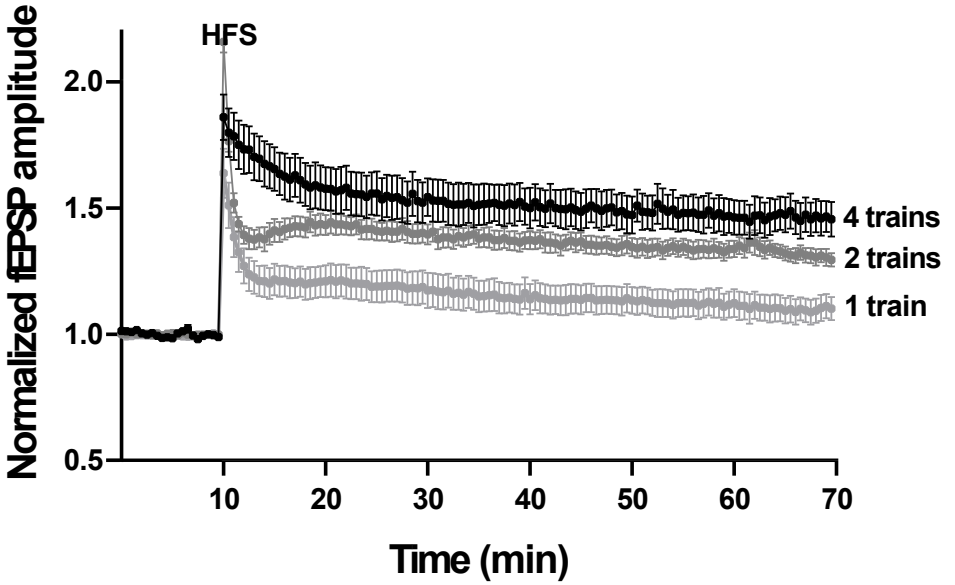
TBS (5x4) : 5 theta-bursts (4 pulses at 100 Hz), delivered at 5 Hz (200 ms interval)

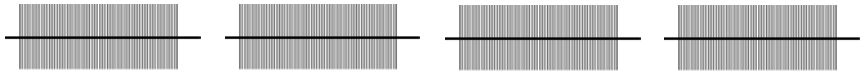


TBS (3x4) : 3 theta-bursts (4 pulses at 100 Hz), delivered at 5 Hz (200 ms interval)

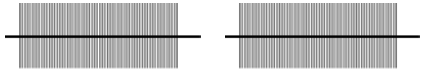
TBS (1x4) : Single theta-burst (4 pulses at 100 Hz)

High Frequency Stimulation (HFS)





4 trains : 4 trains (pulses applied at 100 Hz for 1 second), delivered with 20 seconds interval



2 trains : 2 trains (pulses applied at 100 Hz for 1 second), delivered with 20 seconds interval

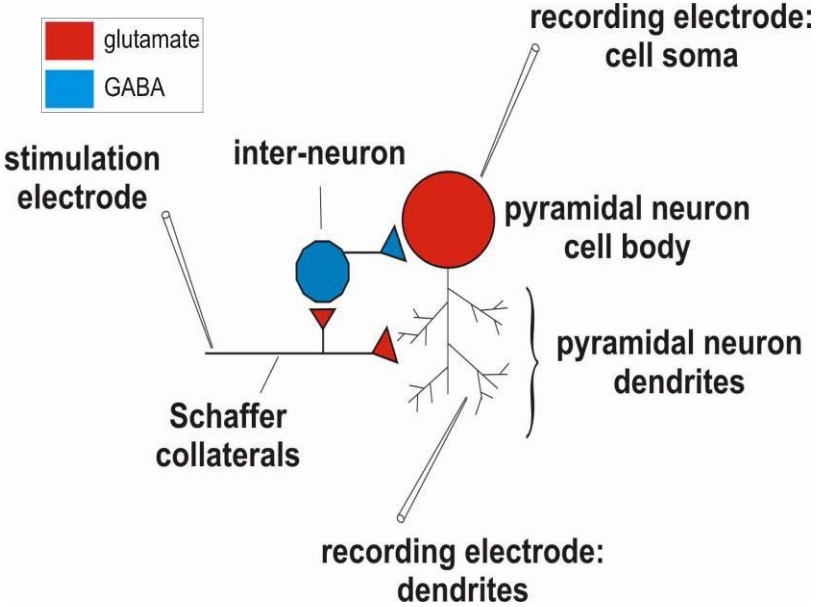
1 train : Single train (pulses applied at 100 Hz for 1 second)

SC-CA1 SYNAPSES

Paired-pulse inhibition

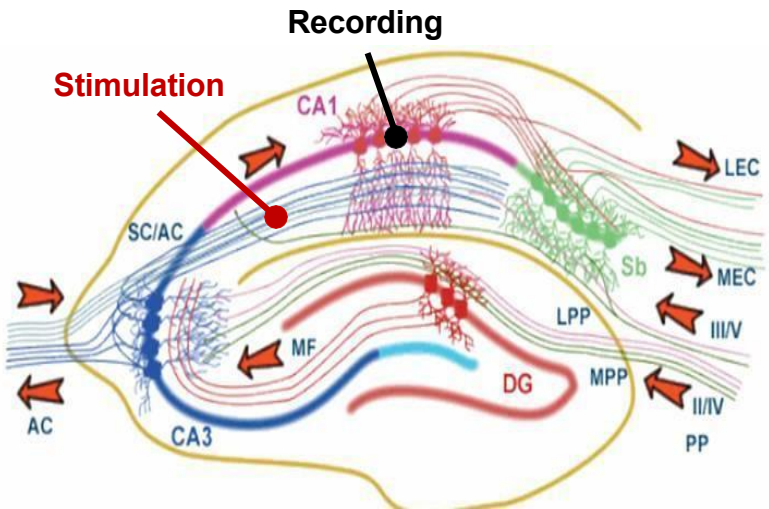
Main summary

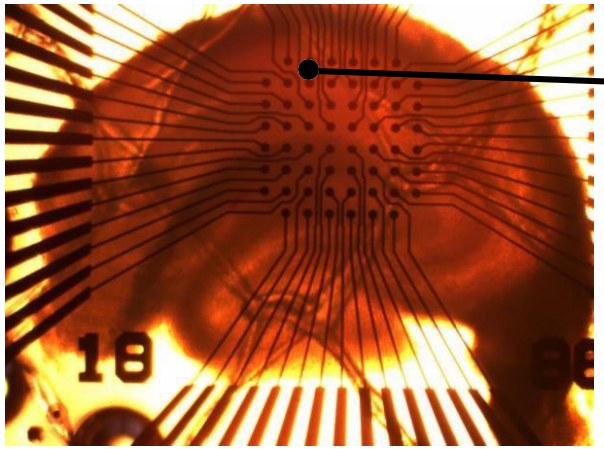
SC-CA1 summary

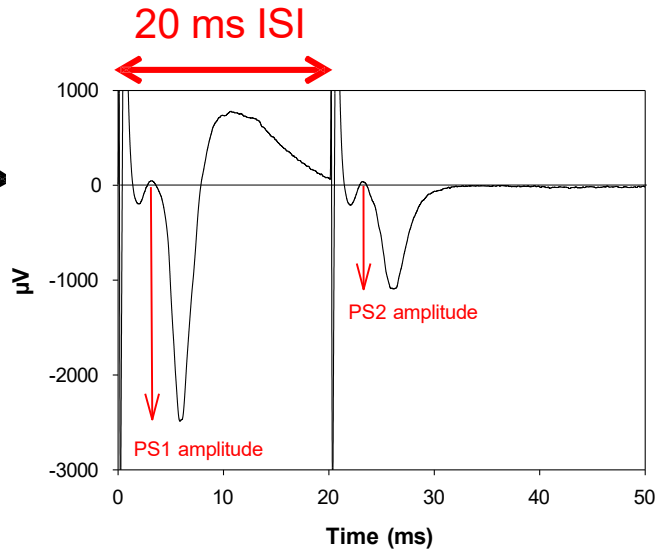


Nearby a detailed scheme of the neuronal network and connections between Schaeffer's collaterals is presented in the graph nearby Note that axons coming from pyramidal neurons of the CA3 region (Schaeffer's collaterals) make synapses on both dendrites of large pyramidal neurons and on small inhibitory interneurons. The paired-pulse protocol allows to reveal the inhibitory component of this network since inhibition related to GABAergic interneurons activation is time-shifted in comparison with direct transmission at dendrites of pyramidal CA1 neurons. There is a two step chemical synapse for inhibition whereas only a one step chemical synapse is involved for direct excitatory transmission.

The Paired-pulse inhibition (PPI) protocol, consisting in two stimuli applied at 20 ms intervals at SC, reveals GABAergic-mediated inhibition of synaptic transmission. The Population Spikes (PS) are recorded from the Stratum Pyramidale.The PS amplitude is strongly decreased for the second evoked response when compared to the first one. The monitoring of the ratio peak 2/peak 1 reveals the effect of compounds at GABAA receptors.





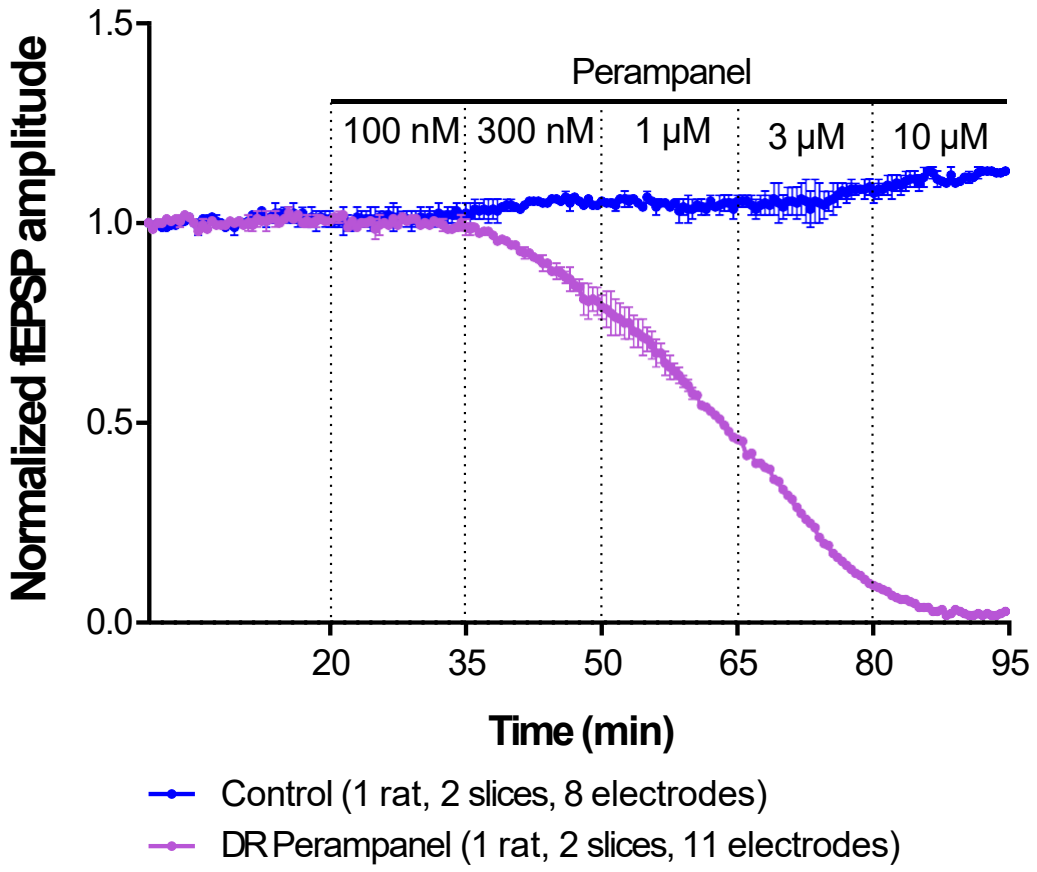


RESULTS

AMPA receptors

Main summary
SC-CA1 summary

Perampanel



Dose-dependent inhibition of fEPSPs by Perampanel – AMPA antagonist receptors

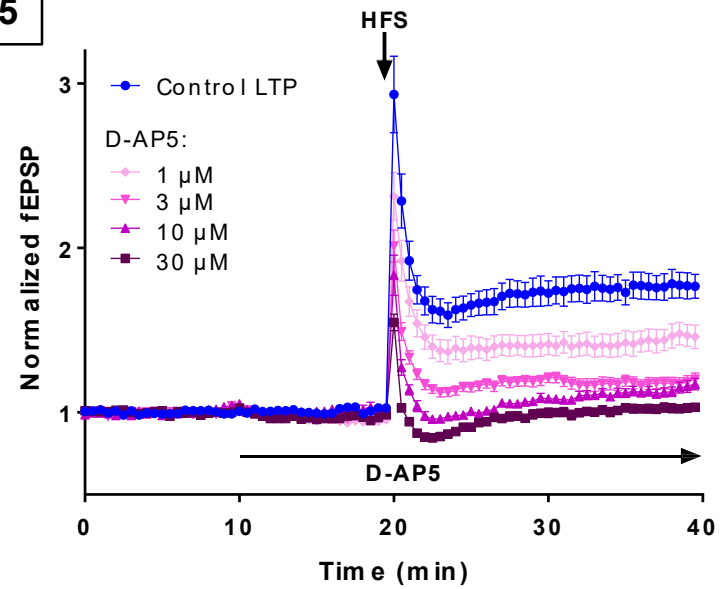
RESULTS

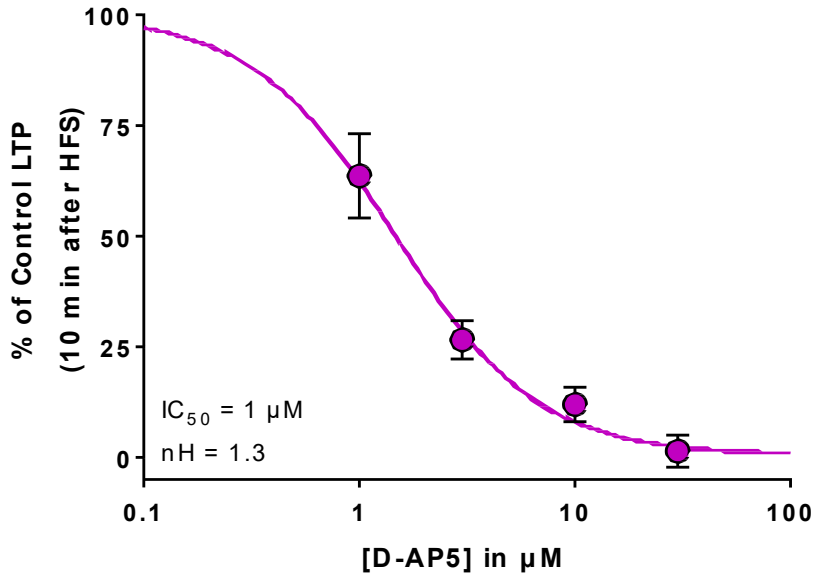
NMDA receptors (1/7)

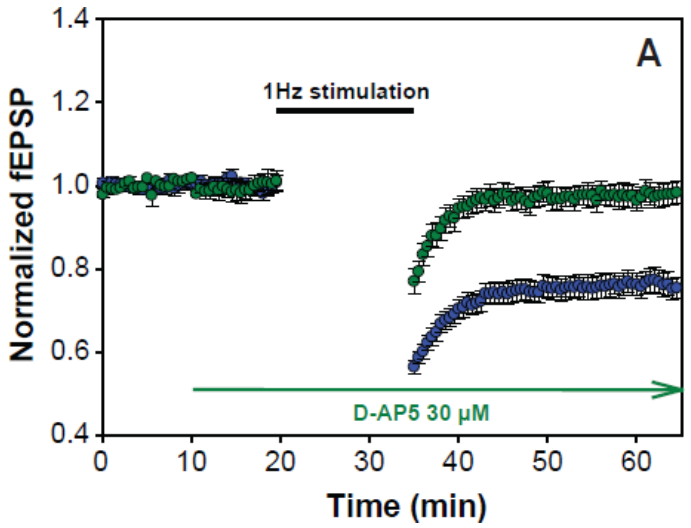
Main summary

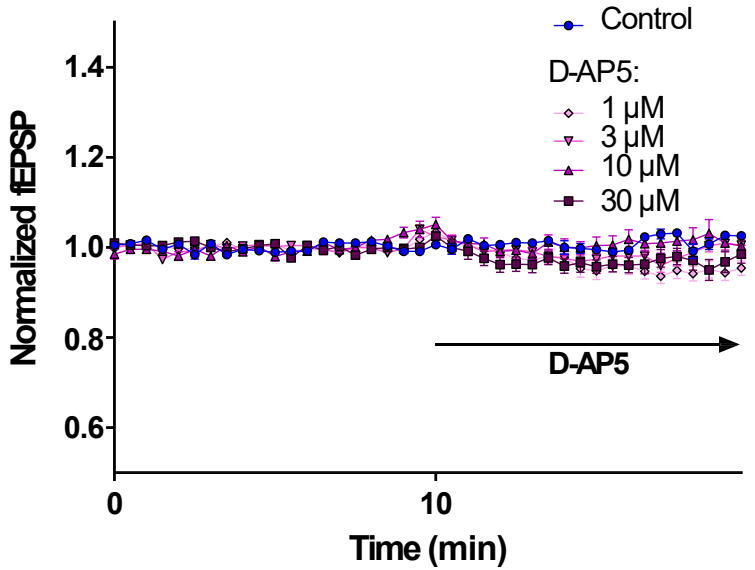
SC-CA1 summary

D-AP5









- **Dose-dependent inhibition of LTP and LTD blockade by the competitive NMDA receptors antagonist D-AP5.**
- D-AP5 did not modify the AMPA-mediated fEPSP

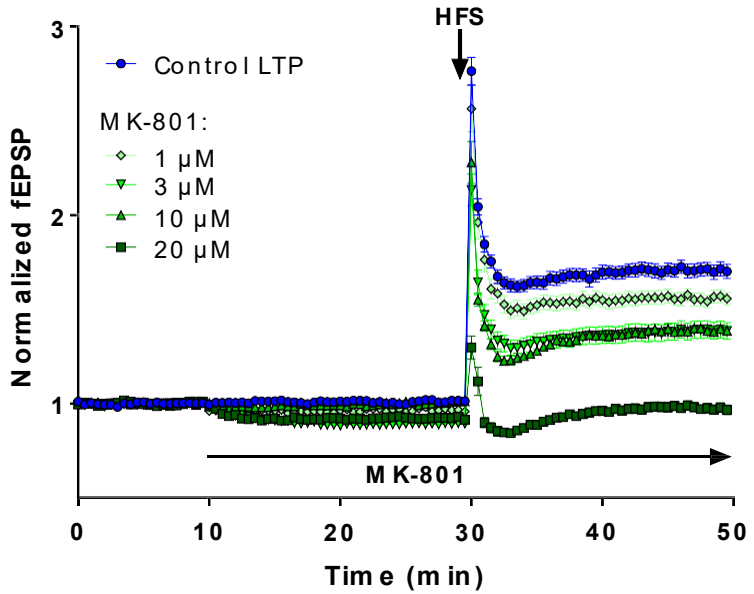
RESULTS

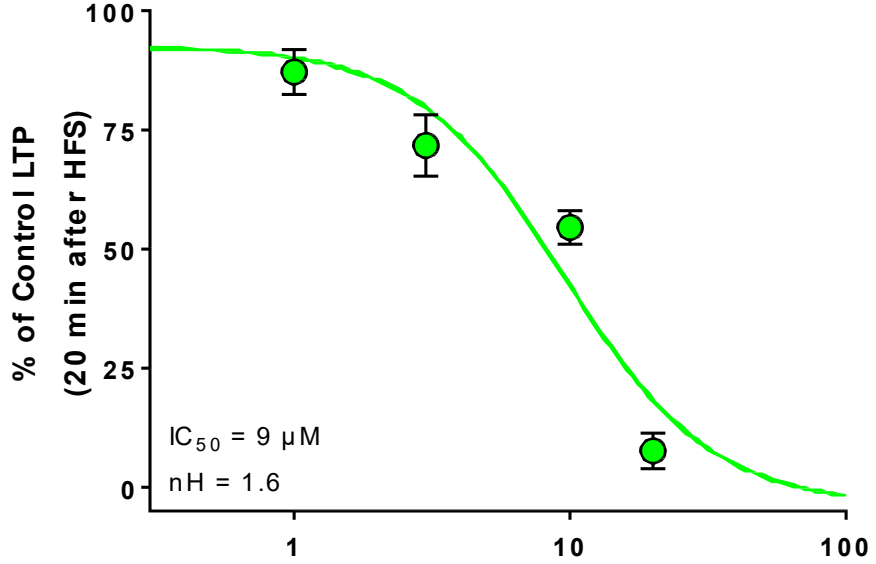
NMDA receptors (2/7)

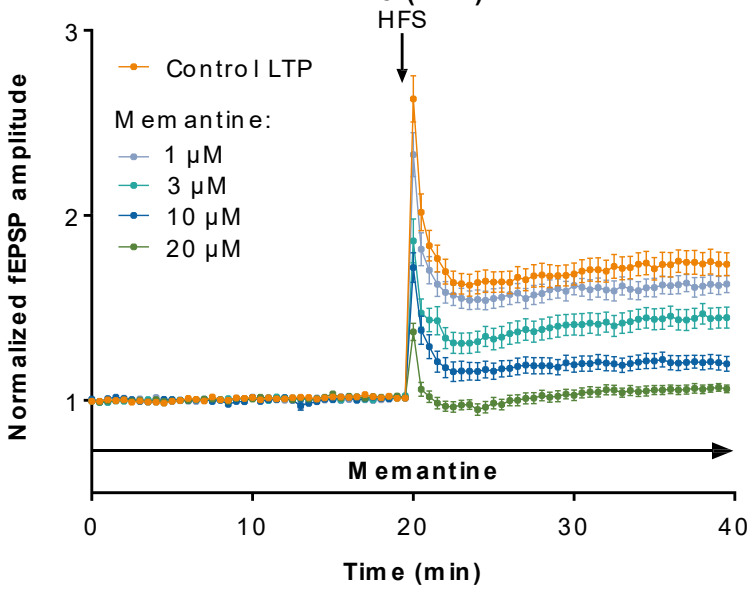
Main summary

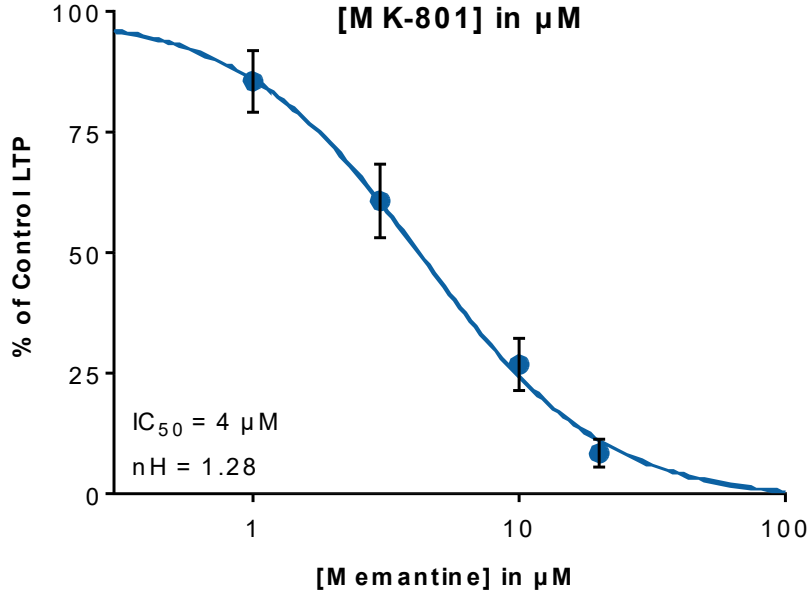
SC-CA1 summary

MK-801, Memantine









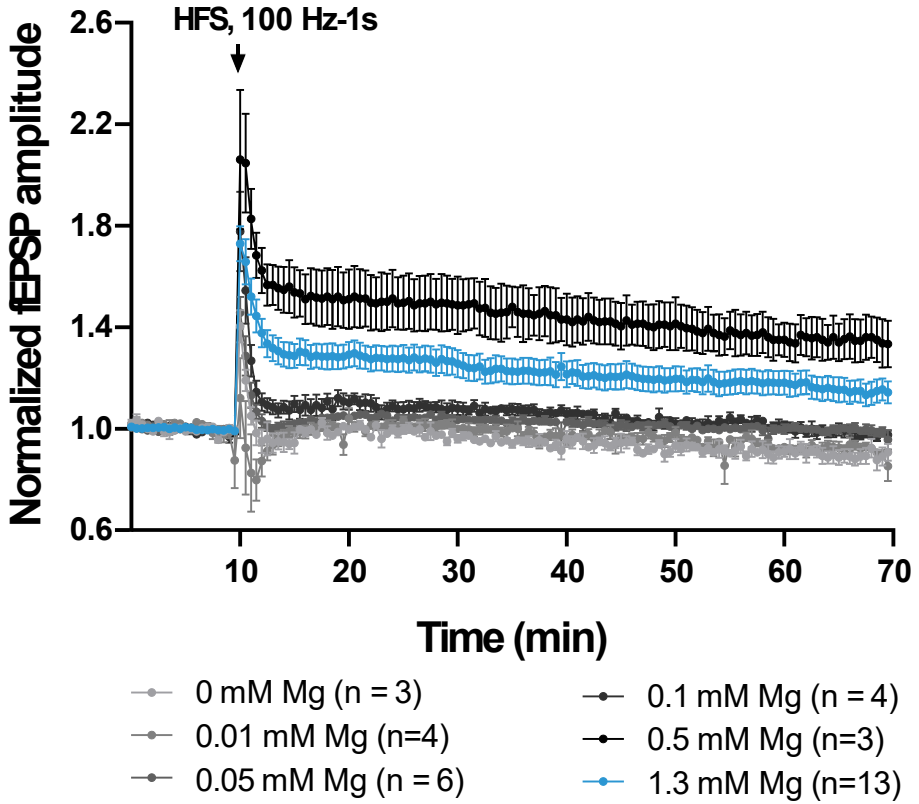
- **Dose-dependent inhibition of LTP by the non-competitive NMDA receptors antagonists MK-801, and memantine.**

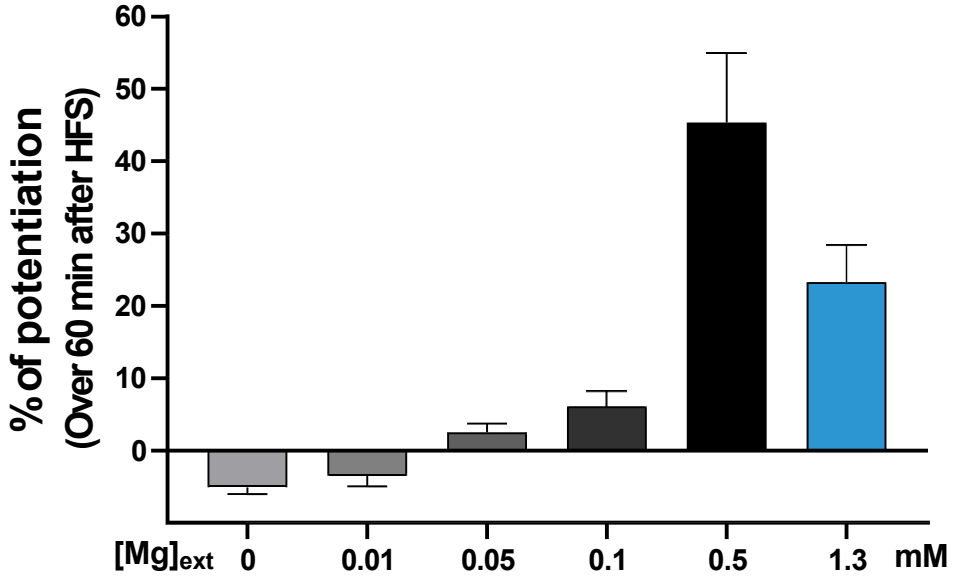
RESULTS

NMDA receptors (3/7)

Main summary
SC-CA1 summary

Magnesium





- **0.5 mM magnesium concentration enhanced the long-term potentiation, the potentiation was reduced for concentrations of magnesium lower than 0.1 mM.**

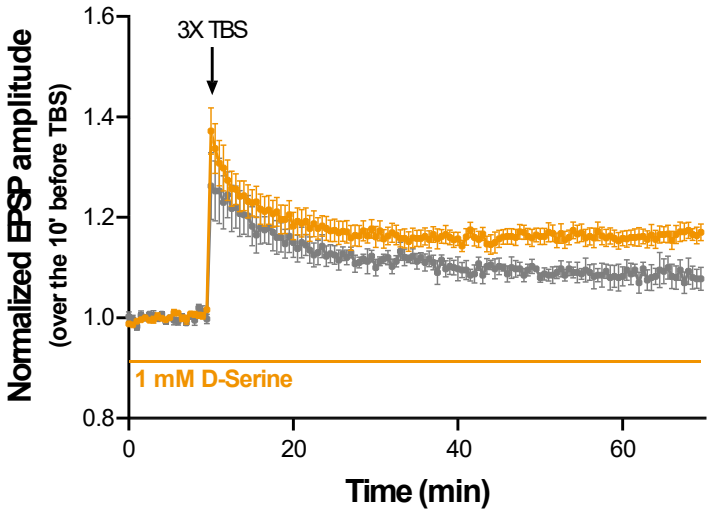
RESULTS

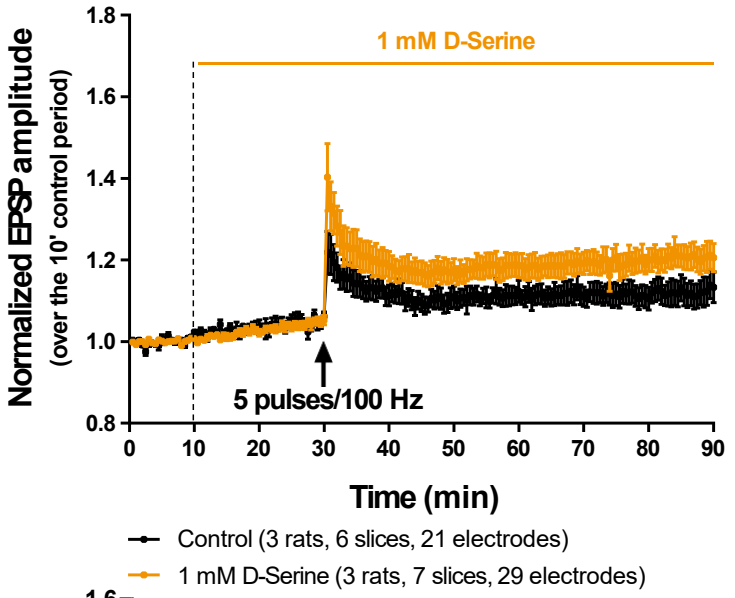
NMDA receptors (4/7)

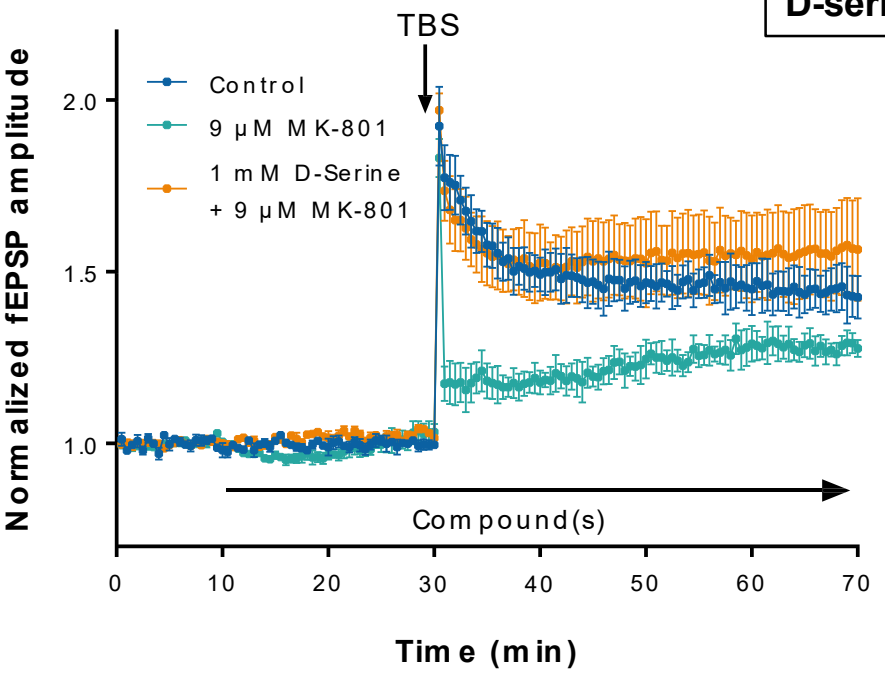
Main summary

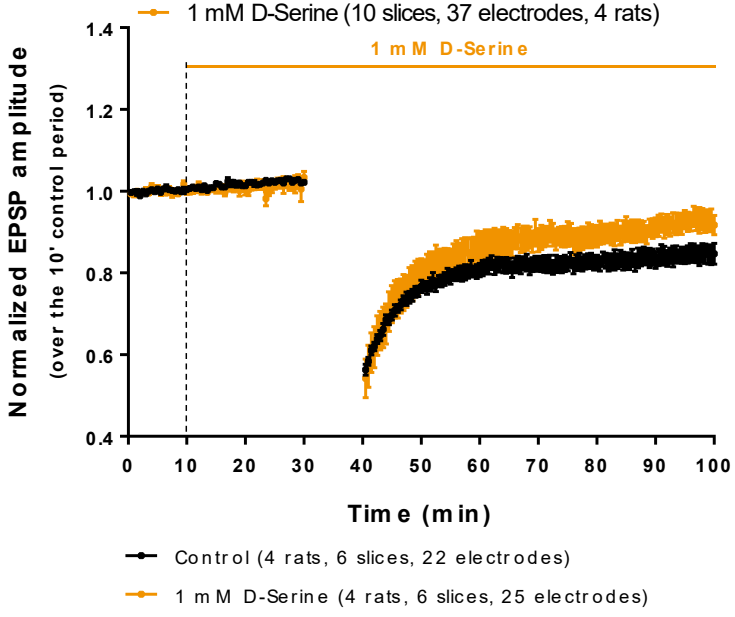
SC-CA1 summary

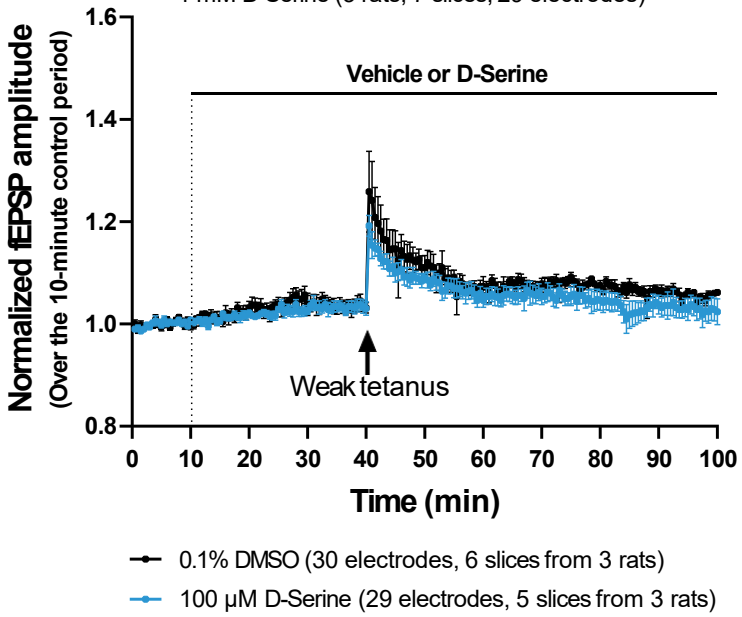
D-serine











- **Pre-exposure with 1 mM D-Serine prevents the MK-801-induced LTP disruption**.
- At 1 mM, D-Serine slightly increase the LTP and decrease the LTD whereas no effect was observed on weak tetanus at 100 µM concentration.
- D-serine do not modify the synaptic transmission.

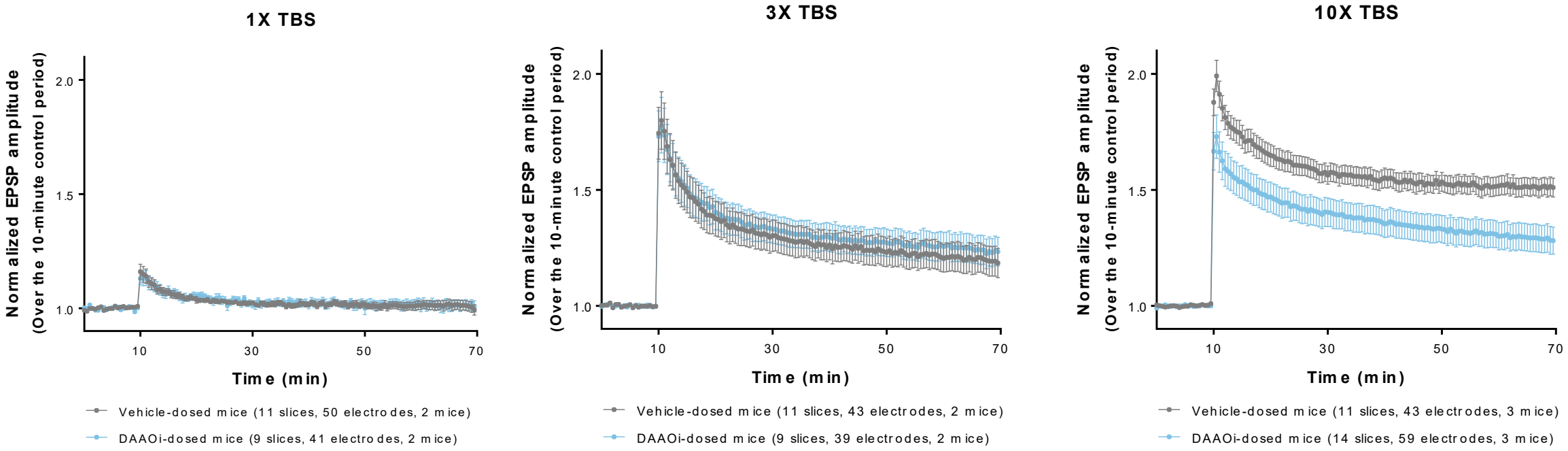
RESULTS

NMDA receptors (5/7)

Main summary

SC-CA1 summary

DAAOi



- **In DAAOi-dosed mice the long-term potentiation is reduced when induced by a 10X TBS.** no differences observed with LTP induced by 1X or 3X TBS

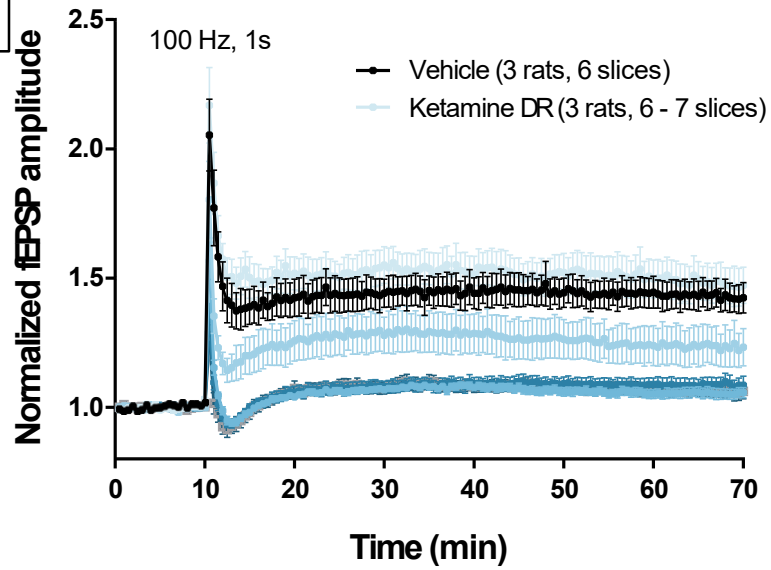
RESULTS

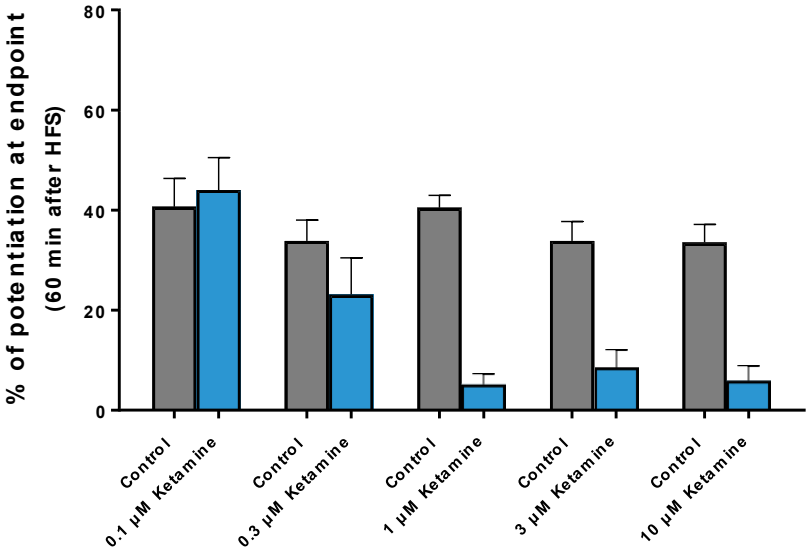
NMDA receptors (6/7)

Main summary

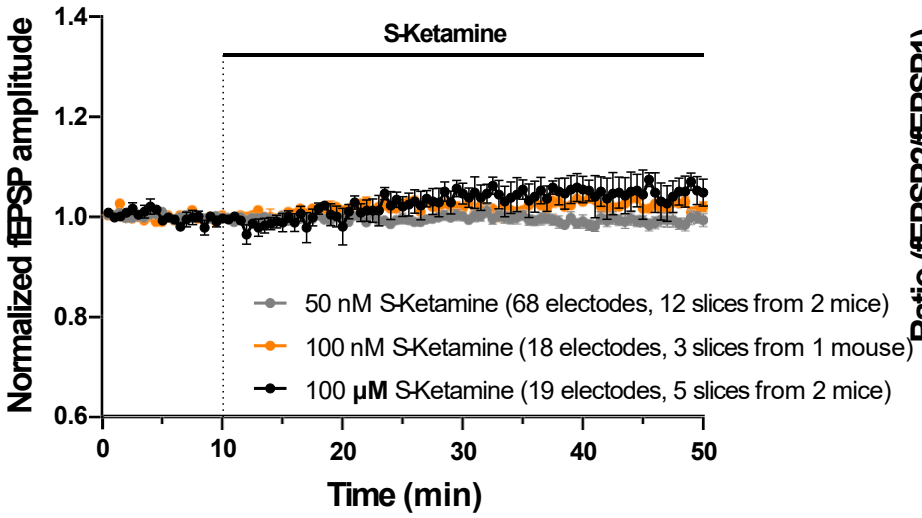
SC-CA1 summary

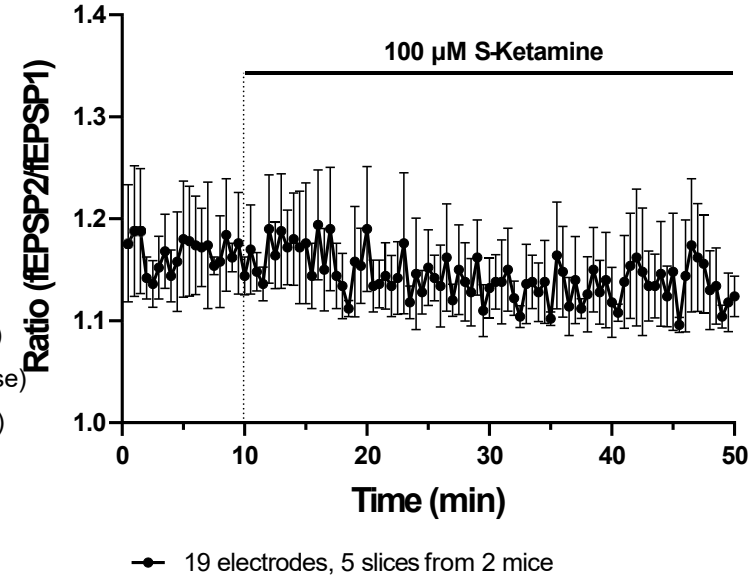
Ketamine





- **Ketamine dose-dependently inhibited the Long-Term Potentiation in the CA1 region of rat hippocampal slices, with an IC50 close to 0.5 µM for Ketamine.**





- **Conversely with Zhang (2017) data Ketamine at low and high doses do not modulate both AMPA EPSPs and the short-term plasticity**

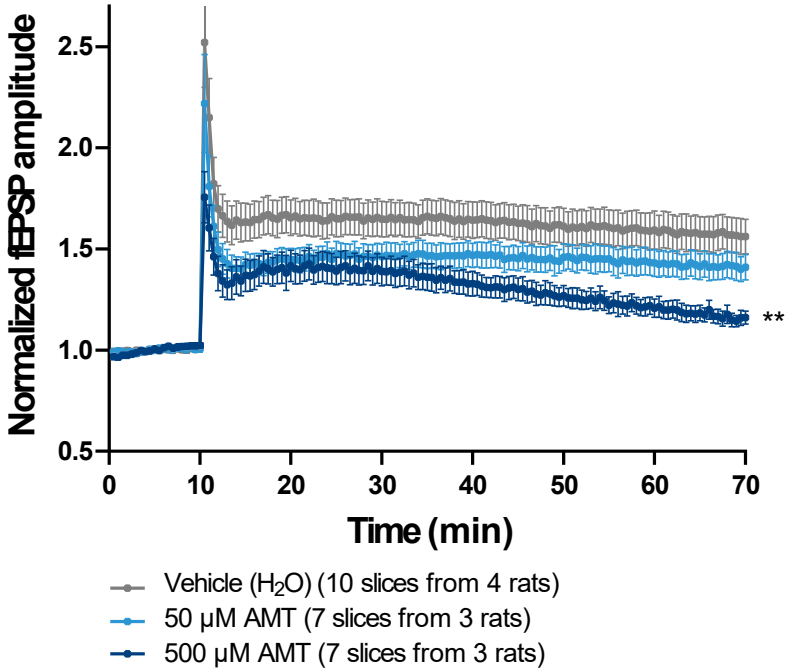
RESULTS

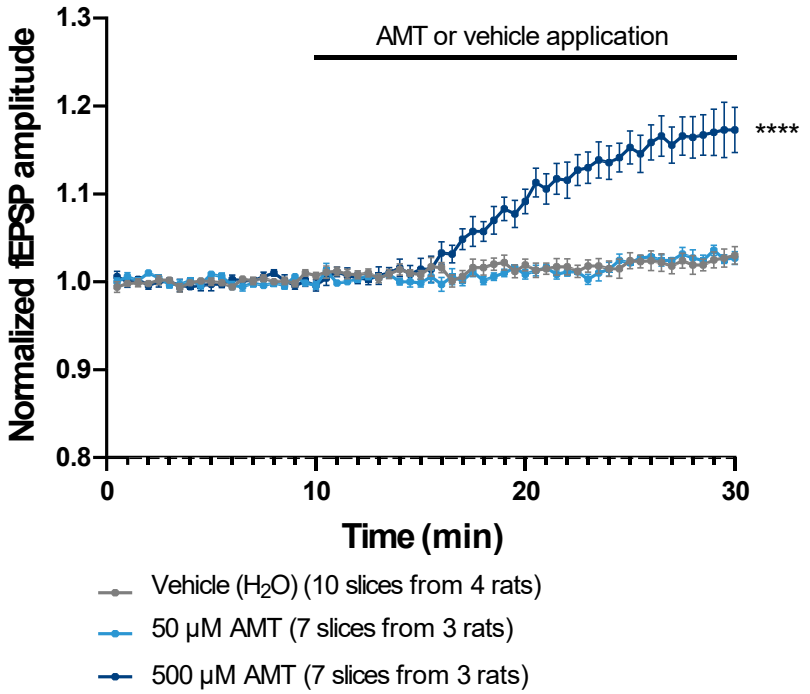
NMDA receptors (7/7)

Main summary

SC-CA1 summary

Amantadine





- In slices exposed to 50 µM amantadine the potentiation of fEPSP was slightly lower than in vehicle slices. This slight difference however remained not significant. (p = 0.2027, Unpaired t-test ; p = 0.2535, Anova).

- In slices exposed **to 500 µM amantadine the potentiation of fEPSP was significantly reduced compared to vehicle slices**. (p = 0.0038, Unpaired t-test ; p = 0.0029, Anova).

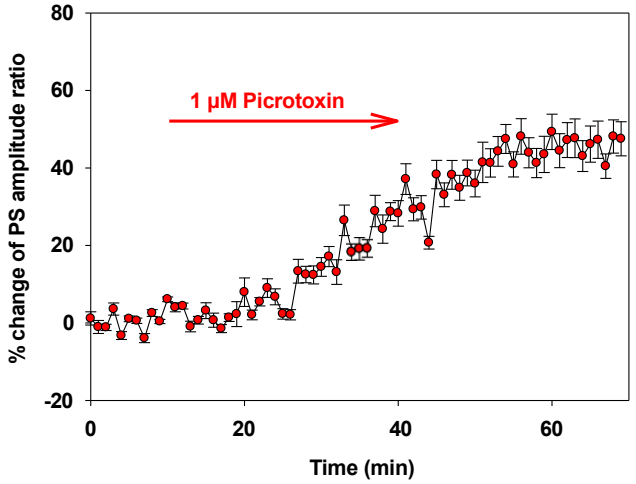
- In slices exposed to 50 µM AMT the amplitude of fEPSP was not modified over 20 minutes. In slices exposed to **500 µM AMT the amplitude of fEPSP significantly increased** over 20 minutes. At end point, the fEPSP amplitude was increased by 17.3 ± 2.6 % (p < 0.0001, Unpaired t-test).

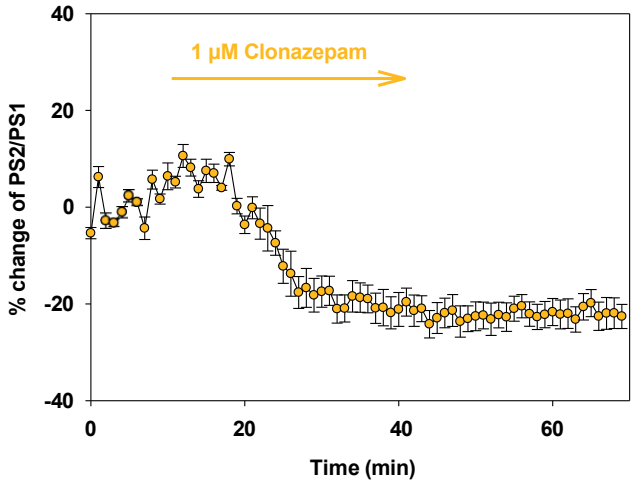
RESULTS

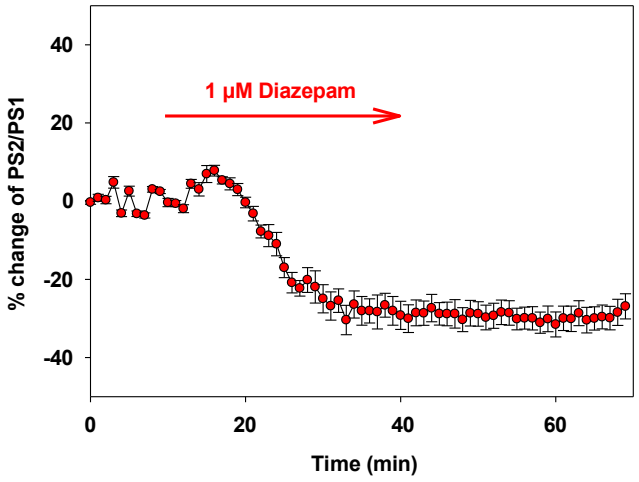
GABA receptors (1/7)

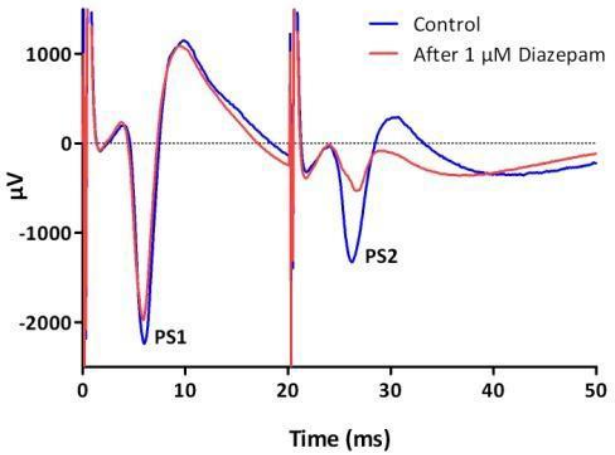
Main summary
SC-CA1 summary

PTX, Clonazepam, Diazepam

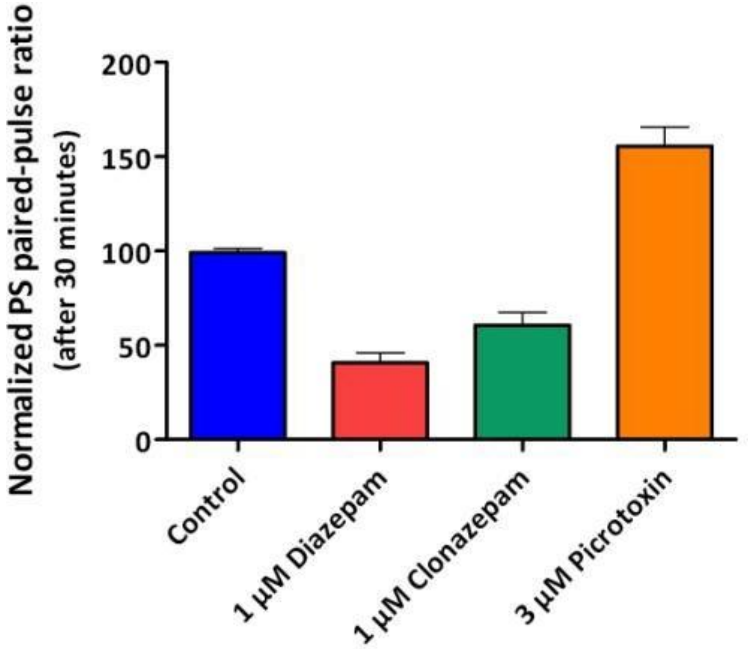








Paired-pulse inhibition



- The second Population Spike (PS) amplitude is decreased compared to the first one since GABAergic interneurons inhibition is still functioning when the second stimulus arrives in the CA1 region. **Thus GABAA Positive Allosteric Modulators (PAM) such as Diazepam or Clonazepam enhance PPI** (and then decrease PS paired-pulse ratio) whereas a **GABAA antagonist such as Picrotoxin suppresses PPI**

RESULTS

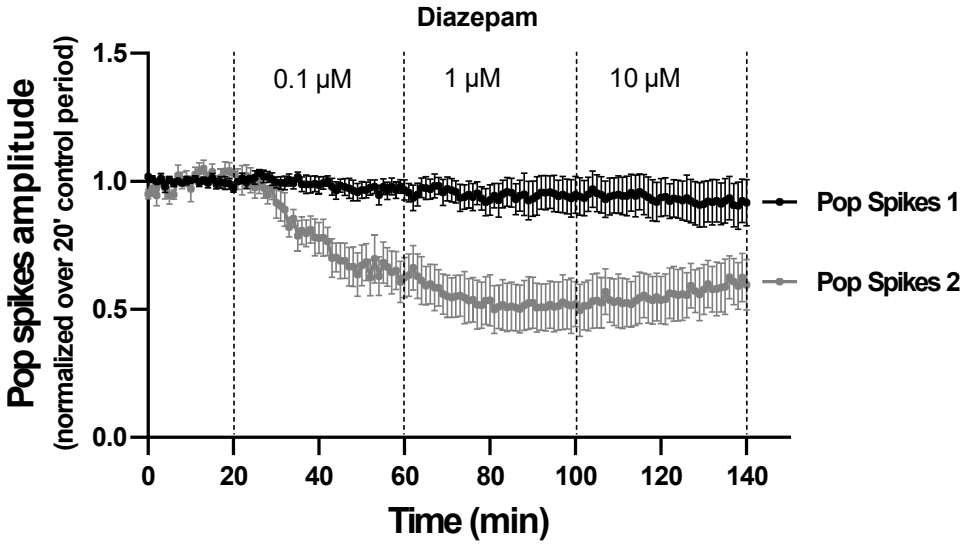
GABA receptors (2/7)

Main summary

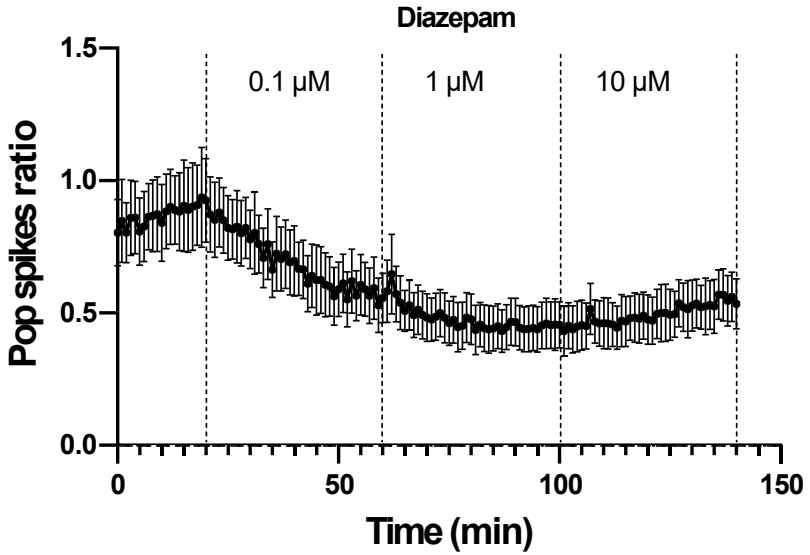
SC-CA1 summary

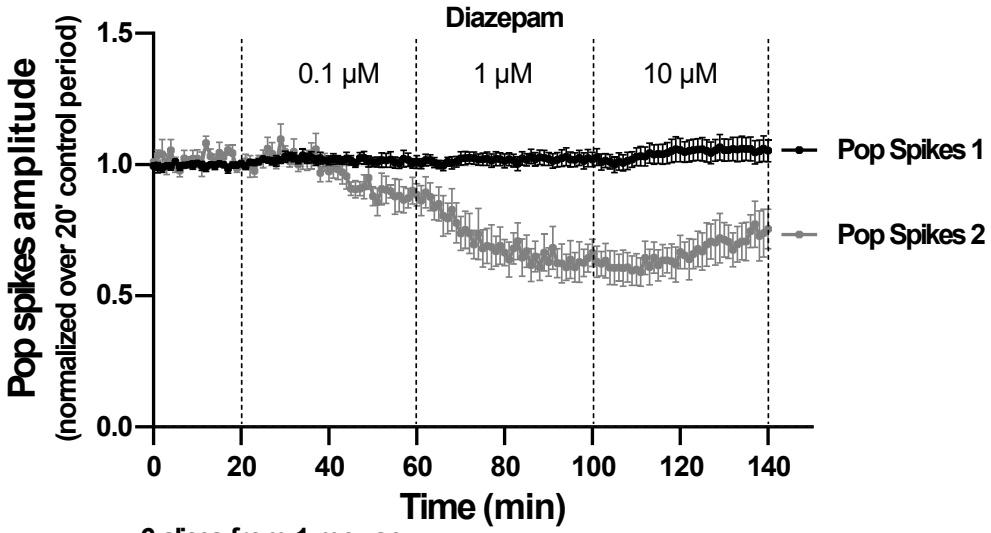
Diazepam

Paired-pulse inhibition

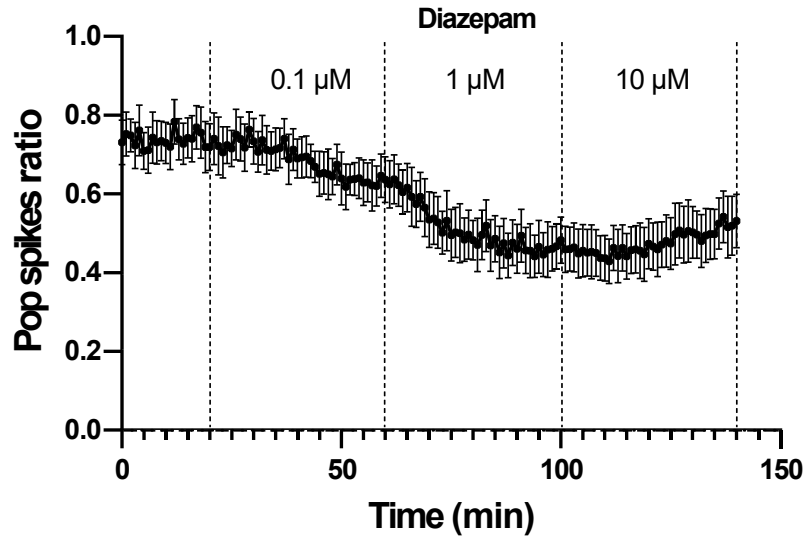


6 slices from 1 rat





6 slices from 1 mouse



- **Diazepam – PAM $GABA_A$ - enhances the inhibition the second population spikes amplitude without affecting the first population spikes response.**

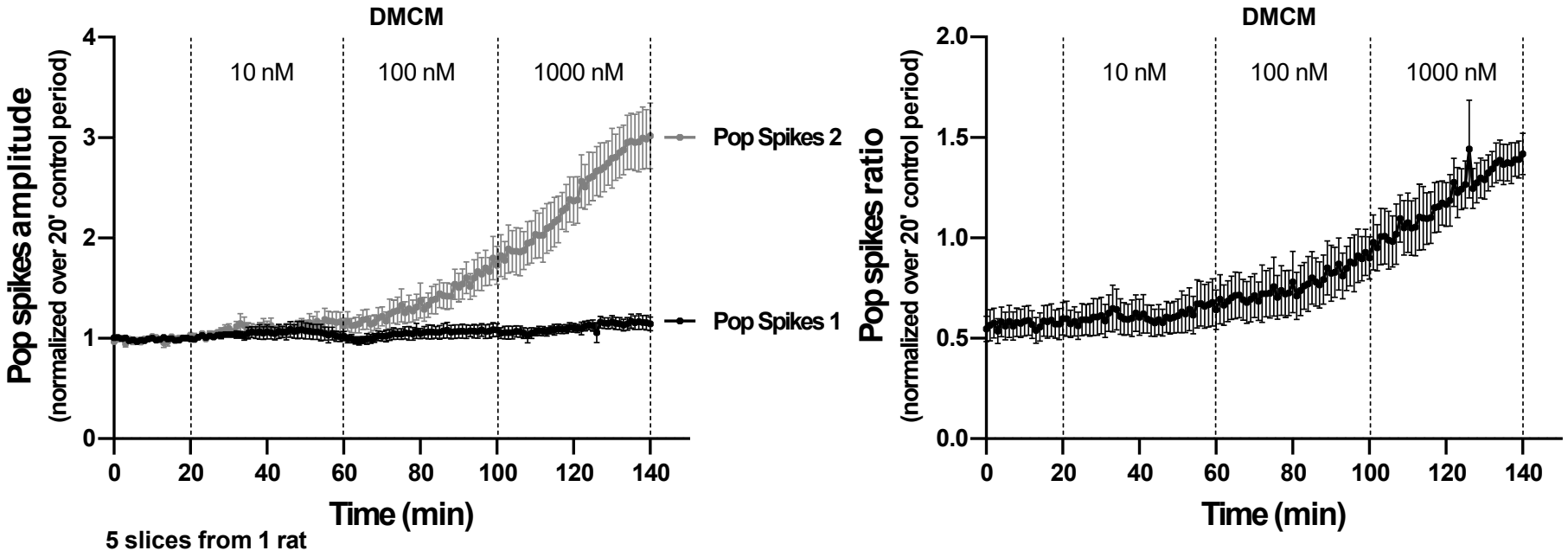
RESULTS

GABA receptors (3/7)

Main summary
SC-CA1 summary

DMCM

Paired-pulse inhibition



- **DMCM – NAM $GABA_A$ - reduces the inhibition the second population spikes amplitude without affecting the first population spikes response.**

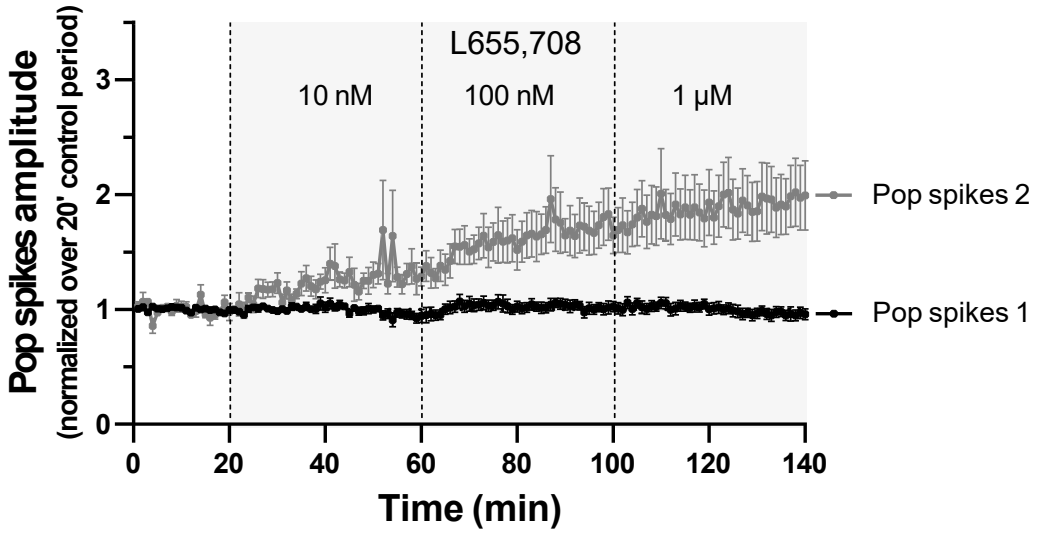
RESULTS

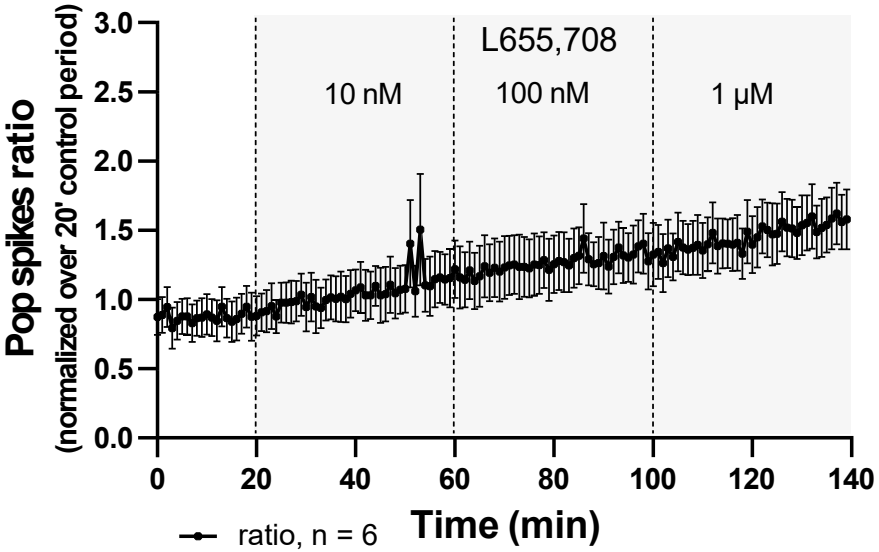
GABA receptors (4/7)

Main summary
SC-CA1 summary

L655,708

Paired-pulse inhibition





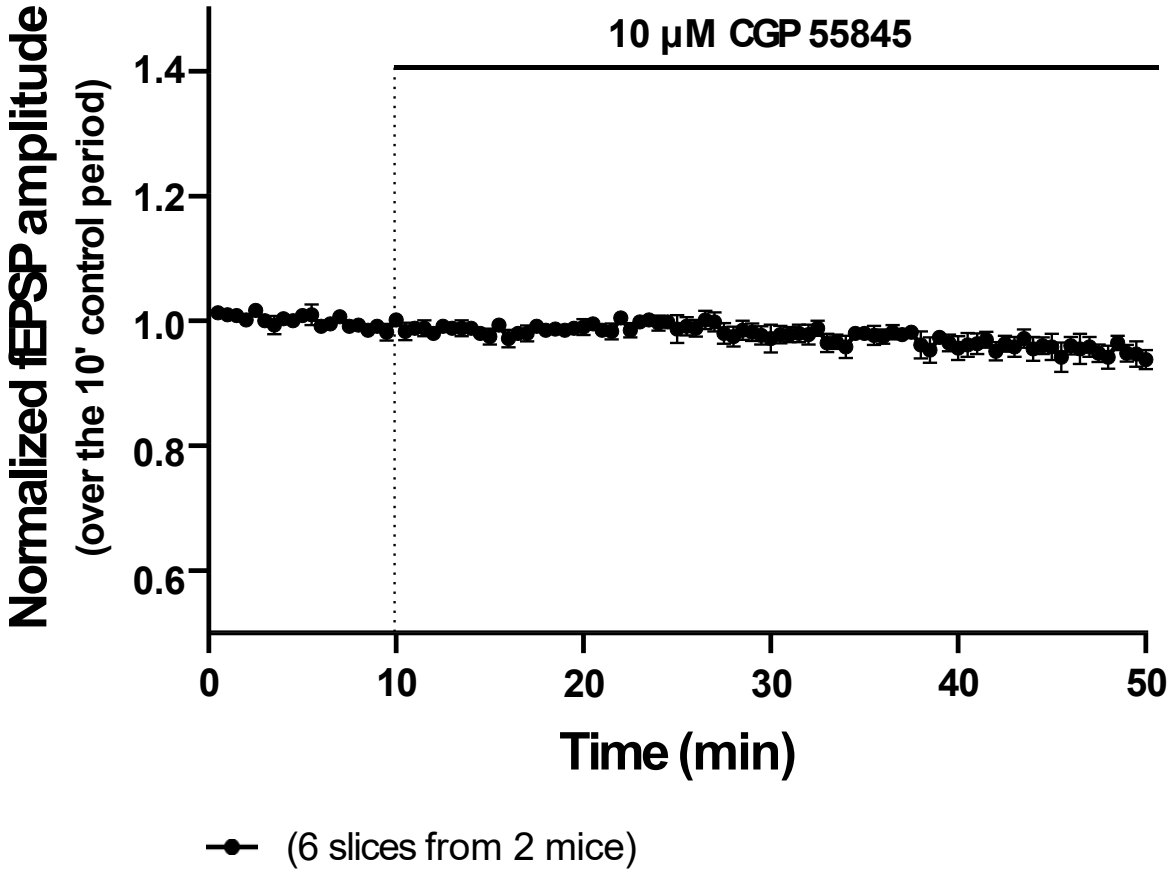
- **L655,708 – a NAM selective for $GABA_A$ receptors containing the α5 sub-unit - reduces the inhibition the second population spikes amplitude without affecting the first population spikes response.**

RESULTS

GABA receptors (5/7)

Main summary
SC-CA1 summary

CGP 55845



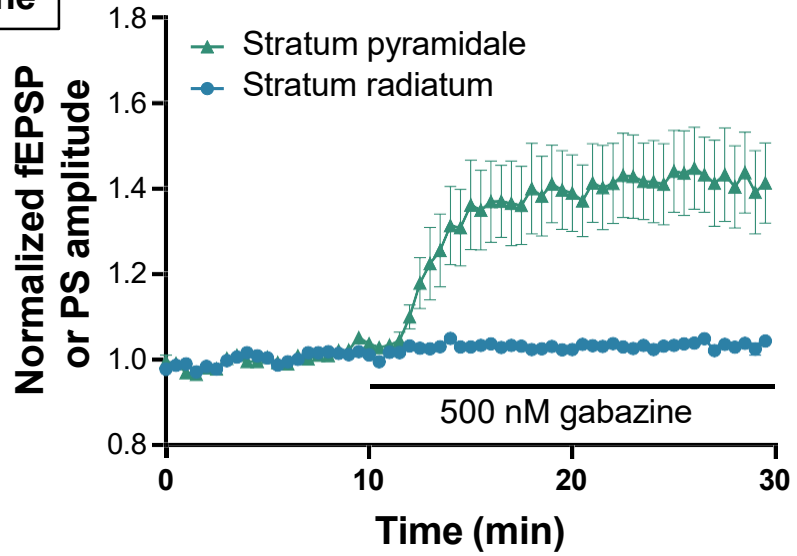
- **CGP 55845 – a $GABA_B$ antagonist – do not modify the fEPSPs amplitude.**

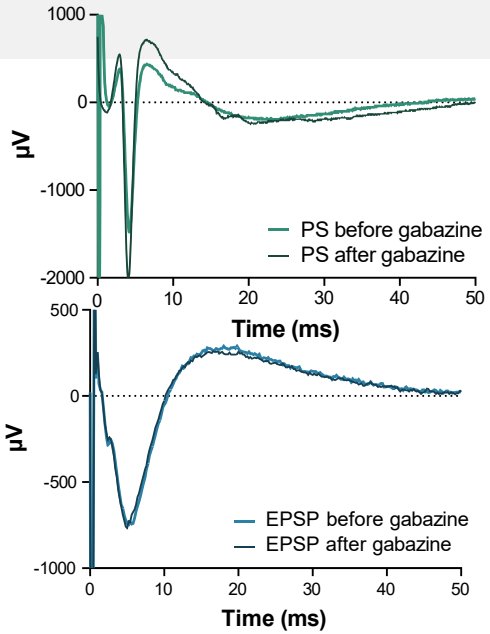
RESULTS

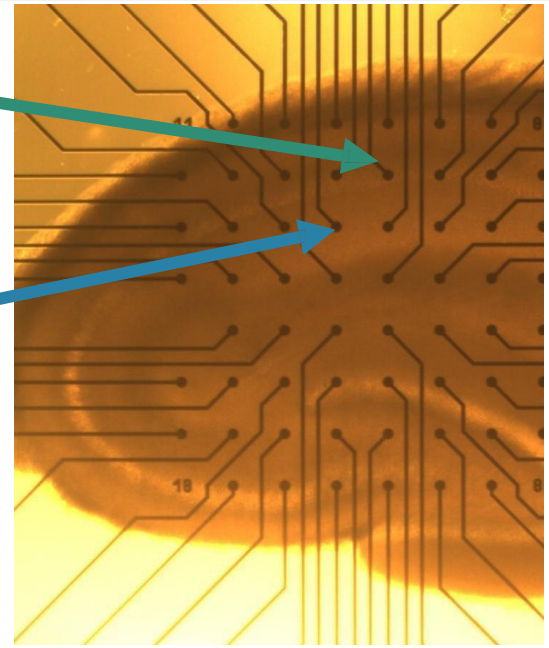
GABA receptors (6/7)

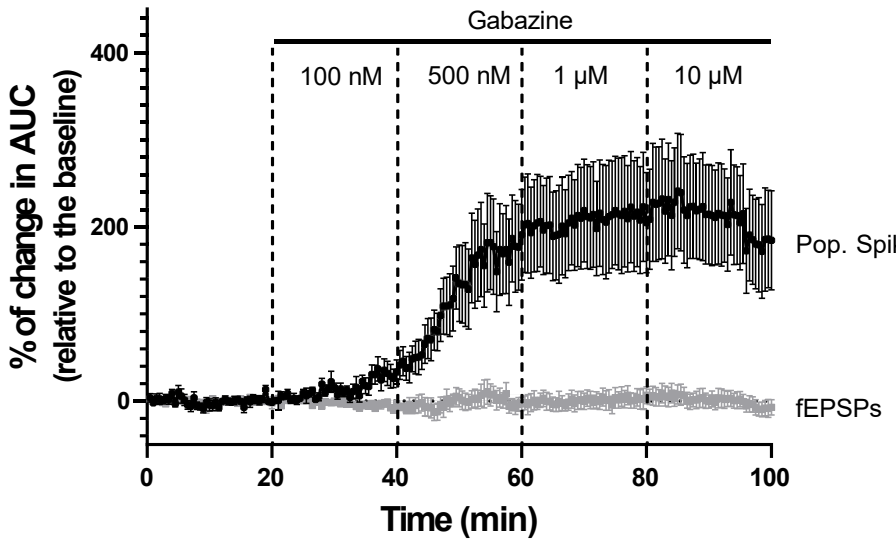
Main summary
SC-CA1 summary

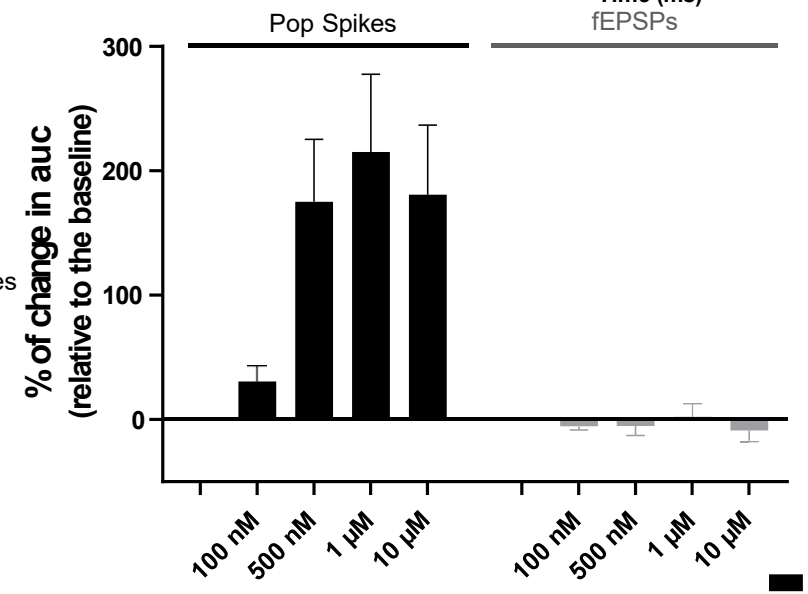
Gabazine











- **Gabazine modulates populations spikes without modifying fEPSPs**

PS (10 electrodes from 4 slices from 2 rats)

EPSP (29 electrodes from 7 slices from 2 rats)

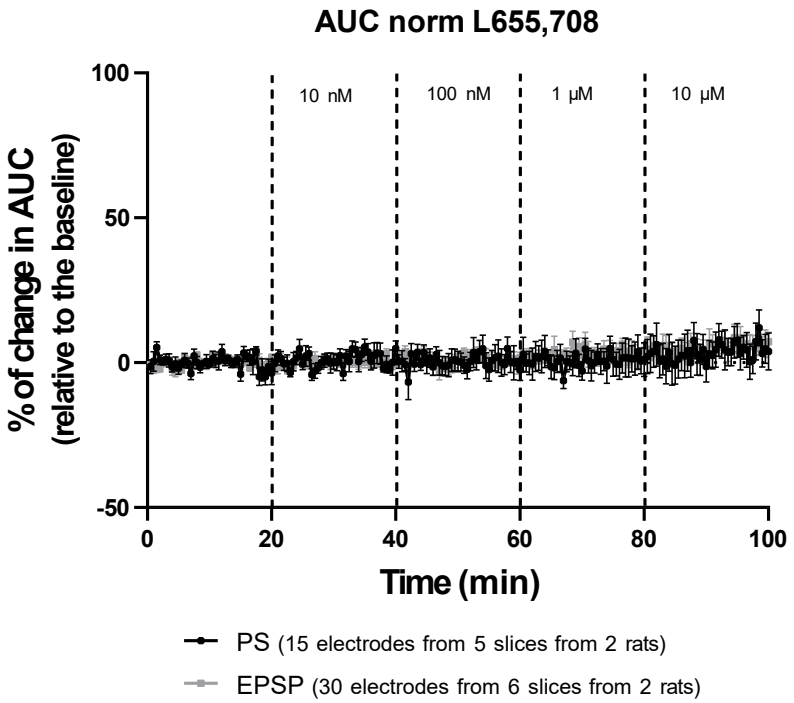
RESULTS

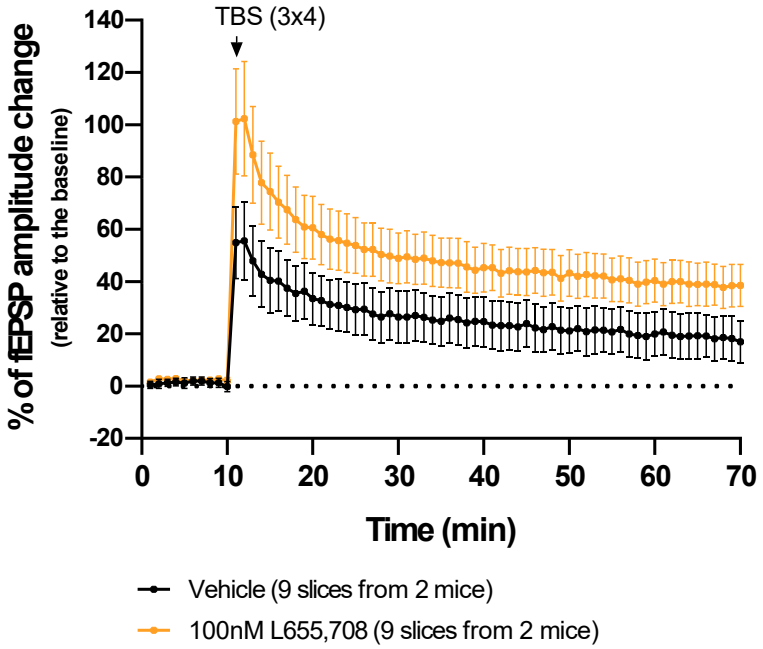
GABA receptors (7/7)

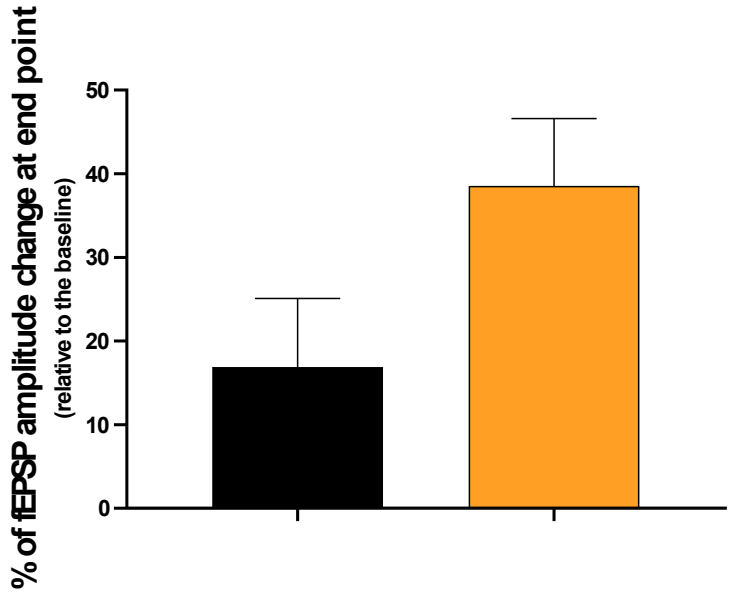
Main summary

SC-CA1 summary

L655,708







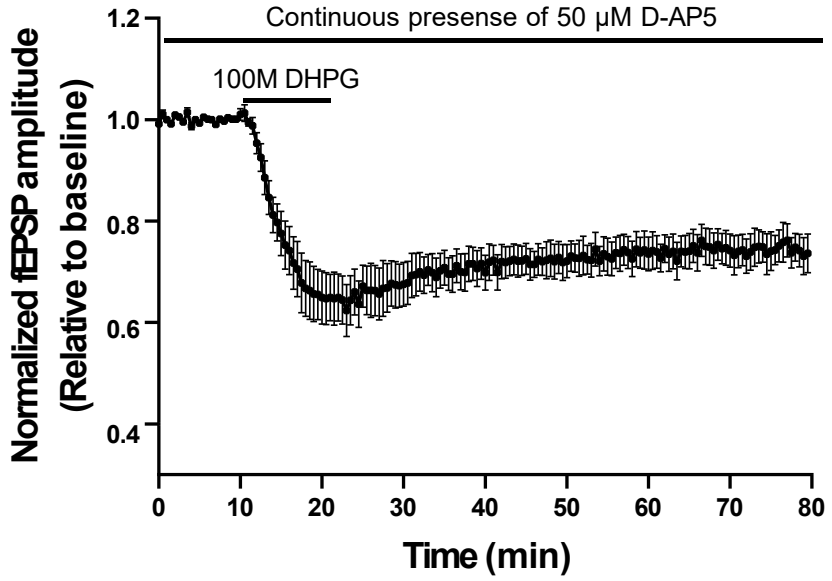
- **L-655,708 – a inverse agonist for $GABA_A$ containing alpha 5 – do not modulate the synaptic transmission but increases long-term potentiation.**

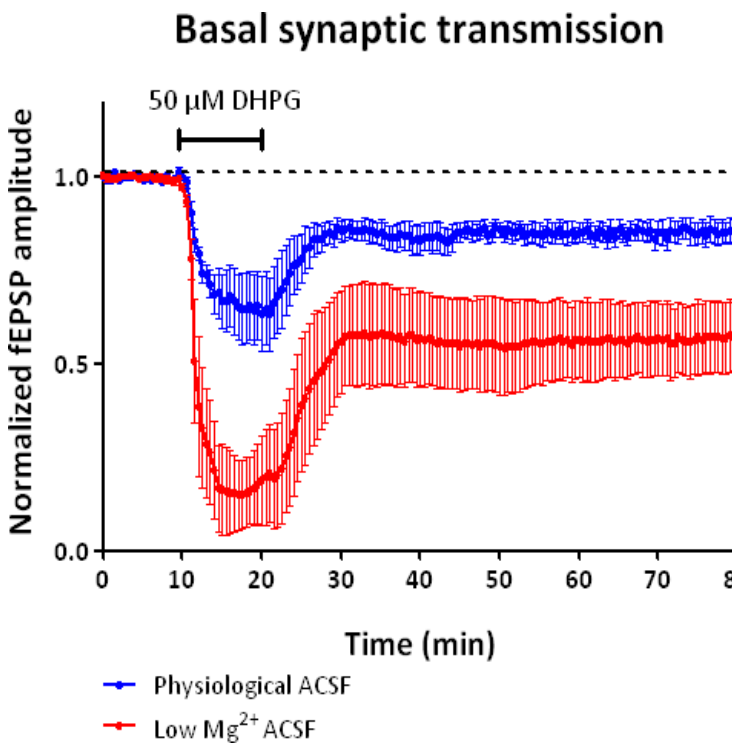
RESULTS

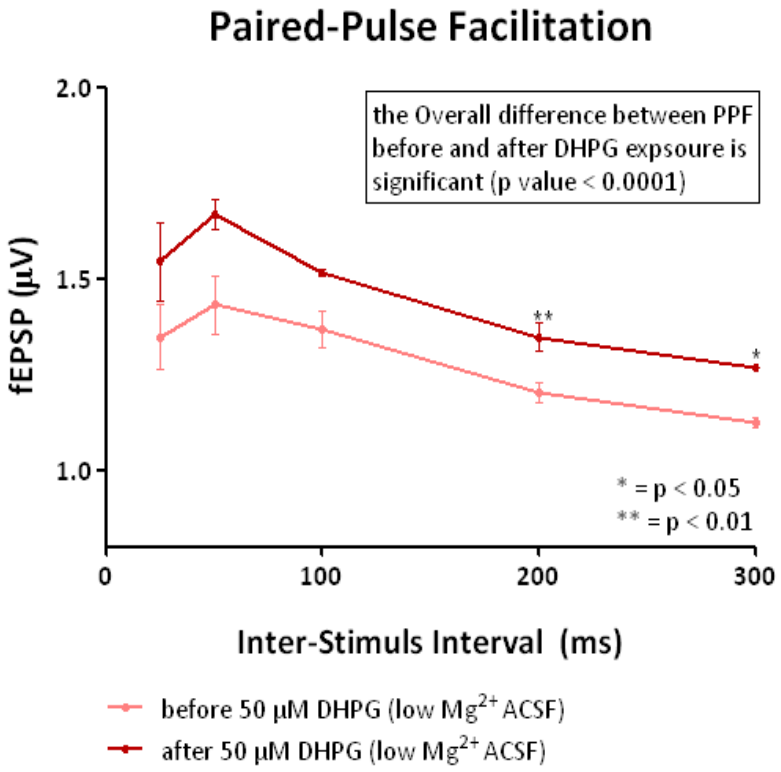
mGluR I (1/2)

Main summary
SC-CA1 summary

DHPG







- **DHPG - Selective group I mGlu agonist – exposed over a 10 min period, induced a long-term depression at the CA1 synapses.**
- **DHPG-induced LTD is enhanced in a low magnesium ACSF**, likely due to a larger calcium entry through NMDA receptors (Palmer, Neuropharmacol., 1997).

- The mechanism of long-term depression induced by DHPG is non-NMDA dependent
- DHPG-induced LTD is mediated, at least in part, by pre-synaptic mGluR I receptors. Paired-Pulse experiments (right panel) clearly highlight the pre-synaptic nature of DHPG effect.

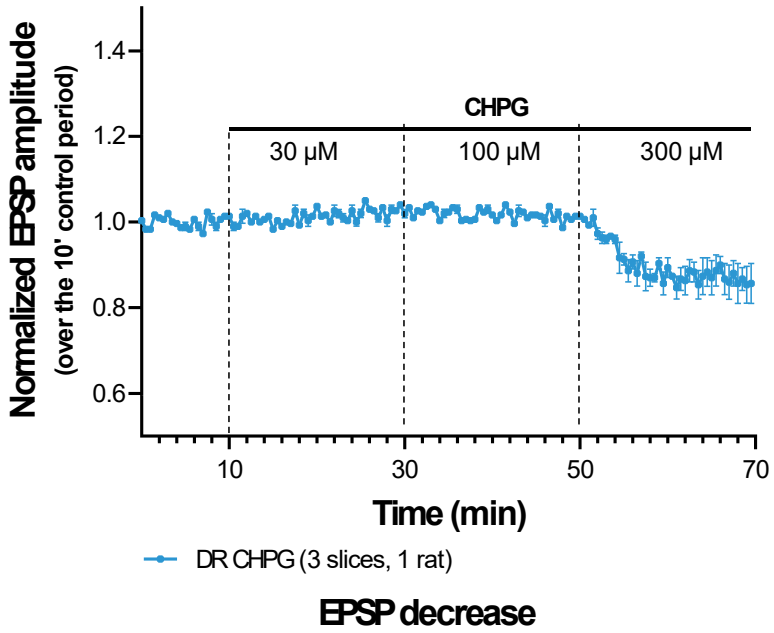
neuroservices ALLIANCE

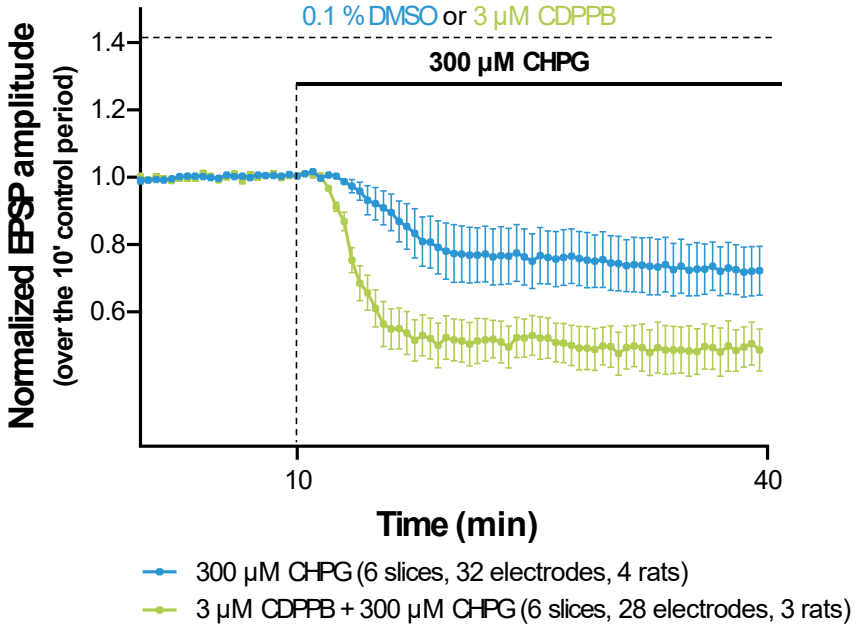
RESULTS

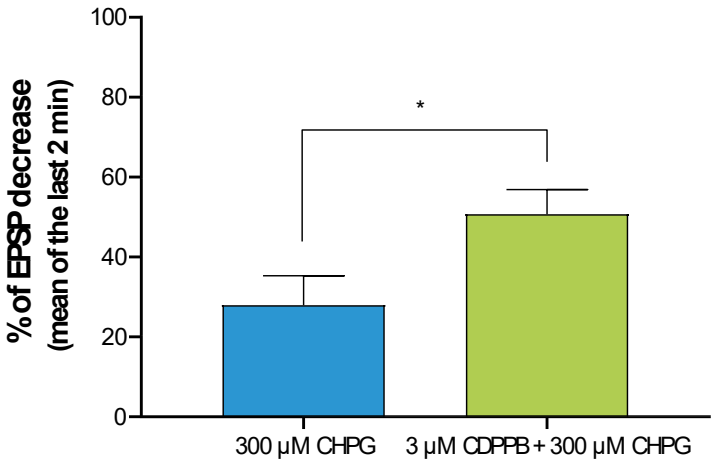
mGluR I (2/2)

Main summary
SC-CA1 summary

CHPG, CDPPB







- **CHPG (a selective mGlu5 agonist) substantially decreased the basal synaptic transmission.**
- **The effect of CHPG was significantly enhanced by CDPPB (a selective positive allosteric modulator at mGlu5 receptor).**

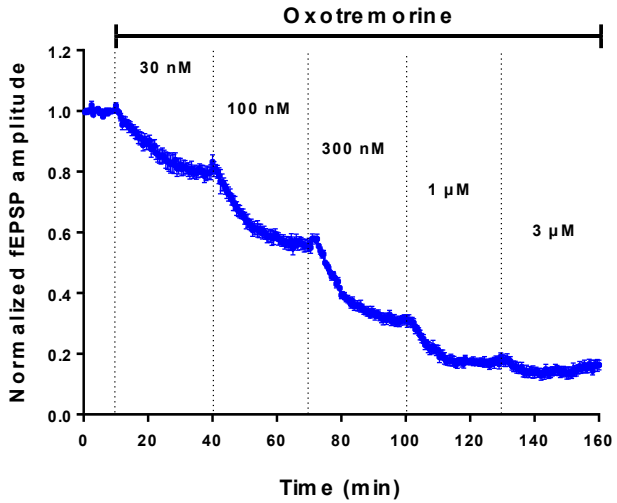
RESULTS

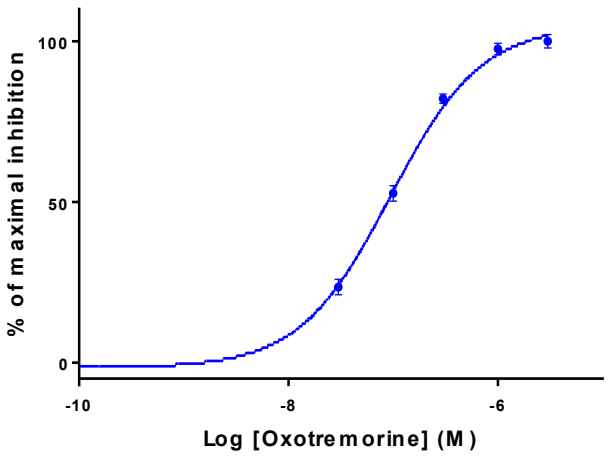
Muscarinic receptors (1/2)

Main summary

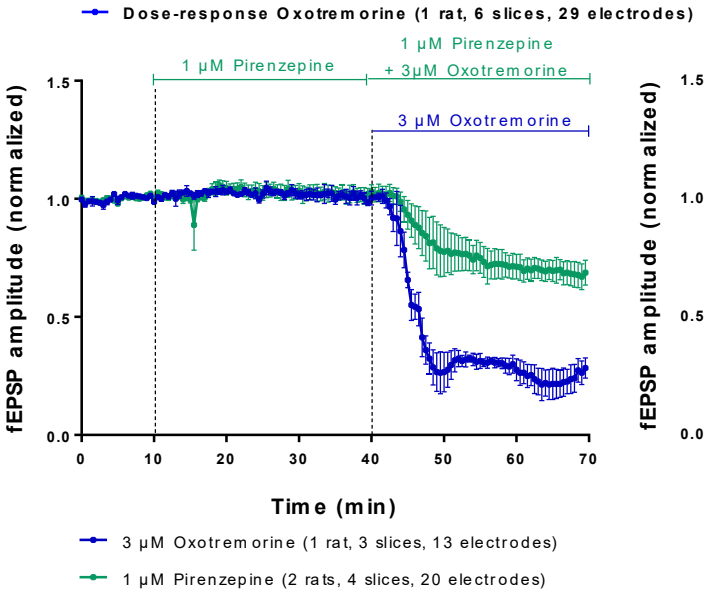
SC-CA1 summary

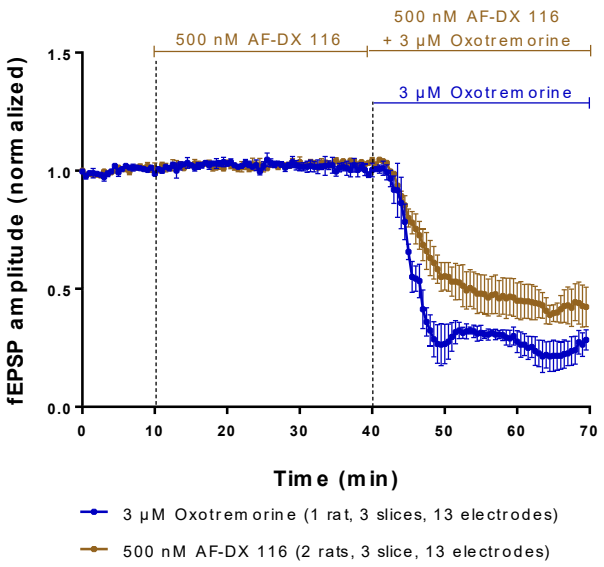
Oxotremorine, Pirenzepine, AF-DX-116, Topicamide

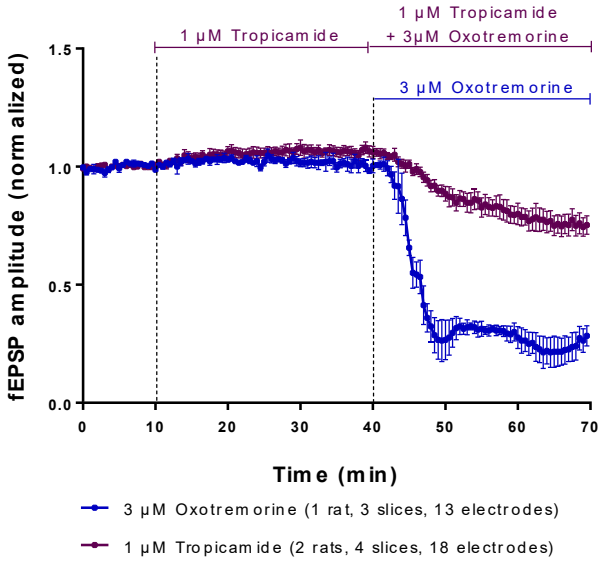


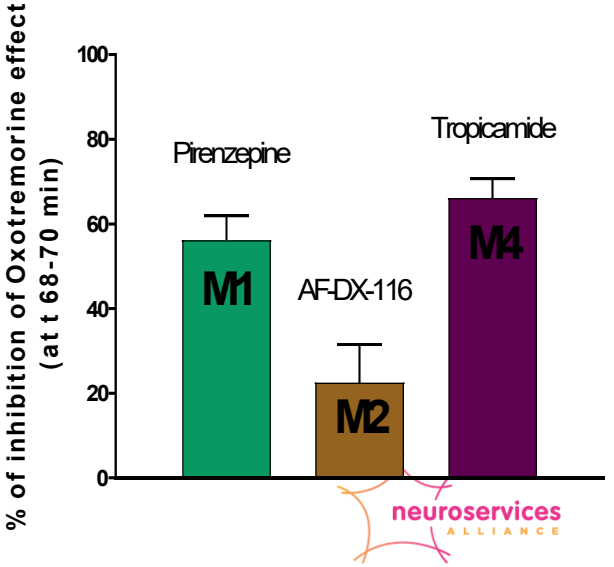


- **Oxotremorine, a non-selective muscarinic receptor (mAChR) agonist, dose-dependently decreased the amplitude of evoked-responses**. (EC50 = 92 nM, EC30 = 40 nM).
- **Pirenzepine, AF-DX-116 and topicamide respectively M1, M2 and M4 mAChR antagonists partially inhibited the effect of 3 µM Oxotremorine.**
- M1 and M4 were the main subtypes of mAChR involved in the Oxotremorine effect observed in the CA1 region of rat hippocampal slices. The contribution of M2 mAChR to Oxotremorine effect was more modest.









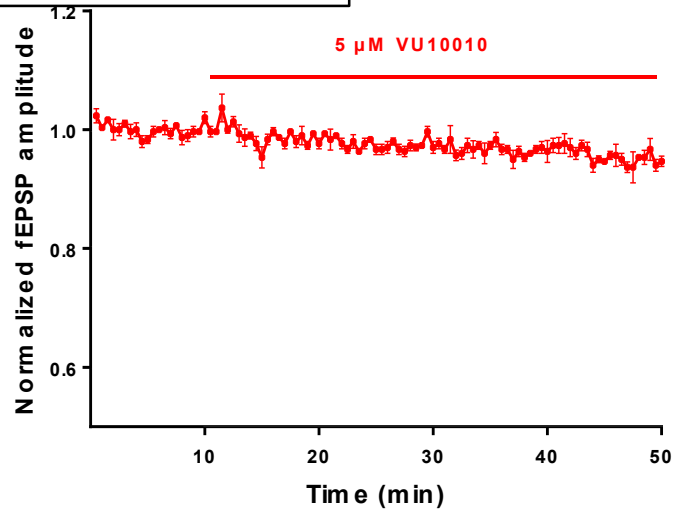
RESULTS

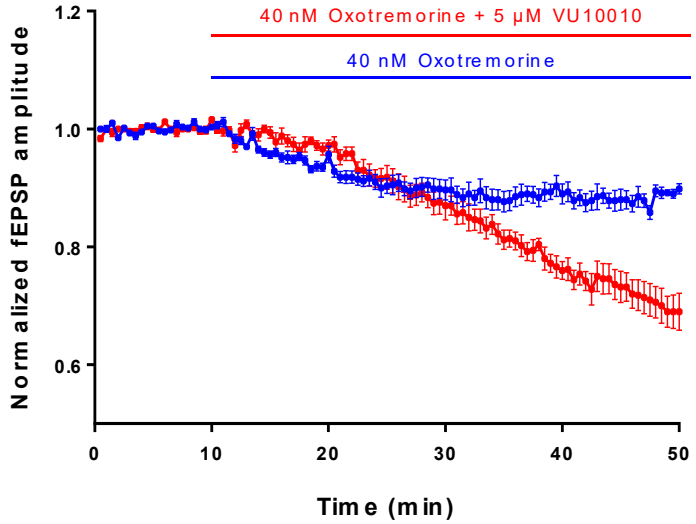
Muscarinic receptors (2/2)

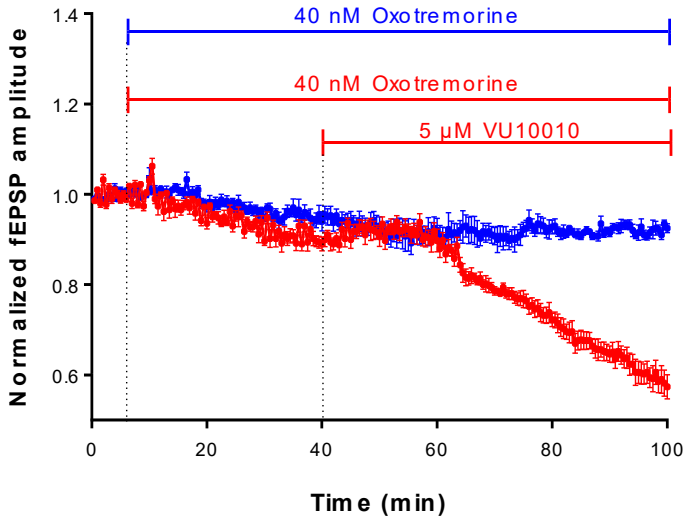
Main summary

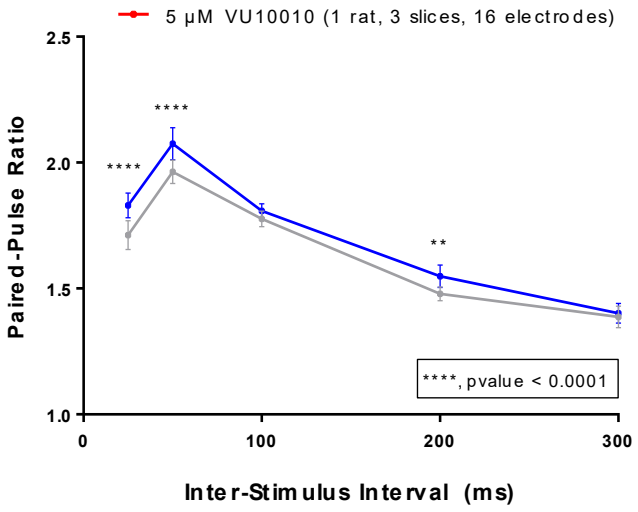
SC-CA1 summary

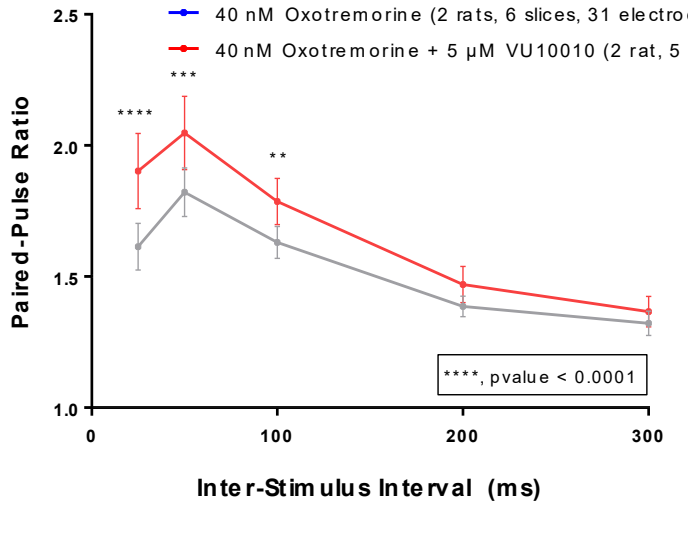
Oxotremorine, VU10010

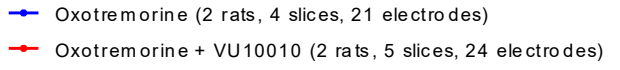












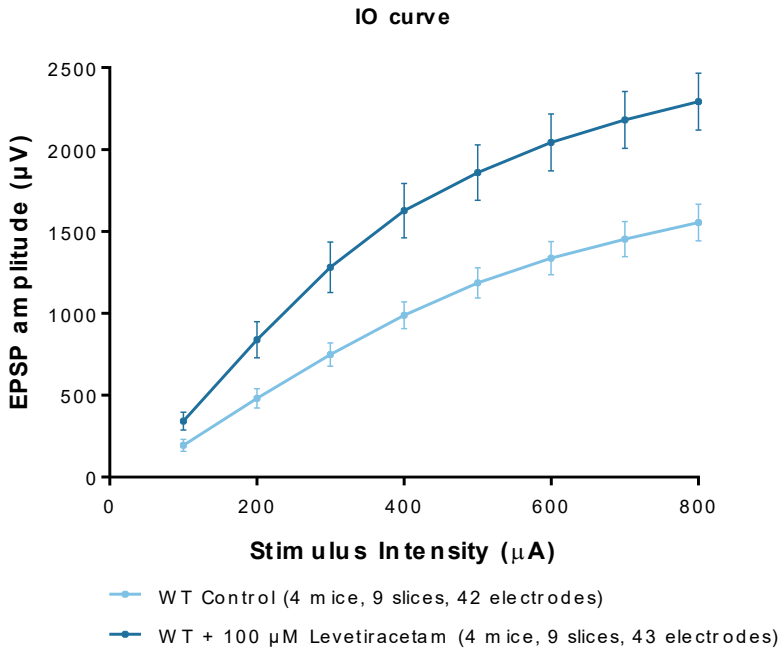
- VU10010 is a selective M4 Positive Allosteric Potentiator. **VU10010 alone (5 µM) did not modify the amplitude of evoked-responses, but enhance the effect or Oxotremorine on syntaptic transmission and short-term plasticity.**

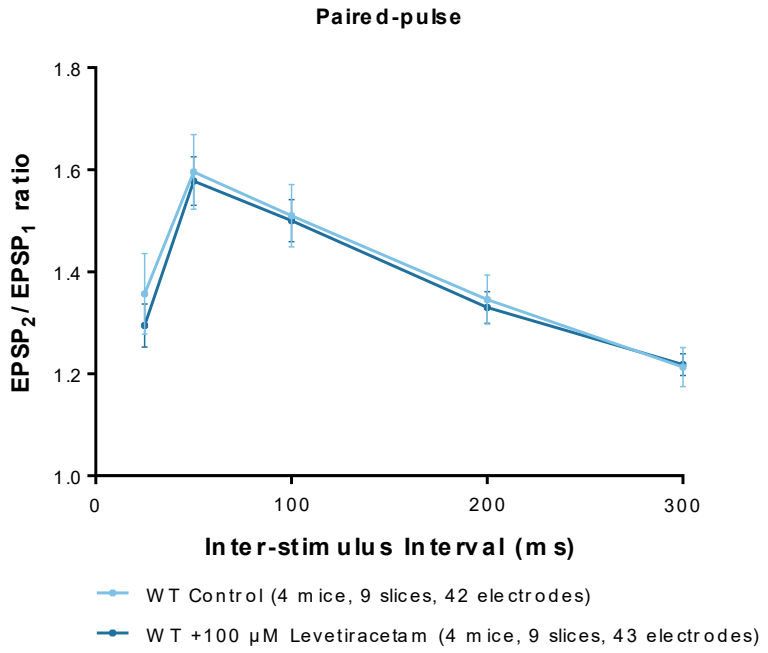
RESULTS

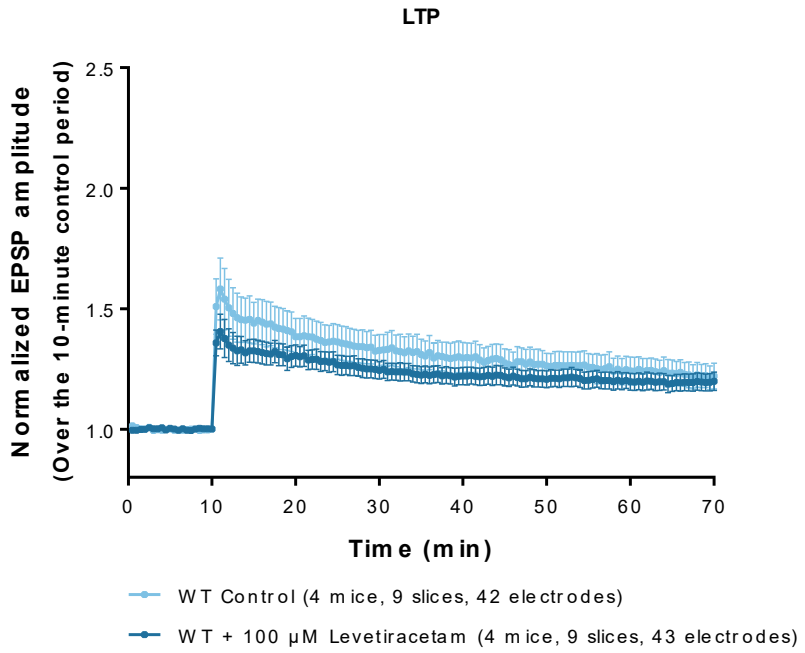
Synaptic vesicle protein 2A

Main summary
SC-CA1 summary

Levitiracetam







- **Input/Output curve was significantly higher in slices preincubated for 3 h with 100 µM Levetiracetam (Two-way ANOVA, $p < 0.0001$).**
- **Paired-pulse properties and long-term potentiation were similar in slices preincubated for 3 h in 100 µM Levetiracetam and in control slices.**

SV2A is a membrane-bound protein that is found on synaptic vesicles and is ubiquitous throughout the CNS4 - it appears to play a role in vesicle exocytosis11,15 and in the modulation of synaptic transmission by increasing the available amount of secretory vesicles available for neurotransmission.7 Stimulation of pre-synaptic SV2A by levetiracetam may inhibit neurotransmitter release,6 but this action does not appear to affect normal neurotransmission. This has led to the suggestion that levetiracetam exclusively modulates the function of SV2A only under pathophysiological conditions.4

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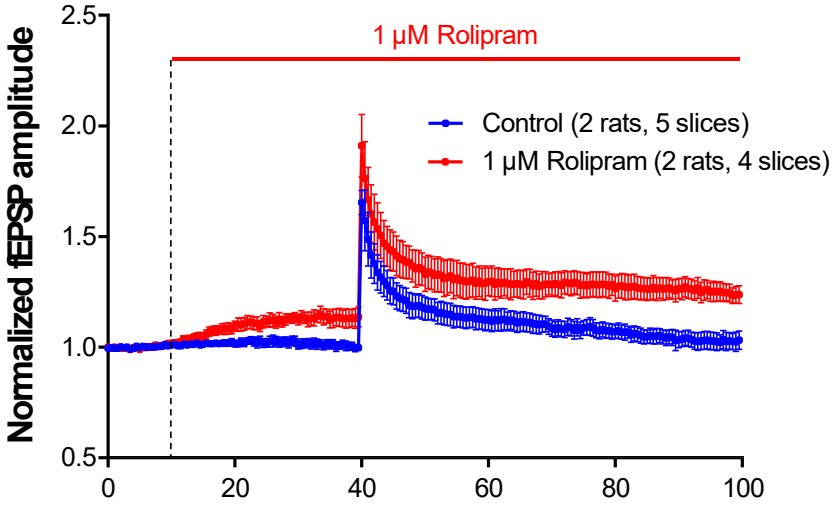
RESULTS

Enzymes & cytokines(1/2)

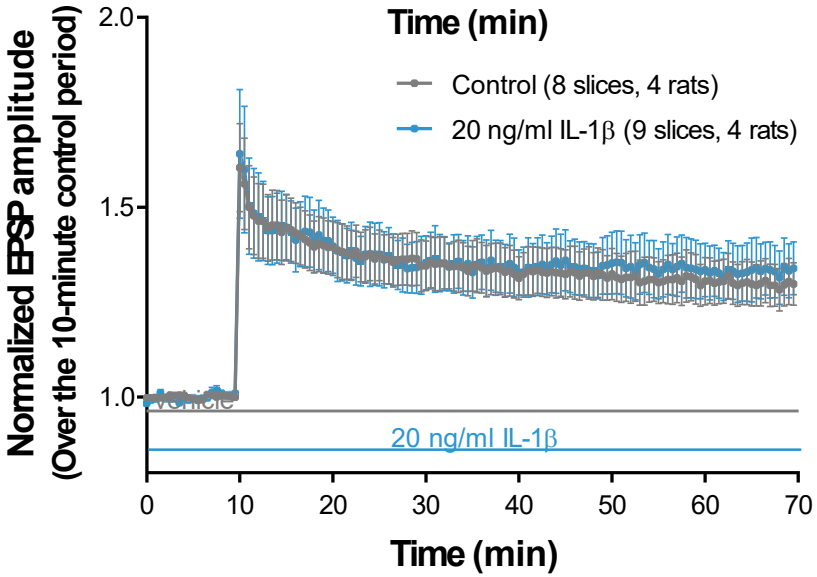
Main summary
SC-CA1 summary

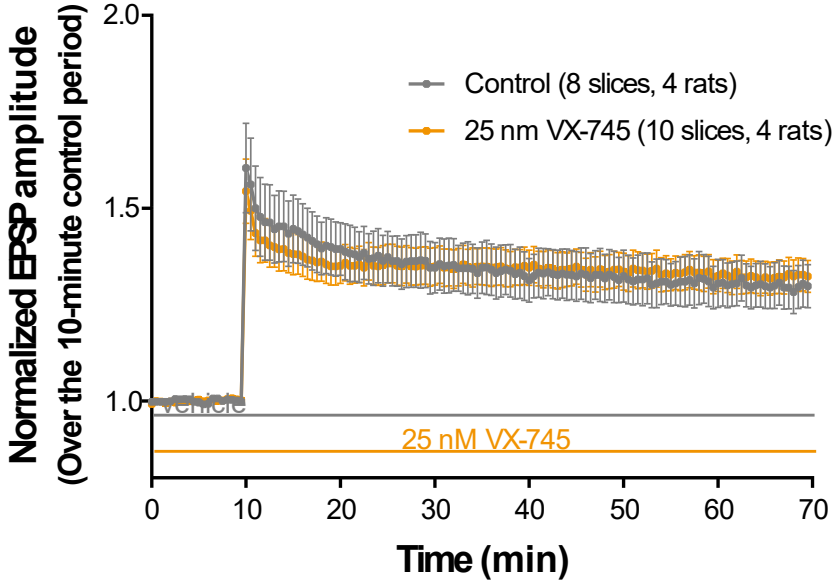
Rolipram, Interleukin 1B, VX-745



- When the weak tetanus is applied with an intensity of 33 % of Imax, the stimulation train induces only Short-Term Potentiation (STP) of evoked-responses. That stimulation intensity corresponds to the threshold stimulation intensity, above which a Long Term Potentiation (LTP) of the evoked responses is elicited.

- **Rolipram – a PDE 4 inhibitor – , at 1 µM, enhances the basal synaptic transmission by about 12 ± 5%** after 30 minutes of exposure**. Rolipram also enhances the potentiation, and turns STP into LTP**. After 60 minutes, the potentiation of evoked responses stabilized, at about 10%.





- **Interleukin 1β and VX-745 - Potent and selective p38α inhibitor – do not modified the long-term potentiation**

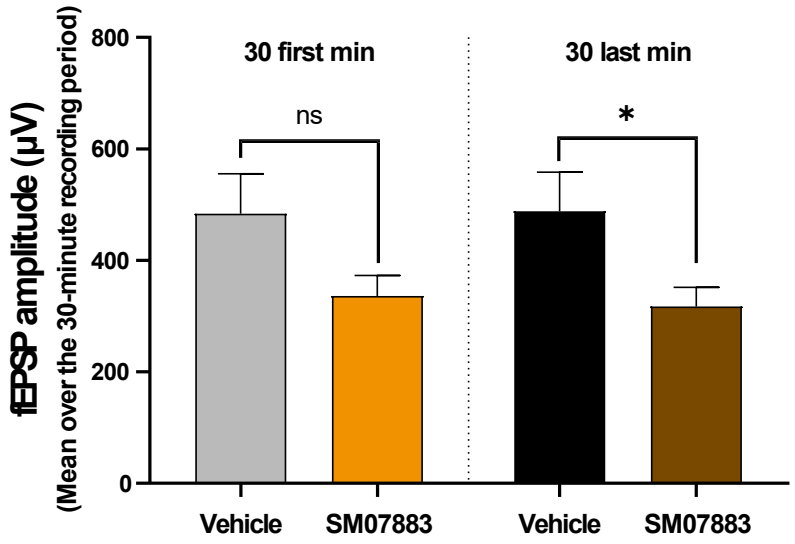
Experiments carried out with 4 weeks-old Sprague Dawley rats
LTP : 1 train of 10 bursts composed each of 4 stimuli at 100 Hz, applied at 200 ms interval, to 40% of Imax

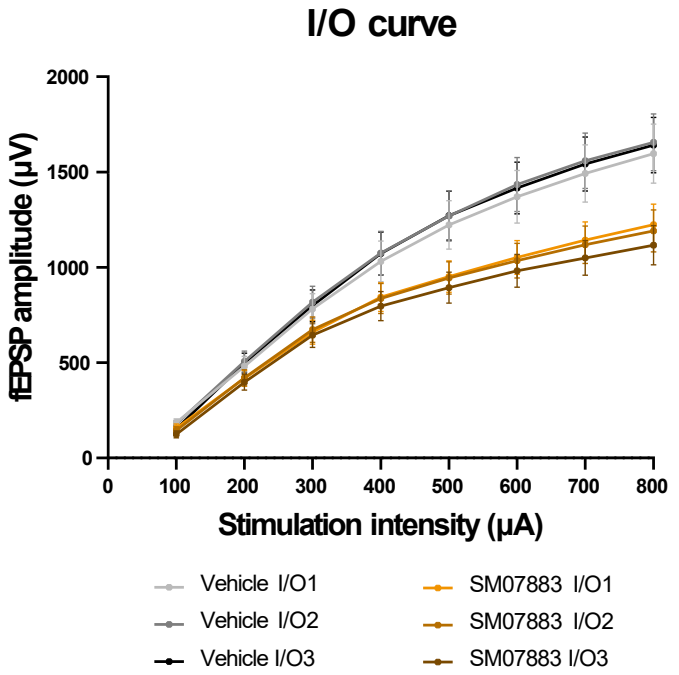
RESULTS

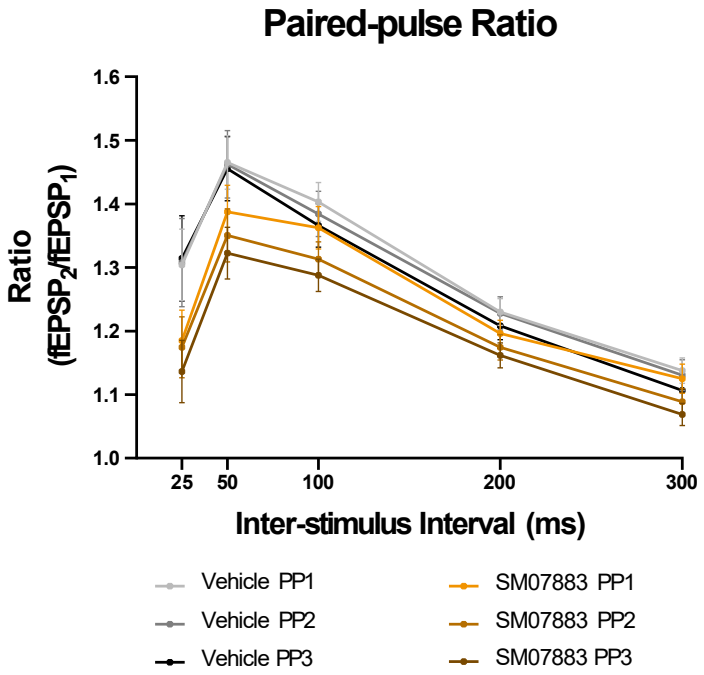
Enzymes & cytokines (2/2)

Main summary
SC-CA1 summary

SM07883







- **The DYRK1a inhibitor, SM07883 modify both the synaptic transmission and the short term plasticity properties** in 6 month-old C57Bl6 mouse hippocampal slices

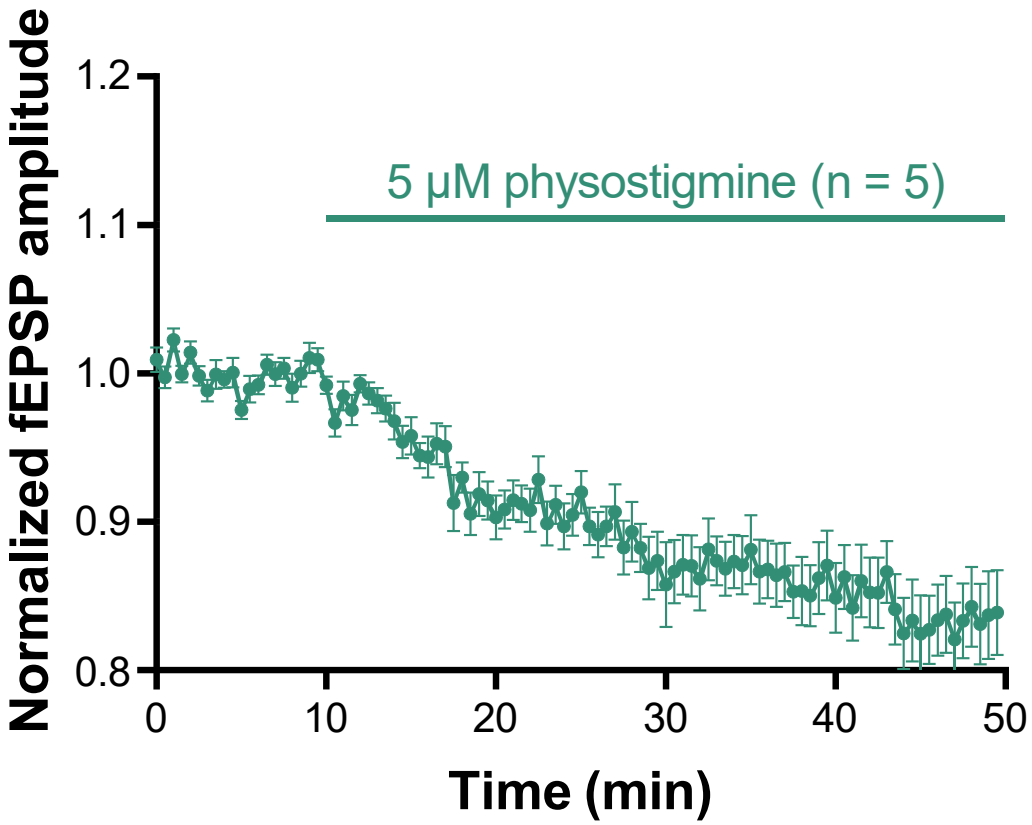
- Evoked-response recordings and successive I/O protocols together demonstrated that SM07883 exposure (through animals dosing and/or application in the medium perfused onto the slices) progressively decreased the amplitude of fEPSPs whereas this parameter remained steady in the presence of vehicle.

- Successive paired-pulse experiments suggest that SM07883 might modulate the synaptic transmission at the pre-synaptic level. Indeed, in the presence of SM07883 the paired-pulse ratio decreased as a function of the duration of compound application, whereas it remained stable in the presence of vehicle only.

RESULTS

Cholinesterase inhibitor

Physostigmine



- **Physostigmine – a cholinesterase inhibitor – reduced the fEPSPs amplitude by about 20 %**

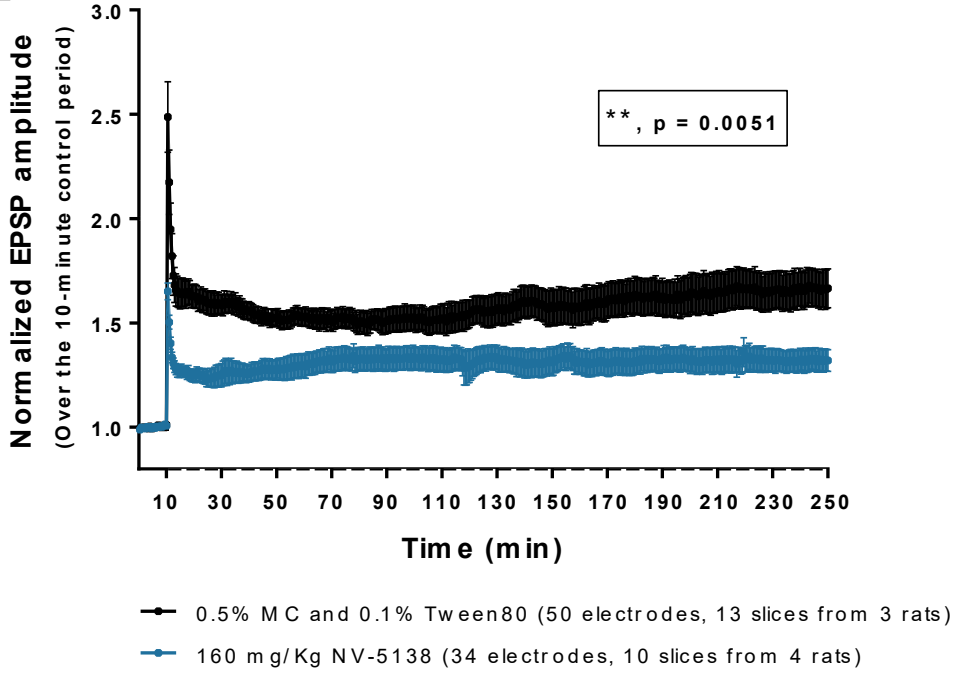
RESULTS

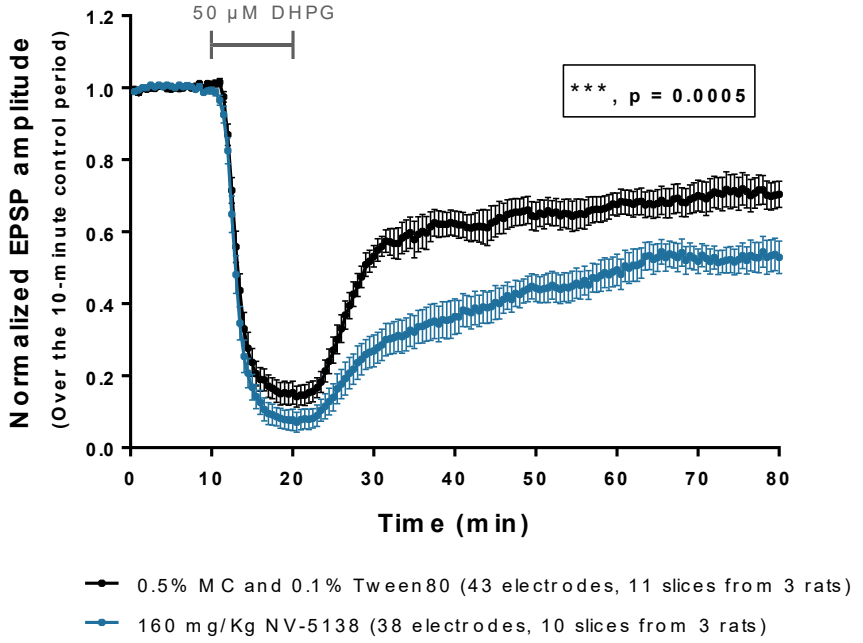
mTORC

Main summary

SC-CA1 summary

NV-5138





- The High Frequency Stimulation (HFS) induced a large potentiation of EPSP amplitude, the potentiation observed was significantly lower in slices from NV-5138-treated animals – that selectively activates mTORC1 - than in the ones from vehicle-treated animals (2-Way ANOVA) for both early and late phase of the LTP.

- The Long-Term Depression (LTD) significantly differ between slices from NV-5138 and vehicle-treated rats (2-Way ANOVA). Indeed, the DHPG-induced depression was much stronger in NV-5138-treated rats than in vehicle-treated.

Experiments carried out with 6 to 8 weeks-old Sprague Dawley rats
HFS : 2 trains of stimulations at 100 Hz for 800 ms, spaced by 60s, to 40% of Imax

neuroservices ALLIANCE

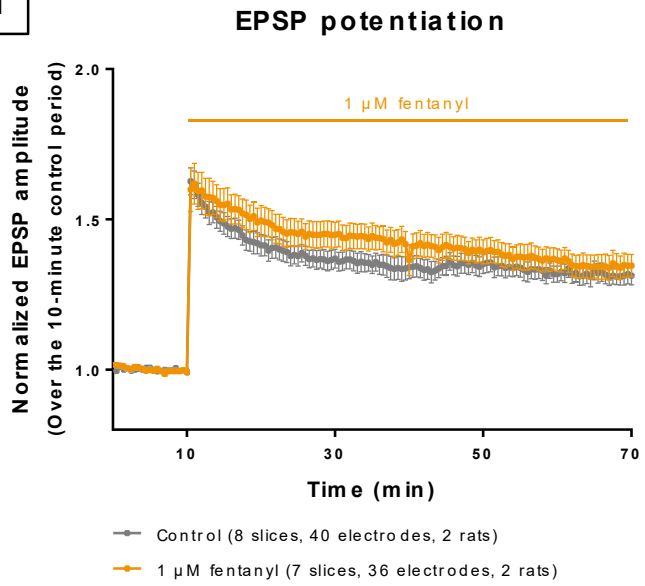
RESULTS

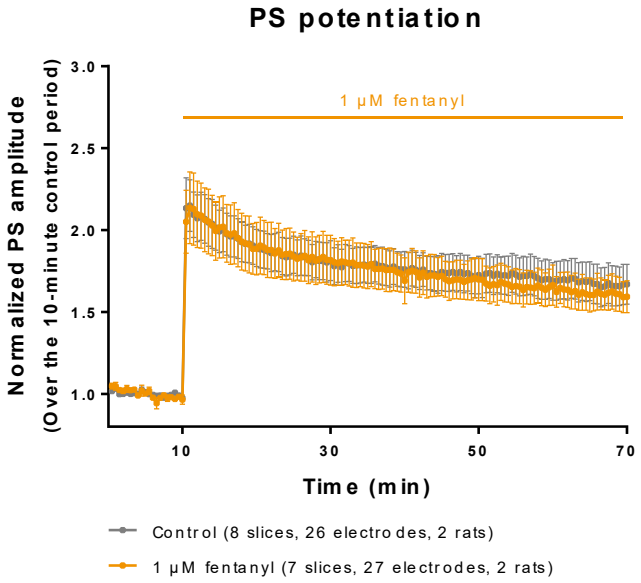
Opioids receptors

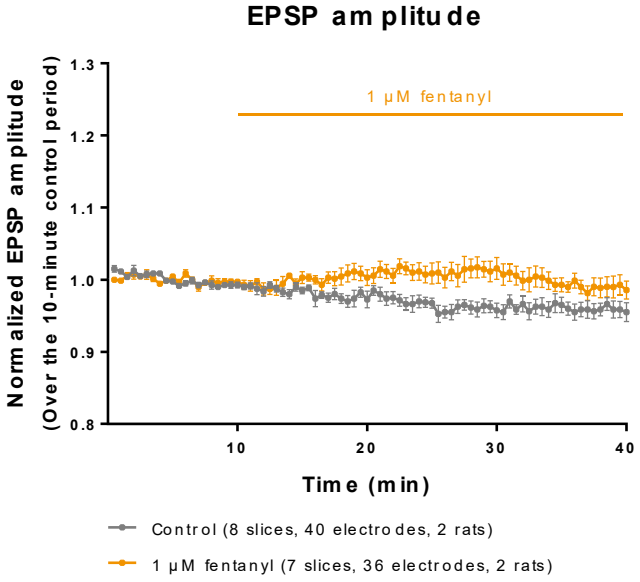
Main summary

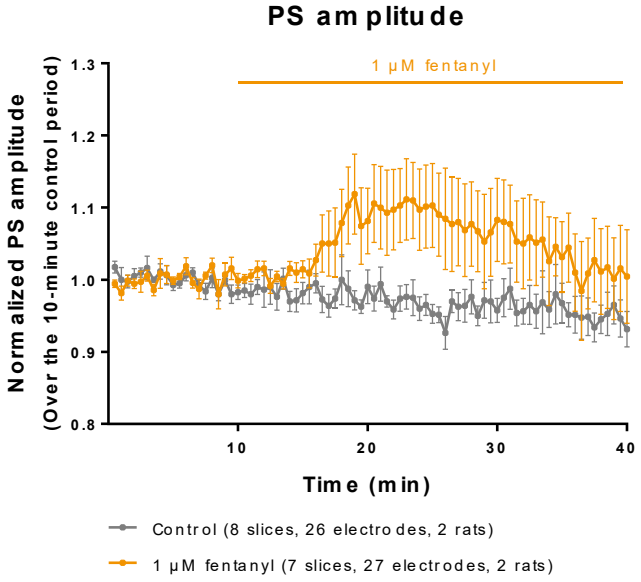
SC-CA1 summary

Fentanyl









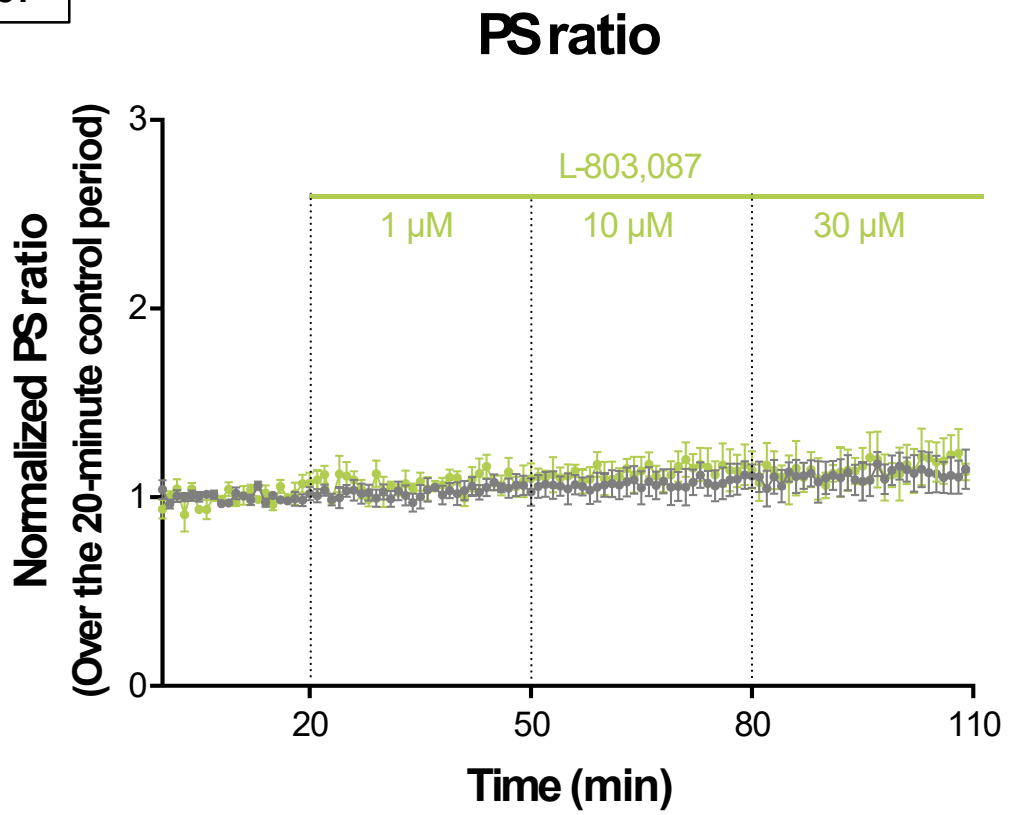
- **1 µM fentanyl did not modify the potentiation of both EPSP and PS.**
- **1 µM fentanyl applied over 30 minutes increased the amplitude of both EPSP and PS but effect was more prominent on the PS.**

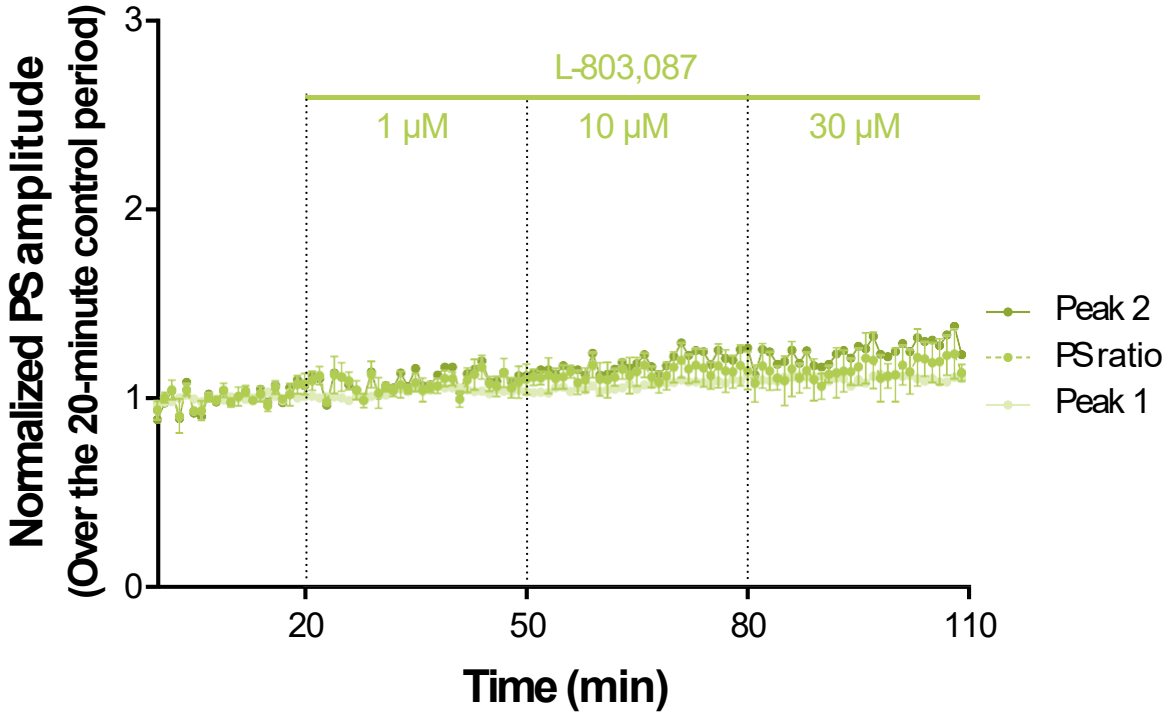
RESULTS

Somatostatin receptors

Main summary
SC-CA1 summary

L-803,087





- In L-803,087-exposed slices – a Potent and selective sst4 agonist- the ratio of paired-PS remained steady over the 110 minutes of recording and superimposed with the vehicle slice. Both fEPSP 1 and fEPSP 2 remain unchanged after the exposure to the sst4 agonist.

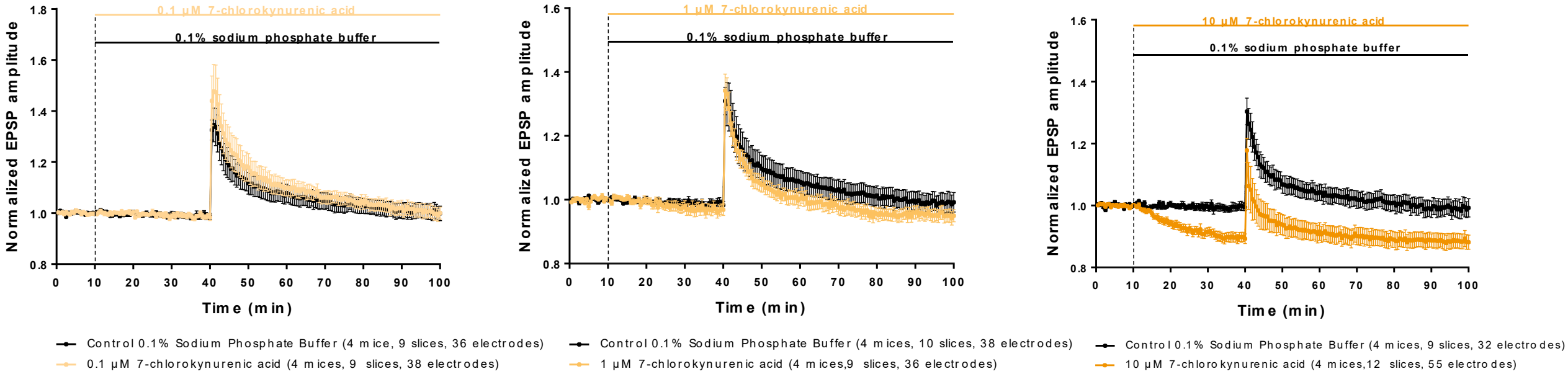
RESULTS

L-glutamate uptake

Main summary

SC-CA1 summary

7-chlorokynurenic acid



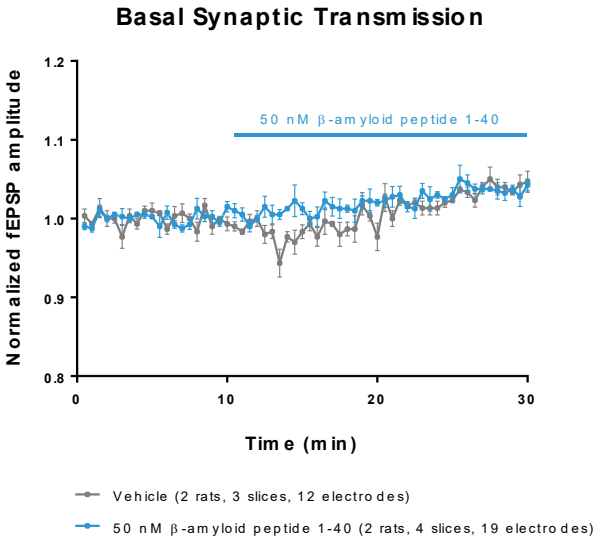
- In the CA1 region of hippocampal slices, 0.1 µM and 1 µM 7-chlorokynurenic acid - Potent competitive inhibitor of L-glutamate uptake - did not modify the basal synaptic transmission, over a 30-minute period. 10 µM 7-chlorokynurenic acid decreased the EPSP amplitude by about 10 %.

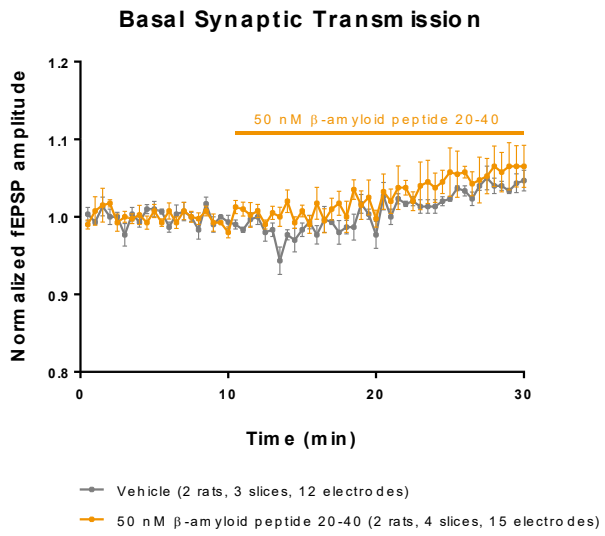
- In overall, the Short-Term Potentiation was in the same range in vehicle and 7-chlorokynurenic acid-exposed slices at any concentration tested.

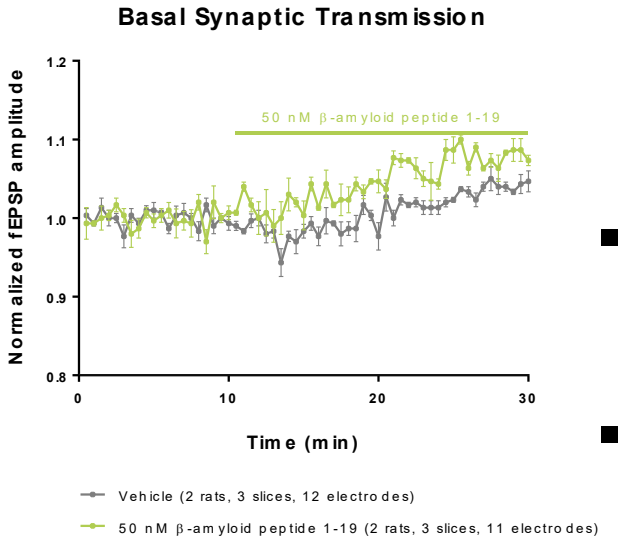
RESULTS

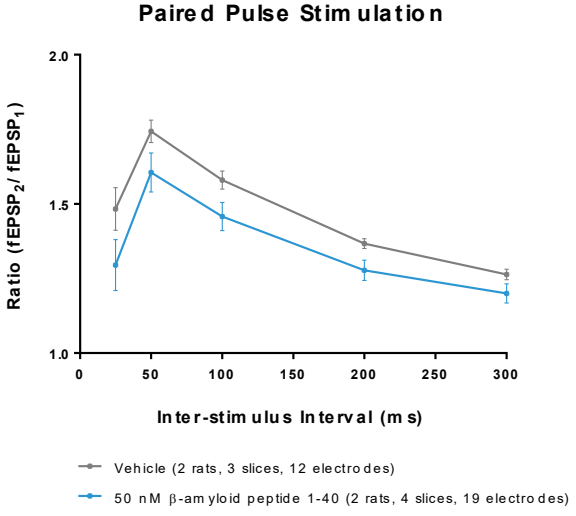
Amyloid-β peptides (1/2)

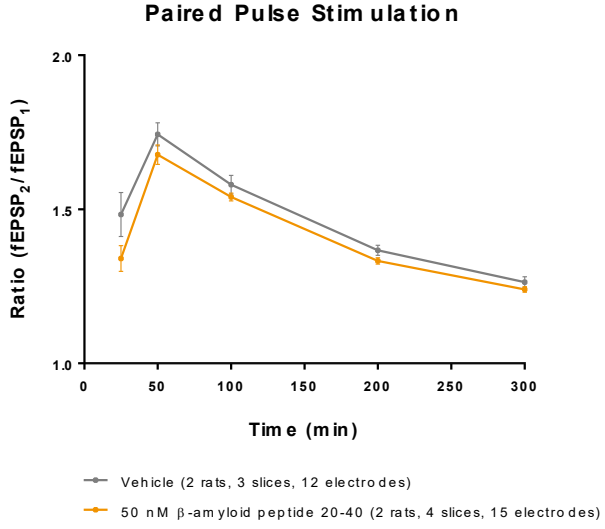
Main summary
SC-CA1 summary

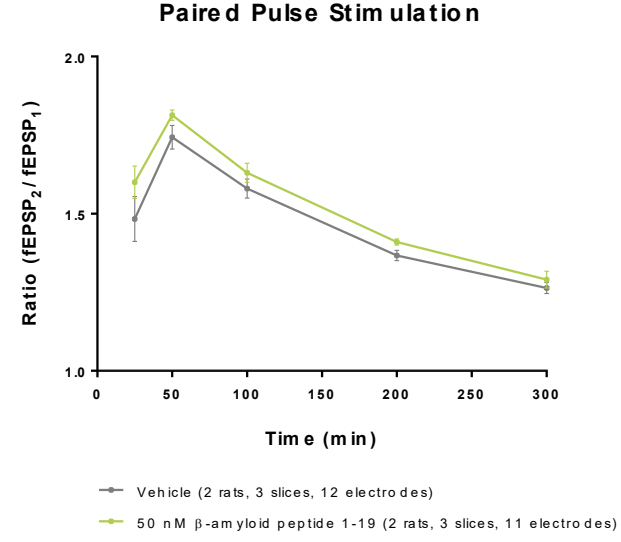










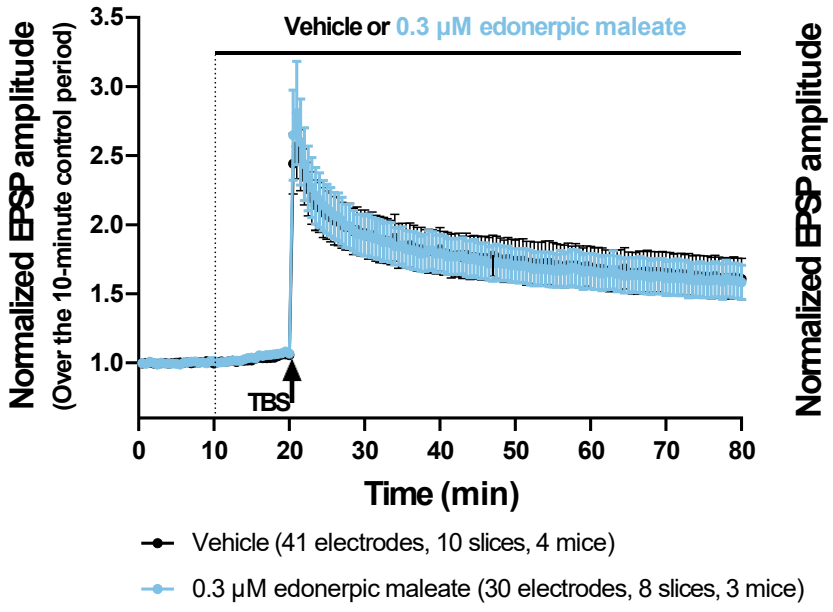


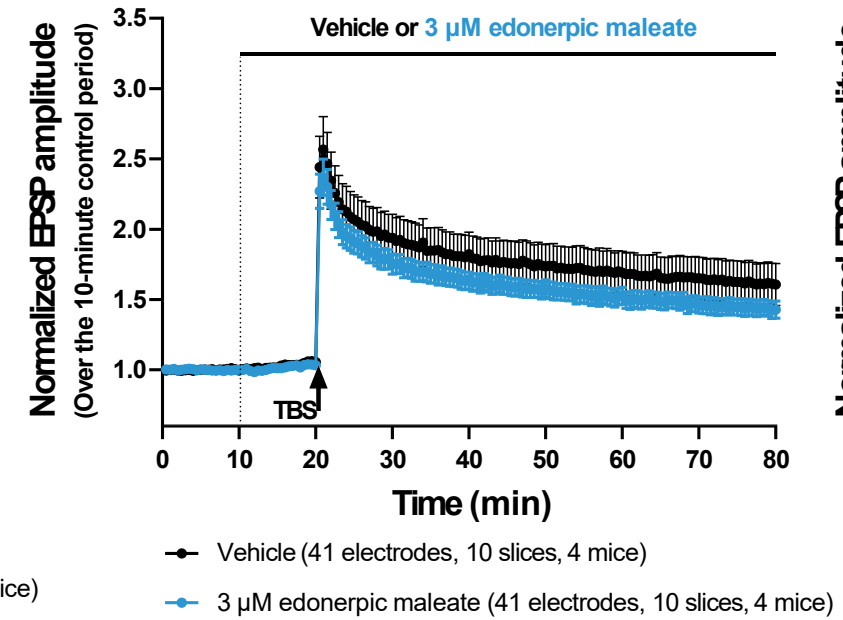
- Amyloid-β peptides (Aβ) - do not modified the amplitude of fEPSPs over 20 minutes exposure.
- The short-term plasticity remained in the same range as well, however Amyloid-β peptides (Aβ) 1-40 trend the reduce the facilitation.

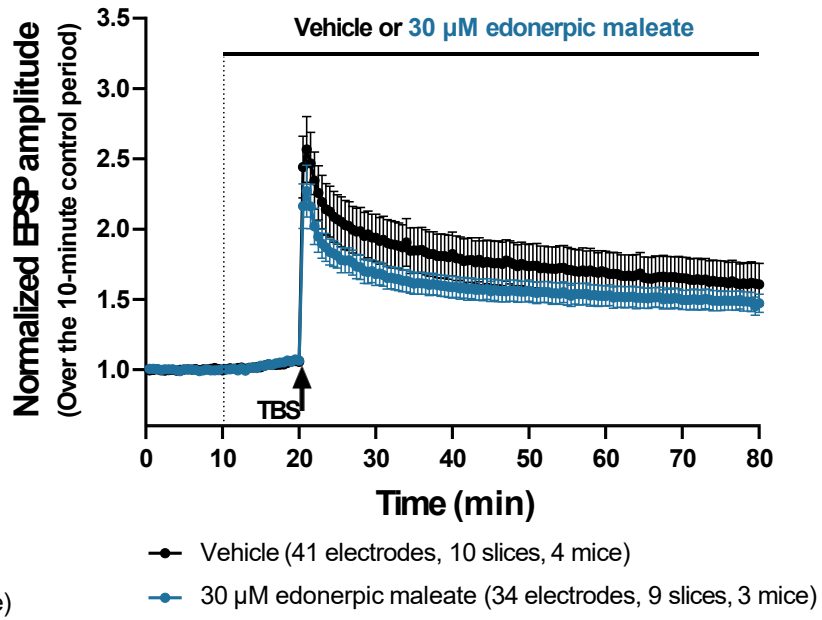
RESULTS

Amyloid-β peptides (2/2)

Main summary
SC-CA1 summary







- None of the 3 tested concentrations of edonerpic maleate - agent which can inhibit amyloid-β peptides (Aβ) - (0.3 µM, 3 µM and 30 µM) modified the amplitude of fEPSPs nor the potentiation triggered by a mild TBS when compared to the vehicle

DENTATE GYRUS SYNAPSES
Perforant path & Mossy fiber

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ALLIANCE

SUMMARY – Dentate gyrus synapses

Main summary

Dentate gyrus synapses

- Information about the MPP and LPP fibers
- Long-term potentiation

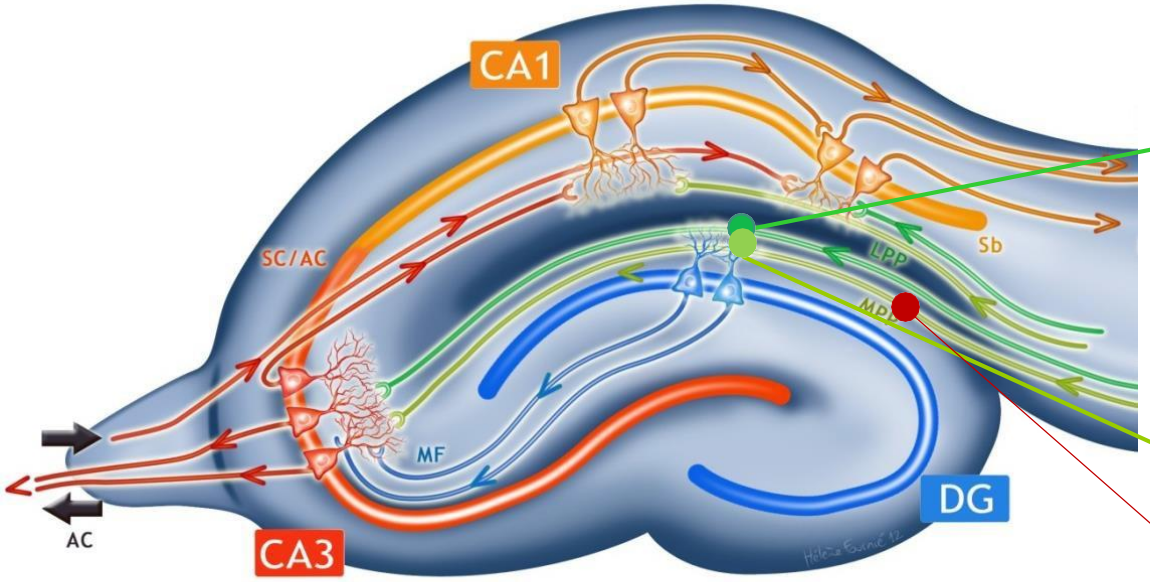
RESULTS

- NMDA receptors antagonists – D-AP5
- mGluR III – L-AP4 / VU0155041 / LSP1-2111
- mGluR II – DCG-IV / LY 379268 / MGS0008 / LY341495
- GABA receptors – Picrotoxin

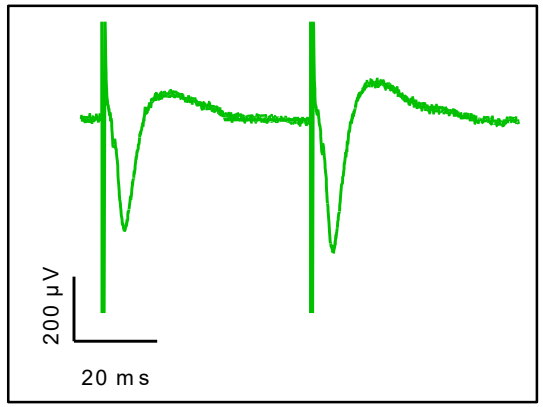
DENTATE GYRUS SYNAPES

Information about the MPP and LPP fibers

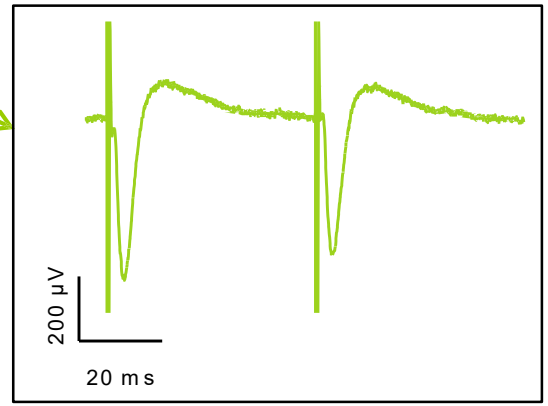
Main summary
Dentate gyrus summary



Lateral Perforant Path (LPP)



Medial Perforant Path (MPP)



- While paired-stimuli are applied with a 50 ms interval, evoked-responses at LPP synapses display a Paired-Pulse Facilitation (PPF), whereas the ones recorded at MPP synapses display a Paired-Pulse depression (PPD).
- Pre-synaptic metabotropic Glu4, 7 and 8 receptors are known to be expressed at Lateral Perforant Path (LPP) synapses within the hippocampus (Corti, Neuroscience, 2002). mGluR4 agonists might be involved in L-AP4 decrease of excitatory synaptic transmission at LPP synapses (Bushell, Neuropharmacol., 1996).
- The discrimination between both pathways can be pharmacologically confirmed : mGluRIII agonists (such as L-AP4) selectively decrease the evoked-responses at LPP whereas mGluRII agonists (such as DCG-IV) selectively decrease the evoked-responses at MPP

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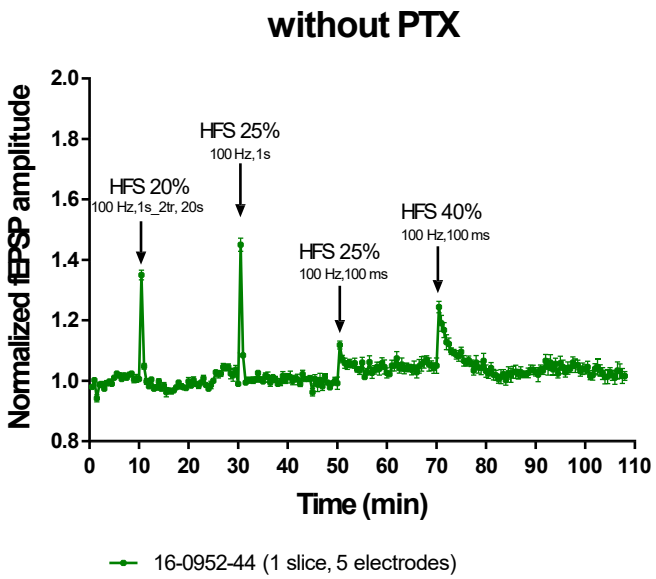
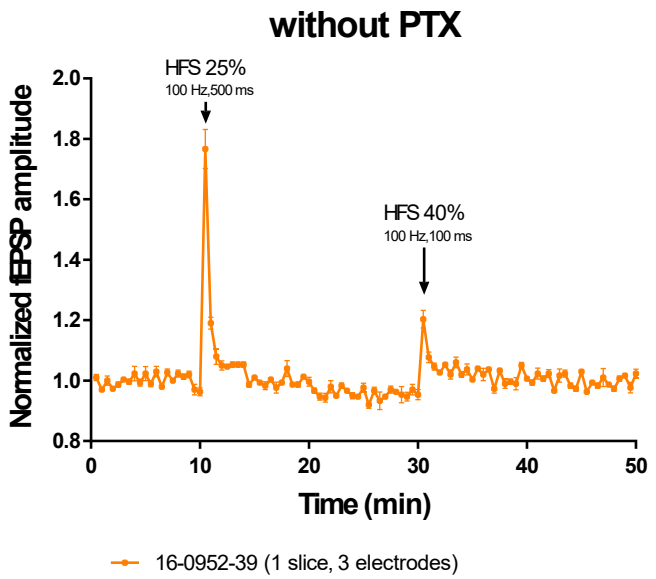
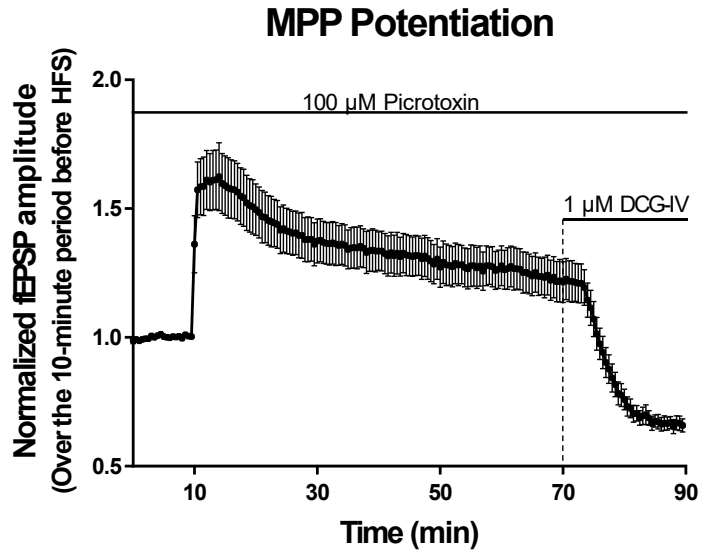
DENTATE GYRUS SYNAPES

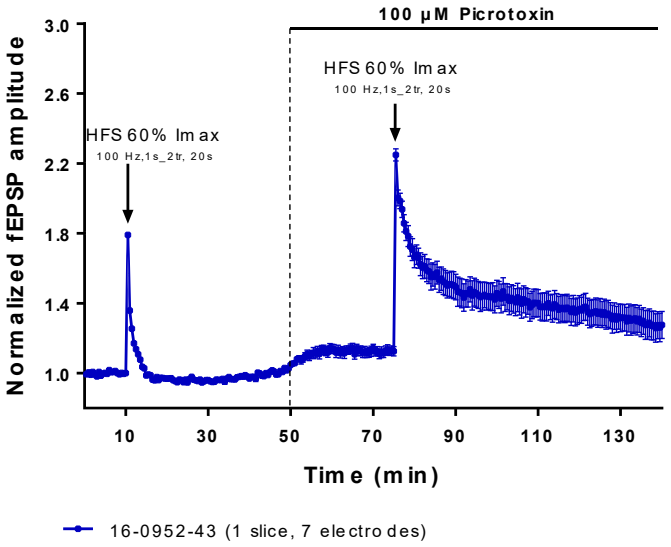
Long-term potentiation

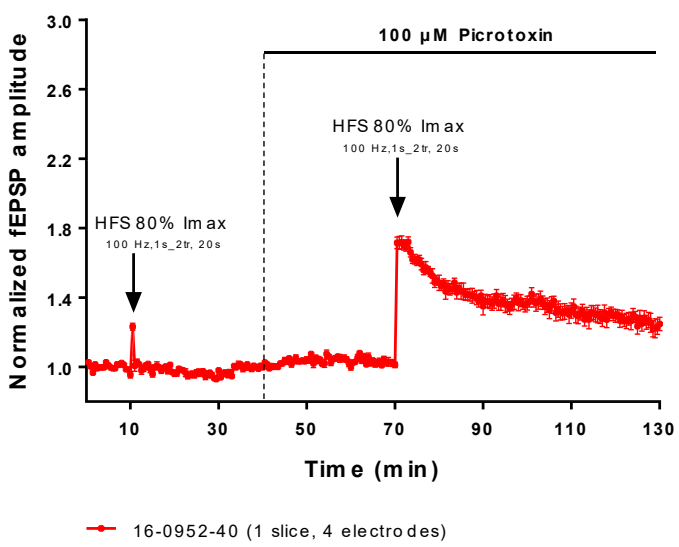
Main summary
Dentate gyrus summary











- In the absence of GABAA receptors antagonist, none of the HFS protocol tested was able to elicit a lasting potentiation (see above, non exhaustive examples of HFS protocols tested).
- The second HFS (same stimulation pattern as the first one) applied in the presence of 100 µM PTX triggered a large and lasting potentiation of the evoked responses, for both tested stimulation intensities (60 and 80% of Imax).
- The blockade of GABAergic tone is required to induce Long-term potentiation in both LPP and MPP

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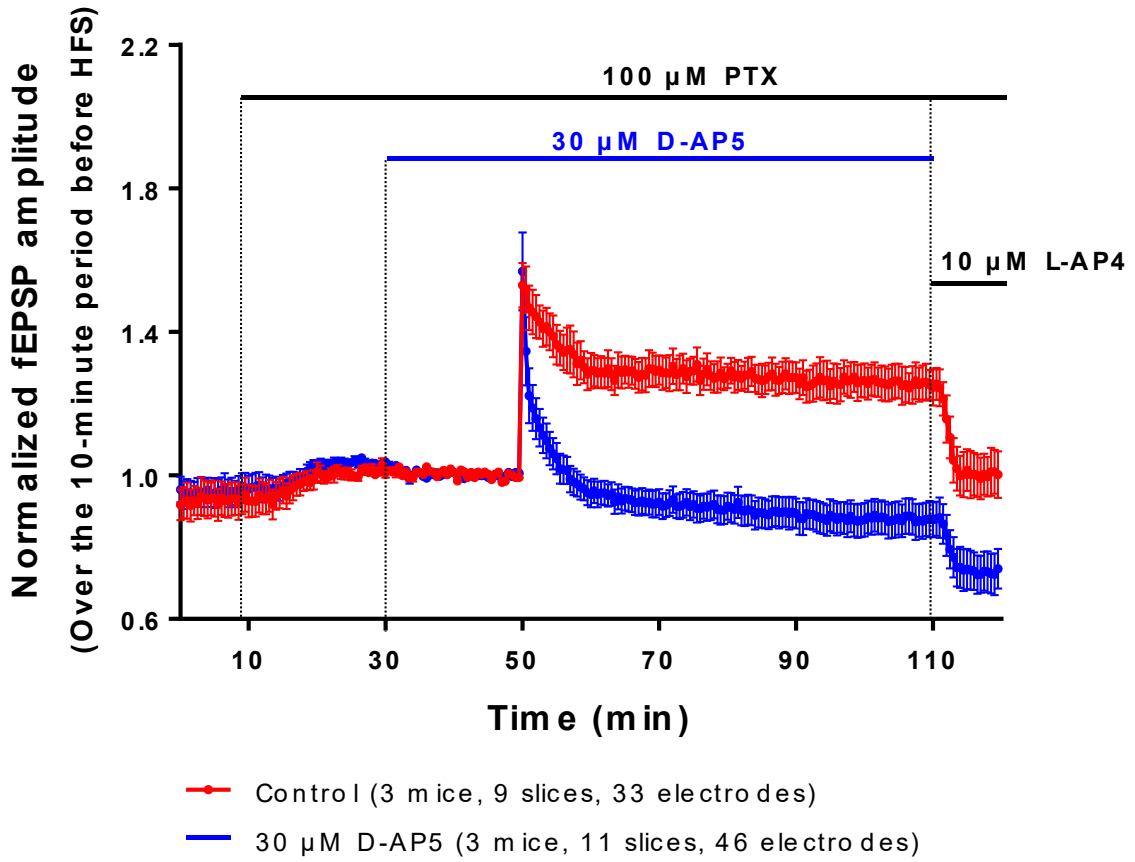
RESULTS

NMDA receptors

Main summary
Dentate gyrus summary

D-AP5



- In the presence of 100 µM Picrotoxin, HFS induced a large potentiation of the fEPSP amplitude, that maintained over 1 hour.
- 30 µM D-AP5 (NMDA receptors antagonist) co-perfused with 100 µM Picrotoxin fully inhibit the HFS. In accordance with literature data (Colino and Malenka, 1993; M. V. BARATTA et Al., J Neurophysiol, 2002) the LTP at the LPP synapses is fully NMDA dependent.
- L-AP4 confirms that the recorded evoked responses results from a stimulation of the LPP pathway.

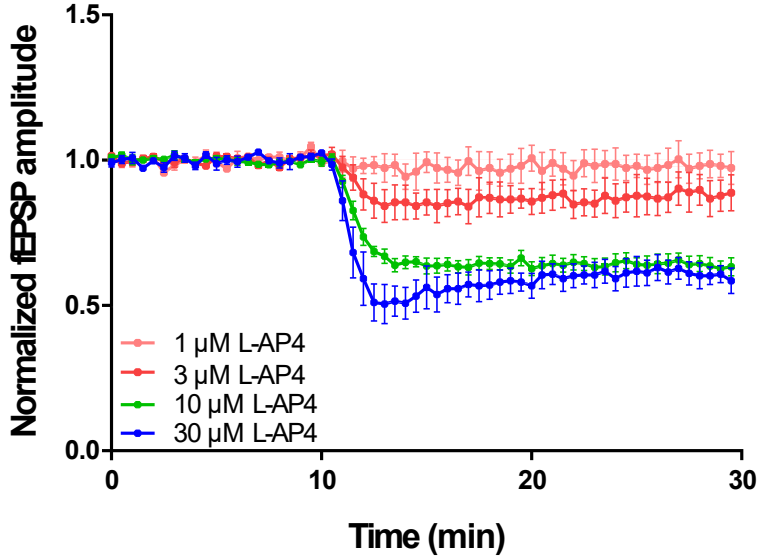
Experiments carried out with 3 to 6 month-old C57/black 6 mice
HFS : 2 trains of stimulation at 100 Hz for 1 second with 20 seconds interval at 80% Imax

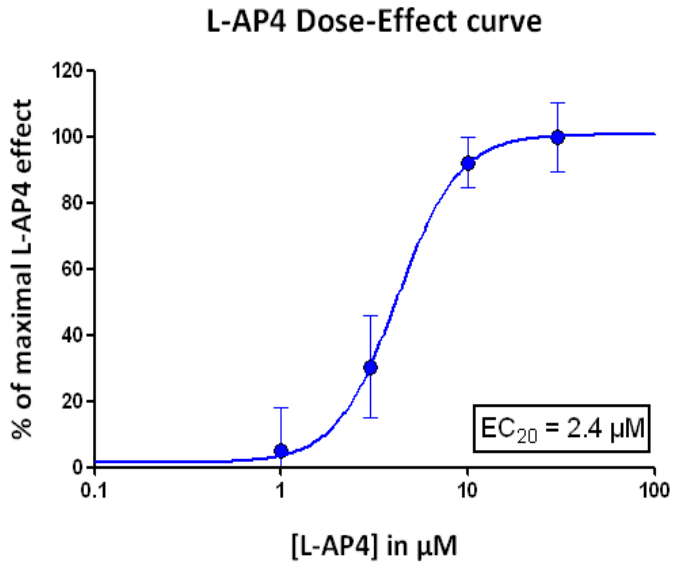
RESULTS

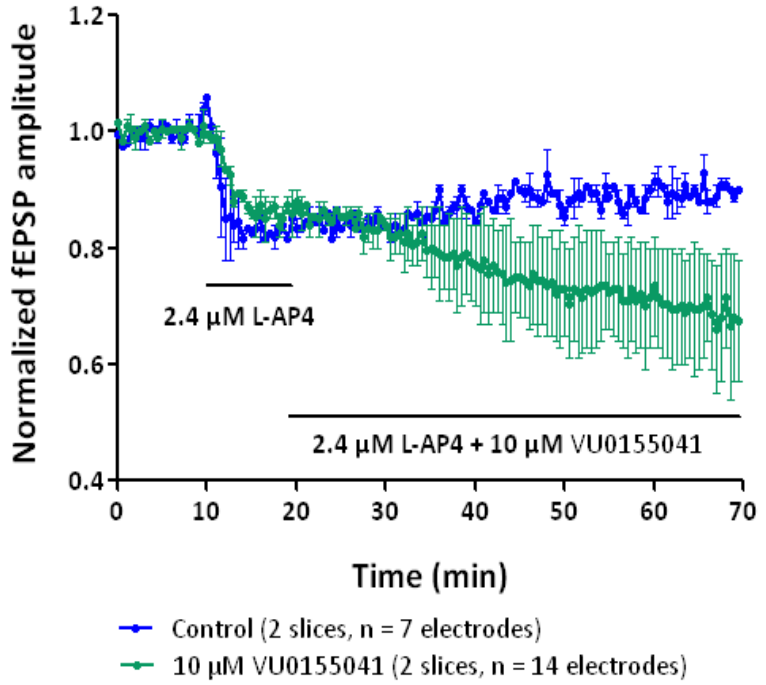
mGluR III – LPP synapses

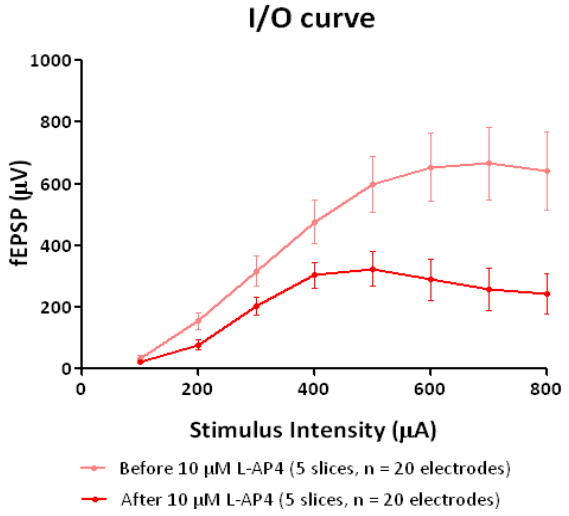
Main summary
Dentate gyrus summary

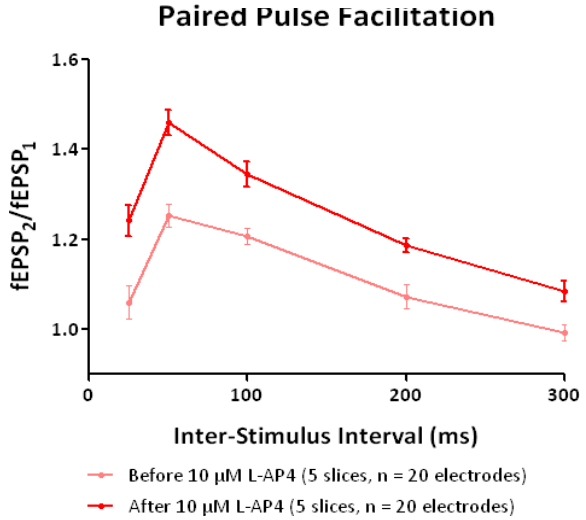
L-AP4, VU0155041











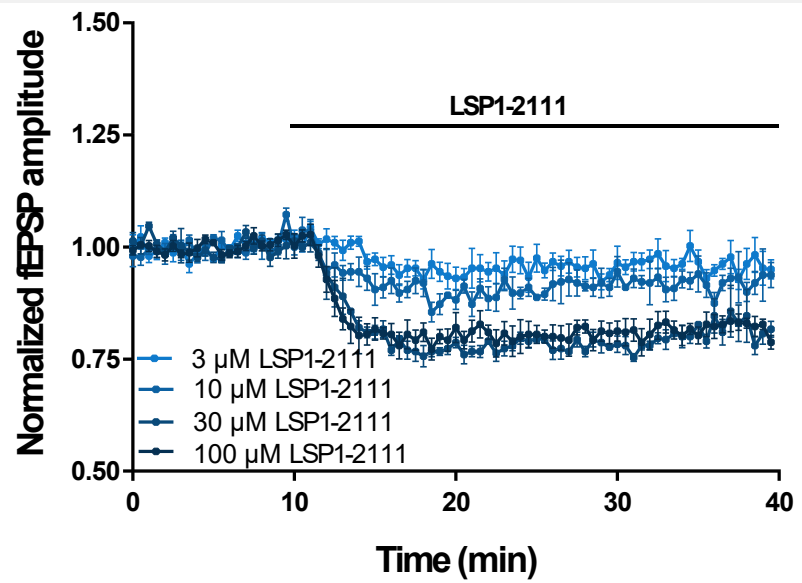
- L-AP4 - a selective agonist of group III metabotropic glutamate receptor - dose-dependently decreases evoked-responses amplitude at LPP synapses, with stronger effect to the higher stimulation intensities consistently with mGluR III presynaptic regulatory functions, to control the release of neurotransmitters. The paired-pulse ratio at LPP synapses is increased confirming the pre-synaptic nature of the L-AP4 effect.
- VU0155041 – a $mGluR_4$ PAM – enhances L-AP4 effect

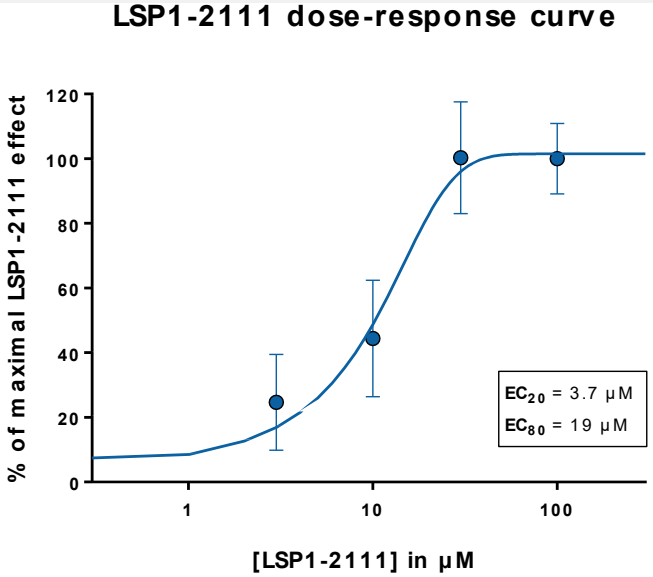
RESULTS

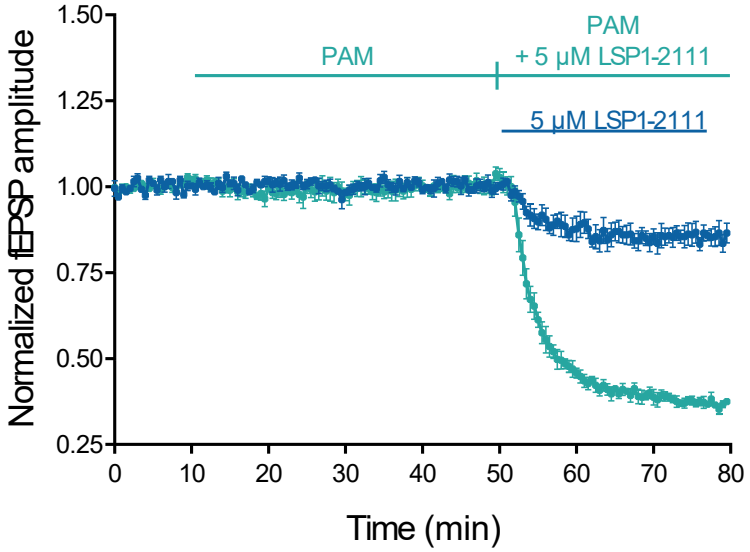
mGluR III – LPP synapses

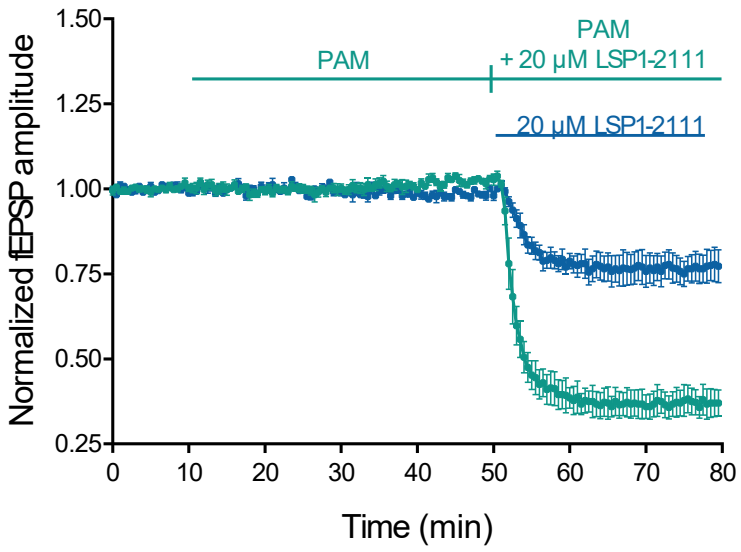
Main summary
Dentate gyrus summary

LSP1-2111









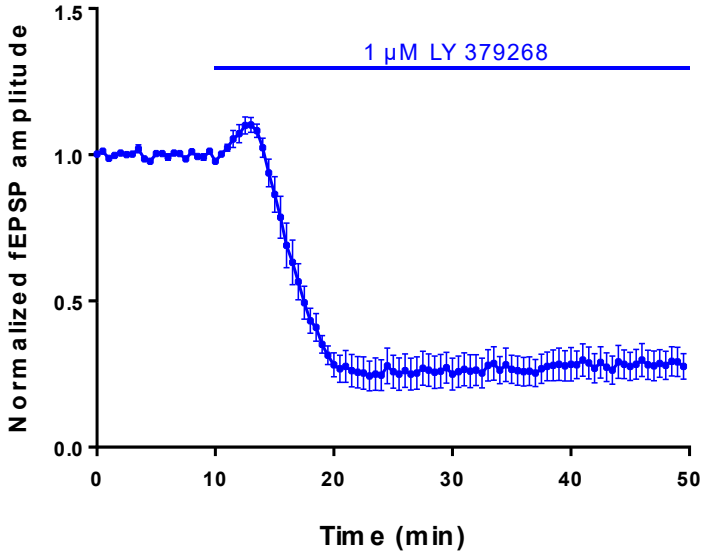
- LSP1-2111 – a potent agonist acting at the orthosteric site of group III mGlu receptors, with a preferential affinity on the mGlu4 receptor - dose-dependently decreases the fEPSP amplitude at LPP synapses.
- Putative mGluR4 PAM enhances the effect of LSP1-2111

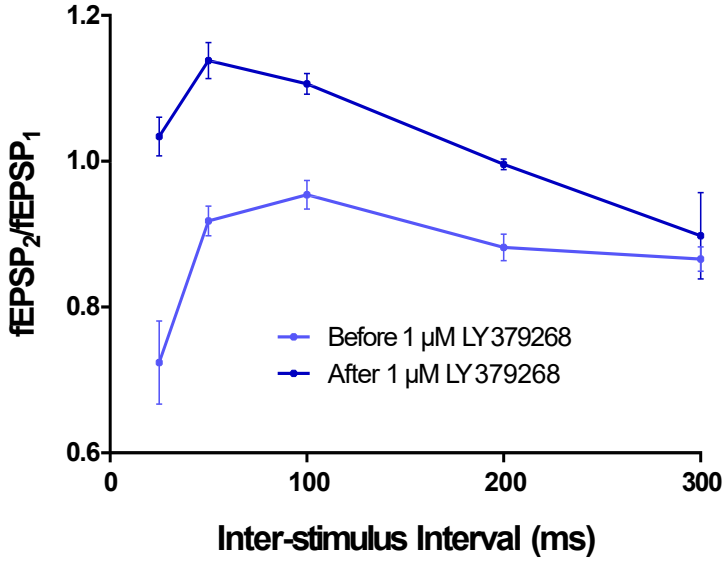
RESULTS

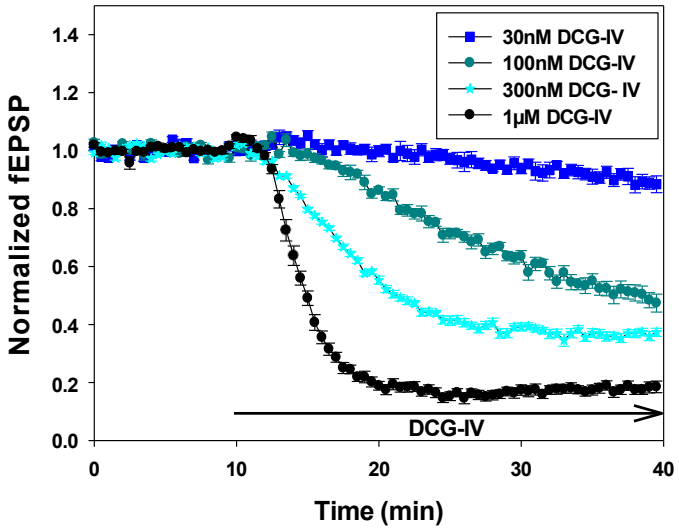
mGluR II – MPP synapses

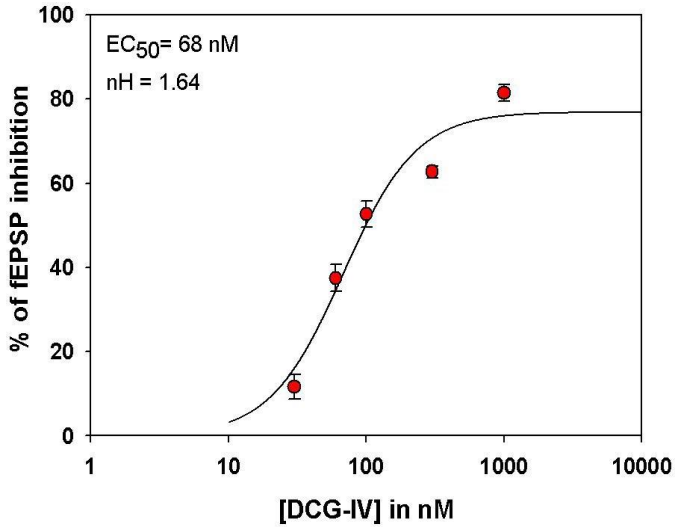
Main summary
Dentate gyrus summary

LY 379268, DCG-IV









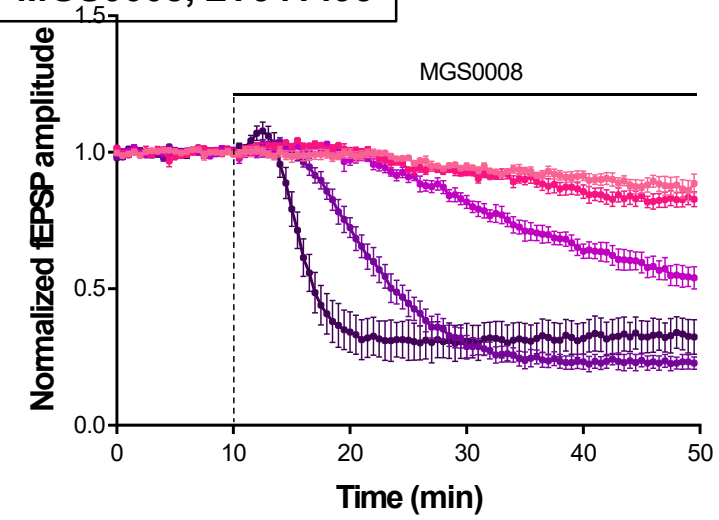
- The highly selective mGluR II agonist LY 379268 drastically decreases the fEPSP amplitude at MPP synapses.Its effect is almost maximal after only 10 minutes. At endpoint, the fEPSP amplitude is decreased by about 75%.
- LY 379268 at 1 µM largely increases the paired-pulse ratio, after a 40-minute exposure. The compound's effect becomes stronger as the inter-stimulus interval decreases. This confirm the pre-synaptic nature of LY 379268 effect.
- DCG-IV is a very potent and selective mGluR II agonist. DCG-IV dose-dependently decreases the fEPSP amplitude.

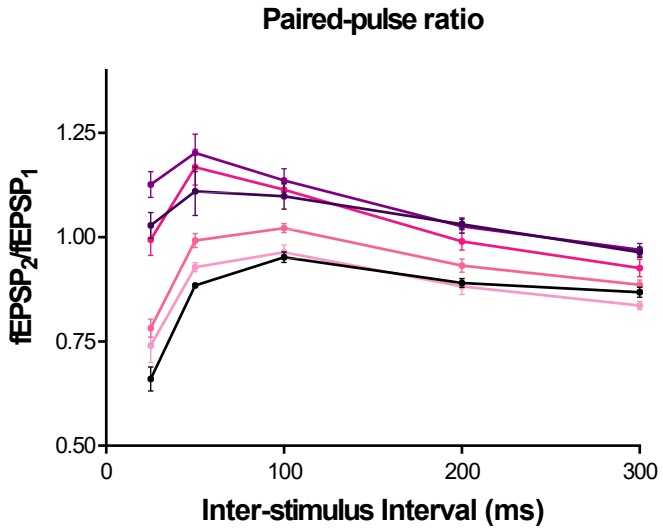
RESULTS

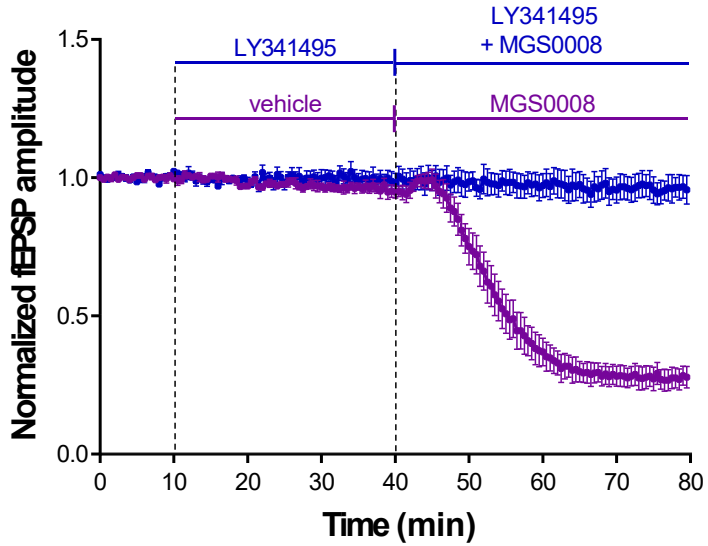
mGluR II – MPP synapses

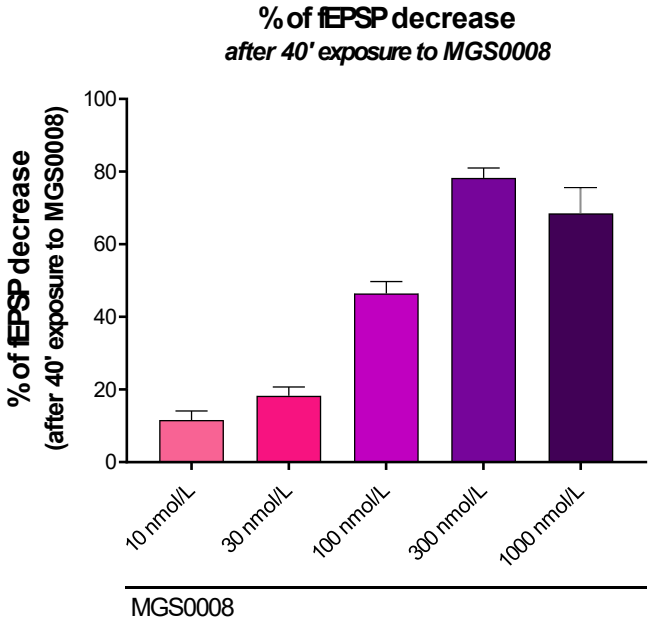
Main summary
Dentate gyrus summary

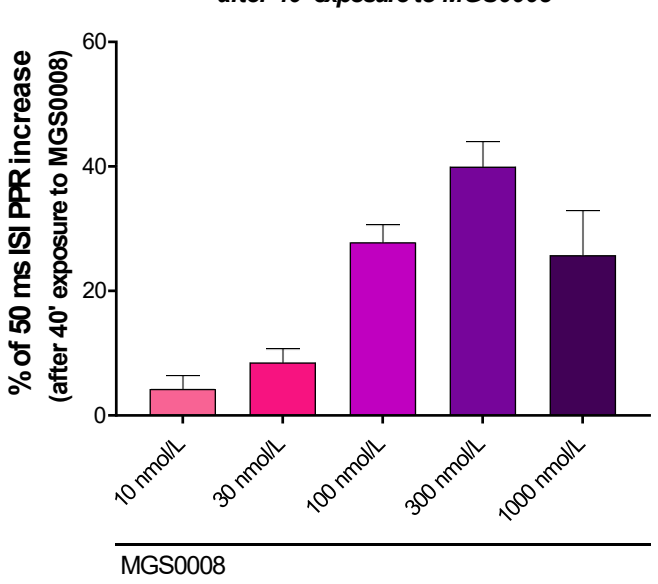
MGS0008, LY341495











- MGS0008 – a selective group II mGluR agonist dose-dependently decreased the fEPSP amplitude recorded in the Dentate Gyrus when stimulating the MPP fibers and increased the PP ratio.
- LY341495 – a potent and selective group II mGluR antagonist - do not modify the fEPSP but fully inhibit the effect of MGS0008

Data averaged from 5 slices from 3 rats for each conditions

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TEMPORO AMMONIC PATHWAY

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ALLIANCE

SUMMARY – Temporo ammonic pathway

Main summary

TEMPORO AMMONIC PATHWAY

- Information about the temporoammonic pathway
- Long-term potentiation

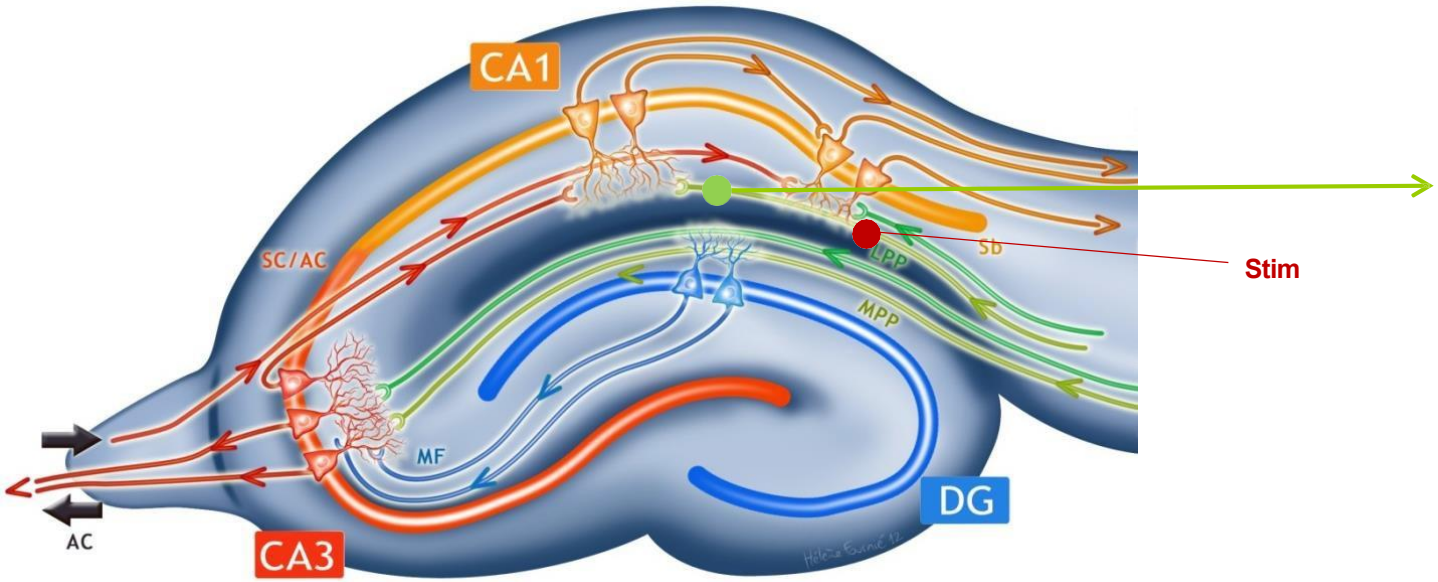
RESULTS

- Adrenergic receptors – A61603

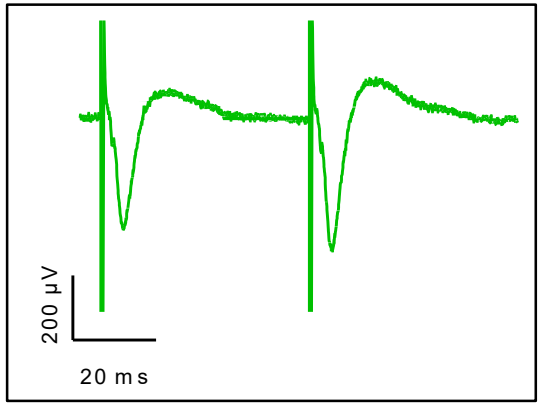
TEMPORO AMMONIC PATHWAY

Information about the Temporo ammonic pathway

Main summary
Temporo ammonic pathway summary



Temporoammonic pathway (TAP)

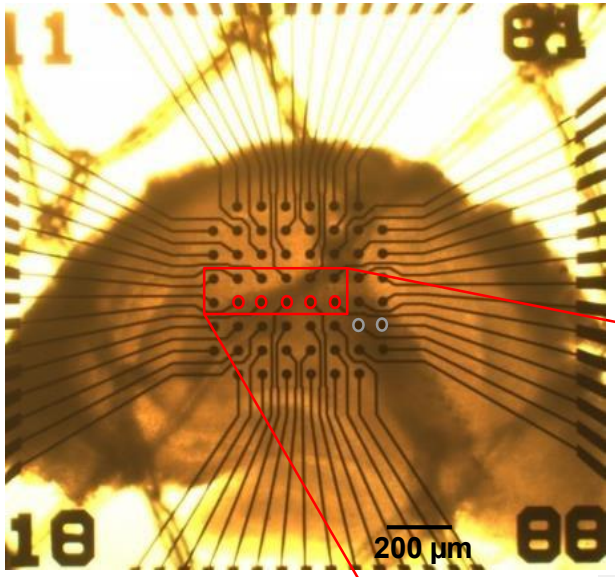


- The hippocampal CA1 region receives cortical information directly via the temporoammonic pathway

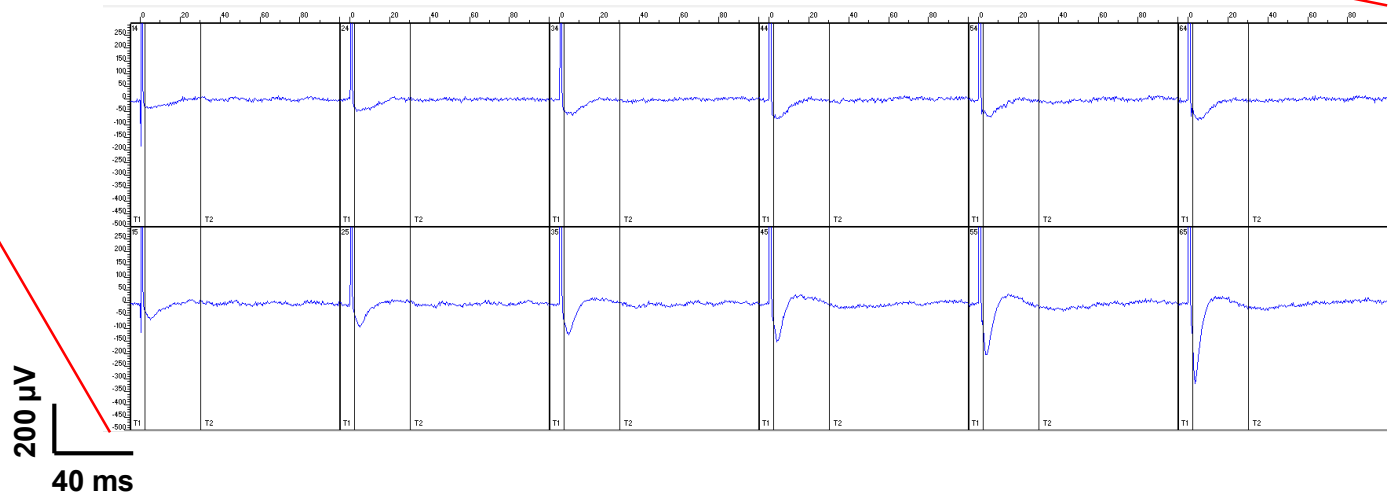
TEMPORO AMMONIC PATHWAY

Information about the Temporo amonic pathway

Main summary
Temporo ammonic pathway summary



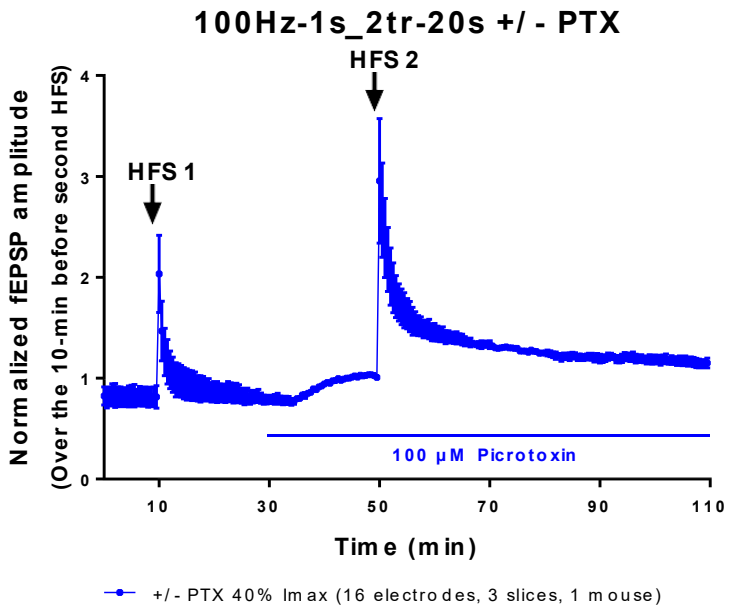
- Electrodes used to selectively stimulate the TAP pathway are surrounded in blue. The electrodes surrounded in red display evoked-responses at TAP synapses, and figured below the picture of the slice.

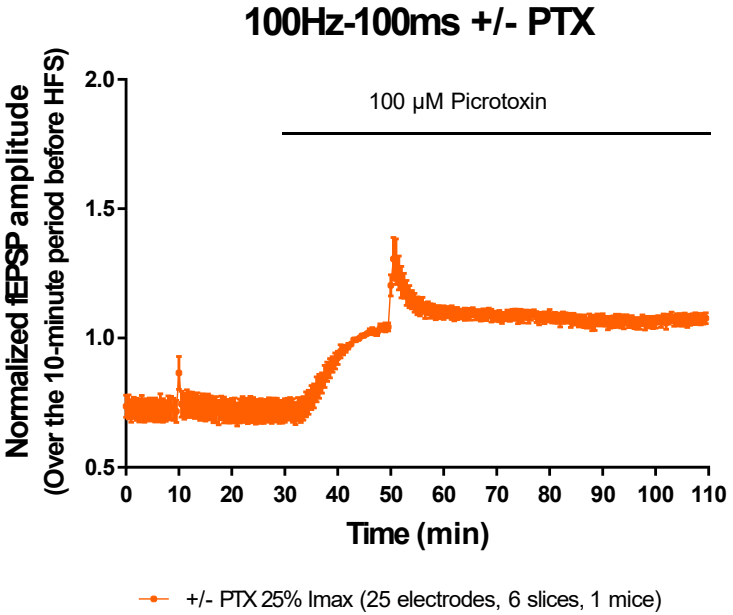


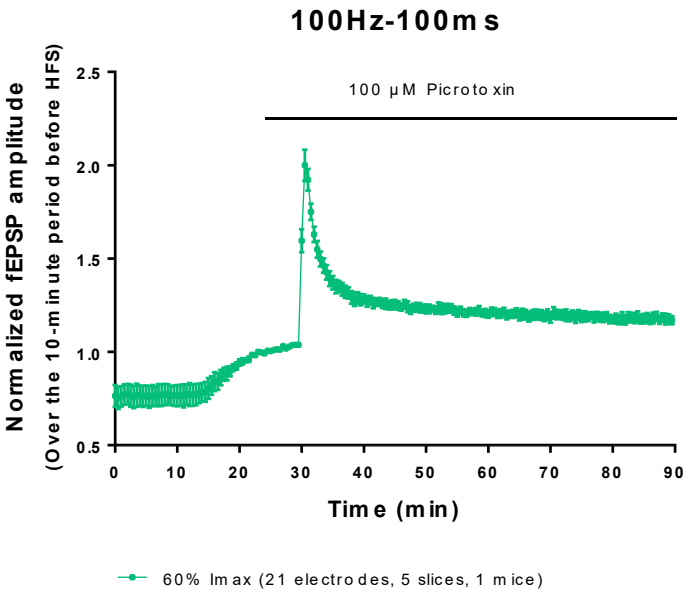
TEMPORO AMMONIC PATHWAY

Long-term potentiation

Main summary
Temporo ammonic pathway summary







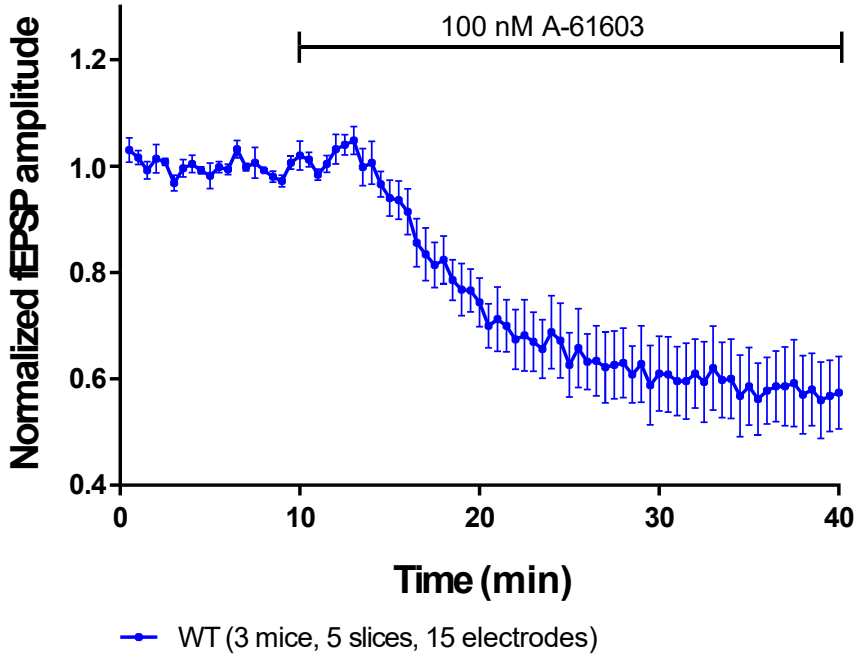
- The blockade of inhibitory tone is required to incude long-term plasticity at the TAP. A second tetanus (same stimulation pattern as the first one) applied in the presence of 100 µM PTX triggered a larger potentiation of the evoked responses.
- The amplitude of the evoked-responses slightly increased upon exposure to 100 µM PTX and rapidly stabilized (after about 10 minutes).
- The fibers needs to be stimulate at an high intensity. the same protocol (100Hz, 100ms) tested with 100 µM PTX, do not induced substantial potentiation at 25 % I max but potentiate fEPSPs at 60% of Imax.

RESULTS

Adrenergic receptors

Main summary
Temporo ammonic pathway summary

A-61603



- A-61603 – $\alpha 1_A$ receptors agonist – decreases fEPSP at the Temporo amonic pathway