Poster P841

In vitro electrophysiological study of hippocampal network activity in a mouse model of STXBP1 haploinsufficiency

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Overview

QUESTION

Does STXBP1 haploinsufficiency affect hippocampal network activity and short-term plasticity?

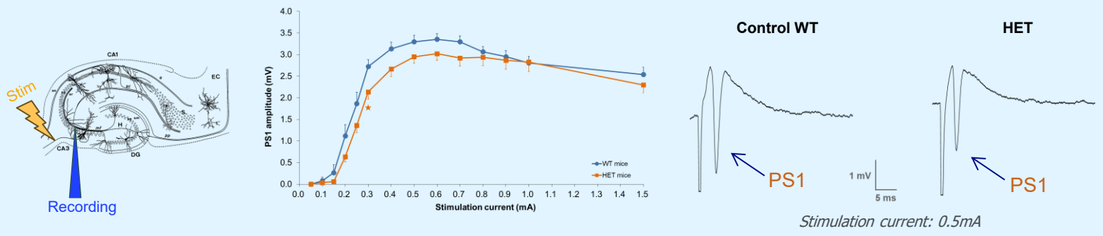
INVESTIGATION

We used conventional extracellular field potential recordings to measure synaptic transmission and short-term plasticity in acute hippocampal slices from STXBP1 HET mice vs littermate WT mice

RESULTS

Synaptic transmission in STXBP1 HET

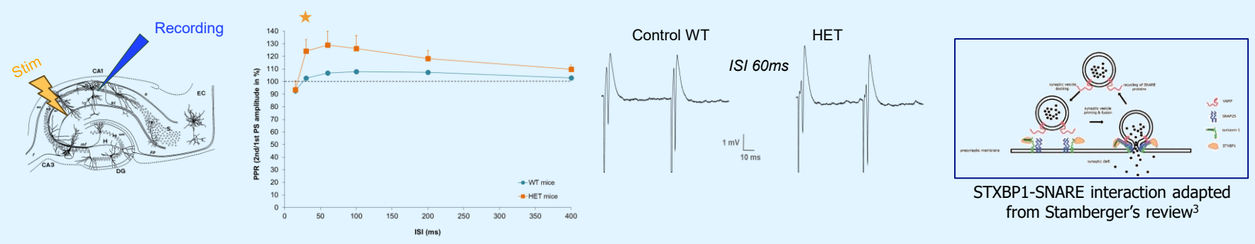
- **Minor decrease of synaptic responses observed in CA3 region from HET mice**
- **This result is in agreement with previous observations performed from HET neurons[1,2]**



- **Synaptic transmission in CA1 and DG regions is not impacted**
- **No spontaneous bursting observed in all investigated hippocampal regions**

Short-term plasticity in STXBP1 HET

- **A significant increase in paired-pulse facilitation (PPF) is observed at CA3 to CA1 synapse**
- **This result is in agreement with previous observations performed from STXBP1 variants[5] and HET[4] neurons, and with the predicted role of STXBP1-SNARE in the presynaptic fusion machinery[3]**



- **Short-term plasticity evaluated at fimbria to CA3 and CA3 to DG synapses is not impacted**

CONCLUSIONS

Overall excitability, synaptic transmission, and short-term plasticity remain unchanged in the hippocampal regions of STXBP1 HET mice, except in CA3 and CA3-to-CA1 synapse, where a reduced synaptic transmission and a potential dysfunction in presynaptic vesicular release were noticed, respectively.

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Background

- STXBP1 haploinsufficiency disorders are associated with neurodevelopmental delay, seizures and intellectual disability. Reduced levels of STXBP1 protein in heterozygous mice (HET) might result in changes in synaptic transmission and in short-term plasticity.
- Previous studies investigating network activity in neurons from STXBP1 HET mice or hIPSC derived STXBP1 HET neurons highlighted the impact of STXBP1 haploinsufficiency on neuronal network activity [1,2,4,5].

Objective

- We investigated the synaptic transmission and short-term plasticity in acute hippocampal slices of a HET mouse strain that has been extensively characterized.
- Aim was to identify potential changes in hippocampal synaptic transmission and short-term plasticity in HET mice.

Methods

Hippocampal slices were obtained from 5 male HET mice and 5 WT littermate 11- to 14-week-old mice.

Sagittal hippocampal slices (350 µm thick) were cut with a vibratome in ice-cold and oxygenated (95% O2, 5% CO2) choline-ACSF composed of (in mM): 126 choline-Cl, 3 KCl, 2.4 CaCl2, 1.3 MgCl2, 1.24 NaH2PO4, 26 NaHCO3, and 10 glucose, pH 7.4

Slices were kept for ~2 h at 32 °C in oxygenated (95% O2, 5% CO2) standard ACSF composed of (in mM): 126 Na-Cl, 3 KCl, 2.4 CaCl2, 1.3 MgCl2, 1.24 NaH2PO4, 26 NaHCO3, and 10 glucose, pH 7.4

The slices were placed in an interface chamber where field excitatory postsynaptic potentials (fEPSPs) were acquired with a glass microelectrode (impedance ~1.5 MΩ) via an Axoclamp 2B amplifier. Recordings were performed at 32°C with perfusion ACSF flowing at a rate of 1.5 mL/min.

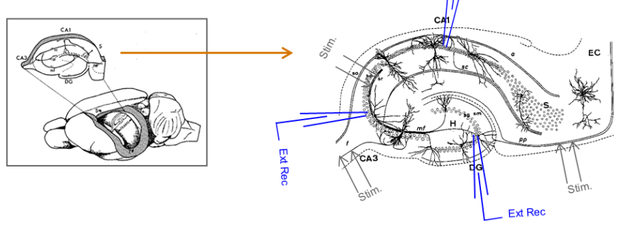


Figure 1 – stimulation and recording areas in hippocampal slice

SYNAPTIC TRANSMISSION AND NEURONAL EXCITABILITY

- Input–output (I/O) functions: increasing intensities of stimulation were applied pre-synaptically (input) in perforant path, fimbria and Schaeffer collaterals and post-synaptic responses (output) were measured in DG, CA3 and CA1 principal layers
- First PS (population spike) or PS1 amplitude and number of PSs according to increasing intensities of stimulation were measured and compared in hippocampal slices from HET and WT mice for assessing the potential changes in synaptic transmission strength

SHORT-TERM PLASTICITY

- Paired-pulse (PP) experiments consisted in 2 pulses paired in quick succession (15–400 ms)
- This experiment was used to determine whether paired pulse depression (PPD, generally observed for inter stimulation intervals (ISI) <30ms at investigated synapses) or paired pulse facilitation (PPF, observed for ISI 30-200ms) were impacted in hippocampal slices from HET mice.

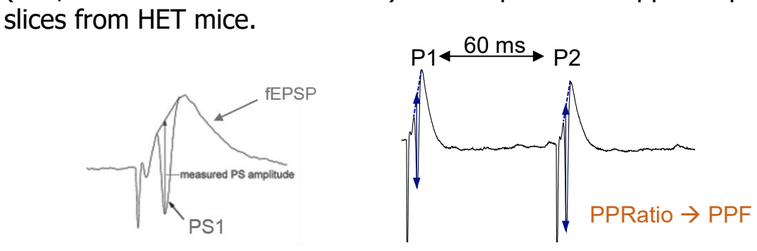
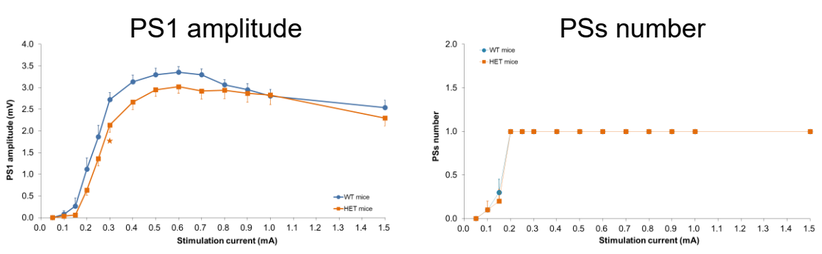


Figure 2 – illustrative examples of LFP recording in CA1

A. PS1 elicited on fEPSP recorded in CA1 pyramidale layer
B. Paired-pulse facilitation induced by 60ms ISI paired pulse stimulation

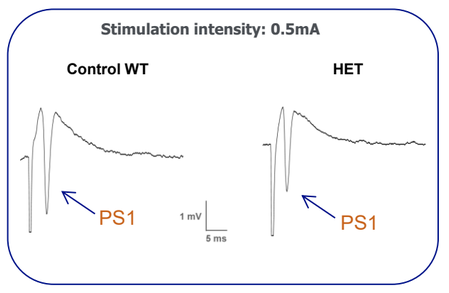
Results on synaptic transmission

CA3: MINOR DECREASE OF I/O RESPONSES IN HET MICE



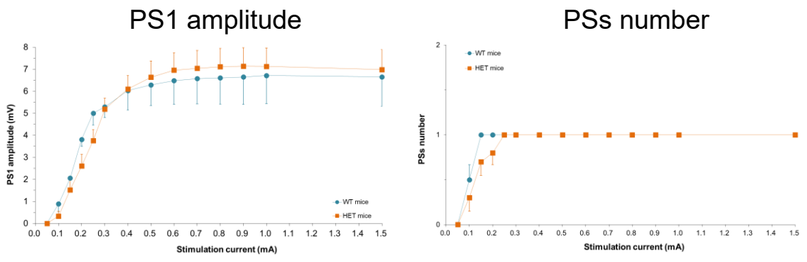
Mean ± SEM, n=10 slices/group from 5 mice/group
T-test, ★ P<0.05
Abbreviations: I/O, input/output; PS, population spike

Figure 3 – PS1 amplitude and number of PSs in CA3



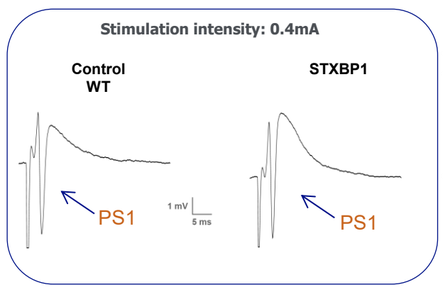
- Small trend towards a decreased PS1 amplitude for low to medium intensities of stimulation
- 1 single PS elicited from evoked fEPSP indicating no difference in neuronal synchronisation and in basal excitability in HET. No threshold change for evoking the PS.
- No spontaneous bursting slices observed both in WT and HET (not illustrated)

CA1: NO DIFFERENCE BETWEEN WT AND HET MICE IN I/O RESPONSES



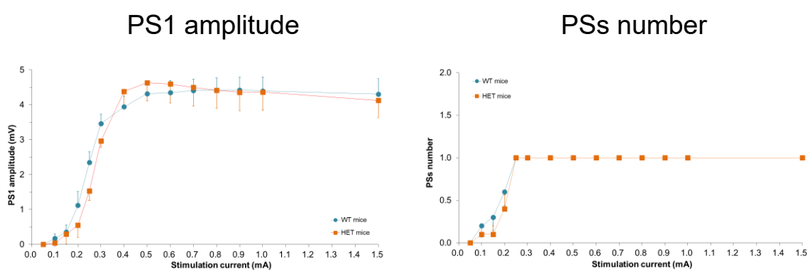
Mean ± SEM, n=10 slices/group from 5 mice/group
Abbreviations: I/O, input/output; PS, population spike

Figure 4 – PS1 amplitude and number of PSs in CA1



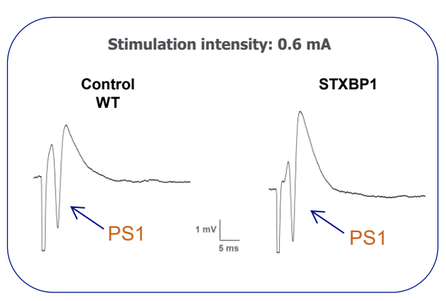
- No change of PS1 amplitude curve
- 1 single PS elicited from evoked fEPSP indicating no difference in neuronal synchronisation and in basal excitability in HET. No threshold change for evoking the PS.
- No spontaneous bursting slices observed both in WT and HET (not illustrated)

DG: NO DIFFERENCE BETWEEN WT AND HET MICE IN I/O RESPONSES



Mean ± SEM, n=10 slices/group from 5 mice/group
Abbreviations: I/O, input/output; PS, population spike

Figure 5 – PS1 amplitude and number of PSs in DG

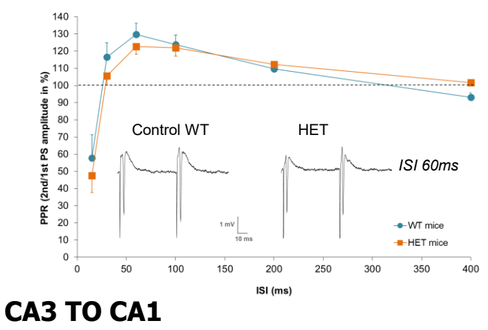


- No change of PS1 amplitude curve
- 1 single PS elicited from evoked fEPSP indicating no difference in neuronal synchronisation and in basal excitability in HET. No threshold change for evoking the PS.
- No spontaneous bursting slices observed both in WT and HET (not illustrated)

Results on short-term plasticity

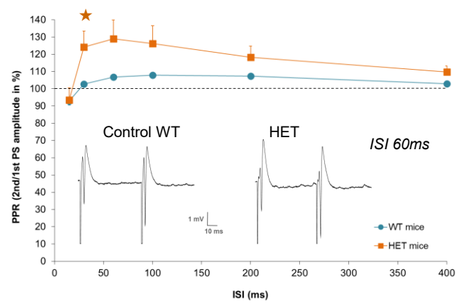
PAIRED-PULSE RATIOS OF PS1 AMPLITUDE IN HIPPOCAMPAL AREAS

FIMBRIA TO CA3



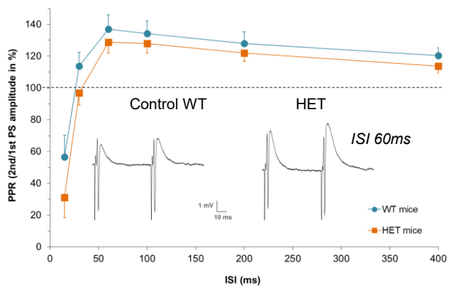
- No significant change of short-term plasticity at fimbria to CA3 synapse

CA3 TO CA1



- A significant increase in paired-pulse facilitation (PPF) is observed at CA3 to CA1 synapse

PERFORANT PATH TO DG



- No significant change of short-term plasticity at perforant path to DG synapse

Mean ± SEM, n=10 slices/group from 5 mice/group
T-test, ★ P<0.05
Abbreviations: ISI, inter-stimulation interval; PPR, paired-pulse ratio; PS, population spike; pp, perforant path

Figure 6 – Paired-pulse ratios of PS1 amplitude

- PPF reflecting the release probability of the presynaptic cells, an increased PPF in CA1 suggests a reduced release probability in HET presynaptic neurons located in CA3 pyramidal layer

Conclusions – STXBP1 HET mice

- Single evoked population spike and absence of spontaneous bursting suggest that general basal excitability in hippocampus is not exacerbated.
- Weak decrease of synaptic transmission (in CA3), in agreement with previous observations performed from HET neurons[1,2]. No change observed in CA1 and DG regions.
- Increased paired-pulse facilitation at CA3-CA1 synapse suggests a reduced release probability of CA3 neurons in agreement with studies from Munc18-1 variants[5], from HET neurons[4], and with the predicted role of STXBP1-SNARE in the presynaptic fusion machinery[3].

References

1. Chen W. et al. *eLife* 2020;9:e48705.
2. Patzke C. et al. *JCI* 2015;125(9):3560-3571.
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5. Kovacevic J. et al. *Brain* 2018:141;1350-1374.

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