

Negative allosteric modulators of $\alpha 5$ GABA type A receptors, basmisanil and ONO-8590580, can prevent β -amyloid-induced long-term potentiation impairments in hippocampal mouse brain slices *ex vivo*

A. O’Connell¹, C. Ní Dhochartaigh¹, É. Mc Inernry¹, O. McNamara¹, L. Quinlan², A. Kwakowsky¹

Ionad Néareolaíochta na Gaillimhe
Galway Neuroscience Centre

¹Pharmacology and Therapeutics, School of Pharmacy and Medical Sciences, Institute for Health Discovery and Innovation, Institute for Clinical Trials, Galway Neuroscience Centre, University of Galway, Galway, Ireland, ²Physiology, School of Pharmacy and Medical Sciences, Institute for Health Discovery and Innovation, Institute for Clinical Trials, Galway Neuroscience Centre, University of Galway, Galway, Ireland

Background

Alzheimer’s disease (AD) is a progressive neurodegenerative disease, accounting for ~70% of dementia cases. The cognitive decline observed in patients with AD is accompanied by an excitatory/inhibitory (E/I) imbalance, particularly in the hippocampus [1-4]. Gamma-aminobutyric acid (GABA) plays a crucial role in maintaining the E/I balance and neuronal activity involved in memory [5,6]. In AD, changes in $\alpha 5$ GABA A type receptor ($\alpha 5$ -GABAAR) expression and activity disturb the E/I balance and impair cognitive processes [7,8]. Therefore, targeting $\alpha 5$ -GABAARs offers a promising therapeutic strategy [9, 10].

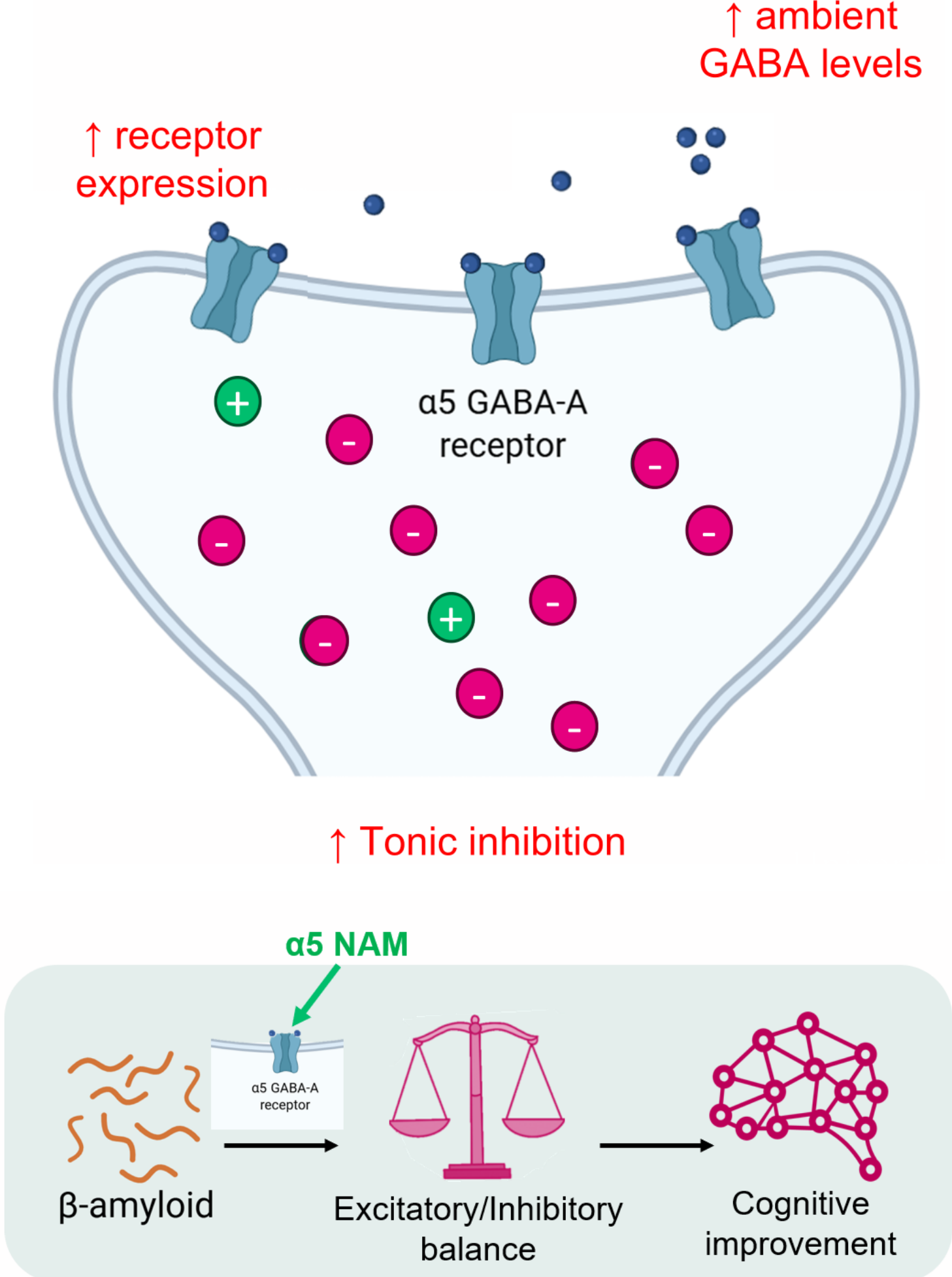


Figure 1 – Rationale for targeting $\alpha 5$ GABA type A receptors in the treatment of Alzheimer’s Disease.

Study Aim: Investigate the effects of basmisanil and ONO-8590580, two promising $\alpha 5$ -GABAAR NAMs, on $A\beta$ -induced cognitive deficits in a well-established acute *ex vivo* model of AD.

Results

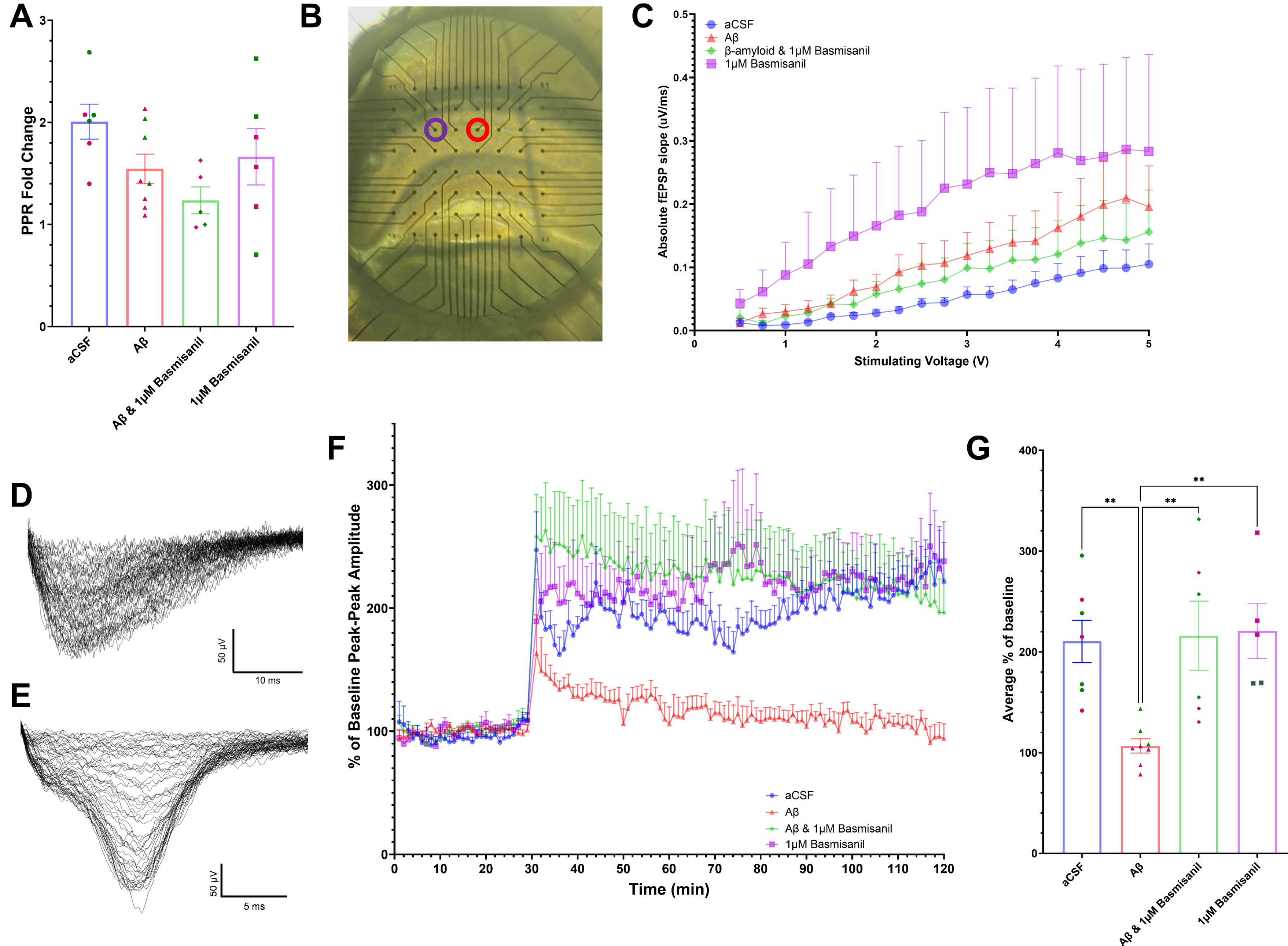


Figure 2 Effect of Basmisanil on β -amyloid1-42-induced long-term potentiation impairments. A) Paired-pulse ratios in the pyramidal layer–CA1 network B) An acute hippocampal slice treated with $A\beta$ 1-42 & basmisanil, the red circle indicates the stimulating electrode and the purple circle indicates the recording electrode. C) Input-output relationships in the pyramidal layer–CA1 network D) Example traces of input-output relationships from an $A\beta$ 1-42-treated slice and E) from an aCSF-treated slice. F) Timeline of normalized CA1 field excitatory postsynaptic potentials (fEPSP) amplitudes in the pyramidal layer–CA1 G) Normalized fEPSP responses for 100-110 minutes. Where applicable, green data points indicate recordings obtained from acute slices prepared from male animals, and pink data points indicate recordings obtained from acute slices prepared from female animals. Data are expressed as mean $\pm$ SEM or + SEM (as determined by one-way ANOVA and Tukey’s multiple comparison test or two-way repeated measures ANOVA, * $p < 0.05$, ** $p < 0.01$).

Research Methodology

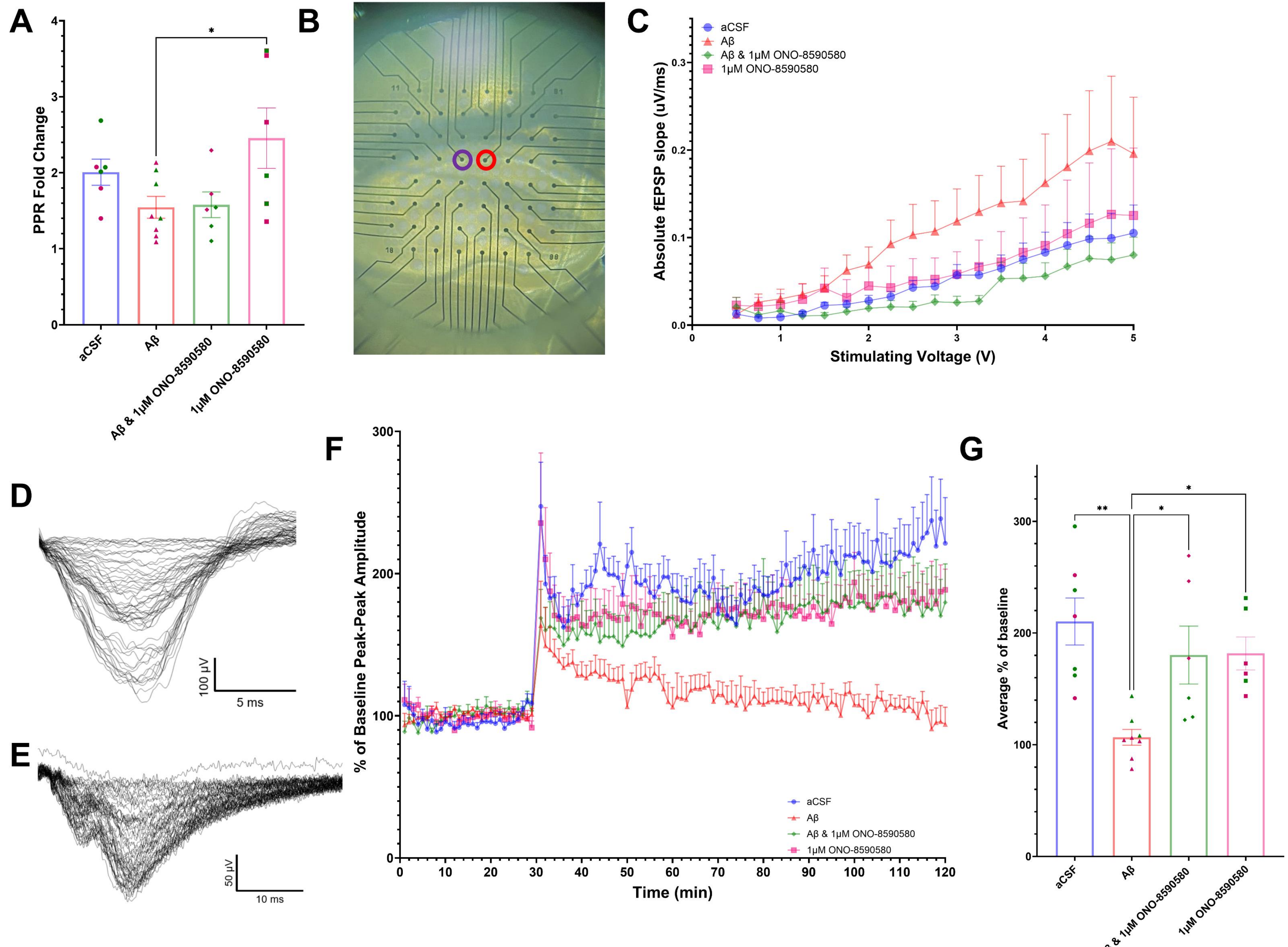
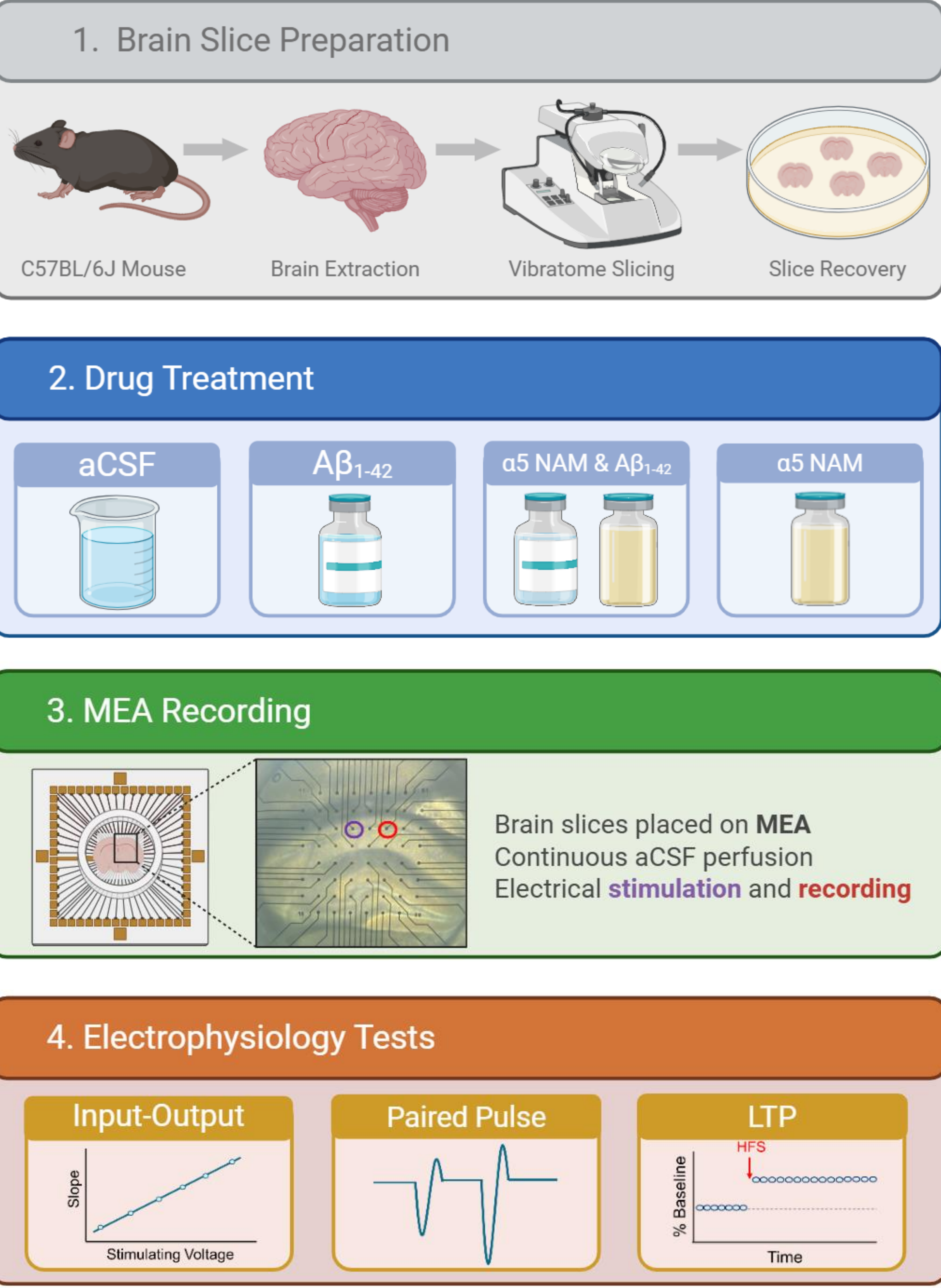


Figure 2 Effect of ONO-8590580 on β -amyloid1-42-induced long-term potentiation impairments. A) Paired-pulse ratios in the pyramidal layer–CA1 network B) An acute hippocampal slice treated with $A\beta$ 1-42 & ONO-8590580, the red circle indicates the stimulating electrode and the purple circle indicates the recording electrode. C) Input-output relationships in the pyramidal layer–CA1 network D) Example traces of input-output relationships from an $A\beta$ 1-42-treated slice and E) from an aCSF-treated slice. F) Timeline of normalized CA1 field excitatory postsynaptic potentials (fEPSP) amplitudes in the pyramidal layer–CA1 G) Normalized fEPSP responses for 100-110 minutes. Where applicable, green data points indicate recordings obtained from acute slices prepared from male animals, and pink data points indicate recordings obtained from acute slices prepared from female animals. Data are expressed as mean $\pm$ SEM or + SEM (as determined by one-way ANOVA and Tukey’s multiple comparison test or two-way repeated measures ANOVA, * $p < 0.05$, ** $p < 0.01$).

Conclusion

In the present study, our observations confirm the pharmacological potential of targeting the $\alpha 5$ -GABAAR in AD. Given the *ex vivo* and acute nature of this study, future studies should focus on the effects of basmisanil and ONO-8590580 following chronic *in vivo* administration. Despite this, the current study supports the idea that $\alpha 5$ -GABAAR NAMs effectively prevent $A\beta$ 1-42-induced disruptions in hippocampal plasticity, underscoring the relevance of basmisanil and ONO-8590580 as potential therapies in AD.

References

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