

Presynaptic muscarinic receptors modulate the feedforward Temporoammonic microcircuit in the hippocampus

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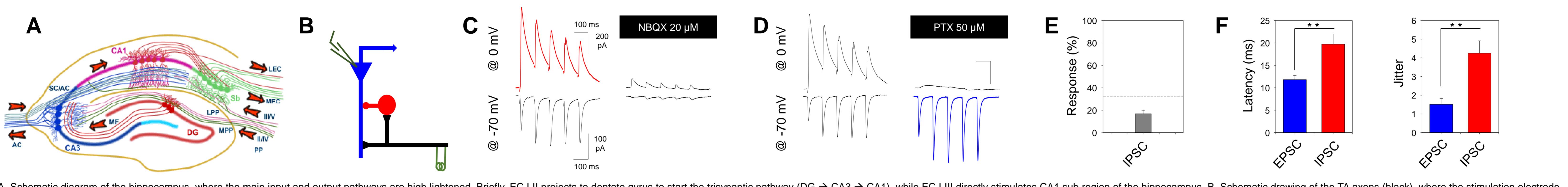
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Summary

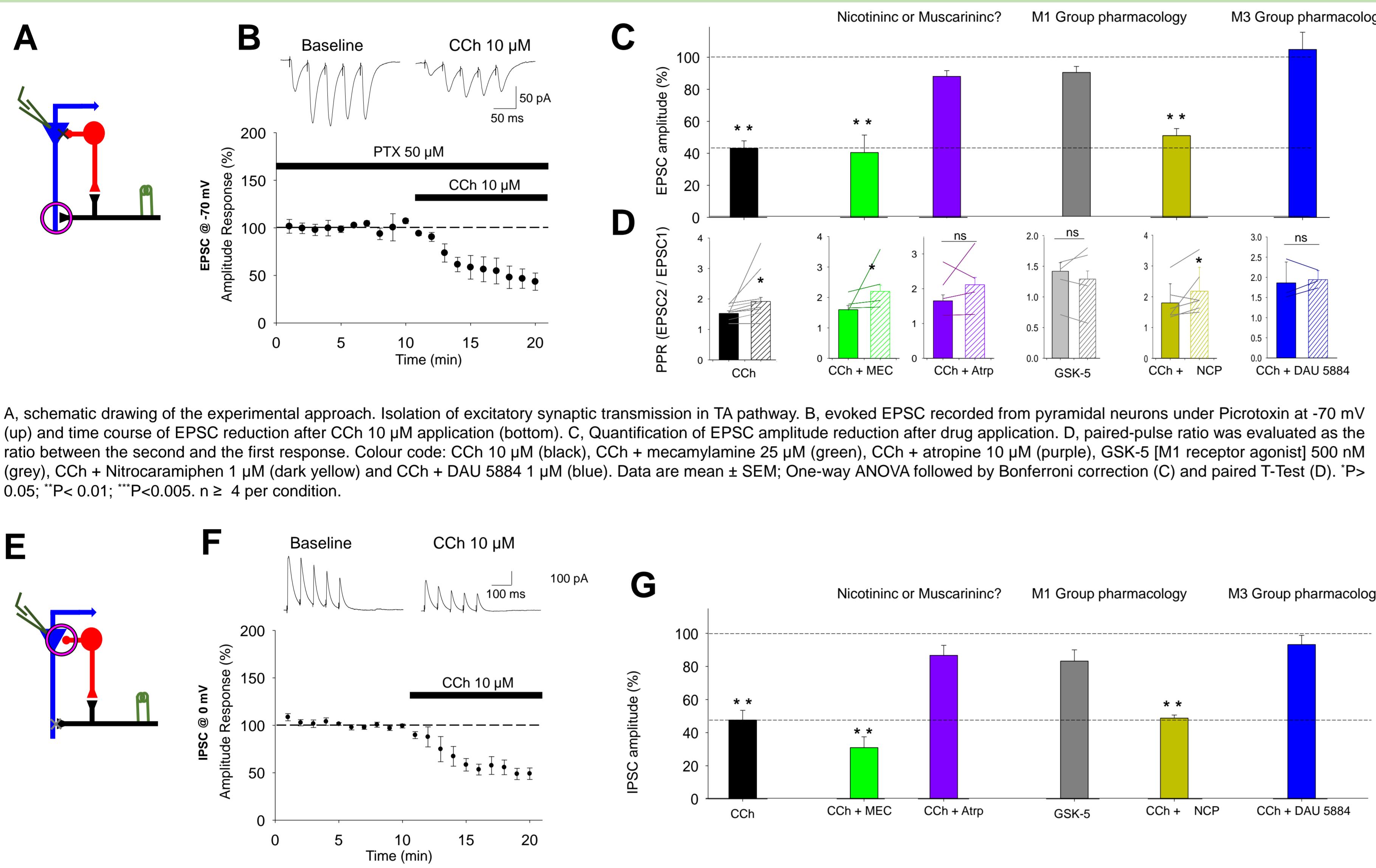
The release of acetylcholine in the hippocampus during awake behaviour is important for encoding memory. Within the hippocampal network, acetylcholine has diverse effects: it increases neuronal excitability, controls synaptic strength and regulates the induction of synaptic plasticity. However, these effects are not ubiquitous and instead are exhibited at individual synapses within the network. The Temporoammonic (TA) pathway carries spatial information from grid cells in entorhinal cortex layer III to CA1 hippocampal place cells synapsing onto the distal dendrites. It is not currently known how acetylcholine regulates synaptic transmission in the temporoammonic pathway or which acetylcholine receptors mediate this regulation. To determine how acetylcholine regulates the TA pathway we made whole cell patch clamp recordings from CA1 pyramidal neurons or selected subset of interneurons in acute hippocampal sagittal slices from adult mice. Electrical stimulation in the Stratum Lacunosum Moleculare was used to isolate monosynaptic excitatory postsynaptic currents (EPSC) or disynaptic inhibitory postsynaptic currents (IPSC). The acetylcholine receptor agonist carbachol (CCh 10 μ M) reduced both excitatory and inhibitory synaptic responses and increased paired-pulse ratio for excitatory responses, indicating a presynaptic locus of action. Specific pharmacological intervention showed that M3 receptor antagonist or genetic deletion of this receptors, blocked CCh induced reduction of synaptic probability of release. Furthermore, we revealed that PV⁺ interneurons are feedforward upon TA pathway stimulation, whose excitatory inputs are inhibited by the activation of M3 receptors. Excitatory and inhibitory responses at pyramidal neurons were similarly reduced by CCh but the increase in paired pulse ratio for excitatory drive produced a facilitation of excitatory-inhibitory balance in response to repetitive stimulation. In addition, CCh produced an increase in the number of spikes in the CA1 pyramidal neurons when TA synapses were repeatedly stimulated over a range of frequencies. We conclude that acetylcholine modulates the temporoammonic pathway by presynaptically located M3 muscarinic receptors.

Experimental design

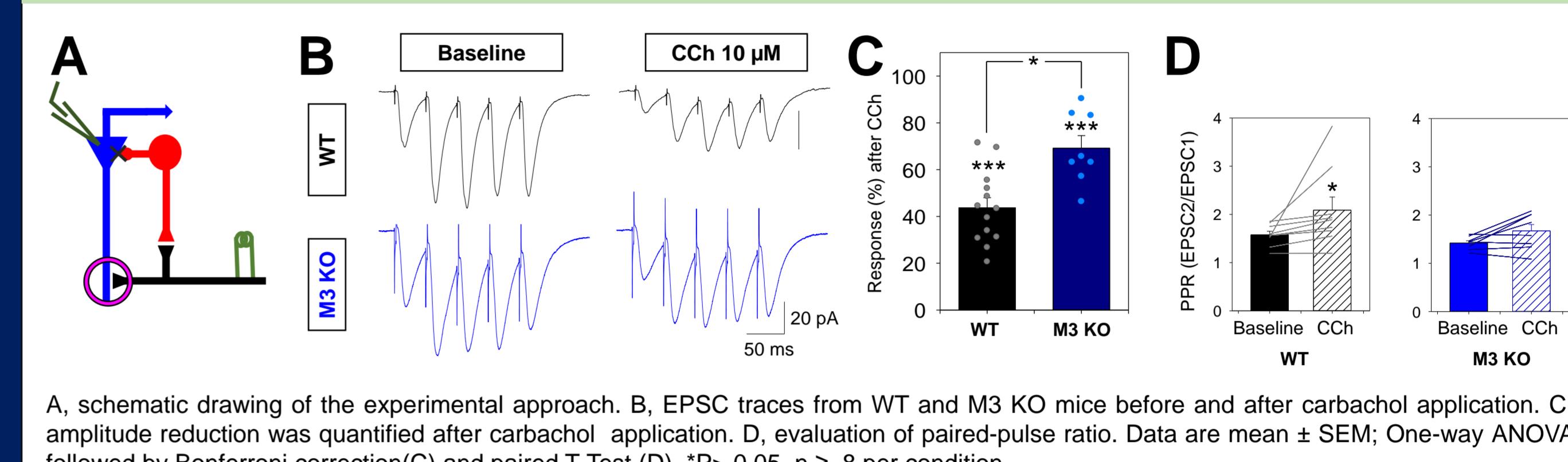


Results

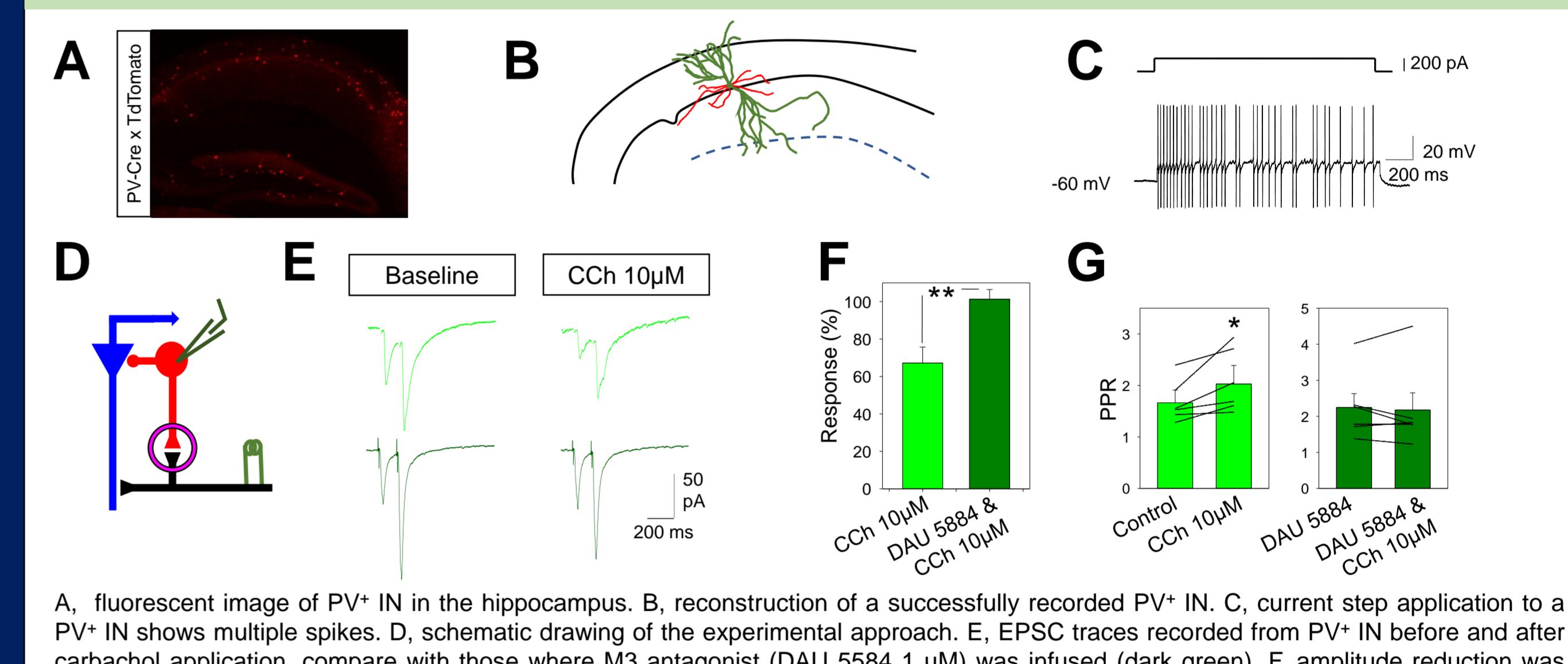
1. TA to CA1 evoked EPSC & IPSC are reduced by 10 μ M Carbachol



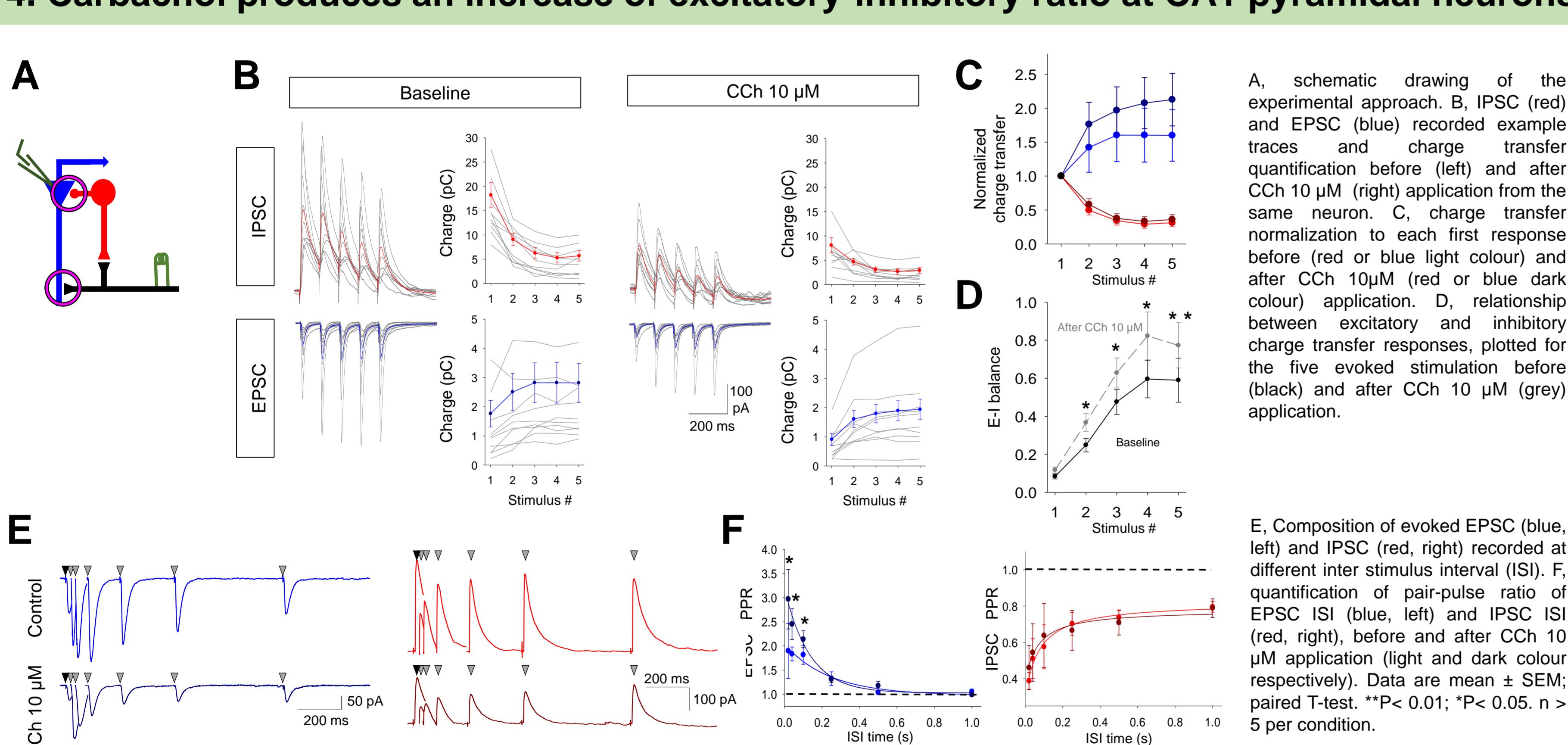
2. M3 KO mice exhibit reduced cholinergic modulation



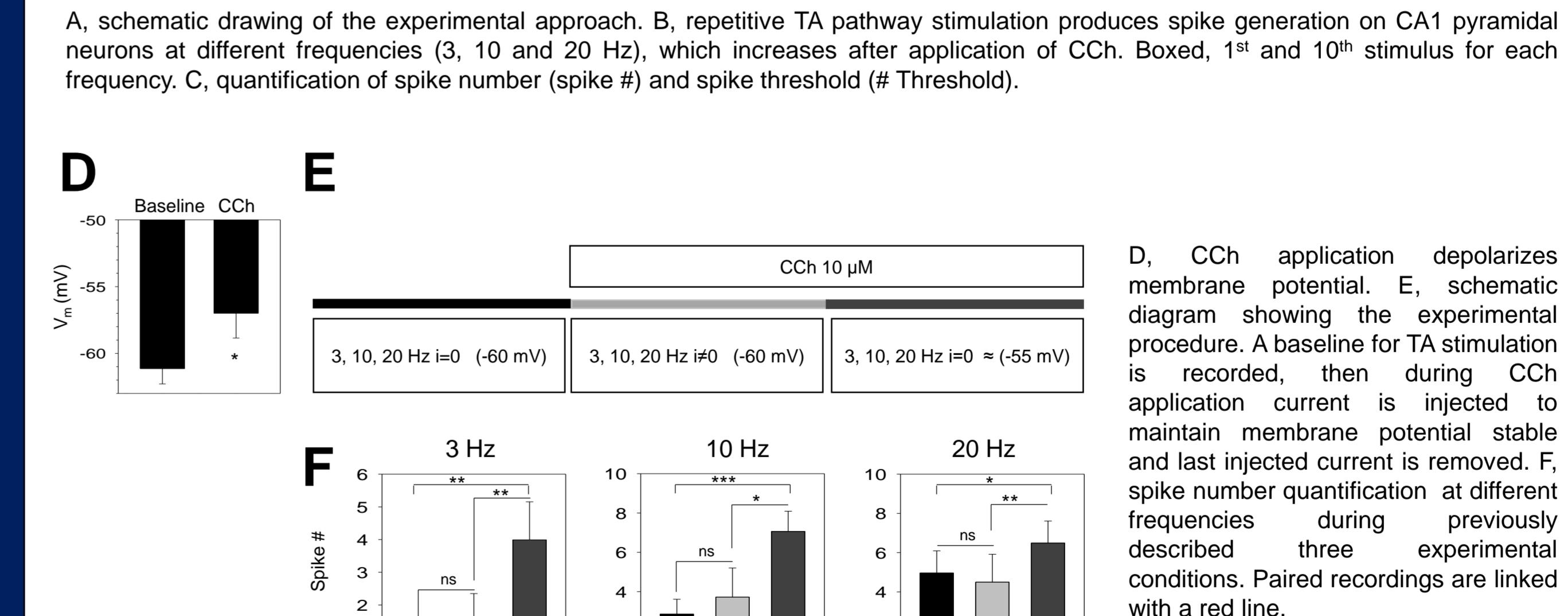
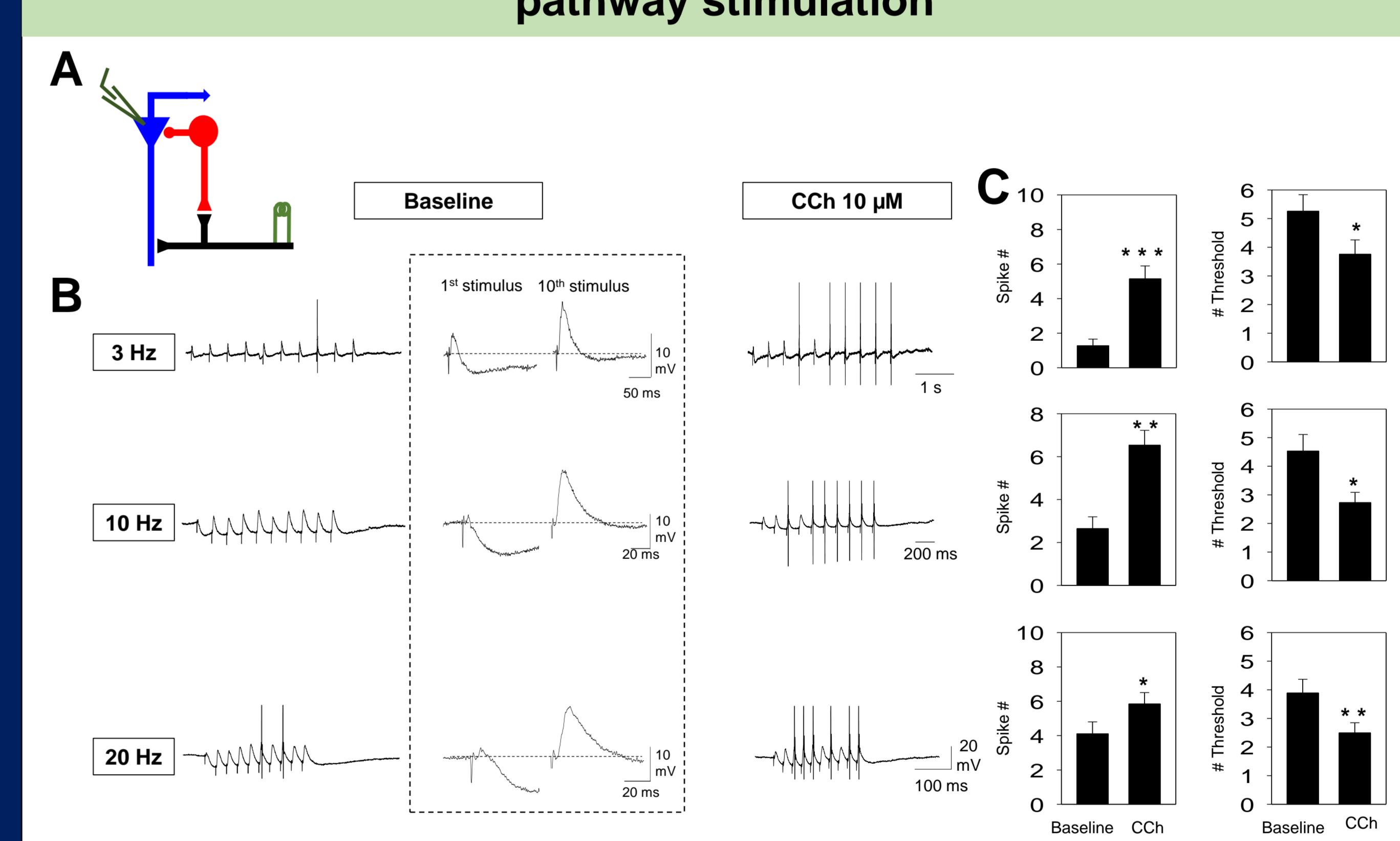
3. Feedforward PV⁺ IN are modulated by M3 activation



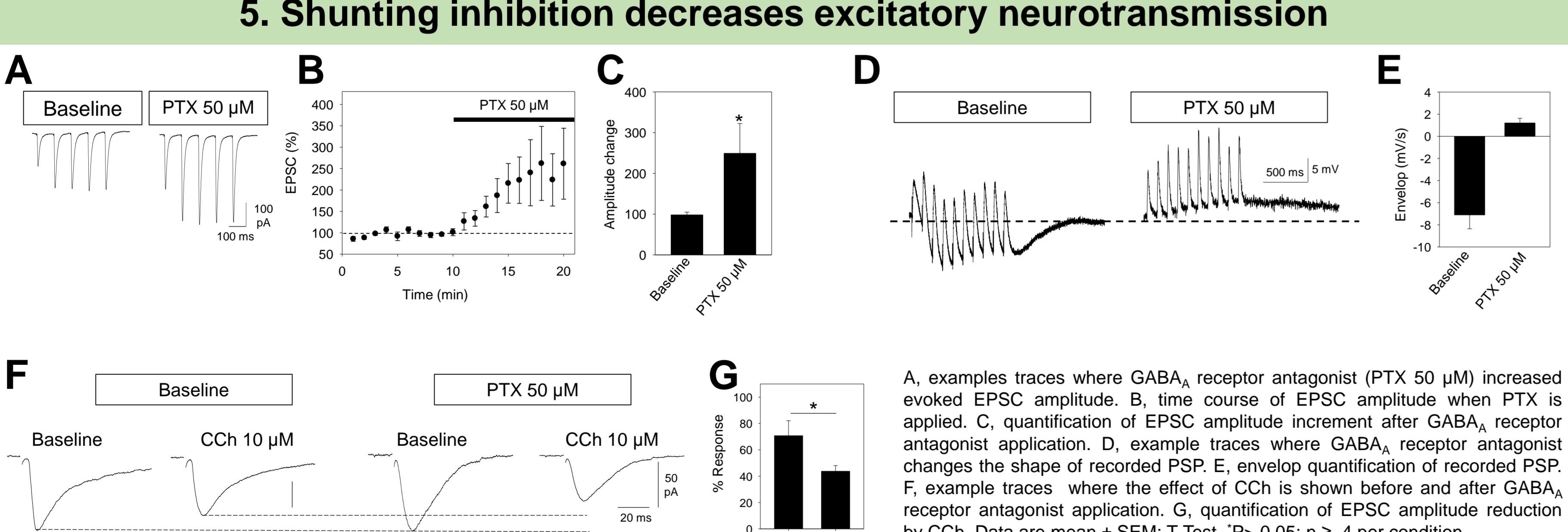
4. Carbachol produces an increase of excitatory-inhibitory ratio at CA1 pyramidal neurons



6. Carbachol increases CA1 spike generation in response to TA pathway stimulation



5. Shunting inhibition decreases excitatory neurotransmission



Conclusions

- TA stimulation yielded monosynaptic facilitating EPSC and disynaptic depressing IPSC responses on CA1 pyramidal neurons.
- Both excitatory and inhibitory synaptic responses from TA pathway were decreased by presynaptically located M3 muscarinic receptors, identified by pharmacological inhibition or genetic deletion.
- PV⁺ IN in the hippocampus are feedforward interneuron in the TA pathway and their excitatory inputs are depressed by M3 muscarinic receptors.
- Repetitive stimulation of TA axons enhanced EPSCs more than IPSCs in CA1 pyramidal cells resulting in an increase of excitatory to inhibitory balance.
- Inhibitory drive shapes excitatory neurotransmission, affecting cholinergic modulatory outcome at feedforward hippocampal microcircuit.
- Cholinergic receptor activation fits in a model where TA inputs are boosted when sensory stimuli are increased, thus causing an increment in spike generation of CA1 pyramidal cells.

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