

# Acetylcholine modulates input selectivity in CA1 of the hippocampus

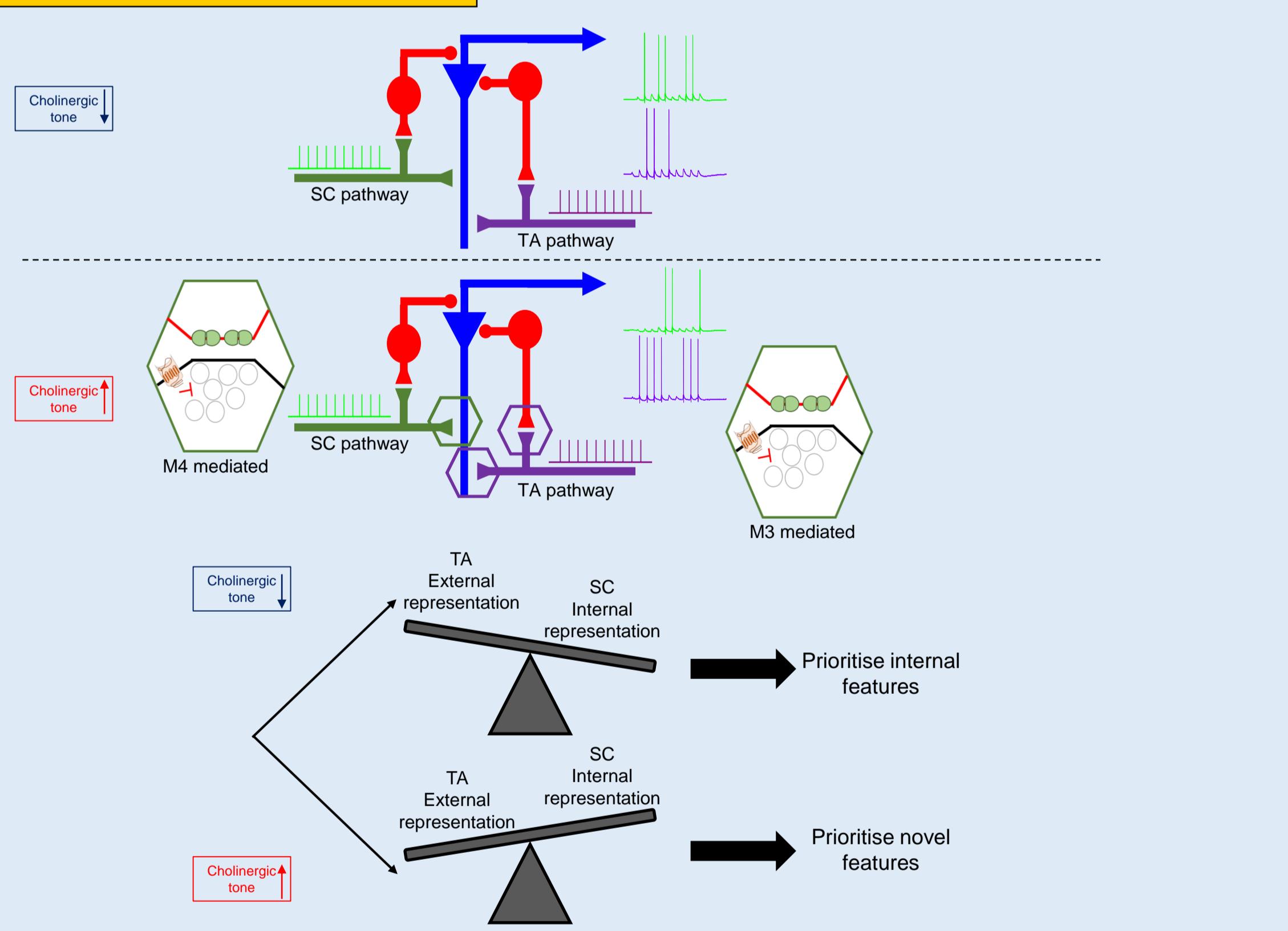
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## Summary

Acetylcholine fundamentally reconfigures cortical circuits to switch their function. In the hippocampus acetylcholine is thought to prioritise input to CA3 and CA1 circuits from sensory modalities containing new information about the environment and away from internally held representations. This reconfiguration enables acetylcholine to signal that previously held representations require updating with new information (Dannenberg et al., 2017). However, the mechanism by which acetylcholine enables this critical switch in function is unclear. In the CA1 region, internally held representations are proposed to enter via the Schaffer collateral (SC) pathway from CA3 whereas new information enters via the temporoammonic (TA) pathway direct from the entorhinal cortex. Therefore, it is predicted that acetylcholine will reduce SC input whilst enhancing TA input to CA1. Previous studies have reported that acetylcholine reduces excitatory synaptic transmission in both SC and TA pathways apparently challenging this prediction. However, these studies did not measure the effects of acetylcholine on feedforward inhibition which have a major role in determining the CA1 response to SC or TA input taking into account the overall excitatory-inhibitory drive. Therefore, our goal was to test the core hypothesis that acetylcholine prioritises TA input over SC input. We used electrical stimulation to obtain monosynaptic excitatory or disynaptic inhibitory postsynaptic currents ( $\text{m}_\text{EPSC}$  or  $\text{d}_\text{IPSC}$  respectively) from SC and TA pathways on the same CA1 pyramidal neuron. The acetylcholine receptor agonist carbachol (CCh) reduced both  $\text{m}_\text{EPSC}$  and  $\text{d}_\text{IPSC}$  synaptic responses for the SC input which resulted in no change to excitatory-inhibitory balance and indeed a decrease in postsynaptic spiking. In contrast, TA  $\text{m}_\text{EPSC}$  and  $\text{d}_\text{IPSC}$  were also reduced by cholinergic receptor activation, but a boost in facilitation of excitatory and the lack of it in the inhibitory drive resulted in an increase of excitatory-inhibitory balance, which produced an increment in postsynaptic spiking. Our data suggest that distinct interneuron populations engaged by SC or TA pathways participate in input selective modulation.

## Conclusions



- Cholinergic receptor activation in CA1 reduces EPSC and IPSC amplitude and charge transfer in TA and SC pathway.
- Repetitive stimulation of SC axons produces a similar increase in the EPSC and IPSC facilitation, producing a slightly increase in the excitatory-inhibitory ratio by the activation of cholinergic receptors.
- Repetitive stimulation of TA axons produces a facilitation of EPSC which is not reproduced by IPSC, producing an increase in the excitatory-inhibitory ratio by the activation of cholinergic receptors.
- Diverse interneuron subtypes are engaged upon SC or TA pathway stimulation and their synaptic physiology is differently regulated by cholinergic receptor activation.
- Inhibitory drive at TA pathway shapes excitatory neurotransmission, affecting cholinergic modulatory outcome at feedforward hippocampal microcircuit.
- Both excitatory and inhibitory synaptic responses from TA pathway were decreased by presynaptically located M3 muscarinic receptors, identified by pharmacological inhibition.
- PV+ and CCK+ IN in the hippocampus are feedforward interneuron in the TA pathway and their excitatory inputs are depressed by cholinergic receptors activation.
- Cholinergic receptor activation reduces SC pathway spike generation while increasing TA pathway spike generation of CA1 pyramidal cells, therefore making CA1 pyramidal cells more responsive to TA pathway in comparison to SC pathway.
- Differential expression of presynaptic muscarinic receptors on SC and TA inputs to CA1 enable acetylcholine to reconfigure the network to favour new information over internally held representations.

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