Cell type-specific cholinergic neuromodulation in the hippocampus: roles in normal and disease states

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"offline"

inactive, quiescent

"online"

active, learning



"theta" oscillations





Interneuron Diversity in the CA1 Hippocampus



Lawrence 2008



adapted from Moser, 2003 Klausberger et al., 2003 Pacing of the hippocampus by the medial septum



adapted from Borhegyi et al., 2004

Cholinergic control of excitation/inhibition balance



Interneuron Diversity in the CA1 Hippocampus



Lawrence 2008

Cell type-specific responses of carbachol/ muscarine in frontal cortex



from Kawaguchi 1997

Interneuron Diversity in the CA1 Hippocampus



Lawrence 2008

mAChR-induced ADPs are hallmark features of O-LM interneurons



mAChR activation increases firing reliability in O-LM interneurons



Lawrence et al., 2006a

Simulation of I_M inhibition and augmentation in O-LM interneuron model



Lawrence Saraga et al. 2006

Interneuron Diversity in the CA1 Hippocampus



Dave Bonislawski and Jordan Pauli

PV BCs and CCK BCs exhibit distinct cholinergic phenotypes A В Muscarine $10_{\mu}M$ **PV-BCs CCK-BCs** 4 n=15 n=29 Norm Adap Coeff - CCK-BCs 3 PV-BCs 500pA 100pA 2 0 0 г \mathbb{C} 8 -Norm Frequency 6 4 -60mV-~ 2 $\oplus \oplus \oplus \oplus \oplus \oplus$ €⊕⊕⊕€ D 8 ADF (mV) 6 5mV 4 2 0 -2 -60mV 500ms Ε 25 **╞**╋╋╋╋╋**┋**_॒ 0 (Vd) ployl⊽ -25 -75 -100 5mV 5mV -60mV ¦-60mV -125 0 2 3 4 -1 500ms 500ms Time (min)

Cea del Rio et al. 2010

The presence of M3 mAChRs distinguishes CCK-BCs from PV-BCs



Cea del Rio et al. 2010

PV BC - CA1 pyramidal cell unitary transmission



Muscarine inhibits unitary PV-GFP-pyramidal cell transmission





A Low Variance Synapse - Yippie!



Variance-mean analysis on unitary PV-pyramidal cell transmission



Mathematical model of mAChR modulation of PV BC transmission



Lee et al. J Comput Neurosci 2009

Emily Stone

Cell-type specificity of cholinergic modulation



Remaining questions:

- receptor localization
- mAChR-sensitive conductances
- presynaptic receptors
- synaptic activation: point-to-point vs. volume transmission
- network contributions
- effects on behavior

Evidence for direct postsynaptic targets of cholinergic terminals in the hippocampus



Frotscher and Leranth 1985

Contrasting modes of cholinergic transmission



Do different interneuron subtypes utilize different modes of cholinergic transmission?

Need to know physiological effect + spatial localization of cholinergic afferents

Ben Holloway

ChR2-YFP injection into the medial septum



Genetic deletion of M1 mAChRs from PV+ cells using the CRE/loxP system



loxP	M1 muscarinic receptor gene	loxP
	Cre recombinase enzyme in PV cells	
	loxP loxP	

Ben Holloway and Kurt Stoll

Cell-type specificity of cholinergic modulation



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Cobb and Lawrence 2010

National Institutes of Health

Christian Cea del Rio



Ludovic Tricoire



Chris McBain



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Fernanda Saraga

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Emily Stone



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April Johnston





Ben Holloway Tavita Garrett

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Miriam Rose Baker

Eric Marceau

Kurt Stoll

NIH NINDS Epilepsy Foundation Alzheimer's Association National Center for Research Resources

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