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ORIGINAL ARTICLE

Cholinergic Modulation of Cortical Function

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Introduction

Extensive physiological research has demonstrated a number of common effects of acetylcholine within cortical structures, including the hippocampus, piriform cortex, and neocortex (Hasselmo, 1995, 1999). This article will provide a description of how the different physiological effects of acetylcholine could interact to alter specific functional properties of the cortex.

The physiological effects of acetylcholine serve to enhance the influence of feed-forward afferent input to the cortex while decreasing background activity by suppressing excitatory feedback connections within cortical circuits. By enhancing the response to sensory input, high levels of acetylcholine enhance attention to sensory stimuli in the environment and enhance encoding of memory for specific stimuli. Interference from prior memory is reduced by suppressing synapses modified by prior learning (Sevilla et al., 2002; Linster et al., 2003).

Acetylcholine Enhances Input Relative to Feedback

Acetylcholine enhances both encoding and attention by enhancing the influence of sensory input relative to the internal processing of stimuli. This results from a variety of physiological effects. Acetylcholine enhances the spiking response of cortical pyramidal cells to afferent input (Krnjevic, 1984). Research in brain slice preparations consistently demonstrates depolarization of pyramidal cells due to cholinergic activation of muscarinic receptors (Cole and Nicoll, 1984).

This slow depolarization of membrane potential enhances the spiking response to excitatory synaptic input. The suppression of spike frequency accommodation also enhances the spiking response to afferent input and has been observed in neocortex and hippocampal region CA1 (Madison and Nicoll, 1984). This also facilitates sustained spiking activity important for maintaining responses necessary for encoding new memories (Klink and Alonso, 1997).

Acting at muscarinic receptors, acetylcholine appears to reduce the processing of information on the basis of prior memories within cortical structures. The selective cholinergic suppression of excitatory feedback, but not afferent input, to the cortex has been demonstrated in slice preparations of the piriform cortex (Hasselmo and Bower, 1992; Linster et al., 2003), and neocortex (Hasselmo and Cekic, 1996; Gil et al., 1997). Within the hippocampal formation, muscarinic suppression of excitatory transmission was reported at connections including the Schaffer collaterals projecting from hippocampal region CA3 to CA1 (Hounsgaard, 1978; Hasselmo and Schnell, 1994; Sevilla et al., 2002). This muscarinic suppression appears to selectively spare silent synapses (Sevilla et al., 2002) while suppressing synapses with more AMPA conductance.

Cholinergic effects at muscarinic receptors have been shown to selectively enhance afferent connections in thalmocortical slices (Gil et al., 1997) and to selectively enhance synaptic transmission in the afferent fiber system in the CA3 region of the hippocampus while having no effect on the intrinsic fiber synapses (Giocomo and Hasselmo, 2005). Nicotinic enhancement of afferent connections could

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complement the muscarinic suppression of intrinsic connections by amplifying input for new information while old information is suppressed. The role of nicotine in enhancing certain memory processes in both humans (Levin et al., 1998) and animals (Buccafusco et al., 1997) could be due to the nicotinic enhancement of the afferent transmission of new sensory information.

Functional Role of Cholinergic Modulation

Numerous human memory studies demonstrate that blockade of muscarinic acetylcholine receptors by systemic administration of the drug scopolamine interferes with the encoding of new verbal information while having little effect on retrieval of previously stored information (Broks et al., 1988; Hasselmo, 1995). Scopolamine appears to primarily affect episodic memory while sparing semantic and procedural memory (Atri et al., 2004). In rats, effects of muscarinic receptor blockade by scopolamine have been observed in tasks where the rat must encode episodic memories.

The importance of the selective suppression of excitatory transmission by acetylcholine has been analyzed in computational models of associative memory function. These models demonstrate that cholinergic suppression of transmission prevents retrieval of previously encoded associations from interfering with the encoding of new associations. Consistent with this, blockade of cholinergic suppression of excitatory synaptic transmission by scopolamine appears to enhance proactive interference (Broks et al., 1988).

Physiological experiments in brain slice preparations have demonstrated enhancement of long-term potentiation by cholinergic agonists at a number of different synaptic pathways, including the Schaffer collateral input to region CA1 (Huerta and Lisman, 1993) and associated fiber connections in the piriform cortex (Hasselmo and Barkai, 1995). This enhancement would naturally be important for the encoding of new information. The suppression of synaptic transmission appears selective for recently modified synapses (Linster et al., 2003) but not silent synapses (Sevilla et al., 2002). This might prevent interference by selectively suppressing retrieval of recently learned information during new encoding.

Encoding is also enhanced by cholinergic activation of intrinsic mechanisms for sustained spiking activity in individual neurons, which allows a longer period for synaptic modification (Klink and Alonso, 1997).

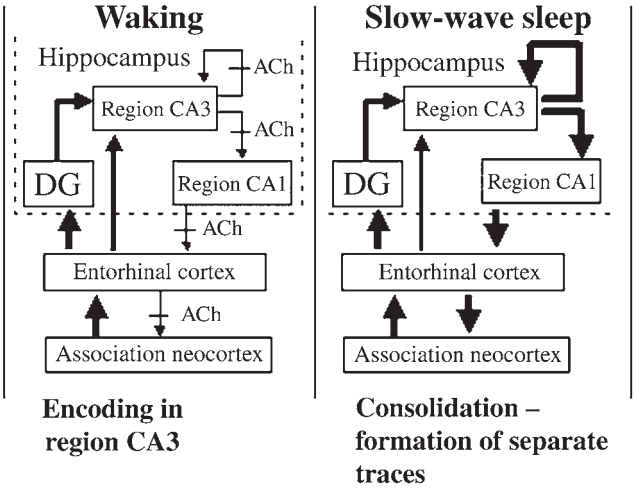

Fig. 1. Schematic of cholinergic modulation of hippocampal dynamics during active waking and slow-wave sleep. Left, During active waking, high levels of acetylcholine set appropriate dynamics for encoding. Sensory information from neocortical structures flows through the entorhinal cortex and dentate gyrus (DG) into hippocampal region CA3, where cholinergic enhancement of synaptic modification helps in the formation of an intermediate-term representation, binding together different elements of an episodic memory. Feedback connections to region CA1, entorhinal cortex, and association cortex are strong enough to mediate immediate retrieval, but cholinergic suppression of these connections prevents interference from previous encoding from dominating over the feed-forward connectivity. Right, During quiet waking or slow-wave sleep, much lower levels of acetylcholine release the suppression of excitatory feedback. This strong excitatory feedback mediates reactivation of memories stored in region CA3 during EEG phenomena, termed sharp waves, which flow back through region CA1 to the entorhinal cortex. This enables the slow consolidation of long-term episodic memory in hippocampal regions and association neocortex.

The functional effect of changes in acetylcholine levels during the sleep/wake cycle is summarized in Fig. 1. High levels of acetylcholine during waking will reduce interference from previously modified synapses while allowing silent synapses to be modified. In contrast, during slow-wave sleep low levels of acetylcholine could be important for the consolidation of previously encoded information, as described in Fig. 1. The loss of cholinergic modulation during slow-wave sleep should enhance the spread of excitatory activity in response to stimulation. This would provide the appropriate dynamics for the formation of additional traces within regions

CA3 and CA1, and could allow the hippocampus to further strengthen internal connections (Buzsaki, 1989; Hasselmo, 1999).

Conclusions

Levels of acetylcholine in the hippocampus and neocortex could change dramatically during different stages of waking and sleep. High levels of acetylcholine during active waking might set appropriate dynamics for attention to sensory input or encoding of new information (Hasselmo, 1999; Linster et al., 2003). At the same time, the cholinergic suppression of excitatory feedback connections prevents interference from internal processing of previously stored information (Hasselmo, 1995, 1999; Sevilla et al., 2002; Linster et al., 2003). Lower levels of acetylcholine during quiet waking and slow-wave sleep might provide a release from this suppression of excitatory feedback, facilitating the process of consolidation (Hasselmo, 1999).

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References

Atri A., Sherman S. J., Norman K. A., Kirchhoff B. A., Nicolas M. M., Greicius M. D., et al. (2004) Blockade of central cholinergic receptors impairs new learning and increases proactive interference in a word paired-associated memory task. *Behav. Neurosci.* **188,** 223–236.

Broks P., Preston G. C., Traub M., Poppleton P., Ward C., and Stahl S. M. (1988) Modeling dementia: effects of scopolamine on memory and attention. *Neuropsychologia* **26,** 685–700.

Buccafusco J. J., Prendergast M. A., Terry A. V., and Jackson W. J. (1997) Cognitive effects of nicotinic cholinergic receptor agonists in nonhuman primates. *Drug Dev. Res.* **38,** 196–203.

Buzsaki G. (1989) Two-stage model of memory trace formation: a role for "noisy" brain states. *Neuroscience* **31,** 551–570.

Cole A. E. and Nicoll R. A. (1984) Characterization of a slow cholinergic postsynaptic potential recorded in vitro from rat hippocampal pyramidal cells. *J. Physiol.* **352,** 173–188.

Gil Z., Conners B. W., and Amatai Y. (1997) Differential regulation of neocortical synapses by neuromodulators and activity. *Neuron* **19,** 679–686.

Giocomo L. M. and Hasselmo M. E. (2005) Nicotinic modulation of glutamatergic synaptic transmission. *Eur. J. Neurosci.* **22,** 1349–1356.

Hasselmo M. E. (1995) Neuromodulation and cortical function: modeling the physiological basis of behaviour. *Behav. Brain Res.* **67,** 1–27.

Hasselmo M. E. (1999) Neuromodulation: acetylcholine and memory consolidation. *Trends Cognitive Sci.* **3,** 351–359.

Hasselmo M. E. and Barkai E. (1995) Cholinergic modulation of activity-dependent synaptic plasticity in rat piriform cortex. *J. Neurosci.* **15,** 6592–6604.

Hasselmo M. E. and Bower J. M. (1992) Cholinergic suppression specific to intrinsic not afferent fiber synapses in rat piriform (olfactory) cortex. *J. Neurophysiol.* **67,** 1222–1229.

Hasselmo M. E. and Cekic M. (1996) Suppression of synaptic transmission may allow combination of associative feedback and self-organizing feedforward connections in the neocortex. *Behav. Brain Res.* **79,** 153–161.

Hasselmo M. E. and Schnell E. (1994) Laminar selectivity of the cholinergic suppression of synaptic transmission in rat hippocampal area CA1: computational modeling and brain slice physiology. *J. Neurosci.* **14,** 3898–3914.

Hounsgaard J. (1978) Presynaptic inhibitory action of acetylcholine in area CA1 of the hippocampus. *Exp. Neurol.* **62,** 787–797.

Huerta P. T. and Lisman J. E. (1993) Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. *Nature* **364,** 723–725.

Klink R. and Alonso A. (1997) Muscarinic modulation of the oscillatory and repetitive firing properties of entorhinal cortex layer II neurons. *J. Neurophysiol.* **77,** 1813–1828.

Krnjevic K. (1984) Neutrotransmitters in cerebral cortex: a general account, in *Cerebral Cortex*, Jones, E. G., and Peters, A., eds., Plenum Press, New York, pp. 39–61.

Levin E. D., Conners C. K., Silva D., Hinton S. C., Meck W. H., March J., and Rose J. E. (1998) Transdermal nicotine effects on attention. *Psychopharmacology* **140,** 135–141.

Linster C., Maloney M., Patil M., and Hasselmo M. E. (2003) Enhanced cholinergic suppression of previously strengthened synapses enables the formation of self-organized representations in olfactory cortex. *Neurobiol. Learn. Mem.* **80,** 302–314.

Madison D. V. and Nicoll R. A. (1984) Control of the repetitive discharge of rat CA1 pyramidal neurons *in vitro*. *J. Physiol.* **354,** 319–331.

Sevilla D. F., Cabezas C., de Prada A. N., Sanchez-Jimenez A., and Bruno W. (2002) Selective muscarinic regulation of functional glutamatergic Schaffer collateral synapses in rat CA1 pyramidal neurons. *J. Physiol.* **545,** 51–63.