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Review on Acetylcholine and Memory

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ABSTRACT

Acetylcholine may set the dynamics of cortical networks to those appropriate for learning of new information, while decreased cholinergic modulation may set the appropriate dynamics for recall. In slice preparations of the olfactory cortex, acetylcholine selectively suppresses intrinsic but not afferent fiber synaptic transmission, while decreasing the adaptation of pyramidal cells. In biologically realistic models of this region, the selective suppression of synaptic transmission prevents recall of previously learned memories from interfering with the learning of new memories, while the decrease in adaptation enhances the response to afferent input and the modification of synapses. This theoretical framework may serve to guide future studies linking neuromodulators to cortical memory function.

KEYWORDS: *Ach Acetylcholine*

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Modeling the cholinergic modulation of memory function

Associative memory models. Ultimately, understanding the role of cholinergic modulation in memory function requires considering this modulation in the context of the function of specific cortical regions. While the functional characteristics of the cortex have not been fully elucidated, we have approached this question specifically with regard to the putative associative memory function of the olfactory cortex ls-23. Experimental work showing selective cholinergic suppression of synaptic transmission within the olfactory cortex ~2 motivated development of computational models, allowing the effect of this modulation on the storage of multiple overlapping input patterns to be analysed 2°-23. This work in turn draws upon a broad background of research on theoretical properties of associative memories z4-27. The networks described in this literature have many features that we believe to be similar to olfactory cortex in particular, and cortical structures in general. For example, these models are capable of forming stable representations of complex input patterns, recalling full memory states when an incomplete or noisy version of the original pattern is provided 24-27. We have proposed that a similar process is essential to recognizing objects based on complex and highly variable olfactory stimuli 18-~3. Abstract associative memories also rely upon a network structure in which the representation of each memory is distributed across a large number of synapses. Numerous neurobiologists have noted very similar structural features in regions of the mammalian cortex believed to be involved in memory or memorylike function ls-23'2s'29. Memory storage in abstract associative memory models is accomplished by modifying synaptic strengths using mechanisms that are very similar to the well-described properties of longterm potentiation (LTP) in biological networks 3°. Limitations on associative memory capacity. Our approach to understanding the implementation of associative memory function has been to explore the ability of a biologically realistic model of olfactory cortex to store memories ~s-23. As with abstract associative memory models, one of the primary issues in memory storage is how the network might optimize memory capacity. For example, the distributed nature of memory storage in

these networks means that regardless of specific network architecture, network activity generated by a new input pattern can be adversely influenced by connections modified by previously stored patterns ~°-23. How this arises is shown in more detail in Box 1. However, in brief, recall of previously learned memories during learning of new memories can result in a positive feedback cycle leading to runaway synaptic modification and a complete lack of response specificity, with any input recalling the elements of all memories stored within the network 2°-23. Before focusing on the more detailed physiological models, it is worth considering how abstract associative memory models have dealt with this problem. First, the problem can be alleviated if the modeler makes sure that the input patterns are non-overlapping (e.g. orthogonal; see for example, Ref. 25). This ensures that no cell is activated by more than one input pattern. In biological systems, however, most real stimuli are not likely to be orthogonal (especially in olfaction). The second approach most abstract modelers have taken to this problem involves clamping network activity to the input pattern and ignoring synaptic transmission at the modifiable connections 24-27. In this way, the synaptic changes made during the storage of previous patterns have very little effect on the storage of the new patterns, thereby avoiding the runaway synaptic modifications that can corrupt the new memory. From what is known about the mechanism of LTP in biology, however, completely turning off synaptic transmission would interfere with the mechanisms of synaptic modification at those synapses, by preventing the activation of postsynaptic NMDA receptors by glutamate 3°. Accordingly, biology must have found another way of dealing with this difficulty, which might ultimately give the network better learning dynamics. Acetylcholine and associative memory function. As described in the remainder of this article, physiological experiments together with modeling of olfactory cortex suggest that the effects of acetylcholine summarized in may play a vital role in preventing the problem of interference between memories during associative memory function in cortical structures. In particular, acetylcholine may serve to modulate cortical networks between those characteristics appropriate for storing a new memory based on new afferent input patterns, and the characteristics appropriate for recall of previously stored patterns. The models demonstrate that without the neuromodulation of cortical networks between the dynamics of learning and recall, memory contamination takes place. (1) Presynaptic effects. In olfactory cortex, acetylcholine suppresses synaptic transmission at the intrinsic and association fiber synapses while having little effect on synaptic transmission at afferent fiber synapses ~2 These intrinsic and association fibers show more robust synaptic modification than afferent fibers 34-36, and our models suggest these synapses are critical for associative memory function in the olfactory cortex 18-23. Similarly, in regions CA1 and CA3 of the hippocampus, acetylcholine suppresses synaptic transmission at synapses of the Schaffer coUaterals s'9, which show robust long-term potentiation 3°. In both of these structures therefore, the presynaptic effects of acetylcholine mimic the approach used to avoid interference in abstract associative memory models: synaptic transmission at modifiable synapses is ignored during learning 24-27 (see Box 1). However, in contrast to abstract models of associative memory, acetylcholine does not completely suppress synaptic transmission, but allows at least some synaptic transmission to remain 9'11'12. As described below, further analysis of the consequences of this partial suppression suggests that including this feature of biology in more abstract networks might actually improve their associative memory performance 23. (2) Postsynaptic effects. In a broad range of cortical preparations, acetylcholine has been shown to suppress the normal adaptation of pyramidal cell firing in response to sustained current injection or synaptic input 12-17,33, This appears to be due to blockade of voltage- and Ca2+-dependent K + currents that normally underlie this adaptation 31'32'37. To date there is no corollary in abstract associative memory models for the postsynaptic effects of acetylcholine. Some models of the effects of other neuromodulatory substances incorporate a constant change in gain of a sigmoid input/output function 38, but these input/output functions do not accurately reflect the characteristics of neuronal adaptation. Our biological modeling suggests that the blockade of voltage- and Ca2+-dependent K + currents serves to counteract decreased levels of neuronal activity due to the suppression of synaptic transmission at intrinsic fiber synapses 12'17'21. This suppression of neuronal adaptation allows neurons receiving afferent input to fire in a more sustained manner, increasing both pre- and postsynaptic activity at intrinsic fiber synapses within the network, and thereby enhancing the rate of learning. In addition, these changes effectively increase the length constant of pyramidal cell membranes, making them more responsive to synaptic input that is more distal on the dendrites, in olfactory cortex these distal dendrites are the specific sites of termination of the afferent input to the network 39.

Relation of the model to other experimental data Data

obtained from neural recordings of the basal forebrain in behaving animals support the possibility that cortical levels of acetylcholine are modulated dependent upon the novelty or behavioral significance of behavioral stimuli 4°"1, a feature essential to this model of cholinergic function. In addition, psychopharmacological research suggests that acetylcholine affects the acquisition of new memories to a greater degree than the recall of previously learned memories :~'7. The cholinergic antagonist scopolamine has been shown to increase the number of false positives (responses to unrewarded stimuli) in several behavioral tasks 4. One interpretation of this result, which is consistent with the role of acetylcholine proposed here, is that these false positives reflect a greater number of spurious correlations between learned patterns. This could explain the greater effect of scopolamine on discrimination learning in tasks in which multiple or irrelevant cues as opposed to single cues are presented 5. A similar interpretation may also explain the greater effect of scopolamine on discrimination of patterns presented at low contrast, where distinctions between different stimuli are less clear and greater interference from previous trials can occur 6. These effects can also be described as relating to 'attention', highlighting the fact that conceptual divisions between memory and attention may not apply so clearly at the physiological le'¢el. With respect to olfaction, scopolamine prevents a change in response dependent upon the novelty or familiarity of an odor 42. Experimental evidence on other modulatory effects of acetylcholine are compatible with the modeling framework presented here. Cholinergic modulation has been shown to enhance LTP of the Schaffer collaterals in the stratum radiatum of CA1 (Ref. 43) and the perforant pathway innervation of the dentate gyrus of the hippocampus 44 at the same time as it reduces the level of synaptic transmission. Along with increased postsynaptic excitability, this would further enhance learning during cholinergic modulation. The effect of cholinergic agents on LTP in the olfactory cortex is currently under investigation. Cholinergic modulation also influences the function of inhibitory interneurons in a complex manner, with simultaneous enhancement of the activity of inhibitory interneurons z4'45 and suppression of inhibitory synaptic transmission 4s. In this model, we have found that increasing inhibitory modulation up to a limit increases the efficiency of memory storage 22'23. This could allow the inhibition to make neuronal activity more sparse, thereby increasing the capacity of autoassociative storage zg. In models of the oscillatory properties of olfactory cortex, suppression of pyramidal cell adaptation 46 and reduction in the strength of intrinsic fiber synaptic transmission 46'47 can cause an increase in theta rhythm oscillations such as that noted with cholinergic agents in the hippocampus 48. We believe that the results presented here could provide additional insights for enhancing the function of more abstract models of cortical function. Our analysis of the effects of acetylcholine suggests that the partial suppression of intrinsic connections may produce better memory storage performance than the full suppression currently employed in abstract models. With partial suppression, acetylcholine can prevent activation of neurons not receiving afferent input, while allowing synapses between neurons receiving input to enhance their own growth 2a (see Box 1). This suggests that the level of cholinergic modulation should be graded depending on the degree of overlap between the new input pattern and existing memories. The feedback regulation of basal forebrain input to cortical structures 4o,41 should be analysed to determine if such tuning of modulation is possible. The framework presented here for acetylcholine may serve as a general framework for considering the Concluding remarks The model presented here provides a coherent framework for describing the role of the coordinated neuromodulatory effects of acetylcholine in cortical memory function. Selective suppression of excitatory intrinsic fiber synaptic transmission prevents recall activity due to previously modified synapses fl'om interfering with the learning of new memories. At the same time, the cholinergic suppression of neuronal adaptation enhances the speed of synaptic modification by allowing a more sustained response to afferent synaptic input. Thus, the neuromodulatory effects of acetylcholine appear to complement one another in enhancing associative memory function in cortical structures.