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EDITORIAL

Synaptic properties and functional consequences of cholinergic signalling in the mammalian CNS

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Acetylcholine (ACh) release regulates a diverse array of functions in the mammalian CNS but the mechanisms underlying cholinergic signalling have remained controversial. In the absence of well-defined model systems of cholinergic synaptic transmission it has long been assumed that the various processes initiated by ACh release lack precision, with ACh activating pre- and postsynaptic receptors over long temporal and spatial scales. Over the last several years, the ability to isolate cholinergic synaptic pathways using either conventional or optogenetic techniques has led to a flurry of studies that have identified the dynamic properties of cholinergic signalling, including the functional consequences on a synaptic, circuit and behavioural level. A representative cross section of this recent work was presented at a minisymposium held during the Society for Neuroscience meeting in November 2013, described in the following set of short reviews. Collectively, they emphasize that ACh, rather than acting as a slow and diffuse neuromodulator, can reliably and precisely regulate synaptic plasticity, activity patterns in individual neurons and local circuits, and specific forms of learning.

The first review (d'Incamps & Ascher, 2014) highlights studies at the motoneuron–Renshaw cell synapse in the spinal cord of neonate mice, a well-established model system for cholinergic synaptic transmission. Presynaptic activity leads to the co-release of glutamate and ACh, with the latter activating both homomeric α7 nicotinic ACh receptors (nAChRs) and heteromeric nAChRs. Pharmacological isolation of the heteromeric nAChR-mediated component reveals biphasic EPSCs, with a fast component decaying with a time constant around 10 ms, followed by a slow component decaying over tens of milliseconds. These two kinetically distinct components are probably mediated by the activation of both low- and high-affinity heteromeric nAChRs near sites of release, or alternatively, by a single heteromeric nAChR displaying two distinct activity modes.

Biphasic postsynaptic responses mediated by the activation of nAChRs have also been demonstrated in neocortex (Arroyo *et al.* 2014). Optogenetic stimulation of basal forebrain cholinergic afferents can generate a fast α7 and a slow non-α7 nAChR-dependent response in layer 1 interneurons. These two responses have very distinct properties: α7 nAChR-mediated EPSCs are highly variable from trial to trial and insensitive to perturbations of acetylcholinesterase (AChE) activity, whereas non-α7 nAChR-mediated EPSCs are reliable and highly sensitive to AChE activity. One interpretation of these findings is that fast responses are mediated by ACh release from ultrastructurally defined synapses, while slow responses are due to a specialized form of volume transmission, generated by ACh release from non-synaptic varicosities.

The diversity of cholinergic synaptic signalling modes is further highlighted by results from the thalamic reticular nucleus (TRN), a brain structure that receives cholinergic inputs from the brainstem and the basal forebrain (Beierlein, 2014). ACh release evoked by single stimuli can generate excitatory–inhibitory (E–I) postsynaptic responses, with excitation mediated by non-α7 nAChRs being rapidly curtailed by inhibition, triggered by postsynaptic M2 muscarinic ACh receptors (mAChRs) and the opening of G protein-coupled inwardly rectifying K^+ (GIRK) conductances. ACh release at these afferents is controlled by autoinhibition, mediated by mAChRs expressed in presynaptic terminals. Functionally, the cholinergic innervation of TRN is quite powerful, as ACh release from individual axons is sufficient to trigger action potentials in TRN neurons. Furthermore, the interaction of nAChRs and mAChRs during brief trains of cholinergic synaptic inputs leads to an entrainment of TRN neuronal activity, showing that cholinergic activity can precisely regulate neuronal firing patterns.

Activation of nAChRs and mAChRs by endogenously released ACh can also modulate glutamatergic synaptic strength over different time scales (Yakel, 2014). In the hippocampus, cholinergic afferents from the medial septum and diagonal band of Broca can induce distinct forms of synaptic plasticity at Schaffer collateral (SC) synapses, highly dependent on the relative timing of cholinergic and glutamatergic afferent activity. For cholinergic inputs activated 100 ms prior to activation of the SC pathway, α7 nAChR-dependent long-term potentiation (LTP) is induced, whereas reducing the time difference to 10 ms leads to α7 nAChR-dependent short-term depression. Studies in cocultures suggest that both forms of plasticity require the coordinated activation of both pre- and postsynaptic nAChRs. Finally, if cholinergic inputs are activated 10 ms after the SC stimulation, mAChR-dependent LTP is observed.

How does cholinergic activation regulate higher cognitive functions such as learning? In neocortex, ACh release from basal forebrain afferents can elicit reliable responses in several types of neocortical interneurons (Poorthuis *et al.* 2014). To examine cholinergic control of neocortical circuits during behaviour, the authors employed a combination of genetic targeting of distinct cell types, two-photon imaging and optogenetics. They show that associative fear learning involves the activation of the cholinergic basal forebrain, leading to a recruitment of layer 1 interneurons in the auditory cortex and the generation of disynaptic inhibition of layer 2/3 parvalbumin-positive (PV) interneurons. As PV neurons play a critical role in controlling ongoing activity in local networks of pyramidal cells, the ultimate effect of phasic ACh release is a disinhibition of pyramidal neurons, which facilitates associative learning in auditory cortex.

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Additional information

Competing interests

None declared.