SYMPOSIUM REVIEW

An update on cholinergic regulation of cholecystokinin-expressing basket cells

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Abstract Information processing and transfer within cortical circuits requires precise spatiotemporal coordination of excitatory principal cell activity by a relatively small population of inhibitory interneurons that exhibit remarkable anatomical, molecular and electrophysiological diversity. One subtype of interneuron, the cholecystokinin-expressing basket cell (CCKBC), is particularly well suited to integrate and impart emotional features of an animal's physiological state to principal cell entrainment through the inhibitory network as CCKBCs are highly susceptible to neuromodulation by local and subcortically generated signals commonly associated with 'mood' such as cannabinoids, serotonin and acetylcholine. Here we briefly review recent studies that have elucidated the cellular mechanisms underlying cholinergic regulation of CCKBCs.

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The mammalian neocortex and hippocampus integrate and process multiple sources of sensory and contextual information via reciprocally connected neuronal networks composed of excitatory glutamatergic principal cells and inhibitory GABAergic interneurons. Such computation requires a delicate balance between excitation and inhibition in which relatively few interneurons are able to rapidly pace and synchronize large populations of principal cells to effectively coordinate central information transfer. The precision of this coordination largely relies upon a remarkable heterogeneity within the GABAergic interneuron population that allows the inhibitory network to dynamically control principal cell excitability in both space and time (Klausberger *et al.* 2005; Klausberger & Somogyi, 2008; Isaacson & Scanziani, 2011).

Spatially, a clear division of labour is evident between interneurons with axonal projections that preferentially target either the perisomatic or dendritic compartments of

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the postsynaptic cells they innervate. This gross anatomical divergence optimally positions dendrite-targeting interneurons to control the efficacy, plasticity and summation properties of principal cell synaptic inputs, and perisomatic targeting interneurons to control network synchronicity and output by coordinating action potential (AP) generation amongst large groups of principal cells (Freund & Buzsaki, 1996; Freund & Katona, 2007). Temporal specialization is determined in part by laminar positioning within a given circuit as this dictates afferent recruitment (e.g. preferential 'feedforward' or 'feedback' drive). However, even two broadly anatomically similar interneurons with overlapping afferent input can exert distinct inhibitory influences on the network due to further divergence in electrophysiological properties conferred by unique expression profiles of channels, receptors, calcium binding proteins and neuropeoptides (McBain & Fisahn, 2001; Freund, 2003; Markram *et al.* 2004). This divergence is particularly evident in comparing the two dominant populations of perisomatically targeting basket cells. Parvalbumin-positive basket cells (PVBCs) are optimally designed for timing precision with their fast membrane time constants, non-accommodating fast-spiking behaviour, and tightly calcium-coupled synchronous GABA release (Bucurenciu *et al.* 2008; Doischer *et al.* 2008; Hu *et al.* 2010). In contrast cholecystokinin basket cells (CCKBCs) are better suited to temporal integration with their slower membrane time constants, accommodating low frequency firing profiles, and loosely coupled calcium-dependent synchronous GABA release with a prominent asynchronous component recruited with repetitive activation (Hefft & Jonas, 2005; Daw *et al.* 2009, 2010; Szabo *et al.* 2010).

Based on these differences it has been proposed that PVBCs mediate a rigid clockwork pacing function for the generation and maintenance of fast cortical oscillations while CCKBCs serve as plastic fine-tuning devices that modulate the PVBC-entrained network (Freund, 2003; Freund & Katona, 2007). Consistent with this model PVBCs are primarily driven in a rapid, efficient and faithful manner by local principal cells with relative immunity to slower signalling neuromodulatory substances (Glickfeld & Scanziani, 2006; Freund & Katona, 2007). In contrast network engagement of CCKBCs occurs with considerable jitter requiring temporally summating coincident activity from multiple excitatory afferent pathways and is strongly influenced by a variety of neuromodulators (Glickfeld & Scanziani, 2006; Freund & Katona, 2007). It is this neuromodulatory tone of CCKBCs that is considered to impart emotional and motivational features of an animal's physiological state to the perisomatic inhibitory system. Indeed CCKBCs are heavily endowed with receptors for many signals commonly associated with 'mood' such as endocannabinoids, serotonin, acetylcholine, noradrenaline and neuropeptide Y. Thus, in addition to their direct influence on the excitatory glutamatergic principal cells, these neuromodulatory substances can influence circuit information processing and transfer through modulation of CCKBC function. Even at embryonic stages as cells fated to become CCKBCs exit the caudal ganglionic eminence (CGE) progenitor pool they express receptors for serotonin and cannabinoids suggesting roles for these signals in CCKBC proliferation, migration and circuit integration (Morozov *et al.* 2009; Lee SH *et al.* 2010; Tricoire *et al.* 2010; Vucurovic *et al.* 2010). Initial attempts to elucidate the effects of various neuromodulators on specific interneuron subpopulations were typically confounded by heterogeneity within the entire population sampled (e.g. McQuiston & Madison, 1999*a*). However, the recent generation of GFP reporter mice to selectively target specific interneuron subtypes combined with strict *post hoc* inclusion standards to limit findings to a uniform interneuron population has facilitated increasingly refined functional interrogation of diverse interneuron subtypes (e.g. McQuiston & Madison, 1999*a*; Lawrence *et al.* 2006*b*; Cea-del Rio *et al.* 2010, 2011). Here we briefly review several recent studies that have exploited this experimental approach to examine the cholinergic regulation of CCK-containing interneuron function.

Muscarinic acetylcholine receptors

Basal forebrain cholinergic input to the neocortex and hippocampus critically regulates arousal, attention and learning (Jones, 2004; Hasselmo, 2006). At the neuronal network level this regulation reflects cholinergically driven changes in the magnitude of cortical oscillations in relation to an animal's behavioural state (Lawrence, 2008). The convergent influence of cholinergic signalling and perisomatic inhibition on network oscillations suggests an important link between the cholinergic and GABAergic systems in dynamically regulating principal cell coordination. Indeed while acetylcholine (ACh) directly modulates glutamatergic transmission, the ability of cholinergic drive to entrain principal cell ensembles also requires direct modulation of GABAergic interneurons through both nicotinic and muscarinic receptors (nACh and mAChRs, respectively).

Initial evidence for direct neuromodulation of CCK-expressing interneurons by ACh came from studies by Kawaguchi, as well as McQuiston and Madison, in the neocortex and hippocampus, respectively (Kawaguchi, 1997; McQuiston & Madison, 1999*a*). In rat neocortex, application of the non-specific AChR agonist carbachol, or the general mAChR agonist muscarine, produced hyperpolarizing, depolarizing, or biphasic responses in CCK-containing GABAergic cells with regular- or burst-spiking properties, without altering the properties of fast-spiking PVBCs (Kawaguchi, 1997). In hippocampal

interneurons, the predominant muscarinic response observed was depolarization, but biphasic responses were also evident in some stratum radiatum interneurons, a portion of which undoubtedly included CCK-containing interneurons (McQuiston & Madison, 1999*a*). In a subset of these interneurons mAChR activation was observed to convert the afterhyperpolarization (AHP) following injection of a square wave current pulse to trigger AP firing into an afterdepolarization (ADP) that frequently resulted in continued firing beyond the duration of the current injection (McQuiston & Madison, 1999*b*). Moreover, changes in interneuron membrane voltage and ADP were also elicited by release of endogenous ACh using bulk stimulation of cholinergic fibres arriving in the hippocampus (Widmer *et al.* 2006). Although these initial studies clearly indicated that GABAergic inhibitory interneurons were targets for cholinergic modulation, what they did not clarify was whether specific homogeneous cohorts of interneurons, identified for example by their anatomical, morphological, or neurochemical content, were modulated in a stereotypic manner by muscarinic receptor activation.

Recent studies have tackled this question head on and demonstrated that subtypes of anatomically/neurochemically identified CCK-positive interneurons display largely overlapping and stereotypic muscarinic receptor response profiles (Widmer *et al.* 2006; Cea-del Rio *et al.* 2010, 2011). The cell bodies of CCK-containing interneurons are distributed throughout almost all subfields of the mammalian CA1 hippocampus with the vast majority of CCK-containing interneurons being captured by the CCKBC and CCK-Schaffer collateral-associated (CCKSCA) cell types (Tricoire *et al.* 2011). Both CCKBCs and CCKSCAs typically have their somatodendritic axis oriented such that they receive their primary excitatory input from the Schaffer collateral axons of CA3 pyramidal cells. While CCKBCs make their axon targets onto a narrow somatic and proximal dendritic domain of pyramidal neurons, the axons of CCKSCAs typically target wide areas of the remaining principal cell dendrites (Fig. 1). This limited overlap in axonal output domains suggests they perform distinct functions in the ongoing neuronal network, despite receiving a common source of afferent drive. Therefore, whether these two neurochemically similar but morphologically distinct cell types respond similarly or distinctly in the face of muscarinic receptor activation was until recently an open question.

Both CCKBCs and CCKSCAs typically express mRNAs for M1 and M3 mAChRs, but show subtle differences in the occurrence of M2, M4 and M5 mAChR mRNAs, all of which are present with greater frequency in CCKSCAs (Cea-del Rio *et al.* 2010, 2011). Muscarine receptor activation increases action potential duration and frequency, reduces spike adaptation, and promotes an ADP generation in both CCKBCs and CCKSCAs (Cea-del Rio *et al.* 2010, 2011) (Fig. 1*A* and *B*). Pharmacological intervention, and recordings from M1, M3 and double M1/M3 mAChR knockout (KO) mice, indicated that these responses are synergistically mediated by both M1 and M3 mAChRs (Cea-del Rio *et al.* 2010, 2011). Specifically, M3 receptor activation controls the muscarinic receptor-mediated increase in firing frequency, whereas both M1 and M3 muscarinic receptor activation is required for the full conversion of the spike AHP into a spike ADP (Fig. 1*C* and *D*). These data stand in sharp contrast to that obtained from PVBCs where M1 muscarinic receptors are the sole mediators of somatodendritic muscarinic receptor-mediated excitation (Cea-del Rio *et al.* 2010).

Activation of somatodendritic mAChRs on CCK interneurons is likely to have important consequences for the roles played by these cells in the cortical network. For example, brief trains of glutamatergic synaptic input delivered concomitantly with mAChR activation triggered long-lasting repetitive firing, which far exceeded the duration of the synaptic stimuli (Cea-del Rio *et al.* 2010). This suggests that prolonged tonic firing of CCK interneurons may result from modest glutamatergic excitatory synaptic drive following a brief episode of cholinergic input. Furthermore, muscarinic receptor modulation amplified 0.5–2 Hz subthreshold membrane oscillatory activity in both CCKBCs and CCKSCAs suggesting that cholinergic tone primes these cells to participate in low frequency network activity (Cea-del Rio *et al.* 2011). Indeed muscarinic receptor activation enhanced the efficiency of CCKBC/SCA recruitment during sinusoidal current injections in the theta frequency range to mimic slow network oscillations (Cea-del Rio *et al.* 2011). Moreover, optogenetically driven ACh release induced bursts of endocannabinoid-sensitive perisomatic inhibitory synaptic currents in CA1 pyramidal cells in the theta frequency range through mAChR activation (Nagode *et al.* 2011).

Although CCKBCs and CCKSCAs show mostly stereotypic responses to muscarinic receptor activation, several notable differences were also observed. In addition to promoting theta engagement, muscarine receptor activation broadened the frequency response preference of CCKBCs, but not that of CCKSCAs, to drive engagement during higher frequency oscillatory activities in the beta range (15–20 Hz) (Cea-del Rio *et al.* 2011). A further difference between the muscarinic profiles of CCKBCs and CCKSCAs was noted in the effects on resting membrane potential. During muscarine application CCKBCs undergo an M1/M3 mAChR-dependent depolarization (Cea-del Rio *et al.* 2010), possibly mediated by closure of Kv7 channels turning off the M-current (Lawrence *et al.* 2006*a*). In contrast CCKSCAs undergo a biphasic membrane voltage

deflection in response to muscarine application, which is driven separately by M1 and M3 mAChRs during the hyperpolarizing and depolarizing phases, respectively (Cea-del Rio *et al.* 2011) perhaps arising through M1-mediated GIRK channel activation (McQuiston & Madison, 1999*b*) followed by M3-mediated inhibition of the M-current (Fisahn *et al.* 2002).

Independent of the somatodendritic response profiles described above muscarine also depresses GABA release from CCKBC presynaptic terminals (Kim *et al.* 2002;

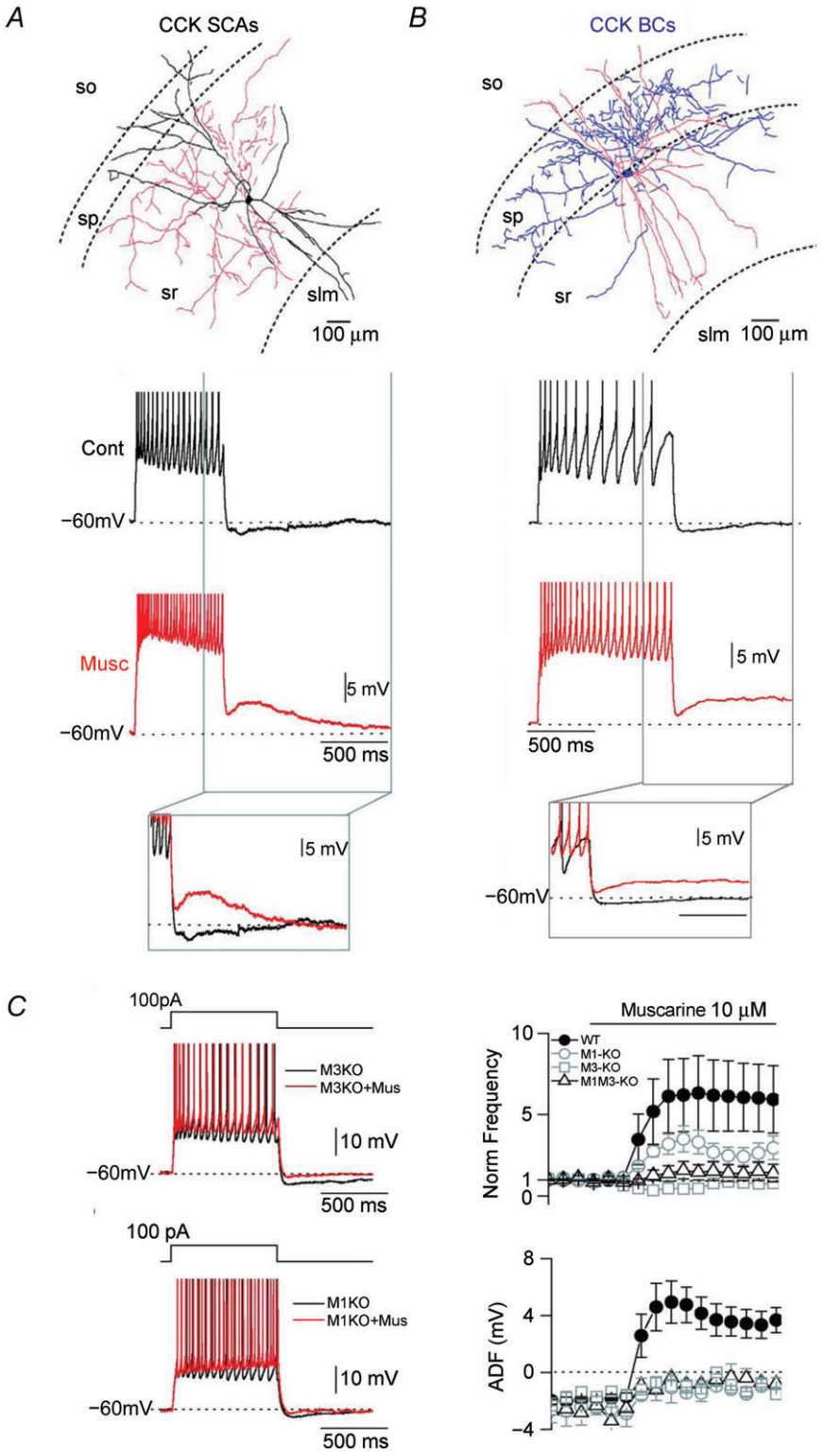

Figure 1.
A **and** ***B*****, upper panels are representative morphological reconstructions of typical CCK-containing Schaffer collateral-associated (CCKSCAs) and basket cells (CCKBCs). Lower series of panels show the voltage response from –60 mV in control (black) and after bath application of 10 μM muscarine (red) for CCKSCAs (left) and CCKBCs (right). Grey boxes represent the overlap of the control and muscarinic afterdeflection to highlight the emergence of the ADP in the presence of muscarine.** ***C*****, left panels: representative traces for mAChR-induced changes in M3 KO CCKSCAs (upper) and M1 KO CCKSCAs (lower). Normalized firing frequency (upper right panel) and ADF summary population plots for control (filled circles), M1 KO CCKSCAs (open circles), M3 KO CCKSCAs (open squares) and M1M3 KO CCKSCAs (open triangles). Data reproduced from Cea-del Rio** ***et al.*** **2010, 2011.**

Neu *et al.* 2007). However, this modulation occurs indirectly by mAChR activation on postsynaptic targets innervated by CCKBCs leading to the liberation of endocannabinoids from these targets and subsequent activation of cannabinoid receptor 1 (CB1) receptors on CCKBC terminals resulting in robust depression of CCKBC release (Kim *et al.* 2002; Chevaleyre *et al.* 2006; Neu *et al.* 2007). This indirect modulation contrasts with PVBCs in which activation of M2 mAChRs directly on the presynaptic terminals is reported to depress GABA release from these cells (Hajos *et al.* 1998; Szabo *et al.* 2010). Interestingly, endocannabinoid/CB1-mediated indirect modulation of CCKBC release has also been implicated in kainate and CCK receptor-driven depression of presynaptic release from CCKBCs (Foldy *et al.* 2007; Karson *et al.* 2008; Daw *et al.* 2010; Lourenco *et al.* 2010, 2011; Lee & Soltesz, 2011). However, while carbachol depresses both synchronous and asynchronous CCKBC release, kainate receptor activation selectively depresses synchronous release without altering the asynchronous component (Daw *et al.* 2010; Szabo *et al.* 2010). Thus, while an increase in cholinergic tone promotes removal of CCKBC inhibitory influence on the network, kainate receptor activation selectively reduces temporal precision of CCKBC output by selectively reducing phasic release. Whether CCK peptide-induced depression of CCKBC release is selective for synchronous release remains to be determined.

Nicotinic acetylcholine receptors

Rapid cholinergic modulation of CCKBC function can also occur through ionotropic nAChRs. Indeed it has recently been reported that the entire cohort of CGE-derived interneurons, which includes the CCKBC subpopulation (Tricoire *et al.* 2011), is robustly excited by nAChR activation (Lee S *et al.* 2010). Early studies reported the presence of nicotinic excitatory potsynaptic currents in hippocampal interneurons primarily mediated through α7 subunit-containing nAChRs (Frazier *et al.* 1998). Subsequent investigation confirmed nAChR-mediated responsiveness of neocortical CCKBCs but pharmacological profiles indicated responses were mediated by α7 subunit-lacking, α4/β2 subunit-containing nAChRs (Porter *et al.* 1999; Férézou *et al.* 2002). Indeed α7 subunit mRNA was detected with less frequency than α4/5- and β2-encoding transcripts in anatomically and molecularly identified nicotinic-sensitive neocortical CCKBCs (Porter *et al.* 1999). Conflicting with this observation is a report that the α7 subunit-encoding mRNA strongly colocalizes with CB1 and CCK transcripts in the hippocampus suggesting divergence in neocortical and hippocampal CCKBC nAChR composition (Morales *et al.* 2008). Recently, in adult mice anatomically confirmed hippocampal CCKBCs were found to exhibit nAChR postsynaptic currents using optogenetic techniques to trigger release from septal cholinergic afferents confirming that hippocampal CCKBC nAChRs are synaptically driven (Bell *et al.* 2011). However, as in neocortex these rapid postsynaptic responses in hippocampal CCKBCs exhibited pharmacological profiles consistent with α4/β2 subunit-containing nAChRs leaving the role of α7 subunit-containing receptors in question (Bell *et al.* 2011). Interestingly, α4/β2 nAChR gain of function mutants serve as a model for autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and exhibit enhanced network synchronization in the delta/theta range (Klaassen *et al.* 2006). As the characteristic phase-locked firing behaviour of CCKBCs during theta oscillations suggests a prominent role for these cells in regulating this rhythm (Klausberger *et al.* 2005), it is tempting to speculate that the ADFNLE phenotype relates in part to enhanced cholinergic recruitment of CCKBCs. Concerning α7 nAChRs, it is possible that these receptors function at extrasynaptic sites (Brumwell *et al.* 2002) and/or participate in early development of CCKBCs regulating their migration and circuit integration by promoting electrophysiological maturation, including establishment of mature chloride gradients (Liu *et al.* 2006; Bortone & Polleux, 2009).

Given their high calcium permeability, an alternative role for α7 subunit-containing nAChRs could be regulation of transmitter release from CCKBC presynaptic terminals (MacDermott *et al.* 1999). Indeed calcium influx through α7 nAChRs, in combination with calcium-induced calcium release from internal stores (CICR), is reported to drive action potential-independent transmitter release from hippocampal mossy fibres (Sharma & Vijayaraghavan, 2003; Sharma *et al.* 2008). Recently, an elegant study by Alger and colleagues specifically examined the contribution of nAChRs to GABA release from interneuron presynaptic terminals (Tang *et al.* 2011). Interestingly, they found that activation of nAChRs on the axons of perisomatically targeting interneurons robustly drives action potential-independent GABA release and additionally modulates action potential-dependent GABA release. However, the contribution of α7-containing nAChRs was minimal. Rather, the cholinergic recruitment of perisomatic GABA release was primarily mediated by α3/β4 subunit-containing nAChR-mediated axonal depolarization with subsequent activation of T-type calcium channels and CICR. Moreover, while nAChR-driven GABA release was convincingly demonstrated to involve PVBCs a role for this phenomenon in driving release from CCKBC terminals remains to be demonstrated.

In conclusion, recent advances in imaging and genetic technology that permit the reliable identification of

specific cohorts of local circuit inhibitory interneurons for electrophysiological interrogation have rapidly advanced our understanding and appreciation of the roles played by many of these cell types in the local cortical circuit. This review brings together recent data from some of these studies regarding modulation of CCK-containing inhibitory neurons by acetylcholine and its associated muscarinic and nicotinic receptors. However, ACh represents only one common cortical neuromodulator and inhibitory interneurons are littered with receptors for numerous others (including 5HT, dopamine, NPY, noradrenaline, to name but a few). It is our hope that by careful study of this armament of neuromodulatory receptors and their downstream response profiles on identified subpopulations of interneurons we will learn much about the roles played by neuromodulatory systems in sculpting the activity of interneurons in the hippocampal and cortical network.

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