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SYMPOSIUM REVIEW

Sticking out of the crowd: the molecular identity and development of cholecystokinin-containing basket cells

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Abstract Certain essential cognitive processes require the precise temporal interplay between glutamatergic (excitatory) pyramidal cells and γ-aminobutyric acid (GABA)-releasing inhibitory interneurons in the hippocampus. Basket cells, the main class of interneurons, target pyramidal cell somata and proximal dendrites and thus are poised to modify network oscillations. Though only present in limited numbers, the impaired development of basket cells can result in changes in the hippocampal circuitry leading to neurological disorders, such as schizophrenia. The diversity of the spatial origins, neurochemical make-up, cytoarchitecture and network contributions amongst basket cells is a provocative example of interneuron heterogeneity in the hippocampus. This review discusses recent data concerned with the developmental trajectories of one subclass, the cholecystokinin-containing basket cell, and emphasizes the significance of the short-range intercellular guidance cues that have recently emerged to impact the formation and function of their inhibitory synapses.

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Abbreviations 2-AG, 2-arachidonoylglycerol; ABHD6, α-β hydrolase domain 6; BDNF, brain-derived neurotrophic factor; CB_1R, type 1 cannabinoid receptor; CCK, cholecystokinin; CGE, caudal ganglionic eminence; COX-2, cyclooxygenase-2; CRF, corticotropin releasing factor; ctx, cortex; D2R, dopamine receptor D2; DAGLα, diacylglycerol lipase α; DSI, depolarization-induced suppression of inhibition; GABA, γ-aminobutyric acid; hip, hippocampus; iLTD, long-term depression of inhibition; IZ, intermediate zone; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; MGL, monoacylglycerol lipase; MSI, metabotropic suppression of inhibition; MZ, marginal zone; nAChR, nicotinic acetylcholine receptor; NPY, neuropeptide Y; PV, parvalbumin; SOM, somatostatin; TrkB, tropomyosin-related receptor kinase B; THC, tetrahydrocannabinol; VGLUT3, vesicular glutamate transporter 3; VIP, vasoactive intestinal peptide; VZ, ventricular zone.

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Functional significance of basket cells in the hippocampal circuitry

Some cognitive processes, including attention and memory formation, require the precise temporal interplay between glutamatergic (excitatory) pyramidal cells and γ-aminobutyric acid (GABA)-releasing inhibitory interneurons in the hippocampus (McBain *et al.* 1999; Freund, 2003; Buzsaki *et al.* 2004; Morellini *et al.* 2010; Murray *et al.* 2011). Although vastly outnumbered by pyramidal cells, the precisely timed activity of interneurons and their innate property to entrain large principal cell ensembles are essential to set the output of the hippocampal circuitry (Freund, 2003; Freund & Katona, 2007).

Interneurons are historically considered as the 'diverse' cell type in the hippocampal circuitry, which have evolved to define specific network modalities through selective positioning, spike timing and input–output relationships. The presently accepted consensus to classify interneurons is based on the 'Petilla' terminology, which classifies GABAergic interneurons by collating their molecular, anatomical and physiological characteristics (Ascoli *et al.* 2008). This approach requires multiparametric analysis of the interneurons' birth places, migratory routes, neurochemical tags, molecular make-up (Table 1), cytoarchitectural features, intrinsic membrane properties and network relationships (Pleasure *et al.* 2000; Anderson *et al.* 2002; Ascoli *et al.* 2008; Tricoire *et al.* 2011).

Using these criteria, at least 22 subtypes of GABAergic interneurons are presently discerned in the hippocampus alone. The term 'basket cell' alludes to the axonal field of these cells being restricted to the soma and proximal dendrites of principal cells, with their synapses enwrapping excitatory perikarya in the pyramidal layer (Gulyas *et al.* 1999; Papp *et al.* 2001). This synapse distribution confers particular power to tune pyramidal cell excitation and network oscillations (Freund, 2003). Basket cells can be divided into neurochemically and functionally distinct classes, the majority expressing parvalbumin (PV) (Nomura *et al.* 1997), a cytosolic fast Ca^{2+} buffer implicated in the generation and maintenance of high-frequency action potential trains known as 'fast-spiking' (>100 Hz). A second class expresses cholecystokinin (CCK), a peptide hormone, and exhibits irregular discharge patterns unusually exceeding 50 Hz (Freund & Buzsaki, 1996; Kawaguchi & Kondo, 2002; Wang *et al.* 2002). A division of function between PV and CCK basket cells has been proposed with PV^+ interneurons controlling the rhythm of network oscillations ('clockwork precision'), while CCK^+ cells sculpt the efficacy of information flow and encoding by fine-tuning network chronosynchrony (Freund, 2003).

Ever since Ramon y Cajal's first description of local-circuit interneurons, the molecular identity and network contributions of GABAergic cells have been studied in postnatal cortical networks. It is only through recent advances of molecular genetics and cell biology that we have come to appreciate the interneurons' different origins, migratory behaviours and cytoarchitectural features (Xu *et al.* 2004; Butt *et al.* 2005; Miyoshi *et al.* 2010; Tricoire *et al.* 2011). Although present in limited numbers, impaired development of GABAergic interneurons in the fetal cerebrum can have permanent impact on the hippocampal circuitry (Peters & Kara, 1985), precipitating neurological disorders (Di Cristo, 2007). This review discusses recent data concerned with the developmental trajectories of CCK^+ basket cells, and emphasizes the significance of recently identified short-range intercellular guidance cues that impact the formation and function of GABAergic synapses.

The historical approach: retrospective neurochemical analysis of CCK^+ basket cells

Do CCK^+ basket cells exhibit unique cytoarchitectural and molecular signalling properties that distinguish them from other basket cells? This is an important question to address to gain insights regarding their circuit parameters, response patterns, as well as development and integration into hippocampal neuronal networks (Table 1). Electrophysiology studies combined with *post hoc* cellular neuroanatomy were the preferred approach to identify unique characteristics of basket cells. However, the advent of molecular array technologies and genetic tagging opened new horizons in the understanding of the birthplaces, migratory routes and terminal differentiation programs of various interneuron subtypes, facilitating the resolution of ambiguities regarding molecular identities.

CCK is the primary marker to classify this group of basket cells (Fig. 1). Recent findings have revealed dual pathways downstream from CCK receptor signalling in the two basket cell populations (Foldy *et al.* 2007). First, CCK inhibits GABA release from CCK^+ basket cells through CCK2 receptors. This mechanism is dependent on type 1 cannabinoid receptor (CB_1R) activation (see below) but independent of GABA release from other interneurons (Lee & Soltesz, 2011). Second, CCK2 receptors on PV^+ basket cells respond to CCK and trigger Ca^{2+} release from intracellular Ca^{2+} stores. This event leads to depolarization by the activation of a non-selective cationic conductance enhancing GABA release (Lee *et al.* 2011). Therefore, the net effect is to shift inhibition from CCK^+ to PV^+ basket cells, leaving CCK signalling poised to modulate complex signalling networks by modifying inhibitory and excitatory signals to fine-tune precise firing patterns.

An intracellular feature of hippocampal CCK^+ basket cells is that a subset contains vasoactive intestinal peptide (VIP) (Freund & Buzsaki, 1996). CCK^+–VIP^+ basket cells can co-express corticotropin-releasing factor

Table 1. Molecular parameters of CCK- and PV-containing cells

CCK^+ small basket cell	References	PV^+ nest/large basket cell	References
Receptors		**Receptors**	
$5\text{-}HT_{3A}$	Morales & Bloom, 1997	M2 muscarinic ACh	Hajos *et al.* 1998
Nicotinic ACh	Porter *et al.* 1999	μ-Opioid	Drake & Milner, 2002
CB_1R	Katona *et al.* 1999		
Oestrogen receptor α	Hart *et al.* 2007		
$GABA_B$	Sloviter *et al.* 1999		
Peptides		**Peptides**	
VIP	Kawaguchi & Kubota, 1997	NPY (subset)	Wang *et al.* 2002
CRF	Kubota *et al.* 2011		
Endocannabinoids		**Endocannabinoids**	
MGL	Gulyas *et al.* 2004	MGL	Gulyas *et al.* 2004
Vesicular transporters		**K^+ channels**	
VGLUT3	Somogyi *et al.* 2004	Kv3.1b	Sekirnjak *et al.* 1997
		Kv3.2	Hernandez-Pineda *et al.* 1999
		Kv3.3	Chang *et al.* 2007

(CRF) (Kubota *et al.* 2011). Once released, CRF and CCK depolarize pyramidal cells through CRF-1 and CCK2 receptors, respectively (Gallopin *et al.* 2006). Conspicuously, CCK^+ basket cells express vesicular glutamate transporter 3 (VGLUT3; Fig. 1) (Harkany *et al.* 2004; Somogyi *et al.* 2004). Although the precise role of VGLUT3 in basket cells remains unknown, experiments using genetic deletion of VGLUT3 indicate that glutamate co-transmission at GABA/glycinergic synapses is necessary for the developing inhibitory circuit in the auditory system (Noh *et al.* 2010).

CCK^+ interneurons also exhibit a unique assembly of cell-surface receptors. These include postsynaptic $\alpha4/\beta2$ nicotinic acetylcholine (nAChR) (Porter *et al.* 1999; Ferezou *et al.* 2002; Bell *et al.* 2011), ionotropic $5\text{-}HT_{3A}$ serotonin (Morales & Bloom, 1997; Vucurovic *et al.* 2010) and oestrogen α receptors (Hart *et al.* 2007), the latter being associated with clusters of synaptic vesicles in perisomatic boutons. However, the specific role of oestrogen receptors on vesicles remains unclear. Serotonin and cholinergic signalling via $5\text{-}HT_{3A}$ and $\alpha4$-nAChR, respectively, elicit fast synaptic excitation of CCK^+–VIP^+ basket cells (Ferezou *et al.* 2002; Varga *et al.* 2009). In contrast, oestrogen α receptor signalling limits presynaptic neurotransmitter release by reducing the likelihood of GABA-laden synaptic vesicle docking (Hart *et al.* 2007).

CCK^+ interneurons express high levels of the CB_1R (Katona *et al.* 1999; Marsicano & Lutz, 1999; Tsou *et al.* 1999). CB_1Rs, a primarily $G_{i/o}$ protein-coupled GPCR receptor subclass, are named after their ability to bind to and transduce the psychotropic effect of Δ^9-tetrahydrocannabinol (THC), the major phytocannabinoid from cannabis (Devane *et al.* 1988; Matsuda *et al.* 1990). The physiological impact of agonist activation of CB_1Rs is profound since these receptors are targeted to the presynaptic terminals of many neurons

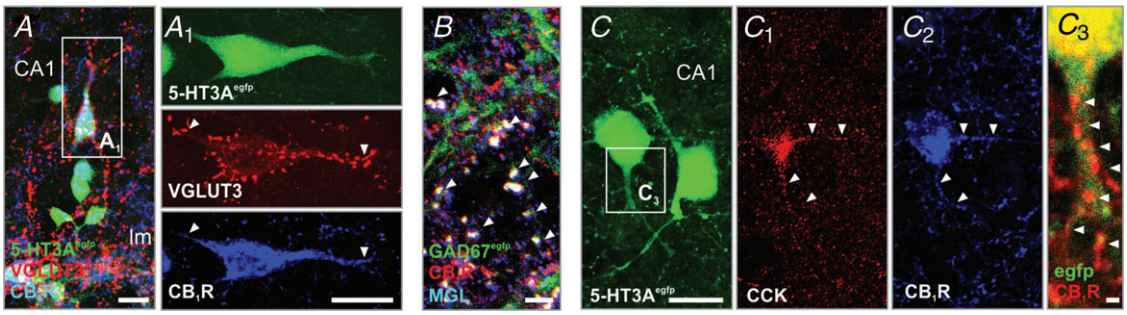

Figure 1. Characteristic molecular markers of CCK^+ interneurons
A, a subpopulation of $5\text{-}HT_{3A}\text{-}EGFP^+$ cells in the hippocampus is immunoreactive for VGLUT3 and CB_1Rs. A_1, arrowheads point to VGLUT3/CB_1R^+ processes. *B*, CB_1R^+/$GAD67^+$ boutons contain the 2-AG degrading enzyme MGL (arrowheads), C–C_3, CCK^+ interneurons express $5\text{-}HT_{3A}Rs$ and CB_1Rs. Arrowheads indicate CB_1R^+ structures. Scale bars: 20 μm (*A*, A_1, *C*), 5 μm (*B*) and 1 μm (C_3).

(including CCK$^+$ basket cells; Fig. 1) where they generally limit neurotransmitter release (Wilson & Nicoll, 2001; Kano *et al.* 2009; Regehr *et al.* 2009). CB_1R activation under physiological conditions is achieved through the 'on-demand' liberation of endogenous cannabinoids ('endocannabinoids'), such as 2-arachidonoylglycerol (2-AG) (Mechoulam *et al.* 1995) and anandamide (Devane *et al.* 1992), from postsynaptic neurons. Endocannabinoid signalling belongs to the emerging family of signalling systems that mediate feedback control of neurotransmitter release through retrograde action: for 2-AG, ligand synthesis at the postsynapse occurs through diacylgycerol lipases α/β (DAGLα/β) in pyramidal cells (Bisogno *et al.* 2003). However, CCK$^+$ interneurons lack DAGLα/β *in vivo* during development and adulthood identifying endocannabinoids as target-derived cues (Yoshida *et al.* 2011). Having traversed the synaptic cleft, 2-AG engages presynaptic CB_1Rs. Endocannabinoid inactivation operates both at postsynaptic and presynaptic loci through the segregated action of the serine hydrolase ABHD6 (Marrs *et al.* 2010) and monoacylglycerol lipase (MGL) (Dinh *et al.* 2002), respectively. CCK$^+$ basket cells express and co-target MGL with CB_1Rs to their presynapses (Gulyas *et al.* 2004; Yoshida *et al.* 2011). Furthermore, cyclooxygenase-2 (COX-2) has been demonstrated to degrade 2-AG (Kozak *et al.* 2000) and its inhibition prolongs depolarization-induced suppression of inhibition (DSI) in a CB_1R-dependent manner affirming that COX-2 is involved in CB_1R-mediated retrograde signalling (Kim & Alger, 2004; Straiker & Mackie, 2009) (Fig. 3).

CCK$^+$ basket cells also express presynaptic $GABA_B$ receptors (Sloviter *et al.* 1999). Although the role of $GABA_B$ receptors remains largely unclear, a coupling to N-type Ca^{2+} channels (Wilson *et al.* 2001) in a Ca^{2+}-dependent manner similar to CB_1Rs (Neu *et al.* 2007) has been reported.

Should I stay or should I go: the developmental program of CCK interneurons

Understanding the mechanisms driving the development of any neuron and its network requires detailed knowledge about the genetic and environmental history of the cell. This is particularly challenging for telencephalic interneurons since it is impossible to deduce the precise birth location of a neuron based on where it is found in the adult structure. Despite these challenges, the origins and genetic programs involved in the developmental control of neocortical interneuron differentiation are beginning to be understood (Batista-Brito & Fishell, 2009). In contrast to pyramidal cells, interneurons migrate long distances tangentially to reach their final destinations by and after birth (Fig. 2). The medial ganglionic eminence (MGE) was long thought to give rise to around 85–90% of all interneurons (Nery *et al.* 2002). However, recent data suggest that as many as 30–40% of cortical interneurons are instead derived from the caudal ganglionic eminence (CGE, Fig. 2) (Lee *et al.* 2010*a*; Miyoshi *et al.* 2010). The phenotypes of CGE-derived interneurons are non-overlapping with their MGE-derived counterparts, and these neurons are generally born later during development (Butt *et al.* 2005; Miyoshi *et al.* 2010; Tricoire *et al.* 2011).

CCK$^+$ basket cells are CGE derived

All cortical CGE-derived interneurons express 5-HT_{3A} receptors, as well as respond to nicotinergic stimulation

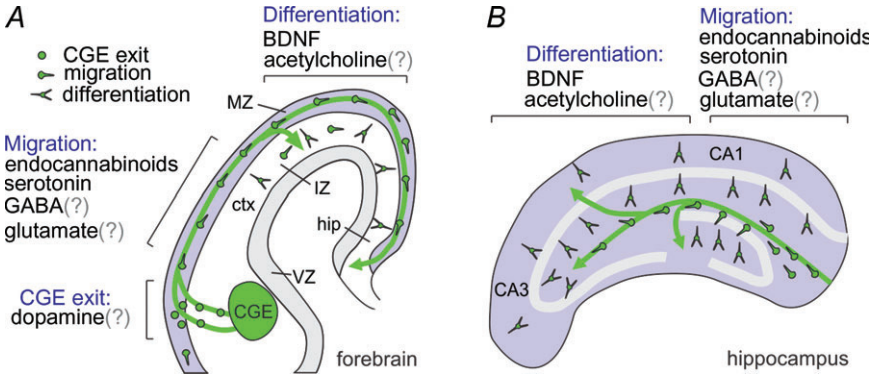

Figure 2. Molecular cues orchestrating CCK$^+$ basket cell development
Overview of the molecular cues involved in the migration and differentiation of basket cells towards the neocortex and the hippocampus. *A* and *B*, basket cells born in the CGE migrate through the marginal zone (MZ) or the intermediate zone (IZ) of the cerebral cortex (Manent *et al.* 2005; Morozov *et al.* 2009) to find their final positions either in the neocortex (*A*) or the hippocampus (*B*). Green trajectories indicate the migratory routes of prospective GABA interneurons. Molecular cues for each developmental state are noted. Question marks query the specificity of cues during CCK$^+$ interneuron development.

(Lee *et al.* 2010*a*). Therefore, the use of a 5-HT_{3A}BAC-EGFP reporter mouse line allowed detailed analyses showing that all VIP^+ cells are born in the CGE (Lee *et al.* 2010*a*; Vucurovic *et al.* 2010). Some of these deep layer VIP cells were shown to co-express CCK. A recent genetic fate mapping study of the hippocampus using GAD65-EGFP and Mash1CreER mice substantiated these findings by showing that CGE-derived cells included most CCK^+ interneurons (Tricoire *et al.* 2011). However, a definitive conclusion about the origin of the entire cortical/hippocampal CCK population remains elusive for a number of reasons: (1) the GAD65-EGFP and Mash1CreER transgenic models suffer from an incomplete labelling of the entire CGE-derived neuron population (Miyoshi *et al.* 2010; Tricoire *et al.* 2011). (2) The 5-HT_{3A}BAC-EGFP mouse has not yet been shown to be as specific for CGE-derived cells in the hippocampus as it is in the cortex. (3) In contrast to available immunohistochemical data, a stringent genetic design found a higher number of GFP-tagged cells in superficial cortical laminae, when crossing CCK-IRES-Cre (Taniguchi *et al.* 2011) with a Dlx5/6-Flpe and a RCE-dual reporter (Miyoshi *et al.* 2010), which expresses EGFP only upon coincident Flpe- and Cre-driven recombination. This suggests that either VIP^- CCK cells escaped detection in earlier studies or there is a population of interneurons transiently expressing CCK during development.

Genetic regulation of interneuron specification

A number of transcription factors are crucial for general cortical interneuron development. These include the Dlx gene family and the proneural gene Mash1 (Long *et al.* 2009). Mice lacking both Dlx1 and Dlx2 have a severe loss of tangentially migrating interneurons (Cobos *et al.* 2007). Similarly, Mash1 null mice have a marked loss of GABAergic cells in the neocortex and hippocampus (Anderson *et al.* 1997; Casarosa *et al.* 1999). The specific genetic program that controls the specification and generation of interneurons derived from the MGE, and involving the sequential activation of Nkx2-1 (initial specification) followed by Lhx6 and Sox6 (migration and differentiation) is beginning to be elucidated (Liodis *et al.* 2007; Du *et al.* 2008; Azim *et al.* 2009; Batista-Brito *et al.* 2009).

The search is still on for a CGE-specific factor equivalent to Nkx2-1. Such a transcription factor is probably repressed by Nkx2-1 since removal of Nkx2-1 after the final cell division of interneuron progenitors dictates the acquisition of a full CGE phenotype in many MGE-derived cells (Butt *et al.* 2008). One gene family that is preferentially expressed in the CGE during development includes the Coup-TF1/2 genes (Kanatani *et al.* 2008). Accordingly, Coup-TF1 removal specifically in interneurons reduces the amount of CGE-derived VIP^+ and CR^+ interneurons (Lodato *et al.* 2011). Coup-TF2 has also been implicated in regulating tangential migration towards the cerebral cortex, and is expressed in a subset of CB_1R^+, as well as CB_1R^-, hippocampal cells (Kanatani *et al.* 2008; Fuentealba *et al.* 2010; Antypa *et al.* 2011). Although the hunt for a CGE-specific 'master regulator' might be rewarding, the hypothesis that CGE fate may be a 'default state' of interneurons derived from the ganglionic eminences also seems plausible.

Developmental cues for CCK^+ basket cells

Although cell-autonomous mechanisms can drive the initial engagement of CGE-derived basket cells in migratory behaviours and cytoarchitectural differentiation, short-range paracrine signals will provide critical cues to instruct the directionality of cell movement, synapse formation and functional integration into neuronal networks (Fig. 2).

Classical neurotransmitters impact interneuron development. In particular, serotonin has been identified as a cue instructing interneuron migration, differentiation and synaptogenesis (Lauder, 1990). Inhibition of serotonin synthesis in pregnant rats leads to a decrease in the migration and terminal differentiation of CCK^+ interneurons in affected offspring (Vitalis *et al.* 2007). A gain-of-function analysis using SLC6A4 knockouts in which serotonin reuptake is blocked ('hyperserotonergic mouse') demonstrated an increase of CGE-derived $GAD65^+$ interneurons in the cerebral cortex (Riccio *et al.* 2009). Data from organotypic slice systems suggest that serotonin's concentration is critical to define the directionality of its action: excessive bath-applied serotonin decreased interneuron migration. This effect was mediated by 5-HT_6 but not 5-HT_{3A} receptors (Riccio *et al.* 2009). Although its direct impact on CCK^+ interneurons is less well understood, dopamine D1 receptor activation promotes interneuron migration from both the MGE and CGE. In contrast, dopamine D2 receptors (D2Rs) limit the tangential migration of interneurons (Crandall *et al.* 2007). Similarly, disrupted dopamine signalling by either inhibition of tyrosine hydroxylase or stimulation of D2Rs limits the size of the Dlx5a/6aIG-GFP^+ GABAergic interneuron pool in zebrafish (Souza *et al.* 2011).

GABA signalling is thought to be excitatory during embryogenesis and early postnatal development (Ben-Ari, 2002). The conversion to an inhibitory mode of GABA action relies on the coincident and opposite expressional regulation of the neuron-specific K^+–Cl^- co-transporter (KCC2, increase) and the Na^+–K^+–Cl^- co-transporter (NKCC1, decrease), resulting in a significant decrease of the intracellular Cl^- concentrations (Liu *et al.* 2006).

Manipulations that limit the loss of NKCC1 prevent the developmental switch of the Cl^- gradient (Liu *et al.* 2006). Cholinergic neurotransmission through nAChRs is needed for the developmental switch. Accordingly, α7-nAChR$^{-/-}$ mice retain high NKCC1 and low KCC2 levels, precluding inhibitory GABA neurotransmission (Liu *et al.* 2006) associated with morphological irregularities in hippocampal neurons (Liu *et al.* 2007). Since CCK$^+$ basket cells express both α7-nAChRs and $GABA_A$ receptors, it is plausible to assume that nicotine stimulation (e.g. maternal tobacco smoking) could compromise the morphological differentiation – particularly synaptogenesis – of this cell type. Short-range GABA signals, acting on $GABA_A$ receptors, are also required to maintain tangential migration through leading process elongation *in vivo* (Manent *et al.* 2005).

Neurotrophins are indispensable for interneuron development. Brain-derived neurotrophic factor (BDNF) powerfully regulates the morphological and neurochemical differentiation of GABAergic interneurons (Marty *et al.* 1996; Berghuis *et al.* 2004). GABA signalling acts upstream to BDNF by repressing BDNF synthesis (Marty *et al.* 1996) to decrease neurite outgrowth. Yet other signalling cassettes can hijack ('trans-activate') the tropomyosin-related kinase B (TrkB) receptor on interneurons in the absence of its cognate ligand. Endocannabinoids are one such class of signalling molecules using TrkB receptors to regulate CCK$^+$ interneuron migration (Berghuis *et al.* 2005). The idea that endocannabinoid signalling via CB_1Rs is involved in interneuron development is reinforced by several findings: firstly, by the ability of THC to induce redistribution of hippocampal CCK$^+$ interneurons *in utero* (Berghuis *et al.* 2005). Secondly, acute exposure of the growth cones of CB_1R^+/CCK$^+$ interneurons to endocannabinoid microgradients evokes chemorepulsive turning or collapsing responses (Berghuis *et al.* 2007). Thirdly, CB_1R activation inhibits neurite outgrowth, and abolishes BDNF-induced axonal growth (Berghuis *et al.* 2005). Cumulatively, these data suggest an antagonistic interplay between endocannabinoid and neurotrophin signalling cassettes in the refinement of interneuron morphology and synaptic wiring. Interestingly, these effects prevail once the synapse forms with remodelled endocannabinoid and BDNF signalling networks participating in negative and positive retrograde feedback loops to control synaptic efficacy, respectively.

Endocannabinoid control of synaptic plasticity

Theta oscillations in the hippocampus occur during exploration and rapid eye movement sleep and are involved in place finding and learning and memory (O'Keefe & Nadel, 1978; Buzsaki, 2002). During these oscillations, pyramidal cells transmit information. PV$^+$ basket cells synchronize the rhythm of the network, while endocannabinoid-sensitive CCK$^+$ basket cells function as fine-tuning devices (Freund, 2003). In anesthetized rodents, CCK$^+$ interneurons fire on the ascending phase of the theta wave, at the moment when hippocampal place cells become activated (Klausberger *et al.* 2005). In contrast, PV$^+$ basket cells fire on the descending phase (Klausberger *et al.* 2003). As we discussed above, CCK$^+$ basket cells play a critical role in feed-forward inhibition by releasing CCK, resulting in the enhancement of GABA release from PV$^+$ interneurons (Foldy *et al.* 2007). Their inhibition of pyramidal cells ceases upon activation of CB_1Rs on their presynaptic terminals, forming a spatial focus of activity. Coincidentally, they maintain inhibitory control over resting place cells through entrainment of PV$^+$ interneurons (Carlson *et al.* 2002; Chevaleyre & Castillo, 2004; Klausberger *et al.* 2005).

Amongst all hippocampal neurons, CCK$^+$ interneurons express the highest known levels of CB_1Rs (Katona *et al.* 1999). This gives rise to diverse mechanisms of endocannabinoid-mediated short- and long-term synaptic plasticity at their synaptic inputs onto pyramidal neurons, including depolarization-induced suppression of inhibition (DSI) (Pitler & Alger, 1992; Ohno-Shosaku *et al.* 2001; Wilson & Nicoll, 2002), metabotropic suppression of inhibition (MSI) (Varma *et al.* 2001; Kim *et al.* 2002) and long-term depression (iLTD) (Chevaleyre & Castillo, 2003; Chevaleyre *et al.* 2007).

Of these, the inhibitory perisomatic inputs deriving from CCK$^+$ basket cells are the best characterized. The CCK$^+$–CA1 pyramidal synapse was one of the first sites shown to express DSI (Pitler & Alger, 1992; Ohno-Shosaku *et al.* 2001; Wilson & Nicoll, 2002). DSI is a form of synaptic plasticity that is induced postsynaptically, but acts presynaptically *via* a messenger traversing the synaptic cleft in a direction opposite to that of the major neurotransmitter ('retrograde messenger'). Accordingly, 2-AG, the likely retrograde messenger (Gao *et al.* 2010; Tanimura *et al.* 2010), is produced in a Ca^{2+}-dependent manner *via* postsynaptic activation of DAGLα, which cleaves the DAG precursor into 2-AG. The release of lipophilic 2-AG is facilitated, yet non-vesicular, contrasting classical vesicle-dependent neurotransmitter release (Neu *et al.* 2007). Once liberated, 2-AG (and other endocannabinoids) activates presynaptic CB_1Rs, which subsequently reduce neurotransmitter release by inhibiting N-type Ca^{2+} channels (Wilson *et al.* 2001). DSI can last for tens of seconds. However, its duration is chiefly determined by the expression of one or more pre- or post-synaptic 2-AG-degrading enzymes (Kim & Alger, 2004; Hashimotodani *et al.* 2007; Straiker *et al.* 2009), which can act in concert to terminate 2-AG signalling. An example of enzymatic cooperativity is shown in Fig. 3, where the two temporally distinct forms of DSI (referred

to as DSI_{fast} and DSI_{slow}) – observed in cultured neurons – are determined by the complement of MGL and COX-2 available to break down 2-AG (Straiker & Mackie, 2009).

Endocannabinoid signalling is not restricted to CCK^+ basket cell to CA1 pyramidal neuron synapses. For instance, CCK^+ basket cell synapses also target other CCK^+ or PV^+ basket cells (Karson *et al.* 2009). Although studying interneuron–interneuron coupling is challenging, evidence for domain-specific plasticity of outputs has begun to appear (Lee *et al.* 2010*b*), including endocannabinoid plasticity at three inputs/outputs of CCK^+ Schaffer collateral-associated interneurons (Ali & Todorova, 2010).

Whilst dendritic spines of pyramidal cells are the consensus sites for DAGL's subcellular accumulation in the neocortex and hippocampus (Yoshida *et al.* 2006), synaptically connected CCK^+ basket cells can express endocannabinoid-mediated DSI in the apparent absence of DAGLα (Daw *et al.* 2009). This phenomenon could be explained by a complex metabolic configuration of synaptic plasticity through the release of other endocannabinoids, such as anandamide (Ali, 2007; Puente *et al.* 2011), or by other forms of endocannabinoid actions like the direct potentiation of postsynaptic $GABA_A$ receptors by 2-AG (Sigel *et al.* 2011). Given that at least ~40% of cultured hippocampal interneurons express the machinery to sustain endocannabinoid signalling in response to depolarization (Straiker & Mackie, 2009), this suggests that many CA1 interneurons may be more than just targets of endocannabinoid signalling.

Perisomatic endocannabinoid-mediated plasticity by CCK^+ basket cells is well positioned to regulate the output of CA1 pyramidal neurons. Their role may be that of an integrator of assorted weaker inputs to support feedback inhibition at key sites of pyramidal neuron output regulation (Glickfeld & Scanziani, 2006). However, endocannabinoid-mediated synaptic plasticity is itself under modulation: endocannabinoid inhibition can be overridden by a high (>20Hz) firing rate in CCK^+ basket cells (Foldy *et al.* 2006). In addition, indirect evidence suggests that postsynaptic CCK receptors can enhance endocannabinoid release (Foldy *et al.* 2007).

Conclusions: disease implications

This review provides a concise summary of the molecular and network features that make CCK^+ basket cells unique, and indispensable for the proper function of hippocampal neuronal networks. If a specific class of interneurons is required to maintain a form of control over the hippocampal circuitry then its loss should manifest in altered behaviours or neuropsychiatric illness.

Endocannabinoids have also been suggested to play a role in the prevention of epileptic activity, particularly in the neonatal period when they can act as a substitute for inhibitory GABA (note that GABA is excitatory during this period; Ben-Ari, 2002). In the immature hippocampus, CB_1R antagonism leads to epileptic discharges, while receptor stimulation reduces network activity (Bernard *et al.* 2005). However, and in accord with the role of endocannabinoids during axon guidance (Berghuis *et al.* 2007; Mulder *et al.* 2008; Keimpema *et al.* 2010), prenatal ('ectopic') stimulation of CB_1Rs by full agonists results in permanent modifications of the hippocampal circuitry such that decreased glutamatergic excitation persists in the offspring (Mereu *et al.* 2003). Therefore, CB_1R signalling appears unexpectedly fundamental for the proper development *and* function of neuronal networks.

Another compelling example of this lies with the molecular pathogenesis of schizophrenia. BDNF and TrkB expression are decreased in schizophrenic patients

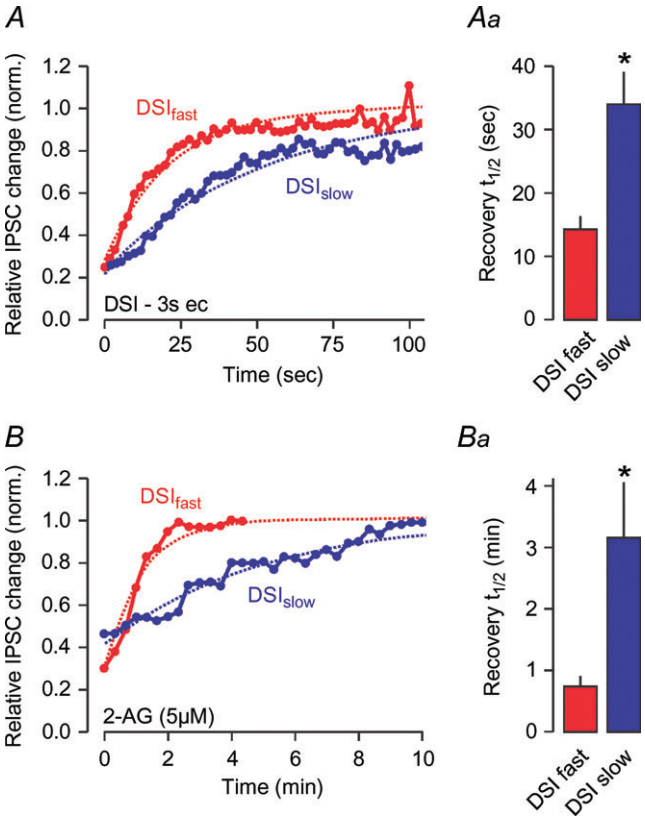

Figure 3. Enzyme-dependent divergent time courses for DSI- and 2-AG-mediated inhibition in DSI_{fast}- and DSI_{slow}-expressing cultured interneurons
A, duration of DSI (3 s depolarization) in DSI_{fast} (red) and DSI_{slow} (blue) neurons, as a result of MGL acting alone (DSI_{slow}) or in combination with COX-2 (DSI_{fast}). *Aa*, bar graph shows $t_{1/2}$ values with 99% confidence intervals. *B*, duration of 2-AG-mediated inhibition in DSI_{fast} *vs.* DSI_{slow} neurons. *Ba*, bar graph shows $t_{1/2}$ values with 99% confidence intervals. ∗99% confidence intervals do not overlap. Reprinted from *Neuroscience* **163**, Straiker & Mackie (2009), Cannabinoid signaling in inhibitory autaptic hippocampal neurons, pp. 190–201, Copyright 2009, with permission from Elsevier.

(Hashimoto *et al.* 2005). In addition, CCK levels are also reduced in schizophrenics (Bachus *et al.* 1997; Fung *et al.* 2010). Since BDNF influences the differentiation of CCK^+ interneurons (Marty *et al.* 1996; Berghuis *et al.* 2005), the decrease in BDNF, together with a decrease in CCK content, argues for the loss of CCK^+ interneurons. This hypothesis is supported by the coincident decrease of CB_1R and CCK mRNAs in schizophrenia (Eggan *et al.* 2008). It is interesting to note that these correlative changes are not a consequence of treating the psychosis but inherent to the disease itself (Bachus *et al.* 1997; Eggan *et al.* 2008). In contrast, higher CCK (Bachus *et al.* 1997) and CB_1R levels (Hungund *et al.* 2004) have been reported in suicide victims, suggesting an increased potential for modulation of GABAergic neurotransmission. These findings suggest that CCK^+ basket cell functions underlie fundamental behavioural and cognitive traits, and that their dysfunction can precipitate devastating neuropsychiatric symptoms.

An emerging consensus is that most, if not all, neuropsychiatric disorders have developmental origins. A developmental component is particularly well characterized in schizophrenia, and centres around the misrouting of interneurons and inappropriate endocannabinoid signalling (Di Cristo, 2007). Further studies focusing on the birth, migration, differentiation and functions of defined subsets of interneurons integrating into the hippocampal circuitry will therefore be essential to drive the development of successful therapeutic interventions.

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