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Chandelier Cells in Functional and Dysfunctional Neural Circuits

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Chandelier cells (ChCs; also called axo-axonic cells) are a specialized GABAergic interneuron subtype that selectively innervates pyramidal neurons at the axon initial segment (AIS), the site of action potential generation. ChC connectivity allows for powerful yet precise modulation of large populations of pyramidal cells, suggesting ChCs have a critical role in brain functions. Dysfunctions in ChC connectivity are associated with brain disorders such as epilepsy and schizophrenia; however, whether this is causative, contributory or compensatory is not known. A likely stumbling block toward mechanistic discoveries and uncovering potential therapeutic targets is the apparent lack of rudimentary understanding of ChCs. For example, whether cortical ChCs are inhibitory or excitatory remains unresolved, and thus whether altered ChC activity results in altered inhibition or excitation is not clear. Recent studies have shed some light onto this excitation-inhibition controversy. In addition, new findings have identified preferential cell-type connectivities established by cortical ChCs, greatly expanding our understanding of the role of ChCs in the cortical microcircuit. Here we aim to bring more attention to ChC connectivity to better understand its role in neural circuits, address whether ChCs are inhibitory or excitatory in light of recent findings and discuss ChC dysfunctions in brain disorders.

Keywords: chandelier cells, axo-axonic cells, interneuron, circuits, schizophrenia, epilepsy

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INTRODUCTION

Discovered in the 1970s, ChCs quickly gained intrigue as a unique and potentially powerful subtype of GABAergic interneurons that selectively innervates pyramidal neurons at the axon initial segment (AIS), directly regulating the site of action potential generation (Szentágothai and Arbib, 1974; Jones, 1975; Somogyi, 1977). In the decades that followed, many studies have uncovered potential roles of ChCs in brain functions (Li et al., 1992; Klausberger et al., 2003; Zhu et al., 2004; Howard et al., 2005; Dugladze et al., 2012; Jiang et al., 2013; Viney et al., 2013), and have led to implications of ChC dysfunctions in brain disorders such as epilepsy and schizophrenia (DeFelipe, 1999; Lewis, 2011; Marín, 2012; Inan and Anderson, 2014). However, many questions remain unanswered. One of the most puzzling questions involves whether these GABAergic interneurons can be excitatory (Szabadics et al., 2006; Woodruff et al., 2010). In addition, how ChCs are incorporated in neuronal circuits is not clear. The diseases that implicate ChC dysfunction also involve other cell types, including other interneuron subtypes (DeFelipe, 1999; Lewis et al., 2012; Del Pino et al., 2013). Recent studies have shed some light onto the excitation-inhibition controversy and ChC connectivity in the cortex, which may facilitate our understanding of ChC functions in neural circuits and ChC connectivity dysfunctions in brain disorders. Here we briefly review ChCs in functional and dysfunctional neural circuits and highlight these new findings.

ChC CONNECTIVITY

ChC connectivity to the AIS of pyramidal neurons has been found in many different brain regions of many different animals, including the human prefrontal cortex (Somogyi, 1977; Fairén and Valverde, 1980; Peters et al., 1982; Somogyi et al., 1982, 1983; Freund et al., 1983; Kosaka, 1983; DeFelipe et al., 1985; Kisvárday et al., 1986; De Carlos et al., 1987; Marin-Padilla, 1987; Lewis and Lund, 1990; Kawaguchi and Kubota, 1998; Inda et al., 2007). The axonal arborization of a ChC forms vertically oriented axon terminal boutons or cartridges, a distinct arrangement resembling candlesticks on a chandelier (Szentágothai and Arbib, 1974; Jones, 1975; Szentágothai, 1975; see **Figure 1**). ChC cartridges align with AISs of pyramidal neurons, allowing a single ChC to innervate the AIS with an average of 3–5 boutons. This innervation average is highly variable. The number of ChC boutons per AIS is not uniform across brain regions, is directly correlated with the size of the pyramidal AIS and may reach as many as 12 (DeFelipe et al., 1985; Fariñas and DeFelipe, 1991; Cruz et al., 2003; Inda et al., 2007; Inan and Anderson, 2014). In addition, this mean value is variable during development, as the number of ChC boutons per AIS is 32% lower in adult compared to 3-month-old monkeys (Fish et al., 2013).

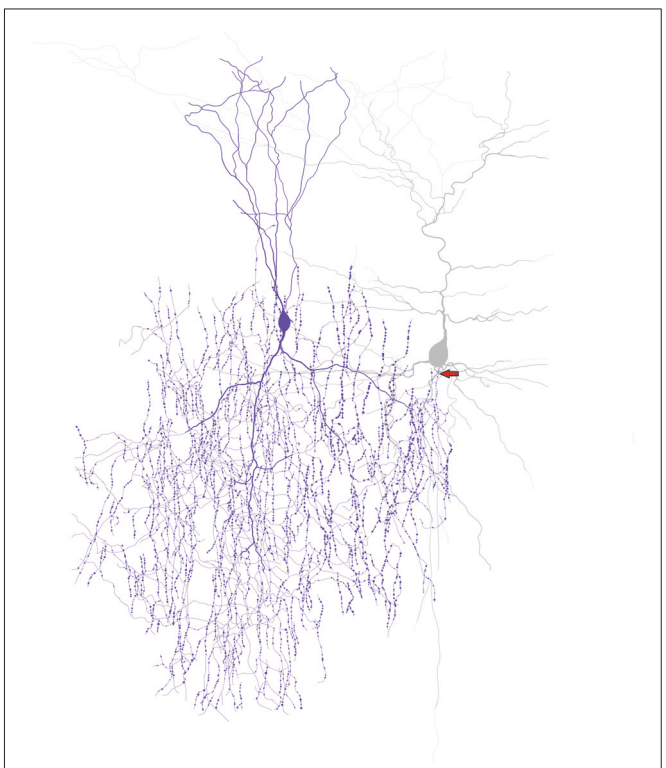

FIGURE 1 | ChCs have unique axonal morphology and innervate pyramidal neurons at the axon initial segment (AIS). Drawing of a ChC (purple) and a connected pyramidal neuron (gray) to illustrate the "chandelier" morphology and the axo-axonic connectivity of ChCs. Arrow indicates the ChC connectivity site at the pyramidal neuron AIS.

A single ChC innervates hundreds of pyramidal neurons (Freund et al., 1983; DeFelipe et al., 1985; Somogyi et al., 1985; Li et al., 1992; Tai et al., 2014). Within the range of its axonal arbor, a ChC contacts 35–50% of pyramidal neurons in the somatosensory cortex through postnatal development (Inan et al., 2013); however, lower innervation values (18–22%) by single ChCs have been reported when examining a wider area of the neocortex in postnatal day 18–23 (P18–23) mice (Blazquez-Llorca et al., 2015). Quantitative analysis showed that this connectivity reaches a peak of 22–35% at 30–60 μm from the ChC soma (Blazquez-Llorca et al., 2015). The selective innervation at the AIS suggests that ChCs tightly regulate the output of pyramidal neurons. Moreover, each pyramidal neuron is innervated by multiple ChCs (Inan et al., 2013). As the number of functional release sites critically regulates the firing probability (Loebel et al., 2009; Bagnall et al., 2011), multiple innervations further contribute to the ability of ChCs to strongly and precisely regulate pyramidal neurons (Buhl et al., 1994).

ChCs innervate pyramidal neurons in cortical layer 2 (L2), L3, L5a and L5b (Jiang et al., 2013; Lee et al., 2015). This innervation of cortical pyramidal neurons shows clustered patterns of both high and very low densities based on the identification of ChC cartridges and their apposition to AISs (Fairén and Valverde, 1980; Somogyi et al., 1982; DeFelipe et al., 1985; Li et al., 1992; Inan et al., 2013; Blazquez-Llorca et al., 2015). This may be due to differences in ChC morphology or distribution as ChCs are not distributed uniformly in certain areas of the cortex (De Carlos et al., 1985). Another possibility is that ChCs may preferentially target certain neuronal groups over others. Although the connectivity between GABAergic interneurons and pyramidal neurons has been hypothesized to be generally non-selective and based primarily on spatial proximity (Sohya et al., 2007; Niell and Stryker, 2008; Liu et al., 2009; Bock et al., 2011; Fino and Yuste, 2011; Packer et al., 2013), this may be greatly overstated (Varga et al., 2010). Indeed, evidence shows that ChCs preferentially contact certain pyramidal neurons over others, such as pyramidal neurons with predominantly intracortical projections in the auditory and visual cortices, and centrifugal cells in the piriform cortex (Sloper and Powell, 1979; Fairén and Valverde, 1980; De Carlos et al., 1985; DeFelipe et al., 1985; Fariñas and DeFelipe, 1991; Wang and Sun, 2012).

Studies examining the inputs to L2/3 ChCs have elucidated some ChC cortical connectivity (see **Figure 2**) and offered some possible functional roles. Using laser scanning photostimulation, L2/3 ChCs in the mouse primary somatosensory cortex were shown to receive excitatory input predominantly from L2/3 and L5a (with relatively weaker excitatory input from L4), and receive inhibitory input primarily from L1 and L2/3 (with relatively weaker input from L5b and L6; Xu and Callaway, 2009). Dendrites from L2/3 ChCs extend branches within the lamina and send a prominent dendrite upward into L1 (Kawaguchi, 1995; Xu and Callaway, 2009; Woodruff et al., 2011; Taniguchi et al., 2013; Markram et al., 2015). These findings led to the hypothesis that the dendrites of L2/3 ChCs, similar to the apical dendrites of pyramidal neurons,

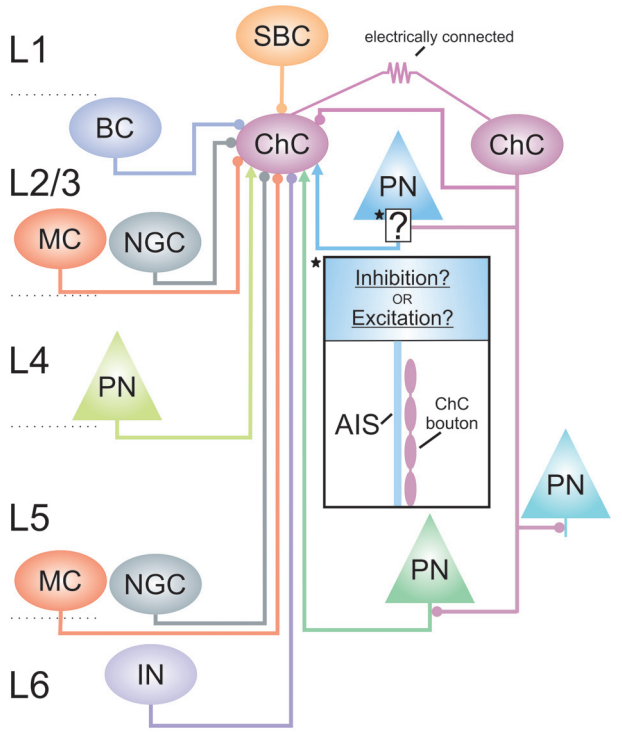

FIGURE 2 | Connectivity of cortical ChCs. Simplified schematic of some of the known connections between L2/3 ChCs and other neurons in the cortex. Arrows at terminals indicate excitation; circles at terminals indicate inhibition. Starred and boxed region and insert highlights the ChC synaptic contact with L2/3 pyramidal neurons in which the GABAergic response is not clear. AIS, axon initial segment; BC, basket cell; ChC, chandelier cell; IN, interneuron of unknown subtype; MC, Martinotti cell; NGC, neurogliaform cell; PN, pyramidal neuron; SBC, single-bouquet cell.

allow ChCs to act as circuit switches by receiving input from other cortical areas via L1. Interestingly, dual recordings from both pyramidal neurons and ChCs in L2/3, revealed that the L1 stimulation strength necessary for activation is significantly less for ChCs compared to pyramidal neurons (Woodruff et al., 2011). Much insight into L2/3 ChC function has come from the examination of inputs with *in vivo* recordings. Using whisker stimulation, Zhu et al. (2004) demonstrated that L2/3 ChCs have large receptive fields with lower acuity than pyramidal neurons and other non-pyramidal neurons. In addition, simultaneous dual recordings *in vivo* showed that L2/3 ChCs respond more robustly to increased cortical excitation than other cortical neurons. These results suggest that L2/3 ChCs have a critical role in balancing excitation and inhibition (Zhu et al., 2004).

Recent studies have greatly advanced our current understanding of ChC cortical connectivity with GABAergic interneurons (see **Figure 2**). The L1 inhibitory input to L2/3 ChCs is now known to come from single-bouquet cells (SBCs; Jiang et al., 2013). Within L2/3, ChCs receive GABAergic inputs from Martinotti cells (MCs), neurogliaform cells (NGCs) and from other ChCs, along with some inputs from basket cells (BCs; Jiang et al., 2015). L2/3 ChCs also receive input from MCs and NGCs from L5 (Jiang et al., 2015). In addition, ChC connectivity through gap junctions has been reported in the hippocampus (Baude et al., 2007), and in the neocortex between ChCs and between ChCs and BCs (Woodruff et al., 2011; Taniguchi et al., 2013). These connectivity patterns may allow for the coordination of ChCs to synchronize the activity of large populations of pyramidal cells (Bennett and Zukin, 2004; Howard et al., 2005).

ChCs are diverse. Along with the diversity in the number of boutons (see above), ChC axons can vary in their complexity and localization in different cortical areas and layers, and depends on the type and age of the animal (Somogyi et al., 1982; DeFelipe et al., 1985; Inda et al., 2007, 2009; Taniguchi et al., 2013). Some genetic markers are thought to be specific for ChCs, such as DOCK7, a molecule essential for ChC cartridge and bouton development (Tai et al., 2014). However, ChCs show some diversity in their biochemical content. For example, studies indicate that only subpopulations of ChCs express certain gene products used as markers for interneuron subtypes, such as parvalbumin (Lewis and Lund, 1990; Del Río and DeFelipe, 1994; Fish et al., 2013; Taniguchi et al., 2013). This diversity in ChCs suggests complex connectivities and possibly distinct functional roles. ChCs originate during the latest stages of cortical neurogenesis and then migrate through defined routes that lead to a specific laminar distribution in the cortex (Inan et al., 2012; Taniguchi et al., 2013). This laminar distribution of ChCs is established prior to their innervation of pyramidal neurons and has led to the hypothesis that ChCs may be composed of different layer-specific subgroups, which establish distinct connectivities and perhaps distinct functional roles in the cortical microcircuit (Taniguchi et al., 2013).

ARE ChCs INHIBITORY OR EXCITATORY?

Whether ChCs are inhibitory or excitatory is not currently agreed upon. ChCs activate $GABA_A$ receptors and a greater understanding of the response mediated by these receptors is needed. Activation of $GABA_A$ receptors in mature neurons is typically associated with inhibition owing to the flow of anions such as Cl^- through the membrane, leaving the membrane potential below threshold (Kaila, 1994). However, $GABA_A$ receptors are capable of mediating excitation if the transmembrane gradient of Cl^- is reversed (Misgeld et al., 1986). GABA-mediated excitation is thought to occur in developing neurons until around P7 due to an intercellular Cl^- regulation that results in the efflux of Cl^-, which raises the membrane potential above threshold (Obata et al., 1978; Mueller et al., 1984; Ben-Ari et al., 1989; Cherubini et al., 1991; Owens et al., 1996; Rivera et al., 1999; Ben-Ari, 2002; Owens and Kriegstein, 2002). Because intracellular Cl^- homeostasis may be altered by experimental procedures, these observations have been questioned (Bregestovski and Bernard, 2012; Dzhala et al., 2012; but see Ben-Ari et al., 2012b). Recently, *in vivo* recordings have demonstrated that GABA generally depolarizes but inhibits postsynaptic neurons

in developing (P3–4) mice (Kirmse et al., 2015). However, concerns about the results of this study have been raised due to experimental procedures that can alter the recorded GABAergic activity (Ben-Ari, 2015). Thus, the effect of GABA observed is highly dependent upon experimental procedures, but currently GABA is generally believed to be excitatory only during development and may be restricted to some cortical plate neurons (Ben-Ari, 2014, 2015). In mature neurons, GABA is mainly inhibitory and is generally believed to be excitatory only under certain circumstances when paired with excitatory input (Gulledge and Stuart, 2003).

ChCs in L2/3, on the other hand, have been shown to be capable of mediating excitatory activity in brain slices from animals well past the developmental period when GABA-mediated excitation is thought to occur (Szabadics et al., 2006). The GABA-mediated excitation by ChCs was attributed largely to differences in the intracellular Cl^- regulation at the postsynaptic AIS (Szabadics et al., 2006; Khirug et al., 2008; Báldi et al., 2010), a cellular subregion known to be molecularly and physiologically unique (Rasband, 2010; Bender and Trussell, 2012; Kole and Stuart, 2012). To avoid changes in intracellular Cl^- concentrations, Szabadics et al. used the gramicidin perforated patch technique (Szabadics et al., 2006). Some subsequent studies in L2/3 using this technique have strengthened their claim (Khirug et al., 2008; Woodruff et al., 2009). However, no direct evidence has been found if this actually occurs *in vivo*. Nevertheless, a possibility for ChC excitation is hypothesized to occur during "down" states, when pyramidal neurons are hyperpolarized and sodium channels are deinactivated (Szabadics et al., 2006; Woodruff et al., 2011).

Because the perforated patch technique may still alter GABAergic activity, concerns with this technique and the results obtained were raised (Glickfeld et al., 2009; Woodruff et al., 2010). Using a novel noninvasive approach that avoids the perturbations with perforated patching, hippocampal ChCs were found to strictly mediate inhibition (Glickfeld et al., 2009; Bazelot et al., 2010; Chiang et al., 2012). Other novel techniques used in the cortex also indicate that ChCs are inhibitory. Using noninvasive methods combined with an innovative technique to activate axo-axonic synapses, Wang et al. (2014) showed that ChCs in the piriform cortex are inhibitory and mediate reversal potentials similar to those mediated by BCs. Noninvasive techniques that replicated *in vivo* conditions indicated that L2/3 ChCs were predominately inhibitory (Woodruff et al., 2011). *In vivo* studies that clearly demonstrate whether ChCs are inhibitory or excitatory are lacking, but some results suggest that ChCs are not excitatory (Klausberger et al., 2003, 2005; Massi et al., 2012; Somogyi et al., 2013; Viney et al., 2013).

ChC-mediated excitation is an enigmatic issue. This is largely due to the complications when recording GABAergic responses. Nevertheless, currently those experiments using the least invasive techniques, along with *in vivo* data, suggest that ChCs are inhibitory, as originally assumed (Somogyi, 1977) and demonstrated above and by others (Buhl et al., 1994; Maccaferri et al., 2000; Tamás and Szabadics, 2004; González-Burgos et al., 2005; Jiang et al., 2013, 2015; Lee et al., 2015).

ChC DYSFUNCTIONS IN BRAIN DISORDERS

ChC dysfunctions are well associated with schizophrenia (Lewis et al., 2005; Lewis, 2011; Marín, 2012). Evidence indicates the GABA membrane transporter 1 (GAT1) is decreased in axon terminals of ChCs (Woo et al., 1998), whereas the $GABA_A$ receptor α2 subunit is increased in pyramidal neurons in schizophrenia (Volk et al., 2002). These pre- and postsynaptic alterations are significantly prominent in L2/3 (Pierri et al., 1999; Volk et al., 2001; Lewis, 2011). The postsynaptic alterations were originally assumed to be compensatory (Volk et al., 2002). If ChCs are excitatory in L2/3, decreased GAT1 may be a compensatory response for decreased excitatory inputs to pyramidal neurons in schizophrenia (Lewis et al., 2012). However, if L2/3 ChCs are inhibitory, then the alterations may be causative or contributory. Future studies will need to examine the effect of these alterations on ChC-mediated GABAergic activity in L2/3.

Schizophrenia is associated with significant changes in neural activity. These changes are shown with both structural and functional alterations and result in abnormal neural network oscillations and synchrony (Meyer-Lindenberg et al., 2001; Uhlhaas and Singer, 2010; Yu et al., 2012). Disruptions in gamma oscillations, which are associated with some of the cognitive dysfunctions in schizophrenia, may result from dysfunctions specifically in ChCs and BCs (Lewis et al., 2012). Schizophrenia patients exhibit many disturbances in cognition, including impairments in attention and sensory processing (Elvevåg and Goldberg, 2000; Javitt, 2009). L2/3 ChCs are part of a cortical interneuronal circuit that is thought to be involved in the selection of attentional and salient signals (Jiang et al., 2013). Dysfunctions of L2/3 ChCs in schizophrenia would then lead to dysfunctions in this circuit, and therefore cause disruptions in attention. The mechanisms underlying schizophrenia are thought to result in part from abnormalities in the development of GABAergic interneuronal circuits (Le Magueresse and Monyer, 2013; Schmidt and Mirnics, 2015). Recent advances in the understanding of ChC development may also lead to hypotheses for how ChC circuitry is altered in schizophrenia. Because the migration of ChCs to L2/3 occurs by P7 when GABA is thought to be excitatory (Anderson and Coulter, 2013; Taniguchi et al., 2013), ChC excitation could have a role in brain maturation and brain disorders (Ben-Ari et al., 2012a).

ChC dysfunction is also implicated in epilepsy (DeFelipe, 1999; Dinocourt et al., 2003). Evidence indicates that ChCs may prevent runaway excitation. ChC axon terminals are lost at the epileptic focus (Ribak, 1985). In addition, *in vivo* recordings show that ChCs fire more robustly than other types of cortical neurons when overall cortical excitation increases (Zhu et al., 2004). Therefore, ChCs may be specifically recruited by epileptic activity to decrease excessive excitation (Paz and Huguenard, 2015). This has led to the hypothesis that ChCs play a critical role

in regulating the balance between excitation and inhibition (Zhu et al., 2004). Dysregulation of the excitation-inhibition balance is thought to underlie epilepsy, along with other brain disorders including schizophrenia (Fritschy, 2008; Yizhar et al., 2011; Lewis et al., 2012). Future studies will need to determine the role of ChC dysfunctions in altering the excitation-inhibition balance and whether ChC dysfunctions underlie other brain disorders that implicate disruptions of the excitation-inhibition balance, such as autism (Rubenstein and Merzenich, 2003). Nevertheless, these results suggest that ChCs are at least predominately inhibitory.

FUTURE DIRECTIONS

A significant impediment that prevents elucidating the link between ChC dysfunctions and brain disorders is the uncertainties in the role of ChCs in the cortical microcircuit, including whether ChCs are inhibitory or excitatory. Ideally, the ability to specifically target ChCs with the identification of specific markers will greatly aid in resolving the role of ChCs in brain functions. One such undertaking is the creation of the Nkx2.1CreERT2 mouse line that can label a portion of interneurons, the majority of which are ChCs (Taniguchi et al., 2013). With the ability to track ChCs from their genesis to postnatal development and incorporation into cortical circuits, understanding the link between dysfunctions in ChC connectivity and brain disorders may be facilitated (Anderson and Coulter, 2013; Taniguchi et al., 2013). Because of the diversity of ChCs and the possibility of subgroups of ChCs with distinct connectivity patterns and functional roles, innovating techniques will be needed in uncovering ChC circuitry. One such technique is the use of simultaneous multiple patch-clamp recording (Wang et al., 2015; Wyskiel et al., 2016), which can not only greatly elucidate ChC connectivity, but can answer some of the lingering questions about its postsynaptic effects. Further advances in our understanding of ChCs will hopefully provide answers in the near future.

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