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The alpha2 nicotinic acetylcholine receptor, a subunit with unique and selective expression in inhibitory interneurons associated with principal cells☆

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ABSTRACT

Nicotinic acetylcholine receptors (nAChRs) play crucial roles in various human disorders, with the α7, α4, α6, and α3-containing nAChR subtypes extensively studied in relation to conditions such as Alzheimer's disease, Parkinson's disease, nicotine dependence, mood disorders, and stress disorders. In contrast, the α2-nAChR subunit has received less attention due to its more restricted expression and the scarcity of specific agonists and antagonists for studying its function. Nevertheless, recent research has shed light on the unique expression pattern of the *Chrna2* gene, which encodes the α2-nAChR subunit, and its involvement in distinct populations of inhibitory interneurons. This review highlights the structure, pharmacology, localization, function, and disease associations of α2-containing nAChRs and points to the unique expression pattern of the *Chrna2* gene and its role in different inhibitory interneuron populations. These populations, including the oriens lacunosum moleculare (OLM) cells in the hippocampus, Martinotti cells in the neocortex, and Renshaw cells in the spinal cord, share common features and contribute to recurrent inhibitory microcircuits. Thus, the α2-nAChR subunit's unique expression pattern in specific interneuron populations and its role in recurrent inhibitory microcircuits highlight its importance in various physiological processes. Further research is necessary to uncover the comprehensive functionality of α2-containing nAChRs, delineate their specific contributions to neuronal circuits, and investigate their potential as therapeutic targets for related disorders.

1. Introduction

Nicotinic acetylcholine receptors (nAChRs) are composed of different subunit combinations, leading to the formation of multiple receptor subtypes. The α7, α4, α6, and α3-containing nAChR subtypes have been extensively studied and found to be physiologically relevant

Abbreviations: 5HTR3A, Serotonin receptor 3A; ChAT, Choline acetyltransferase; Calb1, Calbindin 1; Calb2, Calbindin 2, also known as calretinin; Chrna2/α2-nAChR, Cholinergic nicotinic receptor alpha 2 subunit; Cre, Cyclic recombinase; *Dmrt3*, Doublesex and mab-3 related transcription factor 3; Elfn1, Extracellular leucine-rich repeat fibronectin containing protein 1; FDDI, Frequency-dependent disynaptic inhibition; I_h, Hyperpolarization-activated current/H-current; IPSC, Inhibitory postsynaptic current; IS3, Interneuron-specific type 3; I_{SK}, small conductance calcium-activated potassium current; LTP, Long-term potentiation; MCα2, *Chrna2*+ Martinotti cells; nAChR, Nicotinic acetylcholine receptor; OLM cells, Oriens lacunosum moleculare cells; OLMα2, *Chrna2*+ OLM cells; PV, Parvalbumin; RCα2, *Chrna2*+ Renshaw cells; Sst, Somatostatin; Trpv1, Transient receptor potential cation channel, subfamily V, member 1; VAChT, Vesicular acetylcholine transporter, Slc18a3; VIAAT, Vesicular inhibitory amino acid transporter, Slc32a1; VIP, Vasoactive intestinal peptide.

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in human disorders such as Alzheimer's disease, Parkinson's disease, nicotine dependence, mood, and stress disorders [1]. In contrast, less is known about the α2-nAChR subunit, presumably because of a more restricted expression of α2-nAChR subunits and the shortage of specific agonists/antagonists [2–4].

The gene for the α2-nAChR subunit, *Chrna2*, has quite a unique expression pattern and is found in several discrete populations of inhibitory interneurons. Such neurons, and their influence on principal cell activity, are at the heart of central nervous system function. We exemplify such functions stemming from three inhibitory interneuron populations that selectively express the *Chrna2* subunit. These interneurons, which are involved in motor control, cognitive and emotional memory formation, share several molecular and physiological features. They provide dendritic inhibition to principal cells from which they receive direct monosynaptic excitatory input creating a recurrent inhibitory microcircuit. We summarize current knowledge and hypotheses regarding the α2-nAChR subunit, as well as the role of *Chrna2* expressing cells in neuronal microcircuits.

1.1. Structure

Neuronal nAChR subunits share a similar structure, consisting of a large extracellular N-terminal domain (ligand binding), three hydrophobic transmembrane regions (M1–M3), the variable intracellular loop, a fourth transmembrane region (M4), and a short extracellular C-terminus. The cysteine-loop, shared by the gene superfamily, is formed by a disulfide bond in the large N-terminal domain. The M2 transmembrane segment forms the ionic pore, with some contribution from M1. Intracellular domains vary among subunits, affecting modifications and interactions, including linking to cytoskeletal elements controlling cellular trafficking, surface distribution, and clustering [5]. X-ray crystallography and other techniques have provided insights into the structure of the α2-nAChR subunit. One study presents the X-ray crystal structure of the human neuronal α2-nAChR subunit in complex with the non-selective agonist epibatidine, demonstrating the pentameric assembly and intersubunit interactions in the ligand binding pocket [6]. Structure-guided mutagenesis and electrophysiological data confirmed the functional importance of certain residues, for example the highly conserved tryptophan in position 84 in one of the ligand-binding pocket loops affecting ligand binding affinity and desensitization kinetics. Such studies provide valuable information for modeling nAChRs and developing subtype-specific drugs against nAChR-related diseases [6].

1.2. Pharmacology

Studies investigating the pharmacology of the α2-nAChR subunit and α2-containing nAChRs are scarce. An early study using the *Xenopus* oocyte system to express ligand-gated ion channels investigated the sensitivity of different combinations of rat α and β subunits of nAChRs to various agonists. The α2β2 combination was more sensitive to nicotine, less sensitive to cytisine and equally sensitive to dimethylphenylpiperazinium when compared to acetylcholine. The α2β4 combination was more sensitive to cytisine than to acetylcholine and less sensitive to dimethylphenylpiperazinium compared to acetylcholine, demonstrating that α2β2 and α2β4 nAChRs have widely-divergent pharmacological properties [7]. In another *Xenopus* oocyte study [8], where recombinant human nAChR subunits were expressed, cytisine was the least effective agonist for β2-containing nAChRs, but showed significant activity for other nAChR subtypes, including those containing α2. Acetylcholine was highly efficacious for most nAChR combinations, except for α3β2 where dimethylphenylpiperazinium was more effective [8]. These findings further emphasize that both α and β subunits play a role in the pharmacology of these channels.

In an effort to identify positive allosteric modulators of α4β2 nAChR, NS9283 was discovered, and found to also interact with α2-containing nAChRs [9]. Interestingly, NS9283 improved performance in behavioral tests for episodic memory (social recognition test), sustained attention (five-choice serial reaction time task), and reference memory (Morris water maze) in rats [9]. Previous studies have suggested that α2-nAChR subunit expression in the rodent brain is sparse [2,10]; therefore, the assumption has been that the observed in vivo pharmacological effects of NS9283 were mainly attributed to allosteric modulation of α4β2 nAChRs in rodents. However, studies now show that *Chrna2*+ interneurons, albeit a smaller part of the total number of neurons, are directly involved in cognitive processing and may therefore well be responsible for at least part of the observed in vivo effects [11,12].

1.3. Localization

The α2-nAChR subunit is primarily found in neuronal cells, particularly in the central nervous system. Precise and specific cellular studies on the α2-nAChR subunit are lacking; however, it is presumably located on the postsynaptic cell membrane together with other nAChR subunits. One study investigated the presence and composition of α2-containing nAChRs in the mouse interpeduncular nucleus and olfactory bulbs [10]. The researchers found a modest, but measurable, dependence on the α2-nAChR subunit for high-affinity binding of [125I]epibatidine, indicating the presence of α2-nAChR subunits in these regions. The predominant subtype of α2-nAChRs in the interpeduncular nucleus was α2β2, although some receptors may contain β4-subunits. In the olfactory bulb, α2-nAChR subunits primarily formed α2β4 [10]. Another study compared wild-type mice with mice lacking specific subunits (α2, α4, α6, α7, β2, β4, α5, and β3) using radioligand binding to identify potential nAChR binding sites [13]. Through comparison, the study could semi-quantitatively evaluate each binding site. For example, deletion of the α7-subunit specifically eliminated [125I]α-bungarotoxin binding, deletion of the β2-subunit eliminated the binding of 5[125I]-3-((2S)-azetidinylmethoxy)pyridine (A-85380), and binding of [125I]α-conotoxinMII was mostly eliminated by deletion of either the α6- or β2-subunit. Notably, little or no effect on binding was found when examining mice lacking the α2-nAChR subunit, investigating several brain areas including the cortex, striatum, olfactory, colliculi, and brainstem nuclei. Thus, other subunits are more prevalent to the degree that it is difficult to ascertain the effects of acetylcholine mediated by receptors containing the α2-nAChR subunit. As will be described below, the α2-nAChR subunit is expressed by relatively few interneurons, explaining the lower signals in studies using radioligand techniques.

1.4. Function

The α2-nAChR subunit plays important physiological roles, and has a higher abundance and wider distribution in the primate brain compared to rodents [10,14,15]. Female mice lacking α2-nAChR subunits showed increased cued fear conditioning with nicotine, while male mice did not exhibit significant changes in fear conditioning [16]. In another study by the same group, mice with a hypersensitive α2-nAChR subunit showed impaired contextual fear conditioning, and this effect was rescued by pretreatment with nicotine [17]. Moreover, nicotine withdrawal studies, induced by nAChR blockade with mecamylamine after two weeks of nicotine treatment, revealed that α2-containing nAChR is involved in regulating neuronal activity [18]. During withdrawal, there was increased neuronal activity in the interpeduncular nucleus and dorsal hippocampus, which was absent in mice lacking the α2-nAChR subunit. Conversely, α2-null mutant mice showed suppressed neuronal activity in the dentate gyrus. Interestingly, α2-null mice exhibited heightened neuronal activity in the stratum lacunosum moleculare layer of the hippocampus, regardless of nicotine withdrawal. Moreover, in α2-null mutant mice, the effects of maternal nicotine exposure on learning and memory in adolescent mice are eliminated [19].

A specific missense mutation (rs2472553, Thr22Ile) in the α2-nAChR signal peptide sequence has been associated with nicotine dependence [20]. The threonine to isoleucine substitution affects the receptor's

response to acetylcholine and nicotine, favoring low sensitivity receptor isoforms and potentially contributing to increased susceptibility to nicotine dependence. A genome wide association study of cannabis use disorder, which has a strong genetic component, identified a genetic variant on chromosome 8 associating risk of disease with *CHRNA2* expression [21]. The genetic link is further supported by a study of functional relationships between regulatory and transcribed elements in human corticogenesis, which found physical interaction between the genome-wide significant risk locus on chromosome 8 with the regulatory region of *CHRNA2* [22]. In analyses of the genetically regulated gene expression, reduced expression of *CHRNA2* was found in brain tissue from individuals with cannabis use disorder [21]. The functional connection between cannabis use and α2-containing nAChRs is unknown. However, the study discuss three hypotheses regarding the involvement of *CHRNA2* in cannabis use disorder: (1) cannabis substances may directly interact with α2-containing nAChRs; (2) cannabis could indirectly impact these receptors by affecting neurotransmitter release, particularly dopamine, which is associated with addiction; and (3) there could be a biological link between *CHRNA2* expression and the cannabinoid receptor 1 gene (*CNR1*), a central part of the endocannabinoid system, where the identified risk locus associated with *CHRNA2* expression would be related to increased expression of the cannabinoid receptor 1. Interestingly, a subset of inhibitory interneurons that directly connect and inhibit the *Chrna2*-expressing type of interneurons has been found to express high levels of the cannabinoid receptor 1 [23]. Together, these findings highlight the distinct roles of the α2-nAChR subunit in various physiological processes, including nicotine-related behaviors and neuronal activity regulation and emphasize the need to characterize the underlying neuronal circuits.

1.5. Disease association

A susceptibility locus for schizophrenia on chromosome 8p21–22 has been strongly implicated in affected families. Three candidate genes, prepronociceptin (*PNOC*), *CHRNA2*, and N-acetyltransferase 1 (*NAT1)*, located in this region, were identified as potential contributors to schizophrenia. However, a case-control study using specific markers near these genes did not find any significant differences in allele frequencies between patients and controls, suggesting that DNA variations or mutations in these genes are unlikely to increase susceptibility to schizophrenia [24].

Mutations in the *CHRNA2* gene (as well as in the α4 and β2 subunit genes) have been linked to familial sleep-related epilepsy [15,25,26], as well as to benign familial infantile seizures [27]. Mutations in the *CHRNA2* gene were initially reported to result in increased sensitivity to acetylcholine [15]. In contrast, other studies identified other mutations in the *CHRNA2* gene linked to familial sleep-related epilepsies, where the mutation caused a reduction in their response to nicotine [28,29]. Animal models, however, indicate that expression of mutant nAChRs may cause hyperexcitability by affecting gamma-aminobutyric acid-(-GABA)ergic populations and synaptic architecture in the neocortex and thalamus [26].

Whether a loss- or gain-of-function mechanism is at play is not established, and both options are possible since heteromeric nAChRs can regulate excitatory and inhibitory transmission, and the maintenance of a delicate balance between excitation and inhibition is required for normal neuronal activity. Overactive nAChR in GABAergic cells can lead to hypoexcitability through excessive GABA release in a disinhibitory circuit. A loss-of-function nAChR in the same cells may cause hyperexcitability by reducing feedback inhibition to pyramidal cells. As we shall see below, *Chrna2* expressing interneurons in the cortex are special in that they are intimately connected to principal excitatory cells providing recurrent inhibitory feedback. To carefully characterize *Chrna2* cells and their circuit partners is therefore necessary to fully understand the effects of pharmacological manipulations.

2. Location of α2-nAChR containing cells

In an in-situ study by Ishii et al. [3] as well as in results from the Allen brain expression atlas [30], *Chrna2* mRNA expressing cells are found in discrete populations consisting of a limited number of cells in most major areas of the brain. For example, in the neocortex, *Chrna2* cells are found exclusively in layer 5 in most, if not all, neocortical areas. In the hippocampus, *Chrna2* cells are only found in the stratum oriens. Specific genetic markers are invaluable to establish the role of specific neurons in circuit functionality and *Chrna2* seems to have a quite specific and limited expression to make it a useful marker for understanding circuits and the receptor itself. How specific is its expression in the brain and spinal cord?

2.1. α2-nAChR expressing neurons in the cortex and spinal cord

Single-cell sequencing has emerged as a powerful tool to resolve heterogeneities that exist within cell populations, which can exhibit diverse genetic profiles and functional characteristics. Indeed, a large-scale analysis of the molecular architecture of the mammalian neocortex and hippocampal formation found that most GABAergic neuron types are shared among them and for the most part correlate strongly with the spatial arrangement (both location and layer) of the cell types [31]. In two more specific studies on the hippocampus and cortex, it was found that the often-studied somatostatin (*Sst*) expressing population can be divided into discrete subtypes that selectively contribute to cell-type specific circuits within the cortex and hippocampus [32,33]. In particular, *Chrna*2 stood out as a specific marker for one of the subpopulations in the neocortex and one in the hippocampus. Further, *Chrna2*-cyclic recombinase (Cre) mice was the only driver line used in these studies that were based on the expression of only one gene, *Chrna2*, emphasizing its exclusive and specific pattern of expression.

The production and characterization of *Chrna*2-Cre mice revealed that hippocampal oriens lacunosum moleculare (OLM, Fig. 1A) interneurons and layer 5 Martinotti cells (Fig. 1B) in the neocortex express this gene [34,35]. Additionally, in the spinal cord, Renshaw cells (Fig. 1C), an inhibitory interneuron population discovered 1946 and named 1952 [36,37], selectively express *Chrna2* [38]. These three inhibitory interneuronal populations share additional features, suggestive of a common mechanism for control of principal cell activity that will be discussed later in this review.

2.2. α2-nAChR expressing neurons in other brain areas

Chrna2+ cells are also present in several subcortical structures. For instance, a study that included the developmental expression of *Chrna2* in the amygdala found expression in the anterior and posteriodorsal regions of the medial amygdala nuclei, deriving from the medial subpallium [41]. These areas are associated with reproductive behavior and send inhibitory signals to the medial hypothalamus. *Chrna2* is also expressed in a group of neurons found in the bed nucleus of the stria terminalis. This region is associated with motivated behavior and emotions and it is part of the bed nucleus-amygdala continuum. Preliminary data suggest that these cells are GABAergic projection neurons with firing features similar to OLM cells [Kullander, unpublished data]. Perhaps the region containing the highest density of *Chrna2* cells is the interpeduncular nucleus [2], a region in the brain involved in addiction, anxiety, and mood regulation [42]. There are also clusters of cells in several other areas including the olfactory bulb, septum, substantia innominata, tegmental nuclei, raphe nuclei, spinal trigeminal nucleus, parafascicular nucleus, nucleus of the vertical limb of the diagonal band, and nucleus accumbens, which are largely unstudied [3]. This list is not exhaustive, and more careful analysis will increase the number of locations where *Chrna2* expressing cells are found and characterized. For example, *Chrna2* cells have recently been found in the retina, expressed in a particular subtype of GABAergic amacrine cells [43]. Also, in the

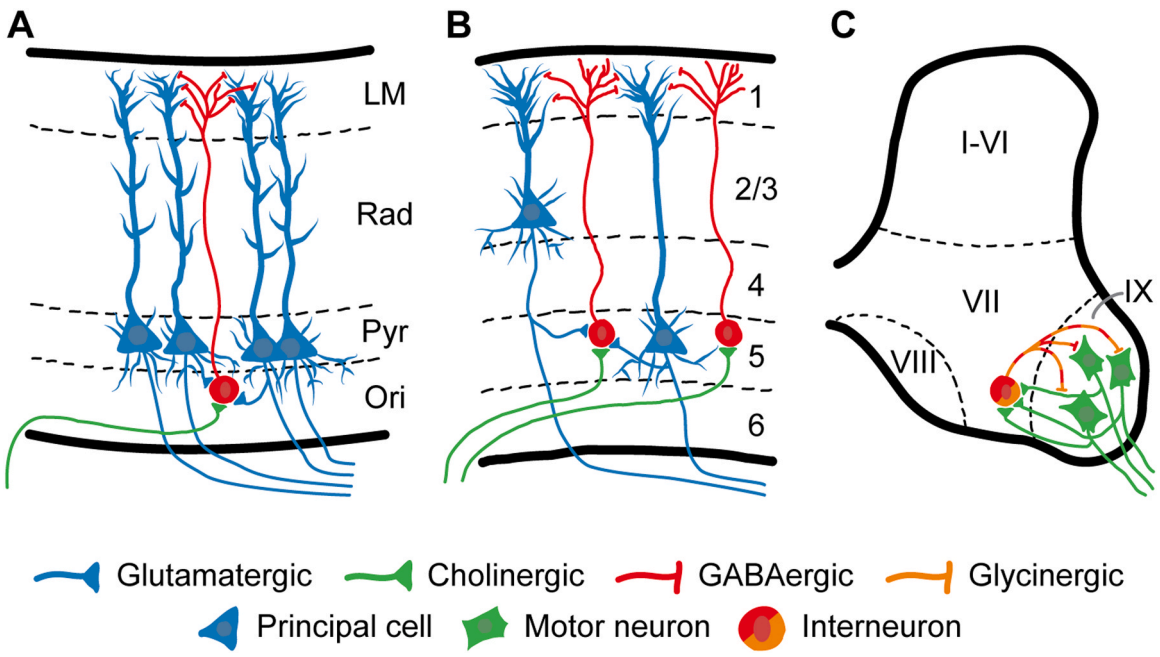

Fig. 1. Anatomical schematic of the *Chrna2* cell types. Illustration of three cell types expressing *Chrna2* (red, orange), their anatomical location and relationship to their corresponding principal cell (blue, green). A) The OLM cell positioned in the hippocampus oriens layer (Ori) connects to pyramidal cells in the pyramidal layer (Pyr) on their apical dendrites in the lacunosum moleculare layer (LM) and receives feedback from pyramidal cells (Rad, stratum radiatum), B) the Martinotti cell positioned in layer 5 of the neocortex connects to pyramidal cells in layer 3 and 5 on their apical dendrites in layer 1 and receives feedback from pyramidal cells, and C) the Renshaw cell in the ventral most part of the spinal cord (lamina VII) connects to motor neurons (lamina IX) and receives feedback from motor neurons [39,40].

main olfactory bulb, *Chrna2* is selectively expressed in deep short-axon cell interneurons with superficial axonal projections to the sensory input layer, where these cells integrate centrifugal cholinergic input with broadly tuned feedforward sensory input to modulate principal cell activity [44]. In the subiculum, *Chrna2* cells display more extensive projections, but similar electrophysiological properties as the below described OLM cells, including inhibitory responses in pyramidal cells mediated by GABA-A and GABA-B receptors [45].

The characterizations made so far of *Chrna2* expressing cells show that such cells are inhibitory and closely associated with principal cells and their activity. However, this is not always the case. For example, cells of the anteroventral cochlear nucleus project to the dorsal cochlear nucleus to control the firing of sound responsive cells [46]. Interestingly, these spherical bushy cells of the anteroventral cochlear nucleus express *Chrna2* and are glutamatergic. Spherical bushy cells are remarkably different from Martinotti, OLM or Renshaw cells. These neurons fire single (or a few) action potentials in response to prolonged stimulation due to a strong low threshold K^+ current mediated by voltage-dependent potassium channels [47]. Little is known about the role of cholinergic innervation through nAChRs on anteroventral cochlear nucleus function, although it has been shown that bushy cells receive both muscarinic and nicotinic synapses from top-down sources [48]. Furthermore, dispersed and heterogenous *Chrna2* cells have been found and characterized in striatal microcircuits [49]. The study identified three distinct subtypes of *Chrna2* cells based on their intrinsic properties, morphology, synaptic connectivity, as well as sensitivity to nicotine. Their role was suggested to provide a broad and diverse modulation of striatal dynamics, but the characterization also showed that striatal *Chrna2* interneurons differ from *Chrna2* populations in other brain regions. In the same study [49], *Chrna2* cells were observed in the globus pallidus externa, and in this case, the intrinsic cellular properties were very similar to that of hippocampal *Chrna2* interneurons. In the next part of this review, we will have a closer look at the three best characterized microcircuits containing *Chrna2*-cells, in the neocortex, hippocampus and spinal cord.

3. α2-nAChR containing cells in the hippocampus – OLM cells

OLM cells were first described by Santiago Ramon y Cajal in 1893 as large somata neurons located in the hippocampal stratum oriens and sending prominent axonal projections to stratum lacunosum moleculare, thus the name OLM.

3.1. Molecular characteristics

Sst expression is commonly referred to as a defining molecular signature of OLM cells [50–52]. Although the *Sst*-Cre mouse line has been used in several studies addressing OLM cells [53,54], OLM cells comprise only around 40% of *Sst*+ interneurons [55,56]. Moreover, emerging evidence suggests that OLM cells in the CA1 region of the hippocampus form a heterogeneous cell population (Table 1), indicating the existence of at least two different OLM subpopulations [11,57–60]. OLM cells that express the calcium-binding albumin protein parvalbumin (PV) [61–63], are thought to comprise one subpopulation of OLM cells [58]. PV+ OLM cells fire phase-locked to an in vitro kainate-induced gamma activity, whereas PV- OLM cells do not [58]. Another study reported that intersectional expression of reelin and *Sst* is restricted to OLM cells and also comprise at least two types: both of them express metabotropic glutamate receptor 1 and *Sst*, but just one expresses PV [64]. Further, a subpopulation of OLM cells expresses serotonin receptor 3 A (5HTR3A), indicating a developmental origin from the caudal ganglionic eminence, whereas another group of OLM cells expresses the transcription factor NK2 homeobox 1 (*Nkx2-1*), suggesting an origin from the medial ganglionic eminence [57]. These two groups of OLM cells are also differentially involved in network oscillations; 5HTR3A+ cells do not fire phase locked to the kainate-induced gamma oscillations in vitro, in contrast to the NK2 homeobox 1+ OLM cells [57]. In addition, a recent study [32] reported that an intersection of NK2 homeobox 1 and neuron-derived neurotrophic factor (*Ndnf*) identified a population of OLM cells that predominantly targeted CA1 pyramidal neurons. *Chrna2* expression is specific to OLM interneurons in the CA1 hippocampal region (OLMα2 cells). Interestingly, OLMα2 cells

Table 1
Molecular characteristics and proposed subdivisions of OLM cells.

Reference	Expression pattern	Functionality
[50–56]	*Sst*+	Defining molecular signature, however only ≈ 40% of *Sst*+ cells have OLM morphology
[58, 61–63]	PV+	Phase-locked to in vitro kainate-induced gamma activity
	PV-	Not phase-locked to in vitro kainate-induced gamma activity
[64]	Reelin+ /metabotropic glutamate receptor 1+ /PV+	Not investigated
	Reelin+ /metabotropic glutamate receptor 1 + /PV-	Not investigated
[57]	5HTR3A+	Origin from the caudal ganglionic eminence Not phase-locked to in vitro kainate-induced gamma activity
	NK2 homeobox 1 +	Origin from the medial ganglionic eminence Phase-locked to in vitro kainate-induced gamma activity
[32]	NK2 homeobox 1 + /Neuron derived neurotrophic factor+	Targeting CA1 pyramidal neurons
[34,65]	*Chrna2*+ /PV-	Hippocampal input gating
[23]	*Chrna2*+ /5HTR3A-	Not investigated
[66]	Neuropeptide Y+	Not investigated
[67]	*Elfn*+	Presynaptic release probability
[68]	*Trpv1*+	Schaffer collateral LTP

rarely express PV [34,65], nor do they fire phase-locked to in vitro induced gamma activity [Kullander, unpublished data]. Thus, the network involvement suggests that OLMα2 cells belong to the PV-, 5HTR3A+ OLM population. However, a recent study investigating single cell transcriptomics [23] does not report overlap between *Chrna2* and 5HTR3A. One recent study [66] has conducted single cell RNA sequencing characterization of anatomically identified OLM cells, using two different transgenic lines, *Sst*-Cre and 5HTR3A-Cre. Interestingly, this study reports consistent expression of neuropeptide Y in OLM interneurons, which was previously not linked with the identity of this cell type. Furthermore, Winterer et al. [66] claims uniform expression of developmental origin-related genes, contradicting the view that OLM cells may originate from multiple neurogenic zones [57]. One source of discrepancy of the results reported by these two studies could be the anatomical location of the neurons investigated. Winterer et al. [66] reported the usage of the medial hippocampal transverse slices, while Chittajallu et al. [57] used horizontal slices from the entire hippocampus. This implies that the aforementioned study [66] did not have access to the ventral hippocampal OLM cells, which may explain their results indicating uniform expression of the developmental origin-related genes. Future studies should investigate whether this is indeed the case.

An additional study [67] has reported that the extracellular leucine-rich repeat fibronectin containing protein 1 (*Elfn1*) is selectively expressed in OLM cells, but see the Allen Brain Atlas [30]. Another recent study [68] reported that the transient receptor potential cation channel, subfamily V, member 1 (*Trpv1*) is also expressed in CA1 OLM interneurons, in which *Trpv1* promotes excitatory innervation. Whether *Trpv1*+ and *Chrna2*+ OLM neurons are overlapping cell populations still remains to be investigated. Anatomical inspection of *Chrna2*+ cells revealed that *Chrna2* displays a gradient-like expression along the dorsoventral axis, comprising the vast majority of OLM cells in the intermediate/ventral hippocampus [11,12,59,65].

3.2. Electrophysiological characteristics

The functional differentiation along the dorsoventral hippocampal axis is relatively new to the field of neuroscience [69], thus, the vast majority of current studies have investigated OLM cells in the dorsal hippocampus. Similar to dorsal OLM cells (Fig. 2B), the action potentials of ventral OLMα2 cells display spike frequency adaptation [34,70,71], but do not display the prominent voltage "sag" of the dorsal OLM cells [65]. These dorsal OLM cells' characteristics indicate a strong contribution of the hyperpolarization-activated current (H-current or I_h) [72,73]. It is presumed that expression of the underlying cyclic nucleotide-gated channel can result in spontaneous firing [72], and equips dorsal OLM cells with an intrinsic resonance frequency at theta [74]. The differences in I_h properties between the dorsal OLM and the more ventrally located OLMα2 cells are in line with several studies reporting electrophysiological differences in pyramidal cells along the dorsoventral hippocampal axis [75–77]. These differences include a larger I_h and higher excitability in the ventral compared to dorsal pyramidal cells. A recent modeling study reported that, depending on the somatic versus dendritic distribution of H-channels on OLM cells, OLM cells fire in low or high theta range, respectively [60]. Putative OLM cells, targeting the distal dendrite, has been suggested to be of a "late--persistent" type compared with other cell types targeting the soma (e.g. basket cells). Such putative OLM cells had an increased probability of spike generation upon repeated stimuli, which allowed for an activation in proportion to the rate of action potentials for subsequent recurrent inhibition of the distal apical dendrite [78,79]. Optogenetic activation of OLMα2 cells induces cholinergic-dependent activity in the lower theta range, so called type 2 theta [11].

3.3. Connectivity

OLM cells are excited by local pyramidal cells and in turn inhibit the distal apical dendrites of pyramidal cells, providing a classic example of feedback inhibition (Fig. 2A). A large proportion (74%) of all OLM cell synapses are made on pyramidal cells, 17% of OLM synapses were unidentifiable, leaving 9% of synapses found on other GABAergic cells [61]. OLMα2 cells inhibit GABAergic stratum radiatum interneurons, allowing disinhibition of the proximal pyramidal cell dendrite [34]. OLM cells also receive inhibitory inputs; a subpopulation of vasoactive intestinal peptide (VIP) and calbindin 2 (*Calb2*, also known as calretinin) positive neurons, referred to as interneuron-specific type 3 (IS3) cells preferentially innervate OLM cells through dendritic synapses [80]. The inhibitory post-synaptic currents (IPSCs) recorded at IS3–OLM synapses had a small amplitude and a small release probability. Those IPSCs, however, summated efficiently during high frequency firing of IS3 interneurons suggesting that dendritic inhibition of OLM cells by IS3 neurons is an important factor in the recruitment of OLM cells in feedback inhibition [80].

Action potentials in CA1 pyramidal neurons evoke an excitatory postsynaptic potential of about 1 mV in the OLM cell (mean amplitude: 0.93 ± 1.06 mV) [81], which alone is unlikely to reach the OLM cell action potential threshold. However, excitatory input onto the OLM cells facilitates repeated firing of the pyramidal neuron. This facilitation is regulated by the *Elfn1* [67]. When measured at the soma of a CA1 pyramidal neuron, the inhibitory postsynaptic potential elicited by a single OLM interneuron has a small amplitude and slow kinetics [82]. Since there is a distance of several hundred micrometers between the input site and the somatic recording site, it is probable that the inhibitory postsynaptic potential is several-fold larger locally at the distal dendrite. About 80 OLM cell synapses are found per pyramidal neuron [55], thus, it is likely that OLM cell-mediated inhibition effectively controls the excitatory input onto the tuft.

In terms of afferent inputs, ventral hippocampal OLMα2 cells were shown to receive excitatory, cholinergic input from the medial septum (described in more detail in Section 3.5 below), while dorsal OLM cells receive glutamatergic input, also from the medial septum [83]. One recent study [84] has shown that GABAergic neurons of the nucleus incertus selectively inhibit *Sst*+ , putative OLM cells in the dorsal hippocampus, both monosynaptically and indirectly, through the inhibition of their excitatory, glutamatergic and cholinergic inputs.

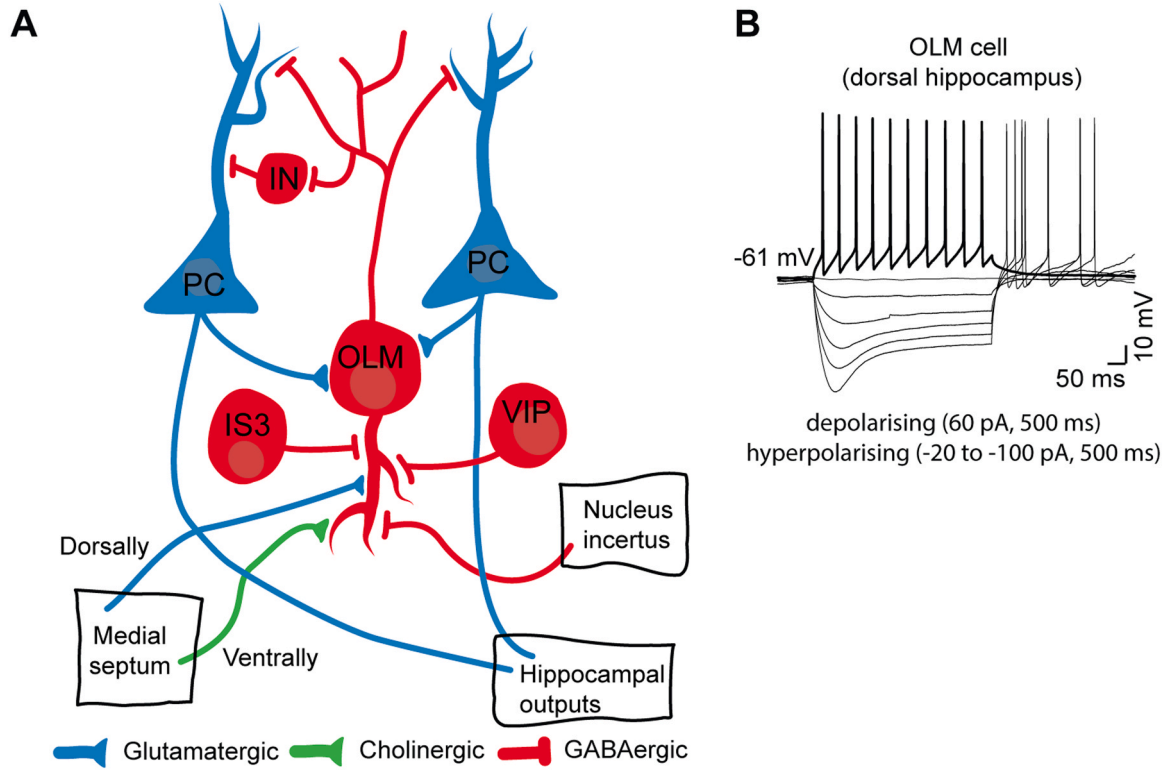

Fig. 2. The OLM circuitry and electrophysiology. A) The OLM cell synapses on pyramidal cells (PC) and other GABAergic cells (among them other inhibitory interneurons (IN) in turn also connecting to pyramidal cells). In turn, they receive input from pyramidal cells, other GABAergic interneurons (VIP+ and *Calb2*+ IS3 cells) as well as long-range projections from the medial septum and nucleus incertus. B) Example electrophysiology trace from an OLM cell in dorsal hippocampus (adapted from [65]). Note the accommodating firing pattern in response to depolarizing current injections.

3.4. Functionality

Within hippocampal networks, using electrophysiology and voltage dye imaging, OLMα2 cells were shown to facilitate Schaffer collateral input carrying context-related information to the CA1 hippocampal region, while inhibiting entorhinal cortex input that conveys environmental information to the CA1 pyramidal neurons [34]. This gating function of the OLMα2 cells was also reflected in the long-term potentiation (LTP) measurements – optogenetic activation increased LTP on Schaffer collateral synapses, while simultaneously decreasing LTP on entorhinal cortex synapses [34,85].

Another suggested role for OLM cells is the synchronization of pyramidal cell activity underlying rhythmogenesis. Different types of hippocampal interneurons fire differentially phase-locked to the ongoing network oscillations in the hippocampus [62,86,87]. OLM interneurons fire strongly phase-locked to theta oscillations (4–12 Hz), while there is no observable coupling to the gamma rhythm [62]. Interestingly, a subset of OLM cells with high excitation were shown to be recruited during hippocampal sharp wave ripples [88]. Although the different coupling of distinctive interneuron classes to hippocampal oscillations are valuable clues about the specific mechanisms of brain rhythms, these studies do not answer whether these interneuron subtypes possess the capacity to drive specific oscillatory activity. Optogenetic activation of OLMα2 cells causally drive slower frequency, cholinergic-dependent type 2 theta oscillations in the ventral hippocampus. Such OLMα2-driven theta activity directly relates to the increased risk-taking behavior in mice exposed to predator odor [11].

Further, OLMα2 cells in the intermediate hippocampus can bidirectionally modulate learning. Activation of OLMα2 cells impairs object and fear-related memory encoding, whereas their inhibition enhances object memory encoding, without affecting fear-related encoding [12]. These findings suggest a pivotal role for OLMα2 interneurons in driving hippocampal rhythmogenesis and controlling cognitive and emotional information processing.

3.5. Cholinergic innervation and presumed role for this input

The hippocampus receives major cholinergic innervation from the medial septum, where lesions in the medial septum result in a complete loss of acetylcholinesterase in the hippocampus that is coupled with a significant decrease in choline acetyltransferase (ChAT) activity [89]. When the fimbria fornix pathway is stimulated, acetylcholine application enhances population spikes in the CA1 hippocampal region, where both pyramidal cells and interneurons depolarize upon acetylcholine application [90]. Cholinergic responses have been identified in several types of hippocampal interneurons [91]. Pharmacological activation of muscarinic receptors in OLM interneurons leads to enhanced action potential firing [92]. Further, the output reliability and precision of action potential firing in response to theta patterned input is improved [93,94]. OLMα2 cells receive direct cholinergic input from the medial septum that was functionally abolished by the nonspecific nAChR antagonist mecamylamine [34]. Intermediate OLMα2 cells seem more responsive to nicotine than their dorsal counterparts, which is in line with behavioral experiments showing that dorsal and intermediate OLMα2 cells differently control learning [12]. This could explain the observation that nicotine administered in the dorsal hippocampus enhanced contextual fear memory, while nicotine administration in the ventral hippocampus impaired memory [95]. Genetic deletion of the α2-nAChR subunit eliminates the facilitation of nicotine-induced LTP in OLM interneurons and leads to memory impairment [17]. In a mouse model of Alzheimer's disease, a significant decrease of cholinergic action on OLM interneurons was reported [96]. One recent study [97] reported nicotine-mediated activation of α2-containing nAChRs on OLM cells in developing brains disrupts the OLMα2 cell-mediated control of

LTP in adolescence that could be linked to impaired memory. Acetylcholine can activate OLMα2 neurons, which leads to increased negative feedback to CA1 pyramidal cells and shunting of hippocampal output to the entorhinal cortex [98].

Furthermore, the cholinergic antagonist atropine completely abolishes theta activity in both anesthetized and immobile rats, demonstrating the cholinergic nature of type 2 theta oscillations [99]. It has been proposed that cholinergic-dependent theta invades CA1 from CA3, whereas cholinergic independent theta originates from the entorhinal cortex [100]. In addition, entorhinal cortex mediated theta was shown to be NMDA-receptor dependent, and glutamatergic activation of medial septal cells acts through the dorsal OLM cells and drive type 1 theta oscillations [83]. This further supports the existence of two different OLM cell populations, one receiving predominant glutamatergic input, prevalent in the dorsal hippocampus and driving type 1 theta; and OLMα2 cells, prevalent in in intermediate and ventral hippocampus, receiving strong cholinergic input from the medial septum and driving type 2 theta. Differences in other inputs, possibly from different brain areas, to multiple OLM cell subpopulations remain to be investigated.

4. α2-nAChR containing cells in the cortex – Martinotti cells

Martinotti cells are multipolar neurons with short branching dendrites and axonal arborizations in neocortical layer 1 that contact the distal tuft dendrites of pyramidal cells in multiple columns (Fig. 3A) [101]. Martinotti cells were first reported by Carlo Martinotti and Santiago Ramon y Cajal [102,103], who described them as a neocortical, cross-laminar projecting neuron with ascending axonal collaterals reaching layer 1 [51,104,105].

4.1. Molecular characteristics

Martinotti cells are ubiquitous to the neocortex, found in layers 2–6 but predominantly reside in layers 2/3 and 5 of the somatosensory, visual, auditory, motor and frontal cortices [101,106–108]. As a result, isolating Martinotti cells from other neocortical interneurons is challenging and relies on the selectivity of specific neurochemical markers. Martinotti cells have been reported to express *Sst* [101,109,110], and several combinations of transgenic lines have been created to attempt to genetically isolate Martinotti cells [51,52,111,112]. These experiments identified that *Sst* is not exclusively expressed by Martinotti cells in the neocortex, as the *Sst*-Cre mouse line marks layer 1–projecting Martinotti cells with cell bodies in both layer 5 and layer 2/3, but also non-Martinotti cells in layer 4 [112]. Additional tools to identify Martinotti cells include the use of the glutamate decarboxylase 1 (Gad1/GAD67) promoter, which still results in various morpho-electrical cell subtypes [51,111]. Besides *Sst*, Martinotti cell types express neuropeptide Y [113,114], calbindin 1 (*Calb1*) [50,109,115] and *Calb2* [101,110,112]. With single-nuclei RNA sequencing it was recently shown that even more candidate genes exist and especially the combination of *Sst* and myosin heavy chain 8 (*Myh8*), synapse differentiation inducing 1-like (*Syndig1l*), *Calb2* or ETS variant 1 (*Etv1*) can be used to target Martinotti cells [33]. Although some of these molecules are widely used as markers, their roles and functions within the cells are often less known. Interestingly, it has been shown that neocortical low-threshold spiking cells, which include the Martinotti cell population, depolarize through the effects of acetylcholine acting via nAChRs [116–118]. Here, several candidate nAChR subunits exist [30,119,120], with *Chrna2* being the most prominent [35]. We found that the *Chrna2*-Cre mouse line marks infragranular Martinotti cells in layer 5 [35] and these cells seem to overlap with the *Sst*-myosin heavy chain 8 subtype that has been described recently [33].

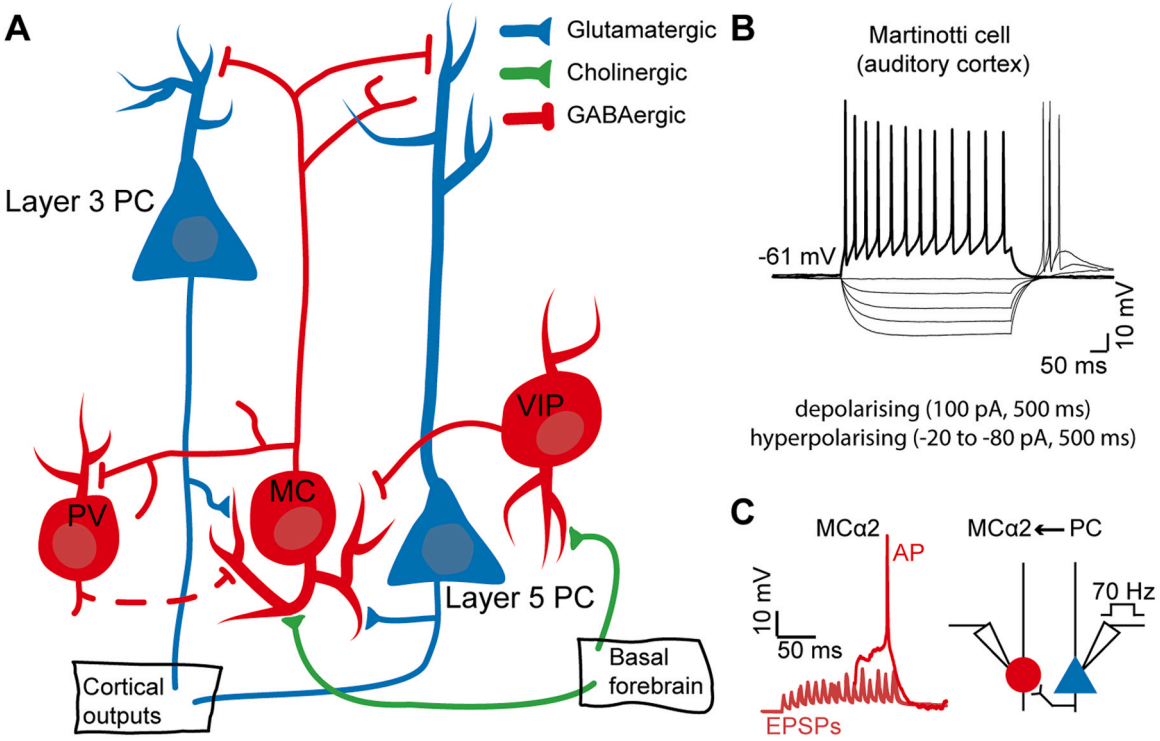

Fig. 3. The Martinotti circuitry and electrophysiology. A) The Martinotti cell (MC) synapses on layer 3 and 5 pyramidal cells (PCs) and other GABAergic cells (among them PV interneurons). In turn, they receive input from pyramidal cells, other GABAergic interneurons (VIP+ and, putatively, PV+ cells) and long-rage cholinergic projections from the basal forebrain. B) Example electrophysiology trace from a Martinotti cell (adapted from [35]). Note the accommodating firing pattern in response to depolarizing current injections. C) Example of an electrophysiology trace from a MCα2 recording showing the facilitating excitatory postsynaptic potentials (EPSPs) triggered from thick-tufted pyramidal cells (PC) and a MCα2 action potential (AP) (adapted from [35]). Here, the PC was stimulated with 70 Hz (see schematic). 12 repetitions from one example PC−MCα2 pair are shown.

4.2. Electrophysiological characteristics

Martinotti cells identified by their expression of *Chrna2* (MCα2) show an accommodating firing pattern (spike-frequency adaptation) with regular action potentials, as well as complex (both a fast and a slow component) afterhyperpolarizations and afterdepolarizations in response to positive and negative current injections, respectively [35] (Fig. 3B-C). Furthermore, MCα2 cells are low-threshold spiking, a feature often used to describe the Martinotti population [101,107,121]. *Sst*+ cells include both slow-spiking Martinotti cells and fast-spiking non-Martinotti cells [112], whereas MCα2 cells are in general slow-spiking. Other electrophysiological properties of *Sst*+ Martinotti cells include non-accommodating firing and a bursting discharge [101], further supporting that there are subtle differences of Martinotti cell types in the different layers of the neocortex. Interestingly, recently it has also been shown that SRY-box transcription factor 6 (*Sox6)* is required to maintain the electrophysiological properties of some of the *Sst*+ cells in the neocortex with *Chrna2*+ cells losing their rebound bursting discharge in conditional SRY-box transcription factor 6 knock-out mice [122].

4.3. Connectivity

The discharge pattern of Martinotti cells is particularly important because they typically receive excitatory inputs from local pyramidal cells and in turn connect to many neighboring pyramidal cells (Fig. 3A). The pyramidal cell—Martinotti cell connectivity has been examined via multi-patch recordings and is highly convergent with many (68%) neighboring pyramidal cells contacting the same Martinotti cell, producing a strongly facilitating signal [123]. This facilitation requires repetitive activity of pyramidal cells to trigger Martinotti cell action potentials [123,124] and distinguishes pyramidal cell—Martinotti cell connectivity from pyramidal cell—basket cell connectivity [123–127].

Furthermore, Martinotti cells contact many (79%) neighboring pyramidal cells and provide feedback and feed-forward inhibition onto their distal dendrites [123]. Together, pyramidal cells and Martinotti cells establish a disynaptic inhibitory mechanism where two or more pyramidal cells can synchronize their firing via intermediate Martinotti cells [123,128]. This mechanism is called frequency-dependent disynaptic inhibition (FDDI) and can be triggered by pyramidal cells with a brief, high frequency burst [123,128]. Especially thick-tufted pyramidal cells play a crucial role for FDDI [129] and optogenetic activation and inhibition of whole populations of MCα2 cells [35] confirmed that FDDI is mediated by thick-tufted (also called subcerebral projection neurons or pyramidal tract neurons) but not thin-tufted pyramidal cells (also called callosal projection neurons or intratelencephalic neurons) [35, 130–133].

4.4. Functionality

The distal inhibition of pyramidal cell dendrites by Martinotti cells is important for shaping local dendritic voltage-activated responses [134]. FDDI combined with dendritic depolarization has shown that Martinotti cells can decrease back-propagating action potential-activated Ca^{2+} spike firing and thereby in turn can also reduce the burst firing of pyramidal cells [134]. Although the particular functionality of FDDI remains uncertain, a possible function could be to keep activity within bounds via negative feedback and as a result synchronize the spike timing of subtype-specific pyramidal cells. Coordinated activity could then result in rhythmicity and intercortical oscillations. In a computer model, inhibition was shown to best control pyramidal cell firing at 10–20 Hz, establishing oscillatory activity in beta frequency [135]. Moreover, beta frequency is regulated by cholinergic modulators [135–137]. Together with the exclusive expression of the α2-nAChR subunit in Martinotti cells, this could suggest a specific role for MCα2 cells in layer 5 by transmitting the modulatory action of cholinergic signaling.

Several studies have investigated the role of Martinotti cells in different behavioral paradigms, mostly targeting layer 2/3 *Sst*+ cells. In the visual cortex for example, layer 2/3 *Sst*+ cells play a crucial role in context-dependent induced gamma rhythm, which could be established through rhythmic inhibition of pyramidal cell dendrites [138]. In the barrel cortex, layer 2/3 *Sst*+ cells show reduced firing during active sensorimotor integration [139]. Based on firing patterns, these layer 2/3 *Sst*+ cells may well represent layer 2/3 Martinotti cells. In active wakefulness experiments it was recently shown that, during whisking, activity of layer 2/3 *Sst*+ cells with Martinotti cell morphology is suppressed [140]. Moreover, also the spiking activity of layer 5 Martinotti cells with “T-shaped” morphology (prominent innervation of layer 1) was suppressed during whisking whereas the spiking activity of layer 5 Martinotti cells with “fanning-out” morphology (prominent innervation of layer 2/3, with less ascending axon reaching layer 1) was increased [140,141]. If MCα2 cells are active or suppressed during whisking remains to be studied but linking morphological and electrophysiological features it seems very likely that MCα2 cells follow the activity patterns of T-shaped Martinotti cells. Recently, it has been shown that MCα2 of the primary auditory cortex increase steady state firing frequency after noise overexposure which leads to decreased firing frequency in thick-tufted but increased firing frequency in thin-tufted pyramidal cells [142], and thus could also modulate the basal forebrain cholinergic system again via these projections [143].

4.5. Cholinergic innervation and presumed role for this input

Several neocortical inhibitory interneurons express nAChRs, suggesting local cholinergic modulation of inhibition in the neocortex [144–146]. In general, acetylcholine has been proposed to preferably excite low-threshold spiking cells through nAChRs, whereas fast spiking cells are modulated through muscarinic receptors [118]. Martinotti cells in both layer 2/3 and layer 5 respond to carbachol and muscarine [146, 147], where cortical disynaptic inhibition has been reported to be mediated by slow, non-α7 nicotinic excitation [144]. Interestingly, VIP+ interneurons also respond to acetylcholine and connect to Martinotti cells [148].

Cholinergic input to the Martinotti cells is most likely coming from the basal forebrain, however, in the rat brain, there is evidence of cortical cholinergic interneurons [149]. Cholinergic interneurons have also been suggested to be present in the mouse cortex [117], however, in situ signals from probes against vesicular acetylcholine transporter (VAChT) and ChAT recognize cholinergic nuclei and interneurons at expected anatomical locations in the striatum, basal forebrain, and brainstem nuclei [30]. Since VAChT and ChAT labeling is absent in the neocortex, a model in which cholinergic input to Martinotti cells is fed from the basal forebrain is more likely.

Chrna2 is particularly expressed by layer 5 Martinotti cells [35]. It has been suggested that during slow-wave activity (in layer 5 prefrontal cortex), nAChR stimulation may affect internal processing, e.g. spike-time dependent plasticity, by adjusting the rules for plasticity [116]. In the same layer, β2-containing nAChRs are expressed, which when active, have been shown to reduce GABA-B receptor-mediated cortical UP states in vitro. Addressed in the GIN mouse line (layer 2/3 and layer 5) as well as in human neocortical slices (layer 2/3), Martinotti cells were shown to depolarize by the activation of β2-containing nAChRs [150].

Mice lacking the α2-nAChR subunit are largely viable, but altered responses during nicotine-associated behaviors have been observed [16]. Interestingly, micro-arousals during non-REM sleep were reduced in homozygous β2-nAChR subunit knock-out mice [151]. Whether these defects are attributable to Martinotti cell dysfunction remains to be investigated.

5. α2-nAChR containing cells in the spinal cord – the Renshaw cell

The observation that motor neuron firing decreased following antidromic stimulation of spinal cord ventral roots, led to the postulation that a central spinal cord component was inherently regulating motor neuron activity [36]. Further work confirmed and extended these observations, reporting that interneuron activation by motor neuron axon collaterals would generate a series of inhibitory discharges back to the motor neuron itself, regulating motor neuron firing. These interneurons, now ubiquitously known as Renshaw cells, are located in the medial, ventral most region of lamina VII adjacent to the motor neuron pools in lamina IX [152–154] and regulate the recurrent inhibition of motor neuron activity.

5.1. Molecular characteristics

Renshaw cells can be identified by their anatomical location combined with immunohistochemical identification that relies on the expression of *Calb1* and the unique expression of large gephyrin clusters [152,153,155–158]. The unequivocal confirmation of Renshaw cells in vitro, however, is through the generation of an evoked monosynaptic response in Renshaw cells from ventral root stimulation [159].

The Renshaw cell population constitutes approximately 10% of the V1 subclass of spinal interneurons that develop from the P1 progenitor domain (reviewed in [160]). During development, Renshaw cells express the transcription factors paired box 6 (*Pax6*), developing brain homeobox 2 (*Dbx2*), and NK6 homeobox 2 (*Nkx6-2*) and, as early born V1 neurons, leave the cell cycle around embryonal day 10 and begin to upregulate *Calb1* expression [155,161,162]. *Calb1*, under the control of the transcription factors forkhead box D3 (*Foxd3*) and MAF bZIP transcription factor B (*Mafb*), is upregulated soon after Renshaw cells begin differentiation and is retained in mature Renshaw cells but downregulated in other early V1 populations [155,161,162]. The other calcium binding proteins PV and CALB2 are also expressed in Renshaw cells [163], where almost all (92%) *Calb1*+ neurons co-expressed PV and half (46%) also co-expressed *Calb2* in postnatal day 15 mice [164]. The mechanisms that control *Calb2* and PV expression in spinal interneurons are largely unknown, however, CALB1 has the strongest immunoreactivity in Renshaw cells [152]. To date, CALB1 has been the best immunohistochemical marker of the Renshaw cell population, despite its differential, widespread and decreasing expression in the ventral horn [161,163–165]. Conditional *Calb1* expression genetically targeted Renshaw cells in adult mice, where a *Calb1*-destabilized Cre combinatorial approach with engrailed 1 (*En1*) or PV increased cellular specificity in targeting the Renshaw cell population [166].

Between postnatal day 10–14, Renshaw cells develop unique, large gephyrin clusters on their cell membrane, which are discriminant from other inhibitory interneurons and motor neurons [156]. The gephyrin clusters on Renshaw cells increase in size during postnatal development, where the proportion of large clusters increases from 5% to 35% from postnatal day 2–15 [157]. Although *Calb1* expression is maintained in Renshaw cells, and large gephyrin clusters are unique on the Renshaw cell membrane, both *Calb1* [163,167] and gephyrin [168] are abundant in the neonatal spinal cord and remain unreliable markers for the Renshaw cell population.

Chrna2 was suggested as a possible Renshaw cell marker due to its expression pattern in the ventral horn [169]. Its expression pattern is restricted to the gray matter ventral rim and labels a small interneuron population reminiscent of Renshaw cells [3169,170]. There is a high overlap between *Chrna2* mRNA, CALB1 and gephyrin immunoreactivity, which confirmed these *Chrna2*+ neurons as Renshaw cells (RCα2) [38]. In contrast to the transient and non-specific expression of both *Calb1* and gephyrin in the ventral horn, *Chrna2* is a specific, reliable and persistent marker of Renshaw cells that does not seem restricted by developmental regulation of transcription factors.

5.2. Electrophysiological characteristics

Renshaw cell activity (Fig. 4B) is tightly regulated, as single motor neuron action potentials reliably activate and drive Renshaw cell firing [40]. Conversely, single Renshaw cell action potentials are sufficient to disrupt the motor signal [171]. The antidromic activation of motor neurons through ventral root stimulation triggers action potentials in Renshaw cells, where action potential trains are characterized by an initial action potential doublet [38,172]. In the *Chrna2*+ population, a proportion (39%) of RCα2 are spontaneously active at rest, similar to other spinal interneurons [38,173–175], and RCα2 reliably follow motor neuron activation, firing trains of action potentials with slight spike adaptation, up to and over 50 Hz [38,176].

Renshaw cells are rhythmically active in response to induced locomotor central pattern generator activity, firing predominantly in phase with the respective ventral root [177]. Many rhythmically active central pattern generator interneurons have electrophysiological properties,

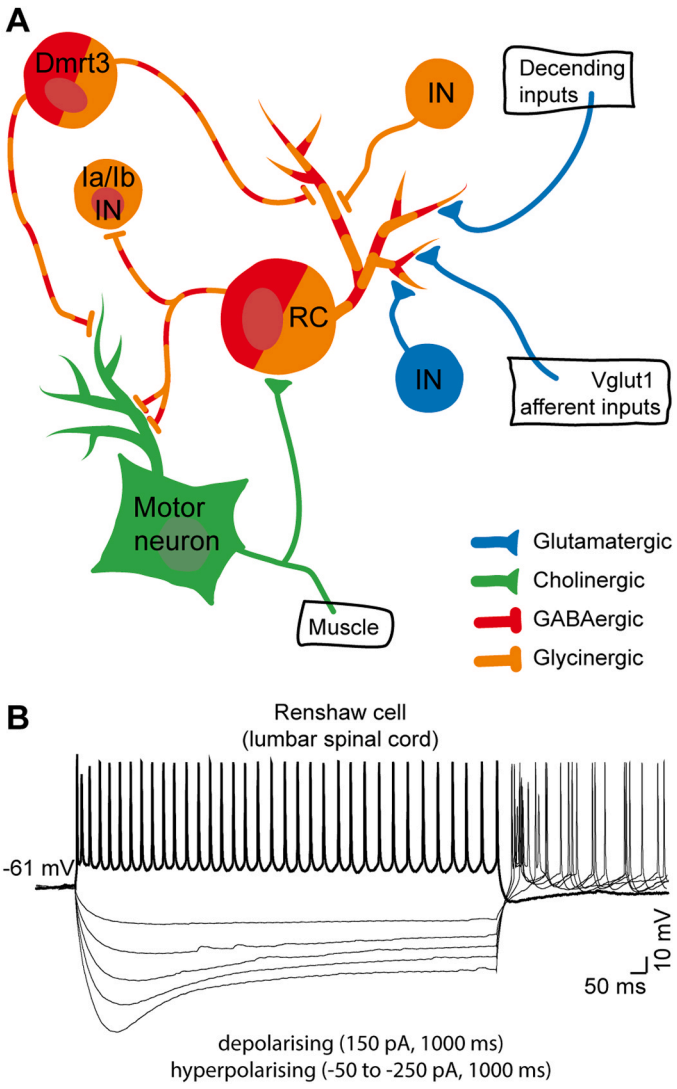

Fig. 4. The Renshaw circuitry and electrophysiology. A) The Renshaw cell (RC) synapses on motor neuron and other inhibitory cells (among them Ia and Ib interneurons (IN)). In turn, they receive input from motor neurons, other inhibitory interneurons (*Dmrt3* cells among others) as well as excitatory interneurons, and long-range projections in the form of descending fibers and afferent, proprioceptive inputs. (Vglut1, vesicular glutamate transporter 1). B) Example electrophysiology traces from a Renshaw cell (adapted from [38]). Note the accommodating firing pattern in response to depolarizing current injections.

including spike adaptation and ionic currents, that independently act to modulate cellular excitability and activity [173,174,178]. RCα2 display a large inward current that repolarizes the membrane from strong hyperpolarization, eliciting a large depolarizing sag in the membrane potential and occasionally causing post-inhibitory rebound potentials at the termination of hyperpolarization [38]. Renshaw cells express hyperpolarization-activated cyclic nucleotide gated channels (*Hcn4*) [179], which in RCα2 conduct a functional, prominent, ZD7288 (I_h antagonist) sensitive I_h [38]. RCα2 I_h was active at a strikingly negative half-activation voltage of $-103.1 +/- 1.2$ mV, this excludes I_h in contributing to the resting membrane potential of RCα2 cells [38]. RCα2 cells do not exhibit burst firing as previously described [177], however, blocking I_h activation slowed RCα2 firing frequency [38].

Renshaw cell firing can also be modulated by currents that act to compensate for profound cellular excitation. RCα2 cells have a small conductance calcium-activated potassium current (I_{SK}) that acts to slow RCα2 firing in response to prolonged depolarizing inputs [38]. Blocking I_{SK} using Apamin, a specific I_{SK} antagonist, impeded the RCα2 action potential afterhyperpolarization potential increasing RCα2 firing and eliciting burst-like rebound action potentials [38].

5.3. Connectivity

Renshaw cells are excited by motor neuron axon collaterals and in turn innervate and inhibit motor neurons [159], Renshaw cells [180,181] and other spinal interneurons [119,172,182] establishing a recurrent inhibition circuit (Fig. 4A). The unique circumferential migration pattern of Renshaw cells [155,161], coupled with the inability of motor neuron axons to leave the ventral horn during early development and their need to find innervation targets [155], facilitates and reinforces the recurrent inhibition circuit. Once migrated at embryonal day 11.5, Renshaw cells are spontaneously active and functionally heterogeneous [183], and can be clustered into distinct, transiently functional classes during early development (embryonal day 11.5–16.5) [184]. With a predicted motor neuron—Renshaw cell ratio of 5:1 [185,186], Renshaw cells receive considerable excitatory input from motor neurons on their proximal dendrites that proliferates during postnatal maturation [187].

Renshaw cells also receive excitatory monosynaptic inputs from descending fibers [188] and excitatory/inhibitory monosynaptic inputs from local spinal interneurons [189,190] on their proximal dendrites. Renshaw cells are innervated by vesicular glutamate transporter 1 (*Slc17a7*/VGLUT1)-expressing proprioceptive afferents on their distal dendrites that initially proliferate, but are subsequently deselected and decline in density after postnatal day 20 [165,187,191]. Thus, Renshaw cells have a significant proximal-distal distribution of innervation, where excitatory afferent inputs are received distally, whilst cholinergic and local inhibitory and excitatory inputs innervate Renshaw cell proximal dendrites.

To complete the recurrent inhibition circuit, Renshaw cells innervate and inhibit the proximal dendrites of both homonymous and heteronymous motor neurons [36,159,171]. Renshaw cells also innervate and inhibit other Renshaw cells, and Ia and Ib inhibitory interneurons [119,172,182,192]. Once a functional circuit is established both the motor neuron and Renshaw cell are primed to act as pre- and postsynaptic targets [155].

5.4. Functionality

Additional spinal circuits function to tightly regulate motor neuron output that work largely independently of the locomotor generating network. The observation that motor neuron firing could be modulated through ventral root stimulation confirmed that a central spinal cord circuit was acting to modulate functional motor neuron output [159,193]. Motor neuron and Renshaw cell connectivity establishes the recurrent inhibition circuit, which has been widely studied through the use of isolated spinal cord preparations in combination with antidromic dorsal and ventral root stimulation.

The unique central circuitry of recurrent inhibition can be exploited to elucidate the role of the Renshaw cell in governing motor neuron activity. The activation of motor neurons by the stimulation of a dorsal root sensory afferent (test stimulus), produces a stereotypical and reproducible motor neuron reflex response, which is recorded by a ventral root recording electrode. This motor neuron response can be altered by the activation of Renshaw cells. A conditioning stimulus applied through stimulation of an adjacent ventral root, activates Renshaw cells through antidromic volleys in neighboring motor neurons. When Renshaw cells are activated prior to motor neuron activation, the Renshaw cells inhibit motor neuron activity, attenuating the motor neuron response reflex [193]. Whilst the activation of Renshaw cells attenuates motor neuron activity, the inhibition of Renshaw cells can facilitate motor neuron firing. Disinhibition of motor neurons by the inhibition of Renshaw cells increases motor neuron activity, however, due to the nature of the Renshaw cell—motor neuron circuit, increased motor neuron firing will inevitably increase Renshaw cell activity.

Although in principle the role of the Renshaw cell in recurrent inhibition appears straightforward, the functionality of the Renshaw cell population has been debated since their discovery. Release of function mechanisms was suggested as an explanation for the observation that lower (or spinal) centers in the nervous system become hyperactive upon loss of higher center influence [194,195]. Renshaw cells and their potential role in disinhibition sprung from recordings in the spinal cord where either recurrent inhibition or facilitation was observed dependent on the motor neuron pool tested [193]. Recurrent inhibition was found when the motor nerves used for testing belonged to the same muscle or muscle group. Recurrent facilitation, however, was found only when the conditioning stimulus was performed in another motor neuron pool, sometimes, but not always, in the antagonistic muscle. Recurrent facilitation was later suggested to be a result of decreased background inhibition, or disinhibition [196,197].

Renshaw cell activity is likely contributing to other neuronal circuits in parallel to the recurrent inhibition circuit. Renshaw cells receive their predominant excitatory drive from motor neuron collaterals, through fast cholinergic (nAChRs) and slower glutamatergic (NMDA and AMPA) transmission, and are also innervated by descending brainstem and cortical (corticospinal tract) inputs. The inherent molecular and electrophysiological profile/nature of the Renshaw cell is primed to respond to inhibitory events. Renshaw cells have distinctive, large gephyrin clusters on their soma and proximal dendrites, suggesting that Renshaw cells receive potent inhibition from other neurons. In support of this, Renshaw cells appear to have an ionic mechanism in place to deal with incoming powerful inhibition, the I_h has a strongly negative half-activation potential which repolarizes the membrane from strong inhibition.

Renshaw cells are rhythmically active during locomotion but are not integral for generating the locomotor rhythm [177,198]. Beyond this, the precise functional role of Renshaw cells remains unclear. Potential roles for the population include shortening the burst duration of motor neurons, coordinating flexor-extensor alternation [177,199], changing the gain of motor pools [200], influencing the de-correlation of motor neuron firing [201] and reducing motor neuron firing during locomotion [202]. Genetic manipulation of the Renshaw cells has been inconclusive in deciphering their role in locomotion. Ablating the V1 population in neonatal isolated mouse spinal cords decreased the locomotor speed but retained normal flexor-extensor alternation [203], whilst adult mice show flexor-extensor related gait difficulties [204]. Hyperpolarizing the V1 interneuron population using optogenetics in mouse isolated spinal cords, slowed locomotor-like rhythm induced through dorsal and ventral root stimulation [205]. Optogenetic inhibition induced hyperpolarization of V1 interneurons during drug-induced fictive locomotion, slowed the locomotor speed and altered the pattern of the locomotor-like rhythm, increasing flexor and extensor dominated

bursts [205]. Thus, the phenotypic and behavioral consequences of V1 ablation cannot be directly attributable to the role of the Renshaw cell.

The *Chrna2*-Cre mouse is the first Renshaw cell specific genetic tool, which broadens the possibilities to decipher their functional role. The targeted silencing of RCα2 cells, through selective deletion of the vesicular inhibitory amino acid transporter (VIAAT; *Chrna2*^{Cre};*Viaat*$^{lx/lx}$ mice), caused no observable motor or locomotor dysfunction in adult mice [206]. Moreover, in isolated neonatal spinal cords, the frequency, rhythm and flexor-extensor patterning of the limbs during induced locomotor-like activity was also unaffected. Increasing the locomotor speed of isolated spinal cords caused similar increases in the locomotor-like activity in *Chrna2*^{Cre};*Viaat*$^{lx/lx}$ mice compared to control, suggesting that Renshaw cells are not central to the regulation or coordination of locomotor patterns [206]. Together these functional data contradict previous reports as they do not support previous theories implicating Renshaw cells in the regulation of flexor-extensor activity [177,198] or support the finding that mice with ablated V1 neurons had gait dependent flexor-extensor difficulties [204]. The selective silencing of RCα2 cells does however support the previous observation that flexor-extensor alternation remains largely unaffected when the V1 population is silenced or ablated [203,205].

5.5. Cholinergic innervation and presumed role for this input

The motor neuron—Renshaw cell synapse was the first example of a fast, cholinergic synapse in the central nervous system [159]. Pharmacological blockade of nAChRs silenced Renshaw cell firing in isolated spinal cords [202], confirming the cholinergic nature of the synapse. Recently, glutamate and/or aspartate have been suggested to be co-released with acetylcholine at central motor neuron synapses, since nAChR antagonists fail to completely inhibit evoked motor neuron activation of Renshaw cells [172,207–209]. The nAchR subunits on Renshaw cells are 3α:2β, which likely accounts for the biphasic character of the synaptic current due to their dual mode of activation [210]. Renshaw cell inhibitory neurotransmission, although initially thought to be solely glycinergic [180,181,211], is both glycinergic and GABAergic [212], which prolongs the inhibitory signal on motor neurons.

The motor neuron—Renshaw cell synapse, and indirectly Renshaw cell function, has been investigated by the application of the nAChR antagonist mecamylamine, which blocks cholinergic transmission [153]. In isolated spinal cords, application of mecamylamine altered the locomotor frequency [177], highlighting the importance of cholinergic transmission in normal motor activity. In *Chrna2*^{Cre};*Viaat*$^{lx/lx}$ mice, however, mecamylamine application had little effect on locomotor-like activity as both control and *Chrna2*^{Cre};*Viaat*$^{lx/lx}$ spinal cords had a similar reduction in locomotor frequency [206]. This suggests that the action of mecamylamine is likely independent of Renshaw cell function, and possibly acts on other locomotor neurons that express other nAChR subtypes (e.g. the α5 subunit).

6. General features of α2-nAChR cells in the central nervous system

6.1. Tonic activity and disinhibition

Chrna2 cells are a subset of inhibitory interneurons that share the characteristics of a close association to principal cells and that display spontaneous and/or tonic activity. Such activity is fed by intrinsic membrane conductance and can be fine-tuned by synaptic inputs and neuromodulatory factors [213]. This raises the question as to whether the regulation of circuit activity and principal cell output through these interneurons is controlled through disinhibition (Fig. 5), a concept

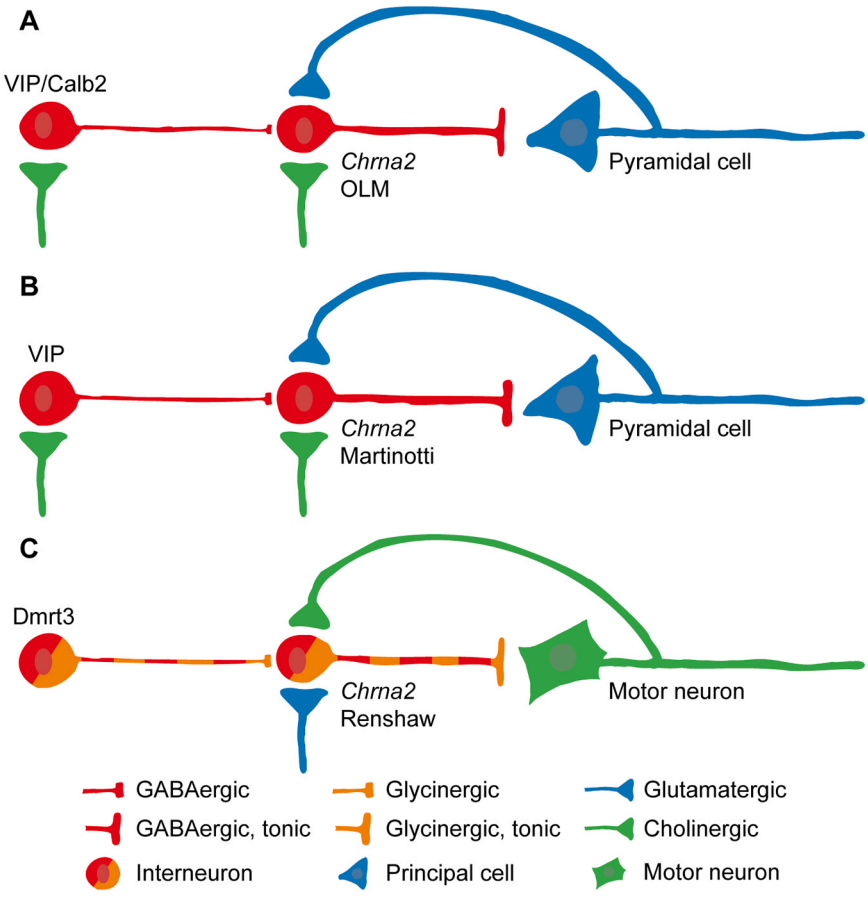

Fig. 5. The common model of recurrent inhibition. Schematic illustration of cell types expressing *Chrna2* (center cells; red, orange) and the proposed common model of recurrent inhibition these cells have with their respective principal cell (rightmost cells; blue, green). The *Chrna2* cells tonically inhibit the principal cell and they in turn provide excitatory input to the *Chrna2* cells that reset or reenforce tonic inhibition. Upstream inhibitory interneurons (leftmost cells; red, orange) provide disinhibition upon excitation and cholinergic innervation provide modulation (green terminals). A) The OLM cell receives inhibitory input from VIP+ and *Calb2*+ neurons and cholinergic modulation from the medial septum. B) The Martinotti cell receives inhibitory input from VIP+ basket cells and cholinergic modulation from basal forebrain. C) The Renshaw cell receives inhibitory input from *Dmrt3* and other interneurons and direct cholinergic input from motor neurons as well as modulatory input from proprioceptive afferents.

suggested by Jackson [194,195] and nowadays a well-known mechanism in basal ganglia circuits for initiation of motor commands. The identification of inhibitory interneurons upstream of spontaneously active inhibitory interneurons supports this idea [214,215].

How does this look for the OLM cell? OLM cells are known to be excited by local pyramidal cells and in turn inhibit the distal apical dendrites of pyramidal cells, providing a classic example of feedback inhibition (Fig. 5a). OLM cells have been found to be tonically active [34,216] and are targeted by long range excitatory cholinergic projections as well as excitatory and inhibitory local interneurons [34,217]. The inhibitory interneurons that target OLM cells include other OLM interneurons, bistratified cells, and interneurons specifically innervating other interneurons [34,64,218,219]. OLM cells receive local inhibitory inputs from IS3 cells co-expressing VIP and *Calb2* [80,218,220] and cells expressing PV [221].

Similar to OLM cells, *Sst*+ Martinotti cells also receive excitatory connections from nearby pyramidal cells, which facilitate their activation. The output connections of Martinotti cells primarily target the distal dendrites of pyramidal cells, providing recurrent lateral inhibition (Fig. 5b) [70]. Optogenetic experiments and concurrent multiple whole-cell recordings of neocortical interneurons, followed by morphological reconstruction, have demonstrated that *Sst*+ cells, including layer 5 Martinotti cells, establish connections with each other and can inhibit various types of interneurons such as PV+ and VIP+ cells [148], thereby promoting circuit disinhibition. Previous research has shown that optogenetic suppression of *Sst*+ interneurons firing in vivo unexpectedly increases the activity of neighboring pyramidal neurons [139]. An in vitro study found that the spontaneous activity of *Sst*+ interneurons strongly suppresses excitatory synaptic transmission between layer 2/3 pyramidal neurons in the somatosensory cortex of mice [222]. These findings have led to the suggestion that the spontaneous activity of *Sst*+ cells provides constant inhibitory influence on pyramidal neurons, effectively disconnecting them from the network during periods of low activity [223]. Furthermore, optogenetic studies using a VIP-Cre mouse model have shown that *Sst*+ interneurons represent the major target of VIP+ interneurons; in particular, the inhibition provided by VIP+ interneurons was much larger in *Sst*+ cells compared with PV+ interneurons in the visual and somatosensory cortices [137,224]. A similar observation was reported in the auditory and medial prefrontal areas [225], where optogenetic activation of VIP+ interneurons elicited IPSCs primarily in *Sst*+ cells; albeit no difference in the amplitude of the evoked IPSCs appeared between *Sst*+ and PV+ interneurons. In addition, optogenetic silencing of VIP+ interneurons strongly reduced the IPSCs recorded in neocortical *Sst*+ cells [137]. Taken together, these studies show that VIP+ /*Calb2*+ IS3 interneurons are well positioned to modulate primarily the activity of local *Sst*+ circuits, providing dendritic disinhibition to cortical pyramidal neurons. Several of the mentioned studies have been made on layer 2/3 pyramidal neurons and *Sst*+ Martinotti cells, and it remains to be established whether MCα2 cells in layer 5 have similar arrangements and responses.

The Renshaw cell "release of function" mechanism implies the presence of tonic activity of inhibitory interneurons and in the initial models, it was thus suggested that Renshaw cells act on tonically active inhibitory interneurons [226]. It was also proposed that Ia inhibitory interneurons could be this source of tonic inhibition [182]. However, others have suggested that Renshaw cells themselves can be tonically active and become disinhibited by upstream inhibitory interneurons, or alternatively, that Renshaw cells are kept in an active state by other inputs, such as dorsal root afferents and a tonic stretch reflex [227–229]. Reciprocal inhibition between motor nuclei is required for alternating activities between flexor and extensor muscles, as well as left-right movements. The innervation of Renshaw cells by inhibitory interneurons adds to what appears to be a relatively simple local circuit; the activation of upstream inhibitory interneurons reverts Renshaw cell activation and attenuate Renshaw cell mediated inhibitory input to the motor neurons. Renshaw cells are innervated by inhibitory doublesex and mab-3 related transcription factor 3 (*Dmrt3*) neurons [230] and receive direct inhibition from other Renshaw cells within the population (Fig. 5c). Therefore, the selective activation of the *Dmrt3* population would decrease Renshaw cell activity. The simultaneous convergence of multiple inhibitory inputs, for example from *Dmrt3* neurons [230] and other surrounding Renshaw cells, strongly activates Renshaw cell I_h which causes the generation of excitatory rebound action potentials, possibly turning strong inhibition into rebound excitation. This complicates the disinhibition of Renshaw cells and confines the action of inhibitory inputs on Renshaw cell activity to a defined physiological range. Since inhibitory input would normally cause inhibition of Renshaw cells and an increase in motor neuron output, a barrage of inhibitory inputs, sufficient to activate I_h, could cause rebound action potentials in Renshaw cells attenuating motor neuron firing.

In summary, disinhibition and tonic activity are likely important parameters for adequate circuit function, in which the *Chrna2*+ Renshaw, Martinotti and OLM cells operate.

6.2. Cholinergic innervation and possible role for microcircuit activity

Cholinergic modulation has significant effects on interneuron activity in the hippocampus, neocortex and spinal cord. The major source of acetylcholine supplying the hippocampal OLM and cortical Martinotti interneurons is the basal forebrain, whereas Renshaw cells receive cholinergic input from local motoneurons [159]. Multiple studies have shown that OLM and Martinotti cells generate large depolarizing responses upon activation of muscarinic acetylcholine receptors [92,147], where both *Chrna*2+ OLM and Martinotti cells depolarize in response to carbachol application [146]. The motor neuron—Renshaw cell synapse was the first example of a fast, cholinergic synapse in the central nervous system [159] where pharmacological blockade using mecamylamine silences Renshaw cell firing [202]. Of note, the first example of a fast cholinergic ionotropic action in the brain was demonstrated in the OLMα2 cells [34].

It has been demonstrated that nAChRs play a role in modulating hippocampal circuits by exciting interneurons, which in turn can lead to the inhibition or disinhibition of pyramidal neurons [231]. Moreover, nicotine can impact hippocampal network activity by continuously activating non-α7-containing nAChRs, which in turn promotes the induction of LTP in OLM cells [232]. But perhaps most interesting were results showing that a specific subgroup of interneurons in the stratum oriens/alveus remains continuously activated by nicotine due to the persistent activation of α2-containing nAChRs. The authors could show that these interneurons establish synaptic connections with pyramidal cells, and that nicotine enhances the inhibitory baseline currents at these synapses while suppressing phasic inhibition [233]. OLMα2 cells are thus modulating inhibitory circuits through the activation of a non-desensitizing α2-containing nAChR subtype, which alter the operation of hippocampal circuits by gating inhibitory circuits. Thus, cholinergic action may well be crucial for the OLM cell to maintain tonic activity. The extent to which acetylcholine release will affect specific interneuron subtypes depend on the density and location of the cholinergic axonal terminals and its inactivating enzyme, acetylcholinesterase.

The influence of cholinergic activation of Martinotti cells might result in a shift in pyramidal cell activity, similar to what has been observed in the hippocampus and the OLMα2 cells. The MCα2 and OLMα2 populations exhibit low-threshold spiking and are excited by acetylcholine through nAChRs [116,118], although *Sst*+ cells in neocortical layer 2/3 and 5 can be modulated by both carbachol, the nicotinic and muscarinic receptor agonist, and muscarine, the agonist for the muscarinic receptors [146,147,234]. Further, oscillations at different frequencies, in which Martinotti cells participate, are regulated by cholinergic modulators [235]. The activation of muscarinic receptors in OLM cells resulted in increased action potential firing, longer lasting

plateau depolarizations and a higher sensitivity to the theta-patterned input [93,236]. Moreover, while muscarinic receptors in OLM cells promote transient theta generation, α7-containing nAChR activation facilitates future theta generation, as revealed using pharmacological and genetic manipulations in freely moving mice [237]. Therefore, both Martinotti cells and OLM cells show state-dependent activity, which can be tuned by acetylcholine [34,61,62,234], and, therefore, result in state-dependent modulation of inhibition to pyramidal cells and target interneurons.

The main source of excitability to Renshaw cells during locomotion arises from cholinergic motor neuron synaptic inputs [177]. Single motor neuron action potentials can reliably drive Renshaw cell firing [40], where Renshaw cells reportedly reliably fire in response to motor neuron inputs upwards of 50 Hz [176]. Renshaw cells fire during locomotor activity and are active during the locomotor phase, where individual Renshaw cell activity is coupled with a functionally synonymous, flexor or extensor, motor neuron group [177]. Since Renshaw cells match motor neuron firing, the generated recurrent inhibition can alter the firing rate and temporal timing of motor neuron spikes, and act to variably change the gain of motor neurons.

6.3. Concluding remarks

Chrna2+ Renshaw, Martinotti and OLM cells all act in circuits that are tightly coupled to rhythmic oscillatory activity, and are modulated by cholinergic influence. At least two hypotheses concerning the general features of interneurons that express *Chrna2* arise from the collected data: 1) inhibitory interneurons use *Chrna2*-mediated signaling to support a sustained tonic activity to achieve a mechanism of disinhibition; and 2) the response profile upon activation is a prerequisite to achieve a microcircuit ready for rhythmic activity and oscillations.

α2-nAChR subunits are expressed in specific and limited locations in the brain, mainly on inhibitory interneurons. Despite their low overall expression levels in a limited number of interneurons, they have been shown to play significant roles in several physiological functions, including modulation of neurotransmitter release, pain processing, addiction-related behaviors, anxiety, stress response, and cognitive function. The consequences of modulating α2-containing nAChRs suggest that they are an important target for therapeutic intervention in various neuropsychiatric disorders, particularly those involving inhibitory interneuron dysfunction.

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Declaration of Competing Interest

The authors declare no competing interests.

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