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REVIEW

Calretinin Expression in the Mammalian Neocortex: A Review

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Summary

In the mammalian neocortex, the calcium-binding protein calretinin is expressed in a subset of cortical interneurons. In the recent years, research on interneurons is one of the most rapidly growing fields in neuroscience. This review summarizes the actual knowledge of the functions of calretinin in neuronal homeostasis and particularly of the distribution, connectivity and physiological properties of calretinin expressing interneurons in the neocortex of rodents and primates, including humans. The possible neuroprotective role of calretinin and the presumed "resistance" of calretinin-expressing interneurons to various pathological processes are also discussed.

Key words

Calcium-binding proteins • Interneurons • Inhibition • Neuroprotection • Neurovascular coupling

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Introduction

Neuronal population in mammalian cerebral cortex consists of two distinct groups. Pyramidal neurons, which constitute approximately 70-80 % of total neuronal population, are uniformly excitatory, using glutamate as a neurotransmitter. The other group is formed by interneurons, also known as local circuit neurons. Most of them are inhibitory, using GABA as a principal neurotransmitter. It is now increasingly appreciated that the GABAergic interneurons play many important roles in cortical neuronal networks both in normal and pathological states. Various strategies to sort GABAergic interneurons into distinct subgroups have been adopted and this process is far from being completed yet. Based on the expression of three different calcium-binding proteins, namely parvalbumin (PV), calbindin D28k (CB) and calretinin (CR), it is possible to divide the cortical GABAergic interneurons into three largely non-overlapping populations (with some limitations, see below). Here we focus on CR and especially on CR-expressing cortical neurons in the neocortex.

EF-hand family of calcium-binding proteins

Calretinin belongs to the so-called EF-hand family of CaBP. The EF-hand is an evolutionary well preserved amino acid domain with a characteristic three-dimensional structure and with a high affinity for calcium ions (Moews and Kretsinger 1975). More than 600 proteins containing EF-hand motive are already known across different species (Carafoli *et al.* 2001). The best known is probably calmodulin, which mediates numerous intracellular processes after binding of Ca^{2+}, hence acting like a Ca^{2+} sensor. The Ca^{2+} sensors are intracellular proteins, which after binding of free calcium ions undergo conformational change and subsequently activate or deactivate various target molecules (enzymes, transport proteins, etc.), thereby affecting various

regulatory processes in the cell. On the contrary, Ca^{2+} buffers are another group of cytosolic Ca^{2+}-binding proteins, which do not show any significant conformational change upon Ca^{2+} binding. Ca^{2+} buffers are involved in shaping both the amplitude and the duration of Ca^{2+} signals and in limiting the spatial spreading of local Ca^{2+} signals (Berridge *et al.* 2000, Schwaller 2009).

Calretinin

Calretinin, first described in 1987, acquired its name based on the structural similarity to calbindin D28k and the site of first detection (retina) (Rogers 1987). Calretinin in general shares many features with calbindin D28k and belongs to calbindin D28k subfamily of CaBP. The gene for CR is located on chromosome 16 (Parmentier *et al.* 1991). CR is composed of 269-271 amino acid residues and contains six EF-hand domains. Four of them bind Ca^{2+} with high affinity in a cooperative manner, one with low affinity and the last one is non-functional, without Ca^{2+}-binding ability (Schwaller *et al.* 1997, Stevens and Rogers 1997). Besides Ca^{2+}-binding properties, CR also shows affinity for copper ion Cu^{2+} (Groves and Palczewska 2001), which upon binding to CR antagonizes Ca^{2+} binding to CR. The mammalian neuronal cytoplasmic concentration of CR was estimated to be in order of tens of micromoles (Hackney *et al.* 2005). Although usually considered to be freely diffusible and uniformly distributed in the cytoplasm, at a certain stage of development it was shown to be highly concentrated beneath the cell membrane (Hack *et al.* 2000).

While PV acts as a so-called "slow" buffer (exerts slow Ca^{2+} binding kinetics) and CB like a "fast" buffer (exerts fast Ca^{2+} binding kinetics), CR was first shown to behave as a fast buffer in modifying presynaptic signaling in frog saccular hair cells (Edmonds *et al.* 2000). However, recently it was found that CR shares some kinetic properties of both slow and fast buffers in modifying dendritic Ca^{2+} transients (Faas *et al.* 2007). Such dual kinetic properties are mainly consequence of the above-mentioned cooperative Ca^{2+} binding by CR. These studies also show that CR affects intracellular calcium signals both pre- and postsynaptically. Further elucidation of CR function came from the studies on CR–/– (Schurmans *et al.* 1997, Schiffmann *et al.* 1999, Gall *et al.* 2003, Cheron *et al.* 2004, 2005), CR+/– (Gurden *et al.* 1998) and CR "rescue" (CR–/– with selective reexpression in certain cellular population) (Aller *et al.* 2003, Bearzatto *et al.* 2006) mice. In these studies, impairment of long-term potentiation in the dentate gyrus and especially abnormal excitability in the cerebellar neuronal network with mild impairment of motor coordination were shown to be a result of CR deficiency in mossy cells of dentate gyrus and granule cells of cerebellar cortex, respectively. Together, these studies indicate that modulation of calcium signaling by CR (and CB and PV) is important for precise timing and plasticity of synaptic events in neuronal networks. To make things more complicated, it seems that CR, similarly to CB, might also act as a calcium sensor protein (Billing-Marczak and Kuznicki 1999).

Another still controversial topic is the possible neuroprotective role of CR. While some studies performed mainly on isolated cells or tissue cultures found neuroprotective effect against calcium-induced cytotoxicity (Lukas and Jones 1994, Isaacs *et al.* 1996, Marini *et al.* 1997, D'Orlando *et al.* 2001, 2002), other works using similar techniques gave opposite results (Mockel and Fischer 1994, Kuznicki *et al.* 1996, Bouilleret *et al.* 2000, Isaacs *et al.* 2000). Finally, neuroprotective effect of CR against cellular damage mediated by very low Ca^{2+} concentration has been described recently (Lema Tome *et al.* 2006, Turner *et al.* 2007).

Calretinin-expressing neurons in the neocortex

After the discovery of calretinin (Rogers 1987), a basic description of CR distribution in rodent brain emerged in the following years from the work of several authors (Pochet *et al.* 1989, Winsky *et al.* 1989, Rogers *et al.* 1990, Jacobowitz and Winsky 1991, Resibois and Rogers 1992) as reviewed by Baimbridge *et al.* (1992) and Andressen *et al.* (1993).

In this paper, the neurons expressing CR will uniformly be described as CR+ neurons, regardless of the method used for CR detection in the particular cited articles (immunohistochemistry, *in situ* hybridization etc.). In this review, we will focus mainly on CR+ neurons in rodents and primates, including human. For information about CR+ neocortical neurons in other species and about their relationship to mammalian brain phylogenesis, see (Hof *et al.* 1999).

Ontogenesis of neocortical calretinin-expressing interneurons

At least in rodents, the CR+ interneurons differ from other interneuronal subtypes in their site of origin. Unlike the pyramidal neurons, which originate in the ventricular zone of the dorsal telencephalon, the precursors of neocortical interneurons proliferate in the ganglionic eminences in the ventral telencephalon and migrate tangentially to neocortex during the embryonic period. While the PV+ and CB+ cells derive predominantly from the medial ganglionic eminence, the CR+ neurons develop in the caudal ganglionic eminence (Xu *et al.* 2003, Wonders and Anderson 2006). While the molecular mechanisms of CR+ interneuronal development and migration are not completely understood yet, the attention was recently drawn to the importance of estrogen receptor β expression for the development of CR+ GABAergic interneurons in rodent brain (Fan *et al.* 2006).

Co-expression of other markers in calretinin-expressing neurons

As already mentioned in the introduction, the three calcium-binding proteins – CR, PV and CB – tend to be expressed in non-overlapping populations of cortical interneurons (Conde *et al.* 1994, Kubota *et al.* 1994, Gabbott and Bacon 1996a, del Rio and DeFelipe 1996, Kawaguchi and Kubota 1997, Zaitsev *et al.* 2005, 2009). However, a low degree of co-localization between CR and CB was described by some authors (del Rio and DeFelipe 1996, 1997a, Cauli *et al.* 1997, Park *et al.* 2002) (for review see DeFelipe 1997). Nevertheless, the usefulness of utilization of PV, CB and CR for categorizing of interneuronal subpopulations was recently validated by gene cluster analysis (Toledo-Rodriguez *et al.* 2004).

In rodents, almost 100 % of CR+ neurons in the neocortex seem to use GABA as a neurotransmitter (Kubota *et al.* 1994, Gonchar and Burkhalter 1997, Gonchar *et al.* 2007). On the other hand, in monkey (Melchitzky *et al.* 2005) and human (del Rio and DeFelipe 1996) neocortex, about 25 % of CR+ neurons were found not to express GABA. These non-GABAergic CR+ neurons are discussed below.

Substantial co-localization of CR with vasoactive intestinal peptide (VIP) and choline acetyltransferase (ChAT) in neocortical neurons was described (Rogers 1992, Kubota *et al.* 1994, Cauli *et al.* 1997, Kawaguchi and Kubota 1997, Gabbott and Bacon 1997, Porter *et al.* 1998, von Engelhardt *et al.* 2007). As long as both VIP and acetylcholine are involved in the regulation of energy metabolism and blood flow dynamics in the cortex (Magistretti 1990, Cauli *et al.* 2004), an important role of CR/VIP/ChAT-positive neurons in "the local regulation of tissue physiology within a radial column of cortex" can be presumed (Gabbott *et al.* 1997b, Cauli *et al.* 2004).

For additional information on co-expression of various neuronal substances (other neuropeptides, receptor subunits etc.) in CR+ neurons, consult following papers (Rogers 1992, DeFelipe 1993, Dun *et al.* 1994, Cauli *et al.* 2000, Gonzalez-Albo *et al.* 2001, Toledo-Rodriguez *et al.* 2004, 2005, Gonchar *et al.* 2007).

Distribution and somatodendritic morphology of calretinin-expressing neurons in the neocortex

CR+ neurons in neocortex are concentrated predominantly in cortical layers II and III, both in rodents and primates. The density of CR+ neurons decreases with increasing depth in neocortex and therefore they are quite rare in infragranular layers, when compared to the supragranular ones. The CR+ neurons most commonly possess bipolar or bitufted (two tufts of dendrites originating from the opposite cellular poles) vertically oriented somatodendritic morphology, with fusiform or oval perikaryon (Jacobowitz and Winsky 1991, Resibois and Rogers 1992, Glezer *et al.* 1992, Kubota *et al.* 1994, Conde *et al.* 1994, Fonseca and Soriano 1995, Leuba and Saini 1996, Gabbott and Bacon 1996a, Gabbott *et al.* 1997a,b, Meskenaite 1997, Park *et al.* 2002, Gonchar and Burkhalter 2003, Zaitsev *et al.* 2005, 2009, Desgent *et al.* 2005). The dendrites often extend to layer I superficially and to infragranular layers deeply. On the contrary, the dendritic tree is quite narrow in horizontal direction. Besides these bipolar neurons, other morphological types of CR+ neurons, most typically multipolar and horizontally oriented neurons, were consistently found in the neocortex in the majority of the above cited studies (Fig. 1).

Interareal and interspecies differencies

The distribution of CR+ neurons is similar but not absolutely homogenous among various neocortical areas. In owl monkey, CR+ neuronal density varies between individual areas with higher values in the visual cortices, lower counts in the prefrontal association cortex and the motor and premotor cortices and lowest counts in the primary somatosensory cortex (Elston and Gonzalez-

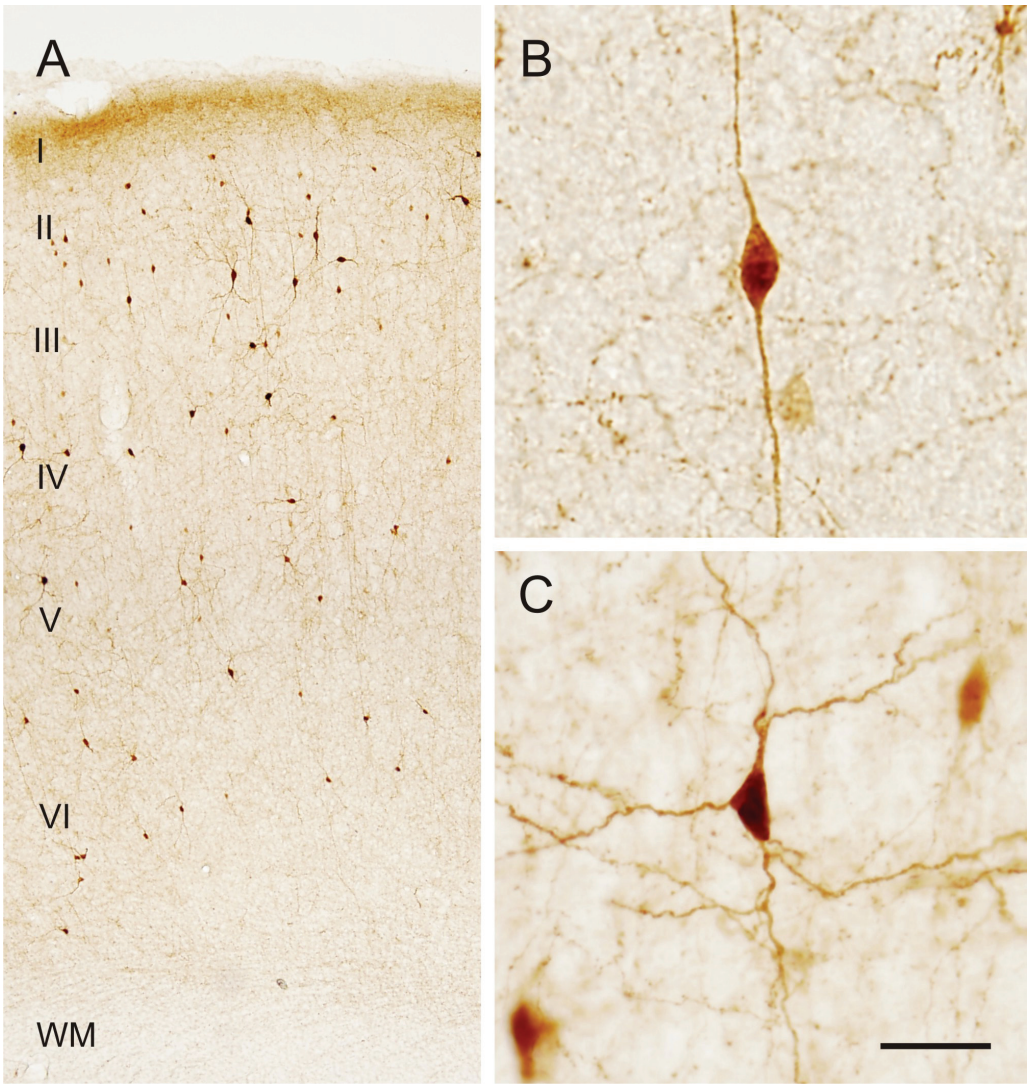

Fig. 1. Representative photomicrograph illustrating the distribution of calretinin-immunoreactive (CR+) neurons in neocortex of the rat **(A)**. Examples of typical bipolar **(B)** and multipolar **(C)** CR+ neurons. Scale bar = 200 μm in A and 25 μm in B and C; I–VI: cortical layers; WM: white matter.

Albo 2003). In human, although the general pattern of CR immunoreactivity was found to be similar in all inspected association areas, the density of CR+ neurons was significantly lower in the frontal than in the temporal, occipital and parietal association cortices (Hof *et al.* 1993, Barinka *et al.* 2009).

Gabbott and coworkers systematically described morphology and distribution of CR+ neurons in the medial prefrontal cortex (mPFC; Brodmann areas 24, 25 and 32) of the rat (Gabbott *et al.* 1997a), monkey (Gabbott and Bacon 1996a,b) and human (Gabbott *et al.* 1997b). Their work confirmed the overall resemblance of neocortical CR+ population among examined species. However, significant difference in overall CR+ neuronal counts between the rat neocortex on one hand and primate (monkey and human) on the other was documented. In mPFC, the CR+ neurons constituted 4 % of the total neuronal population in the rat, but 11 % in the monkey and 8 % in the human. Furthermore, the ratio between CR+, PV+ and CB+ cells in mPFC was found to be about 1.2 : 1.7 : 1 in the rat, but 2.2 : 1.2 : 1 in the monkey. These results correspond well with the findings of other authors (Conde *et al.* 1994, Kubota *et al.* 1994, del Rio and DeFelipe 1996, Gonchar and Burkhalter 1997, Tamamaki *et al.* 2003). Altogether, the CR+ neurons are significantly more numerous in primate frontal cortex when compared to rodents, both absolutely and relatively to the other GABA+ interneuronal types. This seems to be also true in other neocortical fields, e.g. in parietal and temporal associational areas (our unpublished observation in human and rat neocortex).

Connectivity and physiological properties of calretinin-expressing neurons

For determination of individual interneuronal types, the axonal targeting and the connectivity in general are the most relevant indicators (Markram *et al.* 2004). In case of CR+ neocortical neurons, the axon most typically originates from the body or one of the primary dendrites and then forms the descending main trunk with side branches with descending and ascending projection; the tangentially pointing branches are rare and the whole axonal tree usually does not extend beyond the width of the dendritic tree of that particular neuron. However, in vertical direction the axonal tree of one CR+ neuron often spans significant portion of the cortical thickness, in case of the neurons located in supragranular layers also extending to the layers IV, V and VI. It means that the most often found CR+ cells, which possess vertically oriented bipolar or bitufted dendritic branching, also have a similarly oriented axonal arbor (Conde *et al.* 1994, Fonseca and Soriano 1995, Gabbott and Bacon 1996a, Gabbott *et al.* 1997a,b, Meskenaite 1997, Gonchar and Burkhalter 1999, 2003, Zaitsev *et al.* 2005, Caputi *et al.* 2009). Therefore a possible role of these neurons could be to provide the inhibition of projection neurons within the cortical minicolumn and thus to synchronize their activity (Gabbott *et al.* 1997b). One special type of vertically oriented bitufted neurons with especially extensive vertical axonal arborisation (so-called horse-tail) extending deep to the infragranular layers are the double-bouquet cells. In primates, including human (but not in rodents), some of these neurons were found to express calretinin (Conde *et al.* 1994, del Rio and DeFelipe 1997a, DeFelipe *et al.* 1999).

Besides the CR+ neurons with vertically oriented axonal tree, cells with horizontal axonal arborisation (most often with multipolar dendritic morphology) have also been found (Meskenaite 1997, Gabbott *et al.* 1997b). Recently, two different types of CR+ neurons in layers II/III in the mouse neocortex were described (Caputi *et al.* 2009). The first type was the CR+ bipolar neuron with vertically arranged dendritic and axonal arbors, but the second type was multipolar with preferentially horizontal orientation of both the dendritic and the axonal arbors. The bipolar neurons also uniformly co-expressed VIP, which was not found in multipolar CR+ cell in this study. The two types clearly differ in electrophysiological characteristics as well (see below). It means that at least two significantly different populations of CR+ neurons exist in the neocortex (besides Cajal-Retzius cells, see below).

On the basis of their axon targeting, cortical interneurons can be divided into dendrite-targeting (with many subgroups), soma-targeting and axon-targeting interneurons. The CR+ neurons are mostly dendrite targeting, similarly as CB+ neurons, but unlike PV+ neurons which typically innervate soma or axon initial segment of pyramidal neurons. More precisely, the CR+ axonal boutons that form symmetrical GABAergic synapses typically innervate dendritic shafts and less often dendritic spines or somata (Meskenaite 1997). There are noteworthy interareal differences in types of postsynaptic cells innervated by CR+ neurons. While pyramidal neurons (especially their dendrites) were found to represent the main target of CR+ axons in all examined layers in the human temporal neocortex (del Rio and DeFelipe 1997b), the CR+ interneurons innervate mainly pyramidal neurons in infragranular, but preferentially other GABAergic interneurons in supragranular layers of the primary visual cortex (monkey – Meskenaite 1997, rat – Gonchar and Burkhalter 1999). Also in monkey prefrontal cortex, CR+ neurons innervate preferentially other GABAergic neurons in supragranular layers (Melchitzky and Lewis 2008). Therefore, it indicates that at least in some cortical areas and layers the CR+ neurons (by inhibiting other classes of inhibitory interneurons) may exert significant disinhibitory effect on the pyramidal neurons (Meskenaite 1997, Gonchar and Burkhalter 1999). Based on these observations, a "gating cell" function for the CR+ neurons – switching the flow of information between two pathways by inhibiting one of them and disinhibiting the other one – was suggested by Callaway (2004). Analogous situation was also described in the hippocampus, where CR+ interneurons were found to be specialized to control other interneuronal types (Gulyas *et al.* 1996). DeFelipe *et al.* (1999) found in the monkey visual areas that especially the CB+ neurons are densely contacted by CR+ axonal terminals. On the other hand, the large PV+ basket cells did not seem to be contacted by CR+ axonal terminals. Furthermore, the connectivity between the interneuronal populations is not unidirectional, because the CR+ neurons were also substantially innervated by PV+ and CB+ interneurons.

The CR+ interneurons are also innervated by the pyramidal cortical neurons. Interestingly, in the monkey prefrontal cortex, the density of excitatory inputs on CR+ dendrites in supragranular layers was found to be significantly lower (40-90 %) than on the PV+ dendrites

(Melchitzky and Lewis 2003). Similarly, in the visual areas of the rat, unlike the PV+ neurons, the CR+ neurons in layers II/III receive only sparse inputs from the feedback and feedforward excitatory connections (connecting primary and higher-order visual areas). On the contrary, the CR+ neurons in layer I are selectively targeted by feedback connections from higher-order visual areas (Gonchar and Burkhalter 2003).

The synaptic connections between individual interneurons of the same type were described in all interneuronal classes, including CR+ interneurons (Gabbott and Bacon 1996a, Gabbott *et al.* 1997a,b, Meskenaite 1997, Gonchar and Burkhalter 1999, Melchitzky *et al.* 2005, Melchitzky and Lewis 2008, Caputi *et al.* 2009). The inhibitory interneurons also form the so-called electrical synapses or gap junctions. These are preferentially formed between interneurons of the same class and were also found to connect the CR+ interneurons (Caputi *et al.* 2009). Together, the chemical and electrical synapses between CR+ interneurons synchronize the activity of interconnected neurons, which then form a neuronal assembly that consequently modulates the activity of other interneuronal classes as well as of the pyramidal neurons in cortical microcircuits.

While the GABAergic cortical interneurons preferentially form connections with neurons in their close proximity, sparse GABAergic cells with long-range cortico-cortical projections were also found in the neocortex (Peters *et al.* 1990). Interestingly, 14 % of GABAergic long-distance cortico-cortical neurons in the monkey were recently found to be CR+ (none of these neurons were PV+) (Tomioka and Rockland 2007). The exact physiological function of such long-range GABAergic neurons has not been elucidated so far, but various possibly important tasks have been proposed, e.g. synchronization of multiple local neuronal networks with otherwise weakly formed interareal connections (Buzsáki 2006).

In monkey prefrontal cortex it was shown that the CR+ neurons, unlike the other classes of GABAergic interneurons, are not contacted by dopamine terminals (Sesack *et al.* 1995). Nevertheless, they possess the D_5 dopamine receptors (Glausier *et al.* 2009), suggesting that the extrasynaptic dopamine transmission may influence CR+ cortical neurons. On the contrary, the VIP+ and CCK+ interneurons (the majority of which also express CR) were found to be selectively excited by nicotinic receptor stimulation in the rat neocortex (Porter *et al.* 1999).

Besides the above discussed GABAergic CR+ neurons forming inhibitory, symmetric synapses, non-GABAergic CR+ cells and asymmetric excitatory CR+ synapses were also described. In the human temporal neocortex, 26 % of CR+ neurons were found to be non-GABAergic (del Rio and DeFelipe 1996) and 31 % of synapses formed by the CR+ axon terminals were of the asymmetrical type and hence presumably excitatory (del Rio and DeFelipe 1997b). Very similarly, 23 % of CR+ cells were GABAergic and 29 % of synapses formed by the CR+ axon terminals were asymmetric in the monkey prefrontal cortex (Melchitzky *et al.* 2005). In the both cited studies, the CR+ axonal terminals which formed asymmetric synapses, contacted predominantly dendritic spines.

Electrophysiological properties of calretinin-expressing neurons

The PV+ interneurons are uniformly described as fast-spiking: in response to a depolarizing current injection, they show high-frequency firing of action potentials without marked accommodation (lowering) of firing frequency. On the other hand, the CR+ (and CB+) neurons belong to the non-FS cell types (interneurons exerting other than FS pattern). The non-FS interneurons are quite heterogeneous; various spiking patterns, which do not match exactly with expression of any calcium-binding proteins, have been described. In the rodent brain, the CR+ neurons were found to belong to the regular-spiking non-pyramidal (RSNP) cells or to burst-spiking non-pyramidal (BSNP) cells (Kawaguchi and Kubota 1997, Kawaguchi and Kondo 2002). Interestingly, in the already mentioned study (Caputi *et al.* 2009), the two different CR+ neuron types (bipolar and multipolar) in the mouse cortical layers II/III also differed in electrophysiological properties: the bipolar neurons showed bursting firing pattern, while the multipolar neurons had a regular firing pattern. It was suggested that the multipolar CR+ neurons together with one type of PV+ neurons form an interneuronal network which is able to drive synchronized inhibition of pyramidal neurons. In opposite, the bipolar CR+ neurons could act as “disinhibitory” neurons relieving pyramidal cells from inhibition.

In the rat neocortex, the CR+/VIP+ bipolar interneurons have also been described as irregular spiking (IS): an initial burst of action potentials is followed by intermittent action potentials (Cauli *et al.* 1997, 2000, Porter *et al.* 1998).

Toledo-Rodriguez *et al.* (2004) described four major clusters of ion channel genes co-expressed in cortical interneurons of the rat. Three of these clusters contained also one of the three calcium-binding proteins. The "CR cluster" expressed (besides CR) SK2, Kv3.4 and Caα1B ion channel subunits and was associated with accommodation of spiking pattern. The PV and CB clusters differed in both the expression of ion channel subunits and the electrophysiological properties (PV cluster was associated with fast spiking and CB cluster with bursting behavior).

The CR+ neurons were described as classic accommodating/adapting in the monkey prefrontal cortex, the pattern consistent with the RSNP in the rat (Zaitsev *et al.* 2005, 2009). These studies also confirmed a marked correlation between the expression of calcium-binding proteins and the electrophysiological properties of interneurons.

Cajal-Retzius cells

One "special" neuronal population which also expresses CR is formed by the Cajal-Retzius (CjR) cells. These cells differ significantly from the other CR+ neuronal types in various aspects: location exclusively in the first cortical layer, their glutamatergic phenotype, specific role in cortical layers patterning, etc. Interestingly, although the number of CjR neurons dramatically decreases in the early postnatal period and they probably completely disappear from the rodent cortex, in the higher mammalian orders, including primates, a small but significant population of CjR cells can be found also in the adult neocortex (Martin *et al.* 1999, Ábrahám *et al.* 2005). For more information, consult a recent review on CjR cells (Soriano and Del Rio 2005).

Calretinin-expressing neurons in neurologic and psychiatric disorders

The possible changes in expression of calcium-binding proteins in various neurological and psychiatric disorders were studied in detail by many authors. Interestingly, while the CB and especially the PV expression or the number of CB and/or PV expressing neurons decreases, the CR expression seems not to be affected under the conditions of schizophrenia, major depression, Alzheimer disease and multiple sclerosis (Hof *et al.* 1993, Fonseca and Soriano 1995, Beasley *et al.* 2002, Hashimoto *et al.* 2003, Clements *et al.* 2008). In various epileptic conditions, the CR expression or number of CR+ neocortical neurons was shown to be normal or decreased less prominently than the PV and CB expression (Garbelli *et al.* 1999, 2006, Zamecnik *et al.* 2006, Aronica *et al.* 2007, Barinka *et al.* 2009). Whether this "resistance" of CR+ neurons results from the proposed neuroprotective role of CR, or whether it is the specific position of these neurons in cortical microcircuits that protects them from deterioration, has not been sufficiently elucidated yet.

Conclusions

Calretinin plays a role in modulation of synaptic events and signal transduction in neuronal networks. The role of CR in other intracellular Ca^{2+}- sensitive processes and in neuroprotection is still unclear and remains to be defined. With some limitations, the calcium-binding proteins CR, PV and CB can be used as convenient markers for different populations of cortical interneurons, which has already been proved by gene expression profiling, electrophysiological as well as developmental studies. The CR expressing neurons increase in number significantly in primate neocortex, when compared to rodents. In primates, they are the most numerous interneuronal population. By inhibiting other interneurons, at least some of the CR+ interneurons are capable to exert disinhibitory effect on pyramidal neurons, a property not described in any other interneuronal population. The CR+ neurons which co-express VIP (and ChAT) probably play an important role in neurovascular coupling. Besides the majority of CR+ neurons utilizing GABA as a neurotransmitter, smaller proportion of CR+ neurons belongs to the non-GABAergic phenotype. Finally, the CR expressing neurons seem to be more resistant to various neuropathological conditions then the PV and CB interneuronal populations.

Conflict of Interest

There is no conflict of interest.

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References

ÁBRAHÁM H, TÓTH Z, BARI F, DOMOKI F, SERESS L: Novel calretinin and reelin expressing neuronal population includes Cajal-Retzius-type cells in the neocortex of adult pigs. *Neuroscience* **136**: 217-230, 2005.

ALLER MI, JONES A, MERLO D, PATERLINI M, MEYER AH, AMTMANN U, BRICKLEY S, JOLIN HE, MCKENZIE AN, MONYER H, FARRANT M, WISDEN W: Cerebellar granule cell Cre recombinase expression. *Genesis* **36**: 97-103, 2003.

ANDRESSEN C, BLUMCKE I, CELIO MR: Calcium-binding proteins: selective markers of nerve cells. *Cell Tissue Res* **271**: 181-208, 1993.

ARONICA E, REDEKER S, BOER K, SPLIET WG, VAN RIJEN PC, GORTER JA, TROOST D: Inhibitory networks in epilepsy-associated gangliogliomas and in the perilesional epileptic cortex. *Epilepsy Res* **74**: 33-44, 2007.

BAIMBRIDGE KG, CELIO MR, ROGERS JH: Calcium-binding proteins in the nervous system. *Trends Neurosci* **15**: 303-308, 1992.

BARINKA F, DRUGA R, MARUSIC P, KRSEK P, ZAMECNIK J: Calretinin immunoreactivity in focal cortical dysplasias and in non-malformed epileptic cortex. *Epilepsy Res* **88**: 76-86, 2010.

BEARZATTO B, SERVAIS L, ROUSSEL C, GALL D, BABA-AISSA F, SCHURMANS S, DE KERCHOVE D'EXAERDE A, CHERON G, SCHIFFMANN SN: Targeted calretinin expression in granule cells of calretinin-null mice restores normal cerebellar functions. *FASEB J* **20**: 380-382, 2006.

BEASLEY CL, ZHANG ZJ, PATTEN I, REYNOLDS GP: Selective deficits in prefrontal cortical GABAergic neurons in schizophrenia defined by the presence of calcium-binding proteins. *Biol Psychiatry* **52**: 708-715, 2002.

BERRIDGE MJ, LIPP P, BOOTMAN MD: The versatility and universality of calcium signalling. *Nat Rev Mol Cell Biol* **1**: 11-21, 2000.

BILLING-MARCZAK K, KUZNICKI J: Calretinin – sensor or buffer – function still unclear. *Pol J Pharmacol* **51**: 173-178, 1999.

BOUILLERET V, SCHWALLER B, SCHURMANS S, CELIO MR, FRITSCHY JM: Neurodegenerative and morphogenic changes in a mouse model of temporal lobe epilepsy do not depend on the expression of the calcium-binding proteins parvalbumin, calbindin, or calretinin. *Neuroscience* **97**: 47-58, 2000.

BUZSÁKI G: *Rhythms of the Brain*. Oxford University Press, Oxford, 2006.

CALLAWAY EM: Feedforward, feedback and inhibitory connections in primate visual cortex. *Neural Netw* **17**: 625-632, 2004.

CAPUTI A, ROZOV A, BLATOW M, MONYER H: Two calretinin-positive GABAergic cell types in layer 2/3 of the mouse neocortex provide different forms of inhibition. *Cereb Cortex* **19**: 1345-1359, 2009.

CARAFOLI E, SANTELLA L, BRANCA D, BRINI M: Generation, control, and processing of cellular calcium signals. *Crit Rev Biochem Mol Biol* **36**: 107-260, 2001.

CAULI B, AUDINAT E, LAMBOLEZ B, ANGULO MC, ROPERT N, TSUZUKI K, HESTRIN S, ROSSIER J: Molecular and physiological diversity of cortical nonpyramidal cells. *J Neurosci* **17**: 3894-3906, 1997.

CAULI B, PORTER JT, TSUZUKI K, LAMBOLEZ B, ROSSIER J, QUENET B, AUDINAT E: Classification of fusiform neocortical interneurons based on unsupervised clustering. *Proc Natl Acad Sci U S A* **97**: 6144-6149, 2000.

CAULI B, TONG XK, RANCILLAC A, SERLUCA N, LAMBOLEZ B, ROSSIER J, HAMEL E: Cortical GABA interneurons in neurovascular coupling: relays for subcortical vasoactive pathways. *J Neurosci* **24**: 8940-8949, 2004.

CLEMENTS RJ, MCDONOUGH J, FREEMAN EJ: Distribution of parvalbumin and calretinin immunoreactive interneurons in motor cortex from multiple sclerosis post-mortem tissue. *Exp Brain Res* **187**: 459-465, 2008.

CONDE F, LUND JS, JACOBOWITZ DM, BAIMBRIDGE KG, LEWIS DA: Local circuit neurons immunoreactive for calretinin, calbindin D-28k or parvalbumin in monkey prefrontal cortex: distribution and morphology. *J Comp Neurol* **341**: 95-116, 1994.

D'ORLANDO C, CELIO MR, SCHWALLER B: Calretinin and calbindin D-28k, but not parvalbumin protect against glutamate-induced delayed excitotoxicity in transfected N18-RE 105 neuroblastoma-retina hybrid cells. *Brain Res* **945**: 181-190, 2002.

D'ORLANDO C, FELLAY B, SCHWALLER B, SALICIO V, BLOC A, GOTZOS V, CELIO MR: Calretinin and calbindin D-28k delay the onset of cell death after excitotoxic stimulation in transfected P19 cells. *Brain Res* **909**: 145-158, 2001.

DEFELIPE J: Neocortical neuronal diversity: chemical heterogeneity revealed by colocalization studies of classic neurotransmitters, neuropeptides, calcium-binding proteins, and cell surface molecules. *Cereb Cortex* **3**: 273-289, 1993.

DEFELIPE J: Types of neurons, synaptic connections and chemical characteristics of cells immunoreactive for calbindin-D28K, parvalbumin and calretinin in the neocortex. *J Chem Neuroanat* **14**: 1-19, 1997.

DEFELIPE J, GONZALEZ-ALBO MC, DEL RIO MR, ELSTON GN: Distribution and patterns of connectivity of interneurons containing calbindin, calretinin, and parvalbumin in visual areas of the occipital and temporal lobes of the macaque monkey. *J Comp Neurol* **412**: 515-526, 1999.

DEL RIO MR, DEFELIPE J: Colocalization of calbindin D-28k, calretinin, and GABA immunoreactivities in neurons of the human temporal cortex. *J Comp Neurol* **369**: 472-482, 1996.

DEL RIO MR, DEFELIPE J: Double bouquet cell axons in the human temporal neocortex: relationship to bundles of myelinated axons and colocalization of calretinin and calbindin D-28k immunoreactivities. *J Chem Neuroanat* **13**: 243-251, 1997a.

DEL RIO MR, DEFELIPE J: Synaptic connections of calretinin-immunoreactive neurons in the human neocortex. *J Neurosci* **17**: 5143-5154, 1997b.

DESGENT S, BOIRE D, PTITO M: Distribution of calcium binding proteins in visual and auditory cortices of hamsters. *Exp Brain Res* **163**: 159-172, 2005.

DUN NJ, HUANG R, DUN SL, FORSTERMANN U: Infrequent co-localization of nitric oxide synthase and calcium binding proteins immunoreactivity in rat neocortical neurons. *Brain Res* **666**: 289-294, 1994.

EDMONDS B, REYES R, SCHWALLER B, ROBERTS WM: Calretinin modifies presynaptic calcium signaling in frog saccular hair cells. *Nat Neurosci* **3**: 786-790, 2000.

ELSTON GN, GONZALEZ-ALBO MC: Parvalbumin-, calbindin-, and calretinin-immunoreactive neurons in the prefrontal cortex of the owl monkey (Aotus trivirgatus): a standardized quantitative comparison with sensory and motor areas. *Brain Behav Evol* **62**: 19-30, 2003.

FAAS GC, SCHWALLER B, VERGARA JL, MODY I: Resolving the fast kinetics of cooperative binding: Ca^{2+} buffering by calretinin. *PLoS Biol* **5**: e311, 2007.

FAN X, WARNER M, GUSTAFSSON J-Å: Estrogen receptor β expression in the embryonic brain regulates development of calretinin-immunoreactive GABAergic interneurons. *Proc Natl Acad Sci USA* **103**: 19338-19343, 2006.

FONSECA M, SORIANO E: Calretinin-immunoreactive neurons in the normal human temporal cortex and in Alzheimer's disease. *Brain Res* **691**: 83-91, 1995.

GABBOTT PL, BACON SJ: Local circuit neurons in the medial prefrontal cortex (areas 24a,b,c, 25 and 32) in the monkey: I. Cell morphology and morphometrics. *J Comp Neurol* **364**: 567-608, 1996a.

GABBOTT PL, BACON SJ: Local circuit neurons in the medial prefrontal cortex (areas 24a,b,c, 25 and 32) in the monkey: II. Quantitative areal and laminar distributions. *J Comp Neurol* **364**: 609-636, 1996b.

GABBOTT PL, BACON SJ: Vasoactive intestinal polypeptide containing neurones in monkey medial prefrontal cortex (mPFC): colocalisation with calretinin. *Brain Res* **744**: 179-184, 1997.

GABBOTT PL, DICKIE BG, VAID RR, HEADLAM AJ, BACON SJ: Local-circuit neurones in the medial prefrontal cortex (areas 25, 32 and 24b) in the rat: morphology and quantitative distribution. *J Comp Neurol* **377**: 465-499, 1997a.

GABBOTT PL, JAYS PR, BACON SJ: Calretinin neurons in human medial prefrontal cortex (areas 24a,b,c, 32', and 25). *J Comp Neurol* **381**: 389-410, 1997b.

GALL D, ROUSSEL C, SUSA I, D'ANGELO E, ROSSI P, BEARZATTO B, GALAS MC, BLUM D, SCHURMANS S, SCHIFFMANN SN: Altered neuronal excitability in cerebellar granule cells of mice lacking calretinin. *J Neurosci* **23**: 9320-9327, 2003.

GARBELLI R, MERONI A, MAGNAGHI G, BEOLCHI MS, FERRARIO A, TASSI L, BRAMERIO M, SPREAFICO R: Architectural (Type IA) focal cortical dysplasia and parvalbumin immunostaining in temporal lobe epilepsy. *Epilepsia* **47**: 1074-1078, 2006.

GARBELLI R, MUNARI C, DE BIASI S, VITELLARO-ZUCCARELLO L, GALLI C, BRAMERIO M, MAI R, BATTAGLIA G, SPREAFICO R: Taylor's cortical dysplasia: a confocal and ultrastructural immunohistochemical study. *Brain Pathol* **9**: 445-461, 1999.

GLAUSIER JR, KHAN ZU, MULY EC: Dopamine D1 and D5 receptors are localized to discrete populations of interneurons in primate prefrontal cortex. *Cereb Cortex* **19**: 1820-1834, 2009.

GLEZER, II, HOF PR, MORGANE PJ: Calretinin-immunoreactive neurons in the primary visual cortex of dolphin and human brains. *Brain Res* **595**: 181-188, 1992.

GONCHAR Y, BURKHALTER A: Three distinct families of GABAergic neurons in rat visual cortex. *Cereb Cortex* **7**: 347-358, 1997.

GONCHAR Y, BURKHALTER A: Connectivity of GABAergic calretinin-immunoreactive neurons in rat primary visual cortex. *Cereb Cortex* **9**: 683-696, 1999.

GONCHAR Y, BURKHALTER A: Distinct GABAergic targets of feedforward and feedback connections between lower and higher areas of rat visual cortex. *J Neurosci* **23**: 10904-10912, 2003.

GONCHAR Y, WANG Q, BURKHALTER A: Multiple distinct subtypes of GABAergic neurons in mouse visual cortex identified by triple immunostaining. *Front Neuroanat* **1**: 3, 2007.

GONZALEZ-ALBO MC, ELSTON GN, DEFELIPE J: The human temporal cortex: characterization of neurons expressing nitric oxide synthase, neuropeptides and calcium-binding proteins, and their glutamate receptor subunit profiles. *Cereb Cortex* **11**: 1170-1181, 2001.

GROVES P, PALCZEWSKA M: Cation binding properties of calretinin, an EF-hand calcium-binding protein. *Acta Biochim Pol* **48**: 113-119, 2001.

GULYAS AI, HAJOS N, FREUND TF: Interneurons containing calretinin are specialized to control other interneurons in the rat hippocampus. *J Neurosci* **16**: 3397-3411, 1996.

GURDEN H, SCHIFFMANN SN, LEMAIRE M, BOHME GA, PARMENTIER M, SCHURMANS S: Calretinin expression as a critical component in the control of dentate gyrus long-term potentiation induction in mice. *Eur J Neurosci* **10**: 3029-3033, 1998.

HACK NJ, WRIDE MC, CHARTERS KM, KATER SB, PARKS TN: Developmental changes in the subcellular localization of calretinin. *J Neurosci* **20**: RC67, 2000.

HACKNEY CM, MAHENDRASINGAM S, PENN A, FETTIPLACE R: The concentrations of calcium buffering proteins in mammalian cochlear hair cells. *J Neurosci* **25**: 7867-7875, 2005.

HASHIMOTO T, VOLK DW, EGGAN SM, MIRNICS K, PIERRI JN, SUN Z, SAMPSON AR, LEWIS DA: Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. *J Neurosci* **23**: 6315-6326, 2003.

HOF PR, GLEZER, II, CONDE F, FLAGG RA, RUBIN MB, NIMCHINSKY EA, VOGT WEISENHORN DM: Cellular distribution of the calcium-binding proteins parvalbumin, calbindin, and calretinin in the neocortex of mammals: phylogenetic and developmental patterns. *J Chem Neuroanat* **16**: 77-116, 1999.

HOF PR, NIMCHINSKY EA, CELIO MR, BOURAS C, MORRISON JH: Calretinin-immunoreactive neocortical interneurons are unaffected in Alzheimer's disease. *Neurosci Lett* **152**: 145-148, 1993.

CHERON G, GALL D, SERVAIS L, DAN B, MAEX R, SCHIFFMANN SN: Inactivation of calcium-binding protein genes induces 160 Hz oscillations in the cerebellar cortex of alert mice. *J Neurosci* **24**: 434-441, 2004.

CHERON G, SERVAIS L, DAN B, GALL D, ROUSSEL C, SCHIFFMANN SN: Fast oscillation in the cerebellar cortex of calcium binding protein-deficient mice: a new sensorimotor arrest rhythm. *Prog Brain Res* **148**: 165-180, 2005.

ISAACS KR, DE ERAUSQUIN G, STRAUSS KI, JACOBOWITZ DM, HANBAUER I: Differential effects of excitatory amino acids on mesencephalic neurons expressing either calretinin or tyrosine hydroxylase in primary cultures. *Brain Res Mol Brain Res* **36**: 114-126, 1996.

ISAACS KR, WOLPOE ME, JACOBOWITZ DM: Vulnerability to calcium-induced neurotoxicity in cultured neurons expressing calretinin. *Exp Neurol* **163**: 311-323, 2000.

JACOBOWITZ DM, WINSKY L: Immunocytochemical localization of calretinin in the forebrain of the rat. *J Comp Neurol* **304**: 198-218, 1991.

KAWAGUCHI Y, KONDO S: Parvalbumin, somatostatin and cholecystokinin as chemical markers for specific GABAergic interneuron types in the rat frontal cortex. *J Neurocytol* **31**: 277-287, 2002.

KAWAGUCHI Y, KUBOTA Y: GABAergic cell subtypes and their synaptic connections in rat frontal cortex. *Cereb Cortex* **7**: 476-486, 1997.

KUBOTA Y, HATTORI R, YUI Y: Three distinct subpopulations of GABAergic neurons in rat frontal agranular cortex. *Brain Res* **649**: 159-173, 1994.

KUZNICKI J, ISAACS KR, JACOBOWITZ DM: The expression of calretinin in transfected PC12 cells provides no protection against Ca^{2+}-overload or trophic factor deprivation. *Biochim Biophys Acta* **1313**: 194-200, 1996.

LEMA TOME CM, BAUER C, NOTTINGHAM C, SMITH C, BLACKSTONE K, BROWN L, HLAVATY C, NELSON C, DAKER R, SOLA R, MILLER R, BRYAN R, TURNER CP: MK801-induced caspase-3 in the postnatal brain: inverse relationship with calcium binding proteins. *Neuroscience* **141**: 1351-1363, 2006.

LEUBA G, SAINI K: Calcium-binding proteins immunoreactivity in the human subcortical and cortical visual structures. *Vis Neurosci* **13**: 997-1009, 1996.

LUKAS W, JONES KA: Cortical neurons containing calretinin are selectively resistant to calcium overload and excitotoxicity in vitro. *Neuroscience* **61**: 307-316, 1994.

MAGISTRETTI PJ: VIP neurons in the cerebral cortex. *Trends Pharmacol Sci* **11**: 250-254, 1990.

MARINI AM, STRAUSS KI, JACOBOWITZ DM: Calretinin-containing neurons in rat cerebellar granule cell cultures. *Brain Res Bull* **42**: 279-288, 1997.

MARKRAM H, TOLEDO-RODRIGUEZ M, WANG Y, GUPTA A, SILBERBERG G, WU C: Interneurons of the neocortical inhibitory system. *Nat Rev Neurosci* **5**: 793-807, 2004.

MARTIN R, GUTIERREZ A, PENAFIEL A, MARIN-PADILLA M, DE LA CALLE A: Persistence of Cajal-Retzius cells in the adult human cerebral cortex. An immunohistochemical study. *Histol Histopathol* **14**: 487-490, 1999.

MELCHITZKY DS, EGGAN SM, LEWIS DA: Synaptic targets of calretinin-containing axon terminals in macaque monkey prefrontal cortex. *Neuroscience* **130**: 185-195, 2005.

MELCHITZKY DS, LEWIS DA: Pyramidal neuron local axon terminals in monkey prefrontal cortex: differential targeting of subclasses of GABA neurons. *Cereb Cortex* **13**: 452-460, 2003.

MELCHITZKY DS, LEWIS DA: Dendritic-targeting GABA neurons in monkey prefrontal cortex: comparison of somatostatin- and calretinin-immunoreactive axon terminals. *Synapse* **62**: 456-465, 2008.

MESKENAITE V: Calretinin-immunoreactive local circuit neurons in area 17 of the cynomolgus monkey, Macaca fascicularis. *J Comp Neurol* **379**: 113-132, 1997.

MOCKEL V, FISCHER G: Vulnerability to excitotoxic stimuli of cultured rat hippocampal neurons containing the calcium-binding proteins calretinin and calbindin D28K. *Brain Res* **648**: 109-120, 1994.

MOEWS PC, KRETSINGER RH: Refinement of the structure of carp muscle calcium-binding parvalbumin by model building and difference Fourier analysis. *J Mol Biol* **91**: 201-225, 1975.

PARK HJ, KONG JH, KANG YS, PARK WM, JEONG SA, PARK SM, LIM JK, JEON CJ: The distribution and morphology of calbindin D28K- and calretinin-immunoreactive neurons in the visual cortex of mouse. *Mol Cells* **14**: 143-149, 2002.

PARMENTIER M, PASSAGE E, VASSART G, MATTEI MG: The human calbindin D28k (CALB1) and calretinin (CALB2) genes are located at 8q21.3----q22.1 and 16q22----q23, respectively, suggesting a common duplication with the carbonic anhydrase isozyme loci. *Cytogenet Cell Genet* **57**: 41-43, 1991.

PETERS A, PAYNE BR, JOSEPHSON K: Transcallosal non-pyramidal cell projections from visual cortex in the cat. *J Comp Neurol* **302**: 124-142, 1990.

POCHET R, BLACHIER F, MALAISSE W, PARMENTIER M, PASTEELS B, POHL V, RESIBOIS A, ROGERS J, ROMAN A: Calbindin-D28 in mammalian brain, retina, and endocrine pancreas: immunohistochemical comparison with calretinin. *Adv Exp Med Biol* **255**: 435-443, 1989.

PORTER JT, CAULI B, STAIGER JF, LAMBOLEZ B, ROSSIER J, AUDINAT E: Properties of bipolar VIPergic interneurons and their excitation by pyramidal neurons in the rat neocortex. *Eur J Neurosci* **10**: 3617-3628, 1998.

PORTER JT, CAULI B, TSUZUKI K, LAMBOLEZ B, ROSSIER J, AUDINAT E: Selective excitation of subtypes of neocortical interneurons by nicotinic receptors. *J Neurosci* **19**: 5228-5235, 1999.

RESIBOIS A, ROGERS JH: Calretinin in rat brain: an immunohistochemical study. *Neuroscience* **46**: 101-134, 1992.

ROGERS J, KHAN M, ELLIS J: Calretinin and other CaBPs in the nervous system. *Adv Exp Med Biol* **269**: 195-203, 1990.

ROGERS JH: Calretinin: a gene for a novel calcium-binding protein expressed principally in neurons. *J Cell Biol* **105**: 1343-1353, 1987.

ROGERS JH: Immunohistochemical markers in rat cortex: co-localization of calretinin and calbindin-D28k with neuropeptides and GABA. *Brain Res* **587**: 147-157, 1992.

SESACK SR, BRESSLER CN, LEWIS DA: Ultrastructural associations between dopamine terminals and local circuit neurons in the monkey prefrontal cortex: a study of calretinin-immunoreactive cells. *Neurosci Lett* **200**: 9-12, 1995.

SCHIFFMANN SN, CHERON G, LOHOF A, D'ALCANTARA P, MEYER M, PARMENTIER M, SCHURMANS S: Impaired motor coordination and Purkinje cell excitability in mice lacking calretinin. *Proc Natl Acad Sci U S A* **96**: 5257-5262, 1999.

SCHURMANS S, SCHIFFMANN SN, GURDEN H, LEMAIRE M, LIPP HP, SCHWAM V, POCHET R, IMPERATO A, BOHME GA, PARMENTIER M: Impaired long-term potentiation induction in dentate gyrus of calretinin-deficient mice. *Proc Natl Acad Sci USA* **94**: 10415-10420, 1997.

SCHWALLER B: The continuing disappearance of "pure" Ca^{2+} buffers. *Cell Mol Life Sci* **66**: 275-300, 2009.

SCHWALLER B, DURUSSEL I, JERMANN D, HERRMANN B, COX JA: Comparison of the Ca^{2+}-binding properties of human recombinant calretinin-22k and calretinin. *J Biol Chem* **272**: 29663-29671, 1997.

SORIANO E, DEL RIO JA: The cells of Cajal-Retzius: still a mystery one century after. *Neuron* **46**: 389-394, 2005.

STEVENS J, ROGERS JH: Chick calretinin: purification, composition, and metal binding activity of native and recombinant forms. *Protein Expr Purif* **9**: 171-181, 1997.

TAMAMAKI N, YANAGAWA Y, TOMIOKA R, MIYAZAKI J, OBATA K, KANEKO T: Green fluorescent protein expression and colocalization with calretinin, parvalbumin, and somatostatin in the GAD67-GFP knock-in mouse. *J Comp Neurol* **467**: 60-79, 2003.

TOLEDO-RODRIGUEZ M, BLUMENFELD B, WU C, LUO J, ATTALI B, GOODMAN P, MARKRAM H: Correlation maps allow neuronal electrical properties to be predicted from single-cell gene expression profiles in rat neocortex. *Cereb Cortex* **14**: 1310-1327, 2004.

TOLEDO-RODRIGUEZ M, GOODMAN P, ILLIC M, WU C, MARKRAM H: Neuropeptide and calcium-binding protein gene expression profiles predict neuronal anatomical type in the juvenile rat. *J Physiol Lond* **567**: 401-413, 2005.

TOMIOKA R, ROCKLAND KS: Long-distance corticocortical GABAergic neurons in the adult monkey white and gray matter. *J Comp Neurol* **505**: 526-538, 2007.

TURNER CP, CONNELL J, BLACKSTONE K, RINGLER SL: Loss of calcium and increased apoptosis within the same neuron. *Brain Res* **1128**: 50-60, 2007.

VON ENGELHARDT J, ELIAVA M, MEYER AH, ROZOV A, MONYER H: Functional characterization of intrinsic cholinergic interneurons in the cortex. *J Neurosci* **27**: 5633-5642, 2007.

WINSKY L, NAKATA H, MARTIN BM, JACOBOWITZ DM: Isolation, partial amino acid sequence, and immunohistochemical localization of a brain-specific calcium-binding protein. *Proc Natl Acad Sci USA* **86**: 10139-10143, 1989.

WONDERS CP, ANDERSON SA: The origin and specification of cortical interneurons. *Nat Rev Neurosci* **7**: 687-696, 2006.

XU Q, DE LA CRUZ E, ANDERSON SA: Cortical interneuron fate determination: diverse sources for distinct subtypes? *Cereb Cortex* **13**: 670-676, 2003.

ZAITSEV AV, GONZALEZ-BURGOS G, POVYSHEVA NV, KRONER S, LEWIS DA, KRIMER LS: Localization of calcium-binding proteins in physiologically and morphologically characterized interneurons of monkey dorsolateral prefrontal cortex. *Cereb Cortex* **15**: 1178-1186, 2005.

ZAITSEV AV, POVYSHEVA NV, GONZALEZ-BURGOS G, ROTARU D, FISH KN, KRIMER LS, LEWIS DA: Interneuron diversity in layers 2-3 of monkey prefrontal cortex. *Cereb Cortex* **19**: 1597-1615, 2009.

ZAMECNIK J, KRSEK P, DRUGA R, MARUSIC P, BENES V, TICHY M, KOMAREK V: Densities of parvalbumin-immunoreactive neurons in non-malformed hippocampal sclerosis-temporal neocortex and in cortical dysplasias. *Brain Res Bull* **68**: 474-481, 2006.