Dendrites of Neocortical Pyramidal Neurons: The Key to Understand Intellectual Disability

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Abstract

Pyramidal neurons (PNs) are the most abundant cells of the neocortex and display a vast dendritic tree, divided into basal and apical compartments. Morphological and functional anomalies of PN dendrites are at the basis of virtually all neurological and mental disorders, including intellectual disability. Here we provide evidence that the cognitive deficits observed in different types of intellectual disability might be sustained by different parts of the PN dendritic tree, or by a dysregulation of their interaction.

Introduction

The father of modern Neuroscience, Santiago Ramón y Cajal, postulated that neocortical pyramidal neurons (PNs) might play an outstanding role for the accomplishment of higher cognitive functions. He defined these cells, representing the vast majority of neocortical neurons, the “psychic cells” (Cajal 1917). Despite his feeling of shame, aimed at counterbalancing the “audacity of language”, after more than a century we have to recognize that, once again, the claim of the great Spanish scientist was substantially right. On the same line of reasoning, it can be assumed that a functional derangement of PNs is the pathophysiological basis of the cognitive deficit observed in intellectual disability (Granato and De Giorgio 2014).

Intellectual disability (ID), previously referred to as mental retardation, is classically defined as a neurodevelopmental disorder with IQ below 70, although more complex definitions, based on poor adaptive functioning and reduced daily life skills, have been provided by the DSM-5 (American Psychiatric Association 2013) and the American Association on Intellectual Developmental Disabilities (Shogren and Turnbull 2010).

The present point of view deals with the anomalies of neocortical PNs, as observed in experimental studies reproducing known causes of ID, as well as in the brains of affected human individuals. Given that dendritic alterations are considered among the most relevant anatomical and functional counterparts of ID (Kaufmann and Moser 2000) and owing to the great extension and geometric complexity of the dendritic arborizations of PNs, we shall focus primarily on dendritic anomalies. Some excellent reviews cover exhaustively the relationships between dendritic alterations and ID (Kaufmann and Moser 2000, Dierssen and Ramakers 2006, Quach et al. 2021). Our purpose is to provide mechanistic insights into how the disruption of PN dendritic function contributes to the genesis of ID, with a special emphasis on the role of the different parts of the dendritic tree.

Dendrites Of Pns

PNs represent the majority of neocortical neurons and are distributed in all cortical layers except layer 1. Among PNs, the thick-tufted cells are the most thoroughly studied, provide the cortical output directed to subcortical structures, and can be found in the deep part of layer 5 (layer 5b (Spruston 2008, Ramaswamy and Markram 2015)). Thick-tufted PNs are characterized by a prominent apical dendrite
spanning all the way to the pial surface and terminating with a branching apical tuft, whose radium often equals (or exceeds) that of the basal dendrites (Fig. 1). Other classes of PNs are those of layer 2/3 (providing cortico-cortical associative and callosal projections) and those bearing a slender apical dendrite, mainly located in the superficial part of layer 5 (Krieger et al. 2017), see also Fig. 1 in (Shepherd 2013). Modified PNs projecting to the thalamus and claustrum reside in layer 6 (Thomson 2010).

The prototypical PNs, the thick-tufted cells of layer 5, display geometric differences among the basal, oblique, and apical dendritic domains that are clearly recognizable at a first glance (see Fig. 1). In a seminal paper published exactly thirty years ago, Alan Larkman provided a rigorous formal description of such branching pattern differences, pointing out, for instance, that basal dendrites branching points are close to the cell body, whereas intermediate branches of the apical tuft are relatively longer than distal ones (Larkman 1991). It is well known that the dendritic geometry impinges upon the functional properties of neurons (Mainen and Sejnowski 1996). Furthermore, different parts of the dendritic tree of layer 5 PNs are potentially involved in the microcircuitry of different cortical layers. Therefore, it is conceivable that basal and apical dendrites contribute differently to the cortical machinery during physiological cognitive tasks.

Regarding the connections, the basal dendrites receive feedforward input from the receptor surfaces through the thalamic relay. The ascending input is thought to be conveyed indirectly to the dendrites of layer 5 through the canonical cortical circuit (thalamus → layer 4 → layer 2/3 → layer 5 (Thomson and Morris 2002, Lübke and Feldmeyer 2007)). However, layer 5 neurons can be also contacted directly by thalamic afferents (Meyer et al. 2010, Constantinople and Bruno 2013). Conversely, most of the apical tuft of PNs lies in layer 1, where it receives feedback connections from higher cortical areas, conveying input related to attention, context, expectations (Coogan and Burkhalter 1990, Cauller 1995, Cauller et al. 1998). Together, the basal and apical dendritic arborization are in the ideal position to integrate bottom-up and top-down streams of information. The refinement of dendritic recording (Davie et al. 2006) made it possible to ascertain that action potentials can back propagate through the apical dendrite of PNs (Stuart and Sakmann 1994) and to shed light on the interplay between basal and apical dendrites. Using multiple patch-clamp recordings from the soma and the apical dendrite of layer 5 PNs, it has been demonstrated that the coincidence of a back propagated action potential generated at the soma and of an apical dendritic input is able to generate a dendritic calcium spike that, in turn, elicits a burst of somatic spikes (Larkum et al. 1999). This mechanism, originally called backpropagation-activated calcium spike firing (BAC firing) has been considered the electrophysiological basis of the top-down / bottom-up integration operated by a single PN (Larkum 2013). This idea was widened by Bill Phillips and Matthew Larkum, leading to the concept of “apical amplification”, the mean by which the information coming from the external world (bottom-up) is modulated by context-sensitive (top-down) information (Phillips et al. 2016, Phillips 2017). A role of the apical dendrite in cognition and consciousness has been also postulated by (LaBerge 2006). Recently, it has been demonstrated that apical dendritic potentials can gate sensory perception and that such a modulation depends on contextual information (Takahashi et al. 2020). A dysregulation of context-modulated sensory perception and learning abilities can represent a prominent feature of ID (Alevriadou et al. 2004, Carr et al. 2010, Murray et al. 2019).
As to the distribution of ion channels on the membrane of different dendritic compartments, it has been proposed that the apical tuft and basal dendrites are dominated by NMDA receptors and associated potentials, while a calcium initiation zone, located just beneath the apical tuft, is endowed with voltage gated calcium channels (Nevian et al. 2007, Larkum et al. 2009), Fig. 1). Moreover, the correct degree of coupling between basal and apical compartments would be ensured by hyperpolarization-activated HCN channels, responsible for the Ih current and densely distributed on the apical dendrite of PNs (Phillips et al. 2016). Interestingly, these ion channels are developmentally regulated (Atkinson and Williams 2009) and their dysregulation might be involved in the genesis of neurodevelopmental disorders (see below).

In the last years, a conspicuous line of research focused on the dual basal/apical organization of PNs. Changes in the apical amplification process have been implicated in the pathophysiology of several mental disorders, including schizophrenia (Phillips et al. 2016, Mäki-Marttunen et al. 2019). Furthermore, the integration of two different compartments with feedforward and feedback input seems to be ideally suited to bridge the gap between artificial intelligence and neuroscience, since there are similarities between deep learning algorithms and the functional subdivisions observed in PNs (Guerguiev et al. 2017).

Dendrites of pyramidal neurons are covered with spines, which receive most of synaptic inputs and are thought to play a central role in several functions, from electrical filter/isolation to synaptic and structural plasticity (reviewed in (Yuste 2011, Sala and Segal 2014)). The density and distribution of dendritic spines appear to be differently regulated in apical and basal dendrites of PNs during learning (Knafo et al. 2001), in response to hormones (Gould et al. 1990), and in experimental models of neurological illness (Perez-Cruz et al. 2011).

**Pn Dendritic Domains And Id**

From the features outlined above, it is clear that the extensive dendrites of neocortical PNs play a pivotal role in neural computation and higher functions. Therefore, the changes of PN dendrites appear to be central in the genesis of ID. Moreover, a disruption of the interplay between functionally distinct basal and apical compartments might contribute to the pathophysiology of several mental disorders, including ID. Here we focus on PN dendritic alterations in some of the most frequently observed genetic and non-genetic types of ID. Among genetically determined IDs, Down syndrome (DS), caused by trisomy of the human chromosome 21, besides representing the most commonly identified form (Sherman et al. 2007), can be also reproduced by murine models (Dierssen et al. 2001). Notably, dendritic alterations have been reported in both species (reviewed in (Benavides-Piccione et al. 2004)). Interestingly, in the cortex of individuals with DS, the branching of PN dendrites display a higher complexity during the first months of postnatal life, followed by a reduction of dendritic branches thereafter, and dendritic alterations were evident both in the apical and basal dendrites (Becker et al. 1986). In addition to these alterations in branching, a reduction of spine density has been reported in the apical dendrite of humans affected by DS (Suetsugu and Mehraein 1980). It should be noted, however, that PNs of the prefrontal cortex in a murine model of DS display an increased density of spines (Thomazeau et al. 2014). An augmented
number of dendritic spines is a consistent feature of a common inherited cause of ID, the fragile X syndrome (FXS), characterized by mutations of the FMRP, the protein encoded by the FMR1 gene (Bagni and Greenough 2005).

The most common form of nongenetic ID is the consequence of the exposure to alcohol in utero and is nowadays referred to as fetal alcohol spectrum disorders (FASD). Rodent experimental models of FASD allowed to clarify several aspects in the pathogenesis of ID, including those related to PN dendritic anomalies (Valenzuela et al. 2012). Experimental FASD might represent an interesting case of dissociation between dendritic anomalies of basal and apical compartments: after exposure to ethanol during the first week of postnatal life in rats, corresponding to the third trimester of gestation in humans, the basal dendritic branches of PNs are strongly simplified, both in the somatosensory and in the prefrontal cortex (Granato et al. 2003, Granato et al. 2012, Hamilton et al. 2010). Conversely, the spine density of layer 2/3 basal dendrites is not affected (Hamilton et al. 2010, De Giorgio and Granato 2015). Using the same experimental protocols, a specular alteration was observed in the apical dendrites, that featured normal branching properties along with a decreased spine density (Whitcher and Klintsova 2008, Granato et al. 2012, De Giorgio and Granato 2015). It is worth mentioning, however, that in other types of ID, such as congenital/neonatal hypothyroidism, the branching pattern of the apical dendrite is anomalous (Ipiña and Ruiz-Marcos 1986).

Pn Dendrite Physiology And Id

As noted above, active currents generated locally in the dendritic tree can play a fundamental role for the function of PNs. Disruption of dendritic potentials can be the signature of many neurological and mental disorders (Palmer 2014). In the experimental model of FASD, we have demonstrated that the generation of Ca\(^{2+}\) spikes in the apical dendrites of layer 5 PNs is strongly impaired (Granato et al. 2012). A derangement of dendritic Ca\(^{2+}\) signaling has been also reported in the murine model of FXS (Meredith et al. 2007) and might be part of a more complex set of dendritic channelopathies observed in this condition (Brager and Johnston 2014). Calcium spikes are required to induce synaptic plasticity (Kampa et al. 2006, Cichon and Gan 2015). In addition, they support the apical amplification mechanism described above, that in turn is thought to provide the neurobiological basis for context-sensitive perception and learning (Phillips 2017). Interestingly, shutting down the Ube3a protein leads to a selective defect of growth of PN apical dendrites (Miao et al. 2013). The deficiency of the Ube3a protein in humans is associated to the Angelman syndrome, a condition characterized by ID and whose murine model displays a deficit of contextual learning (Jiang et al. 1998). Besides a direct impairment of dendritic calcium electrogenesis, other factors can contribute to the anomalous function of the apical dendrite and to the genesis of ID. For instance, HCN channels, responsible for the Ih current, play a role in the interaction between the basal and the apical dendrites of PNs and some of their variants can be associated to ID (Marini et al. 2018). Another factor ensuring the communication between different dendritic compartments is represented by the backpropagation of axon potential along the apical dendrite. Loss of sodium channels sustaining the backpropagation can also lead to ID (Spratt et al.
Finally, PNs are inserted into a cortical microcircuit to which dendrite-targeting GABAergic interneurons provide a substantial contribution (Palmer et al. 2012). Furthermore, top-down projections from higher cortical areas can engage in a disinhibitory circuit by contacting inhibitory neurons (chiefly VIP-calretinin cells) that, in turn, synapse onto other inhibitory cells, thus activating PN dendrites. Such a disinhibitory circuit might represent part of the neuronal basis for the apical amplification, since it is ideally suited to be involved in recalling past experiences and exploiting contextual cues (Pi et al. 2013, Karnani et al. 2014). Interestingly, an increase in the number of calretinin interneurons has been reported both in a model of FASD and in the Ts65Dn model of DS (Granato 2006, Pérez-Cremades et al. 2010).

**Concluding Remarks**

Considering that PNs are the most abundant neuronal type of the cerebral cortex, and that they bear a massive dendritic tree, it turns out that the vast majority of neocortical volume is made by PN dendrites. In other words, the neocortex seems to be a “dendritic machine” and the involvement of PN dendrites in ID is quite obvious. Times are not yet mature, however, to classify ID according, for instance, to the PN dendritic domain involved, to the spine density, or to the specific interplay between inhibitory interneurons and PN dendrites. Although such a classification might prove useful to steer the clinical and therapeutic interventions, any effort in this direction appears to be challenging. In fact, ID is a permanent condition that is usually established early during neural development, often through intermediate phases showing transient features (see, for example, the dendritic hypertrophy observed in DS). Furthermore, some of the pathologic features might merely represent a byproduct, or a compensation attempt, of primary alterations. This might be the case for the increased number of potentially disinhibitory interneurons observed in DS and FASD.

Studies on PN dendrites in humans affected by ID are shadowed by technical limitations, in particular by the capricious Golgi staining. The refinement of recording and staining techniques, along with the increased possibility of modeling neurons and their dendrites, can help to improve the results of human investigations (Goriounova et al. 2018). Not to mention the fact that animal models of ID allow detailed *in vitro* and *in vivo* explorations of dendritic and spine function. Therefore, the collaboration among clinical, computational, and experimental neuroscientists will warrant a bright future for the research on ID and dendrites.

**Declarations**

**Authors’ contribution**

AG and AM conceived and wrote the manuscript

The authors declare that there is no conflict of interest

Uno de los hechos mejor apreciados entonces fue la revelación de la existencia constante en la corteza cerebral de batracios, reptiles, aves y mamíferos, del *corpúsculo piramidal*, que osé llamar, con audacia
One of the most appreciated facts at that time was the revelation of the constant existence in the cerebral cortex of batrachians, reptiles, birds and mammals, of the pyramidal cell, which I dared to call, with the audacity of language of which today I am a bit ashamed, the psychic cell.

Santiago Ramón y Cajal

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**Figures**

**Figure 1**

3D reconstruction of a thick-tufted PN of layer 5. On the left of the neuron there is the indication of the different sections of the dendritic tree. On the right the main regenerative events occurring in that dendritic domain, according to Larkum et al., 2009. Red: axon