Involvement of cortical fast-spiking parvalbumin-positive basket cells in epilepsy

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Abstract

GABAergic interneurons of the parvalbumin-positive fast-spiking basket cells subtype (PV INs) are important regulators of cortical network excitability and gamma oscillations, involved in signal processing and cognition. Impaired development or function of PV INs has been associated with epilepsy in various animal models of epilepsy, as well as in some genetic forms of epilepsy in humans. In this review, we provide an overview of some of the experimental data linking PV INs dysfunction with epilepsy, focusing on disorders of the specification, migration, maturation, synaptic function or connectivity of PV INs. Furthermore, we reflect on the potential therapeutic use of cell-type specific stimulation of PV INs within active networks and on the transplantation of PV INs precursors in the treatment of epilepsy and its co-morbidities.

Keywords

epilepsy; GABA; interneurons; parvalbumin; basket cells; fast-spiking cells; genes

Introduction

Epilepsy is one of the most common neurological disorders, affecting 0.5–1% of the general population (Theodore et al., 2006). Unfortunately, up to one third of patients with epilepsy remain refractory to current therapies, which generally aim to control seizures but not the factors leading to the emergence of pathological circuits. Uncovering the mechanisms underlying the development of epilepsy is therefore necessary and urgent to improve the treatment and the prognosis of patients with refractory epilepsy.

Epilepsy is a diverse disorder with over 40 recognized epileptic syndromes (Berg et al., 2010). It is characterized by the repeated occurrence of highly synchronized and unprovoked bursts of neuronal activity, known as seizures (McCormick and Contreras, 2001). Focal

seizures typically start in confined brain regions, and remain restricted to these areas (simple focal seizures) or spread to other brain regions (secondary generalization). By contrast, generalized seizures are characterized by the synchronous bi-hemispheric onset of epileptic activity on electroencephalograms (EEG). The mechanisms leading to these different types of seizures and epileptic syndromes still need to be clarified. However, recent genetic studies in patients with epilepsy, and the ongoing investigation of various animal models of epilepsy, have begun to shine light on some of the molecular and cellular determinants of epileptogenesis (the processes leading to epilepsy) and of ictogenesis (the process of seizure initiation).

Epileptogenesis is thought to involve progressive changes in gene expression, neuronal intrinsic properties, connectivity, network organization, astrocytic function and neuro-glial interactions that ultimately set up an imbalance between excitation and inhibition, leading to seizures (McNamara, 1994, Morimoto et al., 2004, Racine et al., 2002, Tasker et al., 1996). The initial trigger for this cascade of events can be an environmental insult (i.e. trauma, anoxia, infection, metabolic disturbances, febrile seizures, status epilepticus) or an intrinsic brain lesion (i.e. malformation, tumor, degeneration). However, in up to half of patients, no underlying cause can be found despite extensive investigations. In such situations, a genetic cause is often suspected and can sometimes be revealed by direct sequencing of candidate genes or by whole-exome/genome sequencing (as reviewed in (Sisodiya and Mefford, 2011)). The genetic etiologies of epilepsy are now recognized to be extremely diverse, including mutations in genes encoding ion channels, receptors, synaptic proteins, transcription factors, cell signaling factors, etc (as reviewed in (El Achkar et al., 2015, Sisodiya et al., 2007, Hani et al., 2015, Helbig, 2015)). The impact of such mutations on specific cell-types within epilepsy-prone networks must be investigated experimentally. Interestingly, recent advances in neurosciences methods, including genome editing to generate new mice models of epilepsy, and techniques such as paired and subcellular patch-clamp recordings, cell array recordings, optogenetics, *in vivo* electrophysiology and imaging technologies have begun to provide detailed descriptions of microcircuit function in both humans and animal models of epilepsy (see reviews: (Paz and Huguenard, 2015a, Rossignol et al., 2014)).

Appropriate brain function depends on highly interconnected and well-organized networks of inhibitory interneurons (INs) and excitatory projection pyramidal neurons (PNs). INs modulate the activity of PNs which transmit information between neuronal assemblies. Imbalances between these network components can give rise to disorders of brain function and neurological diseases, including epilepsy, schizophrenia and autism-spectrum disorder. Abnormalities of GABAergic inhibitory function have been observed in several genetic and experimental animal models of epilepsy and have been postulated to underlie epilepsy in some genetic forms of human epilepsy (see reviews (Powell, 2013, Rossignol, 2011)). Genetic mutations resulting in molecular and functional changes in GABA receptors (Faheem et al., 2014) or in the selective loss or functional impairment of GABAergic INs (Williams and Battaglia, 2013, Bender et al., 2012) may disrupt the regulation of local excitatory circuits, resulting in hyperexcitability of neuronal networks and contributing to epileptogenesis. Here, we review the progress in understanding the molecular factors that regulate cortical INs maturation, excitability, synaptic connectivity and integration within

cortical networks, and how the perturbation of these processes leads to epilepsy, with a focus on parvalbumin (PV)-positive fast-spiking (FS) cortical INs of the basket cell (BC) sub-type (referred to as PV INs in this review).

Cortical interneuron diversity

Glutamatergic neurons constitute ~80 to 90% of the neuronal populations within cortical circuits, whereas GABAergic neurons account for the remaining 10 to 20% (Chu and Anderson, 2015, Druga, 2009). Although the GABAergic INs are a minority, they play vital functions within cortical networks: they provide feed-forward inhibition of incoming thalamocortical afferents and local inhibition within cortical microcircuits; they help generate or regulate specific rhythmic network oscillations important for proper signal processing; and they determine the onset and duration of cortical plasticity periods.

INs are substantially diverse: more than 20 distinct inhibitory cell types have been identified in the cerebral cortex and in the CA1 area of the hippocampus in rodents (Zeisel et al., 2015, Lovett-Barron and Losonczy, 2014). They can be divided into several subtypes sharing specific characteristics pertaining to their morphology, distribution, histochemical marker expression, intrinsic physiological properties, and connectivity ((Ascoli et al., 2008, Somogyi and Klausberger, 2005, Kawaguchi and Kubota, 1997, Butt et al., 2005) and see reviews (Rossignol, 2011, Sultan et al., 2013, Rudy et al., 2011)).

Neocortical GABAergic INs can be classified into several basic types according to their morphology: basket cells, chandelier cells, Martinotti cells, bouquet cells, bipolar cells, neurogliaform cells, etc. (Markram et al., 2004, Benarroch, 2013). They can also be classified based on their marker expression. About 40% of INs are PV-expressing cells, including basket cells and chandelier cells. About 30% of INs express somatostatin (SST), including the dendritic-targeting Martinotti cells, as well as other non-Martinotti cells, as described in the $X98$ and GIN^{EGFP} transgenic mice (Ma et al., 2006). The remaining ~30% of INs expresses the 5HT3A receptor, and includes bouquet cells and neurogliaform cells (Rudy et al., 2011, Lee et al., 2010). In addition, bipolar or bouquet cells frequently express vasointestinal peptide (VIP), and many of them also contain calretinin (CR). Most neurogliaform cells express reelin (see reviews: (Gelman and Marin, 2010, Rudy et al., 2011)).

Moreover, cortical INs differ in terms of their physiological properties, including their discharge patterns in response to depolarization (see reviews: (Fishell and Rudy, 2011, Druga, 2009, Rossignol, 2011)). PV-expressing basket cells and some chandelier cells are fast-spiking (PV-FS); they display high-frequency (>200 Hz) spike trains in response to depolarization, and have little spike frequency adaptation. The fast and high frequency discharges of PV-FS INs rely on the expression of the Nav1.1 voltage-gated sodium (Na^+) channels, several potassium (K^+) channels and calcium (Ca^{2+}) permeable AMPA receptors (Geiger et al., 1995). SST-expressing Martinotti cells show a low-threshold burst firing pattern and a higher resting membrane potential than PV-FS INs; they are more readily activated than PV-FS INs (Fanselow et al., 2008). Bouquet cells show irregular and adapting

spiking and high input resistance. Neurogliaform cells display a slow firing, late spiking firing pattern with slow adaptation (see reviews (Benarroch, 2013, Rossignol, 2011)).

In addition, different INs sub-types preferentially target distinct subareas of PNs, thus enabling a very efficient modulation of cortical activity. For instance, particularly interesting for this review, PV INs (BCs) make basket-like projections that target the soma and proximal dendrites of PNs, exerting a powerful inhibition of PNs excitability. By contrast, PV-positive chandelier cells project on the axonal initial segment (AIS) of PNs, thus modulating the output spike generation and spike timing of PNs. SST-positive Martinotti cells synapse on the dendrites of PNs, where they refine the glutamatergic inputs on cortical PNs and modulate the supralinear dendritic synaptic integration and plasticity of PNs (Lovett-Barron et al., 2012, Larkum, 2013). VIP-containing INs preferentially contact other subtypes of neocortical INs, in particular SST-, but also PV-positive INs, resulting in a net disinhibition of cortical PNs (Francavilla et al., 2015, Lee et al., 2013, Pi et al., 2013).

PV INs, which comprise 40–50% of GABAergic INs in the neocortex, constitute the dominant cortical inhibitory cell type in rodents (see review: (Rudy et al., 2011)). In addition, up to 30% of all INs in the hippocampus express PV (Bezaire and Soltesz, 2013, Katsumaru et al., 1988). Disorders of the specification or function of PV INs have been associated with epilepsy, which is why they will be the focus of this review. PV INs appear to be vulnerable to injury in chronic epileptogenic lesions of the neocortex (Drexel et al., 2011, Trotter et al., 2006, Zamecnik et al., 2006) and in the hippocampus (Andrioli et al., 2007, Scotti et al., 1997). Furthermore, as will be detailed in the following sections, genetic disorders altering the specification, migration, maturation, excitability and connectivity of PV INs have all been shown to cause seizures in rodents, and in some genetic human epilepsies (Figure 1).

Cell type specification

Neocortical GABAergic INs originate in the ventral pallium (ventral forebrain), including in the medial (MGE) and the caudal (CGE) ganglionic eminences, as well as in the preoptic area ((Xu et al., 2004, Anderson et al., 2001, Fogarty et al., 2007, Gelman et al., 2009) and see review: (Batista-Brito and Fishell, 2009)). INs migrate tangentially to the cortical plate, and reach their final destination after radial migration across cortical layers (Anderson et al., 1997a, Anderson et al., 2001).

The MGE generates 70% of all cortical INs, including the PV-positive and the SST-positive INs (Butt et al., 2005, Miyoshi et al., 2007). PV INs derived mainly from the ventral MGE whereas SST INs are preferentially derived from the dorsal MGE, a phenomenon likely mediated by the combinational expression of particular transcription factors within different subdomains of the MGE (Fogarty et al., 2007, Wonders et al., 2008). By contrast, the CGE produces approximately 25% of cortical INs (Butt et al., 2005, Miyoshi et al., 2010, Nery et al., 2002). All CGE-derived INs express the 5HT3A serotonin receptor (Lee et al., 2010). These INs include, amongst others, the VIP-positive INs, the bipolar CR-positive INs and the multipolar neurogliaform cells (Lee et al., 2010, Miyoshi et al., 2010, Miyoshi et al., 2015, Nery et al., 2002). The lateral ganglionic eminence (LGE) is the source of GABAergic

neurons to the striatum, amygdala and olfactory bulb, but does not produce cortical INs (Campbell et al., 1995, Batista-Brito et al., 2008, Wichterle et al., 2001, Wonders and Anderson, 2006, Anderson et al., 1997b, Waclaw et al., 2010).

The specification and the maturation of different sub-types of INs are tightly regulated, and some genes involved in these processes have been linked with epilepsy. The generation of MGE-derived INs relies on the serial expression of 5 important transcription factors: the *Dlx* homeobox genes *Dlx1/2* and *Dlx5/6*, the *NK2* homeobox 1 gene (*Nkx2-1*), the *LIM* homeobox protein 6 gene (*Lhx6*) and its downstream effector SRY-box 6 (*Sox6*) (see reviews: (Rossignol, 2011, Marín, 2012, Xu et al., 2004, Benarroch, 2013, Neves et al., 2013, Batista-Brito et al., 2009)).

The *Nkx2.1* transcription factor, which is expressed only in the MGE, is critical for the molecular specification of the MGE and for the generation of PV- and SST-positive INs (Sussel et al., 1999). Indeed, *Nkx2.1* loss at E10.5 leads to a re-specification of MGE-derived INs into CGE INs sub-types, with gross deficits in PV- and SST-positive INs and a gain of VIP- and CR-positive INs (Butt et al., 2008). This loss of MGE-derived INs results in severe seizures and early mortality within the first 3 weeks of life in *Nkx2.1* conditional mutants (Butt et al., 2008).

The *Lhx6* transcription factor, an effector of *Nkx2.1* (Du et al., 2008), also regulates the specification and the tangential migration of MGE-derived INs. *Lhx6* is expressed by MGE-derived INs as they leave the ventricular zone, and its expression persists into adulthood (Grigoriou et al., 1998). In *Lhx6*$^{-/-}$ mutant mice, the loss of *Lhx6* results in vastly decreased populations of PV- and SST-positive INs in the neocortex and hippocampus, with preserved total GABAergic INs numbers, suggesting a fate-switch phenotype (Liodis et al., 2007). *Lhx6*$^{-/-}$ mutant mice die before P21, most likely from seizures, although this was not formally studied. However, mice carrying an hypomorphic allele of *Lhx6* (*Lhx6*^{LacZ}) display a loss of PV INs in the dentate gyrus of the hippocampus and a widespread deficit of SST INs in the cortex and hippocampus, resulting in disinhibition and spontaneous seizures (Neves et al., 2013). Together, these data from the *Nkx2.1* and *Lhx6* mutant mice suggest that MGE-derived INs are particularly important in regulating cortical excitability and in preventing the development of seizures.

Migration

INs migrate to the cortical plate through the process of tangential migration, and invade the cortical plate using radial migration. The molecular cascades regulating the migration of INs have been extensively reviewed recently (Marin, 2013). Many genes involved in the regulation of INs migration have been linked to epilepsy in rodents and will be reviewed here.

Transcription factors regulating the migration of INs

As discussed above, *Lhx6* regulates INs cell-fate and defines MGE-subtypes of INs (Liodis et al., 2007, Neves et al., 2013). Furthermore, its expression persists in migrating INs and in most MGE-derived mature INs, suggesting that it serves additional roles in INs

development. Indeed, *Lhx6* is a major regulator of MGE-INs migration, both tangential and radial, and it controls the final laminar position and maturation of MGE-derived INs (Alifragis et al., 2004, Liodis et al., 2007, Neves et al., 2013). In *Lhx6*$^{-/-}$ mice, MGE-derived INs have a markedly delayed migration and tend to remain in the lateral cortical plate, failing to reach the medial cortex (Liodis et al., 2007). Furthermore, they fail to populate the middle cortical layers, and tend to remain in the superficial and deep cortical layers (I–II and VI) (Liodis et al., 2007). As stated above, *Lhx6*$^{-/-}$ mice develop epilepsy and die in the first few weeks of age.

The Sry-related HMG-box containing transcription factor *Sox6*, a downstream effector of *Lhx6*, is also expressed in MGE-derived INs as they initiate their migration, and its expression persists into adulthood (Batista-Brito et al., 2009). Conditional *Lhx6*^{Cre}; *Sox6*$^{F/F}$ mutant mice, carrying a targeted deletion of *Sox6* in MGE-derived INs, display a malposition of cortical MGE-derived INs, similar to the one observed in *Lhx6* mutant mice. Indeed, PV and SST INs fail to populate the middle cortical layers and tend to remain in superficial and deep layers. Furthermore, PV INs do not mature properly in *Lhx6*^{Cre}; *Sox6*$^{F/F}$ mutant mice: FS basket cells display a reduction of PV expression and have immature electrophysiological properties with lower firing rates (Batista-Brito et al., 2009). *Lhx6*^{Cre}; *Sox6*$^{F/F}$ mutant mice develop severe lethal seizures leading to death in the third or fourth post-natal week (Batista-Brito et al., 2009).

The Aristaless-related homeobox (*Arx*) transcription factor is one of the many genes up-regulated by *Lhx6* and is thought to mediate some of the effects of *Lhx6* on INs migration (Zhao et al., 2008). *ARX* mutations cause an X-linked disorder with epilepsy, intellectual disability and autism, with or without lissencephaly and agenesis of the corpus callosum in humans (Scheffer et al., 2002, Sherr, 2003). *Arx* plays multiple roles in brain development: it regulates neuronal proliferation and differentiation, as well as neuronal migration, and affects the development of both PNs and INs (Friocourt et al., 2006). In *Arx*$^{-/-}$ mice, CR-, neuropeptide Y- (NPY), and CB-positive INs are severely reduced while PV INs are relatively preserved (Friocourt and Parnavelas, 2010, Colombo et al., 2007, Kitamura et al., 2002). Conditional deletion of *Arx* in INs results in reduced cortical inhibition and epilepsy in hemizygous *Arx*$^{-/y}$; *Dlx5/6*^{CIG} male and in half of *Arx*$^{-/+}$; *Dlx5/6*^{CIG} female mice (Marsh et al., 2009).

The *Dlx* homeobox transcription factors are also major players in the regulation of INs development. *Dlx* genes are expressed in the sub-ventricular and mantle zones of the ganglionic eminences and in subsets of mature GABAergic INs. In particular, the *Dlx1/2* genes are expressed in most immature INs, and become restricted to subsets of SST-, NPY- and CR-positive INs in the post-natal cortex (Cobos et al., 2005b, Cobos et al., 2006). The *Dlx1/2* genes regulate the specification, migration and survival of forebrain INs (Cobos et al., 2007). Indeed, *Dlx1/2* double knock-out mice have a striking reduction of cortical INs (>75%) and of hippocampal INs (>95%), with a near complete blockade of INs migration out of the ventral telencephalon (Anderson et al., 1997a). *Arx* is activated by the *Dlx2* transcription factor (Colasante et al., 2008) and *Dlx1/2*$^{-/-}$ mutant mice show a severe reduction of *Arx* expression in ventral forebrain structures (Cobos et al., 2005a). Interestingly, the INs migration defect observed in *Dlx1/2* mutant mice can be rescued *in*

vitro by the overexpression of the *Arx* gene, suggesting that *Arx* is a major mediator of the effects of *Dlx2* on INs migration (although *Arx* does not rescue the INs specification defect associated with the loss of the *Dlx1/2* genes) (Colasante et al., 2008).

Dlx1/2 genes also induce the expression of the *Dlx5/6* transcription factors in the LGE and MGE sub-ventricular zones (Anderson et al., 1997a). Contrary to the *Dlx1/2* transcription factors, the *Dlx5/6* genes are considered to preferentially control the migration and maturation of PV INs. Indeed, *Dlx5/6*$^{-/-}$ mutant mice display a significant delay in migration of MGE-derived *Lhx6*-positive INs in the deep and superficial migratory streams, partly due to a loss of the Cxcr4 receptor (Wang et al., 2010). This results in reduced numbers of cortical PV INs, and in an altered morphology of the surviving PV INs (increased dendritic branching) (Wang et al., 2010). *Dlx5/6*$^{-/-}$ mutant mice die prenatally and cannot be assessed for epilepsy. However, the heterozygous *Dlx5/6*$^{+/-}$ mice, which have normal numbers of cortical INs but altered cortical inhibition, develop spontaneous electrographic seizures and have a reduced power of cortical gamma oscillations (Wang et al., 2010), implying a dysfunction of PV INs.

Chemotaxis of INs towards the cortical plate

On their way to the cortical plate, INs are influenced by a variety of chemoattractive and chemorepulsive cues. For instance, as they exit the ganglionic eminences, migrating INs start expressing *Sip1*, which represses the expression of the Unc5b receptor that otherwise prevents INs from leaving the ventral telencephalon (van den Berghe et al., 2013). Conditional mutant mice carrying a targeted deletion of *Sip1* in most of the ganglionic eminences (*Gsh2*^{Cre}; *Sip1*$^{fl/fl}$) have a striking reduction in cortical INs and develop spontaneous myoclonic seizures in the first few weeks of life (van den Berghe et al., 2013). Furthermore, neuregulin-1 (NRG1), a trophic factor, exerts short and long-range attraction on INs migrating towards the cortical plate by activating its receptor ErbB4 expressed by migrating INs (Flames et al., 2004). *ErbB4* is one of the direct targets of *Lhx6* and its deregulation could contribute to the INs migratory phenotype in *Lhx6* mutants (Zhao et al., 2008). NRG1 signaling through its receptor ErbB4 also controls various aspects of PV INs function in mature cells, and has been implicated in epilepsy, as detailed in subsequent sections.

The urokinase plasminogen activator receptor (uPAR) (the mouse ortholog of the autism-susceptibility *PLAUR* gene) also appears to be a critical player for INs migration. Indeed, *uPAR*$^{-/-}$ mice show decreased numbers of INs in the parietal and anterior cingulate cortex, mainly affecting PV INs with relative preservation of CR+ and SST+ populations. *uPAR*$^{-/-}$ mice exhibit spontaneous seizures and increased susceptibility to pentylenetetrazol (PTZ)-induced seizures (Powell et al., 2003). The role of uPAR in INs migration had initially been attributed to its activation of the pleiotropic molecule hepatocyte growth factor/scatter factor (HGF/SF), a known INs mitogenic factor *in vitro* (Powell et al., 2001), and to the subsequent binding of HGF/SF to its receptor, MET (Powell et al., 2003). However, more recent evidence from the same authors suggests that MET is not expressed by migrating INs and that HGF/SF promotes the development of excitatory neurons, but not of INs (Eagleson et al., 2011). Therefore, the exact mechanisms by which *uPAR* facilitate INs migration *in vivo*

remain to be resolved. uPAR also appears to promote PV INs maturation since PV INs in the adult *uPAR*$^{-/-}$ mice show decreased GABA expression (in the C57BL/6J background) (Eagleson et al., 2005).

Semaphorins are important repulsive guidance cues involved in growth cone guidance, axonal pathfinding, fasciculation and branching of growing axons (de Wit and Verhaagen, 2003). Semaphorin signaling has also been implicated in the regulation of INs migration. Indeed, the semaphorins 3A and 3F secreted by the striatum repulse INs expressing the neuropilin-1 and neuropilin-2 receptors away from the striatum and towards the cortical plate (Marin et al., 2001, Nobrega-Pereira et al., 2008). Furthermore, the expression of some semaphorins is maintained post-natally, as is the case for Sema 3C and 3F in the cortex and hippocampus (Barnes et al., 2003). Interestingly, these semaphorins are reduced in the hippocampus after kainic acid (KA)-induced status epilepticus (SE), and this may contribute to axonal sprouting post SE (Barnes et al., 2003). *Sema3F*$^{-/-}$ mice display spontaneous seizures (Sahay et al., 2003), which may in part be due to alterations in the migration of INs.

The neuropilins 1 and 2 are semaphorin receptors and are important for INs migration. Whereas neuropilin 1 binds Sema3A, 3C and 3F (Renzi et al., 1999), neuropilin 2 binds Sema 3C and 3F, but only weakly Sema3A (Chen et al., 1997). Neuropilin 1 null mice (*Npn1*$^{-/-}$) are not viable. However, blocking neuropilin 1 expression (using dominant negative mutated proteins) (Marin et al., 2001) or function (using specific antibodies) (Tamamaki et al., 2003) results in altered INs migration, with most INs remaining in the striatum. Neuropilin 2 knock-out mice (*Npn2*$^{-/-}$) have a normal lifespan, but they display a severe disorganization of major fiber tracts, including hippocampal mossy fibers (Chen et al., 2000, Giger et al., 2000). Furthermore, *Npn2*$^{-/-}$ mice have reduced numbers of cortical and hippocampal GABA-, PV- and NPY- positive INs, decreased GABAergic synapses, enhanced susceptibility to KA- or PTZ-induced seizures and increased vulnerability to seizure-related death (Gant et al., 2009, Marin et al., 2001).

The glial derived neurotrophic factor (GDNF) and its receptor GFR α 1, also participate in the guidance of migrating PV INs. Specifically, they are involved in the early differentiation and migration of MGE-INs (Pozas and Ibanez, 2005), and they regulate the final distribution of PV INs (Canty et al., 2009). Although GFR α 1 knock-out mice are not viable, the GFR α 1 "cis-only" mutants, that lack the GFR α 1 receptor in cells that do not express the RET signaling receptor subunit (including INs), are viable. These mutants display hole-like regions devoid of PV-expressing cells in rostral and caudo-lateral cortical regions, in a neuronal activity-dependent fashion (ie. the size of these regions increases after optic nerve transection) (Canty et al., 2009). GFR α 1 "cis-only" mutant mice are more prone to PTZ-induced seizures (Canty et al., 2009).

Neuronal locomotion, neurite extension, neurite branching and nukleokinesis

The migration of INs also involves multiple regulators of neuronal locomotion, the dynamic process of INs migration (see review (Marin, 2013)). INs locomotion starts with the extension and branching of a leading process that probes the environment for guidance cues, followed by the stabilization of a main branch that will guide the INs forward (Lysko et al., 2011). These steps involve an active remodeling of the actin cytosqueleton, regulated by

various Rho-GTPAses, including RhoA, Rac1/Rac3 and cdc42 (Marin et al., 2010, Bellion et al., 2005, Tsai and Gleeson, 2005, Govek et al., 2011, Gallo and Letourneau, 2004, Valiente and Martini, 2009, Tivodar et al., 2015, Vidaki et al., 2012). The Rho-GTPAses are known to be deregulated following seizures in experimental models of epilepsy and in human surgical specimens from epilepsy patients (Zhang et al., 2015, Yuan et al., 2010, Dang et al., 2014). In addition, some of the guidance cues and trophic factors that promote the branching or directionality of the leading process of INs have been associated with epilepsy. For instance, neuregulin-1 (NRG1) is an attractant that promotes branch extension and guides INs on their migratory paths to the cortical plate (Flames et al., 2004).

The stromal-derived factor-1 (SDF1/CXCL12), a chemoattractant expressed in the meninges and in the subventricular/intermediate zones, is a key regulator of INs migration (Stumm et al., 2003, Borrell and Marin, 2006, Tiveron et al., 2006). SDF1/CXCL12 decreases the branching of the leading process of INs by stabilizing the microtubules within the leading process and the actin filaments at the leading process tip, resulting in increased migration speed (Lysko et al., 2014, Lysko et al., 2011). SDF1/CXCL12 acts on INs through its receptor Cxcr4 (Borrell and Marin, 2006). Conditional deletion of *Cxcr4* in MGE-derived INs causes their premature entry in the cortical plate and results in altered regional distribution of INs (Li et al., 2008). A recent study showed that the CXCR4 antagonist AMD3100 reverses some of the pathological landmarks of temporal lobe epilepsy (TLE) (aberrant neurogenesis and distorted dendritic morphology of newborn DG neurons), and that it significantly reduces the duration and frequency of chronic seizures in the intracerebroventricular KA model of epilepsy (Song et al., 2016). Interestingly, although *CXCR4* has not been formally associated with epilepsy in humans, we recently described a young child with severe early-onset epileptic encephalopathy carrying a *de novo* 2q22.2q21.3 chromosomal deletion encompassing the *CXCR4* gene (Michaud et al., 2014). The identification of additional patients carrying deletion or deleterious mutations of the *CXCR4* gene will be necessary to confirm this association with epilepsy.

The second step of INs locomotion is nukleokinesis, or the active movement of the nucleus. Nukleokinesis entails an initial movement of the centrosome in a swelling in the leading process, followed by the traction of the nucleus towards the centrosome. These processes rely on the reorganization of the microtubule network that surrounds the nucleus (the perinuclear cage) and extends between the nucleus and the centrosome. This step involves the action of various organizing complexes and motor proteins, some of which participate in the migration of both PNs and INs and have been linked with epilepsy. In particular, the microtubule-associated proteins (MAP) encoded by the *LIS1* and *DCX* genes have both been associated, in humans, with epilepsy and lissencephaly type I, a disorganization of cortical layers attributed to impairments of PNs migration (see recent review (Kato, 2015)). Neuropathological evidence suggests that mutations in these genes also impair the tangential migration of cortical INs (Marcorelles et al., 2010). Both proteins are known to interact with dynein and to mediate the coupling between the nucleus and the centrosome (Tanaka et al., 2004). Doublecortin, encoded by the *Dcx* gene, binds and stabilizes microtubules (Horesh et al., 1999). Knock-down of *Dcx* in the ganglionic eminences of rat embryos results in delayed migration of INs to the cortical plate (Friocourt et al., 2007). However, in $Dcx^{(-/Y)}$ hemizygous mutant male mice, PV INs numbers are intact, suggesting a normal migration of

INs. By contrast, PNs are disorganized in these animals, with abnormal lamination, altered dendritic morphology and enhanced excitability, suggesting that mechanisms other than disinhibition underlie the enhanced susceptibility to pharmacologically-induced epileptiform discharges in these animals (Bazelot et al., 2012).

Maturation and cell survival

The maturation of cortical PV INs involves the gradual expression of PV and glutamate acid decarboxylase 1 (GAD1), the acquisition of FS membrane dynamics, the progressive innervation of neuronal targets, the development of more complex dendritic morphology, and the development of perineuronal nets (PNNs). These processes are driven by the progressive expression of a variety of transcription factors, channels and membrane proteins (Doischer et al., 2008, Okaty et al., 2009), some of which have been linked with epilepsy, as reviewed here and in subsequent sections.

Maturation of PV INs: focus on the PNN

The PNNs are specialized extracellular matrix structures composed of hyaluronan (HA), link proteins, chondroitin sulfate proteoglycans (CSPGs), and tenascin-R (Tn-R), that surround the soma, dendrites, and AIS of neurons, and form stable structures around synapses, as reviewed in (Wang and Fawcett, 2012, Kwok et al., 2011). PNNs are found in almost all regions of the central nervous system (CNS), but they preferentially surround GABAergic PV INs (Soleman et al., 2013, Pollock et al., 2014). PNNs are critical regulators of synaptic plasticity and the development of PNNs has been linked with the timing of cortical plasticity periods and with epilepsy (see reviews: (Kwok et al., 2011, Dityatev and Fellin, 2008)). For instance, the progressive increase in the ratio of 4-sulfation/6-sulfation of chondroitin sulfate proteoglycans is required to enhance the expression of the transcription factor *Otx2* and to induce the functional maturation towards FS properties of PV INs. Reduction of this 4-sulfation/6-sulfation ratio by overexpressing 6-sulfated chondroitin sulfate proteoglycans impairs the maturation of PV INs and delays the closure of the visual cortical plasticity period (Miyata et al., 2012). Interestingly, *chondroitin 6-O-sulfotransferase-1 (C6ST-1)* transgenic (TG) mice, which overexpress chondroitin 6-sulfated chains and retain a decreased 4-sulfation/6-sulfation ratio, have abnormal PNNs formation, aberrant PV cell maturation and are more susceptible to KA-induced seizures (Yutsudo and Kitagawa, 2015). Furthermore, status epilepticus induces a striking loss of the integrity of the PNNs surrounding PV INs, including alterations in aggregan, HAPLN1 and HAS3 (McRae et al., 2012). These changes are presumed to impair INs function and to contribute to the process of epileptogenesis.

Ambient activity can also regulate the maturation of PV INs. Indeed, the levels of GAD67 and PV in INs have been shown to be activity-regulated and to correlate with the closure of the cortical plasticity periods. For instance, dark-rearing reduces the level of PV expression in the visual cortex and prolongs the visual plasticity period (Tropea et al., 2006). Interestingly, PV knock-out mice are more susceptible to PTZ-induced seizures (Schwaller et al., 2004). The exact mechanisms underlying seizure susceptibility in $Pv^{-/-}$ mice are

uncertain, but might reflect the critical role of PV as a calcium buffer that regulates calcium levels at the synapse and impacts on the dynamics of GABAergic neurotransmission.

Cell survival

A significant proportion of cortical PV INs undergoes programmed cell death during the early post-natal period, with a peak around post-natal day 7 in mice (Southwell et al., 2012). PV INs maturation and survival depends on the trophic support provided by astrocytes (as demonstrated in *Fgfr1^{f/f}; hGfap^{Cre+}* mice (Smith et al., 2014)) and on NMDA-signaling from ambient glutamate (Desfeux et al., 2010). However, the survival of PV INs appears to be mainly regulated by intrinsic cues, the nature of which remains to be determined (Southwell et al., 2012). Preliminary data suggests that PV INs survival is, at least in part, regulated by the *Mef2c* transcription factor in a cell-autonomous fashion (Jaglin et al., 2013). Interestingly, in humans, 5q14.3 chromosomal microdeletions and *MEF2C* point mutations cause early severe epileptic encephalopathy and intellectual deficiency with autistic features (Boutry-Kryza et al., 2015, Paciorkowski et al., 2013, Bienvenu et al., 2013).

In a similar fashion, mice lacking the *Dlx1* gene show an age-dependent selective loss of SST-, NPY-, CR- and RELN-expressing INs (but no changes of PV INs, as these cells do not express the *Dlx1* gene during post-natal ages) (Cobos et al., 2005b). The loss of INs is partly due to enhanced apoptosis of these cells between P21–P30. Furthermore, surviving bitufted INs have poorly differentiated dendrites (shorter total branch length and decreased branching), suggesting a role for *Dlx1* in INs maturation (Cobos et al., 2005b). The loss and aberrant maturation of INs in the *Dlx1^{−/−}* mice results in reduced GABAergic inhibitory transmission in the hippocampus and neocortex and induces epilepsy with generalized seizures (Cobos et al., 2005b). Interestingly, although PV INs appear to be spared in the *Dlx1^{−/−}* mutant mice, recent data suggests that the selective ablation or silencing of SST INs before P10 reduces the density of excitatory thalamic afferents on PV INs, therefore reducing the effective feed-forward inhibition within cortical networks (Tuncdemir et al., 2016). This alteration of PV INs recruitment by thalamocortical afferents might thus contribute to the epileptic phenotype observed in the *Dlx1^{−/−}* mutant mice.

Neuronal Excitability

Amongst the best-described epilepsy genes in human patients are various ion channels genes that encode primary determinants of membrane excitability (e.g., voltage-gated channels, inwardly rectifying ion channels, ligand-gated channels, ion transporters, and ion exchangers). Some of these genes are particularly important in the regulation of PV INs excitability and will be reviewed here.

Voltage-gated sodium channels

Mutations in the *SCN1A* gene, encoding the voltage-gated sodium channel Nav1.1, represent the most common genetic cause of sporadic Dravet's syndrome (DS) and of various forms of familial generalized epilepsy (Generalized Epilepsy with Febrile Seizures (GEFS+), isolated febrile seizures, etc) (Escayg and Goldin, 2010, Bozzi et al., 2012, Claes et al., 2003, Claes et al., 2001, Escayg et al., 2000). Nav1.1 is expressed in PV INs, clustered

at the AIS and sparsely distributed on the cell soma, and is absent from other INs sub-types (Ogiwara et al., 2007). Nav1.1 is also expressed at low levels on PNs, but *Scn1a* loss of function mutations predominantly affect the function of PV INs and do not significantly impair PNs function (Dutton et al., 2012, Yu et al., 2006). Indeed, $Scn1a^{+/-}$ mutant mice display a substantial reduction in sodium current density in hippocampal PV INs, associated with reduced threshold for febrile seizures, spontaneous seizures and premature death (Yu et al., 2006). In addition, mutant mice carrying a humanized *Scn1a* mutation (R1648H, $Scn1a^{rh}$ mice) display a striking alteration of PV INs intrinsic properties, with slower recovery from inactivation and greater use-dependent inactivation of sodium current, as well as decreased action potential (AP) firing rate, resulting in spontaneous generalized seizures and a reduced threshold for febrile seizures and flurothyl-induced seizures (Martin et al., 2010). By contrast, PNs appear largely unaffected in these mutants. Furthermore, the conditional deletion of *Scn1a* restricted to forebrain INs ($Dlx1/2^{Cre}; Scn1a^{fl/+}$) results in generalized seizures and premature death (Cheah et al., 2012). In addition, the conditional deletion of *Scn1a* in PV-positive populations results in reduced seizure threshold to flurothyl or febrile seizure, and induces spontaneous seizures in $Ppp1r2^{Cre}; Scn1a^{fl/+}$ mutant mice. By contrast, conditional deletion of *Scn1a* in PNs ($Emx1^{Cre}; Scn1a^{fl/+}$) does not cause epilepsy (Dutton et al., 2012). Interestingly, the cognitive deficits associated with *SCN1A* mutations have also been linked with impaired excitability of various populations of PV-positive neurons in the septum, hippocampus, amygdala and cortex, leading to disruption of critical network oscillations and altered network function (Bender et al., 2012, Bender et al., 2013, Han et al., 2012). Therefore, the pathogenesis of Dravet syndrome and other *SCN1A*-associated epilepsies is now largely attributed to PV INs dysfunction (Yamakawa, 2011), and therapies aiming at enhancing PV INs excitability are being actively sought for patients with these disorders (Baraban et al., 2013).

Voltage-gated potassium channels

Voltage-gated K^+ channels (Kv) play vital roles in the regulation of neuronal excitability by promoting membrane repolarization after action potentials, thereby shaping spike firing windows. Mutations in various Kv channels have been linked with epilepsy in humans, including *KCNA1* (Kv1.1), *KCNA2* (Kv1.2), *KCNB1* (Kv2.1), *KCNC1* (Kv3.1), *KCND3* (Kv4.3), *KCNQ2* (Kv7.2), *KCNQ3* (Kv7.3) and *KCNH1* (Kv10.1) (Soh et al., 2014, Smets et al., 2015, Saitsu et al., 2015, Syrbe et al., 2015, Eunson et al., 2000).

KCNA1 point mutations cause episodic ataxia with myokimia and variable epilepsy phenotypes in humans (Liguori et al., 2001, Zuberi et al., 1999, Eunson et al., 2000). In addition, $Kcna1^{-/-}$ mice, carrying a deletion of Kv1.1 channels, develop severe epilepsy (Smart et al., 1998). This phenotype has been partly attributed to an increased excitability of the hippocampal CA3 recurrent axon collaterals (Smart et al., 1998). However, in the cortex, Kv1.1 channels are expressed selectively at the AIS of PV INs (Goldberg et al., 2008). Kv1.1 channels dynamically regulate the firing behavior and dampen the excitability of layers II/III cortical PV INs near AP threshold (Goldberg et al., 2008). It is therefore possible that impaired cortical PV INs excitability also contributes to the epilepsy phenotype in $Kcna1^{-/-}$ mice, for instance by inducing rapid depolarization block in hyperexcitable PV INs.

Kv3 channels express delayed-rectifier type currents that promote AP repolarization and are critical determinants of neuronal high-frequency spiking behaviors (as reviewed in (Gan and Kaczmarek, 1998, Rudy et al., 1999, Rudy and McBain, 2001)). Kv3 channels containing Kv3.1 subunits are prominently expressed in cortical and limbic PV-FS INs (Chow et al., 1999, Rudy et al., 1999). *KCNC1* dominant-negative mutations have recently been associated with progressive myoclonic childhood epilepsy in humans (Muona et al., 2015). Kv3.1/3.3 knock-out mice have impaired thalamocortical oscillations and unstable slow-wave sleep (Espinosa et al., 2008). Although they do not display spontaneous seizures, they might have a decreased seizure threshold, but this was not formally tested. Kv3.2 subunits are also highly expressed in limbic and in deep-layer cortical PV INs, where they form heteromultimeric channels with Kv3.1 subunits (Chow et al., 1999, Tansey et al., 2002). Kv3.2-containing channels enable PV INs to sustain high-frequency firing rates (Lau et al., 2000). *KCNC2* mutations have not yet been associated with epilepsy in humans, but ongoing genome studies may reveal such mutations in the near future. Nonetheless, Kv3.2 null mice display decreased cortical inhibition and enhanced seizure susceptibility (Lau et al., 2000). Given the fundamental role of Kv3 channels in promoting high-frequency behaviors in fast-spiking PV INs, modulators of Kv3 potassium channels are actively being sought as potential therapeutic tools for patients with interneuronopathies (i.e. schizophrenia and perhaps epilepsy) (Rosato-Siri et al., 2015).

KCNQ2 mutations are known to cause a variety of epileptic disorders in humans, ranging from a benign form of neonatal seizures (benign familial neonatal epilepsy (BNFE)) due to *KCNQ2* haploinsufficiency, to a severe epileptic encephalopathy due to dominant-negative *KCNQ2* mutations (Bellini et al., 1993, Orhan et al., 2014, Weckhuysen et al., 2012, Weckhuysen et al., 2013, Kato et al., 2013, Saitsu et al., 2012a, Millichap and Cooper, 2012). *KCNQ2* encodes the Kv7.2 potassium channels. KCNQ channels mediate the M-current, a non-inactivating potassium conductance triggered near the AP threshold (Wang et al., 1998). KCNQ channels assemble as tetramers and, in most neurons, Kv7.2 often combines with Kv7.3 to form KCNQ2/3 heteromers (Cooper et al., 2000, Saganich et al., 2001, Wang et al., 1998). Dominant-negative *KCNQ2* mutations are often located in the voltage-sensor of pore domains of the channels, causing electromechanical uncoupling that prevents channel opening on depolarization (Millichap and Cooper, 2012). *KCNQ2* mutations are thought to cause epilepsy by inducing a hyperexcitability of excitatory neurons. Indeed, dominant-negative *Kcnq2* mutations in mice abolish M-currents and cause increased excitability, reduced spike-frequency adaptation and attenuated medium afterhyperpolarization in hippocampal CA1 PNs, resulting in epilepsy and cognitive impairment (Peters et al., 2005). Furthermore, conditional homozygote deletion of *Kcnq2* in PNs is sufficient to cause epilepsy in *Emx1^{Cre}; Kcnq2^{fl/fl}* mice (Soh et al., 2014). However, *Kcnq2* is also expressed in GABAergic INs, as was shown in different sub-population of hippocampal INs (both regular and PV-positive FS INs) (Grigorov et al., 2014, Cooper et al., 2001). In the hippocampus, Kv7 channels regulate interspike intervals of O-LM SST-positive INs (Lawrence et al., 2006). The roles of KCNQ channels in cortical INs remain uncertain. But since SST-INs mediate disinhibition by inhibiting PV INs in cortical layer IV (Xu et al., 2013, Cottam et al., 2013, Pfeffer et al., 2013), hyperexcitability or increased

spike-frequency of SST-INs might be predicted to result in cortical disinhibition in the thalamocortical recipient layer, and could contribute to seizure generation.

Mutations in the *KCNQ3* gene, encoding the associated subunit Kv7.3, have also been linked with epilepsy in humans, including with BNFE, benign familial infantile epilepsy (BFIE), and focal epilepsy with intellectual disability (Bellini et al., 1993, Miceli et al., 2015). The mechanisms underlying *KCNQ3*–associated epilepsy remain uncertain, but they do not involve hyperexcitability of pyramidal cells since *Emx1^{Cre}; Kcnq3^{fl/fl}* mutants do not develop epilepsy and have normal pyramidal cell properties (Soh et al., 2014). The impact of a *Kcnq3* deletion on INs must therefore be investigated.

Neuromodulators of Kv channels directly participate in the regulation of neuronal excitability, including of PV INs excitability (see review:(Cooper and Jan, 2003)). For instance, M1 acetylcholine receptor agonists, such as pilocarpine, inhibit the KCNQ2/Q3 channels (M-channels) and increase the excitability of cortical and CA1 PV INs. This, in turn, induces depolarization block in a significant proportion of PV INs, resulting in disinhibition and seizures (Yi et al., 2014, Yi et al., 2015). The pilocarpine-induced enhancement of PV INs excitability is prevented in *PV^{Cre}; M1^{fl/fl}* conditional knockout mice, which have reduced severity of pilocarpine-induced seizures compared to wild-type mice (Yi et al., 2015). Nonetheless, these mutant mice display cognitive impairment in tasks of novel object recognition and spatial memory (Yi et al., 2014). Of note, muscarinic agonists also robustly inhibit GABA release from cortical PV INs (Kruglikov and Rudy, 2008), compounding the effect of M1 activation on cortical disinhibition.

The brain-derived neurotrophic factor (BDNF) has been shown to decrease the excitability of PV INs in the rat dentate gyrus by activating an M-like current, presumably mediated by the KCNQ2/Q3 channels, thereby controlling PV INs resting membrane potential and excitability (Nieto-Gonzalez and Jensen, 2013, Holm et al., 2009). BDNF is significantly up-regulated following limbic seizures and may contribute to the pathogenesis of TLE (see review: (Scharfman, 2005)). BDNF also plays important roles in the regulation of the extent of PV INs innervation of PNs, as detailed in later sections of this review.

Synaptic connectivity

Synaptogenesis: GABAergic synapse formation and maturation

Loss or change of INs synaptic stability and organization can lead to disturbances in the excitation/inhibition balance and epilepsy. PV INs are critical to cortical local circuits. They are specialized to control cortical rhythms, and they regulate PNs spiking timely and precisely (Freund and Katona, 2007). PV INs respond to single-axon excitatory afferents much more strongly and rapidly than all other types of cortical neurons. They produce high-frequency trains of action potentials, and exert fast, stable and timed inhibitory output onto their target cells (Avermann et al., 2012, Sun et al., 2006). This ensures robust feed-forward inhibition and a resultant widespread cortical inhibition. PV INs are sufficient to generate network oscillations in the gamma frequency range that determine time windows for PNs activation (Cardin et al., 2009, Bartos et al., 2007, Sohal et al., 2009). These gamma oscillations are critical for adequate cortical processing (Cardin et al., 2009, Sohal et al.,

2009), and participate in the processes of attention and memory (Howard et al., 2003). Therefore, selective impairment of PV INs and gamma oscillations may contribute to the cognitive impairments associated with epilepsy (see review: (Holmes, 2015)).

Apart from direct inhibitory control on PNs, PV INs are also mutually connected by GABAergic synapses (Jiang et al., 2013, Tamas et al., 2000) and electrical synapses (Traub et al., 2001, Buhl et al., 2003, Amitai et al., 2002, Szabadics et al., 2001, Tamas et al., 2000). Electrical coupling of PV INs is critical for the generation of gamma oscillations. Indeed, the deletion of connexin-36, impairing gap junction formation, results in decreased power of CA1 gamma oscillations and enhanced sensitivity to PTZ-induced seizures in *Cx36* knock-out mice (Buhl et al., 2003, Jacobson et al., 2010). Moreover, PV INs can specifically form a large number of functional autapses (Jiang et al., 2015, Deleuze et al., 2014). The high connectivity amongst PV INs underlie their ability to synchronize their activity and to generate a coherent inhibitory output within cortical circuits (Bartos and Elgueta, 2012).

The pattern and extent of cortical PV INs innervation of PNs are tightly regulated by neural activity and experience (Baho and Di Cristo, 2012, Chattopadhyaya et al., 2004, Morales et al., 2002). Decreasing the activation of PV INs, either pharmacologically or by reducing afferent inputs with dark-rearing, results in a reduction of the pool of PNs innervated by each PV IN in the visual cortex (Baho and Di Cristo, 2012, Chattopadhyaya et al., 2004). Furthermore, the synaptic release of GABA regulates axonal pruning and GABAergic synapse elimination in the cortex (Wu et al., 2012). The maturation of cortical GABAergic innervation influences the onset and time course of cortical plasticity periods, as demonstrated for ocular dominance plasticity (Katagiri et al., 2007, Hensch and Fagiolini, 2005, Fagiolini and Hensch, 2000). In addition, some of the molecules involved in the activity-dependent maturation of GABAergic innervation have been associated with epilepsy and will be reviewed here.

Polysialic acid (PSA) is an elongated, linear polymer of α-2,8-linked sialic acid, preferentially attached to the neural cell adhesion molecule (NCAM) in vertebrates (Rothbard et al., 1982). This polyanionic and hydrated structure is central to the ability of NCAM and other adhesion molecules to induce intercellular attachment (Acheson et al., 1991, Fujimoto et al., 2001). PSA is involved in many processes entailing changes in cell shape or position, including neuronal migration, axonal fasciculation, axonal guidance, synaptogenesis and activity-dependent plasticity, as reviewed in (Di Cristo et al., 2007). PSA is central in the activity-mediated regulation of cortical GABAergic innervation. Indeed, the premature removal of PSA results in a precocious maturation of perisomatic innervation by PV INs, enhancing inhibitory transmission and causing an earlier onset of ocular dominance plasticity (Di Cristo et al., 2007). Interestingly, the selective ablation of NCAM during inhibitory synapse formation impairs axonal branching and synaptic bouton formation from PV INs (Chattopadhyaya et al., 2013). PSA-NCAM is upregulated in tissue from patients with medial temporal lobe epilepsy (MTLE) and in KA and kindling models of TLE (Le Gal La Salle et al., 1992, Mikkonen et al., 1998, Sato et al., 2002), possibly as a compensatory mechanism to favor stabilization of GABAergic innervation. Importantly, the PSA-NCAM assembly participates in neurotrophin signaling, as reviewed in (Ditlevsen et al., 2008). In particular, PSA-NCAM serves as a co-receptor for GDNF through its GFR α 1 receptor

(Paratcha et al., 2003). GDNF-GFR α 1 signaling participates in axonal growth and synapse formation (Ledda et al., 2007). GDNF is a potent anticonvulsant (Kanter-Schlifke et al., 2007) and PSA-NCAM-dependent GDNF signaling was shown to limit neuronal loss and epileptogenesis in the KA model of epilepsy (Duveau and Fritschy, 2010). Furthermore, the ablation of PSA-NCAM increases acute seizure susceptibility (but not the progression to chronic epilepsy) in the amygdala-kindling model of epilepsy (Pekcec et al., 2007). The degree to which this neuroprotective effect of PSA-NCAM/GDNF signaling relates to its roles in sustaining GABAergic innervation remains to be established.

BDNF and its receptor TrkB are implicated in regulating activity-dependent synaptic plasticity and long-term potentiation (LTP), presumably by enhancing synaptic transmission from more active afferents (Kang et al., 1996, Kang and Schuman, 1995, Korte et al., 1995, Figurov et al., 1996). The activity-dependent expression of BDNF also regulates the expression of GABA in PV INs and controls the levels of cortical inhibition onto PNs, as shown *in vitro* (Rutherford et al., 1997, Rutherford et al., 1998). *In vivo*, the overexpression of BDNF shifts the visual ocular dominance plasticity period to earlier ages, possibly through its effect on the regulation of the maturation of GABAergic innervation (Hanover et al., 1999). Such precocious maturation of inhibitory innervation might have detrimental consequences. BDNF expression is enhanced in the hippocampi of patients with TLE (Martinez-Levy et al., 2016) and excessive activation of TrkB by status epilepticus was shown to promote the development of TLE (Liu et al., 2013). BDNF-TrkB signaling has therefore been identified as an important therapeutic target in the prevention of epileptogenesis. Interestingly, impairing BDNF-TrkB signaling, by uncoupling Trkb from phospholipase C γ 1, prevents the emergence of epilepsy after status epilepticus (Gu et al., 2015). Whether this neuroprotective effect depends on BDNF-TrkB signaling in INs or PNs remains to be investigated.

Disorganization of PV INs innervation may also be a prominent feature of symptomatic epilepsies due to cortical lesions or cortical malformations. For instance, in the undercut (UC) model of chronic post-traumatic epileptogenesis, the inhibitory transmission from FS cells to excitatory regular-spiking (RS) neurons (PNs or spiny stellate neurons) in layer IV of the barrel cortex is impaired. This disinhibition probably reflects presynaptic alterations in FS cells as indicated by a decreased GABA release probability, increased synaptic failures, and a reduced number of presynaptic boutons (Ma and Prince, 2012). In a similar fashion, the prenatal irradiation mouse model of cortical dysplasia displays a significant impairment of the synaptic release properties from PV INs on RS neurons, as illustrated by higher failure rates, decreased connection probability, decreased transmitter release probability, and decreased axonal terminal boutons in biocytin-filled PV INs in the dysplastic cortex. The electrical coupling between PV INs in the dysplastic cortex is also impaired, as shown by a reduction in the connection rates and coupling coefficients (Zhou and Roper, 2014). Of note, cortical INs are less abundant in the dysplastic cortex, and the excitatory drive on surviving FS INs (presumed PV INs) is reduced, further contributing to the disinhibition phenotype (Zhou et al., 2009).

Synaptic function

The functional specification of PV INs is defined by their physiological intrinsic properties, including short membrane time constants, ultra-fast AMPA receptor conductance, an abrupt, non-adapting high-frequency firing; and by their synaptic connectivity and synaptic properties, partly determined by their expression of the P/Q-type $Ca_V2.1$ calcium channels, as reviewed in (Wang et al., 2002, Rossignol, 2011, Rudy et al., 2011). Many molecular determinants of PV INs synaptic function have been associated with epilepsy, and some of these players will be reviewed here.

GABA synthesis occurs via two isoforms of the glutamic acid decarboxylase (GAD) enzyme, GAD65 (*Gad2*) and GAD67 (*Gad1*), in mammals. Although both enzymes are usually expressed by GABAergic cells in an activity-dependent fashion, they differ in their age-dependent expression profile, in their sub-cellular localization and in their kinetics (see review (Pinal and Tobin, 1998)). GAD67, responsible for approximately 90% of GABA synthesis, predominates during early development and after injury, and is expressed both at the cell body and axonal terminals. GAD65 tends to be expressed later and is particularly abundant at nerve terminals where it participates in GABA synthesis under conditions of heightened synaptic activity (Tian et al., 1999). Gad67 constitutive knockout mice (*Gad1⁻/⁻*) do not survive past the perinatal period, but the *in vitro* investigation of hippocampal slices from these animals reveals decreased miniature inhibitory postsynaptic currents (mIPSC) amplitude and reduced levels of GABA in the synaptic cleft of inhibitory synapses (Lau and Murthy, 2012). Mutant mice carrying a heterozygous *Gad1* conditional deletion selectively in PV INs are viable and display substantial deficits in PV INs to PNs synaptic transmission, resulting in an enhancement of PNs excitability in the prefrontal cortex (Lazarus et al., 2015). Whether this deficit is sufficient to enhance seizure susceptibility remains to be investigated. However, constitutive GAD65 knockout mice (*Gad2⁻/⁻*), which do not display significant alterations in baseline mIPSC amplitudes or GABA level presumably due to compensation by GAD67, are more susceptible to PTZ and picrotoxin-induced seizures, suggesting an important role of GAD65 in contexts of high neuronal activity (Asada et al., 1996, Kash et al., 1997).

$Ca_V2.1$ P/Q-type calcium channels regulate neurotransmitter release at the majority of central synapses, but had been demonstrated to be particularly critical to sustain GABA release from PV INs (Zaitsev et al., 2007). Haploinsufficiency of the *CACNA1A* gene, encoding the α1 sub-unit of the $Ca_V2.1$ channels, causes epileptic encephalopathy with episodic ataxia in humans (Damaj et al., 2015, Allen et al., 2013, Jouvenceau et al., 2001). The loss of $Ca_V2.1$ channels can usually be compensated by a gain of function of $Ca_V2.2$ N-type calcium channels (Jun et al., 1999). However, we recently demonstrated that the targeted deletion of *Cacna1a* in MGE-derived cortical INs (*Nkx2.1^Cre; Cacna1a^c/c* mice) results in significant impairment of cortical PV INs synaptic function, with reduced connection probability to PNs and imprecise time-locking of IPSCs in PV INs to PNs pairs, despite compensation by N-type channels (Rossignol et al., 2013). By contrast, the synaptic function of SST INs was preserved in *SST^Cre; Cacna1a^c/c* mutants. We showed that this impairment of cortical and limbic PV INs synaptic function is sufficient to cause generalized epilepsy in *Nkx2.1^Cre; Cacna1a^c/c* mice (Rossignol et al., 2013). Interestingly, mutants

carrying a targeted *Cacna1a* deletion in cortical PNs (*Emx1^{Cre}; Cacna1a$^{c/c}$*) did not develop epilepsy, but displayed decreased cortical excitability. Joint removal of *Cacna1a* in cortical INs and PNs reduced the seizure severity, leading to brief generalized spike-wave absence seizures in *Nkx2.1^{Cre}; Emx1^{Cre}; Cacna1a$^{c/c}$* mice (Rossignol et al., 2013). Therefore, *Cacna1a*-associated epilepsy appears to be due, in part, to the specific cell-type requirement for Ca$_V$2.1 channels in PV INs and the resultant synaptic impairment of cortical PV INs in conditional *Cacna1a* mutants. Interestingly, mice carrying a later post-natal removal of *Cacna1a* restricted to PNs in cortical layer VI (*Cacna1a$^{Ntsr(-/-)}$*) were recently shown to have an enhancement of thalamocortical excitability and to display absence seizures, likely because the cortical excitability of PNs in other cortical layers was preserved (Bomben et al., 2016).

CASK mutations result in severe developmental delay, intellectual deficiency, microcephaly, ponto-cerebellar atrophy and epilepsy in humans (Moog et al., 2011, Najm et al., 2008, Saitsu et al., 2012b, Michaud et al., 2014). CASK is a membrane-associated guanylate kinase (MAGUK) with a conserved multidomain structure that includes a Ca2+/calmodulin-kinase domain, a PDZ and SH3 domain and a guanylate kinase domain (Hata et al., 1996). CASK plays a role in synaptic scaffolding and organization, by interacting with Mints, Veli/Mals and neurexins (Tabuchi et al., 2002, Butz et al., 1998, Hata et al., 1996). *Cask* knock-out mice are not viable due to severe respiratory failure. However, there is a net reduction of spontaneous inhibitory events (sIPSC) and a gain of excitatory events (sEPSC) in *Cask$^{-/-}$* neuronal cultures, suggesting that the loss of *Cask* results in an interneuronopathy (Atasoy et al., 2007).

STXBP1 (syntaxin-binding protein 1) mutations have also been linked with severe epileptic encephalopathy and intellectual disability in humans (Deprez et al., 2010, Hamdan et al., 2009, Mastrangelo et al., 2013, Saitsu et al., 2008). *Stxbp1b* mutant zebrafish develop epilepsy and behavioral impairment (Grone et al., 2016). Stxbp1/Munc18-1 interacts with the synaptic machinery (including SNARE proteins) and is a key regulator of vesicular fusion and neurotransmission (Shen et al., 2015). The exact mechanisms underlying *Stxbp1*-associated epilepsy remain to be resolved. However, the Mint-1 protein, which is preferentially expressed in cortical INs (Ho et al., 2003), interacts both with CASK and Munc18-2/stxbp1 (Butz et al., 1998) and the loss of Mint-1 selectively impairs GABAergic neurotransmission (Ho et al., 2003). Therefore, a GABAergic deficit might underlie the epilepsy associated with perturbations of the CASK/Mint-1/Stxbp1 complex.

Excitatory and inhibitory innervation of PV INs

NRG1, through its receptor ErbB4, regulates PV IN function in multiple ways. First, it increases the intrinsic excitability of PV INs by phosphorylating and inhibiting Kv1.1 channels, thereby decreasing the voltage threshold for action potential in PV INs (Li et al., 2012). Second, it enhances the formation of excitatory synapses on PV INs (Fazzari et al., 2010). Third, it promotes the voltage-dependent release of GABA from PV INs onto PNs (Chen et al., 2010, Woo et al., 2007, Wen et al., 2010, Del Pino et al., 2013). Finally, NRG1–ErbB4 signaling in PV INs also regulates the expression of GABA$_A$ receptor subunits at GABAergic synapses on hippocampal PNs (Okada and Corfas, 2004) and suppresses LTP in

PNs (Chen et al., 2010, Wen et al., 2010, Pitcher et al., 2011). NRG1 and ErbB4 are therefore critical regulators of PV INs excitability and function. In the cortex and hippocampus, *ErbB4* is selectively expressed in PV INs (Vullhorst et al., 2009, Woo et al., 2007, Yau et al., 2003). Mice with targeted deletion of *ErbB4* in PV INs (Pv^{Cre}; $Erbb4^{fl/fl}$) display a variety of cognitive behavioral impairments (hyperactivity, impaired working memory, deficits in pre-pulse inhibition and socialization) (Wen et al., 2010, Del Pino et al., 2013) and are more susceptible to PTZ- and pilocarpine-induced epilepsy (Li et al., 2012), as well as to kindling-induced seizures (Tan et al., 2012).

The density of thalamic afferents onto PV INs is also tightly regulated and is dependent on the integrity of SST INs before the second post-natal week. Indeed, SST INs are strongly activated by thalamocortical projections before P15, and they innervate PV INs and PNs broadly and equally at P6 (whereas they preferentially innervate PNs at P15) (Tuncdemir et al., 2016). Reducing the number of SST INs before the second post-natal week (in SST^{Cre}; *Rosa-DTA* mutants or in SST^{Cre}; $Satb1^{c/c}$ mutants) or impairing their ability to spontaneously release GABA in the extracellular space (SST^{Cre}; $Vgat^{c/+}$ mutants)results in a significant decrease of the thalamic innervation of PV INs (Tuncdemir et al., 2016). We previously demonstrated that $Dlx6^{Cre}$; $Satb1^{c/c}$ mutants, with similar reduction of cortical SST INs, develop epilepsy in the second post-natal week (Close et al., 2012), which might be partly attributable to a reduced excitatory drive on PV INs.

The remodeling of cortical circuits promoting a progressive enhancement of feed-forward inhibition may be a central phenomenon to compensate enhanced excitation within cortical networks in chronic epilepsy. For instance, in the transcortical freeze lesion (FL) rodent model of epilepsy, the increased excitatory connectivity onto PN seems to be partially offset by an increase in excitatory connectivity and a decrease in inhibitory connectivity onto layer V PV FS cells, ultimately resulting in a relative balance between excitation and inhibition in the affected cortical area (Jin et al., 2014). Interestingly, a similar enhancement of excitatory synapse strength on PV INs was noted in cultured neurons from mutant mice carrying a deletion of the neuronal activity-regulated pentraxin (*Narp*) gene (Chang et al., 2010). *Narp* is an activity-regulated immediate-early gene that is preferentially enriched at excitatory synapses on PV INs and that is up-regulated by seizure activity. Notably, $Narp^{-/-}$ mice show an increased sensitivity to kindling-induced seizures (Chang et al., 2010). Together, this data suggests that *Narp* is a critical component of network remodeling following seizures and that it functions by raising excitatory transmission onto PV INs, which rebalances network excitation/inhibition dynamics following seizures (Chang et al., 2010).

Functional networks

The emergence of new techniques to selectively stimulate specific neuronal populations, including optogenetics and DREADD technologies, has raised significant hopes that selective manipulation of INs might represent new therapeutic avenues to correct defective INs function underlying some neuropsychiatric and neurological disorders, including epilepsy (see reviews: (Roth, 2016, Urban and Roth, 2015, Bui et al., 2015, Paz and Huguenard, 2015b)). In this section, we will summarize how modulating the activity of PV INs within neural networks may contribute to the development or prevention of epilepsy.

In recent years, several research groups have used optogenetic manipulations of INs to control seizure activity in various animal models of epilepsy *in vivo* and *in vitro* (Wykes et al., 2016, Krook-Magnuson et al., 2013, Shiri et al., 2015, Shiri et al., 2016, Ewell et al., 2015, Yekhlef et al., 2015, Ledri et al., 2014, Ellender et al., 2014). However, whether the stimulation of PV INs actually prevents or favors seizure generation appears to depend on the specific neuronal state at the onset of stimulation, on the site of stimulation and on the particular seizure models studied.

In a variety of experimental models of epilepsy *in vitro*, PV INs have been shown to fire intensely before seizure onset, which might suggest that they prevent seizure initiation. But because they are able to synchronize network activity (as reviewed in (Avoli and de Curtis, 2011, Jiruska et al., 2013)), it has been suggested that, in some circumstance, enhanced GABAergic signaling might actually trigger seizures. In two different cortical slice models of focal epilepsy (low Mg^{2+} or focal NMDA application), PV INs have been shown to fire actively before seizure onset and to provide an inhibitory barrage to excitation in PNs, preventing seizure propagation (Cammarota et al., 2013, Trevelyan et al., 2006). A similar area of desynchronized firing, the so-called ictal penumbra that surrounds the ictal focus, has also been observed in human patients undergoing multiunit recordings, suggesting that similar inhibitory barrages also occur *in vivo* (Schevon et al., 2012). However, after a period of excessive excitation, PV INs undergo depolarization block and the ensuing failure of PV INs coincides with the onset of seizures (Cammarota et al., 2013). Although this data suggests that PV INs prevent seizure onset, Sessolo et al. showed that the selective optogenetic or electric activation of PV INs at the epileptogenic focus failed to prevent seizures, but rather induced post-inhibitory rebound spiking in PNs, promoting ictal generation in the NMDA slice model of epilepsy (Sessolo et al., 2015). Similarly, the optogenetic activation of PV INs in the entorhinal cortex induces low-voltage fast-onset epileptic discharges in the 4-aminopyridine slice model of epilepsy (Shiri et al., 2015, Yekhlef et al., 2015), a $GABA_A$ receptor-mediated seizure pattern usually attributed to the synchronous activity of GABAergic INs (Gnatkovsky et al., 2008). These low-voltage fast-onset epileptic discharges differ from the glutamatergic-driven hypersynchronous periodic discharges occurring after the application of the $GABA_A$ receptor antagonist picrotoxin, together with $GABA_B$ receptor blockage, or by the optogenetic stimulation of PNs (Shiri et al., 2016, Shiri et al., 2015). This suggests that the stimulation of PV INs might actually trigger specific types of seizure activity. Furthermore, the selective optogenetic activation of PV INs can generate excitatory GABAergic responses onto CA3 PNs, due to a reversal of the chloride equilibrium potential, as shown in hippocampal organotypic slices, a post-traumatic model of epileptogenesis (Ellender et al., 2014). In this preparation, PV INs optic stimulation triggers afterdischarges that propagate across hippocampal networks and that resemble the epileptic activity recorded during the clonic phase of limbic seizures. Together, these studies suggest that, at least in situation of enhanced excitability (low Mg^{2+}, local NMDA application and trauma), the coherent firing of PV INs may trigger seizures.

By contrast, PV INs appear critical in limiting the spread of seizures. Indeed, in cortical low Mg^{2+} cortical slices, PNs are recruited in spatially-restricted modules when the inhibitory barrage fails, leading to a slow progression of the epileptic activity in a step-wise fashion (Trevelyan et al., 2006). The speed of seizure progression inversely correlates with the

inhibitory drive (Trevelyan et al., 2007). Furthermore, the stimulation of PV INs distant from the seizure focus prevents ictal propagation and shortens the duration of seizures at the primary focus in the NMDA slice model, presumably by preventing the propagation of afterdischarges back to the ictal focus (Sessolo et al., 2015).

Despite these controversies on the precise role of PV INs in seizure initiation *in vitro*, on-demand optogenetic activation of hippocampal PV INs or cerebellum PV-expressing neurons (Purkinje cells and INs) *in vivo* decreases the duration of spontaneous seizures in a mouse model of TLE (Krook-Magnuson et al., 2014, Krook-Magnuson et al., 2013), suggesting that the stimulation of PV INs may indeed be an appropriate therapeutic avenue in epilepsy. Furthermore, the transplantation of MGE INs precursors in the cortex of young and adult mice has been shown to reduce or abolish seizures in genetic mice models of epilepsy (Baraban et al., 2009, Hunt et al., 2013, Sebe and Baraban, 2010).

Furthermore, given the central role of PV INs in regulating network activities and in promoting gamma oscillation within different neuronal networks (Buhl et al., 2003, Cardin et al., 2009, Sohal and Huguenard, 2005, Sohal et al., 2009, Traub et al., 2003, Vida et al., 2006, Wulff et al., 2009), and given the suggested implication of gamma oscillations in sustaining various cognitive processes such as information processing, attention and memory (Colgin et al., 2009, Howard et al., 2003, Sohal et al., 2009, Cardin et al., 2009, Fries et al., 2001), it has been postulated that an impairment of PV INs disrupting gamma oscillations may underlie some of the cognitive and behavioral deficits associated with epilepsy. Indeed, several studies have reported that a disruption of the excitatory drive onto PV INs can compromise network oscillations and lead to cognitive and behavioral phenotypes (Yu et al., 2015, Huang et al., 2016, Billingslea et al., 2014, Saunders et al., 2013). Therefore, together with its suggested therapeutic benefit in seizure control *in vivo*, the manipulation of PV INs could potentially be beneficial for the treatment of the co-morbidities of epilepsy. As a proof of concept, the transplantation of MGE-derived INs in genetic models of epilepsy has been shown to correct the behavioral and cognitive phenotypes in adult mice with genetic epilepsy (Hunt et al., 2013).

Perspectives

In conclusion, multiple evidence point to a disruption of the development or function of PV INs as a pathophysiological substrate to the development of epilepsy in various genetic and lesional models of epilepsy, as well as in some genetic forms of epilepsy in humans. While the role of PV INs in the prevention or initiation of seizures *in vitro* remains controversial, the selective stimulation of PV INs or the transplantation of MGE-derived INs precursors have shown significant promises as therapeutic avenues *in vivo*. Therefore, advances in optogenetic and related technologies providing precise temporal and spatial control over particular populations of INs might pave the way for the future use of selective PV INs stimulation in the treatment of patients with epilepsy, particularly in patients where genomic studies reveal mutations in genes known to regulate the development or function of PV INs.

Acknowledgments

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Biographies

E.R. is a clinician scientist at the CHU Ste-Justine, and an assistant professor in the Departments of Neurosciences and Pediatrics at the Université de Montréal. Her work focuses on the genetic basis of pediatric epileptic encephalopathies and on the cellular and network mechanisms underlying these disorders, with a focus on GABAergic interneuron development and function.

X. J. is a post-doctoral fellow, trained electrophysiologist, conducting *in vitro* physiological investigations of various genetic mouse models of epilepsy generated in the Rossignol laboratory.

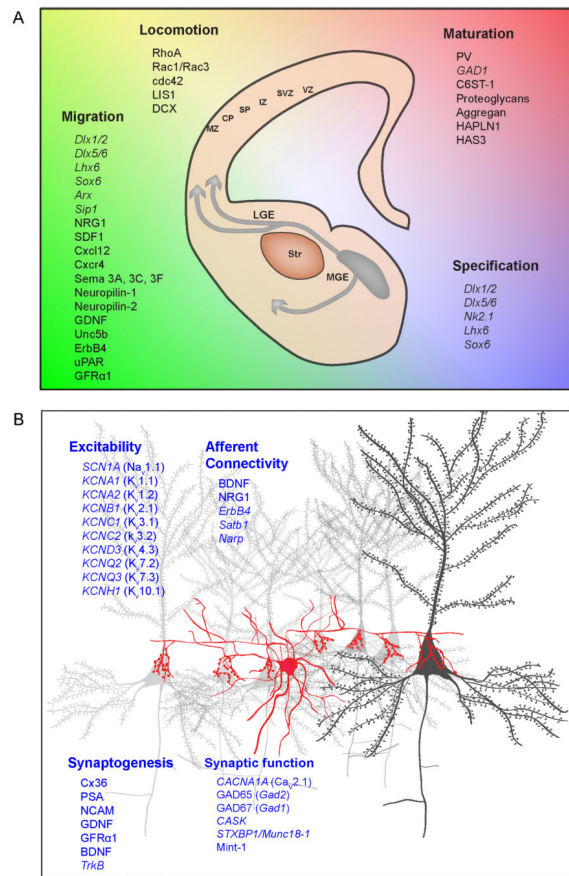M. L. is a research assistant in Dr Rossignol's laboratory.

Figure 1. Molecular determinants of the development and function of cortical parvalbumin-positive fast-spiking basket cells (PV INs) linked with epilepsy

A) Schematic representation of the migratory path of migrating INs from the medial ganglionic eminence (MGE) towards the cortical plate (CP). The MGE-derived INs, expressing the receptors neuropilin1 and 2, avoid the striatum that secretes repulsive semaphorins. Some of the molecular players involved in the control of the specification, migration (chemotaxis and locomotion) and maturation of PV INs that have been implicated in epilepsy are listed here (see text for details). B) Schematic representation of a PV IN basket cell (red) sending projections to the soma of multiple pyramidal cells (black and grey). Some of the sodium and potassium channels associated with epilepsy and governing neuronal excitability are listed here. Furthermore, genes and molecules involved in GABAergic synapse formation (synaptogenesis), synaptic function and afferent connectivity of PV INs are listed here (see text for details). MZ: marginal zone; CP: cortical plate; SP: sub-plate; IZ: intermediate zone; SVZ: sub-ventricular zone; VZ: ventricular zone; LGE: lateral ganglionic eminence; MGE: medial ganglionic eminence; Str: stiatum. See text for the abbreviations of genes and proteins listed here.