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Review

Gene-environment interactions in cortical interneuron development and dysfunction: A review of preclinical studies

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ABSTRACT

Cortical interneurons (cINs) are a diverse group of locally projecting neurons essential to the organization and regulation of neural networks. Though they comprise only ~20% of neurons in the neocortex, their dynamic modulation of cortical activity is requisite for normal cognition and underlies multiple aspects of learning and memory. While displaying significant morphological, molecular, and electrophysiological variability, cINs collectively function to maintain the excitatory-inhibitory balance in the cortex by dampening hyperexcitability and synchronizing activity of projection neurons, primarily through use of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Disruption of the excitatory-inhibitory balance is a common pathophysiological feature of multiple seizure and neuropsychiatric disorders, including epilepsy, schizophrenia, and autism. While most studies have focused on genetic disruption of cIN development in these conditions, emerging evidence indicates that cIN development is exquisitely sensitive to teratogenic disruption. Here, we review key aspects of cIN development, including specification, migration, and integration into neural circuits. Additionally, we examine the mechanisms by which prenatal exposure to common chemical and environmental agents disrupt these events in preclinical models. Understanding how genetic and environmental factors interact to disrupt cIN development and function has tremendous potential to advance prevention and treatment of prevalent seizure and neuropsychiatric illnesses.

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1. Introduction

Disrupted neocortical physiology underlies the neurobehavioral and/or psychiatric pathology associated with a number of common disorders such as epilepsy, schizophrenia, and autism. Though immensely complex, the neocortex is canonically organized along two primary axes: the horizontal laminae and the radial microcircuit columns. Microcircuits, the basic elements of sensory perception and cognition, are composed of functionally entwined excitatory pyramidal neurons and inhibitory interneurons. Pyramidal cells project their axons to distant regions of the cortex or to other parts of the brain and predominantly transmit signals using the neurotransmitter glutamate. Cortical interneurons (cINs), on the other hand, have short, locally connected axons and aspiny to sparsely spiny dendrites. These cells are primarily GABAergic and provide inhibitory input that modulates signal transmission of pyramidal cells (Dreifuss et al., 1969; Chu and Anderson, 2015). Dysfunction of cINs, which are largely responsible for regulating cortical excitability and synchronizing oscillatory activity, is strongly linked to the development of cognitive and behavioral deficits (Markram et al., 2004; Whittington and Traub, 2003; Klausberger and Somogyi, 2008; Wang et al., 2004).

Abnormalities in the neocortical excitatory-inhibitory balance, resulting from cIN defects, are extensively implicated in the pathophysiology of both seizure disorders and neuropsychiatric illnesses (Ongür et al., 2010; Yoon et al., 2010; Yizhar et al., 2011; Bissonette et al., 2014; Jacob, 2016; Hashemi et al., 2016; Konstantoudaki et al., 2016; Takano, 2015) (reviewed by Marín et al. and Inan et al., (Marín, 2012; Inan et al., 2013)). Increasing evidence supports the idea that cIN abnormalities underlie impairment of complex cognitive tasks, including working memory, sensory integration, and language skills. Though interactions between genetic and environmental influences are suspected to be etiologically culpable in the majority of cases of epilepsy, schizophrenia, and autism, previous examinations have focused primarily on the potential impact of these factors during the postnatal period (Van Os et al., 2008). However, several genetic mutations associated with these diseases disrupt the function of genes involved in cIN development (Fazzari et al., 2010; Wen et al., 2010; Cobos et al., 2005). Additionally, recent studies demonstrate that *in utero* exposure to a number of teratogens, such as alcohol, cigarette smoke, and cannabinoids, disrupts cIN development and results in behavioral abnormalities in animal models (Watson et al., 1999; Dufour-Rainfray et al., 2011; Trentini et al., 2016; Lussier and Stevens, 2016; Vargish et al., 2016; Canetta et al., 2016; Smiley et al., 2015). Intriguingly, there is also a growing body of epidemiological data linking human prenatal exposure to these factors to the development of seizure and neuropsychiatric illnesses later in life (Weissman et al., 1999; US Department of Health and Human Services, 2001; Landgren et al., 2010).

This review examines recent data from preclinical studies that support the emerging link between exposure to common chemical and environmental compounds during critical periods of neurodevelopment and cIN abnormalities associated with complex neuropsychiatric conditions. Though current understanding of cIN development remains incomplete, it is posited that genetic programs controlling cell fate are specified during early embryogenesis and modified by local signals during the post-mitotic maturation period when cINs are migrating and integrating into the cortical circuitry (Peyre et al., 2015; Brandão and Romcy-Pereira, 2015). Elucidating gene-environment interactions that disrupt these complex events should be a priority for developmental neuroscientists as solving this intricate etiological puzzle could usher in the development of evidence-based prevention strategies and treatments for myriad diseases.

2. Classification of cortical interneurons

Consistency in classification is vital for understanding how cINs behave within the neural circuitry and elucidating how their dysfunction may contribute to pathological states. Despite a concerted effort over the past two decades, advancement of a single unifying system has been stymied by the innate heterogeneity and often-overlapping phenotypic range of these cells (Battaglia et al., 2013; Kepecs and Fishell, 2014). The Petilla terminology, proposed by a distinguished group of scholars following an international summit in 2005, improved uniformity of nomenclature used to describe cIN subtypes, but clear groupings remain elusive and classification continues to be primarily descriptive (Ascoli et al., 2008).

Extrapolating from what is known about interneuronal specification in the spinal cord (Jessell, 2000), it was initially hypothesized that understanding the developmental origins of cINs would hold the key to defining cardinal classes (Puelles et al., 2000; Marin and Rubenstein, 2002; Flames and Marín, 2005). Accordingly, a primary focus of the field has been exploring how early specification events drive cIN diversity. While several distinct progenitor niches specified through unique transcriptional cascades have been identified, they do not completely account for the observed biological complexity (Peyre et al., 2015; Xu et al., 2004; Butt et al., 2005, 2008; Flames et al., 2007; Miyoshi et al., 2007; Wonders et al., 2008; Welagen and Anderson, 2011; Inan et al., 2012). Additionally, groups of similar cINs within the neocortex and hippocampus have disparate lineages, indicating that different progenitor niches may produce the same subtypes (Tricoire et al., 2010). These observations potentially stem from the presence of highly intricate genetic programs that precisely control cell fate or the remarkable ability of progenitors to respond adaptively to extrinsic influences.

Though no comprehensive classification system yet exists, it is still useful to broadly categorize cINs in terms of neurochemical composition, morphology, and connectivity. Since nearly all cINs express either the calcium-binding protein parvalbumin (PV), the neuropeptide somatostatin (SST), or the ionotropic serotonin receptor 5HT3aR, these markers are frequently used to delineate cINs (listed in Table 1) (Chu and Anderson, 2015; Kelsom and Lu, 2013; Rudy et al., 2011). The PV-expressing cells make up the largest group, accounting for roughly 40% of all cINs. Cells in this group are typically fast spiking and are often divided into two primary populations based on morphology: large basket cells and chandelier cells. Large basket cells tend to synapse at the soma or proximal dendrite of target cells located across multiple layers and are thought to be the dominant source of cortical inhibition (Cruikshank et al., 2007; Gabernet et al., 2005). Cells of the SST-expressing group account for about 30% of cINs, are mostly intrinsic burst spiking or accommodating, often target distal dendrites, and can be subdivided into two main groups: Martinotti and small basket cells (Markram et al., 2004). Lastly, the 5HT3aR-