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Early Actions of Neurotransmitters During Cortex Development and Maturation of Reprogrammed Neurons

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The development of the brain is shaped by a myriad of factors among which neurotransmitters play remarkable roles before and during the formation and maturation of synaptic circuits. Cellular processes such as neurogenesis, morphological development, synaptogenesis and maturation of synapses are temporary and spatially regulated by the local or distal influence of neurotransmitters in the developing cortex. Thus, research on this area has contributed to the understanding of fundamental mechanisms of brain development and to shed light on the etiology of various human neurodevelopmental disorders such as autism and Rett syndrome (RTT), among others. Recently, the field of neuroscience has been shaken by an explosive advance of experimental approaches linked to the use of induced pluripotent stem cells and reprogrammed neurons. This new technology has allowed researchers for the first time to model in the lab the unique events that take place during early human brain development and to explore the mechanisms that cause synaptopathies. In this context, the role of neurotransmitters during early stages of cortex development is beginning to be re-evaluated and a revision of the state of the art has become necessary in a time when new protocols are being worked out to differentiate stem cells into functional neurons. New perspectives on reconsidering the function of neurotransmitters include opportunities for methodological advances, a better understanding of the origin of mental disorders and the potential for development of new treatments.

Keywords: neurotransmitters, hiPSC derived neurons, cortex, GABA, glycine, glutamate, neurogenesis, neurodevelopmental disorder

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INTRODUCTION

The development of the brain cortex is an evolutionarily conserved process that starts during early embryonic stages and continues throughout childhood and adolescent all the way to adulthood (Kast and Levitt, 2019). In such a long process, there are plenty of events in which the developmental path can be altered and thus, the factors that influence the early stages of brain development

can have profound effects on the functioning of an otherwise normal brain. In this context, neurotransmitters are among the most important extracellular cues that control the development of the cortex. Remarkably, these classical communication molecules have been shown to participate in a range of cellular processes that include cellular division, differentiation, neurogenesis, migration, morphological development, synapse formation, synaptic pruning and circuit maturation.

Neurotransmitters are fundamental factors involved in neuronal communication. They are well known and continue to be studied for their role at synapses mediating the transmission of information throughout the entire nervous system. In this regard, undoubtedly synapses are central for the functioning of the brain. Thus, the last 40 years have seen a tremendous advance in our understanding of the role of neurotransmitters at the synapses (Snyder, 2009). However, neurotransmitters are, now for about two decades, beginning to be recognized as pleiotropic extracellular signaling molecules with roles that span far beyond synaptic communication (Ascenzi and Bony, 2017). More in detail, neurotransmitters can act on ionotropic or metabotropic receptors, being the response mediated by the ionotropic receptors in the order of milliseconds and more than 10-times faster compared to metabotropic receptors. This difference in the speed of action relates to their intrinsic properties. While ionotropic actions are based on the flux of ions through the membrane and the subsequent change on resting membrane potential (RMP), metabotropic actions are mediated by the activation of G proteins. Nevertheless, the activation of ionotropic channels can also lead to the activation of downstream signaling cascades that merge onto G protein-mediated signaling. This is particularly relevant during development when ionic gradients are being established and the actions of ionotropic receptors are pleiotropic.

Here, we discuss the role of the most relevant neurotransmitters γ-aminobutyric acid (GABA, glycine and glutamate) focused on the neurogenesis, and synapse development including what begins to be discovered using reprogrammed neurons. Moreover, to keep the length of this review to a reasonable extent and to appropriately cover the recent discoveries, we will focus on ionotropic receptors, the developing cerebral cortex and the models that are currently being put forward to understand this system.

NON-SYNAPTIC FUNCTIONS OF NEUROTRANSMITTERS DURING BRAIN DEVELOPMENT

Early experiments demonstrated that knocking out synaptic release machinery did not interfere with normal embryonic brain development in terms of axon targeting, layering and generation of gross morphological features (Verhage et al., 2000). However, before synapse formation, neurotransmitters are released by non-vesicular transport or through a process not requiring SNARE machinery (Demarque et al., 2002). Thus, although independently of vesicular release, we now know that neurotransmitters can have important effects in the structuring of the brain cortex.

$GABA_A$ Receptors

The GABA is arguably the most important neurotransmitter acting during embryonic development prior to synapse formation. Early experiments demonstrated that GABA was able to tonically activate neurons before synapse formation (Demarque et al., 2002). In line with this, early on it was found that GABA was able to inhibit DNA synthesis through the activation of $GABA_A$ receptors ($GABA_A$; LoTurco et al., 1995). More recently, similar findings have been described on retinal progenitors where more detailed analyses have linked the effects of GABA to the increase of intracellular calcium (Wang et al., 2019), which may as well be involved in the activation of CREB signaling (Jagasia et al., 2009).

Characteristically, both excitatory and inhibitory neurons of the cortex are born away from their final place having to migrate from the ventricular and subventricular zones where they are generated. For excitatory neurons, this means radial migration while for inhibitory neurons this involves a long road ahead in a process named tangential migration. In this context, GABA receptor activation was first found to exert a chemotropic effect on main cortical neurons (Behar et al., 1996). Additionally, it has been shown that activation of $GABA_A$ regulates radial migration at birth by affecting the dynamics of intracellular calcium of migrating neurons (Wang et al., 2003; Heck et al., 2007). Likewise, activation of $GABA_A$ at the rostral migratory stream during early postnatal development has been shown to modulate cell migration leading to the formation of the Islands of Calleja (Hsieh and Puche, 2015). Using the overexpression of a sodium channel as a tool to increase excitability and the frequency of calcium transients, it was found that precocious increase of calcium spikes induced migration arrest and the generation of neural processes (Bando et al., 2016). In line with that, a complementary approach increasing the expression of the potassium chloride transporter KCC2, the major extruder of Cl^- ions in mature neurons, leads to arrested morphological development of pyramidal neurons through the blockage of the excitatory action of GABA during embryonic development of the cortex (Cancedda et al., 2007). A similar role and mechanism of action involving $GABA_A$ activation was described on migratory interneurons (Cuzon et al., 2006; Bortone and Polleux, 2009). In this case, migrating interneurons were shown to be stimulated to migrate during early phases of tangential migration while, upon increased expression of KCC2, they responded to GABA with migration arrest and generation of secondary neurites (Bortone and Polleux, 2009). More detailed experiments aimed at understanding the downstream mechanisms of GABA, during morphological maturation in pyramidal cells and interneurons, have supported the notion that upon GABA receptor activation, the subsequent depolarization triggers the activation of L-type calcium channels, which ultimately affect neurite outgrowth (Maric et al., 2001; Bortone and Polleux, 2009).

On the mechanisms of GABA, a depolarization action linked to the downstream activation of voltage-dependent calcium channels surges as a transversal effect operating during