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Review article

Neuro-immune interactions across development: A look at glutamate in the prefrontal cortex

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ABSTRACT

Although the primary role for the immune system is to respond to pathogens, more recently, the immune system has been demonstrated to have a critical role in signaling developmental events. Of particular interest for this review is how immunocompetent microglia and astrocytes interact with glutamatergic systems to influence the development of neural circuits in the prefrontal cortex (PFC). Microglia are the resident macrophages of the brain, and astrocytes mediate both glutamatergic uptake and coordinate with microglia to respond to the general excitatory state of the brain. Cross-talk between microglia, astrocytes, and glutamatergic neurons forms a quad-partite synapse, and this review argues that interactions within this synapse have critical implications for the maturation of PFC-dependent cognitive function. Similarly, understanding developmental shifts in immune signaling may help elucidate variations in sensitivities to developmental disruptions.

Contents

1. Introduction

Neurodevelopment requires synchrony between multiple processes that must converge in a temporally and spatially specific manner to facilitate the proper formation of neural circuits. One process which has garnered much recent interest is the convergence between developing immune systems with the developing neural circuits (Garay and McAllister, 2010; Peng et al., 2007). The impetus for this research began with clinical studies demonstrating that perturbations in immune function could contribute to developmental disorders like autism and schizophrenia, suggesting that 1) development of one system influences the development of the other, and 2) dysfunction of one system impacts the function of the other (Brown, 2012; Carson et al., 2006; Chess, 1971; Michel et al., 2012). As understanding the intricacies of this bidirectional relationship in normal development must precede understanding the development of pathology, this review focuses on neuro-immune interactions in normal development with specific emphasis on

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glutamatergic synapses as a point of cross-talk between the development nervous and immune systems.

Rodent studies have provided an excellent basis for detailing the underlying mechanisms of this bidirectional relationship across both normal and pathological development and hence will be the focus of the current review. Although development is a continuum, rodent development will be sequestered into five broad developmental periods: *prenatal*, *pre-weanling*, *adolescent*, *adult*, and *aging* (see Spear, 2004, 2000 and Andersen, 2003 for review). In addition, as the phylogenetic age of various brain regions correlates with order of development such as phylogenetically older regions mature first, this review will specifically focus on a phylogenetically young region: the prefrontal cortex (PFC) (Andersen, 2003; Gogtay et al., 2004). The prefrontal cortex is critical for execution of a multitude of higher-order tasks (*e.g.* executive function, working memory) and has a protracted developmental trajectory with rapid maturation during adolescence. This late developmental trajectory of the prefrontal cortex has important consequences for cognition and behavior because structural maturation is concurrent with functional maturation: attention and executive function have delayed maturational periods which parallel the delayed maturation of the frontal lobe (Gogtay et al., 2004; Kolb and Nonneman, 1976; Kolb et al., 2012; Van Eden and Uylings, 1985). Therefore, appropriate convergence of neural and immune signals across the protracted maturation of the prefrontal cortex can have important consequences for the establishment of underlying circuitry and consequentially for the emerging functional capacity of various cognitive tasks during typical development.

The primary argument of this review is that during the various stages of typical rodent development, shifts in the morphological and functional state of glutamatergic terminals, in combination with neuroglia, set the stage for sensitivity to inflammatory signals within this glutamatergic quad-partite synapse. The critical roles of cytokines and immunoresponsive cells in developmental processes suggest that inflammatory signals provide a mechanism which mediates points of vulnerability or resilience to developmental disruptions at this junction.

Two primary glial cells which are closely associated with glutamatergic transmission and actively respond to immune challenges (*e.g.* stress, bacterial exposure, etc.) by producing and reacting to various immune signals (*e.g.* cytokines and chemokines) are astrocytes and microglia (Lee et al., 1993; Sugama et al., 2011). As part of the tri-partite synapse, astrocytes have long been associated with regulation of glutamatergic transmission. The addition of microglia into the relation between astrocytes and glutamatergic terminals expands the glutamatergic tripartite synapse into a quad-partite synapse, as first described by Schafer et al. (2013) (Fig. 1). As the primary immune cells of the central nervous system, incorporating microglia into the dynamics of the glutamatergic synapse inherently links the immune system with the nervous system. The significance of the quad-partite synapse is therefore two-fold 1) it provides a bridge for neuro-immune communication, and 2) the function or dysfunction of this synapse has broad-consequences for coordination of neuronal activity which is necessary for output of cognition and behavior. In the context of this quad-partite synapse, the following sections will first discuss the function of astrocytes and secondly microglia in relation to sensitivity to immune signals.

1.1. Astrocytes exhibit multifaceted functionality

There are several ways by which astrocytes respond to the surrounding environment, many of which are sensitive to extracellular levels of glutamate. This should not be surprising given their role in modulating glutamate homeostasis. These new features have expanded the original "glutamate vacuum" role of astrocytes to include astrocyte-mediated vesicular glutamate release (Bezzi et al., 2004), modulation of the blood-brain barrier permeability (for review, see Abbott et al., 2006), and local regulation of cytokine release (Chung and Benveniste, 1990; Sugama et al., 2011). In addition, astrocytes monitor broad-levels of neural network activity and can communicate with both other astrocytes and microglia via the induction of intracellular calcium waves (Cornell-Bell et al., 1990). While calcium waves can directly facilitate astrocyte-astrocyte communication via gap junctions, they can also indirectly facilitate communication with microglia by stimulating the release of ATP from intracellular stores which can then activate a variety of microglial purinergic receptors (Färber and Kettenmann, 2006; Verderio and Matteoli, 2001).

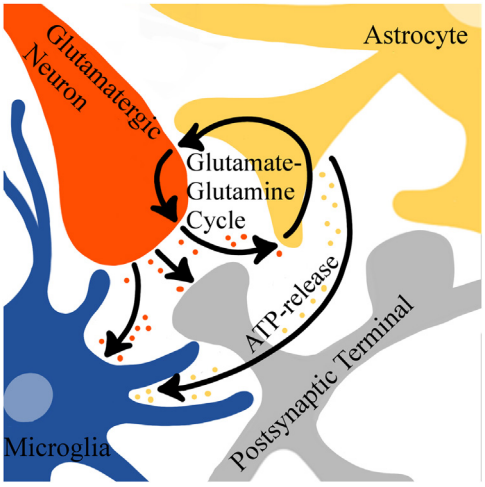

Fig. 1. The quad-partite synapse. This quad-partite synapse consists of the presynaptic (glutamatergic) terminal, postsynaptic terminal, astrocytes, and microglia. Astrocytes and microglia both respond to extracellular glutamate, and astrocytes communicate to microglia via calcium-wave-driven ATP release and activation of purinergic receptors.

1.2. Microglia respond to glutamate in both normal and immune-challenged environments

The second way in which glutamate bridges neuro-immune communications is via microglia. Microglia are immunocompetent cells which were originally described anatomically as progressing from highly ramified to amoeboid morphology in tandem with shifts from non-pathological/resting states to immunologically-activated functions (Leong and Ling, 1992). Since this time, our understanding of microglial morphological shifts and physiological functions has evolved substantially. The idea of ramified microglia as "resting" was overturned after *in vivo* imaging revealed that microglia in healthy brains are highly mobile with the ramified processes rapidly extending and retracting to survey the surrounding environment (Nimmerjahn et al., 2005). Similarly, blanket statements of amoeboid microglia as active have been found to be a vast oversimplification of the variety of phenotypes and functions that microglia can undertake. Currently, the literature has identified three broad classifications of microglia which parallel states of peripheral macrophages: M_0, M_1, and M_2 (as reviewed by Franco and Fernández-Suárez, 2015). M_0 microglial phenotypes exhibit ramified morphology and are characteristic in the healthy adult brain; as such they were once termed either "resting" or "surveying" microglia (Franco and Fernández-Suárez, 2015; Hanisch and Kettenmann, 2007). M_1 microglia are considered classically activated as this phenotype exhibits shifts towards amoeboid morphology which is primarily characterized by the production of pro-inflammatory cytokines as well as high levels of lysosomes which enable phagocytosis. In contrast, the function and morphol-