Uncoupling of EphA/ephrinA Signaling and Spontaneous Activity in Neural Circuit Wiring

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Classic studies have proposed that genetically encoded programs and spontaneous activity play complementary but independent roles in the development of neural circuits. Recent evidence, however, suggests that these two mechanisms could interact extensively, with spontaneous activity affecting the expression and function of guidance molecules at early developmental stages. Here, using the developing chick spinal cord and the mouse visual system to ectopically express the inwardly rectifying potassium channel Kir2.1 in individual embryonic neurons, we demonstrate that cell-intrinsic blockade of spontaneous activity in vivo does not affect neuronal identity specification, axon pathfinding, or EphA/ephrinA signaling during the development of topographic maps. However, intrinsic spontaneous activity is critical for axon branching and pruning once axonal growth cones reach their correct topographic position in the target tissues. Our experiments argue for the dissociation of spontaneous activity from hard-wired developmental programs in early phases of neural circuit formation.

Introduction

The formation and refinement of vertebrate neural circuits involve neural identity specification, axon targeting, and synaptogenesis, processes that are primarily controlled by hard-wired developmental programs. However, developing neurons exhibit spontaneous electrical activity (Spitzer, 2006), and the extent of its influence over genetically encoded developmental mechanisms is currently under debate.

The classical view posits that activity-independent and activity-dependent programs sequentially regulate different aspects of neural development (Katz and Shatz, 1996; Erzurumlu and Kind, 2001). However, recent evidence suggests that spontaneous activity may be more of a critical player at earlier developmental stages than previously thought, influencing the expression and function of transcription factors and axon guidance molecules as well as affecting the concentration of axon guidance receptor secondary messengers such as calcium or cAMP (Nishiyama et al., 2003; Hanson and Landmesser, 2004; Nicol et al., 2007). The representative experiments that raised this idea examined the impact of spontaneous activity on the repulsive signaling mediated by the tyrosine kinase receptor EphA and its ephrinA ligand in both the developing chick spinal motor neurons and the mammalian visual system. Limb-innervating motor neurons of the spinal lateral motor column (LMC) are segregated into dorsal limb muscle-innervating lateral LMC motor neurons and ventral limb muscle-innervating medial LMC motor neurons. The binary decision of motor axon projection to the ventral or to the dorsal limb mesenchyme is mediated, at least in part, by the repulsive signaling from ephrins expressed in the limb to axonally expressed EphA4 receptors (Kao et al., 2012). These motor neurons are electrically active even before they form synapses with their target muscles (O’Donovan and Landmesser, 1987), and it has been proposed that this spontaneous activity may influence their guidance by modulating the expression and/or function of axon guidance receptors such as EphA4 (Hanson and Landmesser, 2004). In the visual system, the classical view proposes that EphA/ephrinA signaling and spontaneous activity in the form of retinal waves act independently and sequentially to form the retinotopic map in the visual targets (McLaughlin et al., 2003; Pfeifferenger et al., 2006; Cang et al., 2008). However, a set of in vitro experiments...