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Review

# Ephrin regulation of synapse formation, function and plasticity

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ABSTRACT

Synapses enable the transmission of information within neural circuits and allow the brain to change in response to experience. During the last decade numerous proteins that can induce synapse formation have been identified. Many of these synaptic inducers rely on trans-synaptic cell–cell interactions to generate functional contacts. Moreover, evidence now suggests that the same proteins that function early in development to regulate synapse formation may help to maintain and/or regulate the function and plasticity of mature synapses. One set of receptors and ligands that appear to impact both the development and the mature function of synapses are Eph receptors (erythropoietin-producing human hepatocellular carcinoma cell line) and their surface associated ligands, ephrins (Eph family receptor interacting proteins). Ephs can initiate new synaptic contacts, recruit and stabilize glutamate receptors at nascent synapses and regulate dendritic spine morphology. Recent evidence demonstrates that ephrin ligands also play major roles at synapses. Activation of ephrins by Eph receptors can induce synapse formation and spine morphogenesis, whereas in the mature nervous system ephrin signaling modulates synaptic function and long-term changes in synaptic strength. In this review we will summarize the recent progress in understanding the role of ephrins in presynaptic and postsynaptic differentiation, and synapse development, function and plasticity.



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## Introduction

The trillions of synaptic connections found in the brain enable neuronal activity to flow between neurons. However, neuronal activity is not the only signal transmitted at synaptic sites. Pre- and postsynaptic specializations contain a host of transmembrane molecules that interact with one another to enable signals to pass between neurons. Trans-cellular signaling between sets of pre- and post-synaptic proteins can

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induce synaptic formation, regulate synapse function and modulate synaptic plasticity (Biederer and Stagi, 2008; Robbins et al., 2010; Yamada and Nelson, 2007). The Eph receptor tyrosine kinases (RTKs) and their ligands, the ephrins, mediate many important signals across synapses. Signaling by both Ephs and ephrins can control a diverse set of synaptic events from the initiation of new synaptic sites to the modulation of synaptic function.

Ephrins fall into two subfamilies: ephrin-As and ephrin-Bs. The ephrin-A subfamily consists of five members that bind and activate EphA RTKs (Fig. 1A). Ephrin-As (ephrin-A1–5) lack a cytoplasmic domain, but are capable of triggering downstream signaling by recruiting Src family and phosphoinositide-3 (PI3) kinases (Davy et al., 1999; San Miguel et al., 2011). The ephrin-B subfamily consists of three proteins that bind and activate the EphB class of Ephs (Fig. 1A). Binding of ephrin-Bs to EphB receptors initiates bidirectional signaling that involves activation of the catalytically active kinase domain on EphBs and phosphorylation of the cytoplasmic tail of ephrin-Bs. Specific functional domains within the intracellular portion of ephrin-Bs enable their signaling (Fig. 1B) (Pasquale, 2008). The known domains within ephrin-Bs include three tyrosine residues enabling the recruitment of Src Homology 2/3 (SH2/SH3) adaptor proteins (Bruckner and Klein, 1998; Holland et al., 1996; Xu and Henkemeyer, 2009), a PDZ binding domain enabling interaction with adaptor-proteins such as glutamate receptor interacting protein 1 (GRIP1) (Aoto et al., 2007; Bruckner et al., 1999), a D-domain for interaction with Erk/MAPK (McClelland et al., 2010), and a Grb4 domain enabling interactions with the G protein-coupled receptor kinase-interacting protein 1 (GIT1) (Cowan and Henkemeyer, 2001; Segura et al., 2007).

Both EphA and EphB RTKs play prominent and well-described roles in the formation and function of excitatory synapses (Dalva et al., 2000; Henkemeyer et al., 2003; Kayser et al., 2006, 2008; Murai et al., 2003). EphA4 is critical for dendritic spine morphogenesis in the hippocampus (Murai et al., 2003) and regulates synaptic plasticity (Filosa et al., 2009; Grunwald et al., 2004). EphBs are required for the formation of many dendritic spine synapses (Henkemeyer et al., 2003; Kayser et al., 2006) and control the formation of excitatory synapses that require the motility of dendritic filopodia (Kayser et al., 2008). EphBs are also important for the formation of spines with normal morphology (Irie and Yamaguchi, 2002; Margolis et al., 2010; Penzes et al., 2003; Tolias et al., 2007) and synaptic plasticity (Grunwald et al., 2001; Henderson et al., 2001). In addition, EphBs regulate the recruitment, localization, and function of NMDA receptors (Dalva et al., 2000; Nolt et al., 2011; Takasu et al., 2002). The role of Eph RTKs in synaptogenesis, spine formation and synaptic function is well documented (Klein, 2009) but it is becoming clear that ephrin ligands play similar roles. In this review we will discuss recent evidence linking ephrins to the formation, maturation, and function of excitatory synapses.

## Expression of Ephs and ephrins in CNS

The pattern of expression of ephrins and Ephs is complex and reflects the diverse functions these proteins play in the developing and mature brain (Flenniken et al., 1996; Liebl et al., 2003; Migani et al., 2007, 2009; Mori et al., 1995). Ephrins and Ephs are expressed pre- and/or post-synaptically at both the developing and mature excitatory synapse (Aoto et al., 2007; Contractor et al., 2002; Grunwald et al., 2001, 2004; Henderson et al., 2001; Kayser et al., 2006, 2008; McClelland et al., 2009, 2010; Segura et al., 2007). Expression pattern of Ephs and ephrins is well defined in the hippocampus (Fig. 1C) (Buchert et al., 1999; Grunwald et al., 2001, 2004; Henderson et al.,

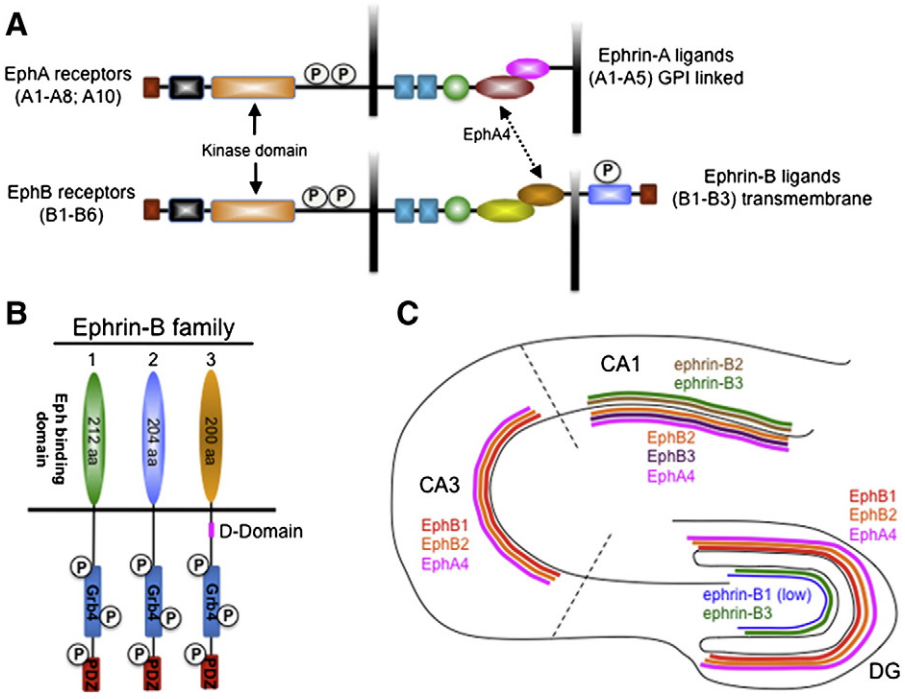


**Fig. 1.** Bidirectional signaling by Eph RTKs and their cell-surface ligands, ephrins. (A) Ephrins fall into two subfamilies based on the Eph RTK they bind. The ephrin-A subfamily consists of five GPI-linked members (ephrin-A1–A5) that bind and activate EphAs (ephrin-A5 that can also bind to EphB2 RTK). The ephrin-B subfamily consists of three family members (ephrin-B1–B3). All ephrin-Bs are transmembrane proteins that bind and activate the EphB class of Ephs and are themselves capable of intracellular signaling. One notable exception to this rule is that all ephrin-B members can also bind and activate EphA4 RTK. (B) Diagrams of the domains within the intracellular portion of ephrin-Bs that enable ephrinBs to function as signaling proteins. These include three tyrosine residues enabling recruitment of Src Homology 2/3 (SH2/SH3) adaptor proteins, a PDZ-binding domain enabling interaction with PDZ domain containing adapter proteins and a Grb4 domain. In addition to the conserved domains, ephrin-B3 contains a D-domain allowing it to interact with Erk2. (C) The expression patterns of Ephs and ephrins in the hippocampus. EphB2 and EphA4 are expressed throughout the hippocampus, while EphB1, EphB3, and ephrin-Bs exhibit regional differences in their expression. In dentate gyrus (DG) ephrin-Bs have well-established pre-synaptic role, while in the CA1 region ephrin-Bs function largely postsynaptically.