N-methyl-D-aspartate receptors (NMDAR) make an essential contribution to activity-dependent gene expression in learning and memory. However, NMDAR are present at both synaptic and extrasynaptic sites, and the subcellular localization of each receptor profoundly and differentially affects the nuclear response to its activation. Activation of synaptic NMDAR induces the expression of cell survival and plasticity genes, while their extrasynaptic counterparts primarily drive the expression of cell death genes, linking the pathway to disease (Hardingham and Bading, 2010). An unresolved issue is how can the distant nucleus discriminate between synaptic and extrasynaptic NMDAR-induced signals?

Jacob is a synapto–nuclear messenger, and previous work has shown that extrasynaptic NMDAR activation induces nuclear translocation of Jacob, which results in sustained dephosphorylation and transcriptional inactivation of the transcription factor CREB, a loss of synaptic contacts, a retraction of dendrites and eventually cell death (Dieterich *et al*, 2008). However, Jacob also transits to the nucleus of CA1 neurons, following induction of Schaffer collateral-dependent long-term potentiation (LTP) but not long-term depression (LTD), and hence acts as a messenger for both synaptic and extrasynaptic NMDAR pathways (Behnisch *et al*, 2011). How does the protein get to the nucleus and what is the molecular basis for these different functions after nuclear import of Jacob? Neuronal importins are present in axons, dendrites, and synapses and they can associate with a dynein motor for active retrograde transport along microtubuli to the nucleus. Jacob utilizes this transport system after activation of both type of receptors and in a recent study we found that Jacob, following its nuclear import, can encode the synaptic and extrasynaptic origin of NMDAR signals (Karpova *et al*, 2013). ERK1/2-kinase binding and ERK-dependent phosphorylation of the serine180 residue in Jacob encodes synaptic but not extrasynaptic NMDAR activation. A stable trimeric complex with proteolytically cleaved fragments of the neurofilament α-internexin is formed, which protects Jacob and active ERK against phosphatase activity during retrograde transport. In the nucleus, this signalosome-like complex enhances 'plasticity-related' and 'CREB-dependent' gene expression as well as synaptic strength. It appears that Jacob operates as a mobile hub that docks NMDA receptor-derived signalosomes to nuclear target sites and it will be interesting to clarify the molecular identity of these complexes, because they are attractive targets for pharmacological interventions in activity-dependent gene transcription.

ACKNOWLEDGEMENTS

This study was supported by the DFG (SFB 779/TPB8), DIP grant, CBBS Magdeburg, MC-ITN NPlast, and the Leibniz Foundation (Pakt für Forschung).

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FUNDING AND DISCLOSURE
The authors declare no conflict of interest.

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Neuropsychopharmacology Reviews (2014) **39,** 245–246; doi:10.1038/npp.2013.204

Maintaining and Modifying Connections: Roles for Axon Guidance Cues in the Mature Nervous System

Upon reaching its target, an axon differentiates to form synaptic connections. Remarkably, recent studies have revealed that proteins initially identified as axon guidance cues are re-emerging as regulators of synaptic plasticity in the adult brain. Canonical axon guidance proteins such as semaphorins, ephrins, and slits, and the prototypical myelin-associated inhibitors of axon regeneration, MAG, Nogo, and OMgp, have been found to influence circuit remodeling and synaptic plasticity in the mature nervous system (Mironova and Giger, 2013). Following a study by Horn *et al* (2013), the netrin receptor DCC now joins this list.

Mechanisms that direct neural development have long been suggested to regulate plasticity in the mature brain. Cajal's (1911) proposal that chemotropism might direct axon extension in the embryo included a hypothesized attractant for commissural axons secreted by floor plate cells in the embryonic spinal cord. In a stunning act of prescience, Cajal (1911) suggested that his putative chemoattractant might also influence synaptic plasticity and learning and memory: 'The ability of neurons to grow in an adult and their power to create new associations can explain learning.' He speculated that 'the mechanisms are probably chemotactile like the ones we observed during histogenesis of the spinal cord'.

Netrins were the first identified floor plate-derived axonal chemoattractants (Lai Wing Sun *et al*, 2011). Although shown to regulate synaptogenesis during development in *Caenorhabditis elegans* and *Drosophila melanogaster*, a role for netrins at synapses in the mature vertebrate CNS had not been investigated. Horn *et al*

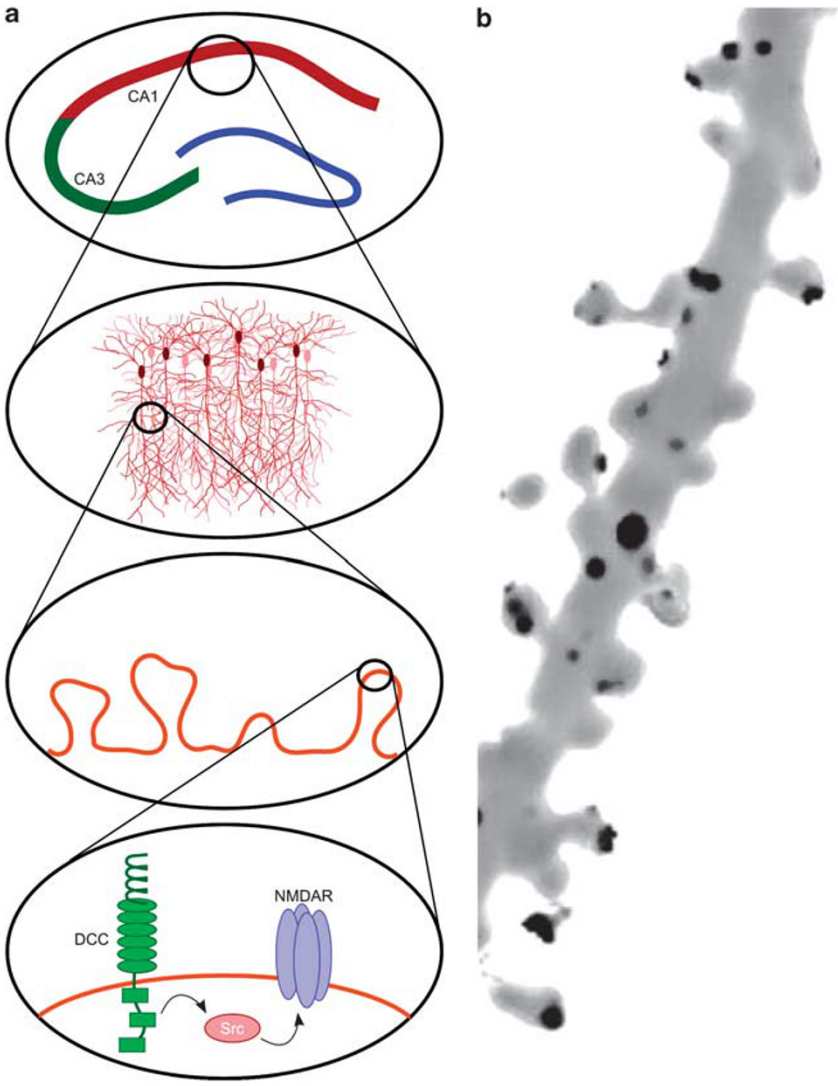

Figure 1. DCC regulates synapse structure, plasticity, and memory. (a) Conditional deletion of DCC selectively from forebrain neurons in the adult mouse causes dendritic spines of hippocampal CA1 neurons to shrink, and interferes with long-term memory formation. In addition, dampened NMDAR function due to reduced DCC-dependent activation of src causes deficient long-term potentiation, a form of activity-dependent plasticity. (b) DCC immunoreactivity (black) enriched at the tips of post-synaptic spines along an fRFP-labeled hippocampal dendrite (adapted from Horn *et al*, 2013).

(2013) report that netrin-1 and its receptor DCC are present at synapses in the adult mouse brain, with DCC enriched in the post-synaptic density. As conventional DCC null mice die at birth, in order to study DCC function in the mature CNS, Horn *et al* (2013) developed a cre-lox conditional DCC knockout to delete DCC only from neurons in the mature mouse forebrain. Following the loss of DCC, dendritic spines were found to shrink, indicating that DCC maintains normal synaptic morphology. Furthermore, DCC activation of the cytoplasmic tyrosine kinase Src was shown to be required for NMDA receptor-dependent long-term potentiation, a form of activity-dependent synaptic plasticity, and for certain forms of learning and memory.

Earlier studies found that conventional adult *DCC* heterozygous mice, which express reduced levels of DCC protein, exhibit a blunted response to amphetamine and fail to sensitize to repeated doses (Flores *et al*, 2005), a form of plasticity thought to influence drug addiction. The findings provided by Horn *et al* (2013) raise the possibility that deficient NMDA receptor function in *DCC* heterozygotes may contribute to defective sensitization. Flores *et al* (2005) also drew similarities between the sensitization defects and models of neural dysfunction in schizophrenia, and NMDA receptor hypofunction has been proposed as an underlying deficit in schizophrenia (Coyle, 2006). Intriguingly, recent reports describe single-nucleotide polymorphisms in the human *DCC* gene associated with schizophrenia, Parkinson's disease, and amyotrophic lateral sclerosis. Ongoing studies aim to identify mechanistic links between psychiatric or neurodegenerative diseases and the synaptic functions of axon guidance proteins.

ACKNOWLEDGEMENTS

Supported by grant 114965 to TEK from the Canadian Institutes of Health Research.

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FUNDING AND DISCLOSURE
The authors declare no conflict of interest.

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Neuropsychopharmacology Reviews (2014) **39,** 246–247; doi:10.1038/npp.2013.212