Targeting NR2B for Memory Improvement

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The NMDA receptor is the central molecular device for controlling synaptic plasticity and memory function, and so understanding the control and action of the NMDA receptor at central synapses may provide clues to therapeutic strategies for treating memory disorders (Li & Tsien, 2009).

The creation of *Doogie* mice has demonstrated that it is possible to manipulate a single NMDA receptor subunit for a broad range of learning and memory enhancement (Tang et al., 1999; Tsien, 2000; Tang et al., 2001; White & Youngentob, 2004; Cao et al., 2007). Since then, scientists have further generated NR2B transgenic rats, nicknamed Hobbie-J, which also exhibited larger LTP and similar enhancement in learning and memory (Wang et al., 2009). This cross-species validation adds to the notion that NR2B may act as a universal key switch for gating memory enhancement in various mammalian brains. On the other hand, conditional knockout of NR2B in the mouse forebrain or hippocampus results in decreased NMDA receptor–mediated charge transfer, reduced cellular LTP, and impaired spatial performance (von Engelhardt et al., 2008).

Proteomics analysis suggests that the core NMDA receptor tetramer associates with a multiprotein complex that includes more than 70 associated proteins, many of which influence trafficking, stability, subunit composition, or function of NMDARs (Husi et al., 2000; Sanz-Clemente et al., 2010). Studies so far have shown that facilitating transport of NR2B to synapses or slowing down the degradation of NR2B at synapses can also be a quite effective means to elevate synaptic NR2B levels and subsequently improve memory function. For example, transgenic mice with the overexpression of KIF-17, a kinesin motor protein involved in

transporting NR2B protein from soma to dendrites, showed a higher NR2B expression at synapses, and these mice possessed superior memory (Wong et al., 2002). Another study reports a significant role for tissue plasminogen activator (tPA) in regulating NR2B trafficking and NMDA receptor complex stability in the hippocampus (Norris & Strickland, 2007). Transgenic mice overexpressing tPA also had better performances in spatial orientation learning tasks (Madani et al., 1999).

In addition, recent studies suggest that the degradation of NMDA receptors is regulated by the Ca^{2+}-dependent protease calpain by rapidly cleaving NMDAR subunits and resulting in a decrease in the number of functional NMDA receptors in the postsynaptic density (Simpkins et al. 2003). This calpain-dependent proteolysis of NR2B is regulated by cyclin-dependent kinase 5 (Cdk5) (Hawasli et al., 2007). A recent study reports that conditional knockout of Cdk5 in the adult mouse brain reduces NR2B degradation, which causes elevation in total surface and synaptic NR2B subunit levels and stronger LTP. These Cdk5 knockout mice also showed better contextual fear conditioning memory, faster fear extinction, and more flexible learning in the reversal water maze task (Hawasli et al., 2007). It is also noteworthy that silencing Cdk 5, a major kinase associated with tau hyperphosphorylation in Alzheimer's disease (AD), has been reported to reduce neurofibrillary tangles in transgenic Alzheimer's mice (Piedrahita et al., 2010).

Interestingly, another transgenic mouse that overexpresses tau-tubulin kinase-1 (TTBK1), another kinase for tau, had increased tau phosphorylation, a higher level of p25 and p35 (both are Cdk5 activators), enhanced calpain I activity, and reduced levels of hippocampal NR2B subunit (Sato et al., 2008). Therefore, it seems that NR2B is also a target for AD-associated changes via calpain, Cdk 5 and tau pathways. On this note, a recent study provided a suggestive association

between a polymorphism in the NR2B promoter region, reduced NR2B expression levels and increased risk of Alzheimer's disease (Jiang & Jia, 2009).

More recently, researchers identified another synaptic transmembrane protein associated with NMDAR protein, Neto1. Neto1 is an interesting molecule because its intracellular domain binds a PSD-95 that is known to directly interact with NMDAR, and its extracellular domain interacts with NR2A and NR2B (Ng et al., 2009). Neto1 knockout mice had diminished synaptic NR2A (but not NR2B) in the hippocampus. Interestingly, administering the ampakine CX546, an AMPA receptor agonist, leads to secondary increase of NMDA currents by relieving the Mg^{2+} blockade of the NR2B-containing NMDARs, subsequently rescuing both LTP deficits and spatial learning deficits in the mutant mice. This was the first report of a pharmacological rescue of inherited plasticity defects and restoration of memory functions by pharmacologically enhancing NR2B-containing NMDA receptor.

Other researchers are actively exploring additional strategies to boost NR2B-containing NMDA receptor functions, such as by transcriptional modification of NR2B/NR2A ratio (Jian et al., 2010) or via optimizing a proper Mg^{2+} in the CSF by supplemental diet (Slutsky et al., 2010). The latter approach can be interesting since the majority of American adults consume less than the estimated average requirement of magnesium, a deficiency in which may have a detrimental effect on memory function.

All together, the above several examples represent current ongoing translational efforts that may one day provide a much-needed solution for treating AD and memory impairments. However, because memory processing is vastly more complicated in the human brain and memory disorders often have diverse causes, much work and many challenges may lie ahead.

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