SYNAPTIC PLASTICITY

MeCP2 and memory mechanisms

File name: NRN_0206_DM1_HL

Word count: 427

Accompanying picture: YES/no

File name of picture:

URLs

Methyl-CpG-binding protein 2 (MeCP2) is an X-linked transcriptional repressor and a regulator of RNA splicing. Loss of function of this protein is a frequent cause of Rett syndrome, a progressive neurological developmental disorder and one of the most common causes of mental retardation in females. New work in mice shows that MeCP2 is necessary for learning and memory, and reveals that its loss of function causes functional and ultrastructural abnormalities in synapses.

Using three hippocampus-dependent behavioural paradigms, Moretti and co-workers describe deficits of spatial memory and contextual fear conditioning in mice expressing a truncated allele of *Mecp2*. These mice also show impairment of social interaction and long-term social memory, consistent with phenotypes observed in Rett syndrome.

Electrophysiological analysis of the CA1 region of the hippocampus in *Mecp2* mutant mice showed increased postsynaptic depolarization and attenuated paired-pulse facilitation,

a simple, short-term form of synaptic plasticity. Together, these data indicate an enhancement of basal synaptic transmission in this region.

Two mechanistically distinct forms of long-term potentiation (LTP) were impaired in the hippocampus of *Mecp2* mutant mice, and LTP was also impaired in primary motor and sensory regions of the cortex. Measures of long-term depression (LTD) that rely entirely on postsynaptic mechanisms for the induction and expression of LTD were normal in *Mecp2* mutant mice. Interestingly, paired-pulse low-frequency stimulation, a measure of LTD that is absolutely dependent on the presynaptic terminal for its induction, revealed an impairment in this form of synaptic plasticity in the CA1 region of mutant mice, which suggests the presence of alterations at the presynaptic terminus.

In addition, electron microscopy revealed changes at an ultrastructural level. Mutant mice showed a reduction in the average length of postsynaptic densities, despite there being no

change in their density or the number of docked vesicles. Therefore, the authors speculate that the close correlation between presynaptic active zone and postsynaptic density size observed in normal synapses is perturbed in these mice.

Together with previous work showing an enhancement of plasticity due to *Mecp2* overexpression, these findings suggest an important role for MeCP2 in the regulation of synaptic function. Analysis of the molecular targets of this protein will improve our understanding of its role in synaptic function. As dysfunction of MeCP2 is associated with mental retardation, mild learning disability and autism, such an understanding might also provide us with insight into the aetiology of a range of neurodevelopmental disorders.

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ORIGINAL RESEARCH PAPER Moretti, P. *et al.* Learning and memory and synaptic plasticity are impaired in a mouse model of Rett syndrome. *J. Neurosci.* **26**, 319–327 (2006)