Insights into activity-dependent neuronal growth through RSRF-supported research

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Brain-derived neurotrophic factor (BDNF) has been a subject of keen interest in neuroscientific circles for several years, turning up in studies of conditions ranging from central hypoventilation syndrome to obsessive-compulsive disorder, depression, bipolar disorder and schizophrenia -- a range of disorders uncannily parallel to those produced by mutations in the "Rett gene," MeCP2.

In 2003, two groups found that MeCP2 regulates BDNF transcription, but sorting out the complex relationship between the two proteins has been quite challenging. New studies from the labs of Michael Greenberg at Children's Hospital Boston and David Katz at Case Western School of Medicine have begun to shed light on the interplay of MeCP2 and BDNF.

Because Rett syndrome (RTT) develops during early childhood, when sensory experiences normally stimulate the development of synaptic circuits, some researchers hypothesized that the fundamental defect in RTT is a failure of synaptic plasticity or maturation. Early support for this hypothesis came from studies showing that MeCP2 expression normally increases as neurons mature. Conversely, RTT patients and mice lacking MeCP2 suffer defects in synaptic plasticity, learning and memory, all of which are dependent on experience – so there is some link between experience and the change in neuronal function it would normally produce that is missing when MeCP2 is not functioning properly.

Zhou et al. (Greenberg lab) have found at least part of that missing link. In a paper just published in Neuron, they show that increases in neuronal activity result in phosphorylation of MeCP2 at a particular residue (S421) which, in turn, increases transcription of certain genes, including Bdnf, that are required for experience-dependent brain maturation. They further show that phosphorylation of MeCP2 at S421 is required for structural modifications of neurons that underlie the maturational process. Moreover, they identified a complex regulatory loop in which BDNF feeds back to trigger phosphorylation of MeCP2, suggesting that BDNF and neuronal activity may cooperate in regulating MeCP2 function. Finally, this study shows that MeCP2 phosphorylation at S421 occurs only in the brain and not in other tissues. Disruption of this specific phosphorylation mechanism could explain why RTT primarily affects brain function, despite the fact that cells throughout the body express MeCP2. The authors also may have found an explanation for the sleep disturbances that are a frequent complication of RTT: one of the brain regions in which they observed activity-dependent phosphorylation of MeCP2 at S421 is involved in regulating circadian rhythms, including the sleep-wake cycle.

New work by Wang et al. (Katz lab) published in the Journal of Neuroscience examines another aspect of how mutations in MeCP2 disrupt BDNF signaling, namely, the relationship between how much BDNF a neuron expresses and how much is released. Normally, synaptic maturation and function are regulated by precise coupling of activity dependent BDNF expression and secretion. This balance is disrupted in MeCP2-deficient neurons, however, by two factors. On the one hand, mutant neurons exhibit a progressive decline in BDNF content after birth; the timing of this decline varies among different brain regions. On the other hand, mutant neurons release a greater percentage of their BDNF content. Thus, early in development, MeCP2 deficient neurons release more BDNF than normal cells. Such hypersecretion of BDNF in newborn MeCP2-deficient neurons may disturb the delicate, tightly

regulated developmental processes elicited by changes in experience-dependent neuronal activity. Eventually, BDNF content declines so much that mutant cells release less BDNF than normal, which is likely to result in synaptic dysfunction. The authors further found that secretory defects are not restricted to neurons that release BDNF. Release of adrenal hormones called catecholamines, which play a key role in the body's response to stress, is also abnormally high in MeCP2- deficient cells. Wang et al. hypothesize that secretory defects could be a common thread contributing to dysfunction of multiple neural systems in RTT.

Source: Rett Syndrome Research Foundation