

# New Findings on the Regulation of Brain-Derived Neurotrophic Factor (BDNF) by MeCP2

Acute Intermittent Hypoxia-Induced Expression of Brain-Derived Neurotrophic Factor is Disrupted in the brainstem of MeCP2 null mice

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IRSF funded investigator John Bissonnette, MD and Agnieszka Balkowiec, MD, PhD of the Oregon Health & Science University have recently published new findings on the regulation of brain-derived neurotrophic factor (BDNF) by MeCP2 in the journal *Neuroscience*.

BDNF is a critical protein that is essential for brain nerve cell development and the way connections are made between these cells that transfer "information" within the brain. In patients diagnosed with Rett syndrome (RTT), BDNF is decreased. Since BDNF is essential to overall brain cell development and function, it is a widely studied protein as a potential therapeutic.

Dr. Bissonnette and his colleagues found that the mutant neurons in a RTT mouse model failed to increase BDNF in a paradigm that markedly increased the neurotrophin in normal mice. In their experimental study, they exposed the animals to an environment of low oxygen to challenge the respiratory system. They found that normal neurons in the areas of the brain that respond to respiratory signals will dramatically increase BDNF upon low oxygen exposure, whereas BDNF protein expression in mutant neurons that lack MeCP2 remains the same.

Respiratory issues are just one symptom that those diagnosed with RTT may contend with. In light of these new findings, low oxygen levels during apneas or other breathing issues may fail to induce BDNF in the respiratory regions of the brain, which then may intensify respiratory dysfunction. Therefore, increasing BDNF levels or its function is a highly studied area to find a potential therapeutic for RTT.

Abstract

Article

Below, we have asked Dr. Bissonnette to comment on the background of BDNF and his recent publication:

Brain-derived neurotrophic factor (BDNF) has long been implicated in the functional changes associated with Rett syndrome. Experiments where isolated brain cells were exposed to chemicals that can mimic neuronal activity have not revealed a unified picture of the role for MeCP2 in BDNF expression in the intact brain. Some years ago, Tracy Baker-Herman, Gordon Mitchell and their colleagues at University of Wisconsin-Madison showed that lowering oxygen for brief intermittent periods resulted in increased BDNF protein in the spinal cord area.<sup>2</sup> We used this experimental approach to determine if the absence of MeCP2 would affect the expression of BDNF. In normal mice, there are two areas of the brainstem that contain respiratory centers, the pons and the medulla, where BDNF was markedly increased following intermittent hypoxia (low oxygen). In contrast, BDNF was unchanged in mice that lacked MeCP2. These results have

implications for the respiratory disturbances in RTT. In a collaborative study between David Kline at the University of Missouri and David Katz at Case Western Reserve University, it was shown that BDNF corrects the abnormality seen in neurons of the nucleus of the solitary tract (NTS), an area in medulla of the brain that also responds to hypoxia.<sup>5</sup> In collaboration with Ana Abdala and Julian Paton at the University of Bristol, we have shown that apneas and irregular breathing in RTT are due to a lack of inhibitory signals to special neurons, and that boosting these signals can corrects these respiratory issues.<sup>1</sup> These results are not necessarily inconsistent with the BDNF hypothesis. Elizabeth Hong in Michael Greenberg's Harvard laboratory showed that disrupting BDNF function resulted in fewer inhibitory signals, and Sacha Nelson with Gina Turrigiano had demonstrated that BDNF enhances inhibitory neuron activity.<sup>3,6</sup> In terms of studies for potential RTT treatments, Abdala et. al. found that enhancing the inhibitory neurotransmitter GABA in RTT mice restored breathing irregularity to normal; however, boosting BDNF with an ampakine treatment did not correct it in RTT mice (Greenberg and Katz). In addition, Rebecca Johnson, Gordon Mitchell, Qiang Chang and co-workers found that a small molecule that activates the BDNF receptor only partially corrected breathing irregularities.<sup>4</sup> Very recently David Katz, together with Frank Longo from Stanford, showed that a separate small molecule that interacts with the BDNF receptor restored the elevated breathing rate in heterozygous MeCP2 deficient female mice to that of normal animals. At the dosing schedule used, however, it did not affect the incidence of apnea.<sup>7</sup> Our recent findings indicate that MeCP2 is necessary for neuronal activity enhancement of BDNF expression. Strategies that increase resting levels of BDNF may be insufficient if a neuronal activity-dependent increase of BDNF is responsible for the functional changes associated with Rett syndrome.

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