New insights into growth factor's role in brain development

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New research sheds light on a neural growth factor called proBDNF, finding that it is present and potentially active during the perinatal period when the brain's circuitry and memory-encoding regions are being refined. Led by Weill Cornell Medical College investigators with those at the National Institutes of Health (NIH) and Memorial Sloan-Kettering Cancer Center (MSKCC), and reported in the Jan. 11 issue of the journal *Nature Neuroscience*, the study could lead to a better understanding of brain development and the formation of memories.

ProBDNF is the precursor form of mature brain-derived neurotrophic growth factor (BDNF), and both are active in the hippocampus and cortex -- areas key to learning, memory and higher thinking. Intriguingly, proBDNF and BDNF encourage different actions; BDNF promotes the differentiation of new neurons and their constituent parts (axons, dendrites and synapses), and proBDNF the pruning of synapses -- a process that occurs particularly in the early stages of life.

"Our results suggest that the nervous system plays an active role in both potentiating and dampening its own activity as necessary," says senior author Dr. Barbara Hempstead, the O. Wayne Isom Professor of Medicine at Weill Cornell Medical College and a leader in the field of neurotrophin research.

Dr. Hempstead and her research team, including lead authors Dr. Jianmin Yang and Dr. Chia-Jen Siao of Weill Cornell Medical College, developed new techniques that enabled them to observe when and where

proBDNF and mature BDNF were being made in a mouse model. They found that proBDNF is most highly expressed in the hippocampus during the postnatal period of the mouse at about days 3 to 21, when large numbers of axons and synapses are being formed. They also found that p75 receptors, a class of receptors that encode a "death domain" in which neurons are killed or pruned, are also active during this period. These results suggest that the expression of proBDNF and p75 are coordinated, with higher and more widespread levels of both molecules seen in the young mouse brain, and lower and more localized levels expressed in the more mature brain.

Since the neurotrophins were discovered many years ago, controversy has existed over a seemingly contradictory role for BDNF. On the one hand, it seems to incite cell death by binding with p75, or dampening synaptic transmission -- important roles identified by co-author Dr. Bai Lu of the NIH's National Institute of Child Health and Human Development. However, the mature form of BDNF also facilitates synaptic transmission and promotes survival and dendritic complexity by activating a class of receptors called the Trk tyrosine kinases.

"Many people in the field wondered how this could be possible," Dr. Hempstead says. "We found that both the 'pro,' or longer precursor form of BDNF, as well as the shorter survival-promoting form of BDNF are secreted by neurons. This gives us a clearer picture that BDNF plays dual roles in the developing brain -- possibly both dampening and enhancing synaptic activity."

Extrapolating her findings from mouse to human, Dr. Hempstead says that this finding provides new insight into how the brain is wired and how this wiring is refined -- particularly during the developmental stages.

"When we're young we all have the ability to learn a multitude of things

and acquire many skills. We can quickly learn languages, how to ride a bicycle or to swim. But as we get older our neuronal circuits become more refined, responsive to the things we do on a repetitive basis," Dr. Hempstead says. "This synaptic strengthening, pruning and refining allow us to have more effective and efficient nerve communication. The question has always been, how do we refine and strengthen synapses that we want to maintain and eliminate those that are 'noise' in the background? Our research provides important clues about how the brain is able to do this."

This paper builds on previous research Dr. Hempstead and her team published in *Science* in 2001 and *Nature Neuroscience* in 2005.

Source: New York- Presbyterian Hospital