CEP-1347 is Added to the Research Pipeline

New research has identified another compound for the research pipeline. Coalition for the Cure senior researchers Leslie Thompson and Elena Cattaneo, along with colleagues at the University of California, the University of Milan, and the University of Tuebingen, have published two articles on CEP-1347 and its positive effect on brain derived neurotrophic factor (BDNF). CEP-1347 was developed to inhibit apoptosis (programmed cell death).. BDNF is a protein in the brain which protects striatal neurons and facilitates neurogenesis, the growth of new neurons.

In the first study (Apostol 2008), CEP-1347 was administered to RD6/2 HD mice over a four week period. Motor symptoms improved and levels of BDNF were increased. The authors also found that CEP-1347 reduced neurotoxicity in cell models and in drosophila.

More preclinical research needs to be done; in future research, the drug will be administered over a longer period of time to determine whether survival time is increased. More work is also planned to determine the precise mechanisms involved. However, the research to date is encouraging because of the effect on BDNF and because the drug was shown to be safe and well-tolerated in Parkinson's patients. Although it was found to be ineffective in Parkinson's, it appears promising for Huntington's Disease.

As the authors point out, there is good evidence for a decrease in BDNF as a major pathology in Huntington's Disease. Dr. Elena Cattaneo and her colleagues have shown how the huntingtin's protein interferes with gene transcription. In HD, a repressor protein known as REST enters the cell's nucleus and suppresses key genes such as the one for BDNF. Strikingly, a mouse model in which the gene for BDNF has been knocked out more closely reproduces the gene transcription problems in HD than in any of the HD mouse models. Other compounds which increase BDNF, such as cysteamine and several SSRI antidepressants have been found to be helpful in HD mouse models.

In addition to the positive results in the first study, the second study (Conforti 2008) suggests that levels of BDNF's messenger RNA in the blood might serve as biomarkers to determine when treatment is necessary and whether it has been effective in restoring BDNF. While levels of the BDNF protein were not detectable in the blood, levels of mRNA were detectable in mouse and rat models and were restored by CEP-1347 treatment.

CEP-1347 was developed as an anti-apoptosis drug by Cephalon pharmaceutical company. It is an inhibitor of mixed lineage kinases that are involved in activating the c-Jun N-terminal kinase (JNK) pathway which leads to apoptosis. It also activates the extracellular signal-regulated kinanse (ERK) pathway. The role of this pathway is more

complex but its activation appears to be neuroprotective in HD. BDNF is a downstream target of the ERK pathway.

CEP-1347 was originally tested for Parkinson's patients and failed in clinical trials in 2005. Scientific commentary has focused on several issues (see Waldmeier 2006). The first is animal modeling in Parkinson's Disease. Since the cause of Parkinson's Disease is not understood, the pathologies of the disease need to be directly reproduced in animal models and that inevitably involves some assumptions which may not be accurate. In the model used a neurotoxin was administered to cause PD like damage. An acute insult to the brain is not the same as a progressive neurodegenerative disorder; studies in HD have shown some clear differences between older neurotoxin models of HD and the newer genetic mouse models.

In contrast, HD researchers are more accurately able to reproduce the disease in animal models since Huntington's Disease is based on one known cause, the expanded polyglutamine tract in the huntingtin's protein gene. Transgenic mice show a progressive disorder.

Another issue raised in the failure of CEP-1347 is whether apoptosis is an appropriate target for treating neurological diseases. It may be that it is too late to target programmed cell death after the onset of the disease. If that is the case, a gene test is available in HD, unlike in PD and treatment could begin earlier. It may be that if apoptosis is blocked, cell death will occur by other pathways. However, in HD, even if the anti-apoptotic properties of the drug fail to modify the disease, the restoration of BDNF could be a significant treatment.

The authors of the commentary on the failure of CEP-1347 in Parkinson's disease suggest that, in the development of treatments for neurodegenerative disorders, it is very important that mechanisms be validated and biomarkers be used to be sure that the drug is reaching its target. The researchers associated with the two HD studies covered here are doing just that with careful preclinical work.

References

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