Hitting receptors in HD

By Lev Osherovich, Senior Writer

Two mouse studies make a case for targeting different glutamate receptors to treat Huntington's disease. In one report, agonizing the AMPA receptor slowed disease progression, whereas another paper suggests that antagonizing the NMDA receptor could have a comparable effect. The findings could open up HD as a new indication for at least two biotech companies: **Cortex Pharmaceuticals Inc.** and **Evotec AG**.

HD is caused by mutations in the *huntingtin* (*HTT*) gene that lead to production of an excessively long, glutamine-expanded version of the protein. The accumulation of mutated, aggregation-prone *HTT* leads to decreases in brain-derived neurotrophic factor (BDNF) and the death of neurons in the striatum.

In the first paper, published in *Proceedings of the National Academy of Sciences*,¹ University of California researchers used Cortex's CX929 ampakine, which increases the sensitivity of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (GRIA; AMPAR) and thereby boosts production of BDNF, to reverse the effects of the mutated *HTT*.

Meanwhile, a **University of Michigan** team published results in the *Journal of Neuroscience* showing that excessive activation of the *N*-methyl-D-aspartic acid receptor (NMDAR) contributes to neurodegeneration in HD. This suggests that antagonizing NMDARs could be another therapeutic option for HD, which may provide Evotec with a new indication for its line of selective NMDAR antagonists.²

Although the studies describe two seemingly different glutamate-dependent mechanisms involved in HD, the results suggest that disease-related imbalances in glutamate signaling could be corrected by fine-tuning either or both receptors.

Boosting BDNF

In the *PNAS* paper, a team from the **University of California, Irvine**, showed that an injection of the ampakine CX929 improved cellular physiology and behavioral tests of learning and memory in mice overexpressing an aggregation-prone mutant form of *HTT* compared with what was seen in untreated controls that also had the mutant *HTT*.

Gary Lynch, professor of anatomy, neurobiology, psychiatry and human behavior at UC Irvine and a senior author on the *PNAS* paper, thinks that stimulation of AMPARs by CX929 boosts production of

BDNF. Indeed, the compound increased BDNF levels in the mouse hippocampus, and the compound's effects mimicked those of direct BDNF treatment in cell-culture assays.

According to Lynch, who is a consultant for Cortex, the neuro-protective effect of CX929 resulted from the higher BDNF levels rather than from chronic AMPAR activation. This is because CX929 is a short-lived molecule that activates AMPARs only transiently but nevertheless leads to long-term improvements.

"The drug has a half-life of less than 15 minutes in rodents and causes no evident changes in behavior during this period," said Lynch. "It causes the brain to increase production of BDNF, a plasticity-promoting factor that is reported to be depressed in HD."

"This work has developed from the concept that treating animals with an ampakine can have long-lasting effects on BDNF expression," said Mark Varney, president and CEO of Cortex. "Huntington's disease mice have a deficit in BDNF, so the obvious question was whether the deficit could be corrected with ampakines."

Varney said stimulating BDNF by agonizing AMPARs circumvents

the challenge of delivering the growth factor or transgenes that encode it to the brain. BDNF itself has failed in multiple clinical trials.³ For example, delivery problems sank **Amgen Inc.**'s Phase III trial of direct BDNF administration to treat amyotrophic lateral sclerosis (ALS) in 1999, leading the company to scrap its BDNF program.

Varney said CX929's short half-life leaves room for improvement and noted that Cortex "now has a series of compounds that have better metabolic stability and give a good increase in BDNF"

Varney said Lynch's results could prompt the company to pursue HD. To that end, the company is working with **CHDI Foundation Inc.**, a not-for-profit company focused on HD, to screen Cortex's library of ampakines for leads.

Richard Morse, director of computational and structural biology at CHDI, said that a decrease in BDNF levels "is a sort of a smoking gun" that accompanies HD pathology and that overexpression of the growth factor "leads to clear amelioration of phenotype" in animal models.

Thus, Morse told *SciBX*, boosting BDNF with ampakines could pay off if the chemical properties of the agonist can be optimized. "The question is how much of an increase in BDNF we can achieve and whether the results are robust enough and avoid eliciting adverse effects," he said.

Lynch said the methods and reagents in his study are covered by Cortex patents.

Curbing the excitement

In an unrelated paper, University of Michigan researchers reported in the *Journal of Neuroscience* that NMDARs may be an alternative target for HD.

According to Roger Albin, professor of neuroscience at the Univer-

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—Giles Hardingham,
University of Edinburgh

sity of Michigan and lead author of the paper, the study supports the idea that excessive stimulation of sensitive neurons in HD patients can lead to neurodegeneration, a process termed excitotoxicity.

"The basic idea is that too much glutamate receptor stimulation kills neurons in the striatum," Albin said. Previous cell-culture studies suggested that the NMDAR was responsible for excitotoxicity, but until now there had been little *in vivo* evidence for the phenomenon, he noted.

To simulate the effects of excitotoxicity, Albin's team introduced an extra copy of an NMDAR subunit called glutamate receptor ionotropic N-methyl-D-aspartate 2B (GRIN2B; NR2B) into a mouse model of HD. This extra subunit is known to cause higher overall levels of glutamatergic neuron activity *in vivo*.⁴

The team found that the extra NMDAR exacerbated HD-like pathology in the mice. After 100 weeks, HD mice that overexpressed NR2B had lower striatal dopamine receptor levels and fewer striatal neurons than HD mice that had normal NR2B levels.

Albin's study "is strong evidence that mutant huntingtin promotes vulnerability of striatal neurons to NMDA receptor-dependent excitotoxicity *in vivo*," said Giles Hardingham, principal investigator at the Centre for Neuroscience Research at the **University of Edinburgh**.

Albin said his findings support the use of NMDAR antagonists to treat HD, a conclusion that could be good news for Evotec, which is developing selective NMDAR antagonists to treat Alzheimer's disease (AD) and depression.

Earlier this month, Evotec announced a deal with **Roche** to advance the biotech's lead compound, EVT-101, into Phase II for depression and to start Phase I trials of a follow-on compound, EVT-103, for unspecified indications. Roche has an option to acquire rights to Evotec's entire EVT-100 series of compounds for all indications.

John Kemp, chief R&D officer at Evotec, said the compounds are selective for NR2B and the Albin study is "encouraging for trying EVT101 in HD. NR2B is a major subtype of the NMDA receptor in the striatum and cortex, so by targeting it you could get some of the neuroprotective effects without the side effects" that other companies have seen in trials of other NMDAR antagonists in which the compounds weren't sufficiently selective for specific neuronal populations.

One nonselective NMDAR antagonist, memantine, is already on the market for AD. The compound was developed by **Neurobiological Technologies Inc.** and is marketed by **Merz GmbH & Co. KGaA** as Axura in Germany, by **Forest Laboratories Inc.** as Namenda in the U.S. and by **H. Lundbeck A/S** as Ebixa in certain European countries.

Memantine is often prescribed off label for HD and is in a 60-patient Phase IV trial for HD-related cognitive and behavioral dysfunction.

Connecting the dots

Although the two studies suggest that AMPARs and NMDARs have opposite roles in HD neurotoxicity, it is unknown to what extent the two pathways overlap. For instance, it remains to be seen whether

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—Roger Albin,
University of Michigan

increasing receptor activation could lead to excitotoxicity in a similar way to NMDARs or whether NMDARs play a role in BDNF production.

Hardingham told *SciBX* that NMDARs ordinarily have a positive effect on neuronal survival but that toxicity develops after "inappropriate levels of NMDA receptor activity"

are exacerbated by changes in receptor expression and glutamate levels caused by the disease.

"The key is to block pathological NMDA receptor activity or signaling while sparing physiological synaptic NMDA receptor signaling," he added.

According to Hardingham, memantine fits the bill by interfering with "excessive, chronic activation of NMDA receptor activity without interfering with physiological trans-synaptic signaling."

Lynch thinks the two receptors act during different phases of neuronal activation, with the BDNF-stimulating effects of AMPAR activation preceding the longer-term effects of NMDAR activity.

It's also uncertain whether higher BDNF levels entirely account for the mechanism of action of Cortex's ampakines. Hardingham believes that ampakines "are likely to induce the expression of other activity-regulated genes besides BDNF" that could confer neuroprotective effects.

Alternatively, Albin suggested that the benefits of BDNF may be specific to the activation of striatal neurons, whereas NDMA-mediated excitotoxicity could involve activation of neurons throughout the forebrain.

"We don't know whether the NMDA pathway interacts with BDNF," he said. "There are multiple mechanisms of pathogenesis and they could all be correct."

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REFERENCES

1. Simmons, D.A. *et al. Proc. Natl. Acad. Sci. USA*; published online March 5, 2009; doi:10.1073/pnas.0811228106
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2. Heng, M.Y. *et al. J. Neurosci.*; published online March 11, 2009; doi:10.1523/JNEUROSCI.5599-08.2009
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3. Lou, K.-J. *SciBX* 2(6); doi:10.1038/scibx.2009.301
4. Tang, Y.P. *et al. Nature* 401, 63–69 (1999)

COMPANIES AND INSTITUTIONS MENTIONED

Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
CHDI Foundation Inc., New York, N.Y.
Cortex Pharmaceuticals Inc. (NYSE-A:COR), Irvine, Calif.
Evotec AG (Xetra:EVT; NASDAQ:EVTG), Hamburg, Germany
Forest Laboratories Inc. (NYSE:FRX), New York, N.Y.
H. Lundbeck A/S (CSE:LUN), Copenhagen, Denmark
Merz GmbH & Co. KGaA, Frankfurt, Germany
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