Huntington’s disease and neurogenesis: 
FGF-2 to the rescue?

Albert R. La Spada*

Departments of Laboratory Medicine, Medicine, and Neurology, and Center for Neurogenetics and Neurotherapeutics, 
University of Washington Medical Center, Box 357110, Room NW120, Seattle, WA 98195-7110

Huntington’s disease (HD) is an autosomal dominant inherited neurodegenerative disorder characterized by involuntary choreiform movements, cognitive impairment, metabolic abnormalities, and a relentlessly progressive course culminating in death 10–25 years after onset. Neuropathology studies of HD have established a stereotypical pattern of neurodegeneration and neuron loss, revealing that medium spiny neurons of the striatum are primarily affected followed by regions of the cerebral cortex (1). The genetic basis of HD is expansion of a CAG trinucleotide repeat within the huntingtin (hnt) gene, resulting in the production of htt protein containing an expanded glutamine tract (2). Such polyglutamine tract expansions are now known to be the cause of nine inherited neurological diseases. As polyglutamine expansions misfold to produce altered peptide conformers that are resistant to the normal cellular processes of protein turnover, “aggregates” or “inclusions” of the aberrant protein accumulate within neurons in HD brain regions (3). The occurrence of misfolded proteins that cannot be properly turned over is an emerging theme in neurodegenerative disease, as Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, prion diseases, and polyglutamine repeat diseases such as HD all share this feature (4).

Although much progress has been made in understanding the molecular genetic basis of HD, efforts to develop a cure or definitive treatment for HD have been complicated by an inadequate understanding of why certain populations of neurons degenerate within the striatum and cortex in HD despite widespread expression of the htt mutant protein throughout the central nervous system (CNS). Furthermore, polyglutamine-expanded htt can produce a myriad of nuclear and cellular abnormalities, accounting for the promulgation of a panoply of potential therapies directed at different aspects of the molecular pathology (5). One intriguing therapeutic option yet to be explored in HD is growth factor stimulation of endogenous neurogenesis. In this issue of PNAS, Jin et al. (6) present the results of a compelling preclinical trial of fibroblast growth factor 2 (FGF-2) in which they demonstrate that growth factor-mediated stimulation of neural stem cell proliferation should be added to the expanding armamentarium of candidate HD therapies.

The existence of populations of multipotent neural stem cells within the adult CNS was first recognized in 1962 (7). As it turns out, dense pools of such multipotent neural stem cells occur in circumscribed regions of the brain: the subventricular zone (SVZ) or subependymal zone (SEZ) and the hippocampal subgranular zone (SGZ). Numerous studies performed on multipotent neural precursors indicate that these cells retain the capacity to differentiate into a wide range of neurons and glia (reviewed in ref. 8). Neurons derived from such neural stem cells are capable of migrating to various regions of the CNS, receiving afferent innervation, forming axonal projections, and expressing neurotransmitters. A decade of work with such neural stem cells both in vivo and ex vivo has revealed that exposure to various combinations of growth factors [e.g., FGFs, epidermal growth factor (EGF), transforming growth factors (TGFs)] and/or neurotrophic factors [e.g., brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF)] permits directed differentiation along either neuronal or astrocytic lineages (9). The success of manipulating stem cells in culture has fueled interest in the ascertainment of undifferentiated stem cells and created a new field known as “regenerative medicine” in which stem cells are coaxed into forming cells of any lineage (including neural cells) and then delivered to regions of injury or degeneration to treat disease. Administration of growth factors to direct endogenous neural stem cells to differentiate into neurons or glia [as was done by Jin et al. (6)] thus differs from cell-replacement therapies based on delivery of ex vivo-derived neural cells to areas of injury or degeneration.

Because FGF-2 had been shown to stimulate proliferation of neural stem cells differentiated into striatal-like neurons and protect striatal neurons in toxin-induced models of HD (10, 11), Jin et al. (6) selected FGF-2 for their study. To test the ability of FGF-2 to promote neurogenesis in the SVZ in HD, they injected FGF-2 s.c. into HD R6/2 transgenic mice. The R6/2 mouse model is widely used for therapeutic trials and displays an early-onset, rapidly progressive HD-like neurological phenotype culminating in death at 12–15 weeks of age (12). The severity of the R6/2 phenotype stems from significant expression of a severely truncated version of the htt gene, containing the amino-terminal 6% of the htt coding region with an ~120-glutamine repeat. Using BrdUrd labeling, they observed a 150% increase in neuron stem cell proliferation in FGF-2-treated HD mice compared with untreated HD mice. This increase was more than five times greater than the proliferation increase noted for FGF-2-treated nontransgenic mice, suggesting that SVZ neural stem cells in HD are primed to proliferate in accordance with an earlier study that reported increased neurogenesis in human HD brains (13). Newly generated neurons were double-cortin- and DARPP-32-positive, verifying their migratory nature and striatal-like properties. Injections of a fluorescent tracer dye into the globus pallidus confirmed that the newly generated neurons were sending axonal projections to the proper neuroanatomical region, further suggesting that FGF-2 could induce endogenous neurogenesis in the SVZ of HD transgenic mice to yield new neurons that migrated into the basal ganglia and projected axons to the expected neuroanatomical location.

After documenting the effect of FGF-2 on SVZ neural stem cells, Jin et al. (6) evaluated FGF-2 as a treatment for HD in a cohort of R6/2 mice, initiating FGF-2 injections at ~8 weeks of age. FGF-2 therapy significantly extended average survival and maximum survival, reduced tremor, and improved motor function (based on rotarod performance) in treated HD R6/2 transgenic mice. As FGF-2 was administered by s.c. injection and HD R6/2 mice suffer from a wide range of metabolic ab__

Conflict of interest statement: No conflicts declared.

See companion article on page 18189.

*E-mail: laspada@u.washington.edu.

© 2005 by The National Academy of Sciences of the USA
further consideration. In an inducible triguing set of findings also deserves of cannabinoid 1 (CB1) receptor expres-
protein aggregates and by restoration by a decrease in nuclear and perinuclear phenotype in HD mice were accompanied a focus of future studies.

generated neurons from SVZ stem cells and determining whether and how newly therapeutic actions of FGF-2 in HD, enhancing cellular proliferation, FGF-2 (6) show that FGF-2 supplementation environments. However, because Jin (6) suggest that FGF-2 supplementation significantly diminished cell death in immortalized striatal-like neurons from homozgyous HD knock-in mice without enhancing cellular proliferation, FGF-2 also has neuroprotective properties independant of neurogenesis. Sorting out the therapeutic actions of FGF-2 in HD, and determining whether and how newly generated neurons from SVZ stem cells sustain degenerating neurons, should be a focus of future studies.

Improvements in the neurological phenotype in HD mice were accompanied by a decrease in nuclear and perinuclear protein aggregates and by restoration of cannabinoid 1 (CB1) receptor expression. The mechanistic basis of this intriguing set of findings also deserves further consideration. In an inducible model of HD, Yamamoto et al. (14) showed that HD mice with pronounced normal motor function and eliminate aggregates upon termination of mutant hit protein expression. Perhaps the FGF-2 treatment regimen, either through its neurogenesis or neuroprotective effects (or both), can sufficiently restore dys-
functional neurons to allow normal cellular processes of protein turnover, metabolism, etc. to be reinstated. Be-
cause endogenous and exogenous cannabinoinds appear to be neuroprotective and can induce neurogenesis (15, 16), restoration of CB1 receptor expression in FGF-2-treated HD mice raises the question of how the cannabinoid pathway might be linked to the recovery process. Future studies could address whether the CB1 receptor effect is a prerequisite for full recovery or is a simply an unrelated epiphenomenon not casually linked to FGF-2 action.

The study by Jin et al. (6) is noteworthy for many reasons. Recent studies done in neurodegenerative disease mouse models suggest that simple manipulations such as environmental enrichment or exercise are sufficient to profoundly impact disease course (17–19). As such interventions likely stimulate endogenous neurogenesis, there is good reason to believe that neural stem cell reserves already residing in the CNS could be called upon in certain disease states to retard progression. That FGF-2 displayed therapeutic efficacy through peripheral administration is encouraging because the difficulty of in situ CNS delivery could conceivably be avoided. However, this is a double-edged sword, because the need for repeated administration and concern over untoward peripheral effects may pose a problem for moving such a therapy from the bench to the bedside. Despite the remaining questions of mechanistic action and potential future translation, the work of Jin et al. (6) suggests that FGF-2 and the role of endogenous neurogenesis in the treatment of neurodegenerative disease are enticing enough to warrant further study and future attention.