21

BDNF in Huntington's Disease: Role in Pathogenesis and Treatment

Maryna Baydyuk and Baoji Xu
Georgetown University
USA

1. Introduction

Huntington's Disease (HD) is a neurodegenerative disorder characterized by motor, cognitive, and psychiatric abnormalities, and is inherited in an autosomal dominant fashion (Borrell-Pages et al., 2006). HD is caused by the CAG trinucleotide repeat expansion in the first exon of the gene encoding huntingtin (htt) (The Huntington's Disease Collaborative Research Group, 1993). This mutation is translated into a polyglutamine (poly Q) stretch near the amino terminus of htt, which results in a toxic gain of function (Gusella & MacDonald, 2000). Although htt is widely expressed in the human body and its mutation is not tissue-specific, the striatum is preferentially affected. The pathological changes in the striatum develop first in the caudate nucleus and then in the putamen, causing a 50-60% neuronal loss in these areas (Mann et al., 1993; Vonsattel & DiFiglia, 1998). Striatal atrophy is due to selective degeneration of medium-sized spiny neurons (MSNs), which comprise 90% of striatal neurons. Interestingly, the MSNs of the indirect pathway, responsible for inhibition of involuntary movement, are preferentially affected, causing motor symptoms of HD such as uncontrollable sequence of movements called "chorea". In the course of the disease, atrophy spreads to other brain regions, including the cerebral cortex, the globus pallidus (GP), and the thalamus (Mann et al., 1993).

The mechanism behind selective degeneration of striatal neurons remains to be elucidated, but it has been suggested that reduced trophic support renders striatal neurons more vulnerable to the toxic actions of mutant htt. Numerous *in vitro* and *in vivo* studies have shown that striatal neurons require brain-derived neurotrophic factor (BDNF) for their survival and function. A deficiency in BDNF-mediated signaling alone is sufficient to cause dendritic abnormalities and neuronal loss in the cerebral cortex and striatum (Baquet et al., 2004; Gorski et al., 2003). Moreover, reduced levels of striatal BDNF were detected in both HD animal models (Apostol et al., 2008; Gharami et al., 2008; Spires et al., 2004) and HD patients (Ferrer et al., 2000). These observations raise the possibility that reduced levels of striatal BDNF may significantly contribute to HD pathogenesis. In support of this view, the progression of HD is accelerated in *Bdnf* heterozygous mice (Canals et al., 2004). Furthermore, alterations of gene expression profile in the striatum have been shown to be similar in HD patients and mice in which the *Bdnf* gene is deleted in the cerebral cortex (Strand et al., 2007). Importantly, the receptor for BDNF, tropomyosin related kinase B (TrkB), is preferentially expressed in striatal MSNs of the indirect pathway, which may explain why this population of neurons is degenerated first in HD patients (Baydyuk et al., 2011).

BDNF found in the striatum is synthesized and anterogradely transported from the cell bodies located in the cerebral cortex, substantia nigra pars compacta, amygdala, and thalamus (Altar et al., 1997; Baquet et al., 2004). Since striatum does not produce BDNF but depends on it for proper function, abnormalities in anterograde transport and reduced gene expression in brain regions supplying BDNF to the striatum might contribute to neuronal dysfunction and death seen in HD (Gauthier et al., 2004; Zuccato et al., 2001). In light of these findings, efforts have been made to test whether increasing BDNF expression represents a valuable strategy for treatment of Huntington's Disease. Indeed, increasing striatal BDNF levels by a transgene, viral delivery, or stimulations that induce *Bdnf* gene expression have been shown to improve disease phenotypes in several HD mouse models (Cho et al., 2007; Gharami et al., 2008; Xie et al., 2010).

This book chapter will review these recent discoveries regarding the role of BDNF deficiency in the pathogenesis of HD and BDNF as a potential therapeutic agent for HD.

2. Wild-type but not mutant htt promotes *Bdnf* gene expression

The pathogenic mechanisms induced by mutant htt are not fully understood but are thought to involve the gain of toxic function and/or the loss of normal activities. Htt is a ubiquitously expressed protein, highly enriched in the brain (DiFiglia et al., 1995). While its exact functions are unknown, htt has been shown to be essential during embryogenesis and possess anti-apoptotic properties during adulthood (Dragatsis et al., 2000; O'Kusky et al., 1999; Rigamonti et al., 2000). Several mechanisms have been proposed for the neurodegenerative effect of the expanded polyQ tract in htt (Rubinsztein, 2002). Discovery of neuronal intranuclear inclusions in HD patients and HD mouse models led to the hypothesis that these protein aggregates might cause neuronal death. However, studies in mice and cultured neurons indicate that the formation of nuclear inclusions does not correlate with neuronal death (Hodgson et al., 1999; Kim et al., 1999; Laforet et al., 2001; Rubinsztein, 2002; Saudou et al., 1998). At present, the molecular basis for the toxic gain of function associated with mutant htt remains unclear.

The loss of a beneficial activity of normal htt has been proposed to contribute to the pathogenesis of HD. Wild type htt is known to regulate transcription of multiple genes, among which the gene encoding BDNF has received special attention (Zuccato et al., 2001). BDNF is a member of the neurotrophin family, which also includes nerve growth factor (NGF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) (Reichardt, 2006). BDNF has been shown to promote neuronal growth, survival, and differentiation by activating its TrkB receptor tyrosine kinase (Patapoutian & Reichardt, 2001). Upon binding to BDNF, activated full-length TrkB triggers multiple intracellular signaling cascades through protein-protein interactions (Chao, 2003). TrkB-initiated signaling pathways have been shown to promote cell survival by up-regulating the activity of survival genes and inhibiting the function of the proteins that lead to programmed cell death (Bhave et al., 1999; Encinas et al., 1999; Yamada et al., 2001). TrkB signaling pathways can also mediate various synaptic reorganization processes, including formation and maintenance of dendrites and dendritic spines (McAllister et al., 1999). In support of these in *vitro* observations, deletion of either the *TrkB* or *Bdnf* gene leads to cell atrophy, dendritic degeneration, and neuronal loss, as shown in the excitatory neurons of the dorsal forebrain (Gorski et al., 2003; Xu et al., 2000).

In rodents and humans, the *Bdnf* gene is transcribed from at least 8 discrete promoters, producing many different *Bdnf* mRNA species that encode the same protein (Aid et al., 2007). The different transcripts are generated in different tissues in a stimulus- and development-specific manner and may have differential subcellular localizations and targets (Metsis et al., 1993; Pattabiraman et al., 2005; Timmusk et al., 1993). Zuccato et al. have shown that wild-type htt enhances *Bdnf* transcription from promoter II, whereas mutant htt suppresses *Bdnf* transcription from promoter II as well as two other *Bdnf* promoters in cultured cells and the cerebral cortex of YAC72 transgenic mice expressing mutant htt with an expanded tract of 72 glutamines (Zuccato et al., 2001). The same group further investigated the mechanism underlying *Bdnf* gene regulation by wild-type and mutant htt, and found that wild-type htt promotes transcription of promoter II by sequestering the repressor element-1 transcription factor/neuron restrictive silencer factor (REST/NRSF) in the cytoplasm, thereby freeing the nucleus of the inhibitory complex and allowing transcription to occur (Zuccato et al., 2003). In contrast, mutant htt is unable to retain REST/NRSF complex in the cytoplasm, leading to aberrant accumulation of REST/NRSF in the nucleus and inhibition of *Bdnf* gene transcription. Interestingly, the effect of htt on *Bdnf* gene expression in cortical neurons is specific since the protein does not affect expression of two other neurotrophins, NGF and NT-3, in cortical neurons (Zuccato et al., 2003). In agreement with these findings, levels of *Bdnf* mRNA are reduced in the cerebral cortices of HD patients (Zuccato et al., 2008). It also has been shown that lower levels of BDNF are associated with higher numbers of CAG repeats in mutant *htt* alleles and correlate with the severity of the disease (Ciammola et al., 2007). It is important to note, however, that this autopsy data should be interpreted with caution. As mutant htt alters electrophysiological properties of cortical neurons (Cummings et al., 2009) and neuronal activity regulates *Bdnf* gene expression (Aid et al., 2007), we should not exclude the possibility that the observed reduction in cortical *Bdnf* mRNA levels may be secondary to neurodegeneration.

Although the contribution of suppressed *Bdnf* transcription to reduced BDNF levels in HD striatum is a widely accepted hypothesis, there are studies that contradict this idea. A reduction in *Bdnf* transcription would predict reduced levels of BDNF protein in cerebral cortices of both HD patients and mouse models. This prediction has been confirmed in one study (Zuccato et al., 2008) but not in another study (Gauthier et al., 2004) using post-mortem tissues from multiple control subjects and HD patients. Furthermore, *in situ hybridization* revealed normal levels of cortical *Bdnf* mRNA in aging YAC128 mice that express the whole human *htt* gene with 128 CAG repeats (Xie et al., 2010). Consistent with this observation, levels of cortical BDNF in YAC128 mice and R6/1 mice, another HD model, were found to be similar to those in WT mice (Gharami et al., 2008; Xie et al., 2010). Further analysis of *Bdnf* gene expression in other HD mouse models at various ages is necessary to clear the discrepancy. Despite the discrepancy in determining cortical *Bdnf* mRNA levels, a significant reduction in striatal BDNF has been consistently shown in both HD patients and animal models.

3. Htt promotes axonal BDNF transport

Studies by Gauthier et al. indicate that in addition to controlling *Bdnf* mRNA production in the cortex, wild-type htt may also regulate BDNF transport along the corticostriatal axes (Gauthier et al., 2004). The idea that htt is involved in intracellular trafficking arose from the subcellular

localization of htt and its association with various proteins of molecular motors. Although present in the nucleus, htt is predominantly found in the cytoplasm, where it interacts with the huntingtin-associated protein-1 (HAP1), a protein involved in axonal transport via association with $p150^{glued}$ subunit of dynactin, which is an essential part of the microtubule-based motor complex (Block-Galarza et al., 1997; Engelender et al., 1997; Li et al., 1998). While htt and other pathogenic polyQ-containing proteins have been shown to affect fast axonal transport (Gunawardena et al., 2003; Szebenyi et al., 2003), the link between deficient trafficking and selective neuronal degeneration has not been established. Gauthier and colleagues show that in normal condition wild-type htt promotes neuronal survival by facilitating the transport of BDNF-containing vesicles along microtubules. Consistent with a loss of function hypothesis, reduction in wild-type htt levels leads to attenuated BDNF trafficking. On the other hand, mutation in htt increases association of polyQ-htt and $p150^{glued}$ via HAP1 and prevents efficient movement of BDNF-containing vesicles along microtubules. They also demonstrate that disruption of BDNF transport leads to decreased neurotrophic support and neurotoxicity, which can be rescued by wild-type htt (Gauthier et al., 2004).

BDNF synthesized in the cortex and transported to the striatum via corticostriatal projections provides the main support for survival of striatal neurons in the adult brain (Altar et al., 1997; Baquet et al., 2004). Importantly, it has been shown that BDNF levels are reduced in the striatum but not in the cortex of HD patients (Gauthier et al., 2004). These observations are in agreement with the notion that both mechanisms, suppressed *Bdnf* gene expression and deficient BDNF transport, might concomitantly contribute to reduced levels of BDNF in the striata of HD patients and mouse models, thus providing strong evidence for BDNF as a crucial factor in the pathogenesis of HD.

4. Possible effects of mutant htt on BDNF maturation

One additional cause for reduced neurotrophic support of striatal neurons in HD may be due to deficits in processing of proBDNF. The proBDNF is a 32-kDa precursor protein that is cleaved to generate the mature BDNF protein of 14 kDa. Whereas the mature form binds to its TrkB receptor and promotes neuronal survival, the uncleaved proBDNF preferentially activates the low-affinity neurotrophin receptor p75NTR (Hempstead 2006), which is a member of the tumor necrosis factor receptor subfamily and is known to induce neuronal death via apoptosis (Frade & Barde, 1998; Teng et al., 2005).

As discussed earlier, immunoblotting analysis has consistently found a reduction in striatal levels of mature BDNF in HD mouse models (Apostol et al., 2008; Gharami et al., 2008; Spires et al., 2004; Xie et al., 2010) and HD patients (Ferrer et al., 2000; Gauthier et al., 2004). However, studies using ELISA assays reported normal striatal levels of BDNF in R6/1 HD mice (Canals et al., 2004; Pang et al., 2006) and increased striatal levels of BDNF in YAC72 mice (Seo et al., 2008). As ELISA assays detect both mature BDNF and proBDNF, this discrepancy suggests that maturation of proBDNF may be impaired in the striatum, leading to accumulation of proBDNF in the striatum. Impaired proBDNF maturation could be detrimental to striatal neurons, because they lose the protective effect of mature BDNF via TrkB receptor signaling and are subject to the apoptotic effect of proBDNF via the p75NTR receptor (Teng et al., 2005). As current BDNF antibodies are still problematic in detecting proBDNF on immunoblots, utilization of tagged *Bdnf* knockin mice (Matsumoto et al., 2008; Yang et al., 2009) will help uncover the effect of mutant htt on BDNF maturation.

A recent study has suggested that proteins involved in proBDNF axonal transport might also play a role in BDNF maturation (Yang et al., 2011). As discussed earlier, htt facilitates axonal transport via its interaction with HAP1 and the mutation in htt alters the formation of proper motor complex and inhibits BDNF transport (Gauthier et al., 2004). Yang et al. found that proBDNF interacts with both HAP1 and sortilin, a binding partner of p75NTR, to form a complex that prevents proBDNF degradation and modulates proBDNF targeting to dendrites and axonal organelles. Furthermore, their data suggest that the complex of proBDNF-HAP1-sortilin might facilitate cleavage and release of mature BDNF (Yang et al., 2011). Thus, it is possible that mutant htt can affect both BDNF maturation and trafficking via its interaction with HAP1.

5. BDNF and selectivity of striatal degeneration

Striatal neurons are not uniformly affected in HD. Immunohistochemical studies using tissues from HD patients have shown a greater decrease in the number of neurons co-expressing the dopamine receptor D2 (Drd2) and enkephalin (Enk) (Reiner et al., 1988). These neurons comprise the indirect pathway, projecting to the external segment of globus pallidus. The indirect pathway acts to terminate basal ganglia associated movements or suppress unwanted sequences of movements (Bolam et al., 2000). Hence, the loss of the indirect pathway neurons leads to disinhibition of the thalamus and increased facilitation of the motor cortex, producing hyperkinesias in HD patients (Calabresi et al., 1996). On the other hand, the direct pathway neurons co-expressing the dopamine receptor D1 (Drd1) and substance P (SP) are less affected in HD. In contrast, striatal interneurons containing acetylcholine, somatostatin/neuropeptide Y, or parvalbumin are spared in patients with HD; a striking phenomenon considering the fact that these cell populations comprise only 5% of striatal neurons (Ferrante et al., 1987a; Ferrante et al., 1987b). These findings suggest that the Drd2/Enk neurons of the striatum may be more vulnerable to the deleterious effects of mutated htt. However, the precise mechanism of this selective neuronal loss is unknown.

Genetic studies using HD mouse models with altered levels of BDNF indicate that BDNF plays an important role in this specificity of degeneration. Depletion of BDNF using heterozygous or forebrain-specific knockout mice results in alterations of striatal gene expression profiling that more closely recapitulates human HD than any other HD models (Strand et al., 2007). Deletion of one copy of the *Bdnf* gene in R6/1 HD mice resulted in early onset of the disease, more severe motor dysfunction, and led to a significant and selective loss of Drd2/Enk striatal neurons (Canals et al., 2004). Data originated in our laboratory show that the loss of striatal neurons was associated with reduced levels of mRNAs for both Enk and Drd2 in YAC128 HD mice (Xie et al., 2010), indicating selective degeneration of striatal neurons in the indirect pathway. Our recent data suggest that selective vulnerability of striatal neurons in the indirect pathway is due to differential expression of the TrkB receptor among striatal neurons. We found that the majority of the TrkB receptor was localized in striatal neurons of the indirect pathway in the adult mouse brain and deletion of TrkB receptor in the developing striatum caused selective loss of this neuronal population (Baydyuk et al., 2011). Together, all these findings indicate that a decrease in striatal BDNF can lead to dysfunction and death of MSNs in the indirect pathway, producing severe motor phenotype as seen in HD. Hence, restoring BDNF levels in the striatum may delay or even stop disease progression.

6. Increasing BDNF expression rescues disease phenotypes in HD mouse models

The evidence discussed above clearly indicates that the reduction in striatal BDNF levels plays a pivotal role in the pathogenesis of HD. Therefore, it is not surprising that efforts have been made to examine whether increasing BDNF expression represents a valuable strategy for treatment of Huntington's Disease. Indeed, increasing striatal BDNF levels via stimulation that induces *Bdnf* gene expression (Duan et al., 2003; Peng et al., 2008; Simmons et al., 2009; Spires et al., 2004) or by viral delivery (Cho et al., 2007) has been shown to improve disease phenotypes in several HD mouse models.

Early symptoms of HD are manifested by cognitive and memory deficits that start before characteristic motor dysfunction (Ho et al., 2003; Lawrence et al., 1998). In HD mouse models, impaired learning and memory, measured as hippocampal long-term potentiation (LTP), occur prior to motor deficits and neuronal loss (Mazarakis et al., 2005; Murphy et al., 2000; Van Raamsdonk et al., 2005). LTP, a form of synaptic plasticity, is potentiated by release of BDNF. Thus, reduced levels of BDNF in HD patients and mice can disrupt synaptic changes important for learning and memory formation. Applying low concentrations of BDNF to hippocampal slices prepared from HD mice fully restores LTP (Lynch et al., 2007). Furthermore, up-regulation of endogenous BDNF levels with an ampakine, a positive modulator of AMPA-type glutamate receptors, rescues synaptic plasticity and reduces learning deficits in HD mice (Simmons et al., 2009).

Altered neurogenesis has been reported in HD mouse models and in human postmortem brains (Curtis et al., 2003; Gil et al., 2005; Phillips et al., 2005). It has been shown that in addition to promoting survival and inducing synaptic plasticity, BDNF also regulates adult neurogenesis (Bath et al., 2011; Henry et al., 2007; Scharfman et al., 2005). The adenoviral delivery of BDNF and Noggin (a known suppressor of gliogenesis) to the striatum of R6/2 HD mice resulted in induction of striatal neurogenesis (Cho et al., 2007). The majority of the newly born neurons differentiated to MSNs and became functional, leading to delayed motor impairment and prolonged survival in R6/2 mice. Similar improvements have been seen in the same HD mouse model after administration of the antidepressant sertraline (Peng et al., 2008). By increasing BDNF levels and stimulating neurogenesis, sertraline treatment resulted in improved motor performance, reduced striatal atrophy, and prolonged survival.

To more directly evaluate the effect of increasing cortical BDNF supply to the striatum on the progression of HD, we overexpressed BDNF in the mouse forebrain by employing a *Bdnf* transgene under the control of the promoter for Ca^{2+}/calmodulin-dependent protein kinase II alpha (Gharami et al., 2008; Xie et al., 2010). This transgene starts to express BDNF in the cerebral cortex in the first postnatal week and reaches plateau in the third postnatal week, as does the endogenous *Bdnf* gene (Huang et al., 1999). It also expresses at low levels in the striatum where the endogenous *Bdnf* gene is mostly inactive (Gharami et al., 2008; Xie et al., 2010). We found that the *Bdnf* transgene was able to greatly increase BDNF levels in the striata of R6/1 and YAC128 mice, indicating that overexpressed BDNF in the cortex is efficiently transported to the striatum despite expression of mutant htt. Importantly, BDNF overexpression reversed brain atrophy, normalized the expression of several important genes in the striatum, and ameliorated deficits in motor coordination in these two HD

mouse models (Gharami et al., 2008; Xie et al., 2010). In addition, overexpression of BDNF in YAC128 mice prevented loss of striatal neurons, normalized spine abnormalities of medium-sized spiny neurons, and significantly improved procedural learning (Xie et al., 2010). In summary, these studies suggest that increasing striatal BDNF supply may have therapeutic potential for HD.

7. Conclusion

Many pathways have been proposed to contribute to the pathogenesis of HD. Recent studies have identified complex molecular mechanisms that mediate neuronal dysfunction and death; these include transcriptional dysregulation, excitotoxicity, impaired axonal transport, and altered synaptic transmission. The findings presented in this chapter support the hypothesis that reduced striatal BDNF plays a crucial role in HD pathogenesis. Currently, drugs used to treat HD act on the symptoms and do not slow or stop the disease progression. Attempting to restore striatal BDNF levels or activate downstream signaling pathways may have therapeutic potential in treating HD patients.

8. Acknowledgment

This work was supported by a grant from the National Institutes of Health (R01 NS050596) to BX.

9. References

Aid T, Kazantseva A, Piirsoo M, Palm K, Timmusk T. (2007). Mouse and rat BDNF gene structure and expression revisited. *Journal of Neuroscience Research,* Vol.85, No.3, (Feb 15), pp.525-535, ISSN 0360-4012

Altar CA, Cai N, Bliven T, Juhasz M, Conner JM, et al. (1997). Anterograde transport of brain-derived neurotrophic factor and its role in the brain. *Nature,* Vol.389, No.6653, (Oct 23), pp.856-860, ISSN 0028-0836

Apostol BL, Simmons DA, Zuccato C, Illes K, Pallos J, et al. (2008). CEP-1347 reduces mutant huntingtin-associated neurotoxicity and restores BDNF levels in R6/2 mice. *Molecular and Cellular Neuroscience,* Vol.39, No.1, (Sep), pp.8-20, ISSN 1095-9327

Baquet ZC, Gorski JA, Jones KR. (2004). Early striatal dendrite deficits followed by neuron loss with advanced age in the absence of anterograde cortical brain-derived neurotrophic factor. *Journal of Neuroscience,* Vol.24, No.17, (Apr 28), pp.4250-4258, ISSN 1529-2401

Bath KG, Akins MR, Lee FS. (2011). BDNF control of adult SVZ neurogenesis. *Developmental Psychobiology,* (Mar 22), ISSN 1098-2302

Baydyuk M, Russell T, Liao GY, Zang K, An JJ, et al. (2011). TrkB receptor controls striatal formation by regulating the number of newborn striatal neurons. *Proceedings of National Academy of Sciences U S A,* Vol.108, No.4, (Jan 25), pp.1669-1674, ISSN 1091-6490

Bhave SV, Ghoda L, Hoffman PL. (1999). Brain-derived neurotrophic factor mediates the anti-apoptotic effect of NMDA in cerebellar granule neurons: signal transduction cascades and site of ethanol action. *Journal of Neuroscience,* Vol.19, No.9, (May 1), pp.3277-3286, ISSN 0270-6474

Block-Galarza J, Chase KO, Sapp E, Vaughn KT, Vallee RB, et al. (1997). Fast transport and retrograde movement of huntingtin and HAP 1 in axons. *Neuroreport,* Vol.8, No.9-10, (Jul 7), pp.2247-2251, ISSN 0959-4965

Bolam JP, Hanley JJ, Booth PA, Bevan MD. (2000). Synaptic organisation of the basal ganglia. *Journal of Anatomy,* Vol.196 (Pt 4), (May), pp.527-542, ISSN 0021-8782

Borrell-Pages M, Zala D, Humbert S, Saudou F. (2006). Huntington's disease: from huntingtin function and dysfunction to therapeutic strategies. *Cellular and Molecular Life Science,* Vol.63, No.22, (Nov), pp.2642-2660, ISSN 1420-682X

Calabresi P, Pisani A, Mercuri NB, Bernardi G. (1996). The corticostriatal projection: from synaptic plasticity to dysfunctions of the basal ganglia. *Trends in Neuroscience,* Vol.19, No.1, (Jan), pp.19-24, ISSN 0166-2236

Canals JM, Pineda JR, Torres-Peraza JF, Bosch M, Martin-Ibanez R, et al. (2004). Brain-derived neurotrophic factor regulates the onset and severity of motor dysfunction associated with enkephalinergic neuronal degeneration in Huntington's disease. *Journal of Neuroscience,* Vol.24, No.35, (Sep 1), pp.7727-7739, ISSN 1529-2401

Chao MV. (2003). Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nature Reviews Neuroscience,* Vol.4, No.4, (Apr), pp.299-309, ISSN 1471-003X

Cho SR, Benraiss A, Chmielnicki E, Samdani A, Economides A, Goldman SA. (2007). Induction of neostriatal neurogenesis slows disease progression in a transgenic murine model of Huntington disease. *Journal of Clinical Investigations,* Vol.117, No.10, (Oct), pp.2889-2902, ISSN 0021-9738

Ciammola A, Sassone J, Cannella M, Calza S, Poletti B, et al. (2007). Low brain-derived neurotrophic factor (BDNF) levels in serum of Huntington's disease patients. *Am J Med Genet B Neuropsychiatr Genet,* Vol.144B, No.4, (Jun 5), pp.574-577, ISSN 1552-4841

Cummings DM, Andre VM, Uzgil BO, Gee SM, Fisher YE, et al. (2009). Alterations in cortical excitation and inhibition in genetic mouse models of Huntington's disease. *Journal of Neuroscience,* Vol.29, No.33, (Aug 19), pp.10371-10386, ISSN 1529-2401

Curtis MA, Penney EB, Pearson AG, van Roon-Mom WM, Butterworth NJ, et al. (2003). Increased cell proliferation and neurogenesis in the adult human Huntington's disease brain. *Proceedings of National Academy of Science U S A,* Vol.100, No.15, (Jul 22), pp.9023-9027, ISSN 0027-8424

DiFiglia M, Sapp E, Chase K, Schwarz C, Meloni A, et al. (1995). Huntingtin is a cytoplasmic protein associated with vesicles in human and rat brain neurons. *Neuron,* Vol.14, No.5, (May), pp.1075-1081, ISSN 0896-6273

Dragatsis I, Levine MS, Zeitlin S. (2000). Inactivation of Hdh in the brain and testis results in progressive neurodegeneration and sterility in mice. *Nature Genetics,* Vol.26, No.3, (Nov), pp.300-306, ISSN 1061-4036

Duan W, Guo Z, Jiang H, Ware M, Li XJ, Mattson MP. (2003). Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. *Proceedings of National Academy of Science U S A,* Vol.100, No.5, (Mar 4), pp.2911-2916, ISSN 0027-8424

Encinas M, Iglesias M, Llecha N, Comella JX. (1999). Extracellular-regulated kinases and phosphatidylinositol 3-kinase are involved in brain-derived neurotrophic factor-mediated survival and neuritogenesis of the neuroblastoma cell line SH-SY5Y. *Journal of Neurochemistry,* Vol.73, No.4, (Oct), pp.1409-1421, ISSN 0022-3042

Engelender S, Sharp AH, Colomer V, Tokito MK, Lanahan A, et al. (1997). Huntingtin-associated protein 1 (HAP1) interacts with the p150Glued subunit of dynactin. *Human Molecular Genetics,* Vol.6, No.13, (Dec), pp.2205-2212, ISSN 0964-6906

Ferrante RJ, Beal MF, Kowall NW, Richardson EP, Jr., Martin JB. (1987a). Sparing of acetylcholinesterase-containing striatal neurons in Huntington's disease. *Brain Research,* Vol.411, No.1, (May 12), pp.162-166, ISSN 0006-8993

Ferrante RJ, Kowall NW, Beal MF, Martin JB, Bird ED, Richardson EP, Jr. (1987b). Morphologic and histochemical characteristics of a spared subset of striatal neurons in Huntington's disease. *Journal of Neuropathology and Experimental Neurology,* Vol.46, No.1, (Jan), pp.12-27, ISSN 0022-3069

Ferrer I, Goutan E, Marin C, Rey MJ, Ribalta T. (2000). Brain-derived neurotrophic factor in Huntington disease. *Brain Research,* Vol.866, No.1-2, (Jun 2), pp.257-261, ISSN 0006-8993

Frade JM, Barde YA. (1998). Nerve growth factor: two receptors, multiple functions. *Bioessays,* Vol.20, No.2, (Feb), pp.137-145, ISSN 0265-9247

Gauthier LR, Charrin BC, Borrell-Pages M, Dompierre JP, Rangone H, et al. (2004). Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. *Cell,* Vol.118, No.1, (Jul 9), pp.127-138, ISSN 0092-8674

Gharami K, Xie Y, An JJ, Tonegawa S, Xu B. (2008). Brain-derived neurotrophic factor over-expression in the forebrain ameliorates Huntington's disease phenotypes in mice. *Journal of Neurochemistry,* Vol.105, No.2, (Apr), pp.369-379, ISSN 1471-4159

Gil JM, Mohapel P, Araujo IM, Popovic N, Li JY, et al. (2005). Reduced hippocampal neurogenesis in R6/2 transgenic Huntington's disease mice. *Neurobiology of Disease,* Vol.20, No.3, (Dec), pp.744-751, ISSN 0969-9961

Gorski JA, Zeiler SR, Tamowski S, Jones KR. (2003). Brain-derived neurotrophic factor is required for the maintenance of cortical dendrites. *Journal of Neuroscience,* Vol.23, No.17, (Jul 30), pp.6856-6865, ISSN 1529-2401

Gunawardena S, Her LS, Brusch RG, Laymon RA, Niesman IR, et al. (2003). Disruption of axonal transport by loss of huntingtin or expression of pathogenic polyQ proteins in Drosophila. *Neuron,* Vol.40, No.1, (Sep 25), pp.25-40, ISSN 0896-6273

Gusella JF, MacDonald ME. (2000). Molecular genetics: unmasking polyglutamine triggers in neurodegenerative disease. *Nature Reviews Neuroscience,* Vol.1, No.2, (Nov), pp.109-115, ISSN 1471-003X

Hempstead BL. (2006). Dissecting the diverse actions of pro- and mature neurotrophins. *Current Alzheimer Research,* Vol.3, No.1, (Feb), pp.19-24, ISSN 1567-2050

Henry RA, Hughes SM, Connor B. (2007). AAV-mediated delivery of BDNF augments neurogenesis in the normal and quinolinic acid-lesioned adult rat brain. *European Journal of Neuroscience,* Vol.25, No.12, (Jun), pp.3513-3525, ISSN 0953-816X

Ho AK, Sahakian BJ, Brown RG, Barker RA, Hodges JR, et al. (2003). Profile of cognitive progression in early Huntington's disease. *Neurology,* Vol.61, No.12, (Dec 23), pp.1702-1706, ISSN 1526-632X

Hodgson JG, Agopyan N, Gutekunst CA, Leavitt BR, LePiane F, et al. (1999). A YAC mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration. *Neuron,* Vol.23, No.1, (May), pp.181-192, ISSN 0896-6273

Huang ZJ, Kirkwood A, Pizzorusso T, Porciatti V, Morales B, et al. (1999). BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. *Cell,* Vol.98, No.6, (Sep 17), pp.739-755, ISSN 0092-8674

Kim M, Lee HS, LaForet G, McIntyre C, Martin EJ, et al. (1999). Mutant huntingtin expression in clonal striatal cells: dissociation of inclusion formation and neuronal survival by caspase inhibition. *Journal of Neuroscience,* Vol.19, No.3, (Feb 1), pp.964-973, ISSN 0270-6474

Laforet GA, Sapp E, Chase K, McIntyre C, Boyce FM, et al. (2001). Changes in cortical and striatal neurons predict behavioral and electrophysiological abnormalities in a transgenic murine model of Huntington's disease. *Journal of Neuroscience,* Vol.21, No.23, (Dec 1), pp.9112-9123, ISSN 1529-2401

Lawrence AD, Hodges JR, Rosser AE, Kershaw A, ffrench-Constant C, et al. (1998). Evidence for specific cognitive deficits in preclinical Huntington's disease. *Brain,* Vol.121 (Pt 7), (Jul), pp.1329-1341, ISSN 0006-8950

Li SH, Gutekunst CA, Hersch SM, Li XJ. (1998). Interaction of huntingtin-associated protein with dynactin P150Glued. *Journal of Neuroscience,* Vol.18, No.4, (Feb 15), pp.1261-1269, ISSN 0270-6474

Lynch G, Kramar EA, Rex CS, Jia Y, Chappas D, et al. (2007). Brain-derived neurotrophic factor restores synaptic plasticity in a knock-in mouse model of Huntington's disease. *Journal of Neuroscience,* Vol.27, No.16, (Apr 18), pp.4424-4434, ISSN 1529-2401

Mann DM, Oliver R, Snowden JS. (1993). The topographic distribution of brain atrophy in Huntington's disease and progressive supranuclear palsy. *Acta Neuropathologica,* Vol.85, No.5, pp.553-559, ISSN 0001-6322

Matsumoto T, Rauskolb S, Polack M, Klose J, Kolbeck R, et al. (2008). Biosynthesis and processing of endogenous BDNF: CNS neurons store and secrete BDNF, not pro-BDNF. *Nature Neuroscience,* Vol.11, No.2, (Feb), pp.131-133, ISSN 1097-6256

Mazarakis NK, Cybulska-Klosowicz A, Grote H, Pang T, Van Dellen A, et al. (2005). Deficits in experience-dependent cortical plasticity and sensory-discrimination learning in presymptomatic Huntington's disease mice. *Journal of Neuroscience,* Vol.25, No.12, (Mar 23), pp.3059-3066, ISSN 1529-2401

McAllister AK, Katz LC, Lo DC. (1999). Neurotrophins and synaptic plasticity. *Annual Reviews Neuroscience,* Vol.22, pp.295-318, ISSN 0147-006X

Metsis M, Timmusk T, Arenas E, Persson H. (1993). Differential usage of multiple brain-derived neurotrophic factor promoters in the rat brain following neuronal activation. *Proceedings of National Academy of Science U S A,* Vol.90, No.19, (Oct 1), pp.8802-8806, ISSN 0027-8424

Murphy KP, Carter RJ, Lione LA, Mangiarini L, Mahal A, et al. (2000). Abnormal synaptic plasticity and impaired spatial cognition in mice transgenic for exon 1 of the human Huntington's disease mutation. *Journal of Neuroscience,* Vol.20, No.13, (Jul 1), pp.5115-5123, ISSN 1529-2401

O'Kusky JR, Nasir J, Cicchetti F, Parent A, Hayden MR. (1999). Neuronal degeneration in the basal ganglia and loss of pallido-subthalamic synapses in mice with targeted disruption of the Huntington's disease gene. *Brain Research,* Vol.818, No.2, (Feb 13), pp.468-479, ISSN 0006-8993

Pang TY, Stam NC, Nithianantharajah J, Howard ML, Hannan AJ. (2006). Differential effects of voluntary physical exercise on behavioral and brain-derived neurotrophic factor expression deficits in Huntington's disease transgenic mice. *Neuroscience,* Vol.141, No.2, (Aug 25), pp.569-584, ISSN 0306-4522

Patapoutian A, Reichardt LF. (2001). Trk receptors: mediators of neurotrophin action. *Current Opinions in Neurobiology,* Vol.11, No.3, (Jun), pp.272-280, ISSN 0959-4388

Pattabiraman PP, Tropea D, Chiaruttini C, Tongiorgi E, Cattaneo A, Domenici L. (2005). Neuronal activity regulates the developmental expression and subcellular localization of cortical BDNF mRNA isoforms in vivo. *Molecular and Cellular Neuroscience,* Vol.28, No.3, (Mar), pp.556-570, ISSN 1044-7431

Peng Q, Masuda N, Jiang M, Li Q, Zhao M, et al. (2008). The antidepressant sertraline improves the phenotype, promotes neurogenesis and increases BDNF levels in the R6/2 Huntington's disease mouse model. *Experimental Neurology,* Vol.210, No.1, (Mar), pp.154-163, ISSN 0014-4886

Phillips W, Morton AJ, Barker RA. (2005). Abnormalities of neurogenesis in the R6/2 mouse model of Huntington's disease are attributable to the in vivo microenvironment. *Journal of Neuroscience,* Vol.25, No.50, (Dec 14), pp.11564-11576, ISSN 1529-2401

Reichardt LF. (2006). Neurotrophin-regulated signalling pathways. *Philos Trans R Soc Lond B Biol Sci,* Vol.361, No.1473, (Sep 29), pp.1545-1564, ISSN 0962-8436

Reiner A, Albin RL, Anderson KD, D'Amato CJ, Penney JB, Young AB. (1988). Differential loss of striatal projection neurons in Huntington disease. *Proceedings of National Academy of Science U S A,* Vol.85, No.15, (Aug), pp.5733-5737, ISSN 0027-8424

Rigamonti D, Bauer JH, De-Fraja C, Conti L, Sipione S, et al. (2000). Wild-type huntingtin protects from apoptosis upstream of caspase-3. *Journal of Neuroscience,* Vol.20, No.10, (May 15), pp.3705-3713, ISSN 1529-2401

Rubinsztein DC. (2002). Lessons from animal models of Huntington's disease. *Trends in Genetics,* Vol.18, No.4, (Apr), pp.202-209, ISSN 0168-9525

Saudou F, Finkbeiner S, Devys D, Greenberg ME. (1998). Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. *Cell,* Vol.95, No.1, pp.55-66, ISSN 0092-8674

Scharfman H, Goodman J, Macleod A, Phani S, Antonelli C, Croll S. (2005). Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. *Experimental Neurology,* Vol.192, No.2, (Apr), pp.348-356, ISSN 0014-4886

Seo H, Kim W, Isacson O. (2008). Compensatory changes in the ubiquitin-proteasome system, brain-derived neurotrophic factor and mitochondrial complex II/III in YAC72 and R6/2 transgenic mice partially model Huntington's disease patients. *Human Molecular Genetics,* Vol.17, No.20, (Oct 15), pp.3144-3153, ISSN 1460-2083

Simmons DA, Rex CS, Palmer L, Pandyarajan V, Fedulov V, et al. (2009). Up-regulating BDNF with an ampakine rescues synaptic plasticity and memory in Huntington's disease knockin mice. *Proceedings of National Academy of Science U S A,* Vol.106, No.12, (Mar 24), pp.4906-4911, ISSN 1091-6490

Spires TL, Grote HE, Varshney NK, Cordery PM, van Dellen A, et al. (2004). Environmental enrichment rescues protein deficits in a mouse model of Huntington's disease, indicating a possible disease mechanism. *Journal of Neuroscience,* Vol.24, No.9, (Mar 3), pp.2270-2276, ISSN 1529-2401

Strand AD, Baquet ZC, Aragaki AK, Holmans P, Yang L, et al. (2007). Expression profiling of Huntington's disease models suggests that brain-derived neurotrophic factor depletion plays a major role in striatal degeneration. *Journal of Neuroscience,* Vol.27, No.43, (Oct 24), pp.11758-11768, ISSN 1529-2401

Szebenyi G, Morfini GA, Babcock A, Gould M, Selkoe K, et al. (2003). Neuropathogenic forms of huntingtin and androgen receptor inhibit fast axonal transport. *Neuron,* Vol.40, No.1, (Sep 25), pp.41-52, ISSN 0896-6273

Teng HK, Teng KK, Lee R, Wright S, Tevar S, et al. (2005). ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. *Journal of Neuroscience,* Vol.25, No.22, (Jun 1), pp.5455-5463, ISSN 1529-2401

The Huntington's Disease Collaborative Research Group. (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell,* Vol.72, No.6, (Mar 26), pp.971-983, ISSN 8458085

Timmusk T, Palm K, Metsis M, Reintam T, Paalme V, et al. (1993). Multiple promoters direct tissue-specific expression of the rat BDNF gene. *Neuron,* Vol.10, No.3, (Mar), pp.475-489, ISSN 0896-6273

Van Raamsdonk JM, Pearson J, Slow EJ, Hossain SM, Leavitt BR, Hayden MR. (2005). Cognitive dysfunction precedes neuropathology and motor abnormalities in the YAC128 mouse model of Huntington's disease. *Journal of Neuroscience,* Vol.25, No.16, (Apr 20), pp.4169-4180, ISSN 1529-2401

Vonsattel JP, DiFiglia M. (1998). Huntington disease. *Journal of Neuropathology and Experimental Neurology,* Vol.57, No.5, (May), pp.369-384, ISSN 0022-3069

Xie Y, Hayden MR, Xu B. (2010). BDNF overexpression in the forebrain rescues Huntington's disease phenotypes in YAC128 mice. *Journal of Neuroscience,* Vol.30, No.44, (Nov 3), pp.14708-14718, ISSN 1529-2401

Xu B, Zang K, Ruff NL, Zhang YA, McConnell SK, et al. (2000). Cortical degeneration in the absence of neurotrophin signaling: dendritic retraction and neuronal loss after removal of the receptor TrkB. *Neuron,* Vol.26, No.1, (Apr), pp.233-245, ISSN 0896-6273

Yamada M, Tanabe K, Wada K, Shimoke K, Ishikawa Y, et al. (2001). Differences in survival-promoting effects and intracellular signaling properties of BDNF and IGF-1 in cultured cerebral cortical neurons. *Journal of Neurochemistry,* Vol.78, No.5, (Sep), pp.940-951, ISSN 0022-3042

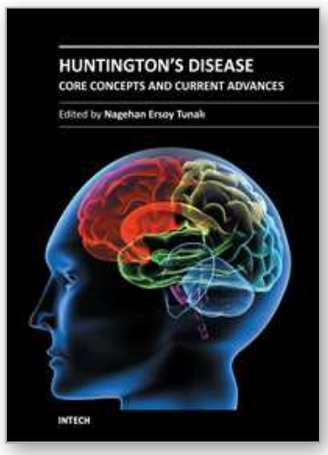
Yang J, Siao CJ, Nagappan G, Marinic T, Jing D, et al. (2009). Neuronal release of proBDNF. *Nature Neuroscience,* Vol.12, No.2, (Feb), pp.113-115, ISSN 1546-1726

Yang M, Lim Y, Li X, Zhong JH, Zhou XF. (2011). Precursor of brain-derived neurotrophic factor (proBDNF) forms a complex with Huntingtin-associated protein-1 (HAP1) and sortilin that modulates proBDNF trafficking, degradation, and processing. *Journal of Biological Chemistry,* Vol.286, No.18, (May 6), pp.16272-16284, ISSN 1083-351X

Zuccato C, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, et al. (2001). Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. *Science,* Vol.293, No.5529, (Jul 20), pp.493-498, ISSN 0036-8075

Zuccato C, Marullo M, Conforti P, MacDonald ME, Tartari M, Cattaneo E. (2008). Systematic assessment of BDNF and its receptor levels in human cortices affected by Huntington's disease. *Brain Pathology,* Vol.18, No.2, (Apr), pp.225-238, ISSN 1015-6305

Zuccato C, Tartari M, Crotti A, Goffredo D, Valenza M, et al. (2003). Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. *Nature Genetics,* Vol.35, No.1, (Sep), pp.76-83, ISSN 1061-4036



Huntington's Disease - Core Concepts and Current Advances
Edited by Dr Nagehan Ersoy Tunali

ISBN 978-953-307-953-0
Hard cover, 554 pages
Publisher InTech
Published online 15, February, 2012
Published in print edition February, 2012

Huntington's Disease is one of the well-studied neurodegenerative conditions, a quite devastating and currently incurable one. It is a brain disorder that causes certain types of neurons to become damaged, causing various parts of the brain to deteriorate and lose their function. This results in uncontrolled movements, loss of intellectual capabilities and behavioural disturbances. Since the identification of the causative mutation, there have been many significant developments in understanding the cellular and molecular perturbations. This book, "Huntington's Disease - Core Concepts and Current Advances", was prepared to serve as a source of up-to-date information on a wide range of issues involved in Huntington's Disease. It will help the clinicians, health care providers, researchers, graduate students and life science readers to increase their understanding of the clinical correlates, genetic aspects, neuropathological findings, cellular and molecular events and potential therapeutic interventions involved in HD. The book not only serves reviewed fundamental information on the disease but also presents original research in several disciplines, which collectively provide comprehensive description of the key issues in the area.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Maryna Baydyuk and Baoji Xu (2012). BDNF in Huntington’s Disease: Role in Pathogenesis and Treatment, Huntington's Disease - Core Concepts and Current Advances, Dr Nagehan Ersoy Tunali (Ed.), ISBN: 978-953-307-953-0, InTech, Available from: http://www.intechopen.com/books/huntington-s-disease-core-concepts-and-current-advances/bdnf-in-huntington-s-disease-role-in-pathogenesis-and-treatment

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen