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Axonopathy in Huntington's disease

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Abstract

Personality changes, psychiatric disturbances and cognitive abnormalities frequently characterise the prodromal phase in Huntington's disease (HD), a devastating monogenic neurodegenerative disorder manifesting with abnormal motor movements and early death. Selective loss of medium-sized spiny striatal neurons has been related to the onset of motor symptoms but it does not completely explain the psychiatric and cognitive changes that often precede motor abnormalities. Here we review the evidence of synaptic and axonal dysfunction and neurite dystrophy preceding neuronal loss in HD patients and models. We discuss possible mechanisms leading to dysfunction of the axonal and synaptic compartments and identify potential novel targets for effective therapeutic intervention.

Background

Huntington's disease (HD) is a devastating hereditary disorder that manifests clinically in the 4^{th} or 5^{th} decade of life with psychiatric, cognitive and motor dysfunctions relentlessly and inexorably progressing to death within 15-20 years of onset. HD follows an autosomal dominant pattern of inheritance with a prevalence of 4-10 per 100000 in Western European populations and it is caused by an unstable expansion of a CAG repeat close to the 5' end of the *IT15* (for "interesting transcript") gene located on the short arm of human chromosome 4. HD is one of at least 9 disorders caused by an expansion in the length of a CAG repeat. Normal individuals have between 8-36 CAG repeats, coding for a polyglutamine (polyQ) stretch, at the N-terminus of the protein product of *IT15*, a 350 kDa protein called Huntingtin (HTT), whereas affected patients have more than 40 CAG repeats (HDCRG, 1993).

The main neuropathological hallmark of HD is the selective degeneration of a subpopulation of striatal neurons, the GABAergic medium sized spiny neurons (MSSN), which leads to marked atrophy of the striatum, while other striatal neurons such as the large aspiny neurons and interneurons are relatively spared. Other affected neuronal populations include the pyramidal neurons of layers III and V of the cortex (Vonsattel, et al., 1985). Microscopically, HD is characterised by the formation of intranuclear and neuropil aggregates where N-terminal fragments of mutant HTT (mHTT) with the expanded polyQ repeat localise. In general, intranuclear aggregates (NII) are bigger in size than neuropil aggregates, but the latter are related to mHTT toxicity, while larger NII probably form in an attempt of the cell to neutralise the toxic action of N-terminal soluble mHTT fragments (Arrasate, et al., 2004, Davies, et al., 1997, DiFiglia, et al., 1997, Saudou, et al., 1998).

Since the discovery of the HD gene and mutation, the mechanism of mHTT toxicity to specific neuronal populations is still largely unclear. However, the subtle onset of behavioural and psychiatric symptoms long before motor impairment suggests that dysfunction of brain

connections controlling emotional and behavioural responses may characterise the early phases of the disease. Indeed synaptic and axonal dysfunction preceding cell loss have been shown, giving a possible explanation to early symptoms and potential novel therapeutic targets to defeat this devastating disorder.

Here we will review reports of early axonal dysfunction in HD patients and *in vivo* and *in vitro* models, we will discuss the evidence of the mechanisms underlying this dysfunction and we will indicate how targeting pathology at this level promises to open a new avenue in the therapeutic treatment of HD.

The normal role of huntingtin in the neurons

Although gain of a toxic function of mHTT primarily causes pathology, a loss of HTT normal function is a contributory factor to HD pathogenesis (Borrell-Pages, et al., 2006, Cattaneo, et al., 2005). HTT is widely expressed in neuronal and non-neuronal tissues and is particularly abundant in neurons of the striatum and layers III and V of the cortex. Within the cell, it has a predominant cytoplasmic and perinuclear distribution, is associated to a variety of organelles including the Golgi complex and the mitochondrion and localises to vesicular structures such as microtubules and synaptic vesicles in neurites and synapses (Zuccato, et al., 2010). HTT distribution in a "beads on a string" fashion in axons and their terminals suggests a role in vesicle axonal transport (DiFiglia, et al., 1995, Sharp, et al., 1995).

Hdh gene inactivation in mice results in developmental retardation and death between embryonic days 8.5 and 10.5 (Duyao, et al., 1995, Nasir, et al., 1995, Zeitlin, et al., 1995), supporting a role in embryonic development and an antiapoptotic function of HTT. Behavioural and cognitive defects in mice heterozygous for a targeted disruption in HTT exon

5 indicate a role of HTT in cognitive processes and suggest that partial loss of HTT function could contribute to the cognitive symptoms of HD patients (Nasir, et al., 1995).

HTT is an essential component of the mitotic spindle (Godin, et al., 2010) and regulates nuclear processes such as gene transcription (Cha, 2007). BDNF transcription in cortical neurons, that provide this trophic factor via the corticostriatal pathway to the striatum, depends on cytoplasmic HTT, which binds to and reduces the translocation of transcriptional regulator REST avoiding its binding to the silencing DNA element RE1/NRSE, its activation and suppression of BDNF transcription (Zuccato, et al., 2001, Zuccato, et al., 2003). Loss of this function could in part lead to decreased BDNF trophic support (Zuccato, et al., 2001).

HTT is present at the postsynaptic density where it interacts with postsynaptic density protein 95 (PSD-95). At this level it is involved in the stimulation of activity-dependent transport of NF-kB out of dendritic spines and its translocation to the nucleus. This function is impaired in the presence of mHTT (Marcora and Kennedy, 2010). Previous data also implicated a postsynaptic role of HTT by interacting with *N*-methyl *D*-aspartate receptors (NMDAR) binding to PSD-95 and regulating NMDAR postsynaptic density (Smith, et al., 2005). Recently, a role of this interaction in mediating excitotoxicity in HD models has been shown (see below). Presynaptic roles of HTT, altered by the HD mutation, have also been documented (Rozas, et al., 2011) and could be affected by loss of normal HTT function.

In the cytoplasm and in the axon, wild type HTT through HAP1 interaction acts in association with microtubule-dependent molecular motors such as kinesins, dynein and dynactin in the regulation of axonal transport and vesicle trafficking (Caviston and Holzbaur, 2009). In this way, HTT regulates the transport of synaptic vesicles, organelles, signalling and trophic factors such as BDNF (Gauthier, et al., 2004) and its loss impairs axonal transport in primary neurons (Her and Goldstein, 2008). HTT function in vesicle trafficking is also mediated by palmitoylation (Yanai, et al., 2006). HTT controls palmitoyl transferase activity of its

interaction partner huntingtin-interacting protein 14 (HIP14) (Huang, et al., 2004), therefore regulating palmitoylation of substrates such as SNAP25 and GluR1 (Huang, et al., 2011) and providing another checkpoint on trafficking of these molecules.

Thus, vital cell processes are supported by the normal function of HTT and affected by its loss contributing to the overall toxicity in HD.

Dystrophic neurites precede neuronal loss in HD

As Alois Alzheimer observed in 1911, an invariable neuropathological finding in HD patients is the gradual and marked atrophy of the striatum, accompanied by the enlargement of the lateral ventricle, shrinkage of the cerebral cortex and the globus pallidus (GP), thinning of corpus callosum and abnormalities of hypothalamus (Vonsattel, et al., 1985). In a series of classical pivotal studies several distinguished morphological alterations of the neurites preceding neuronal loss were identified, particularly at the level of MSSN in post-mortem materials from medium to late stage HD patients. Morphological analysis of dendritic trees of surviving MSSN showed a mixture of regenerative and degenerative changes including recurving of terminal dendritic branches, abnormal growth and formation of new collaterals, and local increase or decrease in spine density, suggesting a biphasic development of dendritic pathology in MSSN, similar to what has been noted also in cortical neurons of Alzheimer's disease (AD) patients and maybe related to cognitive decline (Graveland, et al., 1985).

Similar results were confirmed and extended in posmortem brain specimens from moderate and advanced grade HD patients using staining for Calbindin D28k (Calb), a calcium buffering protein abundant in MSSN and their axons (Ferrante, et al., 1991). In the reduced number of Calb positive MSSN that maintained cell body integrity, intensity of Calb staining

was increased at the terminal dendrites, while it was lost at the level of the axon and proximal dendrites (Ferrante, et al., 1991). A common feature of dystrophic neurites in a wide spectrum of neurodegenerative pathologies is amyloid precursor protein (APP) and ubiquitin (Ub) immunoreactivity (Cochran, et al., 1991). Ub and APP positive aggregates associated with dystrophic neurites and preceding neuronal loss in HD cortex (Cammarata, et al., 1993, Jackson, et al., 1995), and mHTT accumulation in neuritic aggregates in the cortex and subcortical white matter (Sapp, et al., 1997) imply an early pathological process possibly caused by impairment of axonal transport. Notably, the number of mHTT and Ub positive NII is higher in brain of patients affected with a juvenile form of the disease, whereas adult onset patients show less NII and a higher number of HTT and Ub positive dystrophic neurites (DiFiglia, et al., 1997). This observation dissociates the formation of NII from axonal pathology in HD and highlights the independent role that dystrophic neurites/axons play in HD pathology (Sapp, et al., 1999). Loss of enkephalin (ENK) immunoreactivity in the substantia nigra in the absence of cell loss (Waters, et al., 1988) and decreased density of ENK immunoreactive fibres in the external globus pallidus at presymptomatic age (Albin, et al., 1990) suggest degeneration of MSSN axonal projections.

Alterations in dendritic spine density may be related to dysfunction of the corticostriatal glutamatergic input to the neostriatum (Cudkowicz and Kowall, 1990). MSSN receive their main excitatory input from two types of glutamatergic layer V cortical pyramidal neurons (Reiner, et al., 2010). One type of neurons, with only intratelencephalic corticostriatal connections (IT-type), innervates direct pathway neurons, which show a higher resistance to degeneration in HD. The second type of neurons, which send their main axons to the brainstem via the pyramidal tract (PT-type), preferentially innervates indirect pathway striatal neurons, the first to degenerate in HD (Fig. 1). Functional alterations in cortical pyramidal neurons, an increase in cortical excitability, or an altered expression of presynaptic and

postsynaptic glutamate receptors could lead to excessive glutamate stimulation and increased excitotoxicity (reviewed in (Cepeda, et al., 2007)). Cortical pathology has been detected in mildly affected patients and might precede and be more severe than striatal pathology (Cudkowicz and Kowall, 1990, DiProspero, et al., 2004). Severe loss of cortical and subcortical white matter in all degrees of HD has been reported (de la Monte, et al., 1988).

In vivo neuroimaging methods have been used more recently to assess pathology in HD patients and gene carriers. The advantage of these methods is the non-invasiveness and the capability to detect changes both in the gray and the white matter at early time points. With this technology it has been possible to detect white matter atrophy in the prodromal period and reduction of fractional anisotropy, a measure of white matter integrity, possible consequence of axonal injury or withdrawal, in HD patients (Ross and Tabrizi, 2011). Diffusion tensor imaging has consistently shown evidence of white matter disorganisation at an early phase of HD, preceding striatal cell loss (Reading, et al., 2005, Weaver, et al., 2009). White matter abnormalities in early HD patients detected by magnetic resonance imaging (MRI) were correlated to cognitive dysfunction (Beglinger, et al., 2005). Whether white matter change is secondary to early neuronal degeneration of functional circuits, or is a primary event, has not been fully clarified (Ross and Tabrizi, 2011).

Taken together these studies suggest that white matter alterations and presence of dystrophic neurites occur before cell loss, possibly as a result of aggregation of mHTT N-terminal fragments in axons and block of axonal transport. It is important to further clarify the spatio-temporal relationship between neuronal death and neurite dysfunction. The answer to this question will have important therapeutic implications.

Neuronal dysfunction in HD models

Identification of HD gene and mutation makes possible to reproduce the cellular mechanisms of the pathology in cell and animal models (HDCRG, 1993). Despite their limitations, these models provide a useful tool to study the cellular toxicity of the mutant protein in a short frame of time and a useful platform for testing potential pharmacological treatments.

Various genetically modified mouse models expressing mutant human HTT protein have shed light on various aspects of HD pathology (Ferrante, 2009). Mouse models manifest motor and cognitive abnormalities resembling those seen in HD patients. In mice motor and behavioural symptoms often occur at a stage when there is no obvious neuropathological alteration, although at later stages severe atrophy of striatum, cortex, and other brain areas are detectable with histological techniques (Hickey, et al., 2008) and MRI imaging (Cheng, et al., 2011, Sawiak, et al., 2009). N-terminal mHTT aggregates form in the cell nucleus and in the neuropil where they may interfere with vital processes such as axonal transport and synaptic vesicle trafficking. Paradoxically, cell loss is absent in most models, or it occurs at very late stages. It seems likely that neuronal dysfunction rather than neurodegeneration is responsible for the behavioural phenotype of these mice (Crook and Housman, 2011).

MSSN in striatum of the widely used R6/2 mice, which express an N-terminal HTT fragment with a 145 polyQ tract, (Mangiarini, et al., 1996), have a similar atrophic morphology to those of HD patients and are characterised by curved dendrites with decreased branch number and spine density and by the presence of small aggregates along dendrites and axons (Guidetti, et al., 2001, Klapstein, et al., 2001, Meade, et al., 2002). An electron microscopic (EM) study also showed an accumulation of HTT aggregates at the axon terminals accompanied by a reduction in the density of synaptic vesicles. Neuropil aggregates are smaller in size than NII, they accumulate progressively with time and they are visible in the cortex and the striatum in R6/2 mice (Li, et al., 1999). N-terminal aggregates in the axons have been reported in KI mouse models with 72-80 CAG repeats inserted in the endogenous *Hdh* gene, where they

localise also to the GP and SN (Substantia nigra), two areas where NII are absent. This suggests that the neuropil aggregates locate within the long MSSN axons projecting from the striatum, even if the possibility remains that neurons within these regions form neuropil aggregates in the absence of any NII (Li, et al., 2000).

EM analysis in the KI mouse models with 72-80 CAG repeats reveals presence of aggregates in axons undergoing degeneration, even if the number of degenerating axons found seems to be rather small and still at late time points (Li, et al., 2001). Axonal degeneration characterised by organelle disruption and myelin sheath fragmentation has been observed in HD mouse models where neuronal cell death is rarely present (Yu, et al., 2003), suggesting that it occurs earlier and independently from neuronal cell death. Reduction of expression of channel subunits, mainly localised to the axons, in HD mouse models in the absence of neuronal cell death also supports an axonal component in HD pathology (Oyama, et al., 2006). Notably axons in sciatic nerves of asymptomatic R6/2 mice show signs of degeneration, even though these are subtle and rare (Wade, et al., 2008). How these changes in peripheral nerves relate to HD symptoms is not yet clear.

Evidence in *Drosophila* (Gunawardena, et al., 2003) and *C. elegans* (Parker, et al., 2001) as well as in cell lines and primary neurons suggest early neurite toxicity. N-terminal mHTT fragments form aggregates in neurites and cause degeneration (Li, et al., 2000, Li, et al., 2001). Striatal neurons acutely or chronically expressing N-terminal HTT fragments containing polyQ repeats of various lengths are characterised by nuclear and neuritic aggregates, loss of neurofilament staining and neuritic degeneration that precede an apoptotic cell death not related to the formation of NII, although nuclear localisation may be important (Saudou, et al., 1998, Zala, et al., 2005). In neuronal cell lines N-terminal and full-length mHTT form aggregates at the level of the neurites and promote cell toxicity (Cooper, et al., 1998). In addition, mHTT inhibits differentiation and neurite outgrowth in PC12 cells (Song,

et al., 2002, Wyttenbach, et al., 2001, Ye, et al., 2008). This effect may be mediated by a loss of ion channel subunits (Oyama, et al., 2006) or by an abnormal interaction of mHTT with binding partners such as HAP1 that promote neurite outgrowth (Li, et al., 2000, McGuire, et al., 2006, Rong, et al., 2006) through interaction with kinesin and regulation of axonal transport of BDNF (Gauthier, et al., 2004).

Increased sensitivity to the toxic actions of excitatory amino acids in HD models has been widely documented and correlated to abnormalities in expression and function of NMDAR early during the disease progression and to profound abnormalities in NMDAR downstream signaling, culminating in excessive Ca^{2+} influx, mitochondrial membrane depolarization, caspase activation and ultimately cell death, accurately reviewed elsewhere (Fan and Raymond, 2007, Milnerwood, et al., 2010). This could be related to altered glutamate release at cortico-striatal synapses (Cepeda, et al., 2003), reduction in spine density and number (Klapstein, et al., 2001) and decreased expression of astrocytic glutamate transporter (Arzberger, et al., 1997). Notably, alterations of expression and trafficking of NMDAR subunits have been associated to an increased density of NMDAR containing the NR2B subunit at striatal extrasynaptic sites, where their activation triggers an apoptotic cascade (Fan and Raymond, 2007, Hardingham and Bading, 2010, Milnerwood and Raymond, 2010). The toxicity is mediated by an increased association of NMDAR/NR2B with PSD-95 in the presence of mHTT and enhanced extrasynaptic surface NMDAR expression (Fan, et al., 2009). Recent evidence suggests that p38 activation contributes to mHTT-mediated enhancement of extrasynaptic NMDAR/NR2B/PSD-95 toxic signalling (Fan, et al., 2011, Fan, et al., 2012). Increased extrasynaptic NMDAR activity in HD models could have a negative impact on axonal cytoskeletal structure and axonal transport (Takeuchi, et al., 2005).

In conclusion, neuritic and synaptic defects are common in a variety of animal and cell models of HD. The association of aggregates with vesicles and the importance of wild-type

HTT in synaptic function and axonal transport strongly suggest that a transport problem could be the trigger for synaptic dysfunction as well as for axon degeneration. Whether axon dysfunction precedes, follows, or causes synaptic pathology still awaits elucidation.

Deficits of axonal function in HD

All the subcellular compartments, including membrane organelles and cytoskeletal proteins, are trafficked in cells. Because they are in different forms, they are transported either bidirectionally or unidirectionally and either in fast axonal transport or slow axonal transport. It has been well characterized that all the membrane structures, such as synaptic vesicles, mitochondria and endosomes, are transported bidirectionally along microtubules, while cytoskeletal proteins, such as tubulin, actin and neurofilament, and different soluble proteins are shipped in slow axonal transport, the latter can further be subgrouped into slow component a and slow component b.

Neurons are polarized cells with a complex and unique morphology. The long processes (axon and dendrites) extend far away from the cell body. The functional maintenance largely depends on sufficient and timely axonal transport, which ship proteins and different organelles from the cell body to the terminals. Meanwhile, the internalized proteins and signals or "wore-out" organelles are transported back from terminal regions to the cell body for retrograde signalling regulation and reparation. Considering normal fast axonal transport of membranous organelles, three types of functional components are required, --- intact microtubules; anterograde or retrograde transport motor proteins, kinesin and dynein; and membrane organelles (Fig. 2). Among them, transport motor proteins bind to microtubules and organelles at each side; however, the binding affinity and activity are highly regulated and ensure bidirectional trafficking of different organelles (Hirokawa and Takemura, 2005).

Therefore, it is understandable that either of these components being malfunctional will certainly affect normal axonal transport of membrane organelles. In this section we will discuss whether and to which extent each of them affects axonal trafficking in HD.

Impaired transport machinery

In neurodegenerative diseases, including HD, protein misfolding is a common phenomenon, which is involved in protein aggregation. NII of mHTT frequently appear in the nuclei of neurons (DiFiglia, et al., 1997). As discussed above, mHTT aggregates could often be observed in other domains of a neuron, such as axons and synapses (Li, et al., 1999, Li, et al., 2001, Sinadinos, et al., 2009). These protein aggregates can physically interfere with normal axonal trafficking of proteins and membrane bound organelles, such as synaptic vesicles and mitochondria. In *C. elegans* and *Drosophila* models of HD, expression of mHTT causes aggregate formation in axons and leads to impaired axonal trafficking of synaptic vesicles and mitochondria, by increased stalling of transported vesicles (Chang, et al., 2006, Gunawardena, et al., 2003, Li, et al., 1999, Li, et al., 2001, Parker, et al., 2001, Sinadinos, et al., 2009). Interestingly, cytoplasmic/neuropil expression and aggregate formation of mHTT rather than that in the nuclei possess more specific role in blocking axonal transport (Lee, et al., 2004), this is consistent with the notion that neuropil mHTT aggregates may physically interfere with axonal transport. In cortical neurons upon mHTT expression mitochondria trafficking is inhibited and deficits of movement is correlated to the size of aggregates (Chang, et al., 2006). Therefore it is conceivable to hypothesize that a therapeutic approach to restore axonal function in HD is to inhibit the mHTT aggregate formation at least in this compartment.

Intact microtubule is essential for normal function of axonal transport. HTT is associated with microtubules (Gutekunst, et al., 1995, Hoffner, et al., 2002). A normal and highly regulated

interplay between microtubules and molecular motors is crucial for an effective transport. Any alterations on this association will interfere with the normal axonal trafficking. Szebenyi and co-workers demonstrated that mHTT and its aggregates can affect microtubule stability and can also inhibit fast axonal transport and neurite outgrowth (Szebenyi, et al., 2003). Further studies demonstrated that impaired axonal transport is contributed by dysfunctional JNK signalling pathway in neurons (Morfini, et al., 2009). JNK normally phosphorylates kinesin-1, reducing its binding affinity to microtubules. Interestingly, JNK activation substantially increases in cells and animal models of HD (Morfini, et al., 2009). This will cause dissociation of the motor protein kinesin from microtubule tracks and in turn block axonal transport. In non-neuronal cells, mHTT expression and its aggregate formation impair insulin release and associate with high incidence of diabetes (Bjorkqvist, et al., 2005). More evidence has shown that mHTT disrupts insulin-containing granule transport by direct interference with β-tubulin (Smith, et al., 2009). The underlying mechanism may be that mHTT exhibited enhanced, but aberrant interaction between HTT molecules and β-tubulin compared to the wild-type HTT. This abnormal interaction raises the possibility that microtubule-dependent transport is disrupted by mHTT through a physical block and in turn makes the microtubule-based transport less effective in HD (Fig. 3).

It has been showed that HTT associates with various membrane organelles, such as synaptic vesicles (Li, et al., 1999), endosomes (Li, et al., 2009) and mitochondria (Trushina, et al., 2004) and even autophagosomes (Martinez-Vicente, et al., 2010, Ravikumar, et al., 2008). HTT binds to HAP1, a protein that is transported in axons and associates with $p150^{Glued}$ dynactin subunit, an accessory partner of dynein/dynactin motor protein complex (Vallee, et al., 2004) and the kinesin light chain (McGuire, et al., 2006). Therefore, HTT plays a key role in intracellular trafficking of these membranous organelles. Due to the widespread association

of HTT with different types of organelles in different neurons, it appears unlikely that the role of HTT in membrane trafficking is restricted to a specific organelle.

Trafficking of BDNF-containing organelle in HD

Brain-derived neurotrophic factor (BDNF) plays a key role in the survival of striatal neurons (Zuccato and Cattaneo, 2009). BDNF is decreased in the cells that express mHTT in different animal models (Gharami, et al., 2008, Zuccato, et al., 2001, Zuccato, et al., 2005) and patient brains with HD (Ferrer, et al., 2000). BDNF is synthesized as a protein precursor consisting of two domains, the prodomain and the BDNF domain (proBDNF) (Seidah, et al., 1996). The proBDNF is rapidly transported in neurons from the cell body to terminals and it is processed in the cells and become the matured form of BDNF, which then is released in the nerve terminals upon neuronal stimulations (Matsumoto, et al., 2008). Evidence has shown that the single nucleotide (Val66Met) polymorphism in the BDNF gene at codon 66 in the proBDNF sequence leads to a reduction of BDNF transport and activity-dependent release (Egan, et al., 2003). Expression of mHTT with expanded polyglutamine can significantly reduce transport of BDNF. del Toro and co-workers used a live cell imaging technique (fluorescence recovery after photobleaching) and showed that mHTT impaired post-Golgi trafficking of BDNF in a form-specific manner (del Toro, et al., 2006). Val66Val-BDNF form is much more severely affected in trafficking and release by mHTT in contrast to Met66Val-BDNF. Therefore, it appears that different BDNF forms may be involved in differential trafficking machinery in axons and terminals.

Two recent studies have reported that association of HAP1 with proBDNF is required for the intracellular trafficking, axonal transport and activity-dependent secretion of proBDNF (Wu, et al., 2010, Yang, et al., 2011). It appears that HAP1 acts as a BDNF cargo-carrying

molecule analysed with mass spectrometry. Subcellular fractionation analysis showed that deletion of HAP1 influenced the distribution of pro-BDNF in the synaptosomal fraction, indicating that HAP1 plays a role in the trafficking of pro-BDNF-containing vesicles into synapses. mHTT decreases the association of HAP1 with pro-BDNF via interference with the interaction between HAP1 and proBDNF. Further evidence from the same research group showed that the proBDNF forms a complex with HAP1 and sortilin (Yang, et al., 2011). HAP1 null neurons exhibit defective movement of proBDNF-containing vesicles. Co-immunoprecipitation and Western analyses showed that sortilin stabilizes the proBDNF-HAP1 complex and therefore prevent proBDNF degradation. Reduced association among pro-BDNF, HAP1 and sortilin is observed in the HD brains, which may concomitantly result in impaired BDNF transport and increased degradation.

It is worth mentioning that, in contrast to the function of mHTT, wild-type HTT itself enhances the transcription of BDNF via inhibition of the neuron restrictive silencer element (Zuccato, et al., 2003) and facilitates trafficking of BDNF-containing organelles in a phosphorylation-dependent manner (Colin, et al., 2008). Gauthier and colleagues demonstrated that HTT controls neuronal survival by enhancing BDNF vesicular transport along microtubules (Gauthier, et al., 2004). Using biochemical and real-time imaging techniques in cultured cortical neurons or neuroblastoma cells the authors demonstrated that HTT increased the transport efficiency of BDNF-containing vesicles along the microtubules. When expressing mHTT with 109 polyglutamines, BDNF transport is substantially reduced. Further study revealed that the underlying mechanism is that HAP1 induced the recruitment of HTT and $p150^{Glued}$ into these BDNF-containing organelles. mHTT disrupts the association of the HTT/HAP1/$p150^{Glued}$ key motor complex to microtubules. Decreased BDNF trafficking consequently causes a reduction in neurotrophic support and leads to neurotoxicity (Gauthier, et al., 2004).

Mitochondria dynamics in HD

Mitochondria are cytoplasmic organelles and provide energy (ATP) to all the cells in the body, including neurons. It has been long believed that mitochondria are synthesized and formed in the cell body and shipped down to axons and dendrites to the synaptic sites and provide the energy needed locally because most mitochondrial proteins are encoded and localized in the nuclear genome. If so, efficient mitochondria transport and energy supply are essential for normal neuronal function. However, Hollenbeck and his colleague have demonstrated mitochondria biogenesis in distal segment of axons (Amiri and Hollenbeck, 2008). After axotomy, they observed mtDNA replication in axons. Quantitative analysis estimated about one-third of total mtDNA replication occurring in axons of a neuron (Amiri and Hollenbeck, 2008). Therefore it is conceivable that effective mitochondrial trafficking as well as local biogenesis in axons and dendrites are vital for normal function of a neuron.

Mitochondrial transport in axons takes place through a highly regulated plus- and minus-end directed movements along microtubules. The plus-end directed motor, kinesin, and minus-end directed motor, dynein, closely coordinate and control the bidirectional trafficking (Hollenbeck and Saxton, 2005). Many studies have shown that HTT is associated with mitochondria and tightly regulates mitochondria trafficking. Greenamyre and co-workers pioneristically showed direct evidence of mHTT effect on mitochondrial function (Panov, et al., 2002). They demonstrated direct association of HTT on mitochondrial membranes at electron microscopic level. In isolated lymphoblast mitochondria from patients with HD they detected a lower membrane potential compared to mitochondria from the control subjects. Similar phenomena also observed in brain mitochondria isolated from a full-length mHTT transgenic mouse model (YAC72) of HD. More interestingly, the decreased mitochondrial membrane potential, due to impaired mitochondrial calcium handling, occurred much earlier than the onset of motor deficits. In live-cell imaging with cultured cells, expression of mHTT

induces a shift of mobile mitochondria into the stationary status, while the velocity of mitochondria is significantly decreased, particularly at the sites where mHTT aggregates locate (Chang, et al., 2006, Trushina, et al., 2004). Similar phenomena are also observed in the transgenic mouse models of HD. Moreover, the severity of impairment of mitochondria trafficking is closely related to the age of the animal. Loss of mitochondria motility diminishes ATP production and increases oxygen radical formation with age. It appears that both gain-of-function (of mHTT) and loss-of-function (of wild-type HTT) can cause trafficking defects of mitochondria. Using a KI (Q150) mouse model of HD, Orr et al. demonstrate that even prior to aggregate formation, the interaction of soluble mHTT with mitochondria increases with age and interferes with the association of motor proteins (kinesin, p150 and HAP1) with mitochondria (Orr, et al., 2008).

Dynamics of mitochondrial fission and fusion are highly regulated and kept in balance in the physiological condition. Mitochondrial fusion protects cells from toxic insults by diluting the toxin contents. A recent post-mortem study showed that mitochondrial fission and the related genes and gene products, (DRP1 and FIS1) in HD brains appeared increased compared to the control non-HD subjects. Similarly to what happens in patients, also in cell models of HD mitochondrial fragmentation and cristae disruption were observed, accompanied by increased DRP1 dephosphorylation and association to mitochondria and by an increased susceptibility to apoptotic stimuli (Costa, et al., 2010). Conversely, the genes and gene products regulating mitochondria fusion (Mfn1 and Mfn2) decreased in HD (Shirendeb, et al., 2011), implying impaired mitochondrial dynamics in HD.

Vesicular transport in HD

In synapses, besides mitochondria and some specific organelles such as BDNF-containing organelles mentioned above, many more membrane organelles exist. Most abundant portions are synaptic vesicles that store different neurotransmitters and neuropeptides. These organelles are formed in the cell body and transported into the synaptic sites and also undergo vesicular recycling in the synapses. It is well known that HTT is associated with synaptic vesicles (DiFiglia, et al., 1995) and endosomes (Velier, et al., 1998). Upon expression of mHTT the number of immobilized vesicles progressively increased. The motility of mobile vesicles also slowed down (Trushina, et al., 2004). When transmitters are released in the synaptic sites the membrane of synaptic vesicles will be endocytically retrieved into endosomes. In a recent study, Li et al. used fibroblasts from human HD patients to study the effects of mHTT on recycling vesicles (Li, et al., 2009). They observed that mHTT inhibited Rab11 activity and led to deficits in vesicle biogenesis at recycling endosome. Similar changes are also observed in a KI (Q140/Q140) mouse model of HD (Li, et al., 2009). Expression of dominant active Rab11 can normalize Rab11 activity and partially rescue glutamate-induced cell death (Li, et al., 2009). In line with the dysfunction of Rab11 upon mHTT expression, additional neuronal dysfunction is also reported on aberrant trafficking of the neuronal glutamate transporter EAAC1 (Li, et al., 2010) and on dendrite spine loss and neurodegeneration (Richards, et al., 2011).

Although HTT is widely present in different types of cells inside and outside the central nervous system, more robust neuropathology and cell death occur in the neurons of the striatum. Therefore it is interesting to understand whether HTT functions differently with any regional or cell-type preferences. In the context of axonal transport, does mHTT affect one type of neuron more than another? Her and Goldstein recently addressed this issue. They found that mHTT and loss of normal HTT selectively impaired intraneuronal trafficking of the striatal and hippocampal neurons, but not cortical neurons (Her and Goldstein, 2008). The

authors use APP-YFP and BDNF-mCherry to label two types of organelles in cultured neurons of the striatum, cerebral cortex or hippocampus of KI (Hdh150Q) mice or HTT KO (Hdh^{Flox}) mice. Very interestingly, they found that in the mHTT (150Q) expressing neurons the movement of APP and BDNF is impaired in striatal and hippocampal neurons in contrast to the cortical neurons. Loss of HTT impairs APP-containing organelle trafficking and the counter-expression of wild type HTT, rather than mHTT, normalizes APP transport in all three types of neurons. These data indicate that axonal transport in cortical neurons is more resistant to mHTT, in contrast to the striatal and hippocampal neurons. It is unexpected that no alterations are observed for HAP1, $p150^{Glued}$, kinesin and dynactin, which previously have been reported to be altered by mHTT expression or loss of HTT. More experiments are needed to clarify whether other molecules may be involved here and to reconcile this data with previous evidence suggesting defective transport of BDNF in cortical neurons expressing mHTT (Gauthier, et al., 2004, Zala, et al., 2008).

Conclusions and Perspectives

Neuronal dysfunction, neuritic dystrophy and synaptic abnormalities often precede neuronal death in HD patients and models and correlate with behavioural and cognitive impairment. Neuropathological evidence of neuritic dysfunction, Ub and APP immunoreactivity and the presence of aggregates in the neuropil led to the hypothesis that axonal transport defects were the basis of neuronal dysfunction since the early studies (Jackson, et al., 1995). Abnormalities in axonal transport at several levels have been found more recently, confirming this original hypothesis. A failure in axonal transport will reduce delivery of critical cargoes to the most distal sites first, explaining synaptic abnormalities as well as the increased susceptibility of long axonal projections and supporting the notion of HD as a “dying back” type of

neurodegeneration (Han, et al., 2010). The precise spatio-temporal relationship between axonal and synaptic degeneration however still needs to be clarified.

The extended shape and vulnerable nature of axons makes them a target for insults caused by an aggressive extracellular environment. Microglia activation is a hallmark of many neurodegenerative diseases where inflammatory responses play an important part in the disease pathogenesis. In HD, activated microglial cells expressing mHTT have been found in striatum, cortical and subcortical areas and white matter and the number of these cells increase as the disease progresses (Moller, 2010). Microglia activation affects the neurons and their long axons in several ways, such as releasing cytokines or altering phagocytic responses, and induces neuritic beading associated with collapsed cytoskeletal and motor proteins having a detrimental effect on axonal transport (Takeuchi, et al., 2005). This toxicity appears to be mediated by increased glutamate release accompanied by a redistribution of NMDA receptors to extrasynaptic sites (Hardingham and Bading, 2010). Indeed memantine, an antagosit which blocks extrasynaptic NMDAR with high affinity while maintaining synaptic NMDAR transmission, is a promising novel therapeutic strategy (Okamoto, et al., 2009).

Future therapeutic strategies in HD must aim at targeting early synaptic and axonal dysfunctions as well as at fighting neurodegeneration at the later stages of the pathology. Axonal transport defects have to be corrected to achieve effective treatment. Solubilisation of axonal and cytoplasmic aggregates and removal of the blockage to axonal transport may be one such possibilities (Ravikumar, et al., 2008). Stabilisation of microtubules, rail of axonal transport, could be another way to improve defects in HD (Dompierre, et al., 2007). In addition, new knowledge about the molecular players regulating axonal and synaptic degeneration is emerging quickly (Coleman and Freeman, 2010). Shedding light on these

mechanisms may offer yet further therapeutic possibilities to sustain the normal activities of axons and synapses.

In conclusion, a vast body of evidence indicates that dysfunction of the synapse as well as the axon, particularly a disruption in axonal transport, may be the cause of several symptoms occurring early in HD, and therefore may offer a target for future treatment of this devastating disorder.

Abbreviations:

1. HD= Huntington's disease
2. AD= Alzheimer's disease
3. HTT= human huntingtin protein
4. *HTT*= human huntingtin gene
5. IT15= interesting transcript 15
6. mHTT= mutant human huntingtin with an expanded polyQ tract
7. *Hdh*= mouse huntingtin gene
8. polyQ= polyglutamine
9. MSSN= striatal GABAergic medium-sized spiny neurons
10. NII= intranuclear aggregates
11. KI = knock-in
12. KO = knock-out
13. GABA = gamma-aminobutyric acid
14. NMDA = N-Methyl-D-aspartic acid
15. NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells

16. BDNF = Brain-derived neurotrophic factor

17. JNK = c-Jun N-terminal kinase

18. ENK = enkephalin

19. Calbindin D28k = Calb

20. NMDA = *N*-methyl *D*-aspartate

21. NMDAR = *N*-methyl *D*-aspartate receptors

22. PSD-95 = postsynaptic density protein 95

23. DRP1 = dynamin-related protein 1

24. FIS1 = fission protein 1

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Figure Legend

Fig. 1. Schematic representation of the cortical input to striatal neurons and of the major projections of striatal MSSN. The direct and indirect loops of the basal ganglia are

represented on different parts of the brain, for clarity. The location of intranuclear and extranuclear mHTT aggregates, of dystrophic neurites and of fiber loss is also represented. Str= Corpus Striatum, Thal=Thalamus, STN= Subthalamic nucleus, GPi= Globus Pallidus (internal segment), GPe= Globus Pallidus (external segment), SNpc= Substantia Nigra (pars compacta), SNpr= Substantia Nigra (pars reticulata).

Fig. 2. Schematic drawing indicating the machinery of fast axonal transport in a matured neuron. The anterograde motors, kinesins, transport vesicular organelles from the cell body to the terminals along microtubules (to the direction of plus end), while dynein transport membrane organelles retrogradely along microtubules (to the direction of minus end).

Fig. 3. Schematic drawing showing a model of how mHTT affect microtubule-based axonal transport. mHTT (B) binds more strongly to β-tubulin than does wild-type HTT (A), thereby accumulating over time on the microtubules. This causes a physical block to transport and gradually makes intracellular transport less efficient. The figure is adapted from our previous publication (Smith et al., 2009).

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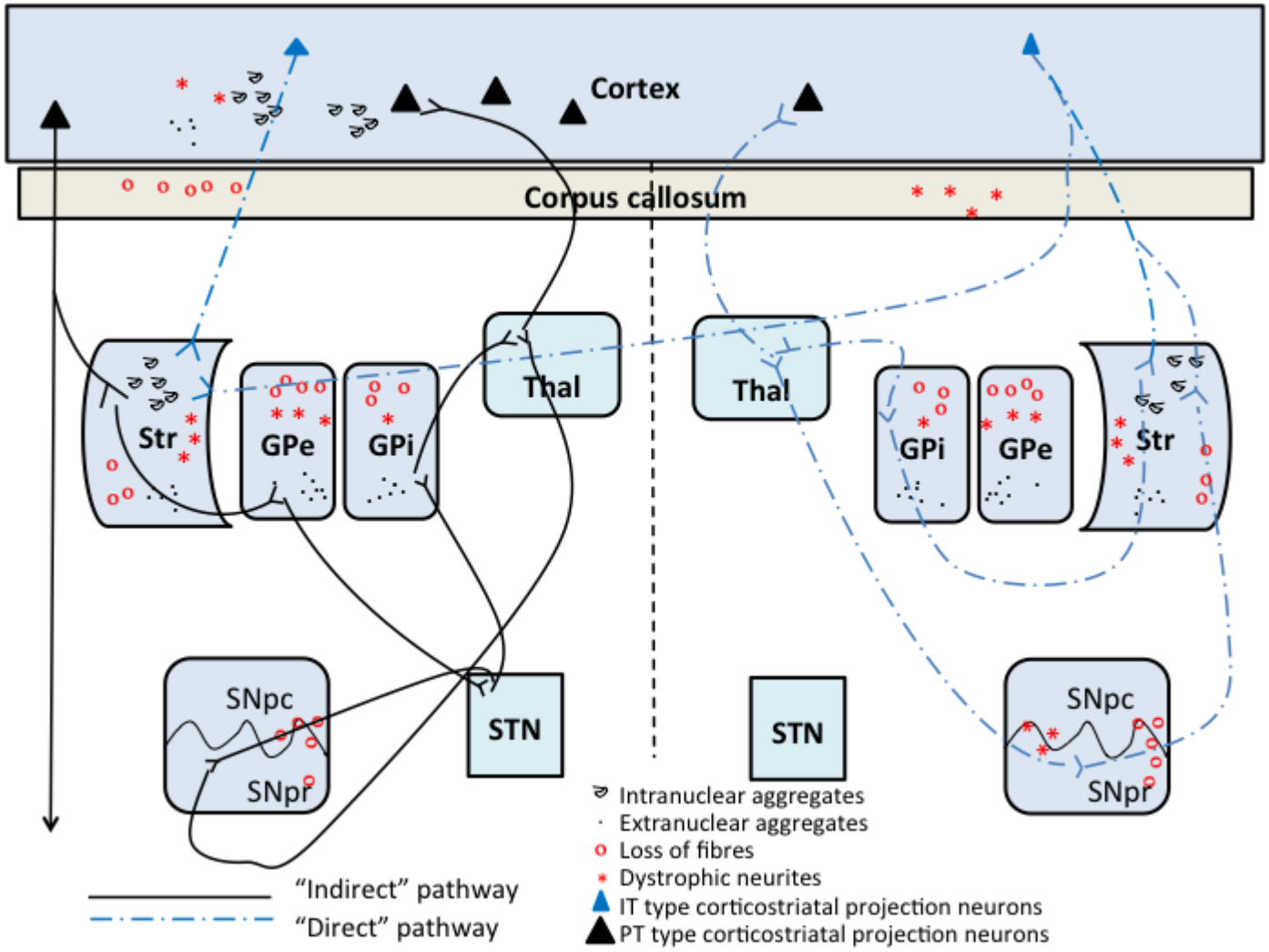
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PT type corticostriatal projection neurons
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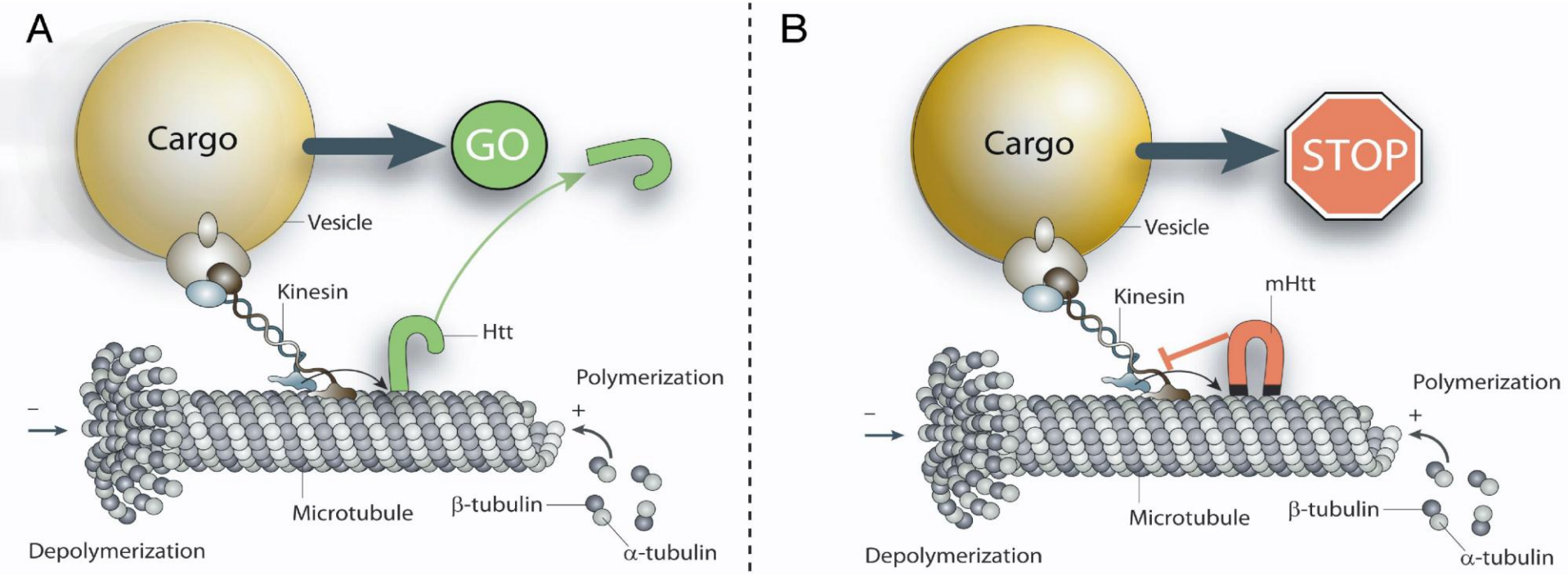
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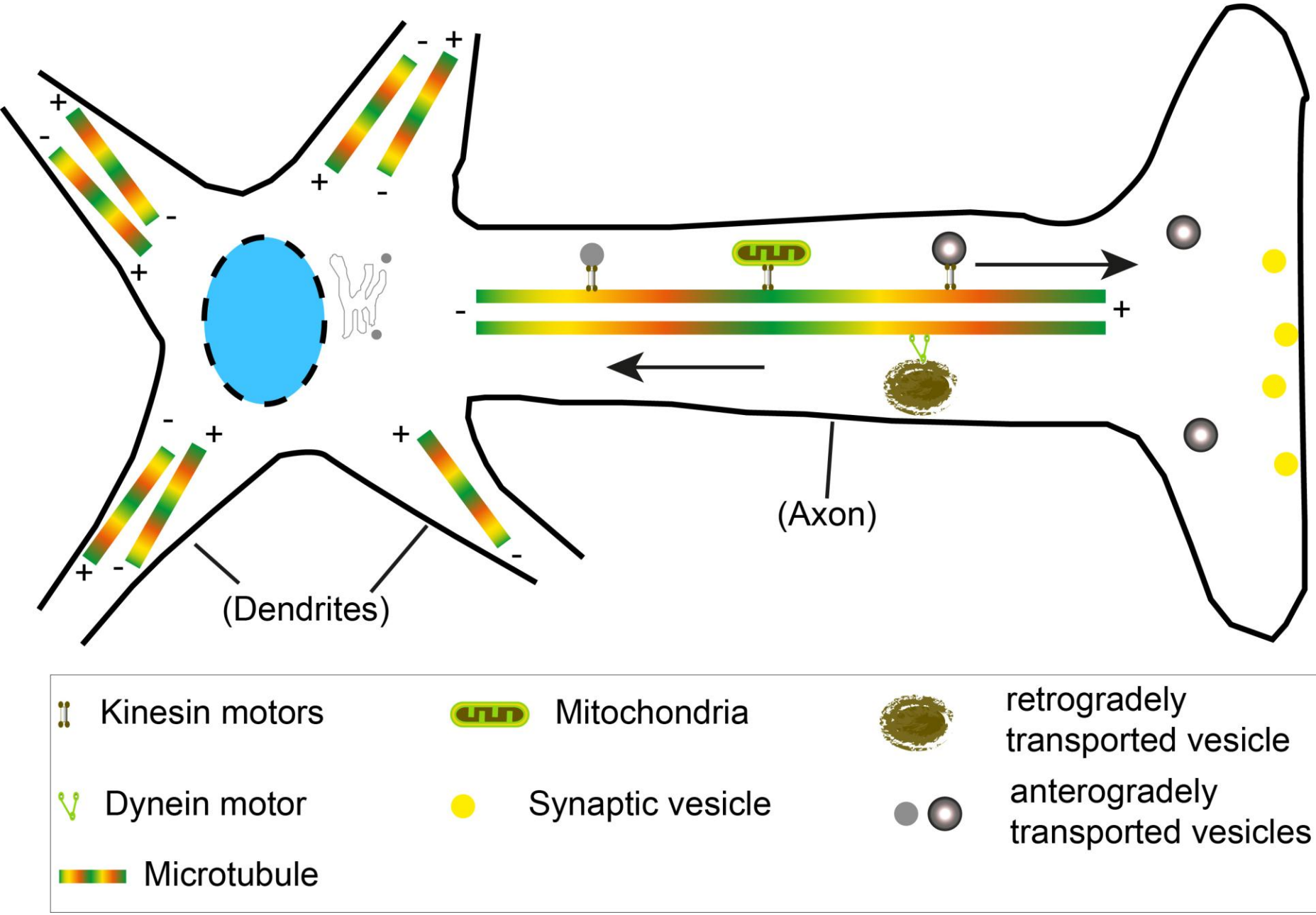
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