HHS Public Access

Author manuscript

Adv Neurobiol. Author manuscript; available in PMC 2019 June 11.

Published in final edited form as:

Adv Neurobiol. 2017 ; 18: 113–142. doi:10.1007/978-3-319-60189-2_6.

"Manganese and the Insulin-IGF signaling network in Huntington's disease and other neurodegenerative disorders"

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Abstract

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease resulting in motor impairment and death in patients. Recently, several studies have demonstrated insulin or insulin-like growth factor (IGF) treatment in models of HD results in potent amelioration of HD phenotypes via modulation of the PI3K/AKT/mTOR pathways. Administration of IGF and insulin can rescue microtubule transport, metabolic function, and autophagy defects, resulting in clearance of Huntingtin (HTT) aggregates, restoration of mitochondrial function, amelioration of motor abnormalities, and enhanced survival. Manganese (Mn) is an essential metal to all biological systems but, in excess, can be toxic. Interestingly, several studies have revealed the insulin-mimetic effects of Mn—demonstrating Mn can activate several of the same metabolic kinases and increase peripheral and neuronal insulin and IGF1 levels in rodent models. Separate studies have shown mouse and human striatal neuroprogenitor cell (NPC) models exhibit a deficit in cellular Mn uptake, indicative of a Mn-deficiency. Furthermore, evidence from the literature reveals a striking overlap between cellular consequences of **Mn-deficiency** (i.e. impaired function of Mn-dependent enzymes) and known HD endophenotypes including excitotoxicity, increased reactive oxygen species (ROS) accumulation, and decreased mitochondrial function. Here we review published evidence supporting a hypothesis that (1) the potent effect of IGF or insulin treatment on HD models, (2) the insulin-mimetic effects of Mn, and (3) the newly discovered Mn-dependent perturbations in HD may all be functionally related. Together, this review will present the intriguing possibility that intricate regulatory cross-talk exists between Mn biology and/or toxicology and the insulin/IGF signaling pathways which may be deeply connected to HD pathology and perhaps, other neurodegenerative diseases (NDDs) and other neuropathological conditions.

1.1 Introduction

Between 1–3 out of 100,000 individuals are diagnosed with Huntington's disease (HD) in the U.S. However, given the autosomal dominant etiology and near 100% penetrance of HD,

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generations of families are devastated by this disease. HD is caused by an expanded tri-nucleotide CAG repeat in the HTT gene. If these repeats surpass 35–40 repeats, there is a near 100% chance that the patient will present with Huntington's disease at some point in their lifetime (usually in middle-late adulthood). While the *HTT*gene was discovered in 1993, there is still no cure for HD though several drugs have been used to treat symptoms (i.e. tetrabenazine for chorea). Furthermore, researchers still do not fully understand 1) the exact function(s) of wild-type HTT is in the human brain or 2) how mutant HTT (HTT >35 CAG repeats) causes neurotoxicity and HD. Two of the posited causes for HD are 1) mitochondrial dysfunction 2) autophagic dysfunction and aggregate accumulation. Recently, a series of studies have shown that insulin/insulin-like growth factor (IGF) treatment in HD models can ameliorate both of these pathogenic mechanisms.

Manganese (Mn) has only been recently implicated in HD, and studies have suggested that a Mn deficiency may underlie some of HD pathology[1–5]. Interestingly, Mn can modulate insulin/IGF homeostasis, shown to be essential for mitochondrial function, and able to stimulate neuroprotective pathways associated with the activation of autophagy, namely insulin/IGF signaling (IIS). This review explores the functional intersection of these two modifiers of HD, (a) Mn biology and (b) insulin/IGF signaling (IIS)—both have been shown to regulate autophagy and mitochondrial health/function. Here we will review a role for Mn and IGF joint dysregulation in HD pathology and briefly explore some the implications of this co-regulation in the context of other neurodegenerative diseases and conditions.

While Huntington's disease will be discussed in detail, other neurodegenerative diseases (NDDs) will also be referenced when studies provide mechanistic understanding of the roles of Mn and IGF/insulin given the shared cellular pathologies between NDDs and HD (i.e. aggregate accumulation, reactive oxygen species, mitochondrial dysfunction). It is plausible that the mechanisms of these NDD pathologies might be quite similar to HD.

1.2.1 IIS signaling and its role in the brain

Insulin and insulin growth factor (IGF) are homologous growth hormones that classically regulate cellular metabolism. Their role in peripheral tissues has been well elucidated. However, only more recently has their role in brain health and development been studied. In the brain, IIS is necessary for synaptic maintenance and activity, neurogenesis, neurite outgrowth, neuronal survival, mitochondrial function and maintenance as well as upper-level processes including memory and feeding behavior and thus dysregulation in neurotrophic support has long been proposed as a mechanism of neurodegenerative diseases[6–31]. Insulin and IGF are mainly produced in the pancreas and liver, respectively, and transported to the brain from the periphery through the blood brain barrier. Alternatively, IGF and insulin can enter the brain through CSF in the choroid plexus. IGF is also produced locally in all brain regions. Upon binding with their respective ligands, IGF receptors (IGFR) and insulin receptors (IR) undergo autophosphorylation at three tyrosine residues required for activation. Subsequently, the IR kinase domain phosphorylates IR substrates (IRSs) which act as secondary messengers, impinging upon a variety of cell signaling pathways including PI3K/AKT, mTOR, and MAPK/ERK to exert their biological effects (e.g. energy metabolism, cell stress responses)[32]. However, individual receptors can heterodimerize forming hybrid IGF/

insulin receptors which can bind either insulin or IGF and activate both the PI3K/AKT and MAPK/ERK pathways. S6, a downstream target of mTOR acts as negative feedback, phosphorylating and inactivating IRSs. Six IGF binding proteins exist (IGFBPs) and act to regulate IGF-R binding and modulate signaling. IGFBPs show a selective expression pattern, being in distinct portions of the brain where they presumably act on specific IIS signaling within anatomical subsets of neurons. These proteins have a higher affinity for IGF than do IGF receptors, allowing tight control of IGF bioavailability. The regulation of neuronal IGFBPs is still quite unknown but evidence suggests specific mechanisms for each protein including control by epigenetic markers and neuronal activity of specific cell types[33,34].

Most kinases in humans are either magnesium (Mg) or Mn dependent. Though most are Mg dependent, several are preferentially activated by Mn including ATM and mTOR[35,36]. While little research has been done to explore the role of Mn as a signaling molecule its inherent role in kinase activation suggest Mn is essential for cell signaling. Several other proteins are also activated by Mn including Arg, MRE11, Mn-SOD, glutamine synthetase, pyruvate decarboxylase, protein phosphatase 1, and many integrin-related proteins[37–46]. Interestingly Mn has been shown to activate several of the same pathways as IGF/insulin including AKT, mTOR, and ERK/MAPK, and even the insulin/IGF receptor itself— all of which have been found to be neuroprotective in HD[46–56].

1.2.2 Mn and insulin/IGF homeostasis.

Mn toxicity has been linked to neuronal cell death and neurodegenerative conditions for several decades—namely Parkinson's disease (PD) and manganism. Though recent studies have yielded greater understanding of toxic effect of Mn on neuronal function, very little is known about basic, neuronal Mn homeostasis. While brain imaging studies have revealed where Mn accumulates within the brain, there is disagreement on what sub-compartment(s) Mn primarily accumulates within a neural cell. The field is in some contention as some studies suggest mitochondria while others suggest within the nucleus[57–59]. Surprisingly few studies have examined whether Mn primarily accumulates in neurons vs glial cells. Lastly, there is poor understanding of how Mn is transported within a cell, primarily due to the high promiscuity of Mn transporters for other metal ions[37,60]. Muddying this understanding, at present there is only one transporter which seems specific for Mn, SCL30A10, an efflux transporter. Interestingly, mutations in this transporter lead to Mn accumulation *in vitro* and *in vivo* and have been linked to increased brain Mn and PD in patients[60–63]. The answers to these basic questions could offer invaluable understanding of Mn biology in the context of both diseased and healthy brains.

Evidence of a role for Mn-dependent regulation of IIS has been steadily amassing since the 1980's. Baly and colleagues showed Mn-deficiency caused glucose intolerance and reduced insulin production in rats, mimicking diabetic-like phenotypes[64–67]. In addition, rats fed a Mn-deficient exhibited reduced pancreatic insulin output following a glucose stimulus. Furthermore, they and others found Mn to be an insulin-mimetic, promoting insulin excretion and activating insulin-related metabolic kinases[64–69]. Around this same time, another study showed that Mn-deficient rats exhibited decreased circulating IGF-1 and

insulin and increased IGFBP3—potentially suggesting Mn might regulate circulating IGF-1 levels via modulating IGFBP3 activity[70]. Later, Lee and colleagues reported that Mn supplementation could protect against diet-induced diabetes in mice via increased insulin excretion, amelioration of glucose intolerance, and increased expression of Mn superoxide dismutase (MnSOD), a Mn-dependent anti-oxidant enzyme in mitochondria[71]. These results were consistent with reports that diabetic patients were responsive to oral Mn treatment as well as reports of reduced blood Mn in diabetic patients[72–74]. Concurrently, other groups established that Mn deficiency was associated with reductions of IGF1 in serum and Mn supplementation could increase IGR-R and IGF1 expression in the hypothalamus of rats[53, 54, 56, 70, 75–78] *However, the mechanisms by which Mn increases IGF1 and insulin levels remain unknown.* Together, these findings suggest a functional link between Mn and the regulation of IGFl/insulin levels in both peripheral tissues and brain. While such studies clearly link Mn to diabetes and hypothalamic/pubertal development, the role of this potent regulatory mechanism has never been studied in the context of a neuronal disease or manganese toxicity.

1.3.1 HD pathobiology

HD is an autosomal dominant neurodegenerative disease which results in hyperkinetic movements, behavioral changes in cognition and mood, and ultimately death. An expanded trinucleo-tide (CAG) repeat in the *Huntingtin* gene (*HTT*) resulting in a mutant HTT protein (mHTT) causes HD. Higher CAG repeats are correlated with increased disease severity and younger age of onset though both are highly variable even between patients with similar repeat size[79,80]. Usually, the disease manifests in adulthood (though juvenile cases do occur), and gives rise to a combination of motor, cognitive, and psychiatric symptoms which ultimately result in death. A hallmark symptom of HD is chorea, uncontrolled hyperkinetic movements, which has been associated with mHTT-dependent cell death within the striatum. Degeneration in other brain regions (cortex, hypothalamus) usual follows, contributing to the variability in symptoms. As HTT is ubiquitously expressed, the basis for the selective neurotoxicity of mHTT for striatal medium spiny neurons (MSNs) and a handful of other neuronal sub-populations remains a mystery[80–84].

1.3.2 Mn dysregulation in HD.

Mn dysregulation has only recently been implicated in HD. In normal brains, Mn accumulation is enriched in the basal ganglia—the part of the brain which most severely degenerates in HD—suggesting Mn serves an important role in this brain region[59,85, 86]. Recently a set of studies revealed a Mn transport deficit, **indicative of a brain-specific Mn deficiency**, in an HD immortalized striatal neuroprogenitor cell line (STHdhQ111/Q111), in HD hiPSC-derived striatal NPCs cells, and also in the striata of YAC128Q mouse model of HD[1, 4]. The mechanism of this Mn-transport deficit has been difficult to resolve as so little is known about Mn sub-cellular transport. Analysis of Mn homeostasis is complicated by the high promiscuity of proposed Mn transporters for other essential metals[37, 60, 87, 88].

However, Mn is known to activate several of the signaling pathways dysregulated in HD including ATM/p53 and AKT/mTOR[1, 53, 54, 88–90]. STHdh Q111/Q111 and hiPSC-derived

striatal neuroprogenitor HD cell models exhibit decreased net Mn up-take leading to diminished ATM activation, a Mn-responsive kinase upstream of p53 and other cellular stress response proteins[1]. Similar to ATM/p53, Mn robustly activates AKT and mTOR, both of which are neuroprotective in HD[91–98]. AKT activation can increase HTTSer421 phosphorylation, shown to facilitate axonal transport, restoring mitochondrial and autophagic function in HD models[92, 95–97, 99–102]. In contrast, Guilarte and colleagues reported decreased HTTSer421 phosphorylation by Mn in YAC128 mouse cortical and hippocampal primary cultures, though striatal levels were not assessed[4, 5]. Lastly, reinstatement of aberrant mTOR activity in HD models restores autophagic function, enhances aggregate clearance, and increases MSN health, though some reports have shown mTOR inhibition to be neuroprotective in HD[91,103,104].

1.3.3 IIS dysregulation in HD.

Recently, several groups observed impaired IIS in HD. Paradoxically, reduced IGF1 expression has been detected in patient caudate tissue and skin-fibroblasts as well as other non-human HD models, while increased IGF1 has been found peripherally in HD and this has been correlated with cognitive decline[96,105,106]. Previous studies have shown mutant HTT disrupts intracellular transport and secretion of insulin while others have shown Mn can act as a potent insulin-mimetic *in vivo*[69]. Additionally, several groups reported robust neuroprotective effects of IGF1 treatment in HD cell and mouse models via increased 1) AKT/ERK signaling 2) IRS2/VPS34 (Class III PI3K) signaling and 3) increased HTT Ser421 phosphor-ylation. Upregulation of these pathways increased autophagic function, aggregate clearance and ameliorated mitochondrial dysfunction[96, 97, 100, 101, 107–111]. Administration of IGF and insulin can also rescue microtubule transport, amelioration of motor abnormalities, MSN health, and enhanced survival in cell and rodent models. IGF1 is also neuroprotective in models of other NDDs[112–119].

1.3.4 Autophagy deficits in HD, potential links to Mn and IIS.

The inability to clear toxic mHTT aggregates may be a principle mechanism of HD-related cell death though there is contention about which form(s) and fragment(s) are truly toxic and which are a compensatory/protective reaction to cellular toxicity[120–123]. Autophagy, a process by which cells degrade complex organelles and proteins to base nutrients, is also the primary process in clearing mHTT aggregates[121, 123–129]. HTT acts as a scaffold for autophagy and this activity is altered or impaired by mHTT, potentially exacerbating pathogenesis[126, 130–133]. In HD, autophagic impairment causes failure of cargo-recognition and lysosomal function resulting in the accumulation of cellular waste and protein aggregates[134]. This may trigger a feed-forward pathogenic loop with ever increasing mHTT levels further impairing clearance[126].

IGF treatment incurs robust amelioration of autophagy defects in HD models. Rothman and colleagues observed that IGF1 upregulates autophagy via an IRS2/VPS34-dependent mechanism in HD cells, resulting in a marked increase in aggregate clearance. This is an AKT/mTOR-independent process, though both AKT and mTOR are activated by IGF1[107]. Additionally, other groups have shown that upregulation of mTOR in HD models increases autophagy and aggregate clearance, rescuing HD-related phenotypes even though mTOR

canonically acts as a negative regulator of autophagy by inhibiting ULK1[91,135]. Interestingly, published studies indicate Mn both increases and decreases autophagy in neuronal systems in a biphasic, time-dependent manner[55, 136]. Given this regulation of autophagy by Mn and Mn-responsive pathways, it seems plausible that correcting Mn homeostasis in HD models may ameliorate aspects of autophagic dysfunction. To date however, there has been only a handful of studies exploring the role of Mn in autophagy—and the majority have been done in the context of Mn toxicity, instead of Mn essentiality[55, 137]. Given clear ties of Mn biology to pathways upstream of autophagy, future studies should interrogate the role of Mn in autophagy during normal neuronal function, in addition to disease states. In particular, we need to establish whether Mn plays a role in basal autophagy or only in the context of Mn toxicity.

1.3.5 Mitochondrial pathology in HD, possible links to Mn and IIS

Mitochondrial dysfunction is another mechanism by which mHTT may cause selective neurodegeneration in HD. Mitochondrial dysfunction may contribute to neurodegenerative diseases (NDD) for several reasons; 1) High mitochondrial respiration is needed to accommodate high ATP usage in neurons, 2) mitochondria, out of all organelles, produce the highest amount of intracellular reactive oxygen species (ROS), 3) mitochondria are a critical regulator of cell death, a common feature of most NDDs, 4) mitophagy (mitochondrial selective autophagy) is often defective in NDD, and 5) perturbations in various metabolic processes, indicative of mitochondrial dysfunction, are often associated with NDD[138–140]. In HD, specifically, overt metabolic effects such as rapid weight changes and defects in glucose homeostasis have been observed in HD patients and models[141–151]. Also, WT HTT has been shown essential for mitochondrial health[152]. To this end, several basic studies and clinical trials have investigated metabolic targets as potential therapeutics for HD including creatine and Coenzyme Q10, but have found little success[153–159].

Several landmark studies demonstrate IGF1 restores mitochondrial health in HD models[97, 100, 101]. Given the IIS-mimetic effects of Mn, correcting Mn homeostasis may ameliorate some facets of mitochondrial dysfunction in HD. This hypothesis is consistent with established roles for Mn in mitochondria: 1) Mn accumulates in mitochondria more so than other organelles supporting a functional need in this organelle; 2) Mn has anti-oxidant functions via the Mn-dependent, mitochondrial enzyme, MnSOD; and 3) Mn is essential for the function at least two gluconeogenesis enyzmes[37, 57,58,60,88]. Rego and colleagues have reported a series of studies providing a mechanistic understanding of how IGF is capable of such robust amelioration of HD symptoms[100, 101, 139, 153, 160–169]. They found HD models exhibit reduced ATP/ADP ratio, decreased O2 consumption, increased mitochondrial ROS and fragmentation, aberrant lactate/pyruvate levels and decreased mitochondrial membrane potential— all of which indicates mitochondrial dysfunction. Each of these was shown to be ameliorated by IGF treatment via upregulation of PI3K/AKT signaling in cellular and mouse models of HD.

1.4.1 IIS signaling and Mn in other NDDs

Abnormal levels of IGF/insulin and decreased IIS signaling (namely, reduced AKT signaling) have been observed in all neuro-degenerative diseases including PD, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), spinocerebellar ataxias (SCA), and other NDD-like conditions such as ataxia telangiectasia (AT). In the case for many models of these diseases, IGF or insulin have been successfully used to ameliorate pathologies *in vitro* and *in vivo;* and they have been used or targeted in clinical trials[114,170–172]. Unfortunately, these clinical trials have reported little success. One possible reason for this is control of IGF-1 bioavailability by IGFBPs. This could be overcome by using a modified IGF-1-like peptide which is unable to bind IGFBPs[173]. Furthermore, although many studies have shown perturbation in metal ion homeostasis in these diseases, few have explored a more specific role for Mn dysregulation. Recent studies elucidating Mn or IGF/Insulin dysregulation in NDDs will be reviewed next, emphasizing developments in recent years.

1.4.2 PD and IIS/Mn

PD is a neurodegenerative disorder resulting in bradykinesia and motor rigidity affecting an estimated 10 million people worldwide. Symptoms of the disease mostly occur in late adulthood as a threshold of dopaminergic neurons in the substantia nigra degenerate. Unlike HD, there is no clear genetic predisposition for most cases of PD, though mutations in some genes are correlated to increased risk for PD. Given this and the late-onset of the disease, many studies have focused on environmental modifiers of the disease[174]. PD has long been associated with perturbations in metal ion homeostasis—particularly iron (Fe) and Mn. Mn toxicity causes parkinsonian-like symptoms and a disease-state known as manganism, but most agree that its pathology is different from that seen in PD. This is mainly because neurodegeneration in PD occurs primarily in the dopaminergic neurons of the substantia nigra while Mn toxicity manifests within the globus pallidus. Furthermore, at least some patients with Mn induced parkinsonism do not produce Lewy bodies and can be unresponsive to levodopa treatment[175–177]. While these two diseases may be distinct, several lines of evidence support a role for Mn dysregulation in PD. Chronic exposure to Mn is associated with increased risk for PD. Also, Mn toxicity has been linked to reduced tyrosine hydroxylase and dopamine levels and DAT cell surface expression but reports regarding impaired neuro-transmission and viability in dopaminergic neurons have been inconsistent[37, 177–181]. Mn toxicity has also been associated with increased alpha synuclein build-up, but it is unclear if this response is neuroprotective or enhances neurodegeneration[182–184].

IGF has been studied in the context of PD as well. Previous studies have revealed neuroprotective effects of IGF in PD models and associated with increased dopaminergic survival in the substantia nigra[112, 182, 185–187]. However, the majority of recent studies mainly focus on plasma IGF-1 levels as a biomarker for PD progression. Several groups published studies suggesting IGF-1 levels were increased in the sera of PD patients compared to control[188, 189]. Furthermore, studies revealed that increased plasma IGF-1 levels correlate with cognitive decline and motor symptoms[188, 190]. While these studies have

great utility as a clinical tool and seem to be quite sensitive, they have added minimal mechanistic insight as to if or why IGF-1/insulin and related signaling may be dysregulated or pathogenic consequences. Thus, continued basic and mechanistic experiment to understanding of IGF's role in PD are needed to resolve inconsistencies and provide detail.

AKT has received considerable attention in the PD field via its neuroprotective roles in the brain. Aside from reduced p-AKT levels found in post-mortem PD brains, several studies have linked increased AKT and IIS signaling to both reduced dopaminergic cell death, reduced alpha synuclein toxicity and complex interactions with PD-related proteins including PARKIN, PINK1, and DJ1[112,185, 191–195].

1.4.3 AD and IIS/Mn

AD results primarily from the degeneration of hippocampal neurons which leads to severe cognitive defects in late-adulthood. Disease is defined by two hallmark pathological features, neurofibrillary tangles (hyperphosphorylated tau) and amyloid beta plaques, two aggregates which incur neurotoxic stress. Heavy metals have also been associated with AD and its aggregate pathology, though few studies have examined Mn levels or dysregulation[196,197]. However, two recent studies investigated plasma Mn levels in AD and reported opposing results. Dehua and colleagues reported elevated Mn levels which were correlated with increased amyloid beta expression and reduced cognition while Bush et al reported reduced Mn levels in sera but no difference in patient erythrocytes[198, 199].

AD may have the most significant ties to IGF dysregulation of all NDDs. AD has been heavily correlated to diabetic status and mechanistic understanding of metabolic dysfunction in AD has led to it being referred to as "type 3 diabetes", a form of diabetes that specifically affects the brain[200]. In recent years, studies have focused primarily on the effects of IGF/insulin on amyloid beta accumulation and the use of IGF-1 levels as a biomarker for disease risk and progression. Two studies in 2009 reported that reduced IGF signaling protects against AB accumulation, potentially by acting on the plaques themselves, condensing them to less toxic forms[201–204]. These were contrary to a flurry of studies in the early-mid 2000's revealing IGF resistance and ameliorative effects by IGF treatment on AB accumulation and cognitive function[115,205–212]. A few years later, insulin resistance and reduced IIS signaling was found in postmortem AD brain tissue and soon after that, lower serum IGF-1 levels were correlated to an increased risk for AD and dementia while higher levels were associated with greater brain volume[212, 213]. Interestingly, increased IGF has been reported in CSF of patients[214,215]. Thus, even though conflicting results have been reported, these studies reveal that AD is deeply tied to IGF biology.

Contrary to PD, excessive AKT signaling has been observed in AD. Several studies have reduced or inhibited IIS signaling and observed delays in symptoms and reduced AB pathology[206,216, 217]. These results, of course, are contrary to aforementioned studies utilizing IGF treatment in AD models. Such conflicting results may be explained by an initial hyperactivation of IIS signaling which eventually desensitizes the pathway. In this way, both IIS inhibition early or IIS treatment late in disease progression may result in ameliorative effects. However, further research will have to be done across disease progression to see if this is indeed the case.

1.4.4 ALS and IIS/Mn

ALS is a neurodegenerative disease which affects more than 12,000 people in the U.S. Disease onset is more variable than other diseases and can often occur in younger people. The cause of ALS is unknown but pathology is attributed to loss of motor neurons in the brain and spinal cord resulting in loss of voluntary muscle control and, in late-stage, patients are unable to move or breathe without ventilator support. ALS has also been associated with metal ion dysregulation. Again, few studies focused on Mn levels but a few studies have reported increased Mn in CSF and plasma while the other reports no change in Mn but significant increases in copper and zinc and a reduction in selenium[218–221].

IGF dysregulation and insulin resistance has been reported in ALS[222–224]. These data led to a few *in vivo* studies using IGF-1 treatment in ALS models. While subcutaneous injection into the periphery with IGF-1 was largely found to be ineffective, direct intrathecal injections directly into the CSF resulted in some decrease in motor atrophy[170,225]. Given these results, a few clinical trials have been attempted in ALS but have found little success[171, 226,227]. One reason may be that these treatments are given peripherally instead of intrathecally[173]. More recently, IGF2 has been found to be neuroprotective in ALS models[113].

1.4.5 Autophagy in other neurodegenerative diseases

Autophagy has been linked to every neurodegenerative disease—namely because most NDDs develop aggregate pathology which is often processed by autophagy. While autophagy is activated as a protective process in order to maintain healthy homeostasis of the cell, if hyperactivated can result in autophagy-mediated cell death. Thus, interactions between aggregates and autophagy play a precarious role in NDDs[228]. Recent studies have begun to explore the effects of metal toxicity on autophagy as well[55, 137]. In PD, autophagy has primarily been investigated in the context of mitophagy (mitochondrial specific autophagy). PD has been linked to mitochondrial toxicity and dysfunction which incurs mitophagy in an attempt to remove unhealthy mitochondria from the neurons to reestablish cellular integrity. PARKIN and PINK1, two proteins associated with familial forms of PD, are essential members of the mitophagy process[229–234]. In AD, autophagy is known to regulate both the secretion and degradation of AB which adds increased complexity to its role in disease pathology. Several studies have revealed increased autophagasome accumulation in AD models, but these results have been inconsistent across disease progression[235–238]. Recently, ALS studies have revealed that two ALS associated proteins, TDP-43 and SOD1, are often dysregulated in ALS patients and models[239–241]. Interestingly, mutations in these proteins (amongst several other observed ALS mutation-associated proteins) cause aberrant autophagic processing in neuronal and spinal cord neurons[242]. Further studies are needed to elucidate mechanistic understanding of these complex relationships to determine whether dysregulated autophagy is a pathogenic mechanism or compensatory “rescue” response. Future investigation must interrogate autophagic flux rather than commonly used end-point measurements as the directionality and capacity of autophagy is necessary for forther understanding and therapeutics. The connections that have been drawn between autophagy and Mn or IGF/insulin warrant continued exploration

but studies should consider potential co-regulation of Mn and IGF/insulin on autophagy processes and dysregulation.

1.5.1 Manganese toxicity and IGF

Little investigation has been done to examine the role of IGF in manganese toxicity. Tong and colleagues found Mn toxicity caused reduced ATP and insulin/IGF receptor expression. Additionally, as mentioned before, Hiney and colleagues have been revealing a role for Mn-induced toxicity in hypothalamic development via IGF/mTOR related pathways[56,53, 54, 56, 76–78]. It is likely that Mn toxicity in other brain regions are regulated a similar manner. Given that Mn accumulates in the brain primarily in the basal ganglia, not the hypothalamus, it seems likely that and IGF/Mn interaction may play even more crucial roles in other brain regions, particularly in aged model systems. Thus, future studies on Mn toxicity and IGF could be informative on developmental toxicity, chronic environmental exposures, and overall brain health.

1.5.2 The co-regulation of ATM, Mn, and insulin/IGF

Interestingly ATM, a Mn activated kinase, has been linked to both IGF/insulin and Mn signaling. Previous studies have shown that Mn induced p53 activity is regulated by ATM. Furthermore, this Mn-induced activity is blunted in HD due to lack of bioavailable Mn[1]. Separately, low levels of the IGF-1 receptor and loss of IGF-1 sensitivity have been observed in Ataxia Telangiectasia (AT), the disease resulting from loss of function mutations in ATM, and in loss-of-function ATM models[243–246]. Additionally, studies have shown patients with AT have significantly decreased IGF-1 levels[247–250]. Additionally, others have shown ATM is essential for IGF and IGF-R transcription by phosphorylating and relieving transcription factors and complexes including p53 from their respective promotors, allowing for transcription[243, 244, 251–254]. Concurrently, downregulation of IGF-R results in increased radiosensitivity and decreased ATM protein levels (mRNA was unchanged) revealing a potential circular regulation between ATM and IGF-R[244, 255, 256]. Also, given that ATM is required for full activation of AKT, it seems likely that the connections between ATM, Mn, and IGF carry some biological relevance in the context of Mn/IGF co-regulation in NDD[257]. Mn could act as an initiating signaling molecule within this cascade where Mn activates ATM/p53 which results in increased IGF/IGF-R transcription and subsequent activation of the PI3K/AKT pathway. This hypothetical, albeit plausible, interaction could explain how a Mn deficiency in HD might contribute to decreased IIS (AKT/mTOR) and Mn-induced ATM/p53 signaling.

1.5.3 IIS signaling, Mn and cancer

Given the striking parallels and potential co-regulation between Mn and IIS and the pronounced and well-studied roles of IIS in cancer progression, one must wonder if there is role for Mn/IIS co-regulation in cancer etiology. As a pro-growth signaling pathway, IIS is often highly upregulated in cancers particularly during tumor progression[258]. However, most findings suggest Mn is not significantly carcinogenic, even to exposed workers. In fact, Mn deficiency leads to a higher risk. A plethora of studies, namely clinical examination of Mn levels in cancer patients, support the role for Mn deficiency in cancer via reduced MnSOD

activity and enhanced ROS accumulation in various cancer types[259–263]. Of note, Mn has been shown to be essential for the activation of ATM and MRE11, two DNA-damage repair proteins, and able to increase phosphorylation of p53, the most-well studied tumor suppressor gene which exerts control on cell cycle supporting a role for Mn deficiency in cancer. In fact, many cancers contain mutations in these same proteins. Somewhat paradoxically, HD is associated with reduced Mn bioavailability and reduced risk for cancers[264]. Accumulating data, studies, and clinical trials support a hypothesis that perturbations in IIS and metal ion homeostasis separately contribute to both NDDs and cancer in somewhat opposite fashions while a dearth of investigation exists to study their potential co-regulation in either disease.

1.6 Conclusions

The roles for IGF and Mn separately in HD are far from being fully elucidated. However, the sizeable overlap between their homeostasis and downstream effects supports a need to consider their coregulation in the context of diseased and healthy states. Neuroprotective cell signaling (i.e. AKT, mTOR, ERK/MAPK), mitochondrial health, and autophagic function have been implicated in all NDDs repeatedly by multiple groups. Past and present research has revealed an essential role for IIS in coordinating these cellular processes. However, little attention has been given to Mn role even though distinct lines of evidence substantiate its essentiality in these very same processes and even the upstream regulation of insulin/IGF. There is not enough evidence one way or another to draw a clear conclusion whether Mn may be at the heart of IIS dysregulation in NDDs, but there is certainly enough to warrant serious consideration of its role as a contributing factor.

It is still unclear how Mn is exerting its effects on IGF/insulin levels and signaling. Is Mn acting at the levels of transcription, translation, or post-translationally? The intriguing possibility that Mn might regulate IGF and IGF-R transcription through ATM/p53 is one that merits further study as it may have implications in not only NDDs but cancer and diabetes as well. Furthermore, given the widespread transcriptional targets of p53, Mn could be widely essential for the transcription of various proteins. Mn could also be exerting its control post-transcriptionally - potentially at the blood brain barrier or via interactions with IGF binding proteins. Clegg and colleagues reported that Mn deficiency resulted in increased IGF-BP3 which they suspected might reduce IGF bioavailability[70]. However, little investigation has been done to follow up on these findings or explore Mn’s role on other IGF-BPs which could offer a clear mechanism of Mn’s regulation of IGF.

We discussed here many examples of overlap between HD etiology, IGF/insulin biology, and Mn homeostasis. While these connections have been more fully elucidated in HD, the inherent overlap between NDD pathology suggests similar roles for Mn and IGF/insulin in other NDDs. However, as reviewed here, there is preliminary evidence that these NDDs often exhibit different trends in Mn and/or insulin/IGF homeostasis— for example PD is associated with increased Mn while HD is associated with Mn-deficiency. However, these observations lead to the following additional questions——1) are we exploring IGF/insulin and Mn dysregulation at the “right” times during disease progression 2) are we inspecting the levels of Mn or IGF/insulin in the correct tissues and 3) is this dysregulation truly a

contributor to disease pathology or simply a downstream effect of a higher mechanism? If IGF/insulin and/or Mn are truly dysregulated in NDDs, one would imagine that there are defined stages of disease progression when specific defects can be observed. Mn or insulin/IGF could be affected early on in the disease prior to symptoms, during early symptom manifestation, or during late-stage progression once significant brain atrophy has occurred (or across the entirety of disease progression). Furthermore, it is likely that this dysregulation may differ in not only magnitude, but directionality, between each stage of the disease as molecular signaling attempts to compensate or desensitize. While serum and plasma levels offer a potential biomarker of brain Mn dysregulation, further studies must examine how these levels correlate to what is seen in actual brain tissue. Studies have found that changes in IGF by age, sex, diet, BMI, and secondary disease status can cause immense variability between patients, particularly in peripheral samples[118]. Several heavy metals are reported to accumulate in the brain with age and can differ by similar confounds suggesting peripheral Mn may also be an inappropriate measurement for brain Mn. Furthermore, regulation of IGF/insulin and Mn across the blood brain barrier has been somewhat elucidated, but strict regulation of these molecules is needed to establish brain integrity suggesting that they might be very different from what is seen in serum/plasma or even CSF. Confirming consistencies between serum, plasma, blood, CSF and the brain should be done in rodent models across disease progression to validate IGF/insulin and Mn biomarkers—substantiating their use in clinical studies. For other NDDs, a higher mechanistic understanding of IGF/insulin and Mn biology should be explored at the molecular and cellular levels, similar to what has been done in the HD field. Lastly, given the extended time it takes prior to NDD manifestation, one must ask whether observed defects in IGF/insulin or Mn are either a cause of the disease or instead a consequence of the neurodegeneration. This is a difficult question to answer given the inherent difficulty in working with aged models—namely mouse models which often do not fully recapitulate the pathology observed in humans.

Currently, available methods and technology make it quite difficult to truly investigate these questions in a high-through put manner. Highly sensitive biomarkers for Mn and IGF/insulin levels in the brain are likely required to observe changes across disease progression which are currently unavailable. The high variability and contradictory data of IGF/insulin levels in serum/plasma compared to brain suggest these are not always appropriate measurements for brain levels. While existing techniques can quantify levels of Mn in tissues or cells (ICP-MS, graphite furnace, cellular fura-2 Mn extraction assay (CFMEA)) as well as techniques that allow a cellular/sub-cellar resolution of Mn localization (XANESX-ray absorption near edge structure), high costs and complexities related to maintaining *in vivo* patterns has limited understanding of Mn brain homeostasis[2]. Thus, creative approaches will be necessary to answer the outstanding questions.

References

1. Tidball AM, Bryan MR, Uhouse MA, Kumar KK, Aboud AA, Feist JE, Ess KC, Neely DM, Aschner M and Bowman AB (2015). A novel manganese-dependent ATM-p53 signaling pathway is selectively impaired in patient-based neuroprogenitor and murine striatal models of Huntington's disease. Human Molecular Genetics. 24 (7): 1929–1944. [PubMed: 25489053]

2. Kwakye GF, Li D and Bowman AB (2011). Novel high-throughput assay to assess cellular manganese levels in a striatal cell line model of Huntington's disease confirms a deficit in manganese accumulation. NeuroToxicology. 32 (5): 630–639. [PubMed: 21238486]

3. Williams BB, Kwakye GF, Wegrzynowicz M, Li D, Aschner M, Erikson KM and Bowman AB (2010). Altered Manganese Homeostasis and Manganese Toxicity in a Huntington's Disease Striatal Cell Model Are Not Explained by Defects in the Iron Transport System. Toxicological Sciences. 117 (1): 169–179. [PubMed: 20547568]

4. Williams BB, Li D, Wegrzynowicz M, Vadodaria BK, Anderson JG, Kwakye GF, Aschner M, Erikson KM and Bowman AB (2010). Disease-toxicant screen reveals a neuroprotective interaction between Huntington's disease and manganese exposure. Journal of neurochemistry. 112 (1):227–237. [PubMed: 19845833]

5. Stansfield KH, Bichell T, Bowman AB and Guilarte TR (2014). BDNF and Huntingtin protein modifications by manganese: implications for striatal medium spiny neuron pathology in manganese neurotoxicity. Journal of neurochemistry. 131 (5): 655–666. [PubMed: 25099302]

6. Greenwood BN and Fleshner M (2008). Exercise, Learned Helplessness, and the Stress-Resistant Brain. NeuroMolecular Medicine. 10 (2): 81–98. [PubMed: 18300002]

7. Trejo JL, Llorens-Martín MV and Torres-Alemán I (2007). The effects of exercise on spatial learning and anxiety-like behavior are mediated by an IGF-I-dependent mechanism related to hippocampal neurogenesis. Molecular and cellular neurosciences. 37 (2): 402–411. [PubMed: 18086533]

8. Xiang Y, Ding N, Xing Z, Zhang W, Liu H and Li Z (2010). Insulin-Like Growth Factor-1 Regulates Neurite Outgrowth and Neuronal Migration From Organotypic Cultured Dorsal Root Ganglion. International Journal of Neuroscience. 121 (2): 101–106. [PubMed: 21110707]

9. Xing C, Yin Y, Chang R, Gong X, He X and Xie Z (2007). Effects of insulin-like growth factor 1 on synaptic excitability in cultured rat hippocampal neurons. Experimental neurology. 205 (1): 222–229. [PubMed: 17335809]

10. Xing C, Yin Y, He X and Xie Z (2006). Effects of insulin-like growth factor 1 on voltage-gated ion channels in cultured rat hippocampal neurons. Brain research. 1072 (1): 30–35. [PubMed: 16438944]

11. Liou J-C, Tsai F-Z and Ho S-Y (2003). Potentiation of quantal ecretion by insulin-like growth factor-1 at developing motoneurons in Xenopus cell culture. The Journal of physiology. 553 (Pt 3): 719–728. [PubMed: 14514875]

12. Ozdinler HP and Macklis JD (2006). IGF-I specifically enhances axon outgrowth of corticospinal motor neurons. Nature neuroscience. 9 (11): 1371–1381. [PubMed: 17057708]

13. Skeberdis VA, Lan J, Zheng X, Zukin RS and Bennett MV (2001). Insulin promotes rapid delivery of N-methyl-D- aspartate receptors to the cell surface by exocytosis. Proceedings of the National Academy of Sciences of the United States of America. 98 (6): 3561–3566. [PubMed: 11248117]

14. Sosa L, Dupraz S, Laurino L, Bollati F, Bisbal M, Cáceres A, Pfenninger KH and Quiroga S (2006). IGF-1 receptor is essential for the establishment of hippocampal neuronal polarity. Nature neuroscience. 9 (8): 993–995. [PubMed: 16845384]

15. Liu W, Ye P, O'Kusky JR and D'Ercole JA (2009). Type 1 insulin-like growth factor receptor signaling is essential for the development of the hippocampal formation and dentate gyrus. Journal of Neuroscience Research. 87 (13): 2821–2832. [PubMed: 19437543]

16. Dentremont KD, Ye P, D'Ercole AJ and O'Kusky JR (1999). Increased insulin-like growth factor-I (IGF-I) expression during early postnatal development differentially increases neuron number and growth in medullary nuclei of the mouse. Brain research Developmental brain research. 114 (1): 135–141. [PubMed: 10209251]

17. O'Kusky JR, Ye P and D'Ercole AJ (2000). Insulin-like growth factor-I promotes neurogenesis and synaptogenesis in the hippocampal dentate gyrus during postnatal development. The Journal of neuroscience : the official journal of the Society for Neuroscience. 20 (22): 8435–8442. [PubMed: 11069951]

18. Hurtado-Chong A, Yusta-Boyo MJ, Vergaño-Vera E, Bulfone A, Pablo F and Vicario-Abejón C (2009). IGF-I promotes neuronal migration and positioning in the olfactory bulb and the exit of

neuroblasts from the subventricular zone. European Journal of Neuroscience. 30 (5): 742–755. [PubMed: 19712103]

19. Oishi K, Watatani K, Itoh Y, Okano H, Guillemot F, Nakajima K and Gotoh Y (2009). Selective induction of neocortical GABAergic neurons by the PDK1-Akt pathway through activation of Mash1. Proceedings of the National Academy of Sciences. 106 (31): 13064–13069.
20. Chiu S-L, Chen C-M and Cline HT (2008). Insulin Receptor Signaling Regulates Synapse Number, Dendritic Plasticity, and Circuit Function In Vivo. Neuron. 58 (5): 708–719. [PubMed: 18549783]
21. Ciucci F, Putignano E, Baroncelli L, Landi S, Berardi N and Maffei L (2007). Insulin-like growth factor 1 (IGF-1) mediates the effects of enriched environment (EE) on visual cortical development. PloS one. 2 (5).
22. Hodge RD, D'Ercole JA and O'Kusky JR (2004). Insulin-like growth factor-I accelerates the cell cycle by decreasing G1 phase length and increases cell cycle reentry in the embryonic cerebral cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience. 24 (45): 10201–10210. [PubMed: 15537892]
23. D'Ercole AJ, Ye P, Calikoglu AS and Gutierrez-Ospina G (1996). The role of the insulin-like growth factors in the central nervous system. Molecular neurobiology. 13 (3): 227–255. [PubMed: 8989772]
24. D'Ercole JA, Ye P and O'Kusky JR (2002). Mutant mouse models of insulin-like growth factor actions in the central nervous system. Neuropeptides. 36 (2–3): 209–220. [PubMed: 12359511]
25. Root CM, Ko KI, Jafari A and Wang JW (2011). Presynaptic Facilitation by Neuropeptide Signaling Mediates Odor-Driven Food Search. Cell. 145 (1): 133–144. [PubMed: 21458672]
26. Jiu Y-M, Yue Y, Yang S, Liu L, Yu J-W, Wu Z-X and Xu T (2010). Insulin-like signaling pathway functions in integrative response to an olfactory and a gustatory stimuli in Caenorhabditis elegans. Protein & Cell. 1 (1): 75–81. [PubMed: 21203999]
27. Marks DR, Tucker K, Cavallin MA, Mast TG and Fadool DA(2009). Awake Intranasal Insulin Delivery Modifies Protein Complexes and Alters Memory, Anxiety, and Olfactory Behaviors. The Journal of Neuroscience. 29 (20): 6734–6751. [PubMed: 19458242]
28. Haj-ali V, Mohaddes G and Babri SH (2009). Intracerebroventricular insulin improves spatial learning and memory in male Wistar rats. Behavioral Neuroscience. 123 (6): 1309. [PubMed: 20001114]
29. Dhamoon MS, Noble JM and Craft S (2009). INTRANASAL INSULIN IMPROVES COGNITION AND MODULATES -AMYLOID IN EARLY AD. Neurology. 72 (3): 292–294.
30. Zhao W, Chen H, Xu H, Moore E, Meiri N, Quon MJ and Alkon DL (1999). Brain insulin receptors and spatial memory. Correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats. The Journal of biological chemistry. 274 (49): 34893–34902. [PubMed: 10574963]
31. Deijen JB, de Boer H and van der Veen EA (1998). Cognitive changes during growth hormone replacement in adult men. Psychoneuroendocrinology. 23 (1): 45–55. [PubMed: 9618751]
32. Fernandez AM and Torres-Alemán I (2012). The many faces of insulin-like peptide signalling in the brain. Nature reviews Neuroscience. 13 (4): 225–239. [PubMed: 22430016]
33. Baxter RC (2014). IGF binding proteins in cancer: mechanistic and clinical insights. Nature reviews Cancer. 14 (5): 329–341. [PubMed: 24722429]
34. Clemmons DR, Busby WH, Arai T, Nam TJ, Clarke JB, Jones JI and Ankrapp DK (1995). Role of insulin-like growth factor binding proteins in the control of IGF actions. Progress in growth factor research. 6 (2–4): 357–366. [PubMed: 8817679]
35. Chan DW, Son SC, Block W, Ye R, Khanna KK, Wold MS, Douglas P, Goodarzi AA, Pelley J, Taya Y, Lavin MF and Lees-Miller SP (2000). Purification and characterization of ATM from human placenta. A manganese-dependent, wortmannin-sensitive serine/threonine protein kinase. The Journal of biological chemistry. 275 (11): 7803–7810. [PubMed: 10713094]
36. Sato T, Nakashima A, Guo L and Tamanoi F (2009). Specific Activation of mTORC1 by Rheb G-protein in Vitro Involves Enhanced Recruitment of Its Substrate Protein. Journal of Biological Chemistry. 284 (19): 12783–12791. [PubMed: 19299511]
37. Horning KJ, Caito SW, Tipps KG, Bowman AB and Aschner M (2015). Manganese Is Essential for Neuronal Health. Annual review of nutrition. 35: 71–108.

38. Paull TT and Gellert M (1998). The 3' to 5' exonuclease activity of Mre 11 facilitates repair of DNA double-strand breaks. Molecular cell. 1 (7): 969–979. [PubMed: 9651580]
39. Trujillo KM, Yuan SS, Lee EY and Sung P (1998). Nuclease activities in a complex of human recombination and DNA repair factors Rad50, Mre11, and p95. The Journal of biological chemistry. 273 (34): 21447–21450. [PubMed: 9705271]
40. D'Antonio EL, Hai Y and Christianson DW (2012). Structure and function of non-native metal clusters in human arginase I. Biochemistry. 51 (42): 8399–8409. [PubMed: 23061982]
41. Kanyo ZF, Scolnick LR, Ash DE and Christianson DW (1996). Structure of a unique binuclear manganese cluster in arginase. Nature. 383 (6600): 554–557. [PubMed: 8849731]
42. Neulen A, Blaudeck N, Zittrich S, Metzler D, Pfitzer G and Stehle R (2007). Mn2+-dependent protein phosphatase 1 enhances protein kinase A-induced Ca2+ desensitisation in skinned murine myocardium. Cardiovascular research. 74 (1): 124–132. [PubMed: 17321507]
43. Wozniak-Celmer E, Oidziej S and Ciarkowski J (2001). Theoretical models of catalytic domains of protein phosphatases 1 and 2A with Zn2+ and Mn2+ metal dications and putative bioligands in their catalytic centers. Acta biochimica Polonica. 48 (1): 35–52. [PubMed: 11440182]
44. Maydan M, McDonald PC, Sanghera J, Yan J, Rallis C, Pinchin S, Hannigan GE, Foster LJ, Ish-Horowicz D, Walsh MP and Dedhar S (2010). Integrin-Linked Kinase Is a Functional Mn2+-Dependent Protein Kinase that Regulates Glycogen Synthase Kinase-3β (GSK3β) Phosphorylation. PLoS ONE. 5 (8).
45. Wedler FC and Ley BW (1994). Kinetic, ESR, and trapping evidence for in vivo binding of Mn(II) to glutamine synthetase in brain cells. Neurochemical research. 19 (2): 139–144. [PubMed: 7910378]
46. Dormond O, Ponsonnet L, Hasmim M, Foletti A and Rüegg C (2004). Manganese-induced integrin affinity maturation promotes recruitment of alpha V beta 3 integrin to focal adhesions in endothelial cells: evidence for a role of phosphatidylinositol 3 kinase and Src. Thrombosis and haemostasis. 92 (1): 151–161. [PubMed: 15213856]
47. Bae J-H, Jang B-C, Suh S-I, Ha E, Baik H, Kim S-S, Lee M-y H (2006). Manganese induces inducible nitric oxide synthase (iNOS) expression via activation of both MAP kinase and PI3K/Akt pathways in BV2 microglial cells. Neuroscience letters. 398 (1–2): 151–154. [PubMed: 16417967]
48. Cordova FM, Aguiar AS, Peres TV, Lopes MW, Gonçalves FM, Remor AP, Lopes SC, Pilati C, Latini AS, Prediger RD, Erikson KM, Aschner M and Leal RB (2012). In vivo manganese exposure modulates Erk, Akt and Darpp-32 in the striatum of developing rats, and impairs their motor function. PloS one. 7 (3).
49. Crittenden PL and Filipov NM (2011). Manganese modulation of MAPK pathways: effects on upstream mitogen activated protein kinase kinases and mitogen activated kinase phosphatase-1 in microglial cells. Journal of applied toxicology : JAT. 31 (1): 1–10. [PubMed: 20589745]
50. Exil V, Ping L, Yu Y, Chakraborty S, Caito SW, Wells KS, Karki P, Lee E and Aschner M (2014). Activation of MAPK and FoxO by manganese (Mn) in rat neonatal primary astrocyte cultures. PloS one. 9 (5).
51. Jang B-CC (2009). Induction of COX-2 in human airway cells by manganese: role of PI3K/PKB, p38 MAPK, PKCs, Src, and glutathione depletion. Toxicologv in vitro : an international journal published in association with BIBRA. 23 (1): 120–126.
52. Cordova FM, Aguiar AS, Peres TV, Lopes MW, Gonçalves FM, Pedro DZ, Lopes SC, Pilati C, Prediger RD, Farina M, Erikson KM, Aschner M and Leal RB (2013). Manganese-exposed developing rats display motor deficits and striatal oxidative stress that are reversed by Trolox. Archives of toxicology. 87 (7): 1231–1244. [PubMed: 23385959]
53. Dearth RK, Hiney JK, Srivastava VK, Hamilton AM and Dees WL (2014). Prepubertal exposure to elevated manganese results in estradiol regulated mammary gland ductal differentiation and hyperplasia in female rats. Experimental Biology and Medicine. 239 (7): 871–882. [PubMed: 24845367]
54. Srivastava VK, Hiney JK and Dees WL (2016). Manganese stimulated Kisspeptin is mediated by the Insulin-like growth factor1/Akt/mammalian target of rapamycin pathway in the prepubertal female rat. Endocrinology.

55. Zhang J, Cao R, Cai T, Aschner M, Zhao F, Yao T, Chen Y, Cao Z, Luo W and Chen J (2013). The Role of Autophagy Dysregulation in Manganese-Induced Dopaminergic Neurodegeneration. Neurotoxicity Research. 24 (4): 478–490. [PubMed: 23604964]

56. Hiney JK, Srivastava VK and Dees WL (2011). Manganese induces IGF-1 and cyclooxygenase-2 gene expressions in the basal hypothalamus during prepubertal female development. Toxicological sciences : an official journal of the Society of Toxicology. 121 (2): 389–396. [PubMed: 21402727]

57. Gunter TE, Gavin CE and Gunter KK (2009). The case for manganese interaction with mitochondria. NeuroToxicology. 30 (4): 727–729.

58. Kalia K, Jiang W and Zheng W (2008). Manganese accumulates primarily in nuclei of cultured brain cells. NeuroToxicology. 29 (3): 466–470. [PubMed: 18400301]

59. Morello M, Canini A, Mattioli P, Sorge RP, Alimonti A, Bocca B, Forte G, Martorana A, Bernardi G and Sancesario G (2008). Sub-cellular localization of manganese in the basal ganglia of normal and manganese-treated rats An electron spectroscopy imaging and electron energy-loss spectroscopy study. Neurotoxicology. 29 (1): 60–72. [PubMed: 17936361]

60. Chen P, Chakraborty S, Mukhopadhyay S, Lee E, Paoliello MM, Bowman AB and Aschner M (2015). Manganese homeostasis in the nervous system. Journal of neurochemistry. 134 (4): 601–610. [PubMed: 25982296]

61. DeWitt MR, Chen P and Aschner M (2013). Manganese efflux in Parkinsonism: Insights from newly characterized SLC30A10 mutations. Biochemical and Biophysical Research Communications. 432 (1): 1–4. [PubMed: 23357421]

62. Leyva-Illades D, Chen P, Zogzas CE, Hutchens S, Mercado JM, Swaim CD, Morrisett RA, Bowman AB, Aschner M and Mukhopadhyay S (2014). SLC30A10 Is a Cell Surface-Localized Manganese Efflux Transporter, and Parkinsonism-Causing Mutations Block Its Intracellular Trafficking and Efflux Activity. The Journal of Neuroscience. 34 (42): 14079–14095. [PubMed: 25319704]

63. Quadri M, Federico A, Zhao T, Breedveld GJ, Battisti C, Delnooz C, Severijnen L-A, Di Toro Mammarella L, Mignarri A, Monti L, Sanna A, Lu P, Punzo F, Cossu G, Willemsen R, Rasi F, Oostra BA, van de Warrenburg BP and Bonifati V (2012). Mutations in SLC30A10 Cause Parkinsonism and Dystonia with Hypermanganesemia, Polycythemia, and Chronic Liver Disease. The American Journal of Human Genetics. 90 (3): 467–477. [PubMed: 22341971]

64. Baly DL (1984). Effect of Manganese Deficiency on InsulinSecretion and Carbohydrate Heomostasis in Rats. JNutrition.

65. Baly DL, Keen CL and Hurley LS (1986). Effects of manganese deficiency on pyruvate carboxylase and phosphoenolpyruvate carboxykinase activity and carbohydrate homeostasis in adult rats. Biological Trace Element Research. 11 (1): 201–212. [PubMed: 24254514]

66. Baly DL, Lee I and Doshi R (1988). Mechanism of decreased insulinogenesis in manganese-deficient rats. Decreased insulin mRNA levels. FEBS letters. 239 (1): 55–58. [PubMed: 2460371]

67. Baly DL, Schneiderman JS and Garcia-Welsh AL (1990). Effect of manganese deficiency on insulin binding, glucose transport and metabolism in rat adipocytes. The Journal of nutrition. 120 (9): 1075–1079. [PubMed: 2204694]

68. Keen CL, Baly DL and Lönnerdal B (1984). Metabolic effects of high doses of manganese in rats. Biological Trace Element Research. 6 (4): 309–315. [PubMed: 24264109]

69. Subasinghe S, Greenbaum AL and McLean P (1985). The insulinmimetic action of Mn2+: involvement of cyclic nucleotides and insulin in the regulation of hepatic hexokinase and glucokinase. Biochemical medicine. 34 (1): 83–92. [PubMed: 2996512]

70. Clegg MS, Donovan SM, Monaco MH, Baly DL, Ensunsa JL and Keen CL (1998). The influence of manganese deficiency on serum IGF-1 and IGF binding proteins in the male rat. Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine (New York, NY). 219 (1): 41–47.

71. Lee S-H, Jouihan HA, Cooksey RC, Jones D, Kim HJ, Winge DR and McClain DA (2013). Manganese Supplementation Protects Against Diet-Induced Diabetes in Wild Type Mice by Enhancing Insulin Secretion. Endocrinology. 154 (3): 1029–1038. [PubMed: 23372018]

72. Ekmekcioglu C, Prohaska C, Pomazal K, Steffan I, Schernthaner G and Marktl W (2001). Concentrations of seven trace elements in different hematological matrices in patients with type 2

diabetes as compared to healthy controls. Biological trace element research. 79 (3): 205–219. [PubMed: 11354346]

73. Koh ES, Kim SJ, Yoon HE, Chung JH, Chung S, Park CW, Chang YS and Shin SJ (2014). Association of blood manganese level with diabetes and renal dysfunction: a cross-sectional study of the Korean general population. BMC endocrine disorders. 14: 24. [PubMed: 24606630]
74. Rubenstein AH, Levin NW and Elliott GA (1962). Manganese-induced hypoglycaemia. Lancet (London, England). 2 (7270): 1348–1351.
75. Srivastava VK, Hiney JK and Dees WL (2013). Early Life Manganese Exposure Upregulates Tumor-Associated Genes in the Hypothalamus of Female Rats: Relationship to Manganese-Induced Precocious Puberty. Toxicological Sciences. 136 (2): 373–381. [PubMed: 23997110]
76. Lee B, Hiney JK, Pine MD, Srivastava VK and Dees LW (2007). Manganese stimulates luteinizing hormone releasing hormone secretion in prepubertal female rats: hypothalamic site and mechanism of action. The Journal of Physiology. 578 (3): 765–772. [PubMed: 17110411]
77. Lee B, Pine M, Johnson L, Rettori V, Hiney JK and Dees LW (2006). Manganese acts centrally to activate reproductive hormone secretion and pubertal development in male rats. Reproductive toxicology (Elmsford, NY). 22 (4): 580–585.
78. Srivastava VK, Hiney JK and Dees LW (2011). Prepubertal ethanol exposure alters hypothalamic transforming growth factor-α and erbB1 receptor signaling in the female rat. Alcohol. 45 (2): 173–181. [PubMed: 20926228]
79. Bates G, Tabrizi S and Jones L (2014). Huntington's disease. Huntington's disease.
80. Landles C and Bates GP (2004). Huntingtin and the molecular pathogenesis of Huntington's disease. EMBO reports. 5 (10): 958–963. [PubMed: 15459747]
81. Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, Nance M, Ross CA, Scahill RI, Wetzel R, Wild EJ and Tabrizi SJ (2015). Huntington disease. Nature reviews Disease primers. 1: 15005.
82. Kumar A, Singh S, Kumar V, Kumar D, Agarwal S and Rana M(2015). Huntington's disease: An update of therapeutic strategies. Gene. 556 (2): 91–97. [PubMed: 25447911]
83. Cattaneo E, Zuccato C and Tartari M (2005). Normal huntingtin function: an alternative approach to Huntington's disease. Nature reviews Neuroscience. 6 (12): 919–930. [PubMed: 16288298]
84. Gusella JF and MacDonald ME (2009). Huntington's disease: the case for genetic modifiers. Genome Medicine. 1 (8): 80. [PubMed: 19725930]
85. Prohaska JR (1987). Functions of trace elements in brain metabolism. Physiological reviews. 67 (3): 858–901. [PubMed: 3299411]
86. Larsen NA, Pakkenberg H, Damsgaard E and Heydorn K (1979). Topographical distribution of arsenic, manganese, and selenium in the normal human brain. Journal of the Neurological Sciences. 42 (3): 407–416. [PubMed: 512674]
87. Takeda A (2003). Manganese action in brain function. Brain Research Reviews. 41 (1): 79–87. [PubMed: 12505649]
88. Tidball AM, Bichell T and Bowman AB (2015). Manganese in Health and Disease. rsc. 540–573.
89. Cordova FM, Aguiar AS, Peres TV, Lopes MW, Gonçalves FM, Remor AP, Lopes SC, Pilati C, Latini AS, Prediger RDS, Erikson KM, Aschner M and Leal RB (2012). In Vivo Manganese Exposure Modulates Erk, Akt and Darpp-32 in the Striatum of Developing Rats, and Impairs Their Motor Function. PLoS ONE. 7 (3).
90. Guilarte TR (2010). APLP1, Alzheimer's-like pathology and neurodegeneration in the frontal cortex of manganese-exposed non-human primates. NeuroToxicology. 31 (5): 572–574. [PubMed: 20188756]
91. Lee JH, Tecedor L, Chen Y, Monteys A, Sowada MJ, Thompson LM and Davidson BL (2014). Reinstating aberrant mTORC1 activity in Huntington's disease mice improves disease phenotypes. Neuron. 85 (2): 303–315. [PubMed: 25556834]
92. Humbert S, Bryson EA, Cordelières FP, Connors NC, Datta SR, Finkbeiner S, Greenberg ME and Saudou F (2002). The IGF-1/Akt Pathway Is Neuroprotective in Huntington's Disease and Involves Huntingtin Phosphorylation by Akt. Developmental Cell. 2 (6): 831–837. [PubMed: 12062094]

93. Blázquez C, Chiarlone A, Bellocchio L, Resel E, Pruunsild P, García-Rincón D, Sendtner M, Timmusk T, Lutz B, Galve-Roperh I and Guzmán M (2015). The CBi cannabinoid receptor signals striatal neuroprotection via a PI3K/Akt/mTORC1/BDNF pathway. Cell death and differentiation. 22 (10): 1618–1629. [PubMed: 25698444]

94. Gines S, Ivanova E, Seong I-S, Saura CA and MacDonald ME (2003). Enhanced Akt Signaling Is an Early Pro-survival Response That Reflects N-Methyl-D-aspartate Receptor Activation in Huntington's Disease Knock-in Striatal Cells. Journal of Biological Chemistry. 278 (50): 50514–50522. [PubMed: 14522959]

95. Humbert S and Saudou F (2003). Huntingtin phosphorylation and signaling pathways that regulate toxicity in Huntington's disease. Clinical Neuroscience Research. 3 (3): 149–155.

96. Lopes C, Ribeiro M, Duarte AI, Humbert S, Saudou F, Pereira de Almeida L, Hayden M and Rego AC (2014). IGF-1 intranasal administration rescues Huntington's disease phenotypes in YAC128 mice. Molecular neurobiology. 49 (3): 1126–1142. [PubMed: 24347322]

97. Ribeiro M, Rosenstock TR, Oliveira AM, Oliveira CR and Rego AC (2014). Insulin and IGF-1 improve mitochondrial function in a PI-3K/Akt-dependent manner and reduce mitochondrial generation of reactive oxygen species in Huntington's disease knock-in striatal cells. Free radical biology & medicine. 74: 129–144. [PubMed: 24992836]

98. Saavedra A, García-Martínez JM, Xifró X, Giralt A, Torres-Peraza JF, Canals JM, Díaz-Hernández M, Lucas JJ, Alberch J and Pérez Navarro E (2009). PH domain leucine-rich repeat protein phosphatase 1 contributes to maintain the activation of the PI3K/Akt pro-survival pathway in Huntington's disease striatum. Cell death and differentiation. 17 (2): 324–335. [PubMed: 19745829]

99. Zala D, Colin E, Rangone H, Liot G, Humbert S and Saudou F (2008). Phosphorylation of mutant huntingtin at S421 restores anterograde and retrograde transport in neurons. Human Molecular Genetics. 17 (24): 3837–3846. [PubMed: 18772195]

100. Naia L, Ferreira IL, Cunha-Oliveira T, Duarte AI, Ribeiro M, Rosenstock TR, Laço MNN, Ribeiro MJ, Oliveira CR, Saudou F, Humbert S and Rego AC (2015). Activation of IGF-1 and insulin signaling pathways ameliorate mitochondrial function and energy metabolism in Huntington's Disease human lymphoblasts. Molecular neurobiology. 51 (1): 331–348. [PubMed: 24841383]

101. Naia L, Ribeiro M, Rodrigues J, Duarte AI, Lopes C, Rosenstock TR, Hayden MR and Rego CA (2016). Insulin and IGF-1 regularize energy metabolites in neural cells expressing full-length mutant huntingtin. Neuropeptides.

102. Gauthier LR, Charrin BC, Borrell-Pagès M, Dompierre JP, Rangone H, Cordelières FP, Mey J, MacDonald ME, Leβmann V, Humbert S and Saudou F (2004). Huntingtin Controls Neurotrophic Support and Survival of Neurons by Enhancing BDNF Vesicular Transport along Microtubules. Cell. 118 (1): 127–138. [PubMed: 15242649]

103. Pryor WM, Biagioli M, Shahani N, Swarnkar S, Huang W-C, Page DT, MacDonald ME and Subramaniam S (2014). Huntingtin promotes mTORC1 signaling in the pathogenesis of Huntington's disease. Science signaling. 7 (349).

104. Sarkar S, Ravikumar B, Floto RA and Rubinsztein DC (2008). Rapamycin and mTOR-independent autophagy inducers ameliorate toxicity of polyglutamine-expanded huntingtin and related proteinopathies. Cell death and differentiation. 16 (1): 46–56. [PubMed: 18636076]

105. Pouladi MA, Xie Y, Skotte NH, Ehrnhoefer DE, Graham RK, Kim JE, Bissada N, Yang XW, Paganetti P, Friedlander RM, Leavitt BR and Hayden MR (2010). Full-length huntingtin levels modulate body weight by influencing insulin-like growth factor 1 expression. Human molecular genetics. 19 (8): 1528–1538. [PubMed: 20097678]

106. Saleh N, Moutereau S, Azulay JP, Verny C, Simonin C, Tranchant C, Hawajri EN, Bachoud-Lévi AC, Maison P and Group H (2010). High insulinlike growth factor I is associated with cognitive decline in Huntington disease. Neurology. 75 (1): 57–63. [PubMed: 20603485]

107. Yamamoto A, Cremona ML and Rothman JE (2006). Autophagy-mediated clearance of huntingtin aggregates triggered by the insulin-signaling pathway. The Journal of cell biology. 172 (5): 719–731. [PubMed: 16505167]

108. Duarte AI, Petit GH, Ranganathan S, Li JY, Oliveira CR, Brundin P, Björkqvist M and Rego AC (2011). IGF-1 protects against diabetic features in an in vivo model of Huntington's disease. Experimental Neurology. 231 (2): 314–319. [PubMed: 21763311]
109. Alexi T, Hughes PE, van Roon-Mom WM, Faull RL, Williams CE, Clark RG and Gluckman PD (1999). The IGF-I amino-terminal tripeptide glycine-proline-glutamate (GPE) is neuroprotective to striatum in the quinolinic acid lesion animal model of Huntington's disease. Experimental neurology. 159 (1): 84–97. [PubMed: 10486177]
110. Metzler M, Gan L, Mazarei G, Graham RK, Liu L, Bissada N, Lu G, Leavitt BR and Hayden MR (2010). Phosphorylation of Huntingtin at Ser421 in YAC128 Neurons Is Associated with Protection of YAC128 Neurons from NMDA-Mediated Excitotoxicity and Is Modulated by PP1 and PP2A. The Journal of Neuroscience. 30 (43): 14318–14329. [PubMed: 20980587]
111. Warby SC, Doty CN, Graham RK, Shively J, Singaraja RR and Hayden MR (2009). Phosphorylation of huntingtin reduces the accumulation of its nuclear fragments. Molecular and Cellular Neuroscience. 40 (2): 121–127. [PubMed: 18992820]
112. Quesada A, Lee BY and Micevych PE (2008). PI3 kinase/Akt activation mediates estrogen and IGF-1 nigral DA neuronal neuroprotection against a unilateral rat model of Parkinson's disease. Developmental neurobiology. 68 (5): 632–644. [PubMed: 18278798]
113. Allodi I, Comley L, Nichterwitz S, Nizzardo M, Simone C, Benitez JA, Cao M, Corti S and Hedlund E (2016). Differential neuronal vulnerability identifies IGF-2 as a protective factor in ALS. Scientific reports. 6: 25960. [PubMed: 27180807]
114. Bassil F, Fernagut P-O, Bezard E and Meissner WG (2014). Insulin, IGF-1 and GLP-1 signaling in neurodegenerative disorders: Targets for disease modification? Progress in Neurobiology. 118: 1–18. [PubMed: 24582776]
115. Gasparini L and Xu H (2003). Potential roles of insulin and IGF-1 in Alzheimer's disease. Trends in Neurosciences. 26 (8): 404–406. [PubMed: 12900169]
116. Aleman I (2012). Insulin-Like Growth Factor-1 and Central Neurodegenerative Diseases. Endocrinology and Metabolism Clinics of North America. 41 (2): 395–408. [PubMed: 22682637]
117. Homolak J, Janes I and Filipovic M (2015). The role of IGF-1 in neurodegenerative diseases. Gyrus. 3 (3): 162–167.
118. Bernhard FP, Heinzel S, Binder G, Weber K, Apel A, Roeben B, Deuschle C, Maechtel M, Heger T, Nussbaum S, Gasser T, Maetzler W and Berg D (2016). Insulin-Like Growth Factor 1 (IGF-1) in Parkinson's Disease: Potential as Trait-, Progression- and Prediction Marker and Confounding Factors. PLOS ONE. 11 (3).
119. Reger MA, Watson GS, Green PS, Wilkinson CW, Baker LD, Cholerton B, Fishel MA, Plymate SR, Breitner JCS, DeGroodt W, Mehta P and Craft S (2007). Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology. 70 (6): 440–448. [PubMed: 17942819]
120. Truant R, Atwal R, Desmond C, Munsie L and Tran T (2008). Huntington's disease: revisiting the aggregation hypothesis in polyglutamine neurodegenerative diseases. The FEBS journal. 275 (17): 4252–4262. [PubMed: 18637947]
121. Arrasate M and Finkbeiner S (2011). Protein aggregates in Huntington's disease. Experimental neurology. 238 (1): 1–11. [PubMed: 22200539]
122. Bano D, Zanetti F, Mende Y and Nicotera P (2011). Neurodegenerative processes in Huntington's disease. Cell Death & Disease. 2 (11).
123. Lim J and Yue Z (2015). Neuronal Aggregates: Formation, Clearance, and Spreading. Developmental Cell. 32 (4): 491–501. [PubMed: 25710535]
124. Cortes CJ and Spada AR (2014). The many faces of autophagy dysfunction in Huntington's disease: from mechanism to therapy. Drug discovery today. 19 (7): 963–971. [PubMed: 24632005]
125. Cuervo A and Zhang S (2015). Selective autophagy and Huntingtin: learning from disease. Cell Cycle. 14 (11).
126. Martin DDO, Ladha S, Ehrnhoefer DE and Hayden MR (2014). Autophagy in Huntington disease and huntingtin in autophagy. Trends in neurosciences. 38 (1): 26–35. [PubMed: 25282404]

127. Ravikumar B and Rubinsztein DC (2006). Role of autophagy in the clearance of mutant huntingtin: a step towards therapy? Molecular aspects of medicine. 27 (5–6): 520–527. [PubMed: 16973207]

128. Sarkar S and Rubinsztein DC (2008). Huntington's disease: degradation of mutant huntingtin by autophagy. The FEBS journal. 275 (17): 4263–4270. [PubMed: 18637946]

129. Williams A, Sarkar S, Cuddon P, Ttofi EK, Saiki S, Siddiqi FH,Jahreiss L, Fleming A, Pask D, Goldsmith P, O'Kane CJ, Floto R and Rubinsztein DC (2008). Novel targets for Huntington's disease in an mTOR-independent autophagy pathway. Nature Chemical Biology. 4 (5): 295–305. [PubMed: 18391949]

130. Rui Y-NN, Xu Z, Patel B, Chen Z, Chen D, Tito A, David G, Sun Y, Stimming EF, Bellen HJ, Cuervo AM and Zhang S (2015). Huntingtin functions as a scaffold for selective macroautophagy. Nature cell biology. 17 (3).

131. Gelman A, Rawet-Slobodkin M and Elazar Z (2015). Huntingtin facilitates selective autophagy. Nature cell biology. 17 (3): 214–215. [PubMed: 25720962]

132. Ochaba J, Lukacsovich T, Csikos G, Zheng S, Margulis J, Salazar L, Mao K, Lau AL, Yeung SY, Humbert S, Saudou F, Klionsky DJ, Finkbeiner S, Zeitlin SO, Marsh LJ, Housman DE, Thompson LM and Steffan JS (2014). Potential function for the Huntingtin protein as a scaffold for selective autophagy. Proceedings of the National Academy of Sciences. 111 (47): 16889–16894.

133. Saudou F and Humbert S (2016). The Biology of Huntingtin. Neuron. 89 (5): 910–926. [PubMed: 26938440]

134. Martinez-Vicente M, Talloczy Z, Wong E, Tang G, Koga H, Kaushik S, de Vries R, Arias E, Harris S, Sulzer D and Cuervo A (2010). Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease. Nature neuroscience. 13 (5): 567–576. [PubMed: 20383138]

135. Sasazawa Y, Sato N, Umezawa K and Simizu S (2015). Conophylline Protects Cells in Cellular Models of Neurodegenerative Diseases by Inducing Mammalian Target of Rapamycin (mTOR)-independent Autophagy. Journal of Biological Chemistry. 290 (10): 6168–6178. [PubMed: 25596530]

136. Gorojod RM, Alaimo A, Porte Alcon S, Pomilio C, Saravia F and Kotler ML (2015). The autophagic-lysosomal pathway determines the fate of glial cells under manganese-induced oxidative stress conditions. Free radical biology & medicine. 87: 237–251. [PubMed: 26163003]

137. Zhang Z, Miah M, Culbreth M and Aschner M (2016). Autophagy in Neurodegenerative Diseases and Metal Neurotoxicity. Neurochemical research. 41 (1–2): 409–422. [PubMed: 26869037]

138. Filosto M, Scarpelli M, Cotelli M, Vielmi V, Todeschini A, Gregorelli V, Tonin P, Tomelleri G and Padovani A (2011). The role of mitochondria in neurodegenerative diseases. Journal of Neurology. 258 (10): 1763–1774. [PubMed: 21604203]

139. Johri A and Beal FM (2012). Mitochondrial Dysfunction in Neurodegenerative Diseases. Journal of Pharmacology and Experimental Therapeutics. 342 (3): 619–630. [PubMed: 22700435]

140. Martin LJ (2012). Chapter 11 Biology of Mitochondria in Neurodegenerative Diseases. Progress in Molecular Biology and Translational Science. 107: 355–415. [PubMed: 22482456]

141. Saleh N, Moutereau S, Durr A, Krystkowiak P, Azulay J-P, Tranchant C, Broussolle E, Morin F, Bachoud-Lévi A-C and Maison P (2009). Neuroendocrine Disturbances in Huntington's Disease. PLoS ONE. 4 (3).

142. Farrer LA (1985). Diabetes mellitus in Huntington disease. Clinical genetics. 27 (1): 62–67. [PubMed: 3156696]

143. Hurlbert MS, Zhou W, Wasmeier C, Kaddis FG, Hutton JC and Freed CR (1999). Mice transgenic for an expanded CAG repeat in the Huntington's disease gene develop diabetes. Diabetes. 48 (3): 649–651. [PubMed: 10078572]

144. Lalic NM, Marie J, Svetel M, Jotic A, Stefanova E, Lalic K, Dragasevic N, Milicic T, Lukic L and Kostic VS (2008). Glucose Homeostasis in Huntington Disease: Abnormalities in Insulin Sensitivity and Early-Phase Insulin Secretion. Archives of Neurology. 65 (4): 476–480. [PubMed: 18413469]

145. Podolsky S, Leopold N and Sax D (1972). INCREASED FREQUENCY OF DIABETES MELLITUS IN PATIENTS WITH HUNTINGTON'S CHOREA. The Lancet. 299 (7765): 1356–1359.

146. Pouladi MA, Xie Y, Skotte N, Ehrnhoefer DE, Graham RK, Kim J, Bissada N, Yang WX, Paganetti P, Friedlander RM, Leavitt BR and Hayden MR (2010). Full-length huntingtin levels modulate body weight by influencing insulin-like growth factor 1 expression. Human Molecular Genetics. 19 (8): 1528–1538. [PubMed: 20097678]

147. Mochel F, Charles P, Seguin F, Barritault J, Coussieu C, Perin L, Bouc Y, Gervais C, Carcelain G, Vassault A, Feingold J, Rabier D and Durr A (2007). Early Energy Deficit in Huntington Disease: Identification of a Plasma Biomarker Traceable during Disease Progression. PLoS ONE. 2 (7).

148. Goodman A, Murgatroyd PR, Medina-Gomez G, Wood NI, Finer N, Vidal-Puig AJ, Morton JA and Barker RA (2008). The metabolic profile of early Huntington's disease- a combined human and transgenic mouse study. Experimental Neurology. 210 (2): 691–698. [PubMed: 18284928]

149. Gaba AM, Zhang K, Marder K, Moskowitz CB, Werner P and Boozer CN (2005). Energy balance in early-stage Huntington disease. The American journal of clinical nutrition. 81 (6): 1335–1341. [PubMed: 15941884]

150. Josefsen K, Nielsen MD, Jørgensen KH, Bock T, Nørremølle A, Sørensen SA, Naver B and Hasholt L (2007). Impaired glucose tolerance in the R6/1 transgenic mouse model of Huntington's disease. Journal of neuroendocrinology. 20 (2): 165–172. [PubMed: 18034868]

151. Oláh J, Klivényi P, Gardián G, Vécsei L, Orosz F, Kovacs GG, Westerhoff HV and Ovádi J (2008). Increased glucose metabolism and ATP level in brain tissue of Huntington's disease transgenic mice. FEBS Journal. 275 (19): 4740–4755. [PubMed: 18721135]

152. Ismailoglu I, Chen Q, Popowski M, Yang L, Gross SS and Brivanlou AH (2014). Huntingtin protein is essential for mitochondrial metabolism, bioenergetics and structure in murine embryonic stem cells. Developmental Biology. 391 (2): 230–240. [PubMed: 24780625]

153. Koroshetz WJ, Jenkins BG, Rosen BR and Beal FM (1997). Energy metabolism defects in Huntington's disease and effects of coenzyme Q10. Annals of Neurology. 41 (2): 160–165. [PubMed: 9029064]

154. Schilling G, Coonfield ML, Ross CA and Borchelt DR (2001). Coenzyme Q10 and remacemide hydrochloride ameliorate motor deficits in a Huntington's disease transgenic mouse model. Neuroscience letters. 315 (3): 149–153. [PubMed: 11716985]

155. Andreassen OA, Dedeoglu A, Ferrante RJ, Jenkins BG, Ferrante KL, Thomas M, Friedlich A, Browne SE, Schilling G, Borchelt DR, Hersch SM, Ross CA and Beal MF (2001). Creatine increase survival and delays motor symptoms in a transgenic animal model of Huntington's disease. Neurobiology of disease. 8 (3): 479–491. [PubMed: 11447996]

156. Ferrante RJ, Andreassen OA, Jenkins BG, Dedeoglu A, Kuemmerle S, Kubilus JK, Kaddurah-Daouk R, Hersch SM and Beal MF (2000). Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience. 20 (12): 4389–4397. [PubMed: 10844007]

157. Tabrizi SJ, Blamire AM, Manners DN, Rajagopalan B, Styles P, Schapira AHV and Warner TT (2003). Creatine therapy for Huntington's disease: clinical and MRS findings in a 1-year pilot study. Neurology. 61 (1): 141–142. [PubMed: 12847181]

158. Verbessem P, Lemiere J, Eijnde BO, Swinnen S, Vanhees L, Leemputte VM, Hespel P and Dom R (2003). Creatine supplementation in Huntington's disease: a placebo-controlled pilot trial. Neurology. 61 (7): 925–930. [PubMed: 14557561]

159. Ferrante RJ, Andreassen OA, Dedeoglu A, Ferrante KL, Jenkins BG, Hersch SM and Beal FM (2002). Therapeutic effects of coenzyme Q10 and remacemide in transgenic mouse models of Huntington's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience. 22 (5): 1592–1599. [PubMed: 11880489]

160. Ferreira IL, Nascimento MV, Ribeiro M, Almeida S, Cardoso SM, Grazina M, Pratas J, Santos M, Januário C, Oliveira CR and Rego CA (2010). Mitochondrial-dependent apoptosis in Huntington's disease human cybrids. Experimental Neurology. 222 (2): 243–255. [PubMed: 20079354]

161. Damiano M, Galvan L, Déglon N and Brouillet E (2010). Mitochondria in Huntington's disease. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 1802 (1): 52–61. [PubMed: 19682570]
162. Kim J, Moody JP, Edgerly CK, Bordiuk OL, Cormier K, Smith K, Beal FM and Ferrante RJ (2010). Mitochondrial loss, dysfunction and altered dynamics in Huntington's disease. Human Molecular Genetics. 19 (20): 3919–3935. [PubMed: 20660112]
163. Reddy HP, Mao P and Manczak M (2009). Mitochondrial structural and functional dynamics in Huntington's disease. Brain research reviews. 61 (1): 33–48. [PubMed: 19394359]
164. Martin WWR, Wieler M and Hanstock CC (2007). Is brain lactate increased in Huntington's disease? Journal of the neurological sciences. 263 (1–2): 70–74. [PubMed: 17655868]
165. Milakovic T and Johnson GVW (2005). Mitochondrial respiration and ATP production are significantly impaired in striatal cells expressing mutant huntingtin. The Journal of biological chemistry. 280 (35): 30773–30782. [PubMed: 15983033]
166. Weydt P, Pineda VV, Torrence AE, Libby RT, Satterfield TF, Lazarowski ER, Gilbert ML, Morton GJ, Bammler TK, Strand AD, Cui L, Beyer RP, Easley CN, Smith AC, Krainc D, Luquet S, Sweet IR, Schwartz MW and Spada AR (2006). Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1α in Huntington's disease neurodegeneration. Cell Metabolism. 4 (5): 349–362. [PubMed: 17055784]
167. Lou S, Lepak T, Eberly LE, Roth B, Cui W, Zhu X-H, Öz G and Dubinsky JM (2016). Oxygen Consumption Deficit In Huntington Disease Mouse Brain Under Metabolic Stress. Human molecular genetics.
168. Ferreira LI, Cunha-Oliveira T, Nascimento MV, Ribeiro M, Proença TM, Januário C, Oliveira CR and Rego CA (2011). Bioenergetic dysfunction in Huntington's disease human cybrids. Experimental Neurology. 231 (1): 127–134. [PubMed: 21684277]
169. Gouarné C, Tardif G, Tracz J, Latyszenok V, Michaud M, Clemens L, Yu-Taeger L, Nguyen H, Bordet T and Pruss RM (2013). Early Deficits in Glycolysis Are Specific to Striatal Neurons from a Rat Model of Huntington Disease. PLoS ONE. 8 (11).
170. Nagano I, Shiote M, Murakami T, Kamada H, Hamakawa Y, Matsubara E, Yokoyama M, Morita K, Shoji M and Abe K (2013). Beneficial effects of intrathecal IGF-1 administration in patients with amyotrophic lateral sclerosis. Neurological Research. 27 (7): 768–772.
171. Sorenson EJ, Windbank AJ, Mandrekar JN, Bamlet WR, Appel SH, Armon C, Barkhaus PE, Bosch P, Boylan K, David WS, Feldman E, Glass J, Gutmann L, Katz J, King W, Luciano CA, McCluskey LF, Nash S, Newman DS, Pascuzzi RM, Pioro E, Sams LJ, Scelsa S, Simpson EP, Subramony SH, Tiryaki E and Thornton CA (2008). Subcutaneous IGF-1 is not beneficial in 2-year ALS trial. Neurology. 71 (22): 1770–1775. [PubMed: 19029516]
172. Hölscher C (2014). First clinical data of the neuroprotective effects of nasal insulin application in patients with Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association. 10 (1 Suppl): 7.
173. Rauskolb S, Dombert B and Sendtner M (2016). Insulin-like growth factor 1 in diabetic neuropathy and amyotrophic lateral sclerosis. Neurobiology of disease.
174. Sulzer D (2007). Multiple hit hypotheses for dopamine neuron loss in Parkinson's disease. Trends in neurosciences. 30 (5): 244–250. [PubMed: 17418429]
175. Guilarte TR and Gonzales KK (2015). Manganese–Induced Parkinsonism Is Not Idiopathic Parkinson's Disease: Environmental and Genetic Evidence. Toxicological Sciences. 146 (2): 204–212. [PubMed: 26220508]
176. Cersosimo MG and Koller WC (2005). The diagnosis of manganese-induced parkinsonism. Neurotoxicology. 27 (3): 340–346. [PubMed: 16325915]
177. Kwakye GF, Paoliello MM, Mukhopadhyay S, Bowman AB and Aschner M (2015). Manganese-Induced Parkinsonism and Parkinson's Disease: Shared and Distinguishable Features. International journal of environmental research and public health. 12 (7): 7519–7540. [PubMed: 26154659]
178. Bowman AB, Kwakye GF, Hernández E and Aschner M (2011). Role of manganese in neurodegenerative diseases. Journal of Trace Elements in Medicine and Biology. 25 (4): 191–203. [PubMed: 21963226]

179. Aschner M, Erikson KM, Hernández E, Hernández E and Tjalkens R (2009). Manganese and its Role in Parkinson's Disease: From Transport to Neuropathology. NeuroMolecular Medicine. 11 (4): 252–266. [PubMed: 19657747]
180. Guilarte TR (2010). Manganese and Parkinson's Disease: A Critical Review and New Findings. Environmental Health Perspectives. 118 (8): 1071–1080. [PubMed: 20403794]
181. Zhang D, Kanthasamy A, Anantharam V and Kanthasamy A (2011). Effects of manganese on tyrosine hydroxylase (TH) activity and TH-phosphorylation in a dopaminergic neural cell line. Toxicology and Applied Pharmacology. 254 (2): 65–71. [PubMed: 21310168]
182. Tong M, Dong M and de la Monte SM (2009). Brain insulin-like growth factor and neurotrophin resistance in Parkinson's disease and dementia with Lewy bodies: potential role of manganese neurotoxicity. Journal of Alzheime's disease : JAD. 16 (3): 585–599. [PubMed: 19276553]
183. Harischandra DS, Jin H, Anantharam V, Kanthasamy A and Kanthasamy AG (2015). α-Synuclein Protects Against Manganese Neurotoxic Insult During the Early Stages of Exposure in a Dopaminergic Cell Model of Parkinson's Disease. Toxicological Sciences. 143 (2): 454–468. [PubMed: 25416158]
184. Peres T, Parmalee NL, Martinez-Finley EJ and Aschner M (2016).Untangling the Manganese-α-Synuclein Web. Frontiers in Neuroscience. 10: 364. [PubMed: 27540354]
185. Ayadi AE, Zigmond MJ and Smith AD (2016). IGF-1 protects dopamine neurons against oxidative stress: association with changes in phosphokinases. Experimental brain research. 234 (7): 1863–1873. [PubMed: 26894890]
186. Offen D, Shtaif B, Hadad D, Weizman A, Melamed E and Gil -Ad (2001). Protective effect of insulin-like-growth-factor-1 against dopamine-induced neurotoxicity in human and rodent neuronal cultures: possible implications for Parkinson's disease. Neuroscience letters. 316 (3): 129–132. [PubMed: 11744219]
187. Krishnamurthi R, Stott S, Maingay M, Faull RLM, McCarthy D, Gluckman P and Guan J (2004). N-terminal tripeptide of IGF-1 improves functional deficits after 6-OHDA lesion in rats. Neuroreport. 15 (10): 1601–1604. [PubMed: 15232291]
188. Ma J, Jiang Q, Xu J, Sun Q, Qiao Y, Chen W, Wu Y, Wang Y, Xiao Q, Liu J, Tang H and Chen S (2015). Plasma insulin-like growth factor 1 is associated with cognitive impairment in Parkinson's disease. Dementia and geriatric cognitive disorders. 39 (5–6): 251–256. [PubMed: 25661865]
189. Godau J, Herforth M, Kattner B, Gasser T and Berg D (2010). Increased serum insulin-like growth factor 1 in early idiopathic Parkinson's disease. Journal of neurology, neurosurgery, and psychiatry. 81 (5): 536–538.
190. Picillo M, Erro R, Santangelo G, Pivonello R, Longo K, Pivonello C, Vitale C, Amboni M, Moccia M, Colao A, Barone P and Pellecchia M (2013). Insulin-like growth factor-1 and progression of motor symptoms in early, drug-naïve Parkinson's disease. Journal of Neurology. 260 (7): 1724–1730. [PubMed: 23400497]
191. Gong L, Zhang QL, Zhang N, Hua WY, Huang YX, Di PW, Huang T, Xu XS, Liu CF, Hu LF and Luo WF (2012). Neuroprotection by urate on 6-OHDA-lesioned rat model of Parkinson's disease: linking to Akt/GSK3β signaling pathway. Journal of Neurochemistry. 123 (5): 876–885. [PubMed: 23094836]
192. Nakaso K, Ito S and Nakashima K (2008). Caffeine activates the PI3K/Akt pathway and prevents apoptotic cell death in a Parkinson's disease model of SH-SY5Y cells. Neuroscience letters. 432.
193. Timmons S, Coakley MF, Moloney AM and Neill C (2009). Akt signal transduction dysfunction in Parkinson's disease. Neuroscience Letters. 467 (1): 30–35. [PubMed: 19800394]
194. Xiromerisiou G, Hadjigeorgiou GM, Papadimitriou A, Katsarogiannis E, Gourbali V and Singleton AB (2008). Association between AKT1 gene and Parkinson's disease: aprotective haplotype. Neuroscience letters. 436.
195. Xu Y, Liu C, Chen S, Ye Y, Guo M, Ren Q, Liu L, Zhang H, Xu C and Zhou Q (2014). Activation of AMPK and inactivation of Akt result in suppression of mTOR-mediated S6K1 and 4E-BP1 pathways leading to neuronal cell death in in vitro models of Parkinson's disease. Cellular signalling. 26.

196. Bandmann O, Weiss K and Kaler SG (2015). Wilson's disease and other neurological copper disorders. The Lancet Neurology. 14 (1): 103–113. [PubMed: 25496901]

197. Dieter HH, Bayer TA and Multhaup G (2005). Environmental Copper and Manganese in the Pathophysiology of Neurologic Diseases (Alzheimer's Disease and Manganism). Acta hydrochimica et hydrobiologica. 33 (1): 72–78.

198. Hare DJ, Faux NG, Roberts BR, Volitakis I, Martins RN and Bush AI (2016). Lead and manganese levels in serum and erythrocytes in Alzheimer's disease and mild cognitive impairment: results from the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing. Metallomics. 8 (6): 628–632. [PubMed: 26962965]

199. Chui D, Yang H, Wang H, Tuo JI, Yu J, Zhang S, Chen Z and Xiao W (2013). The dishomeostasis of metal ions plays an important role for the cognitive impartment. Molecular Neurodegeneration. 8 (S1): 1–1. [PubMed: 23281774]

200. Suzanne M and Wands JR (2008). Alzheimer's disease is type 3 diabetes—evidence reviewed. Journal of diabetes science and technology. 2.

201. Schubert M, Gautam D, Surjo D, Ueki K, Baudler S, Schubert D, Kondo T, Alber J, Galldiks N and Küstermann E (2004). Role for neuronal insulin resistance in neurodegenerative diseases. Proceedings of the National Academy of Sciences of the United States of America. 101.

202. Cohen E, Du D, Joyce D, Kapernick EA, Volovik Y, Kelly JW and Dillin A (2010). Temporal requirements of insulin/IGF-1 signaling for proteotoxicity protection. Aging Cell. 9 (2): 126–134. [PubMed: 20003171]

203. Cohen E, Paulsson JF, Blinder P, Burstyn-Cohen T, Du D, Estepa G, Adame A, Pham HM, Holzenberger M, Kelly JW, Masliah E and Dillin A (2009). Reduced IGF-1 Signaling Delays Age-Associated Proteotoxicity in Mice. Cell. 139 (6): 1157–1169. [PubMed: 20005808]

204. Freude S, Schilbach K and Schubert M (2009). The role of IGF-1 receptor and insulin receptor signaling for the pathogenesis of Alzheimer's disease: from model organisms to human disease. Current Alzheimer research. 6 (3): 213–223. [PubMed: 19519303]

205. Moloney AM, Griffin RJ, Timmons S, O'Connor R, Ravid R and O'Neill C (2010). Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to IGF1 and insulin signalling. Neurobiology of aging. 31.

206. Neill C (2013). PI3-kinase/Akt/mTOR signaling: impaired on/off switches in aging, cognitive decline and Alzheimer's disease. Experimental gerontology. 48 (7): 647–653. [PubMed: 23470275]

207. Torres-Aleman I (2007). Targeting insulin-like growth factor-1 to treat Alzheimer's disease. Expert opinion on therapeutic targets. 11 (12): 1535–1542. [PubMed: 18020976]

208. Craft S and Watson GS (2004). Insulin and neurodegenerative disease: shared and specific mechanisms. The Lancet Neurology. 3 (3): 169–178. [PubMed: 14980532]

209. de la Monte SM and Wands JR (2005). Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. Journal of Alzheimer's Disease. 7.

210. Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR and de la Monte SM (2005). Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. Journal of Alzheimer's Disease. 8.

211. Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, Xu JX, Wands JR and de la Monte SM (2005). Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease-is this type 3 diabetes? Journal of Alzheime's disease. 7.

212. Vidal J-SS, Hanon O, Funalot B, Brunel N, Viollet C, Rigaud ASS, Seux M-LL, le-Bouc Y, Epelbaum J and Duron E (2016). Low Serum Insulin-Like Growth Factor-I Predicts Cognitive Decline in Alzheimer's Disease. Journal of Alzheimer's disease : JAD. 52 (2): 641–649. [PubMed: 27031487]

213. Liu Y, Liu F, Grundke-Iqbal I, Iqbal K and Gong CX (2011). Deficient brain insulin signalling pathway in Alzheimer's disease and diabetes. The Journal of Pathology. 225 (1): 54–62. [PubMed: 21598254]

214. Åberg D, Johansson P, Isgaard J, Wallin A, Johansson J-O, Andreasson U, Blennow K, Zetterberg H, Åberg DN and Svensson J (2015). Increased Cerebrospinal Fluid Level of Insulin-like Growth

Factor-II in Male Patients with Alzheimer's Disease. Journal of Alzheimer's disease : JAD. 48 (3): 637–646. [PubMed: 26402100]

215. Johansson P, Åberg D, Johansson J-O, Mattsson N, Hansson O, Ahrén B, Isgaard J, Åberg DN, Blennow K, Zetterberg H, Wallin A and Svensson J (2013). Serum but not cerebrospinal fluid levels of insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 (IGFBP-3) are increased in Alzheimer's disease. Psychoneuroendocrinology. 38 (9): 1729–1737. [PubMed: 23473966]
216. Griffin RJ, Moloney A, Kelliher M, Johnston JA, Ravid R, Dockery P, O'Connor R and O'Neill C (2005). Activation of Akt/PKB, increased phosphorylation of Akt substrates and loss and altered distribution of Akt and PTEN are features of Alzheimer's disease pathology. Journal of Neurochemistry. 93 (1): 105–117. [PubMed: 15773910]
217. Rickle A, Bogdanovic N, Volkman I, Winblad B, Ravid R and Cowburn RF (2004). Akt activity in Alzheimer's disease and other neurodegenerative disorders. Neuroreport. 15 (6): 955–959. [PubMed: 15076714]
218. Roos PM, Lierhagen S, Flaten T, Syversen T, Vesterberg O and Nordberg M (2012). Manganese in cerebrospinal fluid and blood plasma of patients with amyotrophic lateral sclerosis. Experimental Biology and Medicine. 237 (7): 803–810. [PubMed: 22859739]
219. Peters TL, Beard JD, Umbach DM, Allen K, Keller J, Mariosa D, Sandler DP, Schmidt S, Fang F, Ye W and Kamel F (2016). Blood levels of trace metals and amyotrophic lateral sclerosis. NeuroToxicology. 54: 119–126. [PubMed: 27085208]
220. Miyata S, Nakamura S, Nagata H and Kameyama M (1983). Increased manganese level in spinal cords of amyotrophic lateral sclerosis determined by radiochemical neutron activation analysis. Journal of the Neurological Sciences. 61 (2): 283–293. [PubMed: 6644329]
221. Nagata H, Miyata S, Nakamura S, Kameyama M and Katsui Y (1985). Heavy metal concentrations in blood cells in patients with amyotrophic lateral sclerosis. Journal of the Neurological Sciences. 67 (2): 173–178. [PubMed: 3981218]
222. Reyes ET, Perurena OH, Festoff BW, Jorgensen R and Moore WV (1984). Insulin resistance in amyotrophic lateral sclerosis. Journal of the neurological sciences. 63 (3): 317–324. [PubMed: 6374040]
223. Adem A, Ekblom J, Gillberg PG, Jossan SS, Höög A, Winblad B, Aquilonius SM, Wang LH and Sara V (1994). Insulin-like growth factor-1 receptors in human spinal cord: changes in amyotrophic lateral sclerosis. Journal of Neural Transmission. 97 (1): 73–84. [PubMed: 7888151]
224. Bilic E, Bilic E, Rudan I, Kusec V, Zurak N, Delimar D and Zagar M (2006). Comparison of the growth hormone, IGF-1 and insulin in cerebrospinal fluid and serum between patients with motor neuron disease and healthy controls. European Journal of Neurology. 13 (12): 1340–1345. [PubMed: 17116217]
225. Nagano I, Ilieva H, Shiote M, Murakami T, Yokoyama M, Shoji M and Abe K (2005). Therapeutic benefit of intrathecal injection of insulin-like growth factor-1 in a mouse model of amyotrophic lateral sclerosis. Journal of the neurological sciences. 235.
226. Saccà F, Quarantelli M, Rinaldi C, Tucci T, Piro R, Perrotta G, Carotenuto B, Marsili A, Palma V, Michele G, Brunetti A, Morra V, Filla A and Salvatore M (2012). A randomized controlled clinical trial of growth hormone in amyotrophic lateral sclerosis: clinical, neuroimaging, and hormonal results. Journal of Neurology. 259 (1): 132–138. [PubMed: 21706151]
227. Borasio GD, Robberecht W, Leigh PN, Emile J, Guiloff RJ, Jerusalem F, Silani V, Vos PE, Wokke JH and Dobbins T (1998). A placebo-controlled trial of insulin-like growth factor-I in amyotrophic lateral sclerosis. European ALS/IGF-I Study Group. Neurology. 51 (2): 583–586. [PubMed: 9710040]
228. Harris H and Rubinsztein DC (2011). Control of autophagy as a therapy for neurodegenerative disease. Nature reviews Neurology. 8 (2): 108–117. [PubMed: 22187000]
229. Chinta SJ, Mallajosyula JK, Rane A and Andersen JK (2010). Mitochondrial α-synuclein accumulation impairs complex I function in dopaminergic neurons and results in increased mitophagy in vivo. Neuroscience letters. 486 (3): 235–239. [PubMed: 20887775]
230. Deas E, Wood NW and Plun-Favreau H (2010). Mitophagy and Parkinson's disease: the PINK1-parkin link. Biochimica et biophysica acta. 1813 (4): 623–633. [PubMed: 20736035]

231. Geisler S, Holmström KM, Skujat D, Fiesel FC, Rothfuss OC, Kahle PJ and Springer W (2010). PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. Nature cell biology. 12 (2): 119–131. [PubMed: 20098416]

232. Michiorri S, Gelmetti V, Giarda E, Lombardi F, Romano F, Marongiu R, Nerini-Molteni S, Sale P, Vago R, Arena G, Torosantucci L, Cassina L, Russo MA, Dallapiccola B, Valente EM and Casari G (2010). The Parkinson-associated protein PINK1 interacts with Beclin1 and promotes autophagy. Cell death and differentiation. 17 (6): 962–974. [PubMed: 20057503]

233. Narendra D, Tanaka A, Suen D-F and Youle RJ (2009). Parkin-induced mitophagy in the pathogenesis of Parkinson disease. Autophagy. 5 (5): 706–708. [PubMed: 19377297]

234. Vives-Bauza C and Przedborski S (2010). Mitophagy: the latest problem for Parkinson's disease. Trends in molecular medicine. 17(3): 158–165. [PubMed: 21146459]

235. Wolfe DM, Lee Jh, Kumar A, Lee S, Orenstein SJ and Nixon RA (2013). Autophagy failure in Alzheimer's disease and the role of defective lysosomal acidification. European Journal of Neuroscience. 37 (12): 1949–1961. [PubMed: 23773064]

236. Spilman P, Podlutskaya N, Hart MJ, Debnath J, Gorostiza O, Bredesen D, Richardson A, Strong R and Galvan V (2010). Inhibition of mTOR by Rapamycin Abolishes Cognitive Deficits and Reduces Amyloid-β Levels in a Mouse Model of Alzheimer's Disease. PLoS ONE. 5 (4).

237. Yang D-S, Stavrides P, Mohan PS, Kaushik S, Kumar A, Ohno M, Schmidt SD, Wesson D, Bandyopadhyay U, Jiang Y, Pawlik M, Peterhoff CM, Yang AJ, Wilson DA, George-Hyslop P, Westaway D, Mathews PM, Levy E, Cuervo AM and Nixon RA (2011). Reversal of autophagy dysfunction in the TgCRND8 mouse model of Alzheimer's disease ameliorates amyloid pathologies and memory deficits. Brain : a journal of neurology. 134 (Pt 1): 258–277. [PubMed: 21186265]

238. Yu HW, Cuervo A, Kumar A, Peterhoff CM, Schmidt SD, Lee J-H, Mohan PS, Mercken M, Farmery MR and Tjernberg LO (2005). Macroautophagy—a novel β-amyloid peptide-generating pathway activated in Alzheimer's disease. The Journal of cell biology. 171.

239. Gomes C, Escrevente C and Costa J (2010). Mutant superoxide dismutase 1 overexpression in NSC-34 cells: Effect of trehalose on aggregation, TDP-43 localization and levels of co-expressed glycoproteins. Neuroscience Letters. 475 (3): 145–149. [PubMed: 20363292]

240. Wang X, Fan H, Ying Z, Li B, Wang H and Wang G (2010). Degradation of TDP-43 and its pathogenic form by autophagy and the ubiquitin-proteasome system. Neuroscience Letters. 469 (1): 112–116. [PubMed: 19944744]

241. Gal J, Ström AL, Kwinter DM, Kilty R, Zhang J, Shi P, Fu W, Wooten MW and Zhu H (2009). Sequestosome 1/p62 links familial ALS mutant SOD1 to LC3 via an ubiquitin-independent mechanism. Journal of Neurochemistry. 111 (4): 1062–1073. [PubMed: 19765191]

242. Chen S, Zhang X, Song L and Le W (2012). Autophagy Dysregulation in Amyotrophic Lateral Sclerosis. Brain Pathology. 22 (1): 110–116. [PubMed: 22150926]

243. Luo X, Suzuki M, Ghandhi SA, Amundson SA and Boothman DA (2014). ATM Regulates Insulin-Like Growth Factor 1-Secretory Clusterin (IGF-1-sCLU) Expression that Protects Cells against Senescence. PLoS ONE. 9 (6).

244. Peretz S, Jensen R, Baserga R and Glazer PM (2001). ATM-dependent expression of the insulin-like growth factor-I receptor in a pathway regulating radiation response. Proceedings of the National Academy of Sciences. 98 (4): 1676–1681.

245. Miles PD, Treuner K, Latronica M, Olefsky JM and Barlow C (2007). Impaired insulin secretion in a mouse model of ataxia telangiectasia. American journal of physiology Endocrinology and metabolism. 293 (1): 4.

246. Zhou T, Chou J, Zhou Y, Simpson DA, Cao F, Bushel PR, Paules RS and Kaufmann WK (2007). Ataxia telangiectasia-mutated dependent DNA damage checkpoint functions regulate gene expression in human fibroblasts. Molecular cancer research : MCR. 5 (8): 813–822. [PubMed: 17699107]

247. Ehlayel M, Soliman A and Sanctis V (2014). Linear growth and endocrine function in children with ataxia telangiectasia. Indian Journal of Endocrinology and Metabolism. 18 (7): 93–96.

248. Kieslich M, Hoche F, Reichenbach J, Weidauer S, Porto L, Vlaho S, Schubert R and Zielen S (2010). Extracerebellar MRI—Lesions in Ataxia Telangiectasia Go Along with Deficiency of the

GH/IGF-1 Axis, Markedly Reduced Body Weight, High Ataxia Scores and Advanced Age. The Cerebellum. 9 (2): 190–197. [PubMed: 19898915]

249. Nissenkorn A, Levy-Shraga Y, Banet-Levi Y, Lahad A, Sarouk I and Modan-Moses D (2016). Endocrine abnormalities in ataxia telangiectasia: findings from a national cohort. Pediatric Research. 79 (6): 889–894. [PubMed: 26891003]
250. Schubert R, Reichenbach J and Zielen S (2005). Growth factor deficiency in patients with ataxia telangiectasia. Clinical & Experimental Immunology. 140 (3): 517–519. [PubMed: 15932513]
251. Goetz EM, Shankar B, Zou Y, Morales JC, Luo X, Araki S, Bachoo R, Mayo LD and Boothman DA (2011). ATM-dependent IGF-1 induction regulates secretory clusterin expression after DNA damage and in genetic instability. Oncogene. 30 (35): 3745–3754. [PubMed: 21460853]
252. Shahrabani-Gargir L, Pandita TK and Werner H (2004). Ataxia-telangiectasia mutated gene controls insulin-like growth factor I receptor gene expression in a deoxyribonucleic acid damage response pathway via mechanisms involving zinc-finger transcription factors Sp1 and WT1. Endocrinology. 145 (12): 5679–5687. [PubMed: 15345673]
253. Bhat MA, Rios JC, Lu Y, Garcia-Fresco GP, Ching W, Martin M, Li J, Einheber S, Chesler M, Rosenbluth J, Salzer JL and Bellen HJ (2001). Axon-Glia Interactions and the Domain Organization of Myelinated Axons Requires Neurexin IV/Caspr/Paranodin. Neuron. 30 (2): 369–383. [PubMed: 11395000]
254. Ching J, Luebbert SH, Zhang Z, Marupudi N, Banerjee S, Hurd R, Collins IV, Roy L, Ralston L and Fisher JS (2009). Ataxia telangiectasia mutated (ATM) is required in insulin-like growth factor-1 (IGF-1) signaling through the PI3K/Akt pathway. The FASEB Journal. 23.
255. Chitnis MM, Lodhia KA, Aleksic T, Gao S, Protheroe AS and Macaulay VM (2014). IGF-1R inhibition enhances radiosensitivity and delays double-strand break repair by both non-homologous end-joining and homologous recombination. Oncogene. 33 (45): 5262–5273. [PubMed: 24186206]
256. Valenciano A, Henríquez-Hernández L, Moreno M, Lloret M and Lara P (2014). Role of IGF-1 Receptor in Radiation Response. Translational Oncology. 5 (1): 1–9.
257. Halaby M-J, Hibma JC, He J and Yang D-Q (2008). ATM protein kinase mediates full activation of Akt and regulates glucose transporter 4 translocation by insulin in muscle cells. Cellular Signalling. 20 (8): 1555–1563. [PubMed: 18534819]
258. Vara J, Casado E, de Castro J, Cejas P, Belda-Iniesta C and González-Barón M (2004). PI3K/Akt signalling pathway and cancer. Cancer treatment reviews. 30 (2): 193–204. [PubMed: 15023437]
259. The association between deficient manganese levels and breast cancer: a meta-analysis. The association between deficient manganese levels and breast cancer: a meta-analysis.
260. Behrend L, Mohr A, Dick T and Zwacka RM (2005). Manganese superoxide dismutase induces p53-dependent senescence in colorectal cancer cells. Molecular and cellular biology. 25 (17): 7758–7769. [PubMed: 16107721]
261. Ho C-mJ, Zheng S, Comhair SA, Farver C and Erzurum SC (2001). Differential expression of manganese superoxide dismutase and catalase in lung cancer. Cancer research. 61 (23): 8578–8585. [PubMed: 11731445]
262. Hu Y, Rosen DG, Zhou Y, Feng L, Yang G, Liu J and Huang P(2005). Mitochondrial manganese-superoxide dismutase expression in ovarian cancer: role in cell proliferation and response to oxidative stress. The Journal of biological chemistry. 280 (47): 39485–39492. [PubMed: 16179351]
263. Weydert CJ, Waugh TA, Ritchie JM, Iyer KS, Smith JL, Li L, Spitz DR and Oberley LW (2006). Overexpression of manganese or copper-zinc superoxide dismutase inhibits breast cancer growth. Free radical biology & medicine. 41 (2): 226–237. [PubMed: 16814103]
264. Sørensen AS, Fenger K and Olsen JH (1999). Significantly lower incidence of cancer among patients with Huntington disease. Cancer. 86 (7): 1342–1346. [PubMed: 10506723]