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Genetic and Toxicological Models of Neurodegenerative Diseases: Stepping Stones Toward Finding a Cure

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CONTENTS

6.1 INTRODUCTION

The etiology of idiopathic forms of neurodegenerative disorders is multifactorial. Combinations of environmental and genetic factors as well as the aging process contribute to the pathology involved. While the possible interconnection of such events makes it difficult to distinguish the single factors, the advances made in molecular biology techniques make it possible to at least identify how mutations in single genes alter homeostasis and lead to diseased states.

The first part of this chapter aims at describing transgenic animal models of specific neurodegenerative disorders. These molecular models further the understanding of how a particular gene and its products are involved in the promotion of neurodegeneration. Such models not only delineate the mechanism of pathogenesis,

but can also provide a strong tool for development of pharmaceutical and nutritional supplementation, which may attenuate the rate of neurodegeneration.

The second part of this chapter focuses on environmental toxins that selectively affect the central nervous system. Epidemiological studies involving both identical and nonidentical twins suggest that environmental agents are important contributors to the onset and progression of neurodegenerative disorders. Xenobiotic factors may either play a direct role in initiation of neurodegeneration or can exacerbate underlying mechanisms in the disease process.

6.2 MOLECULAR MODELS OF NEURODEGENERATIVE DISORDERS

The two hallmarks of Alzheimer's disease (AD) are neurofibrillary tangles (NFT) and senile plaques (SP). The former are composed of paired helical filaments (PHFs) made of hyperphosphorylated tau proteins, and the latter are a core of aggregated amyloid-β (Aβ) peptides surrounded by reactive glia. Epidemiological studies have shed some light on the pathogenesis of familial forms of AD and it has been demonstrated that abnormalities in specific genes are responsible. These in turn have led to the development of transgenic animals overexpressing mutated forms of such disease-associated genes that help unravel the possible mechanisms underlying disease progression.

In order to study amyloid deposition, which leads to eventual senile plaque formation, several lines of amyloid precursor protein (APP) over mutated mice have been designed. One such model is the APP23 mouse that expresses a mutant form of the human APP. As they age, these animals develop amyloid plaques predominantly in the hippocampus and neocortex (Bondolfi et al., 2002). β-site-APP cleaving enzyme (BACE) has been shown to be involved in the processing of APP (Vassar et al., 1999). In a double transgenic mouse model, it has been demonstrated that overexpression of BACE in the APP23 animals leads to a robust cleaving of APP. This in turn causes an increase in the formation of Aβ1-42, the more amyloidogenic form of the protein, in the brain of these mice (Bodendorf et al., 2002). It is possible that such accelerated Aβ formation can lead to earlier deposition of amyloid plaques.

While APP mutation leads to Aβ production and plaque formation, transgenic animals expressing mutant human tau protein form NFT. In a mouse transgenic model overexpressing a mutated form of the human tau protein isolated from frontotemporal dementia parkinsonism brains, aggregated forms of the protein were found in hippocampal neurons. These irregular-looking cells contained NFT similar to those which characterize AD. Abnormal histology was accompanied by decrease in neural activity and behavioral impairments (Tanemura et al., 2002). However, mice expressing normal human tau accumulated phosphorylated tau proteins but did not form NFT, even in the presence of mutated presenilin-1 (Boutajangout et al., 2002). Thus, it appears that overexpression of the mutated form of the tau protein is essential for NFT formation in transgenic animals.

While the pathology of AD consists of both senile plaques and neurofibrillary tangles, transgenic animal models have largely been selected for either amyloid deposition or NFT formation. The brain of double transgenic animals that express

both mutated APP and tau proteins show a greater similarity to the AD brain in that NFT and amyloid plaques as well as neuronal loss are all present (Lewis et al., 2001).

While AD is associated with accumulation of Aβ protein, Parkinson's disease (PD) is associated with the accumulation of alpha synuclein (α-syn). This is an evolutionarily well-conserved phosphoprotein expressed in the brain and believed to play an important role in synaptic plasticity. Mutations in the α-syn gene, lead to aggregation of the protein and Lewy body formation, and have been linked to relatively uncommon genetic variants of Parkinson's disease (Kahle et al., 2000). In primary human embryonic cells derived from the mesencephalon, it has been demonstrated that dopaminergic neurons are selectively vulnerable to α-syn overexpression (Zhou et al., 2002).

In an effort to understand the mechanism by which dopaminergic cells are more sensitive to the mutant form of the protein, Tabrizi and colleagues (2000a) created stable human-derived cells expressing either wild-type or mutant α-syn. They found that in the latter case, dopamine was much more toxic than in the cell lines expressing wild-type α-syn. This suggests that the mutation might make the cells more sensitive to dopamine toxicity and consequent degeneration. Recently, a group of scientists have developed a transgenic mouse expressing an alpha synuclein mutation that leads to adult-onset development of disease which closely mimics PD symptoms (Lee et al., 2002). These transgenic animals may provide new insights into the cause and possible treatment of the disorder.

While aggregation of Aβ is a component of AD pathology, and accumulation of α-synuclein is associated with PD, there are patients exhibiting both features. In a double transgenic mouse model overexpressing both APP and α-syn, the animals developed impairments in learning and memory and there was an earlier onset of motor deficits compared to animals only overexpressing alpha synuclein. In isolated cell lines, Aβ causes aggregation of α-synuclein and its intracellular accumulation (Masliah et al., 2001). Thus, agents that block over-production of Aβ may also be useful for treatment of other neurodegenerative disorders such as PD.

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease in which motor neurons in the brain and spinal cord are selectively destroyed. Approximately 98% of the cases are idiopathic. Familial forms have been linked to a mutation in the copper-zinc superoxide dismutase (SOD1) gene. A transgenic model for the disease, expressing mutant human SOD1, has been established. These mice are referred to as G93A and are used to study the pathology of the disease and possible cures. Although the mechanism of neuronal death in ALS is unknown, the availability of these transgenic mice has lead to new findings showing that a multitude of events may be occurring in the pathogenesis of the disease.

The formation of advanced glycation end products is selectively increased in the astrocytes of both ALS patients with the SOD1 mutation and in the transgenic mouse model, while this parameter is unaltered in residual neuronal cells (Shibata et al., 2002). It has been questioned whether expression of SOD mutations in motor neurons can lead to their demise (Lino et al., 2002). While high levels of mutant protein accumulate in these cells, this does not lead to the pathological lesions found in motor neurons of ALS patients or the transgenic animals. Thus, it appears that neuronal death may not be a consequence of nonfunctional SOD aggregation.

However, neuronal nitric oxide synthase (nNOS), an enzyme that can effect peroxynitrite production and thus oxidative changes, increases steadily in spinal motor neurons of the G93A mice with disease progression. The subsequent increase in NO and thence peroxynitrite production may contribute to the demise of the motor neurons (Sasaki et al., 2002).

There is other evidence that motor neuron cell death associated with ALS is due to oxidative stress. In the transgenic G93A animals, mitochondrial respiration and ATP synthesis are impaired. Since most of the active SOD1 is localized in the intermembrane space of mitochondria, and the mutated enzyme may lose its antioxidant function, this may lead to reactive oxygen species (ROS) damage to organelles (Mattiazi et al., 2002). These defects in mitochondria and ATP synthesis are not observed in presymptomatic animals or those carrying the wild type human SOD1 gene. Therefore, the mitochondrial derangement effect appears to be a consequence of the disease process rather than an initiating factor. A causal relationship has, however, been established between oxidative damage and motor neuron degeneration. Mouse motor neuron-like cells, transfected with the mutant human SOD1, have increased levels of oxidative stress and mitochondrial dysfunction compared to cells transfected with the wild-type gene. This leads to cell death, which can be prevented by simultaneous overexpression of antioxidant genes or by treatment with the spin-trapping molecule, DMPO. This species not only inhibits cell death but delays paralysis and enhances survival in G93A transgenic mice (Liu et al., 2002).

6.3 ENVIRONMENTAL TOXINS AS MODELS OF NEURODEGENERATION

A relation between aluminum (Al) exposure and human health has been postulated. In several instances one can observe a direct causal role between exposure to the metal and abnormal neurological symptoms (Alfrey et al., 1976; Rifat et al., 1990; Russo et al., 1991; Bishop et al., 1997; Authier et al., 2001). Epidemiological studies report a good correlation between chronic exposure to Al in the drinking water and a higher incidence of AD (Armstrong et al., 1996; McLachlan et al., 1996; Rondeau et al., 2000). High levels of aluminum have been shown in postmortem brain samples from Alzheimer's patients (Good et al., 1992) but this issue is controversial (Bjertness et al., 1996). However, the metal has been shown to play a role in the formation of the pathological lesions characteristic of AD.

Perl and Brody (1980) originally described the presence of aluminum in neurofibrillary tangles. The frontal cortex of renal dialysis patients not displaying dialysis encephalopathy has been analyzed in order to determine whether or not exposure to high levels of aluminum causes changes in the tau protein similar to those seen in AD. In the white matter, there was a correlation between an increase in the amount of truncated tau protein and an increase in aluminum content. Although the gray matter did not show an increase in truncated tau, there was a decrease in the level of normal tau (Harrington et al., 1994). Circular dichroism and NMR spectroscopy studies reveal that aluminum does bind to tau and, by doing so, produces the aggregation of the protein (Madhav et al., 1996).

Aluminum also modulates the levels of Aβ. Both *in vivo* and *in vitro* analysis reported that aluminum did not effect the processing or expression of APP (Neill et al., 1996). However, a more recent study found that Al exacerbates oxidative stress, Aβ deposition, and plaque formation in the brain of transgenic mice that overexpress APP (Pratico et al., 2002). Aluminum has also been shown to cause aggregation of Aβ (Mantyh et al., 1993; Kawahara et al., 1994; Bondy and Truong, 1999).

Al exposure has been proposed to play a role in the progressive neurodegenerative disease found in Guam and neighboring islands, amyotrophic lateral sclerosis and Parkinsonism dementia complex (ALS/PDC), whose pathology includes deposition of neurofibrillary tangles which contain Al (Strong and Garruto, 1997). However, since the incidence of the disease has declined in the regions where the disease was most prevalent, while the concentration of the metal in the soil and drinking water remains constant, the link has weakened. In contrast, there is a strong link between the use of the cycad plant in food supplies and geographic incidence of the disease (Zhang et al., 1996).

The strongest epidemiological link between ALS/PDC and an environmental toxin comes from the correlation between consumption of the cycad seed and prevalence of the disease. Another interesting hypothesis is that the consumption of flying foxes by the Chamorro people may have resulted in ALS-PDC. These animals feed on the cycad seed and thus accumulate a high concentration of the neurotoxin. Since the number of flying foxes has decreased and the animals are no longer consumed, the prevalence of the disease has gone down (Cox and Sacks, 2002). The disease incidence was high among the Chamorros of the Western Pacific islands of Guam and Rota. The number of cases has substantially decreased since World War II, which brought about the Americanization of the diet of the Chamorro population (Spencer et al., 1987).

Dietary administration of the Cycas amino acid beta-*N*-methylamino-L-alanine (BMAA) fed to macaque monkeys led to symptoms resembling ALS/PDC (Spencer et al., 1987). However, it was later demonstrated that this component of the cycad plant is probably not the causative factor since much of it is removed during processing (Duncan et al., 1990) and the level of cycasin (Figure 6.1) is approximately ten times greater than the levels of BMAA (Kisby et al., 1992). Therefore, the actual toxin in the cycad plant, which is responsible for the disease, has as yet not been definitively identified but appears to be cycasin (Wilson et al., 2002).

Male mice fed a diet containing washed cycad flour developed progressive motor as well as cognitive impairment and neurodegeneration was extensive in the hippocampus, spinal cord, neocortex, substantia nigra, and the olfactory bulb (Wilson et al., 2002). The exact mechanism of cell death is unknown. One study has shown that cycasin can inhibit DNA repair. The ability to repair DNA is also reduced in the brains of ALS/PDC, ALS, and AD patients. Neuronal cell death may be a consequence of enhanced DNA damage (Kisby et al., 1999). Interestingly, the decrease in cycasin-induced DNA repair co-occurs with accumulation of phosphorylated tau (Esclaire et al., 1999).

The most important finding linking an exogenous toxin to PD occurred when it was discovered that a group of young individuals developed symptoms of the disease

Cycasin	MPTP
CH₂OH ...	CH₃ ...
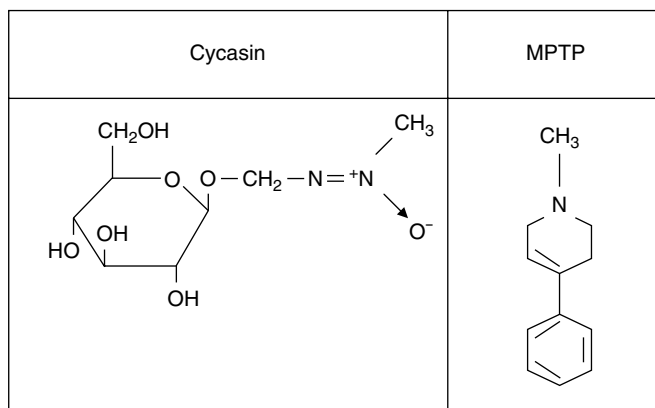
Figure 6.1 The chemical structure of cycasin and 1-methyl-4-phenyl-1,2,3,6-tetrahydro-
pyridine (MPTP).

after using an impure form of synthesized heroin. The toxin was identified to be the
activated form of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Figure 6.1).
Monoamine oxidase B was responsible for the transformation reaction of the com-
pound to the 1-methyl-4-phenylpyridinium ion (MPP⁺), which is transported to and
concentrates within dopaminergic neurons through neurotransmitter uptake mecha-
nisms. Thus, the toxic effect of MPP⁺ is very specific to the nigrostriatal pathway,
which is rich in dopaminergic cells.

It is important to assess if genetic mutations linked to PD may make an organism
more prone to environmental insults leading to cell death. In one study it was
demonstrated that following treatment with MPTP, the level of neuronal death in
the substantia nigra was the same in a transgenic animal model expressing mutant
alpha-synuclein, and wild-type control animals (Rathke-Hartlieb et al., 2001). There-
fore, it appears that mutations in the α-syn, associated with familial PD, do not
enhance susceptibility to MPTP. It may be that the genetic and nongenetic variants
of PD, while presenting with the same progressive dopaminergic damage, are in fact
initiated by unrelated processes.

6.4 COMMON MECHANISTIC LINKS BETWEEN
NEURODEGENERATIVE DISEASES

One feature characterizing a wide range of disorders is enhanced oxidative
damage. There is evidence of increased free radical injury in AD brain tissue (Marcus
et al., 1998; Smith et al., 1998; Nunomura et al., 1999a). Whether this is a cause or
the end result of the disease process is not certain. However, in Down's syndrome,
which leads to early onset of AD, evidence of oxidative stress is found long before
neuropathological changes (Busciglio and Yankner, 1995; Odetti et al., 1998; Nuno-
mura et al., 2000). There is a significant increase in the level of free 4-hydroxy-
nonenal (HNE), an end product of lipid peroxidation, in the amygdala, hippocampus
and the hippocampal gyrus of AD patients compared to age-matched controls

(Markesbery and Lovell, 1997). When AD brains are treated with antibodies against 4-hydroxynonenal, neurofibrillary tangles, but also neurons lacking them, display elevated HNE-pyrrole immunoreactivity in comparison with age-matched controls (Sayre et al., 1997). Oxidative damage to macromolecules is thus not merely a consequence of a pre-existing deficit but may actually participate in the progression of the disease.

A recent study has looked at dietary components that may be related to AD and reported that low folic acid levels are linked to increased susceptibility to AD. It has been proposed that folic acid deficiency impairs DNA repair and thus potentiates neurodegeneration by enhancing Aβ-induced oxidative modification of DNA bases (Kruman et al., 2002). While aggregated forms of this peptide are known to generate free radicals, a new study shows that the monomeric Aβ1-40 actually functions as an antioxidant and, similar to vitamin E and glutathione, protects neurons against Fe(II)-induced oxidative damage (Zou et al., 2002). Therefore, it appears that the production of Aβ that occurs in normal brain may have a beneficial physiological role and only when the protein begins to form fibrils, it can then serve as a foci for increased and possibly detrimental ROS production.

The increasing evidence for oxidant events in AD is paralleled by findings that aluminum enhances cerebral pro-oxidant status. Aluminum treatment of experimental animals can cause increased cortical ROS production or lipid peroxidation (Ohtawa et al., 1993; Gupta and Shukla, 1995; Bondy et al., 1998a). Also, treatment of cell lines of CNS origin with the metal can promote ROS generation (Xie et al., 1996; Campbell et al., 1999).

In isolated cerebrocortical synaptosomes, the metal does not directly cause oxidative events but appears to markedly enhance the capacity of iron to produce ROS (Oteiza, 1994; Bondy and Kirstein, 1996). The mechanism of this promotion appears to be the stabilization of ferrous iron which is more potent in promoting the generation of ROS compared to ferric iron (Yang et al., 1999). This potentiation of oxidative events by Al is not limited to iron but can occur with other transition metals including chromium and copper (Bondy et al., 1998b). Both Al and Aβ stabilize iron in its ferrous form and by this means potentiates Fe-induced ROS production (Bondy et al., 1998c; Yang et al., 1999). The concept that the role of Al in the pathology of AD may be mediated by oxidative stress is supported by a recent study demonstrating that in transgenic mice overexpressing APP, Al enhances Aβ levels and plaque formation. This is prevented by co-exposure to vitamin E (Pratico et al., 2002).

The concept of oxidative stress as a common endpoint in different neurodegenerative diseases is strengthened by the observation that the levels of 8-hydroxy-2-deoxyguanosine (8-OHDG) and 8-hydroxyguanosine (8-OHG) are increased in patients with AD, PD, and ALS (Kikuchi et al., 2002). In PD, the lipid peroxidation end-product 4-HNE is immunolocalized with Lewy bodies and oxidative stress may play a role in their formation (Castellani et al., 2002). Coenzyme Q10, an important cofactor of the electron transport chain and an antioxidant (Beal, 2002), protects not only against MPTP toxicity in mice but also enhances survival in ALS transgenic animals. Thus, there is some evidence that oxidative stress may be a condition leading to subsequent neurodegeneration and antioxidants may ameliorate this effect.

Increased ROS formation in neuronal cells overexpressing normal human or mutated alpha synuclein genes (Junn and Mouradian, 2002) implies that this protein is involved in enhancing oxidative stress. This mirrors the pro-oxidant effect of Aβ on neuronal cells and further strengthens the link between oxidative stress in different neurodegenerative disorders.

An age-related increase in inflammation within the brain has been repeatedly reported (David et al., 1997; Streit et al., 1999; Sharman et al., 2002). NF-κB is a transcription factor involved in the innate immune response (Baeuerle and Henkel, 1994; Medzhitov and Janeway, 1998; Hatada et al., 2000). There is a significant correlation between the amount of activated NF-κB and a key inflammatory enzyme, COX-2, in both the aging and AD brain (Lukiw and Bazan, 1998). The number of activated astrocytes is increased in AD brains and these are associated with senile plaques and cerebral microvessels (Cullen, 1997).

Cytokines are synthesized by activated glia in response to pathogens and trauma and both IL-1 as well as IL-6 levels are elevated in the AD brain (Cadman et al., 1994). Chronic production of these factors by activated glial cells may result in cytotoxicity because they recruit ROS producing macrophages which may lead to neuronal cell loss (Dunn, 1991). Systemic inflammation increases serum amyloid A (SAA) and in a transgenic mouse overexpressing the SAA1 gene, during an acute inflammatory response, amyloid A deposits appear in the brain. The nonsteroidal anti-inflammatory drug indomethacin inhibits this deposition (Guo et al., 2002). Inflammation can be exacerbated by exogenous stressors such as Al. The metal has been shown to promote Aβ production and plaque deposition in APP transgenic mice (Pratico et al., 2002). Furthermore, intracerebroventricular injection of Al salts leads to activation of glial cells in the rat brain (Platt et al., 2001). Al caused an increase in TNFα production and NF-κB activation in a human glioblastoma cell line (Campbell et al., 2002) and mice exposed to A1 in drinking water (Campbell et al., 2004).

Transgenic models of AD suggest that inflammatory events are involved in aging and pathology of the disease. Tg2576 mice show increases in cytokine mRNA levels at 16 months but not at 6 months (Sly et al., 2001). Microglial activation was not observable until mice were 12 months or older in an animal model expressing both mutated APP and presenilin-1 protein (PS1), although aggregated amyloid deposits were present around dystrophic neurites as well as activated astrocytes at an early age (Gordon et al., 2002). Therefore, it is possible that inflammatory processes do not necessarily initiate the pathological lesions in AD but may enhance the progression of the disease.

There is some evidence that controlled microglial activation may actually be advantageous to an aging brain. In APP and PS1 double transgenic mice, intracranial injection of lipopolysaccharide (LPS) in the hippocampus reduced Aβ levels compared to animals which were only injected with saline (DiCarlo et al., 2001). Furthermore, two independent groups have demonstrated that in the ALS transgenic mouse model, treatment with glial derived neurotrophic factor (GDNF) has protective effects (Manabe et al., 2002; Acsadi et al., 2002). It appears that limited and

confined inflammation may be beneficial. However, unresolved pathological lesions may lead to chronic activation of uncontrollable inflammatory events that can actually accentuate existing problems in the diseased brain.

Activated glial cells have been proposed to play a role in PD as well as AD. In a recent study it was demonstrated that the injection of LPS in the supranigral area of rat brains resulted in microglial and astroglial proliferation. These reactive glial cells express increased iNOS immunoreactivity and 3-nitrotyrosine formation leading to subsequent neuronal death (Iravani et al., 2002). The iNOS appears to be an important toxic mediator since pretreatment of animals with an iNOS inhibitor, substantially reduced the extent of cell death. Enhanced production of NO may potentiate already existing oxidative stress and this in turn may be the underlying cause of the decrease in neuronal viability.

It has been demonstrated that metamphetamine and MPTP-induced peroxynitrite formation may be a direct causative factor in dopaminergic neuron toxicity by nitrosylating the human dopamine transporter and thus rendering it ineffective (Park et al., 2002). Inhibition of glial cell activation in the mouse brain decreases MPTP-induced neurotoxicity by blocking the formation of iNOS and interleukin 1β (Wu et al., 2002), both of which are products of NF-κB-promoted gene transcription. In neuroblastoma cells, the MPP ion has been shown to activate NF-κB and the stress-activated c-Jun N-terminal kinase (Cassarino et al., 2000). However, another study looked at the effect of LPS induced toxicity in dopaminergic cells and showed that inhibition of iNOS did not enhance survival of these neurons. Instead, the levels of the cytokines TNF-α and IL-1β appeared to mediate some of the neurotoxicity observed (Gayle et al., 2002). Microglial activation is also believed to play a role in ALS-associated motor neuron death. An inhibitor of microglial activation, minocycline, has been shown not only to delay the onset of the disease but also to dose-dependently increase survival of the G93A transgenic mice (Van Den Bosch et al., 2002). Thus cell death that accompanies neurodegeneration and toxic insult may in part be mediated by chronic and uncontrollable glial activation.

6.5 CONCLUSION

The availability of selectively mutated transgenic animals has allowed the development of novel models of neurodegenerative diseases (Table 6.1). Certain environ-

Table 6.1   Example of Several Genes that Are Altered in Transgenic Animal Models Specific for the Indicated Neurodegenerative Diseases

Disease	Mutated or Overexpressed Genes
Alzheimer's disease (AD)	• Amyloid precursor protein (APP) • Beta-site-APP cleaving enzyme (BACE) • Presenilin-1 (PS1) • Tau
Parkinson's disease (PD)	• Alpha synuclein (α-syn)
Amyotrophic lateral sclerosis (ALS)	• Copper-zinc superoxide dismutase (SOD1)

Table 6.2   Environmental Agents Linked to Specific Neurodegenerative Disorders

Environmental Factors	Specific Neurodegenerative Disease
Aluminum (Al)	• AD
	• ALS/PDC
Cycasin	• ALS/PDC
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)	• PD

mental toxins have also been shown to have utility by mimicking the distinctive pathophysiology of these disorders (Table 6.2). Both genetic and chemically induced models, using experimental animals, have been developed for several other neurological diseases including Huntington's disease (HD). Many of the features of HD can be reproduced in the R6/1 transgenic mouse leading to an abnormally expanded CAG repeat within the ITI5 gene. Amplification of this gene sequence leads to elongated polyglutamine chains on the widely expressed 349-kd protein, huntingtin (Tabrizi et al., 2000b). In a parallel manner much of the histopathology of HD can be reproduced in a rodent model after systemic treatment with 3-nitropropionic acid, 3-NP (Borlongan et al., 1995). 3-NP is a mitochondrial toxin, specifically inhibiting succinic dehydrogenase, and children exposed to this neurotoxin following consumption of mildewed sugar cane in China have shown neurological impairment (Ludolph et al., 1991). The relation between effecting HD-like changes by genotypic alterations on a specific gene, or by use of an inhibitor of an enzyme common to all cells is unclear. However, both models of HD as well as the parent disease show evidence of oxidative damage in affected striatal regions, and drugs that cause amelioration of behavioral and chemical deficits of the 3-NP model are also effective in treating the mouse mutant model (Keene et al., 2002). The symptomatology of HD in these model systems may be initiated by several unrelated means, and this opens the possibility of study of interplay between genotypic and environmental factors.

Using both genetic and chemical tools, new insights into the mechanistic basis of neurodegeneration have been gained. Two consistent findings are that both oxidative stress and inflammatory events play an important role. These common findings suggest that the combination of a multifaceted dietary regimen together with pharmaceutical intervention may delay disease processes and this dual approach may be applicable to many forms of neurodegenerative disorders.

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