

Neurodegenerative Diseases Of The Brain: Genetic And Environmental Factors 11

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11.1. Introduction

Neurodegenerative diseases of the brain are those that involve the slowly progressing loss of neurons usually of a functional structure or system. In parallel the protracted clinical course of the disease is seen. The aetiologies of neurodegenerative diseases remain unknown and generally these diseases are classified on the basis of the localization of neuronal loss. This approach facilitates the neuropsychological study of the relationship of structure or system to function. However, lesions are rarely confined to one system; classifications of neurodegenerative diseases may be based on the major system that is affected but with the acknowledgement of involvement of other parts of the brain. Of the numerous neurodegenerative diseases (Cervós-Navarro and Urich, 1995) perhaps Alzheimer's disease, Huntington's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS) are the best known.

Alzheimer's disease is a neurodegenerative disorder characterized by progressive chronic cognitive dysfunction. Schneck *et al.* (1982) have described a series of stages of cognitive decline beginning with forgetfulness, progressing to the confusional stage and then to dementia. Forgetfulness, as the label suggests, is characterized by forgetting where things have been placed, names, appointments, etc. However, at this stage the symptoms are not so severe that they interfere greatly with employment or daily life. The symptoms may cause anxiety in the afflicted individual. In the confusional stage, memories for recent events are often lost or distorted and there may be word-finding difficulties. Orientation and concentration may be impaired. In the dementia stage, the patient becomes disoriented and confused. Recent memory loss is further advanced making it impossible to have normal conversations. Behavioural problems such as anxiety, restlessness and even psychotic symptoms may be seen.

Probable Alzheimer's disease usually is diagnosed on the basis of the symptoms described above. Repeated computerized tomography (CT) scans or magnetic resonance imaging (MRI) of the brain usually shows progressive atrophy especially in the temporal and parietal cortices (Cervós-Navarro and Urich, 1995). A definitive diagnosis requires the neuropathological confirmation of senile plaques and neurofibrillary tangles originally described by Alzheimer. In more recent years, a number of neurotransmitters have been implicated (Bierer *et al.*, 1995). In particular, cholinergic neurons of the basal forebrain have been found to be lost in excess of the loss seen in normal aging (McGeer *et al.*, 1984). This finding led to the cholinergic hypothesis linking brain cholinergic systems and memory (Coyle *et al.*, 1983; Bierer *et al.*, 1995; Beninger *et al.*, Chapter 17).

Huntington's disease is a neurodegenerative disorder characterized by uncontrolled rapid, arrhythmic, jerky and often repetitive movements of major muscle groups or individual muscles. In parallel with the development of choreic movements, speech, affect, memory and personality changes occur leading eventually to dementia. CT scans reveal generalized cerebral atrophy especially in the corpus striatum producing dilation of the ventricles (Vonsattel *et al.*, 1985). Positron emission tomography (PET) has shown a large decrease in glucose utilization in the corpus striatum and a smaller decrease in the frontal cortex. A number of neurotransmitter-related changes, for example decreased concentrations of dopamine, homovanillic acid, choline acetyltransferase, GABA and substance P, have been seen in Huntington's disease but whether these are causes or effects of the neurodegenerative process remains unknown.

Parkinson, in 1817, described the shaking palsy that became known as the disease bearing his name. Parkinson's disease is characterized by resting tremor, akinesia, rigidity and postural abnormalities. Changes in mood may occur (Ehmann *et al.*, 1990; Cummings, 1992). In the advanced stages of the disease, expression is impoverished, there may be propulsion or retropulsion of movement and increased salivation. CT scans show cortical and subcortical atrophy. There is a predominant loss of the ventrolateral substantia nigra dopaminergic projection to the putamen (Rinne, 1993). Other neurotransmitters also are implicated by the observation of decreases in the number of noradrenergic neurons of the locus coeruleus and serotonergic neurons of the dorsal raphe. Many mechanisms for the pathogenesis of Parkinson's disease have been proposed including environmental factors, aging, oxidative stress and excitotoxicity, but the causes remain unknown.

ALS was first described by Charcot and Joffroy in 1869. It is characterized by muscle weakness and sometimes pain. This is followed, depending on the location of the lesions, with weakness plus muscle atrophy and fasciculation or spastic paresis. Muscle tone increases and tendon reflexes are exaggerated. CT scans and MRI show cortical involvement often extending beyond the motor cortex to include frontal and temporal regions (Kato *et al.*, 1993). Blood flow to the motor cortex is reduced as detected by PET (Kew *et al.*, 1994). Atrophy of the anterior spinal roots always is present (Cervós-Navarro and Ulrich, 1995). Proposed mechanisms for the pathogenesis include oxidative stress, excitotoxicity and immune dysfunction. As is the case for Alzheimer's, Huntington's and Parkinson's disease, the causes of ALS are, at present, unknown.

11.2. A possible role for mitochondrial mutations

Recently, Cassarino and Bennett (1999) proposed a possible role for mitochondria in neurodegenerative diseases that provides a common mechanism underlying the course of cell loss in a variety of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and ALS. In the past forty years a number of human diseases have been found to be associated with inherited mitochondrial DNA mutations (Luft, 1997). As many of these diseases involve selective populations of cells within the central nervous system and since these cells are highly dependent on energy, it is possible for a systemic mitochondrial mutation to lead to cell loss within specific regions.

Mitochondria are the source of energy for cells and brain cells are particularly energy-dependent. Mitochondrial dysfunction can lead to impaired electron transport mechanisms and the production of damaging free radicals. Neurons have relatively fewer antioxidant enzymes (Martilla *et al.*, 1988) making them particularly susceptible to the

ravages of free radicals. Cassarino and Bennett (1999) suggest that this situation can lead to "...a vicious cycle of increasing oxidative damage (that) may slowly damage neurons over a period of years, leading to the eventual neuronal cell death characteristic of the sporadic, age-related neurodegenerative diseases" (p. 3). Oxidative stress resulting from the production of free radicals has been implicated in Alzheimer's disease (see Rupniak *et al.*, Chapter 6), Parkinson's disease and ALS, all of which exhibit free radical-mediated cellular damage (Beal, 1995).

The mitochondrial genome may play an important role in neurodegenerative diseases. Mitochondrial electron transport capabilities decrease with age and the production of free radicals increases (Beal, 1995). In individuals with inherited mitochondrial DNA mutations, the combination of these susceptibilities with the age-associated decrease in mitochondrial anti-oxidant capacity may lead to neurodegeneration. In Parkinson's disease, for example, cells of the substantia nigra contain the highest levels in the brain of mitochondrial DNA mutations (Cortopassi *et al.*, 1992). The combination of these mutations and age-related decreases in electron transfer capabilities may lead to the characteristic loss of dopaminergic neurons of the substantia nigra in Parkinson's disease (Cassarino and Bennett, 1999). The final test of the mitochondrial mutation hypothesis of neurodegenerative diseases will come with the sequencing of mitochondrial DNA.

11.3. A role for trinucleotide repeats

A number of neurodegenerative diseases, including Huntington's disease, have been found to be associated with trinucleotide (CAG) repeat expansions. Furthermore, the greater the number of repeats, the earlier the onset of the disease and the more rapid the course (Zoghbi and Orr, 2000). These trinucleotide repeats may contribute to the pathogenesis of neurodegenerative diseases.

The Huntington's disease gene (HD) codes for the protein huntingtin that appears to be necessary for development. Thus, mice with the murine homologue of HD deleted die during development and replacement with the wild-type gene results in proper development (White *et al.*, 1997). Huntingtin is found in the cytoplasm of cell bodies, dendrites and axons where it is associated with microtubules and synaptic vesicles suggesting a possible role in synaptic transmission. Interestingly, huntingtin is not associated with mitochondria reducing the likelihood that it is involved in oxidative metabolism. The regions in which huntingtin is found to be most abundant include the striatum where it is found in large neurons and medium spiny neurons, the cortex where it is found in pyramidal neurons and the cerebellum where it is found in Purkinje cells (Vonsattel and DiFiglia, 1998).

Huntingtin has been found to be associated with some proteins in the brain. For example, Li *et al.* (1995) showed that huntingtin-associated protein 1 interacts with huntingtin although its function is unknown. In some cases, including huntingtin-associated protein 1, the interaction of the protein with huntingtin is associated with the expansion of polyglutamine tracts produced by CAG repeats.

Transgenic mice with the human huntingtin promoter including expanded CAG repeats evidenced expression of a shortened huntingtin protein with an expanded glutamine tract (Mangiarini *et al.*, 1996). These transgenic mice showed severe behavioural pathologies reminiscent of Huntington's disease. Symptoms included gait disturbances, resting tremor, stereotypical grooming, sudden shuddering movements and seizures. As the mice aged, symptoms became more severe and included weight loss. Control transgenic

mice without the expanded CAG repeats showed none of these behavioural pathologies. Ultrastructural studies of these transgenic mice with the expanded CAG repeats revealed huntingtin staining localized to dense neuronal intracellular inclusions in the nucleus in contrast to the diffuse cytoplasmic distribution of huntingtin in the control animals (Davies *et al.*, 1997). The neuronal inclusions were most common in cortical neurons, striatum, Purkinje cells and spinal cord.

How might trinucleotide repeats lead to the neuropathologies associated with Huntington's and other neurodegenerative diseases? Zoghbi and Orr (2000) point out that all pathogenic models of neurodegeneration involve the idea that the CAG repeats lead to a "gain of function". Thus, the disease results from a mutated protein performing a new function. What feature(s) of trinucleotide repeats and the proteins they produce confer(s) their toxicity? One possibility is that the polyglutamine tract acts as a substrate for transglutaminase that reacts in the presence of active enzyme to become cross-linked with polypeptides containing lysyl groups. Products of this reaction will lead to the formation of aggregates (Green, 1993). Aggregates may not be sufficient or necessary for neuronal degeneration. However, polyglutamine diseases like Huntington's disease as well as other neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and ALS involve the gradual accumulation of proteins either within the cytoplasm or nucleus of the cell or in the extracellular space. These proteins may interact with other proteins, like huntingtin discussed above, to produce alterations that decrease their degradation. It will be the job of future studies to identify how the production of altered proteins by CAG repeats influences protein interactions and degradation to provide a definitive answer to the question posed at the beginning of this paragraph.

11.4. Epidemiology of Neurodegenerative Diseases

Both the idea that neurodegenerative diseases might be related to mitochondrial dysfunction issuing possibly from mutations of mitochondrial DNA and that neurodegenerative diseases might be related to protein dysfunctions resulting from expanded trinucleotide repeats in nuclear DNA provide a possible common mechanism for a variety of neurodegenerative diseases. From this point of view, the chapter by Utti and Wszolek (Chapter 12) is of particular interest. These authors discuss the etiology of neurodegenerative overlap syndrome. They review evidence of overlap among Alzheimer's disease, Parkinson's disease and ALS, pointing out common features of pathological aging in these disorders, common neurochemical observations including elevated plasma cysteine/sulphate ratios, and overlap in mitochondrial respiration chain abnormalities. They review results implicating abnormalities in zinc and iron metabolism in each of these three disorders (cf., Chapter 25 by Fredriksson *et al.*). Finally, they review genetic observations showing a number of kindred studies revealing overlap among Alzheimer's disease, Parkinson's disease and ALS. Results support the suggestions by Cassarino and Bennett (1999) and Zoghbi and Orr (2000) that common dysfunctions in mitochondrial or nuclear DNA, respectively, may underlie a number of neurodegenerative disorders.

In Chapter 13, Calne discusses hereditary and environmental causes of neurodegenerative disorders. He points out the different gradient of cell loss seen in the substantia nigra in Parkinson's disease versus that seen in normal aging as evidence that neurodegenerative disorders involve more than simply an acceleration of the normal aging process. Calne reviews intriguing recent evidence that there is a higher risk of Parkinson's

disease in certain occupational groups including teachers, clergy and health-care workers who have in common a high level of exposure to many people. Included in this group was logging and mining camp workers, who live in close quarters. Parkinson's disease also has a higher prevalence among people living in colder climates. Calne takes these data to suggest that circumstances that lead to a higher risk of exposure to viruses – broad exposure to the public or cold temperatures – increase the risk for Parkinson's disease.

Lobo *et al.* (Chapter 15) focus on the epidemiology of Alzheimer's disease in search of evidence relevant for understanding neurodegeneration. They identify important evidence for environmental factors including regional differences in prevalence and incidence in Europe. There is a higher incidence of Alzheimer's disease in males than in females. Lobo *et al.* identify a number of possible neuroprotective factors including the anti-oxidant vitamin E or histamine H2 blocking agents. Red wine also has been found to have possible neuroprotective effects when taken in moderate amounts (Orgogozo *et al.*, 1997); Lobo *et al.* point out that this was reported from Bordeaux and needs to be replicated with Carinena wine from Zaragoza! The authors end with a discussion of how epidemiological studies can inspire eventual clinical trials of potential therapeutic agents.

11.5. Genetics of neurodegenerative diseases

Chapters 12 (Uitti and Wszolek), 13 (Calne), 14 (Bazzett and Albin) and 15 (Lobo *et al.*) all deal with the issue of genetic factors in neurodegenerative diseases. In the context of their discussion of neurodegenerative overlap syndrome, Uitti and Wszolek (Chapter 12) report on two kindreds with overlap of neurodegenerative disorders and the observation that the abnormal gene was found on the same chromosome in both families. These and related findings are summarized in their Table I. Calne (Chapter 13) focuses on the familial forms of Parkinson's disease and reviews studies implicating particular genes. Two of the products of these genes have been identified, α -synuclein and parkin, but the functions of these proteins remain poorly understood. Lobo *et al.* (Chapter 15), focusing on Alzheimer's disease, discuss the gene coding for apolipoprotein E and the implications for a genetic predisposition to the disease. Genetic studies continue to provide clues to the mechanisms underlying the development and progression of neurodegenerative diseases.

In their excellent chapter, Bazzett and Albin (Chapter 14) focus on Huntington's disease, an adult-onset autosomal dominant neurodegenerative disorder caused by expanded CAG repeats in the huntingtin gene as discussed above. They provide a review of the neuronal and behavioural pathology in Huntington's disease and then discuss the possible role of excitatory amino acids in the disorder. They discuss the problem of regional (striatal) excitotoxic damage and evidence for the possibility that mitochondrial dysfunction leading to cell death is not uniform throughout the brain with aging, providing a resolution to the problem. Bazzett and Albin discuss animal models of Huntington's disease, dealing first with the excitatory amino acid striatal lesion model first reported by Coyle and Schwarcz, 1976) and then with mitochondrial inhibitor animal models. Finally, they provide an overview of Huntington's disease genetics and some of the mouse models already mentioned above. The chapters provide a good survey of the latest studies of possible genetic factors in neurodegenerative diseases and begin to point in the direction of common mechanisms of neuronal dysfunction in a number of different neurodegenerative diseases.

11.6. Neonatal experience and possible neurodegeneration

In recent years it has become more and more clear that early exposure to a wide range of agents, either through introduction of the agent itself (*e.g.*, iron, cocaine) or through indirect release of the agent (corticosteroids) as a result of environmental experiences (stress) can have enduring effects on the nervous system and adult functioning. In the following section, several chapters deal with this aspect of neurodegeneration, providing clues to the possible mechanisms that underlie neurodegenerative diseases.

Fredriksson, Schröder and Archer (Chapter 25) focus on iron. Given that elevated levels of iron have been found in brain regions where cell damage is associated with neurodegenerative disorders, for example in the substantia nigra in Parkinson's disease (*e.g.*, Drayer *et al.*, 1986), and that iron is implicated in mitochondrial function, studies of the effects on development of iron would seem particularly appropriate. Fredriksson *et al.* present the results of studies of postnatal treatment with iron in a number of behavioural paradigms. Iron given on days 10-12 postnatally resulted in a reduction of habituation and radial maze learning in tests given in adulthood. When mice given postnatal iron were treated as adults with MPTP, it was more toxic than in controls not receiving the postnatal iron treatment. Toxicity was indicated by greater decreases in locomotor activity and greater losses of striatal dopamine. Possible mechanisms involving free radical formation through effects on glutathione, for example, are presented. Results suggest possible beneficial effects of iron chelators or antioxidants in preventing the neurodegenerative effects of iron.

In Chapter 24, Kosofsky and his co-workers present the results of a study of prenatal cocaine exposure on responses to stress of adult mice. Experimental animals gained less weight and showed less freezing to foot shock. Behavioural changes were not associated with an altered corticosterone response to stress. In related studies, Le Moal and his co-workers (Chapter 20) assessed behaviour in adult rats whose mothers, while pregnant with them, were exposed to restraint stress. Other groups were exposed to handling stress as neonates. These early manipulations affected responses of the hypothalamic-pituitary-adrenal axis in adulthood. Dopamine receptor subtype densities also were affected. In some experiments, neonatally stressed rats did not differ from controls when tested in adulthood but did differ when tested on the radial maze in old age, suggesting possible gradual, neurodegenerative effects of the early experience. Particularly intriguing was the report of Koehl *et al.* (Chapter 20) that prenatally stressed rats were more likely to self-administer psychomotor stimulants. Results point to enduring effects of early experience that may contribute to the eventual degeneration of neurons and the symptoms that result.

11.7. Adult experience and possible neurodegeneration

In the previous section, the papers reviewed present data suggesting that early experience can have enduring and damaging effects on the nervous system that are manifested as changes in adulthood or old age. In this section, several of the chapters present compelling evidence that adult exposure to a number of abused compounds similarly can have enduring negative effects on the brain.

In Chapter 22, Seiden, Lew and Malberg discuss the effects of methamphetamine and methylenedioxymethamphetamine (MDMA), popularly known as Ecstasy, in this regard. One of the ways that these compounds influence neurotransmission is by acting at

the transporter site to produce reverse transport of dopamine (for methamphetamine) and serotonin (for MDMA). Extensive studies show that the neurotoxic effects of these and a number of related compounds occur when core body temperature is high. Furthermore, the neuroprotective effects of agents such as dizocilpine, ketamine and α -methyl-p-tyrosine, that protect against methamphetamine or MDMA toxicity when co-injected with them, are mediated by the ability of these agents to decrease core temperature. Seiden and his co-workers present the results of extensive studies of the role of core temperature and its interaction with ambient temperature in neurotoxicity. They conclude that, "There is an inverse relationship between ambient temperature and MDMA neurotoxicity; the lower the dose of MDMA that is administered, the higher ambient temperature must be for neurotoxicity to occur. Conversely, the higher the dose of MDMA that is administered, the lower the ambient temperature will be for neurotoxicity to occur." As MDMA commonly is used today in the context of large parties, termed "raves", where many people are crowded together and ambient temperature is likely to be high, the work of Seiden *et al.* has important implications for potential neurotoxic consequences of participation in drug taking under these circumstances.

Ricaurte and McCann (Chapter 23) focus on the damaging effects of MDMA on serotonergic neurons. They review briefly the methods of interspecies dose scaling to lead to their conclusion that humans are using MDMA doses within the toxic range as determined from animal studies. They then review the evidence for neurotoxicity produced by MDMA in humans. Thus, well controlled studies of cerebrospinal fluid levels of the serotonin metabolite 5-hydroxyindoleacetic acid show a decrease; in the same studies, metabolites of dopamine or norepinephrine were not found to be decreased. PET studies show decreased levels of the serotonin transporter in people with a history of MDMA use. Some pharmacological challenge studies have been carried out evaluating the prolactin response to fenfluramine in former users of MDMA; fenfluramine is an analogue of amphetamine that releases serotonin. MDMA users showed a blunted prolactin response to fenfluramine suggesting that hypothalamic serotonergic function had been altered in these individuals and suggesting further that MDMA had induced serotonergic neurotoxicity. MDMA users showed some impairment on a number of cognitive tests including various tests of memory and attention. Sleep studies may provide an indirect index of serotonergic function as serotonin is strongly implicated in the control of sleep (Jouvet and Renault, 1966). Ricaurte and McCann report altered sleep in MDMA users and altered sleep responses to serotonergic drugs suggesting a change in serotonin function in these individuals. Taken together, the results point to a possible serotonergic neurotoxicity with MDMA use. The current widespread abuse of MDMA underscores the importance of these results.

In Chapter 17, Beninger *et al.* focus on the cognitive effects of neurotoxic lesions of the nucleus basalis magnocellularis (nbm). They provide a basis for understanding the often confusing picture emerging from studies using different neurotoxins (*e.g.*, ibotenic acid, quisqualic acid) and reporting large differences in cognitive effects (*e.g.*, level of memory impairment) in spite of comparable decreases in cortical markers for cholinergic function. Thus, different excitotoxins differentially affect cholinergic projections from the nbm to the cortex and amygdala. At the doses normally used in behavioural studies, both excitotoxins would produce a large depletion of cortical choline acetyltransferase (ChAT), a marker for cholinergic neuronal loss, but, whereas ibotenic acid also would produce a large decrease in amygdaloid ChAT, quisqualic would produce a smaller decrease. Thus, the differential effects of the two excitotoxins, when injected into the nbm, on memory is associated with

the level of cholinergic neuron loss that they produce in the amygdala. In support of the hypothesis that amygdaloid cholinergic afferents are important for memory, studies with the excitotoxin phthalic acid, that produces large depletions of amygdala ChAT but small effects on cortical ChAT show large memory impairments (Mallet *et al.*, 1995). Finally, studies with the cholinergic immunotoxin 192 IgG-saporin have shown relatively mild mnemonic impairments following nbm or intraventricular administration. 192 IgG-saporin produces its toxic effects through its action on neurons bearing nerve growth factor (NGF) receptors and it is the cholinergic neurons projecting to the cortex, not those projecting to the amygdala that bear NGF receptors (Heckers *et al.*, 1994). Thus, results with the immunotoxin are consistent with those from studies with different excitotoxins. This chapter provides some insights into the differential contribution of corticopetal versus amygdalopetal cholinergic projections to memory and it provides a basis for understanding the diverse effects reported in studies using these agents to test memory and other cognitive abilities.

Continuing with the focus on the underlying neurochemical mechanisms of normal and abnormal cognitive function, Moghaddam (Chapter 18) discusses the possible role of metabotropic glutamate receptors in schizophrenia. She reviews the heterogeneous anatomical and cellular distribution of the eight subtypes of these receptors and suggests that this arrangement will allow for modifications of glutamatergic neurotransmission in a functionally selective manner. Glutamatergic dysfunction has been implicated in schizophrenia by, for example, the observation that glutamatergic agents can produce symptoms similar to those seen in schizophrenia. This provides a rational basis for targeting glutamatergic receptors to normalize activated glutamate neurotransmission. Moghaddam reviews results from studies with the mGluR2/3 selective metabotropic glutamate receptor agonist LY354740. This compound reversed the behavioural effects in rats of the glutamate antagonist phencyclidine, a schizophrenogenic agent. Thus, it may be possible to target metabotropic glutamate receptors in a regionally and functionally specific manner to normalize abnormal glutamatergic neurotransmission thought to be associated with disorders such as schizophrenia.

In Chapter 21, Rodríguez de Fonseca *et al.* explore the role of endogenous cannabinoids as modulators of dopaminergic and glutamatergic neurotransmission and suggest a possible neuroprotective role for these substances. Agonists acting at cannabinoid receptors in the brain influence the firing rate of dopaminergic neurons. Their action appears to be via presynaptic receptors located on GABAergic neurons projecting from the striatum to the substantia nigra pars reticulata. Dopamine also affects cannabinergic function; thus, D₂ agonists increase extracellular anandamide in the striatum. Focusing on the mesocortical pathway, there is also evidence that brain cannabinoid receptor agonists increase the firing rate of these neurons; this effect was blocked by a μ -opiate antagonist, implicating a cannabinoid-opiate interaction. Based on the identified neurotransmitter interactions involving the cannabinoids, the authors conclude with a discussion of the possibility of targeting the endogenous cannabinoid system in developing treatments for dopamine-related diseases. Of particular relevance to the topic of this book is the finding by Nagayama *et al.* (1999) of neuroprotection derived from stimulation of cannabinoid receptors in the brain. Future studies will continue to unravel the complex interactions of the cannabinoid system with excitatory amino acids and monoamines in the brain providing a rich basis for the development of new pharmacotherapeutic strategies for the treatment of neurodegenerative disorders.

11.8. Responses to neurodegenerative injury

Chapters 16 (Ferrer) and 19 (Delgado-Garcia *et al.*) in this section explore the brain's natural responses to injury with an eye for discovering potential treatments to prevent pathological neuronal loss. Delgado-Garcia *et al.* review the remodelling response of neurons to axotomy or target removal. Following axotomy of abducens neurons, the firing pattern of axotomized motor cells changes. There is gradual recovery over a two-three month period. Recovery of electrophysiological properties corresponds with re-establishing connections by the axotomized neurons. Whether there is functional recovery depends upon the pattern of re-innervation. If the original target is re-innervated by the severed axons, there will be both electrophysiological and functional recovery. However, if re-innervation is of another target, although the firing pattern of the axotomized neurons returns to normal, their function is not restored. Thus, the observation of rewiring of a damaged target can be dissociated from functional recovery.

Following brain damage, increased brain levels of brain-derived neurotrophic factor (BDNF) and of the mRNA for its tyrosine kinase (TrkB) receptors are seen. Trophic factors bind to and activate specific membrane receptors that, in turn, activate intracellular pathways involved in cell survival, maturity and growth. In Chapter 16, Ferrer points out that there is actually a reduction of BDNF in ischemic adult rats or gerbils or in hypoxic or ischemic developing rats in brain regions where the cells will die; however, levels of BDNF increase in brain regions that may survive. Results suggest that BDNF may produce neuroprotection in parts of the damaged brain. Brain cholinergic neurons bear the appropriate receptors for BDNF and are sensitive to the beneficial effects of BDNF. As cholinergic neurons are known to be lost in Alzheimer's disease (Coyle *et al.*, 1993), it might be expected that BDNF also would be involved. Ferrer reviews studies of post mortem tissue from Alzheimer's patients showing decreased BDNF mRNA and protein in the hippocampus suggesting impaired BDNF signalling in Alzheimer's. Results suggest that the delivery of trophic factors and the activation of their receptors may be useful in treatment.

11.9. Conclusions

Many aspects of neurodegenerative diseases are considered in the following chapters. These diseases include Alzheimer's disease, Huntington's disease, Parkinson's disease and ALS. There may be a common mechanism in mitochondrial mutations in all of these disorders leading to oxidative stress and cell loss. Alternatively, or additionally, there may be a common mechanism in trinucleotide repeats leading to the formation of damaging proteins. Epidemiological studies point to the possibility that neurodegenerative diseases may have genetic and environmental determinants. Genetic analyses clearly identify genetic factors in neurodegenerative diseases and are beginning to isolate the gene products that contribute to neuronal loss. Studies of neonatal or adult exposure to environmental factors implicates a number of substances (*e.g.*, iron in neonates, abused drugs in adults) in neurodegenerative cell loss. Further studies of responses to neuronal injury begin to identify the mechanisms and substances involved. This entire enterprise provides multiple leads for the development of neuroprotective pharmacotherapeutics for the treatment and eventual prevention of neurodegenerative diseases. This exciting line of research is sure to provide many new insights into the mechanism of brain damage and recovery that will lead eventually to improved treatment for some of the most devastating of human diseases.

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