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Gene-Environment Interplay in Neurogenesis and Neurodegeneration

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Factors associated with predisposition and vulnerability to neurodegenerative disorders may be described usefully within the context of gene-environment interplay. There are many identified genetic determinants for so-called genetic disorders, and it is possible to duplicate many elements of recognized human neurodegenerative disorders in either knock-in or knock-out mice. However, there are similarly, many identifiable environmental influences on outcomes of the genetic defects; and the course of a progressive neurodegenerative disorder can be greatly modified by environmental elements. Constituent cellular defense mechanisms responsive to the challenge of increased reactive oxygen species represent only one crossroad whereby environment can influence genetic predisposition. In this paper we highlight some of the major neurodegenerative disorders and discuss possible links of gene-environment interplay. The process of adult neurogenesis in brain is also presented as an additional element that influences gene-environment interplay. And the so-called priming processes (*i.e.*, production of receptor supersensitization by repeated drug dosing), is introduced as yet another process that influences how genes and environment ultimately and co-dependently govern behavioral ontogeny and outcome. In studies attributing the influence of genetic alteration on behavioral phenotypy, it is essential to carefully control environmental influences.

Keywords: Neurodevelopment Neurodegeneration; Neurodevelopment; Neurogenesis; Alzheimer disease; Huntington disease; Tau neuropathy; Priming

INTRODUCTION

Most of the neurodegenerative disorders that have received some degree of documentation, such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) are characterized by neuronal damaged caused putatively by toxic, abnormal, aggregate-prone proteins or 'clusters'. A recent review by Petrucelli and Dawson (2004) outlines and describes three different aspects of neurodegenerative mechanisms involved in these disorders, as follows: (1) the genetic configuration underlying the abnormal processing and accumulation of misfolded proteins in the neurodegenerative diseases, using PD as a model disorder, (2) an understanding and consideration of the cellular mechanisms for disposal of abnormal proteins, and the effects of toxic protein accumulation on the ubiquitin proteasome system and neuronal survival, and (3) the development and challenges offered by cell culture and animal models leading to rational and effective treatment strategies. In the realm of neurodegeneration, there are known genetically-associated disorders such as ALS/motor neuron disease, HD, early-onset PD, myasthenia gravis, and others. ALS/motor neuron disease can be inherited or acquired by consumption of foods containing a high content of abnormal excitatory amino acids. HD is an autosomal dominant disorder, caused by abnormal expansion in the length of a CAG triplet repeat sequence in a gene on chromosome 4 (*i.e.*, the *huntingtin* gene). Myasthenia gravis can be autosomal and dominantly inherited; or caused by thymus-derived

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autoimmune production of anti-AChR (acetylcholine receptors). PD is usually idiopathic although there are inheritable types (Graham and Lantos, 2002; see Palomo *et al.*, 2003).

There are also a number of human prion-associated disorders including Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), and kuru. CJD and GSS are dominantly inherited disorders; or they, like kuru, can be acquired by infection (Graham and Lantos, 2002). In other circumstances, genetic and mutational alterations appear to have contributed to a range of disorders affecting the brain, including Down's Syndrome, focal cerebral and global ischemia, and ALS (Groner *et al.*, 1985; Epstein *et al.*, 1987; Chan PH *et al.*, 1993; Gurney *et al.*, 1994; Wong *et al.*, 1995; Bruijn *et al.*, 1997; Murakami *et al.*, 1997). An outline of the neurotoxic action underlying neuronal injury and the eventual neuroprotective/neurorestorative propensities of various molecular mechanisms is outlined (Beal *et al.*, 2000).

Neurodevelopmental disorders include attention-deficit hyperactivity disorder (ADHD), perhaps certain motor/dyskinesic aspects of schizopsychotic disorders with Parkinson-like neuroleptic syndromes, perhaps anxiety disorders including obsessive compulsive disorder (OCD), and elements of affective disorders, including mania (see Palomo *et al.*, 2002b). Drug-induced developmental disorders include fetal alcohol syndrome. Treatments in ontogeny with GABA mimetics or NMDA receptor antagonists are known to produce extensive neuronal apoptosis in brain (Olney *et al.*, 2002), and such neuronal loss can carry forward into behaviorally-associated (dysfunctional) disorders (see Palomo *et al.*, 2002a). The role of apoptosis in HD, too, has been addressed extensively (*cf.* Hickey and Chesselet, 2003). It is not unthinkable that many aspects of neurodegenerative disorder originate, on a cellular level, from neurodevelopmental liabilities that occurred under earlier periods of individuals' brain development, for example due to interferences of either a predominantly genetic or environmental (pharmacological) nature to the preprogramming of neuronal death or to direct toxic cell death. Thus, Fredriksson and Archer (2004) treated mouse pups on either postnatal days 10 or 11 with either the NMDA antagonists, dizocilpine (MK-801, 3 x 0.5 mg/kg) or ketamine (50 mg/kg), or ethanol (3 x 2.5 mg/kg). Fluoro-jade staining indicated marked apoptotic neurodegeneration in several brain regions following sacrifice of some of the pups 24 hours later. The functional analyses indicated marked deficits and hyperactivity in spontaneous motor behaviour; the hyperactivity was in all cases abolished by a low dose of d-amphetamine (0.1 mg/kg). Marked deficits in radial maze learning were obtained, and the deficit induced by MK-801 was abolished by d-amphetamine. In the circular swim, there was no deficit in the acquisition of the task but relocation of the submerged platform induced marked deficits in the Mk-801, ketamine and ethanol treated mice. These NMDA-antagonist-induced postnatally mediated effects are discussed in terms of a useful model of ADHD.

Not to be ignored is the potential of a variety of substances, not restricted to substances of abuse, to produce long-lived changes in the brain after only several exposures (Palomo *et al.*, 2002a; 2004). For example, when rats are treated repeatedly, once daily for several consecutive days, with even low doses of the dopamine D_2 receptor agonist quinpirole (in ontogeny, at old age, or at any stage of ontogeny), there are life-long accentuated responses to subsequent quinpirole treatments (Kostrzewa *et al.*, 1993; 2003; 2004; Brus *et al.*, 2003). Such changes represent a neurotoxic outcome, but these changes are not necessarily accompanied by neurodegenerative changes, or even changes in dopamine D_2 receptor binding parameters (Kostrzewa and Brus, 1991). This highlights the potential of perhaps a library of substances that are able to produce life-long exaggerated (or inhibited) responses in later life, following exposures during ontogeny, even exposure *in utero*.

These above examples demonstrate that both genetics and environment are important in the etiology of neurodegenerative disorders, with both genes and environment coordinately interacting in many of the disorders (Graham and Lantos, 2002). In this paper a few examples of some of the links or suspected links between genetics and environment in the etiology of neurodevelopmental or neurodegenerative disorders are presented and discussed.

The flip side of the coin, neurogenesis, was thought until recently to be specifically an ontogenetic aspect of central nervous system development. However, during the last 5-10 years there has been convincing evidence that new neurons are produced in adulthood - not only in lower vertebrates but in mammalian species including man (Eriksson *et al.*, 1998; Gould *et al.*, 2001; Zhao *et al.*, 2003). Moreover, neurogenesis is now considered to be a viable mechanism accounting for the clinical effect of antidepressants and mood stabilizers (Chen *et al.*, 2000; Malberg *et al.*, 2000; Moore *et al.*, 2000; Czeh *et al.*, 2001; Santarelli *et al.*, 2003).

Over the past 20 plus years, although much has been determined on mechanisms attending neurogenesis and neurodegeneration particularly in regards to pro- and

anti-apoptotic factors, there is still much to be learned. In discussing neurogenesis it is reasonable to state that our current understanding of this process in adult mammalian brain is still quite primitive. A caveat is that (drug-) induced neurogenesis will not necessarily overcome the dying of neurons in neurodegenerative disorders. In reality, induced neurogenesis is region-specific, and as such, the outcome is varied. Therefore, new neurons and new axonal growth will not necessarily result in regeneration of the dying neural tracts and restoration of function. In the case of antidepressant-induced or lithium-induced neurogenesis, the end-point is a change in mood. Therefore, there are aspects of neurodegenerative disorders and elements of psychiatric disorders accompanying the theme of neurodegeneration and neurogenesis.

HUNTINGTON'S DISEASE (HD)

Symptoms of HD usually begin in midlife and include motor dysfunction (including ataxia, lack of coordination, chorea and rigidity), cognitive deficits progressing to dementia, and psychiatric disturbances (*cf*. Ross *et al.*, 1997). The mutation associated with HD occurs nears the *N*-terminus of the large protein, *huntingtin* (*htt*), and expansions beyond a threshold of 36 CAGs induce the disorder (Huntington's Disease Collaborative Research Group, 1993). The normal *htt* protein appears to play a role during embryogenesis as well as in gene regulation and vescicular trafficking in mature cells (Zuccato *et al.*, 2001; 2003). Mice with a CAG repeat expansion in the coding region of HPRT, a 'housekeeping' enzyme not associated with any neurological disease, also develop a progressive neurodegenerative phenotype (Ordway *et al.*, 1997), *i.e.*, expanded polyglutamine tracts appear to have innate neurotoxicity. An expanded polyglutamine confers a toxic 'gain-of-function' on the disease protein, which progressively and selectively disrupts the functioning of vulnerable populations of neurons. Postmortem brains of HD patients indicate substantial atrophy with marked, selective loss of GABAergic, medium spiny, neurons of the caudate and putamen (Vonsattel *et al.*, 1985; Vonsattel and DiFiglia, 1998). Although *htt* is widely expressed in the embryo, adult nervous system, and periphery, neurons of the cerebral cortex and medium spiny neurons are preferentially damaged in HD (Bates *et al.*, 2002; Bates, 2003). The spatiotemporal expression patterns of *htt* and other CAG repeat disease genes do not correspond to the spatiotemporal vulnerability of specific neuronal populations in the diseased brains. Note that *the number of repeat units is highly predictive for the age-of-onset of the disorder* (*e.g.*, Andrews *et al.*, 1993; Duyao *et al.*, 1993; Snell *et al.*, 1993; Rubinsztein *et al.*, 1996; Arning *et al.*, 2004). Variation in repeat length provides a molecular basis for the phenomenon of "anticipation" wherein other factors contribute, especially in cases with pathological CAG repeats in the range 35-45 (Kehoe *et al.*, 1999). Selective vulnerability of neuronal populations may be mediated by disrupted functioning of a subset of synapses subsequent to aberrant gene expression and protein regulation.

Cortical degeneration of neurons projecting to the basal ganglia is seen in the deeper layers, *i.e.*, layers 3, 5 and 6. Less affected areas include the globus pallidus, subthalamic nucleus and amygdala. Structural determinations and aggregations of the mutant *htt* protein (*cf*. Perutz, 1994; Scherzinger *et al.*, 1997; 1999: Yu *et al.*, 2003), as well as brain pathology determination of HD patients and transgenic mice expressing mutant *htt* protein, show the *htt* immunoreactive aggregates in nuclei of neurons throughout the CNS (Davies *et al.*, 1997; Becher *et al.*, 1998; ; Gutekunst *et al.*, 1999). *Htt* inclusions are distributed also throughout the cytoplasm of most neuronal populations, outnumbering nuclear inclusions (Gutekunst *et al.*, 1999). Immunocytochemical studies have suggested that a proteolytic event occurs within exon 2 of full-length mutant *htt* to create an aggregating fragment (Hodgson *et al.*, 1999; Sieradzan *et al.*, 1999; Lunkes *et al.*, 2002). Further, the brains of mice expressing the N171-fragment of *htt* accumulate a predicted protein product and a *C*-terminally truncated product (Schilling *et al.*, 1999). Although there is a great deal of available research, animal models (*e.g.*, Burright *et al.*, 1995; Schilling *et al.*, 2001b; Wang *et al.*, 2002) of HD appear limited in the extent to which they model the disorder: 'Knock-in' or YAC transgenic mice demonstrate some of the early features of the disorder but the behavioral phenotype is generally of late onset and does not progress to premature death (Lin *et al.*, 2001). The R6/2 and N171-82Q mouse models develop changes in motor performance and die prematurely (Jankowsky *et al.*, 2002). Recently, Schilling *et al.* (2004), using the HD-N171-82Q model, compared the efficacy with which environmental, pharmacological and genetic interventions ameliorated the functional and pathological features. Thus, an enriched environment, as well as treatment with coenzyme Q10 (an energy metabolism enhancer), improved the motor skills of these mice, although longevity was not prolonged. Several other pharmacological treatments, including remacemide (glutamate receptor antagonist), celecoxib (cyclo-oxygenase-2,

COX-2, inhibitor) and chlorpromazine (prion inhibitor) were ineffective (Schilling *et al.*, 2004, see also Van Dellen *et al.*, 2000a and Schilling *et al.*, 2001a). Other genetic and environmental factors contributing to the pathogenesis of HD in the clinic and laboratory setting have been outlined (Van Dellen and Hannan, 2004).

Disrupted neuronal gene expression in HD mice covers both receptor and synaptic signal transduction pathways (Cha *et al.*, 1998; Bibb *et al.*, 2000; Chan EY *et al.*, 2002). The loss of specific receptor expression precedes loss of neurons and onset of clinical symptoms. For example, there is downregulation of cannabinoid CB_1 receptors in the basal ganglia of both HD patients and mouse models (Glass *et al.*, 1993; 2000; 2004; Denovan-Wright and Robertson, 2000; Lastres-Becker *et al.*, 2002a,b). Decreased ionotropic and metabotropic glutamate receptor binding in molecules mediating synaptic and intraneuronal signaling in striatum, cortex and other regions is seen in HD mice (Van Dellen *et al.*, 2000b; Luthi-Carter *et al.*, 2002a,b). This evidence implies extensive inter- and intra-neuronal signaling deficits, with pre- and post-synaptic function disruptions in HD mice. Altered synaptic densities with associated pathological changes in neuronal morphology in postmortem HD patient brains and various lines of transgenic HD mice is observed (Ferrante *et al.*, 1991; Guidetti *et al.*, 2001; Klapstein *et al.*, 2001 Spires *et al.*, 2004). Medium spiny neurons, the cell population in the striatum most affected in HD (but is also highly affected in PD), receives extensive input from the cortex - which supports the notion that the cumulative effects of receptor changes and synaptic dysfunction could mediate chronic neurotoxicity.

Using striatal primary neuronal cultures from HD94 mice (*i.e.*, *htt* exon 1 protein with a 94 polyglutamine repeat, HD94-*htt*), Díaz-Hernández (2004) showed that HD94-*htt* immunocytolocalization was primarily in nuclei and intraneuronal aggregates. Also, there was no change in proteasome proteolytic activity and no change in expression of LMP2 proteasome subunits of the cultured cells, unless IFN-γ was added - indicating that the induction of proteasome activity requires an extacellular mediator. This synergism between an immune modulator (IFN-γ) and the ubiquitin-proteasome system is important in the pathogenesis associated with HD.

Huntington's disease-like 2 (HDL2) is an autosomal dominantly inherited disorder (Margolis *et al.*, 2001) caused by trinucleotide repeat expansions (Holmes *et al.*, 2001), and bears strong resemblance to clinical phenotype, inheritance pattern, and neuropathological features of HD. The genetic mutation associated with HDL2 has been characterized as a CTG/CAG trinucleotide repeat expansion within the *junctophilin-3* (JPH3) gene on chromosome 16q24.3 (ibid). Intranuclear inclusions immunoreactive for expanded polyglutamine repeats are observed in the brains of HDL2 patients (Walker *et al.*, 2002). JPH3, the protein product of the gene associated with HDL2, would seem to modulate calcium regulation in junctional membranes: mice lacking JPH3 show impaired motor coordination (Nishi *et al.*, 2002). Walker *et al.* (2003) have described the clinical features of the disorder to include chorea, dystonia, parkinsonism and cognitive deficits with marked phenotypic variations in the patients. With one exception (patient of Mexican descent), all patients reported are of African ancestry, with no patients of Caucasian ancestry yet found (Bauer *et al.*, 2002). The hereditary HD 'phenocopies' include distinguishing features: dementia, depression, chorea, dystonia, parkinsonism, expanded/normal HDL2 triplets and acanthocytosis (Kambouris *et al.*, 2000; Moore *et al.*, 2001; Richfield *et al.*, 2002).

The potential for neurogenesis through transplantation of embryonic neurons or stem cells offers a promising therapeutic strategy for the neurodegenerative disorders (Svendsen *et al.*, 1997; Freed *et al.*, 2001). The discovery of endogenous stem/progenitor cells in the hippocampus and subependymal layer of the basal ganglia in the adult mammlian brain offers the possibility that these undifferentiated cells may generate neurons for cell replacement in HD; neural stem cells in the rodent brain subependymal layer, adjacent to the caudate nucleus, were found to proliferate and differentiate into neurons (Arvidsson *et al.*, 2002; Parent *et al.*, 2002; Curtis *et al.*, 2003). Recently, Curtis *et al.* (2003) examined postmortem control and HD human brain tissue using the cell cycle marker proliferating cell nuclear antigen (PCNA), the neuronal marker βIII-tubulin, and the glial cell marker, glial fibrillary acidic protein (GFAP). They observed a significant increase in cell proliferation in the subependymal layer in HD compared with control brains. The extent of cell proliferation increased with neuropathological severity and increasing CAG repeats in the HD gene, with the HD group. Furthermore, PCNA+ cells were shown to coexpress βIII-tubulin or GFAP, an indication of neuronal and glial cell generation in the subependymal layer of the human brain. Taken together, these findings present evidence for increased progenitor cell proliferation and neurogenesis in the HD adult brain (ibid, but see also Eriksson *et al.*, 1998 and Luthi-Carter *et al.*, 2000).

Recent evidence indicates that environmental factors may modify the onset and progression of HD, and pos-

sibly other neurodegenerative disorders. Both molecular and cellular mechanisms may mediate the polyglutamine-induced toxic 'gain-of-function' and associated gene-environment interplay in HD (Li JL *et al.*, 2003). The key aspects of the disorder seem to include abnormal protein-protein interactions, selective disruptions of gene expression and 'pathological plasticity' of synapses in specific brain regions (*cf*. Hannan, 2004a). The development of "enviromimetics" may mimic the effects of specific environmental stimuli (*e.g.*, environmental enrichment), thereby instigating therapeutic strategies and deepening the interactive understanding and functional significance of neurogenesis (*cf*. Van Praag *et al.*, 2000; Kempermann *et al.*, 2004; see below). Histological quantifications of enrichment studies (*e.g.*, Van Dellen *et al.*, 2000a) indicate the delay of degenerative loss of cerebral volume in HD mice. Further analyses in R6/1 HD mice and early-onset R6/2 HD mice confirm a robust effect of environmental enrichment (Hockly *et al.*, 2003). Nevertheless, a primary conceptualization of the molecular and cellular mechanisms would appear to present a key step in the eventual development of new therapies for HD (Bates and Hockly, 2003; Hersch, 2003). Certainly, questions pertaining to eventual pharmacological therapeutic measures are particularly pertinent (Hannan, 2004b).

Tau-Associated Neurodegeneration

Neurofibrillary tangles are composed of abnormal aggregates of the cytoskeletal protein, tau (Lee *et al.*, 2001; Stamer *et al.*, 2002). In AD, insoluble neurofibrillary tangles composed of hyperphosphorylated forms (see below) of tau accumulate initially within the entorhinal cortex and CA1 subfield of the hippocampus (Grundke-Iqbal *et al.*, 1986; Braak and Braak, 1991). An aberrant folded conformational change in tau, recognized with antibody MC1, appears to be one of the earliest tau pathological events (Jicha *et al.*, 1997; 1999; Uboga and Price, 2000; Weaver *et al.*, 2000). Thus, a variety of alterations in tau, reducing its binding affinity to microtubules, lead to depolymerization of microtubules that contribute to the neuronal loss seen in AD (Drechsel *et al.*, 1992; Biernat *et al.*, 1993; Bramblett *et al.*, 1993). Among the family of microtubule associated proteins (MAPs) are MAP1A, MAP1B, MAP2 and tau - the latter being preferentially located in axons (Binder *et al.*, 1985) and associated in part with cytoarchitectural structure. In a number of neurodegenerative disorders known as tauopathies, tau becomes hyperphosphorylated and forms aberrant fibrillar polymers that deposit in neurons and glia. As described by Ferrer (2004) there are several tauopathies: AD, Pick's disease (PiD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD), and familial frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) (with tau gene FTDP-17 mutation (Spillantini and Goedert, 1998; Buée *et al.*, 2000; Lee *et al.*, 2001; Ingram and Spillantini, 2002; Togo *et al.*, 2002; Ghetti *et al.*, 2003). In all of these tauopathies there is increased expression of stress-activated kinase, c-jun *N*-terminal kinase (SAPK/JNK) and kinase p38 in neurons and glia containing hyperphosphorylated tau. Because there is increased expression of phosphorylated SAPK/JNK and p38 in the region of ßA4 deposits and in the brain of transgenic mice (Tg2576) with the double APP Swedish mutation, ßA4 amyloid is thought to trigger stress kinase activation and tau phosphorylation in the region where there are amyloid deposits.

A recent study by Avila *et al.* (2004) shows through *in vitro* experiments that phosphotau is actually prone to assemble into fibrillar polymers. However, because the tau gene is transcribed into nuclear RNA by alternative splicing, there are a variety of mRNA species which, when transcribed, result in the production of tau isoforms with different numbers of exons. Some isoforms are expressed only in early ontogeny and other isoforms are preferentially expressed (Andreadis *et al.*, 1995; Yoshida and Goedert, 2002). Tau isoforms expressed in peripheral nerves are different from those expressed in brain (Nuñez, 1988; Goedert *et al.*, 1992c).

Caspases, cysteine aspartate proteases critically involved in apoptosis, may be divided into initiator and executioner caspases; the former initiating apoptosis by activating executioner caspases, and the latter acting on downstream effector substrates causes apoptotic progression leading to cell shrinkage, nuclear fragmentation and membrane blebbing (Kerr *et al.*, 1972). Much evidence now indicates that caspases are activated in the AD brain (Rohn *et al.*, 2001; Su *et al.*, 2001), and that components of the neuronal cytoskeleton, including tau, are targeted by caspases following apoptotic stimuli (Fasulo *et al.*, 2000; Gastard *et al.*, 2003; Utsumi *et al.*, 2003). Though the role of tau caspase-cleavage remains unresolved, there is evidence implicating it in tangle pathology (Gamblin *et al.*, 2003). Recently, Rissman *et al.* (2004) tested the hypothesis that caspase-cleavage of tau is an early event in tangle formation in both AD and a transgenic model of the disorder. They found that caspase-cleaved tau catalyzes filament formation, adopts a conformation seen in

early-stage tangles, and may be hyperphosphorylated. Caspase-cleavage of tau colocalizes with amyloid-ß (Aß) and developing tangles in both transgenic mice and AD brain. In primary cortical neurons, Aß-induced caspase activation leads to tau cleavage and generates tangle-like morphology (Rapoport *et al.*, 2002; Rohn *et al.*, 2002; but see also McLaughlin, 1997). The hyperphosphorylation of tau, through promotion of paired helical filament self-assembly, is the prevailing hypothesis in the development of tangle pathology (Alonso *et al.*, 2001). Findings by Rissman *et al.* (2004), however, have demonstrated that ΔTau may be phosphorylated after caspase-cleavage, implying that the production of Δtau does not preclude subsequent phosphorylation.

Brain tau isoforms are divided into two domains: the projection domain containing the amino terminal two-thirds of the molecule [subdivided into regions either proline-rich or with a high number of acidic residues]; and the microtubule-binding domain containing the carboxy terminal one-third of the molecule [subdivided into either a true tubulin-binding region or an acidic carboxy terminal region].

Tau assembly and aggregation as a hyperphosphorylated aggregate occurs primarily in a 2-step process. Several kinases are involved in tau hyperphosphorylation. The first step in hyperphosphorylation of tau proceeds via a proline directed protein kinase (PDPK kinase) (*e.g.*, GSK3) or a non-PDPK kinase (NPDPK kinase) (*e.g.*, protein kinase A, PKA). Lithium, an inhibitor of GSK3, and also H89, an inhibitor of PKA, each inhibit formation of phosphorylated tau. In a second step, in the presence of hydroxynonenal (HNE) - a lipid peroxidation product oft found in Alzheimer patients, hyperphosphorylated tau forms aggregates. A 'rescue' pathway, involving dephosphorylation of phosphotau by phosphatase 2A (PP2A), prevents aggregation since dephosphorylated tau does not assemble. When this pathway is inhibited *in vitro* by okadaic acid, there is an increase in phosphorylated tau aggregates (Avila *et al.*, 2004).

Extracellular signal-regulated mitogen-activated protein kinases (MAPK/ERK1 and MAPK/ERK2, p44, p42), stress-activated protein kinases c-jun *N*-terminal kinase (SAPK/JNK) and p38 kinase phosphorylate tau (Goedert *et al.*, 1997; Lovestone and Reynolds, 1997; Reynolds *et al.*, 1997a,b; 2000; Jenkins *et al.*, 2000; Buée-Scherrer and Goedert, 2002).

Expression of MAPK/ERK, SAPK/JNK, p38 in AD

The fibrillization of tau protein is a hallmark injury in AD (Kopke *et al.*, 1993; Buee *et al.*, 2000; Garcia-Sierra *et al.*, 2000; Galvan *et al.*, 2001). In addition to the cAMP-dependent protein kinase pathway (Shaywitz and Greenberg, 1999), the MAPK cascade also activates CREB (Impey *et al.*, 1999; Roberson *et al.*, 1999). The signaling components of the MAPK cascade, including the extracellular regulated protein kinase (ERK), are expressed at high levels in the brain and CNS (Banes *et al.*, 1999; Wolf *et al.*, 1999). MAPK, that play a critical role in intracellular signaling, are activated by phosphorylation in response to external stressors. For example, traumatic brain injury increases significantly phosphorylated-ERK, but not p38 MAPK levels in rat brain (Otani, 2004). Furthermore, there is an ever-increasing consensus that indirect activation of monoamine receptors by antidepressant treatments increase neurotrophic factors that activate the MAPK cascade (Pullarkat *et al.*, 1998; Russo-Neustadt *et al.*, 1999; Thome *et al.*, 2000). These monoamine receptors may influence the MAPK pathway independent of neurotrophic factors, *e.g.*, through the influence of noradrenaline on the phosphorylation of ERK (Zhong and Minneman, 1999; Tolbert *et al.*, 2003).

There is increased expression of MAPK/ERK, SAPK/JNK, p38 and PKA in tau deposits and NFTs (Hensley *et al.*, 1999; Knowles *et al.*, 1999; Perry *et al.*, 1999; Zhu *et al.*, 2000; 2001; 2002; Atzori *et al.*, 2001; Ferrer *et al.*, 2001a,b; Pei *et al.*, 2001) and in AD, PSP, CBD and PiD (Atzori *et al.*, 2001; Ferrer *et al.*, 2001a,b; Hartzler *et al.*, 2002). Phosphorylated protein kinases are associated with tau deposits in AGD (Ferrer *et al.*, 2003). In a transgenic mouse expressing tau protein with three mutations in the tubulin binding region, present in FTDP-17 disorders, lithium reduces formation of filamentous tau aggregates. This, therefore, indicates that GSK3 kinase plays a role not only in tau phosphorylation but also in tau assembly per se (Avila *et al.*, 2004). In reference to preventive treatments of neurodegenerative disorders, GSK3 and H89 represent potential targets for preventing formation of tau aggregates in tauopathies, such as AD.

Neurofibrillary degeneration and related tauopathies, *e.g.*, frontotemporal dementia, correlates directly with dementia (Tomlinson *et al.*, 1970; Tolnay and Probst, 1999). The activity of protein phosphatase (PP)-2A is compromised in the AD brain and may be one cause of the abnormal hyperphorylation of tau and the consequent neurofibrillary degeneration. Recently, Li L *et al.* (2004) demonstrated that the uncompetitive NMDA antagonist, memantine, inhibits and reverses the PP-2A inhibition-induced abnormal hyperphosphorylation and accumulation of tau in organotypic cultures of rat

hippocampal slices. These restorative effects of memantine were not detected with either 5,7-dichlororkynurenic acid or D(-)-2-amino-5-phosphopentanoic acid, NMDA receptor antagonists that are active at the glycine binding site and the glutamate binding site, respectively. Their results indicate: (i) memantine inhibits and reverses PP-2a inhibition-induced abnormal hyperphosphorylation of tau/neurofibrillary degeneration, and (ii) the compound may have applications for treatment of AD and other tauopathies.

ALZHEIMER'S DISEASE

AD is characterized by loss of synapses and the presence of senile plaques and neurofibrillary tangles (NFTs) in brain (Duyckaerts, 2004). NFTs are composed of hyperphosphorylated tau aggregates of paired helical filaments (PHFs) (Duyckaerts, 2004). The main component of senile plaques is amyloid-ß (ßA or ßA4), derived from α- or γ-secretase cleavage of the ßA precursor protein (ß-APP) protein (Herreman *et al.*, 2000; Zhang *et al.*, 2000). APP transgenic mice are characterized by Aß deposition, amyloid plaques and learning deficits (Games *et al.*, 1995; Hsiao *et al.*, 1996; Sturchler-Pierrat *et al.*, 1997; McGowan *et al.*, 2003). Amyloid suppresses the induction of genes critical for memory consolidation in APP + PS1 transgenic mice (Dickey *et al.*, 2004). Thus, the deposition of ßA-protein is fundamental to the development of AD, on the basis of genetic evidence (Selkoe, 1996; Helpern *et al.*, 2004; Kowalska, 2004; Reddy *et al.*, 2004). For example, Yamamoto *et al.* (2004) report that a membrane-mimicking environment, generated in the presence of detergents or a ganglioside, is sufficient for induction of amyloid fibril formation from soluble Aß-protein. Hereditary variants of the protein, caused by amyloid precursor gene mutations, including Dutch (E693Q), Flemish (E692G) and Arctic (E693G) types, demonstrate mutually different aggregation behaviour in these environments. The Arctic type Aß-protein, in contrast to the wild-type and other variant forms, shows a markedly rapid and higher level of amyloid fibril formation in the presence of sodium dodecyl sulphate or GM1 ganglioside, all of which indicates the presence of favourable local environments for Aß-protein fibrillogenesis.

There are considered to be five genetic risks for AD: 1) mutations in the APP gene, 2) mutation in *presenilin 1* gene, or 3) in the *presenilin 2* gene (Bertran and Tanzi, 2003), 4) alleles for apolipoprotein (ApoE), and 5) polymorphism of a gene on chromosome 12 encoding α-2 macroglobulin. Recent association studies showed that single nucleotide polymorphisms in the glutathione-*S*-transferase Ω1 and glutathione-*S*-transferase Ω2 gene regions are associated with age-of-onset in both AD and PD (Li YJ *et al.*, 2003). The presence of insoluble protein aggregates within neurons is a common hallmark of the neurodegenerative disorders (Taylor *et al.*, 2002). These aggregates may represent a common final pathway by compromising the axonal transport through trapping of molecules which are essential for cellular function, such as 'chaperons' and the proteases. The AD-causing mutations in the APP render valuable clues as to disease mechanisms, further implying the relevance of Aß-protein toxicity in sporadic AD. The highly penetrant mutations of early-onset AD and/or PD implicate either Aß or APP, and α-synuclein as a cause of toxicity and loss of neurons. The APOE*E4 as a risk factor for AD brings cholesterol and lipid metabolism into the equation for Aß toxicity (LaDu *et al.*, 2000). Glutathione-*S*-transferase Ω1 appears involved in the activation of interleukin 1, and glutathione-*S*-transferase Ω1 variations may alter the efficiency of interleukin 1 post-translational processing (Laliberte *et al.*, 2003), contributing to inflammatory, neurotoxic hazard.

Human ApoE gene at locus 19q13.2, associated with AD and coronary heart disease, exists in three common isoforms, E2, E3, and E4, which are encoded by a gene (APOE) with three alleles, ε2, ε3, and ε4, with varying frequencies in populations around the globe (Corbo and Scacchi, 1999). Individuals who are carriers of the ε4 allele are known to be at an increased risk for developing late onset AD (Strittmatter *et al.*, 1993; see Kamboh, 2004), although the mechanism remains unknown. ApoE binds Aß and it has been suggested that ApoE is involved in the initiation of Aß fibril formation (Evans *et al.*, 1995). This function has been demonstrated *in vitro* (Ma *et al.*, 1996), with E4 exhibiting the strongest promotion of fibril formation. The carriership of ε4 is implicated too in the presentation of motor neuron disease where possession of at least one copy is associated with bulbar rather than limb onset (AlChaalabi *et al.*, 1996). ApoE exerts an isoform specific antioxidant role: E2 providing most protection and E4 least protection (Miyata and Smith, 1996), consistent with the observation that there is a markedly later age-of-onset seen among ε2 carriers, as opposed to ε4 carriers (Corder *et al.*, 1993; but see also Schneider *et al.*, 1995). For example Sleegers *et al.* (2004) found a strong familial clustering of various forms of dementia in an isolated Dutch population, of which a high percentage of late-onset AD could be explained by

APOE*4, but 55% of the origin was still unknown (see also Kamboh, 2004). ApoE is associated with the deposition of Aß which is more prevalent with ε4 carriers; expression of ApoE is dramatically elevated in response to brain injury and damage (Nicoll *et al.*, 1995).

Age-of-onset, gender and ethnicity appear relevant aspects of the apoE genotype. There is a gender difference in prevalence and age-of-onset for AD: women with the ε3ε4 genotype show age-of-onset as early as ε4ε4 homozygotes whereas in men the ε3ε4 genotype provides the same (late) onset as ε3ε3 (Payami *et al.*, 1996). Finally, the carriership of ε4 has been implicated also in Pick's disease, corticobasal degeneration and progressive supranuclear palsy (Schneider *et al.*, 1995). The greater the number of ε4 alleles an individual possesses, the younger the age of the individual at disease onset. Age-of-onset of AD tends to occur later among persons with the ε2/ε3 genotype (Borgaonkar *et al.*, 1993; Corder *et al.*, 1993, 1994). Carriers of the ε4 allele have a higher risk of AD than individuals with the most common genotype, ε3ε3, and carriers of the ε2-allele have a lower risk (Ou *et al.*, 1998; Wilson *et al.*, 1994). These tendencies appear in various ethnic groups. In a meta-analysis, it was reported that the apoE ε4 effect is greater among Caucasians than among Japanese older populations (Farrer *et al.*, 1997). In populations aged 80 years or more, the frequency of occurrence of ε4 carriers is lower and that of ε2 is higher, than in younger people (Asada *et al.*, 1996; Gerdes *et al.*, 2000). Tanaka *et al.* (2003) have carried out case-control studies to ascertain gene-environment interactions in disease-susceptibility for AD based on the apolipoprotein E gene in Japan that identify gene and environmental risk factors.

The AD brain is afflicted by extensive oxidative stress, as indexed by protein oxidation, lipid peroxidation, DNA and RNA oxidation, advanced glycation end-products, protein nitration, mitochondrial abnormalities, reactive oxygen species (ROS) formation and other markers (*e.g.*, Markesbery, 1997; Butterfield *et al.*, 2001; Butterfield and Lauderback, 2002;).The 42-amino acid form of the Aß [Aß(1-42)], central to the pathogenesis of AD, is coupled to the extensive oxidative stress that is expressed in the form of Aß-associated free radical induced neurodegeneration in the AD brain (Varadarajan *et al.*, 2000). Aß-peptide toxicity is mediated by free radical damage to cell membranes (Mark *et al.*, 1997; Bruce-Keller *et al.*, 1998; Reich *et al.*, 2001). Consistent with a free radical process, Aß causes lipid peroxidation in brain cell membranes, and this is blocked by free radical antioxidants (Butterfield *et al.*, 1994; Avdulov *et al.*, 1997; Butterfield, 1997; Koppal *et al.*, 1998; Lauderback *et al.*, 2001; Pocernich and Butterfield, 2003). The oxidative and neurotoxic properties of Aß(1-41) seem to be derived from the single methionine residue at position 35 of the 42-mer (Yatin *et al.*, 1999; Butterfield and Kanski, 2002). Thiobarbituric acid reactive substances (TBARS), an index of lipid peroxidation, are increased in the frontal lobe, but not cerebellum of AD patients (Subbarao *et al.*, 1990), as well as being increased in the sensory and occipital cortex (Balazs and Leon, 1994). Reactive aldehydes like 4-hydroxynonenal (HNE), a major product of lipid peroxidation, and 2-propenal (acrolein), due to free radical attack on polyunsaturated fatty acids, are longer lasting than free radicals and may act at sites distant to their formation (Butterfield and Stadtman, 1997; Pocernich and Butterfield, 2003). Free HNE (Markesbery and Lovell, 1998) and protein-bound (Montine *et al.*, 1997; 1998; Sayre *et al.*, 1997) concentrations are elevated in several brain regions and ventricular csf in AD patients, and may relate to APOE allele type (Montine *et al.*, 1999; Tamaoka *et al.*, 2000). Finally, glutathione *S*-transferase, with a high detoxifying activity against HNE (Bruns *et al.*, 1999), is significantly reduced in the AD brain (Lovell and Markesbery, 1998). Significantly, a vast accumulation of evidence indicates that Aß(1-42)-induced lipid peroxidation, with resultant free radical and reactive aldehyde formation, must offer an important factor in the neurodegeneration observed in AD (Butterfield *et al.*, 2002), not least with regard to characteristics of environment (Kanski *et al.*, 2002).

In the context of brain aging and dementia, nitric oxide (NO) and other reactive nitrogen species seem to also play crucial roles in neuromodulation, transmission and plasticity but are involved too in neurodegeneration and inflammation. Acute and chronic inflammation causes elevated NO formation and nitrosative stress. Both NO and its toxic metabolite, peroxynitrite, inhibit the mitochondrial respiratory chain, with resultant cellular energy deficiency and cell death; peroxynitrite susceptibility is dependent upon reduced intracellular glutathione and cellular stress resistance pathways. Neurons have evolved integrated processes, 'longevity assurance' processes, that are composed of "vitagenes" and include members of the HSP system, *e.g.*, HSP70 and HSP32, that detect and control diverse types of stress. HSP32, heme oxygenase-1 (HO-1), induction generates the potent antioxidant, bilirubin, thereby offering neuroprotective potential pertinent to role of the HO-1 gene in age-related oxidative and nitrosative stress. Consistent with the notion of endogenous cellular defense mechanisms (Calabrese *et*

al., 2004), the maintenance/recovery of vitagenes activity may delay the aging process and decrease the occurrence of age-related neurodegenerative disorders.

Cholinergic dysfunction remains a consistent feature of AD (*e.g.*, Coyle *et al.*, 1983). The co-localization of acetylcholinesterase (AchE) with Aß deposits in AD brains (Mesulam, 1986; Moran *et al.*, 1993), as well as the capability of AChE to affect the processing of APP (Mori *et al.*, 1995) and aggregation of Aß peptides (Inestrosa *et al.*, 1996) offers a link between APP and cholinergic neurotransmission (Blusztajn and Berse, 2000). Transgenic mice expressing the *C*-terminal fragment of the APP showed increased tissue levels of AChE (Sberna *et al.*, 1998). Double transgenic expressing both mutations of human APP and α-synuclein showed a prominent age-dependent degeneration of cholinergic neurons in the nucleus basalis and caudate-putamen (Masliah *et al.*, 2001). In the APP23 mouse model of cerebral amyloidosis, modest Aß plaque-associated cholinergic changes in the aged neocortex were observed, but no loss of cholinergic basal forebrain neurons (Boncristiano *et al.*, 2002). Luth *et al.* (2003) using ultrastructural detection of ChAT-immunostaining in cerebral cortical sections of transgenic mice demonstrated degeneration of ChAT-immunoreactive fibres in the environment of Aß plaques and activated glial cells that suggests the involvement of Aß and/or inflammation in the specific degeneration of cholinergic synaptic structures (see also Apelt *et al.*, 2002).

One conceivable approach towards treating/preventing AD is through immunization against Aß. In APP transgenic mice, Aß immunization reduced the Aß burden. Also, in AD patients, Aß immunization reduced the number of senile plaques and number of tau-immunoreactive neuritis, and reduced expression of SAPK/JNK-P and p38-P, but did not alter the number of NFTs in the cerebral cortex (Nicoll *et al.*, 2003; Ferrer *et al.*, 2004). Pharmacogenomic studies predict that the therapeutic response in AD is genotype-specific and that the expression of genes involved in the regulation of drug metabolism can affect efficacy and safety issues in pharmacotherapy. Constitutive genomics may be determinant for onset of dementia in conjunction with environmental and cardiovascular factors (*e.g.*, Cacabelos *et al.*, 2004). The accumulation of novel approaches to models of AD pathology, pertaining to efficient gene-delivery systems using lentiviral vectors, offers much in bettering our understanding of mechanisms in AD as well as in identifying additional targets for AD treatments (Shaughnessy *et al.*, 2004).

NEUROGENESIS AND THE ROLE OF ANTIDEPRESSANT EFFECTS

Adult neurogenesis in the hippocampus has been documented in birds (Barnea and Nottebohm, 1994), rodents (Altman and Das, 1965; Kuhn *et al.*, 1996) and primates, including humans (Eriksson *et al.*, 1998; Gould *et al.*, 1999; Kornack and Rakic, 1999). The production of new neurons is influenced by a diversity of environmental and behavioural conditions (McEwen, 1994; Cameron and McKay, 1998; Arvidsson *et al.*, 2001; Taupin and Gage, 2002; Brown *et al.*, 2003). The insertion of new neurons can modulate the capability of the adult hippocampal network to handle the storage of new memories or the clearance of old memories (Feng *et al.*, 2001; Shors *et al.*, 2001). Linking neurogenesis to neuronal activity may adapt the adult network both to physiological demands and pathological insults (Parent *et al.*, 1997; Gould *et al.*, 2000, 2001; Temple, 2001; Alvarez-Buylla *et al.*, 2002). Neurogenesis may be modulated by hormones, growth factors, neurotransmitters as well as by environmental factors, and under pathological conditions (Liu J *et al.*, 1998; Aberg *et al.*, 2000; Van Praag *et al.*, 2000, 2002). Furthermore, several interventions that modulate hippocampal neuronal activity levels affect also adult neurogenesis (Cameron *et al.*, 1995; Van Praag *et al.*, 1999; Madsen *et al.*, 2000; Seaberg and Van Der Kooy, 2002). Nevertheless, gene-environment interplay in neurogenesis poses a number of methodological considerations (Cooper-Kuhn and Kuhn, 2002; see also Kandel, 2001). In addition to *in vivo* studies, cells with stem cell properties have been characterized extensively *in vitro* after isolation from different brain regions and at different stages of development (Reynolds and Weiss, 1996; Palmer *et al.*, 1999). These isolated cells have been shown to differentiate into neurons under defined culture conditions and to synapse with each other or with co-cultured neurons (Mistry *et al.*, 2002; Song *et al.*, 2002a, b).

There is obvious environmental influence on our mood in general and in the development and maintenance of mood disorders and other psychiatric illnesses. As stated by Reid (2004) "...plastic brain mechanisms should prove central to contemporary conceptualizations of psychiatric disorder". Drevets *et al.* (1997) localized an area of abnormally reduced activity and ~45% reduced grey matter volume in the prefrontal cortex ventral to the genu of the corpus callosum in both familial unipolar and bipolar depressives. Atropy was also seen in the left temporal cortex, including hippocampus, of people with recurrent major depression (Sheline *et al.*, 1996; Shah *et al.*, 1998). The observations that pharmacologi-

cal interventions may enhance neurogenesis are particularly interesting, since antidepressant treatments are efficacious (Malberg *et al.*, 2000), in addition to electroconvulsive therapy (*e.g.*, Madsen *et al.*, 2000). The implication of neurogenesis in cognition has prompted attempts to ascertain the role of the cholinergic system on neurogenesis. Cooper-Kuhn *et al.* (2004) have proposed that the cholinergic system plays a survival-promoting role for neuronal progenitors and immature neurons within regions of adult neurogenesis, similar to the effects observed previously during brain development (*cf.* Mirescu *et al.*, 2004).

Stress and the Hippocampus

Stress hormones are associated with damage to hippocampal neurons (Reagan and McEwen, 1997; Sapolsky, 2000). In rats housed in isolation for several weeks, there was a reduction in the number of new neurons in the dentage gyrus and corresponding impairment of spatial learning; while a return to group housing reversed these deficits (Lu *et al.*, 2003). Other forms of stress mirror the effects of isolation housing (Gould *et al.*, 1997; 1998; Tanapat *et al.*, 2001).

In people with post-traumatic stress disorder (PTSD) there is a tendency for a decrease in hippocampal volume (Bremner, 2002), although there is controversy about whether reduced hippocampal volume precedes stress-induced PTSD; or is a consequence of PTSD.

Complicating the debate about genes and environment is the issue of epigenetic inheritance. For example, female rodents with high licking-and-grooming surrogate mothers themselves become high licking-and-grooming mothers with low anxiety offspring regardless of whether their biological mother was low or high licking-and-grooming (Francis *et al.*, 1999; see Gross and Hen, 2004). However, offspring of high licking-and-grooming mothers raised by low licking-and-grooming mothers did not have high anxiety (Anisman *et al.*, 1998; Liu D *et al.*, 2000).

Although antidepressants produce their pharmacological effect after the first dose (*i.e.*, block of serotonin reuptake by selective serotonin reuptake-inhibitors, SSRIs; enhanced serotonin reuptake after tianeptine; selective block of norepinephrine reuptake; block of norepinephrine and serotonin reuptake by tricyclic antidepressants; inhibition of monoamine oxidase [MAO] by MAO-inhibitors), there is ordinarily a delay of at least 10-14 days before the onset of antidepressant action. This time delay indicates that there is probably some reorganization occurring in brain, and this is now thought to be due to increased neurogenesis - an effect seemingly produced by all antidepressants, prominently in the hippocampus (Malberg *et al.*, 2000; Brody *et al.*, 2001; Czeh *et al.*, 2001; Martin-Aparacio *et al.*, 2001; Santarelli *et al.*, 2003). Similarly, lithium increased grey matter volume in the brain of bipolar patients (Moore *et al.*, 2000).

Gene-environment interactions can take several different forms. In boys with a low activity allele of the MAO-A gene, maltreatment was a risk factor for adult anti-social behavior, while maltreatment was not a risk for later anti-social behavior in boys with the high activity allele (Caspi *et al.*, 2002). Also, genetics may indirectly influence environmental situations. For example, a person with a particular genetic make-up may choose a stressful social or work environment known to increase the risk for major depression (Kendler and Karkowski-Shuman, 1997). Kendler *et al.* (2001) estimate that up to 20% of tenetic influence over psychiatric outcome could be by *outside-the-skin* mechanisms *vs* the *within-the-skin* route.

CONCLUSIONS

The interplay of genetic inheritance and environmental influence is becoming evermore complex. In many experimental paradigms it seems to be increasingly difficult to separate a genetic influence from an environmental influence on development. Some environmental exposures (*i.e.*, a priming process) produce life-long outcomes with there being virtually no 'biological footprint' (*i.e.*, anatomical or identifiable biochemical change). And the recognition of neurogenesis in adult brain further complicates all of these elements with facets of new learning and memory - to add to the uncertainty of gene-environment interplays. Exacting studies, carefully controlling the above elements, are needed to resolve the many complexities in addressing the most important components that influence neuronal processes leading to (or preventing) neuronal apoptosis and other biological events attending neurodegenerative or psychiatric disorders.

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