

## 29. Neurotoxicity and functional concomitants in neurodegenerative brain disorders

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Neurotoxicity may play a role in several of the dopamine (DA) disease states. The connection is not difficult to envision for Parkinson's disease, is arguable for schizophrenia but tenuous for depression and drug abuse. The role of DA in epileptic seizures was not touched upon in this volume but should be considered (see below). In this closing chapter, progressive neurodegeneration will be applied as a central conceptual 'hub' from which the various chapters of this volume may radiate. Concurrently, another concept, that of 'neurodegenerative overlap', will be borne in mind. For example, Uitti *et al.* (1995) have discussed 'shared' epidemiological, clinical and neuropathological features in Parkinson's, Alzheimer's and Motor Neuron disease that, far from giving distinct etiologies and pathogeneses, have produced individual patients showing features of a neurodegenerative overlap syndrome (but note also Eisen and Calne, 1992). These patients also had a strong family history of neurodegenerative disease supporting a putative genetic link.

Possible neurodegeneration has been entertained even in discussions of dopaminergic substrates in drug abuse; different aspects are treated in the chapters by Fernández-Ruiz *et al.* (Chapter 17), Koob *et al.* (Chapter 20), Manzanares *et al.* (Chapter 12) and, to a lesser extent, in that by Broekkamp and Berendsen (Chapter 11). Fernández-Ruiz *et al.* pursue the comparative neurodevelopmental course of fetuses, neonates, juveniles and adults, pertaining to cannabinoid exposure effects upon DA and other neurotransmitters (*e.g.*, Fernández-Ruiz *et al.*, 1994, 1995; Rodríguez de Fonseca *et al.*, 1993). These studies show long term changes in behavioural and dopaminergic activity (Navarro *et al.*, 1994, 1995; Rodríguez de Fonseca *et al.*, 1994; Romero *et al.*, 1995) as well as the neuroendocrine alterations (Romero *et al.*, 1994) following early cannabinoid exposure. Koob *et al.* (Chapter

20) discuss investigations of DA receptor subtype involvement in the reinforcing properties of cocaine, as shown previously (Caine and Koob, 1994a,b). Thus, the activation of DA receptor subtypes in the shell of the nucleus accumbens was examined through application of DA antagonists or agonists, locally or systemically, to block or potentiate the effects of cocaine.

Manzanares *et al.* (Chapter 12) have set out to determine the effects of agonists acting at kappa opioid receptor sites of the DA nigrostriatal, mesolimbic, tuberoinfundibular, periventricular and hypophysial systems; this is a further demonstration of the breath of the neurobiological analyses pursued in this volume. The effects of kappa agonists (*e.g.*, U-50,488), antagonists (nor-binaltorphimine) and dynorphin antibodies upon behaviour, dopaminergic activity (Manzanares *et al.*, 1991a, b, 1992a, b) and the role of gender differences (Manzanares *et al.*, 1993) are reviewed in their chapter. Sigma receptor sites also are important in terms of the DA pathways outlined by Manzanares *et al.* Thus, Weiser *et al.* (1995) found that the sigma ligands, 1,3-di-o-tolylguanidine and (-)-deoxy-N-benzylnormetazocine, caused significant increases in contralateral turning and in tyrosine hydroxylase activity. They showed that the occupancy of sigma receptors in the substantia nigra is implicated in activation of DA synthesis in dopaminergic terminals in the striatum; these results were interpreted as supporting the contention that sigma activity in the substantia nigra activates DA-mediated responses in the striatum. Maj *et al.* (1993) indicated that 1,3-di-o-tolylguanidine and rimcazole (also a selective sigma ligand) produced behavioural effects like those seen with typical neuroleptic compounds, *i.e.*, antagonism of apomorphine-induced aggression and climbing, and antagonism of apomorphine-induced catalepsy. Further, selective sigma agonists, *e.g.*, (+)-pentazocine, 1,3-di-o-tolylguanidine, decreased the firing rate of DA neurons in the substantia nigra whereas the selective antagonist, BMY 14802, increased firing rate (Steinfels *et al.*, 1989; but see also Terleckyj and Sonsalla, 1994, below). In contrast, Broekkamp and Berendsen (Chapter 11) have analysed the functional consequences resulting from 5-HT pathway innervation of DA nerve fibres, and vice versa (Hervé *et al.*, 1988; Ferré *et al.*, 1994), using the catalepsy, circling-behaviour, and microdialysis methods (but see also Chapter 16, by Luthman *et al.*). These findings have reinforced the other evidence that 5-HT<sub>1A</sub> receptor stimulation indirectly enhances activity only in the mesolimbic DA system, as postulated from electrophysiological data (Arborelius *et al.*, 1993).

The issue of neurotoxicity is addressed directly through examination of the phenylethylamine derivatives, methamphetamine, methylenedioxymethamphetamine and amphetamine, and the amphetamine derivatives, *e.g.*, methylenedioxymphetamine, parachloroamphetamine and fenfluramine in the chapter by Lew *et al.* (Chapter 9). As indicated by Lew *et al.*, the prevention of neurotoxicity embraces a 'rich' pharmacology. For instance, in the dopaminergic neuropathology produced by methamphetamine, the sigma receptor ligand (+/-)-BMY 14802

attenuated the neurotoxic effects although clorgyline did not do so (Terleckyj and Sonsalla, 1994). These authors found also that (+/-)-BMY 14802 pretreatment of mice prevented the reduction of D<sub>1</sub> and D<sub>2</sub> receptor number produced by systemic administration of N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. In this regard, the recent study by Sprague and Nichols (1995) demonstrating the protection afforded by L-Deprenyl against serotonergic neurotoxicity induced by 3,4-methylenedioxymethamphetamine further broadens the range of possible neuroprotective agents. Luthman *et al.* (Chapter 16) investigate the consequences of perinatal 6-hydroxydopamine on the function and neurochemistry of the developing DA systems. Thus, the adaptive changes accruing to DA and 5-HT innervation in various brain regions are described in the light of other related evidence (Kostrzewa, 1995; Luthman *et al.*, 1994; Luthman *et al.*, 1995). To continue a characterisation of the neonatal 6-hydroxydopamine-induced denervation method, the chapter by Archer *et al.* (Chapter 6) examines movement disorders that may result from a dopaminergic-glutamatergic imbalance, by examining behavioural effects of glutamate antagonists in lesioned and nonlesioned animals.

## Schizophrenia

Some evidence for a neurodegenerative component in schizophrenia has been found (*e.g.*, Deakin *et al.*, 1989; Jesta and Lohr, 1989). An interesting case is made by Olney and co-workers (Farber *et al.*, 1995; Olney and Farber, 1995) for glutamate receptor involvement that has produced much critical analysis in the chapter by Crow (Chapter 28), [but examine also the chapter by Deakin (Chapter 23) in this context]. Recently, Ellison (1995) has argued for and described a phencyclidine-dizocilpine model of schizophrenia involving different aspects of neurotoxicity. However, neurodegeneration may be of limited explanatory power in this respect (see Crow, 1995). Crow's chapter also lays to rest the DA hypothesis of schizophrenia, at least in its more rudimentary form. On the other hand the chapter by Sokoloff and Schwartz (Chapter 10) offers the possibility for a more complex DA hypothesis. These authors outline the primary structure, gene organisation, signalling systems and neuropharmacology of the multiple dopamine receptor-sites over different brain regions, comparing genetic linkage with putative disorder states, function and receptor-binding affinities (Sautel *et al.*, 1995; Sokoloff and Schwartz, 1995). The evidence for a neurodevelopmental component in schizophrenia (as described also in Crow's chapter) seems to enjoy a broader base (*e.g.*, Chua and Murray, 1995; but see also Davis *et al.*, 1995) and the chapter by Davies and Murray (Chapter 27) outlines the evidence and future goals most succinctly. The notion of schizophrenia as a neurodevelopmental disorder where damage to brain regions that occurs early in development may interact with

subsequent maturational processes that occur later was proposed by Weinberger (1987) and derives strong support from several sources (Jorgen Engel and Jianhua Zhang, personal communication). Possibly, the chapters by Andreasen *et al.* (Chapter 26) and Ebmeier and Ebert (Chapter 25) provide descriptions of what may be the end-point of a neurodegenerative process. Each article presents the methodology to eventually derive such an objective.

Three major neurobiological differences between schizophrenic patients and normals are found, *i.e.*, reduced hemispheric asymmetry, hypofrontality (Weinberger and Berman, 1988) and ventricular enlargement (*e.g.*, Bornstein *et al.*, 1992). Despite the less-than-satisfactory attempts to relate hypofrontality to specific symptoms, hypofrontality seems to possess robust support from imaging evidence (see Chapter 26). Many researchers stress the circuits that may be affected, *e.g.*, fronto-temporal-basal ganglia or the prefrontal-temporolimbic cortex. Others have investigated the occurrence of schizophrenic symptoms (auditory hallucinations, thought disorders) with temporal lobe abnormalities (Barta *et al.*, 1990; DeLisi *et al.*, 1989; Shenton *et al.*, 1992). Using the dichotic listening task as modified for studying brain disorder conditions (Hugdahl, 1988, 1992; Hugdahl and Wester, 1992; Reinvang *et al.*, 1994), Hugdahl and co-workers (Green *et al.*, 1994) recently studied a consonant-vowel version of the dichotic test in hallucinating and nonhallucinating patients. It was found that the nonhallucinating patients display a right-ear advantage (REA) as would be expected from a normal left hemisphere superiority. On the other hand, hallucinating patients did not demonstrate an ear advantage, possibly indicative of failure of left temporal superiority, in keeping with reduction in brain asymmetry. However, a subgroup of patients that was tested both during hallucinations and their absence, did not show variations in brain asymmetry. Given the conflicting results concerning dichotic listening performance and psychotic states (*e.g.*, Bruder, 1983; Colbourne and Lishman, 1979; Lishman *et al.*, 1978; Wexler, 1986), the application of dichotic listening to analyses of the same patients when hallucinating or not may offer potential advantages. The wealth of evidence (*cf.* Hugdahl, 1995) showing that DA disease states, among others, affect dichotic listening might suggest that this technique would be useful in pharmacological studies.

Recently, in an attempt to reconcile two major hypotheses of brain disorder in schizophrenia, the abnormal structural neurodevelopment and functional concomitants, Weinberger and Lipska (1995) have utilised the evidence from postmortem studies as well as from neuropsychological and neuroimaging analyses, to propose a model of schizophrenia involving a structural-functional dysconnection of the prefrontal-temporolimbic cortex region. Thus, morphometric studies have indicated changes in the mesial temporal (Alschuler *et al.*, 1990) and prefrontal cortex (Benes and Bird, 1987), abnormal development in the parahippocampal cortex (Akbarian *et al.*, 1993; Arnold *et al.*, 1991; Jakob and Beckmann, 1986) and a laminar shift in neuronal density in the cingulate cortex

(Benes *et al.*, 1991). *In vivo* imaging studies, employing computer-tomography and magnetic resonance imaging, have demonstrated consistent reductions of cortical volume in the brains of schizophrenics (Zigun and Weinberger, 1993), most particularly in the mesial temporal cortex (Bogerts *et al.*, 1990; Breier *et al.*, 1992), prefrontal cortex (Andreasen *et al.*, 1986; Raine *et al.*, 1992) and with widespread abnormalities over the cerebral cortex (Weinberger *et al.*, 1979; Zipursky *et al.*, 1992). Similarly, neuropsychological tests have shown widespread deficits, not just limited to memory and attention (*e.g.*, Gold *et al.*, 1992; Goldberg *et al.*, 1990, 1993; Saykin *et al.*, 1991). The model proposed by Weinberger and Lipska (1995) outlines a dysconnectivity, rather than a 'non-connectivity' view of the disorder, similar in some respects to the 'dysmyelination' observed in metachromatic leukodystrophy disorder (Hyde *et al.*, 1991).

To this end, Weinberger and co-workers (*e.g.*, Lipska and Weinberger, 1993a; Lipska *et al.*, 1992, 1993, 1994) have utilised the neonatal administration of the excitotoxin, ibotenic acid, to the ventral hippocampal region causing relatively limited destruction and sparing presynaptic afferents, synapses and transit fibres. It must be noted that the lesion, cortical and developmental, influence behaviour normally associated with DA function but in a time-dependent fashion: prepuberty there was no evidence of deficits but postpuberty the same animals showed enhanced reactions to environmental stress and amphetamine (here Chapter 22 by Kalivas and Sorg makes relevant reading). Similarly, both apomorphine-induced stereotypy and resistance to neuroleptic-induced catalepsy emerge after puberty (Lipska and Weinberger, 1993b). Castration before puberty did not prevent the development of these abnormal behaviours (Lipska and Weinberger, 1994a). Weinberger (1995) has suggested that these results implicate brain 'programs', multiple complex refinements in neuronal and glial processes that plateau by early adulthood, of necessity for functional maturation of intracortical connectivity. It appears, therefore, that a developmental dysfunction of the temporo-limbic cortex involving circuit-dysconnectivity may be induced in rats to exhibit post-puberty abnormalities resembling the DA disease state of schizophrenia. Genetic-environmental factors influencing DA functions were found to be relevant: a rat-strain characterised by hyperresponsivity to DA interventions required a more limited lesion to exhibit the behavioural syndrome (Lipska and Weinberger, 1994b). Finally, the expression of this particular syndrome is antagonised by neuroleptic compounds, and interestingly, the supersensitivity to DA agonists following chronic neuroleptic administration (compared to non-lesioned rats) that was evident after haloperidol withdrawal was not seen following clozapine withdrawal (Lipska and Weinberger, 1994c). Taking into account findings that antipsychotic agents modulate DNA transcription in a region of the nucleus accumbens that receives the converging inputs of the prefrontal and temporolimbic cortices (Fink-Jensen and Kristensen, 1994; Robertson and Fibiger, 1992; Robertson *et al.*, 1994), Weinberger and Lipska (1995) have suggested that an

indirect compensation for the malfunctioning communication between those regions, as offered for instance by clozapine, may provide a therapeutic mechanism for drug action.

Both Alzheimer's disease and schizophrenia involve a neuropathology of the entorhinal-hippocampus limbic regions (*cf.* Kovelman and Scheibel, 1984). Structural changes in the hippocampus, parahippocampal gyrus and entorhinal cortex but also other limbic regions have been shown in schizophrenic patients (reviewed by Bogerts, 1993; Jeste and Lohr, 1989). It has been suggested that possibly all schizophrenics present abnormalities in medial temporal lobe structures around the entorhinal cortex (Roberts, 1991). Factor analyses of symptoms of schizophrenia (Malla *et al.*, 1993) indicated three clusters of symptoms: psychomotor poverty (poverty of speech, flatness of affect, decreased spontaneous movement); disorganisation (disorder of thought-form and inappropriate affect); and, reality distortion (delusions and hallucinations). PET-imaging studies indicated that the left parahippocampal region, including the entorhinal cortex, correlated with schizophrenia symptoms, particularly the left parahippocampal gyrus correlated strongly with reality distortion (Liddle *et al.*, 1992). In Alzheimer's, the entorhinal cortex is severely affected (Braak and Braak, 1991). The extent of hippocampal and entorhinal cortex degeneration of these patients has been correlated with performance, smell identification and odor match-to-sample tests (Kesslak *et al.*, 1991). Other evidence points to olfactory dysfunctions, with regard to anatomical sites and functional concomitants, in schizophrenia and Alzheimer's (*e.g.*, Doty, 1991; Feldman *et al.*, 1991; Kopala and Clark, 1990; Kopala *et al.*, 1993). Parallel alterations in site and/or function in these disorders serve to highlight the possible contribution of the phencyclidine-dizocilpine model (Ellison, 1995), albeit on a rather circumstantial basis, in the disease state in the light of aged-schizophrenia populations (but see also the chapter by Davies and Murray). Certainly, the connection between glutamate and neurotoxicity will remain under focus.

## **New antipsychotic compounds**

The chapters of Ellenbroek and Cools (Chapter 21), Jackson *et al.* (Chapter 15), Ögren (Chapter 13) and Goldstein (Chapter 14) deal with preclinical aspects of antipsychotic compound development. Of these, the chapter by Ellenbroek and Cools examines in detail the validity of animal models used currently, for example latent inhibition and prepulse inhibition (*cf.* Hoffman and Ison, 1980; but see also Jackson *et al.* in this regard). The latter model (*cf.* Geyer and Markou, 1995; Geyer *et al.*, 1990; Lipska *et al.*, 1995) has rapidly been gaining wide acceptance as an antipsychotic test situation with practicality, reliability and validity. Clinical validity has been exhibited in studies where schizophrenic patients and 'schizotypal'

subjects demonstrated weaker prepulse inhibition than normals (*e.g.*, Braff *et al.*, 1992; Bolino *et al.*, 1994; Cadenhead *et al.*, 1993). Prepulse inhibition circumstantially implicates DA systems in schizophrenia since amphetamine (Mansbach *et al.*, 1988) or DA D<sub>2</sub> agonists (Peng *et al.*, 1990) are disruptive, and these effects, induced also by apomorphine, are blocked by D<sub>2</sub> antagonists (Swerdlow *et al.*, 1991). Similarly, Johansson *et al.* (1994, 1995, and chapter by Jackson *et al.*) demonstrated the effects of antipsychotic compounds, *e.g.*, remoxipride, upon disruptions induced by phencyclidine. Recently, Humby *et al.* (1996) monitored extracellular DA levels, using *in vivo* brain microdialysis, from rat nucleus accumbens during prepulse inhibition. It was shown that startle stimuli reduced accumbens DA relative to baseline but that a prepulse (before-startle) inhibited the reduction. They concluded: acoustic startle stimuli induced transient reductions of DA in the accumbens and the prepulse stimuli blocked these neurochemical changes (Humby *et al.*, 1996). In their chapter, Ellenbroek and Cools also describe results from other, more genetically-oriented test models. In particular, the derivation of an "apomorphine-susceptible", as opposed to an "apomorphine-unsusceptible" strain of rats has provided both fascinating results as described in the chapter, and promise of future test models.

The other three chapters, by Jackson *et al.*, Ögren and Goldstein, are more focussed upon predictive validity and the identification, synthesis and establishment of new series of compounds for treating schizophrenia, especially "clozapine-like" drugs (but see Moore *et al.*, 1993). The chapters by Moghaddam *et al.* (Chapter 24) and Kalivas and Sorg (Chapter 22) seek to integrate neurobiological circuitries for both clinical and preclinical accounts of schizophrenia and psychosis. Moghaddam *et al.*, implicate NMDA-receptor modulation in the prefrontal cortex by studying delayed alternation tasks following MK-801 or ketamine plus treatment with DA antagonists (Bennett *et al.*, 1995; Krystal *et al.*, 1995). Here, as in other papers (see below) the glutamatergic control of DA release and its relevance to disorders are presented. In Kalivas and Sorg, the functional interconnections of the hippocampal-corticostratial-mesencephalic circuit are investigated for understanding the development and expression of the disorder. Kalivas and co-workers (Chapter 22) have both here and earlier (Steketee and Kalivas, 1991; Steketee *et al.*, 1991) outlined conditions through which stress or psychostimulants may modulate psychotic behaviour, in this case by local injections of pertussis toxin into the ventral tegmental area, thereby enhancing sensitization. Zhang *et al.* (1995) applied pertussis toxin locally into the VTA and studied effects upon acoustic startle and prepulse inhibition. By itself, pertussis toxin caused minimal effects upon startle or prepulse inhibition but in combination with d-amphetamine caused a disruption. Apomorphine, whether administered to sham or toxin treated rats disrupted prepulse inhibition. It was suggested that pertussis toxin may 'disinhibit' the mesocorticolimbic DA system thereby mobilising psychostimulant-mediated psychotic behaviour. Thus, neurodevelopment and

genetic factors are complemented by environmental agents (Davis *et al.*, 1995; Kalivas, 1995). Finally, the interactions between putative antipsychotic compounds and behavioural alterations induced by MK-801 are described in the chapter by Klint *et al.* (Chapter 7).

One recurring theme has been the importance of clozapine, not just as a 'treatment-of-choice' atypical neuroleptic (*cf.* Safferman *et al.*, 1991), but also as a molecular-pharmacological profile upon which to design other potential antipsychotic compounds. In this regard, emerging preclinical evidence has an interesting story to tell, for example as in the chapters by Ellenbroek and Cools (Chapter 21), Jackson *et al.* (Chapter 15), Goldstein (Chapter 14), Ögren (Chapter 13) and Klint *et al.* (Chapter 7). One may query: how does clozapine behave in an established, traditional test of antipsychotic potential such as two-way conditioned active avoidance (*cf.* Arnt, 1982; Fibiger *et al.*, 1975; Janssen *et al.*, 1966; Kuribara and Tadokoro, 1981)? Unlike the "typical" neuroleptic compounds, chlorpromazine and haloperidol, clozapine antagonised conditioned avoidance responding (CAR) at respective doses about 6 and 18 times lower than it antagonised apomorphine-induced (1 mg/kg) hyperactivity or stereotypic behaviour, but see also the paper by Blackburn and Phillips (1989). Despite the suggestion of D<sub>1</sub>-mediation in the CAR effects of clozapine (Iorio *et al.*, 1991), other evidence implicates the high affinity of clozapine for nondopaminergic receptors (Coward *et al.*, 1989; Leysen *et al.*, 1993; Meltzer *et al.*, 1989). Thus, an interactive role of muscarinic, alpha-adrenergic, 5-HT<sub>2</sub>, or 5-HT<sub>1A</sub> receptors with one or more, most likely D<sub>2</sub>, DA subreceptors in CAR has been proposed.

## Parkinson's disease

Alberto Portera-Sánchez' paper (Chapter 2) is quite unique within the volume, dealing as it does with the somewhat difficult epidemiology of PD. He covers descriptive epidemiology, describing both incidence and prevalence, mortality, and analytic epidemiology, including risk factors, race and ethnic source, well-water and pesticides, MPTP consumption, cellular energy metabolism (but see below), medications as etiological factors, infections, genetic/hereditary influences, the associations of PD with other diseases and smoking, the enigma of dietary factors and a possible geographic delineation (see also Chapter 6, Archer *et al.*). Here, the resemblance to Wilson's disease and chronic manganese poisoning (Huang *et al.*, 1989, 1993), with clinical features including bradykinesia, rigidity, impaired postural reflexes and dystonia, ought to be considered. Recent evidence indicates that autonomic disturbances (sympathetic skin response and RR interval variation) occurring in manganism are both less frequent and less severe than those of PD (Chu *et al.*, 1996). In the search for an etiology of PD, incidence and mode-of-inheritance epidemiological studies, *i.e.*, genetic epidemiology, highlight a



powerful environmental influence (Wilhelmsen and Wszolek, 1995), but see also the interesting editorial by Uitti (1995).

Regarding possible etiological factors, it is of interest that delta9-tetrahydrocannabinol-induced catalepsy in mice has been suggested as an experimental model of parkinsonism (Kinoshita *et al.*, 1994a), similar to that induced by haloperidol. Here, however, it was found that the competitive NMDA antagonists (*e.g.*, CPP and AP-7) enhanced the cataleptic effect. In contrast, the noncompetitive NMDA antagonist, MK-801, blocked this cataleptic effect (Kinoshita *et al.*, 1994b). It should be remembered that the NMDA antagonists blocked both D<sub>1</sub> and D<sub>2</sub> antagonist induced catalepsy (Moore *et al.*, 1993; see also Chapter 6 by Archer *et al.* for a review). In connection with the Ca<sup>++</sup> involvement (discussed in the chapter by Portera-Sanchez), recent evidence by Kupsch *et al.* (1995) describes an astonishing degree of protection by the Ca<sup>++</sup>-L-type channel blocker, nimodipine, against MPTP-induced neurotoxicity at the level of the substantia nigra, but not the neostriatum, in mouse brains: in the nigral tissue, the number of tyrosine hydroxylase-positive cells/section was unaffected; in the striatum, DA, DOPAC, HVA and 5-HT were all affected. Concomitantly, survival rates of MPTP-nimodipine mice were in excess of those of MPTP mice, as inferred in the paper by Portera-Sánchez. He has produced a valuable background to the papers that present the clinical (López-Lozano, Chapter 3) and preclinical accounts (Chapters 4, 5, and 8, respectively, by McArthur *et al.*, Fredriksson *et al.*, and Fredriksson *et al.*).

Fredriksson *et al.* (Chapter 8) discuss the status of DA agonist effectiveness in animal models of PD, including the neonatal 6-OHDA lesion, the unilateral nigral 6-OHDA lesion with turning behaviour, reserpine-induced depletions in CD-1 mice, and MPTP-induced selective DA lesions in C57/BL6 mice. The emerging picture is that of a DA D<sub>2</sub> preponderance over DA D<sub>1</sub>, and Fredriksson *et al.* make an interesting case for closer analysis of the currently available medication, cabergoline. This compound is further analysed in primate studies in the paper by McArthur *et al.* (Chapter 4), where it is shown to have produced dramatic changes in the behaviour of MPTP-treated primates. The viability of neuroprotective factors is discussed by Fredriksson *et al.* (Chapter 5) who failed to obtain neuroprotective effects with noncompetitive and competitive glutamate antagonists, although L-Deprenyl and alpha-phenyl-butyl-tert-nitrone (PBN) were efficacious (see also below). Unfortunately, the fascinating results of Scheel-Kruger *et al.*, presented at the meeting, were not available. It was shown that the novel and potent DA reuptake inhibitor, NS 2214, administered 30 min prior to MPTP, offered protection 10-20 times in excess of that by other candidates, *e.g.*, nomifensine, diclofensine and GBR 12909. It will be of great interest to ascertain the protective potential of this compound under conditions of chronic or subchronic administration.

## Cognition

The chapter by Izquierdo and Chaves (Chapter 18) relates to several aspects of DA disease states by addressing the cognitive state in preclinical studies, considerations that were touched upon by several clinical papers and by previous reviews of different types of memory (Izquierdo and Medina, 1995). In describing pharmacological effects on working versus reference memory following manipulations in frontal, temporal, amygdala, hippocampal and septal sites 1995; (McCarthy, 1995; Squire and Alvarez, 1995), this chapter provokes a possible reappraisal of the function (or dysfunction) of memory in DA disease state. The issue of memory loss in DA disease states needs to be pursued more explicitly and is being pursued by some researchers (Gibb, 1993; Gibb and Lees, 1991).

The chapter by Beninger and Nakonechny (Chapter 19) reviews the results of studies examining effects of  $D_1$ - and  $D_2$ -like receptor agonists or antagonists upon incentive learning in operant conditioning. These studies included: 1) responding for food and water; 2) responding for electrical stimulation of the brain; 3) responding to self-administer drugs; 4) responding for conditioned rewards; and, 5) place conditioning. They demonstrate that both DA  $D_1$ - and  $D_2$ -like antagonists impair control of the responding by rewarding stimuli but that the effects of  $D_1$ -like antagonists may be more specific to reward. For DA agonists the situation is more complex: operant responding was augmented by  $D_2$ -like agonists, but impaired by  $D_1$ -like agonists. To demonstrate the involvement of cAMP-dependent protein kinase activation in incentive learning, they show that doses of the inhibitor, Rp-cAMPS, blocked place preference conditioning obtained from intra-accumbens injections of amphetamine (20  $\mu$ g/0.5  $\mu$ l/side). Within this context, mechanisms of neuroplasticity, and possibly neurotoxicity may be distinguished eventually.

Pertinent both to frontal lobe dysfunction in DA disorders and cognitive deficits in PD (*cf.* Dubois *et al.*, 1991; Karayanidis, 1989), performance requiring intact frontal lobe function is disrupted in DA disease state (Brown and Marsden, 1990; Gotham *et al.*, 1988; Taylor *et al.*, 1990). An attentional model, suggesting a deficient attention resource allocation for internally-guided behaviour, has been outlined (Brown and Marsden, 1988, 1991); the attentional impairment (*e.g.*, Goldenberg, 1990) was considered secondary to an impairment in central 'executive' system. To separate the cognitive impairment from motor components, studies employing event-related potentials (ERPs) have investigated attention to a low probability target tone, 'oddball' stimulus against a background of frequent non-target stimuli (Amabile *et al.*, 1990; Ebmeier, 1992; Ebmeier *et al.*, 1992). The target tone elicits a negative peak after around 200 ms, "N2", and a large positive peak after around 300 ms, "P3", post stimulus. P3 latencies are prolonged in PD patients (Hansch *et al.*, 1982), although following the exclusion of dementia P3 latency was not delayed (O'Donnell *et al.*, 1987). P3 latency prolongation has also

been correlated with the 'off', as opposed to the 'on', phase (Starkstein *et al.*, 1989). N1 amplitude has been derived as a general state measure of stimulus discrimination capacity, as well as stimulus feature selection ability (Näätänen and Picton, 1987). Recently, Wright *et al.* (1996) studied non-demented, idiopathic PD patients using an auditory 'oddball' procedure. PD patients showed attenuations of N1 amplitude to both target and non-target tones, suggestive of an early information-processing deficit. N2 latency was lengthened which was taken to indicate an increase in the time required to categorize stimuli. In view of the notion that N1-amplitude generation is located in the frontal cortex (Näätänen, 1992) and the implications of frontal lobe dysfunction in PD (*e.g.*, Owen *et al.*, 1992), the importance of both the disease state and site will undoubtedly unfold (see also Heindel *et al.*, 1989; Morris *et al.*, 1988). Thus, Fournet *et al.* (1996) have investigated medicated PD patients on a dual task paradigm that minimised motor effort and combined verbal, visual or spatial span with two conditions of articulatory suppression. A reduction in central processing resources, as reflected by less span of attention in PD patients, was not accompanied by a deficit of the central executive, possibly due to a task-dependency of use of medication.

The cognitive disturbances that overlap PD, dementia and Alzheimer's disease are of strikingly recurring incidence (Beatty *et al.*, 1989; Boller *et al.*, 1980; Pirozzolo *et al.*, 1982; but see also Chapter 5, by Fredriksson *et al.*). Recently, in an attempt to separate the locus of memory deficits in dementia in PD, Hugdahl *et al.* (1993) adapted the dichotic listening task to present different word-lists to either right or left ear, alternatively forwards or backwards, in order to measure memory performance of young subjects and of PD patients and age-matched controls. The purpose was to assess whether dysfunctions of long-term memory (Riklan *et al.*, 1989) or immediate memory (Wilson *et al.*, 1980) predominated. The word-lists presented by Hugdahl *et al.* (1993) allowed measurement of free recall so that 'primacy', *i.e.*, better recall of the early part of the list, or 'recency', *i.e.*, better recall of the later part of the list, effects could be compared. The results were unambiguous: (1) mean percent correct overall recall for male and female subjects was a declining function of age and PD condition. (2) While recency effects were clearly present for all three groups of patients, the primacy effect of patients presented word-lists to the right ear was notably absent in PD patients and initially disrupted in the older subjects. The authors concluded that the memory impairments of older subjects and PD patients (in increasing severity) point to disruptions of the long-term store and, most relevant to considerations of DA disease states, could be related *specifically to the DA disorder condition*. Certainly, their findings support these conclusions.

## Free radicals, energy metabolism and protective devices

Investigations of free radical involvement in neuronal cell death are proliferating exponentially (Coyle and Puttfarcken, 1993). The observed neurotoxicity of various agents appears to have developed from defective energy metabolism (Albin and Greenamyre, 1992; Tipton and Singer, 1993). Several brain disorder conditions are implicated. Thus, Huntington's disease, an inherited disorder characterised by progressive striatal atrophy accompanied by severe neuronal loss and gliosis, may be derived from NMDA-related mechanisms. For example, intrastriatal injections of quinolinic acid, an NMDA receptor agonist, induces several neurochemical and histological features that characterise the disorder (Beal *et al.* 1991; Ferrante *et al.* 1993). Energy loss conditions, that may arise through a variety of mechanisms, could lead to activation of NMDA receptors, and excitotoxic neuronal damage (Zeevalk and Nicklas, 1990, 1991). In PD, understanding of the disorder has been advanced significantly by investigations of the 'MPTP condition', clinically and in the laboratory (Langston, 1985; Snyder and D'Amato, 1986). MPTP, administered systemically or locally, causes selective destruction of the nigrostriatal, and to a lesser degree the mesolimbic, dopaminergic neurons in primates and some rodent species or strains (Heikkila *et al.*, 1984; Langston *et al.*, 1984). On being taken up by the nigrostriatal system, MPTP is converted by the action of MAO-B to MPP<sup>+</sup>, a potent presynaptic DA uptake substrate (Tolliver *et al.*, 1993) whose uptake properties are enhanced through binding to neuromelanin (D'Amato *et al.*, 1986). Its selective action may derive from the specific ability of the nigrostriatal dopaminergic nerve terminals to take up and retain MPP<sup>+</sup> at concentrations high enough to bring about neuronal death. Here, accumulating, it disrupts oxidative phosphorylation by inhibiting Complex I of the mitochondrial electron transport chain (Gluck *et al.*, 1994), which in turn leads to decreased levels of ATP (Chan *et al.*, 1991). ATP-loss has been assayed also in mouse brain synaptosomes following incubation in the presence of either MPTP or MPP<sup>+</sup> (Scotcher *et al.*, 1990).

The evidence has been gathered from various agents that hinder free radical accumulation: For example, Dykens *et al.* (1987) showed that damage to cerebellar neurons, induced by kainic acid, could be attenuated by such agents as superoxide dismutase, allopurinol, or hydroxyl radical ( $\cdot\text{OH}$ ) scavengers like mannitol. The putative involvement of such compounds as NMDA-antagonists, L-Deprenyl or PBN is discussed above (Fredriksson *et al.*, Chapter 5). In a recent study, Fredriksson and Archer (1996) studied the effects of subchronic administration with the spin trap agent, PBN, upon behavioural deficits in spontaneous motor activity and radial maze performance in aged (15-month-old) mice. It was found

that the compound alleviated both types of deficit, as compared with young (3-month-old) mice. Thiffault *et al.* (1995) found that MPTP induced a three-fold increase in superoxide dismutase activity in the striatum of C57 BL6 mice.

### ***Effects of S-PBN upon lesions induced by various agents***

A number of different compounds that impair mitochondrial energy metabolism may induce secondary excitotoxic lesions in the striatum (Storey *et al.*, 1992; Beal *et al.*, 1993a; Schulz *et al.*, 1994): MPP<sup>+</sup>; malonate, an inhibitor of Complex II of the mitochondrial electron transport chain; 3-acetylpyridine (3-AP), an inhibitor of nicotinamide; and the so-called excitotoxins: alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), N-methyl-D-aspartate (NMDA) and kainic acid. Malonate is a competitive inhibitor of succinate dehydrogenase that may induce striatal lesions through excitotoxicity. S-PBN, administered in 3 injections of 100 mg/kg, 1 hr before and 2 and 5 hr after intrastriatal injections, significantly protected against the striatal lesions (as indexed by lesion volume) induced by NMDA (200 nmol), AMPA (25 nmol), kainic acid (2.5 nmol), 3-AP (18 umol), MPP<sup>+</sup> (90 nmol) and malonate (3 umol) (Schulz *et al.*, 1995). The neuroprotective effects of S-PBN prior to malonate were found to be a function of 1, 2 or 3 injections of the 100 mg/kg dose. Combining S-PBN with MK-801 (2 x 4 mg/kg) increased the striatal protection against malonate and 3-AP induced lesions while MK-801, by itself, gave a similar degree of protection to that of S-PBN. Further, S-PBN (100 mg/kg) injected ip 1 hr before malonate attenuated the formation of 2,3-dihydroxybenzoic acid (DHBA), a specific marker for  $\cdot\text{OH}$  radicals. However, the loss of ATP in the lesioned striatum was not protected by S-PBN (3 x 100 mg/kg). MK-801, but not S-PBN, reduced drastically the spontaneous firing rate of neurons in the caudate nucleus (Schulz *et al.*, 1995). The effects of MK-801 in counteracting malonate-neurotoxicity are in contrast to the failure to protect against the effects of MPTP (Fredriksson *et al.*, Chapter 5).

Kainic acid and NMDA enhance the generation of free radicals *in vivo* (Hammer *et al.*, 1993; Sun *et al.*, 1992). Bondy and Lee (1993), studying brain synaptosomes using a fluorescent probe demonstrated that exposure to NMDA, AMPA or kainic increased oxidative stress, whereas Lafon-Cazal *et al.* (1993a) indicated that NMDA exposure caused superoxide generation in cerebellar neuron cultures. Further, the exposure of rat striatum to glutamate has been shown to yield hydroxyl radicals and provoke striatal damage (Lancelot *et al.*, 1995). It is known that several putative free radical scavengers, *e.g.*, alpha-tocopherol, ascorbic acid, ubiquinone, or 21-amino steroids have attenuated glutamate toxicity *in vitro* (Favitt *et al.*, 1992; Majewska and Bell, 1990; Puttfarcken *et al.*, 1993). The neuroprotective effects of spin-trapping agents, such as S-PBN and PBN, against glutamate and NMDA toxicity, *in vitro*, are evident (Yue *et al.*, 1992), not least

because they showed ready penetration into rat brain following administration (Cheng *et al.*, 1993). Further, Knecht and Mason (1993) found that these compounds reacted with unstable free radicals to produce nitroxides, as imaged with electron paramagnetic resonance.

### ***Effect of inhibitors of nitric oxide synthetase on MPTP-toxicity***

Recently, Schulz *et al.* (1995) studied three aspects of MPTP-induced neurotoxicity: (1) whether or not 7-nitroindazole (7-NI), a potent and selective inhibitor of neuronal nitric oxide synthetase (NOS), *in vivo* and *in vitro* (Babbedge *et al.*, 1993; Moore *et al.*, 1993) could inhibit the depletion of DA and metabolites following MPTP, systemically. (2) The content of nitrotyrosine in relation to tyrosine as an index of peroxynitrite generation after MPTP treatment. (3) The ability of 7-NI to antagonise the production of nitrotyrosine. MPTP was administered to groups of mice either 4 x 20 mg/kg or 6 x 10 mg/kg, at 2-hr intervals. 7-NI (25 or 50 mg/kg) or peanut oil was administered 12 hr before the first MPTP injection and every 8 hr for 48 hr after the final injection. The compound produced a dose-dependent alleviation of DA, homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) loss following both the severe (4 x 20 mg/kg) and moderate (6 x 10 mg/kg) MPTP dose regimes. MPTP (severe regime) also increased significantly the ratio of nitrotyrosine-to-tyrosine in mouse striatum by 31%. Both the 25 and 50 mg/kg dosages blocked completely the elevated ratio of nitrotyrosine-to-tyrosine. Although L-Deprenyl produced an inhibition of MAO-B activity, 7-NI was not shown to do so at all (Schulz *et al.*, 1995) indicating the neuroprotection was independent of the inhibition of this enzyme. Taken together with the finding that mice lacking the neuronal NOS gene are resistant to ischemic injury (Huang *et al.*, 1994), and that transgenic mice with increased dismutase are resistant to MPTP-toxicity (Przedborski *et al.*, 1992), these findings implicate and suggest mechanisms of NO mediation in neurodegenerative disorders.

Nitric oxide has been found to be involved in neuronal cell death in the presence of excessive glutamate stimulation (Dawson *et al.*, 1993; Lafon-Cazal *et al.*, 1993a). Both glutamate and NO are involved in radical formation inducing neurotoxicity mediated through  $\text{Ca}^{++}$  influx. Sawada *et al.* (1996) have investigated dopaminergic and non-dopaminergic neuronal death as caused by glutamate and NO-generating agents in cultured embryonic rat mesencephalon cells. Glutamate produced neurotoxic effects on both dopaminergic and non-dopaminergic neurons, with greater effect on dopaminergic neurons. NO-generating agents (S-nitroso-cysteine and sodium nitroprusside) displayed neurotoxic effects upon the non-dopaminergic neurons. Thus, DA and nonDA neurotoxicity underlying neurodegeneration in the disease state implies a multi-site and agent involvement further complicating attempts at describing etiology.

### ***Neuroprotective potential of current antiepilepsy compounds***

Since dopaminergic neurotransmission is known to be involved in epileptic seizure generation (Turski *et al.*, 1988), and since MPTP-induced DA depletion abolished or reduced strychnine and maximal electroshock seizures, respectively, but not bicuculline or picrotoxin seizures (Fariello *et al.*, 1987), it is not surprising that some anticonvulsive compounds may have relevance for the DA disease states. There are several currently-used agents effective against epileptic seizures that may be found eventually to have some degree of neuroprotective or neurorescue applicability.

First, compounds such as lamotrigine, carbamazepine and phenytoin have been implicated in the inhibition of glutamate release or transmission (*e.g.*, Leach *et al.*, 1986; Potter *et al.*, 1991; Meldrum, 1994; Macdonald, 1995) and in neuroprotection (*e.g.*, Leach *et al.*, 1993). For instance, lamotrigine inhibits veratrine-induced release of glutamate at an IC<sub>50</sub> value of 25  $\mu$ M (Meldrum *et al.*, 1992). Preclinically, the inhibition of veratrine-induced glutamate-release by the lamotrigine analogue, BW1003C87 (IC<sub>50</sub> of 1.6  $\mu$ M) further suggests a protective role against injury-evoked excitotoxicity (Lustig *et al.*, 1992). The effectiveness of lamotrigine, carbamazepine and phenytoin in blocking 4-aminopyridine (4-AP) induced de novo synthesis and release of glutamate, aspartate and GABA was reported recently (Kapetanovic *et al.*, 1995). 4-AP is a voltage-dependent potassium channel blocker that causes tonic-clonic and electrographic seizures *in vivo*, and evokes epileptiform activity and the release of glutamate, aspartate and GABA *in vitro*. Several other compounds, used to treat epileptic seizures, such as phenobarbital, felbamate, valproate, diazepam and ethosuximide were without effect on glutamate synthesis (Kapetanovic *et al.*, 1995). Finally, the ability of lamotrigine to retard the dystonia occurring in response to mild stimulation in a mutant hamster model of generalised dystonia may be due to a simultaneous inhibition of glutamate and GABA release (Richter *et al.*, 1994). In the clinical setting (Zipp *et al.*, 1993), the blocking action of lamotrigine on presynaptic glutamate release may help to explain the putative anti-parkinsonian effect. Felbamate, an anti-convulsive agent that acts as an antagonist at the glycine-binding site of the NMDA receptor complex (McCabe *et al.*, 1993; Rho *et al.*, 1994) has been shown to attenuate haloperidol (D<sub>2</sub>), but not SCH 23390 (D<sub>1</sub>), induced catalepsy in three different tests (Kretschmer, 1994), thereby indicating a further anti-parkinsonian potential of this type of compound. This possibility must not be overlooked since the NMDA-antagonists themselves possess some neurodegenerative properties (*cf.* Olney *et al.*, 1991).

Second, the possible MAO-B inhibitory action of certain antiepileptics should be considered, since an anticonvulsant propensity was reported early on for

MAO-inhibitors (Prockop *et al.*, 1959; Chow and Hendley, 1959). Perhaps the first implication of a putative MAO-B involvement was demonstrated with milacemide (Van Dorsser *et al.*, 1983; Colombo *et al.*, 1990; O'Brien *et al.*, 1994) which was suggested to possess anticonvulsive properties for generalised seizures (Löscher, 1985), despite inconclusive results in humans (Roba *et al.*, 1986). Löscher and Honack (1995) have shown potent anti-seizure effects of the currently viable neuroprotective agent, L-Deprenyl, in amygdala-kindled rats. On the other hand, lamotrigine is known to possess some MAO-B inhibition action, albeit limited. In this regard, it is interesting to observe that lamotrigine (38 mg/kg, sc, ED<sub>50</sub>=6 mg/kg) protected against DA depletion induced by a mild dose of MPTP (15 mg/kg, sc), as did phenytoin at a dose of 67 mg/kg (Jones-Humble *et al.*, 1994); both compounds have MAO-B inhibitory properties (Azzaro and Gutrecht, 1975; Jossan *et al.*, 1987). A similar protective effect of phenytoin (50 mg/kg) and phenobarbital (50 mg/kg) against MPTP-toxicity (30 mg/kg), but not diazepam (20 mg/kg), sodium valproate (300 mg/kg) or carbamazepine (25 mg/kg) has been observed (Melamed *et al.*, 1986). These authors suggested a probable mediation via MAO-B inhibitory action. In contrast, carbamazepine (156 mg/kg), riluzole (33 mg/kg) and nicardipine (0.1 mg/kg), the Ca<sup>++</sup> channel blocker, were without effect; note however, the regionally-selective effects of nimodipine, described above.

Third, antiepileptic compounds may exert neuroprotective properties through modulation of sodium, potassium and/or calcium channels, as has been shown for lamotrigine. Use-dependent inhibition of neuronal sodium channels has been observed for carbamazepine (McLean and Macdonald, 1986), for phenytoin, which reduces the frequency of sustained repetitive firing of action potentials in isolated neurons maintained in culture (Macdonald, 1988; McLean and Macdonald, 1983), and for lamotrigine (Leach *et al.*, 1986). It should be noted that the peripherally-acting L-type Ca<sup>++</sup> channel blocker, nifedipine, has an anti-ischemic activity. Phenytoin, too, inhibits preferentially L-type calcium currents in cardiac and skeletal muscle (Rivet *et al.*, 1990). These studies focus upon the important role of Ca<sup>++</sup> in neuronal cell death (Orrenius and Nicotera, 1994). It has been shown too that the new anticonvulsant compound, zonisamide, while increasing DA, HVA and 5-HIAA levels extracellularly in the hippocampus and striatum, had no effect on Ca<sup>++</sup>-dependent DA release (Okada *et al.*, 1992).

### ***Effects of coenzyme Q10 and/or nicotinamide on defective energy metabolism***

There are several indications that impaired oxidative phosphorylation and energy depletion may produce excitotoxic lesions *in vivo* (e.g., Beal, 1992; Beal *et al.*,



1993b; Greene *et al.*, 1993). Investigations of patients with mitochondrial disorders have suggested possible coenzyme Q10 therapy (Bresolin *et al.*, 1988; Nishikawa *et al.*, 1989) or that administration of nicotinamide, in combination with riboflavin (Penn *et al.*, 1992), may induce both neurochemical and clinical improvements. Coenzyme Q10 is an essential component of the electron transport chain, serving both as electron donor and acceptor (*cf.* Przyrembel, 1987). The potential protective relevance of the compound includes some 'bridging' of electron transport chain defects, as well as improving membrane fluidity and an antioxidant action (Frei *et al.*, 1990). In order to study whether defective energy metabolism contributes significantly to neuronal injury and possible cell death, Beal *et al.* (1994) studied the effects of pretreatment with coenzyme Q10 and nicotinamide, by themselves or in combination, upon lesion volume following malonate-induced striatal lesions. They observed that coenzyme Q10 dose-dependently (200 and 400 mg/kg) reduced lesion volume as did nicotinamide (500 mg/kg), but not riboflavin. A multi-injection procedure (4 injections) produced a clear dose-related protection from 50 up to 250 mg/kg (ip). The combination of coenzyme Q10 (200 mg/kg) with nicotinamide (4 x 200 mg/kg) was more effective than each compound by itself. Malonate-lesioned striatum also showed significant depletions (43%) of ATP compared to non-lesioned striatum. Pretreatment with coenzyme Q10, but not nicotinamide, at the same doses, alleviated the ATP loss. Combining coenzyme Q10 with nicotinamide increased dramatically ATP levels of both the lesioned and non-lesioned striatum (Beal *et al.*, 1994).

These intriguing results by Beal and his co-workers, especially when considered together with their other findings, should be eventually complemented with functional data. The beneficial effects of coenzyme Q10 would seem to include an increased activity of mitochondrial electron transfer *in vivo* and *in vitro* (Nakamura *et al.*, 1989) and ATP production in cultured cardiac myocytes (Okamoto *et al.*, 1993), improvements in some patients with mitochondrial myopathies or encephalomyopathy (Ihara *et al.*, 1989), protection against heart ischemia and reperfusion (Ohhara *et al.*, 1981) as well as glutamate neurotoxicity in cultured cerebellar neurons (Favitt *et al.*, 1992), and, finally, in improving the energy metabolism of patients suffering from mitochondrial cytopathies (Barbiroli *et al.*, 1994). The putative benefits of other compounds affecting neuronal metabolism and synaptic mitochondria are being pursued: For example, the co-dergocrine mesylate, hydergine, has been claimed to enhance stores of ATP (Meier-Ruge *et al.*, 1975), stabilise the cAMP content of nerve cells (Markstein and Wagner, 1978), improve brain glucose utilization (Kawashima *et al.*, 1988; Nagasawa *et al.*, 1989) and cerebral blood circulation (Sinzinger, 1985). All of these investigations serve to demonstrate the increasing weight that is being laid upon the possibility that neuronal energy metabolism and mitochondrial events underlie the functional deficits in neurodegenerative disorders.

Other aspects of metabolism affect MPTP toxicity: oxidative polymorphism of the debrisoquine type requires the isozyme, P450IID6 of the microsomal oxidative complex (Relling, 1989). Defective debrisoquine metabolism may develop PD earlier (Barbeau *et al.*, 1985; Benítez *et al.*, 1990), although this may not necessarily be the case (Gudjonsson *et al.*, 1990; Kallio *et al.*, 1991). Notwithstanding this, a genetic implication (genotype wt/CYP2D6B) involving altered debrisoquine metabolism in PD (Armstrong *et al.*, 1992; Smith *et al.*, 1992) or young-onset PD (Agúndez *et al.*, 1995) suggests that debrisoquine oxidative polymorphism induces differential susceptibility. Further, Alzheimer's disease patients with lewy bodies show an over-representation of the CYP2D6B mutant allele (Saitoh *et al.*, 1995). In the laboratory, it has been shown that dark-adapted female rats, an animal model of impaired debrisoquine oxidation (Al-Dabbagh *et al.*, 1981), are more vulnerable to both MPTP (Jiménez-Jiménez *et al.*, 1991) and tetrahydroisoquinoline (Ohta *et al.*, 1990), both neurotoxins that interfere with debrisoquine 4-hydroxylation (Fonne-Pfister *et al.*, 1987). Recently, Jiménez-Jiménez *et al.* (1996) investigated the acute effects of MPTP (10, 20 or 30 mg/kg, injected at 12 hr intervals) in ovariectomized and laparotomized female dark-adapted rats. It was found that ovariectomy reduced the percentage of animals surviving and ovariectomy + MPTP reduced survival further, and, additionally reduced DA and 5-HT and metabolite levels in the striatum. However, ovariectomy altered debrisoquine metabolic rates, *i.e.*, through a partial blockade of depletion in surviving rats, thereby inducing a resistance to MPTP in dark-adapted rats. Despite the potential consequences of these results for considerations of neurotoxicity and neuroprotection, several questions remained to be solved; for example, why is a species, rats that is insensitive to MPTP being employed?

In the aging ('neurodegenerative') process, several parameters of synaptic mitochondrial morphology - total synaptic contact area, the fraction of cytoplasmic volume occupied by mitochondria, their numerical density, etc. - are shown to be affected (*cf.* Bertoni-Freddari *et al.*, 1993; Scheff *et al.*, 1990). The situation is reflected by clinical evidence (Parker *et al.*, 1989; Schapira *et al.*, 1990; Shoffner *et al.*, 1991). These synaptic deteriorations of the aging process (DeKosky and Scheff, 1990; Bertoni-Freddari *et al.*, 1990, 1994) remain to be elucidated in what one terms for convenience "DA-related disorders" *i.e.*, PD, Huntington's, schizophrenia and even disorders of drug abuse. In the clinical setting, the alleviation of focal cerebral ischemia or traumatic brain injury has benefitted from the use of preclinical models of stroke (*cf.* Muir and Lees, 1995). Thus, antagonists of NMDA receptors have given consistent neuroprotective effects, whether of the noncompetitive (aptiganel hydrochloride, dextrorphan) or competitive (selfotel, d-CPPene) type. Further, the consideration of these 'ancillary' disease states should provide both constructive and predictive improvements for the treatment arsenal.

## Final comment

The present discussion was initiated with the consideration of DA disease states as neurodevelopment-neurodegenerative afflictions, to a greater or lesser extent influenced by the individual's genetic background. We attempted to align the preclinical clues alongside the clinical realities. Suffice it to say, the observations such as the frontal cortex synaptic morphology changes in aging arouse particular interest in the patient population showing smaller prefrontal cortex size, after corrections for brain size changes (Andreasson *et al.*, 1994), as a final template of disease. Certainly, one essential awareness that the DA disorders meeting provoked may be exemplified by the constant risk factors at molecular, cellular, regional, hemispheric and functional levels that require further analysis in the developmental-neuropathological perspective.

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