Interactive monoaminergic systems in movement disorders

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The chapters assembled to explore the interactive basis of the movement disorders offer a disparate collection of disease states: including monoamine systems in the treatment of the epileptic disorders, newer preclinical options in reversing the hypokinesis of animals with inflicted parkinsonism, neuropharmacological mechanisms underlying symptom-profiles and idiosyncrasies arising from long-term L-Dopa regimes, the multiple dopamine subreceptor systems in concert with other systems in behavioural sensitization as relevant to the disease state, and the receptor changes traumatically induced (denervation or environment-associated) but manifested as a self-injurious behaviour syndrome. This particular disease state, by virtue of the experimental manipulation (the unilateral 6-hydroxydopamine (6-OHDA) DA lesion, is on its neurological basis which is shared with other states like Lesch-Nyhan disease (Nyhan, 1973), and the Gilles de la Tourette syndrome (Robertson, 1992), placed within the section on movement disorders. As shown by the coverage of this animal preparation in the following chapters, the importance of the unilateral 6-OHDA lesion has had profound consequences for the understanding of the disorder state (*cf.* Schwarting and Huston, 1996).

Ebert and Löscher have contributed a comprehensive account (Chapter 33) of monoaminergic involvement in the most well-established animal models of epilepsy. Historically tracing the findings initiated from reserpine administration, they describe indications obtained after manipulations of monoamines against the background of disease-induced shifts of GABA and glutamate dysfunction in excitatory-inhibitory electrochemical balance. The animal models described include: the genetically epilepsy prone rat with audiogenic seizures, the maximal electroshock seizure test, and the tests involving induction of seizures through application of chemical agents such as pentylenetetrazole, pilocarpine or kainic acid, as well as the highly mechanism-oriented kindling model of complex partial seizures. One consensus from the review of numerous studies was that brain noradrenergic

pathways were clearly implicated and to a lesser extent dopaminergic and serotonergic systems, but the major interactive monoaminergic avenue would appear to be provided by noradrenergic-serotonergic systems. Since the synergistic effects of co-administrations of NMDA antagonists and several established and putative anticonvulsant agents with subthreshold or threshold doses of L-Dopa, administered acutely or chronically, respectively, were directed upon by the experiments based upon functional applications of the mouse MPTP model of parkinsonism (Archer and Fredriksson, Chapter 34; Fredriksson and Archer, Chapter 35), a curious link with that of Ebert and Löscher may be noted. As indicated, several converging lines seem compatible with the idea that anticonvulsant agents may provide a dual efficacy as well as neuroprotective benefits.

Behavioural sensitization as a receptor adaptive function to effects of psychoactive drugs in the brain as a property affecting and affected by the disorder was the underlying biological operation that was exploited to gain access to descriptions and explanations for the neurobiological processes investigated by the three chapters considered here. In the chapter by Schmidt and Tzschentke (Chapter 40) that monoamine-glutamate focus shifts to considerations of performance of motor behaviour as opposed to specific alterations (place-learning but not cue-learning impairments) of instrumental maze learning in consequence of regional administrations of dopamine-receptor affecting and NMDA-receptor affecting compounds. They have formulated a working hypothesis of the role of DA in the basal ganglia within this framework: By this, it is assumed that DA does not influence outcome ("what actually happens", p. 6) but rather to indicate the "goodness" or the "badness" the outcome of a stimulus-response turned out to be, thereby assigning DA within the basal ganglia an unique role in facilitating 'wanted' or discouraging ("inhibiting") unwanted behaviour. In examining the induction of catalepsy by haloperidol, they used repeated treatments to cause behavioural sensitization (also referred to as plasticity) and then tested with MK-801 to block plasticity: this did not occur and reviewing other findings (*e.g.*, Wise *et al.*, 1996) they finally conclude that MK-801 rather than blocking sensitization renders it state-dependent.

Cognitive dysfunction in PD seems by some accounts relatively selective (Boyd *et al.*, 1991; Brown and Marsden, 1990), and by a recent estimate (Lieberman, 1997) occurs in 19% of PD patients. For instance, immediate-recall word list learning was defective in early-stage PD (Cooper *et al.*, 1991; Hartikainen *et al.*, 1993; Lees and Smith, 1983). On the other hand, delayed-recall appears normal (Taylor *et al.*, 1987, 1990) or even above normal (Cooper *et al.*, 1991) while persons with minor or absent motor symptoms show neither deficits in immediate or delayed recalled recall (Stern *et al.*, 1990). In view of established deficits accompanying early PD (*e.g.*, Levin *et al.*, 1989) and the involvement of selegiline (Dalrymple-Alford *et al.*, 1995), together with the co-occurrence of the motor symptoms, possibly the range of compounds found effective in MPTP parkinsonism (see Fredriksson and Archer, Chapter 35, above) may be considered too in this context. Further, in recent studies of MPTP/6-OHDA and young and aged mice/rats in tests of instrumental learning and motor behaviour (Fredriksson *et al.*, 1996; Fredriksson and Archer, 1997; Luthman *et al.*, 1997). In the Wisconsin Card Sorting test, untreated early-stage

PD patients show performance deficits (Malapani *et al.*, 1994), both in producing fewer categories and more errors of perseveration (Tsai *et al.*, 1994). These considerations plus the estimate that PD patients with dementia run a 2-5 times greater risk of death (Louis *et al.*, 1997) implicate the seriousness of the disease state. Thus, in this context of dysfunctional cognition in parkinsonism the threat to well-being in dementia complications was highlighted recently by Lieberman (1997) in assessing prevalence of dementia, incidence of dementia and pathology of dementia in PD. The type of dementia involved was regarded as a subcortical type, being distinguished from cortical dementia on the basis of degree, sequence and pattern of cognitive impairment, memory loss, emotional, behavioural and personality change (Brown and Marsden, 1988). Lieberman (1997) postulates two types of PD dementia: (1) characterized by cortical Levy bodies, and (2) characterized by cortical senile plaques and neurofibrillary tangles, and in doing so argues that PD dementia be referred to as a cortical, rather than subcortical, type.

In the chapter by Sokoloff *et al.*, (Chapter 38), three interactive aspects of dopaminergic receptors are described: (1) Coexisting D_1 and D_3 receptors in ventral striatal neurons mediate both synergistic and opposite responses; (2) D_1/D_3 receptor interplay in the induction and expression of behavioural sensitization, and (3) The D1R/D3R interplay in psychiatric disorders: focus on drug abuse and schizophrenia. The second of these aspects is most directly pertinent to the movement disorders and intrinsic to any eventual understanding of the enigmatic vagaries of the L-Dopa response. Chase and Oh (Chapter 39) pursue the theme of sensitization-based adaptations but focus upon regulatory mechanisms that involve the signalling pathways linking the adjacent dopaminergic and glutamatergic receptors of the basal ganglia. Special concern is placed upon the sites of dopaminergic and glutamatergic convergence, the distal dendrites of the medium spiny neurons in the striatum and the neuroanatomical matrices through which substantia nigra pars compacta DA neurons modulate the input via glutamate projections descending from areas of the cerebral cortex. These authors underline the necessity of intermittent rather than continuous L-Dopa (sensitization characteristic) in the motor response alterations of the hemiparkinsonian rats, the putative enhanced NMDA receptor sensitivity and the signal transduction cascades involving cyclic AMP-protein kinase A (PKA) in the particular form of receptor plasticity incorporated in the disorder and its substrate (Oh *et al.*, 1997).

As indicated by Casas *et al.*, (Chapter 36) and Prat *et al.*, (Chapter 37) self-injurious behaviour (often referred to as Lesch-Nyhan disease), is a neurological-psychiatric disorder with similarities to several other conditions (*cf.* Luthman *et al.*, 1989, 1991, 1996). In an interactive sense, self-injurious behaviour covers several neurotransmitter systems but has been associated typically with some degree of induced hypersensitivity of the DA systems (Breese *et al.*, 1990, 1991; Criswell *et al.*, 1992). Casas *et al.*, demonstrate a form of conditioned –undrugged environment-related self-injurious behaviour– wherein the behaviour is first induced to apomorphine (on Days 7, 14, or 28) and then tested for in the undrugged state. A very high dose of apomorphine is applied here, *i.e.*, 2.5 mg/kg. The authors suggest that undrugged self-injurious behaviour may represent conditioned respons-

es mediated by hypersensitive mesostriatal DA receptors. It would appear that this effects also demonstrate that drug-sensitization effects, already discussed by these authors in a different context, addiction (Casas *et al.*, 1995), may offer clues as how the condition may occur 'spontaneously' in the clinical context as the consequence of drug-environment or monoamine-environment induced sensitization. Certainly, the described experimental conditions surrounding apomorphine administration seem to implicate some manner of sensitization effects (Robinson and Berridge, 1993). In this vein, it is somewhat perplexing to note that Ellis *et al.*, (1997; but see also Lees, 1993) report that apomorphine treatment of parkinsonian patients alleviated or abolished the neuropsychiatric complications that were marked in all of their patients. Previous reports (Ray Chaudhuri *et al.*, 1990; Stibe *et al.*, 1988) indicated that all patients who tolerated the compound showed fewer neuropsychiatric adverse effects in Parkinson's disease although Ruggieri *et al.*, (1989) found severe mental confusion and hallucinations in patients treated with apomorphine + L-Dopa. However, all twelve patients of the Ellis *et al.*, (1997) study (four females, eight males; age range –39 to 78 years; duration of PD range– 3 to 23 years), all of whom had been administered L-Dopa (from 200 to 1800 mg/day), and most of whom had received either pergolide or bromocriptine by themselves or in combination with amantadine or selegiline, showed undeniable improvements (some patients, unable to tolerate L-Dopa, had taken apomorphine alone for over six years).

Since both depressive and intellectual factors are involved, an oft-recurring consideration for many students of the parkinsonian condition refers early indicators of the disease state, or in another sense, the non-motor, premorbid indications (*cf.* Hubble *et al.*, 1993; Vieregge, 1994). Retrospective analysis of personality-trait factors suggests less talkativeness and flexibility but more even-temperedness, caution, generosity, excessive control and depression prior to onset of motor symptoms (Hubble *et al.*, 1993; Poewe *et al.*, 1983; Todes and Lees, 1985). Recently, Vieregge *et al.*, (1997) investigated whether or not assessments of cognitive flexibility, memory performance, mood, somatic complaints, personality trait may be applied to screen individuals at genetic risk for developing idiopathic PD. Certain performance measures, *e.g.*, verbal fluency (lower scores) and Wisconsin Card Sorting tests (fewer categories and more errors), were significantly worse than age-matched and sex-matched controls. However, the global assessment of the neuropsychological tests, mood changes, somatic complaints, personality traits and fine motor ability did not facilitate the identification of individuals at putative genetic risk for the disorder. This finding, of course, is not the same as saying that the two groups studied: first-degree relatives of PD families (mean age: 52.6 years) and relatives of sporadic PD patients (mean age: 52.1 years), would not eventually develop PD. In each case the PD patients themselves had mean Hoehn-Yahr scores of 3.0 ± 1.5/1.1. The personality traits upon which both groups of relatives to PD patients differed from controls were: impulsiveness and strain (more), extroversion (less) and emotionality (more). In the above connection, a genetic, subclinical, low-dopamine syndrome with sub-threshold motor alteration parkinsonism has been described (Morrish *et al.*, 1994; Sawle *et al.*, 1992) wherein motor

asymptomatic family members showed an abnormal striatal dopamine metabolism. Despite certain inadequacies that the authors themselves are careful in discussing, it would seem that with sufficient neurobiological and neuropathological markers and a more strenuous design the premorbid identification of parkinsonian disorder may well be achieved.

References

Boyd JL, Cruikshank CA and Kenn CW (1991) Cognitive impairment and dementia in Parkinson's disease. *Psychological Medicine*, **21**, 911-921.

Breese GR, Criswell HE, Duncan GE and Mueller RA (1990) A dopamine deficiency model of Lesch-Nyhan disease - The neonatal 6-OHDA-lesioned rat. *Brain Research Bulletin*, **25**, 477- 484.

Breese GR, Criswell HE and Mueller RA (1991) Evidence that lack of brain dopamine during development can increase the susceptibility for aggression and self-injurious behaviour by influencing D1-dopamine receptor function. *Progress in Neuropsychopharmacology & Biological Psychiatry*, **14**, S65-S80.

Brown RG and Marsden CD (1988) Subcortical dementia. *Neuroscience*, **25**, 363-387.

Brown RG and Marsden CD (1990) Cognitive function in Parkinson's disease: from description to theory. *Trends in Neurosciences*, **13**, 21-29.

Casas M, Guardia J, Prat G and Trujols J (1995) The apomorphine test in heroin addicts. *Addiction*, **90**, 831-835.

Cooper JA, Sagar HJ, Jordan N, Harvey NS and Sullivan EV (1991) Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. *Brain*, **114**, 2095- 2122.

Criswell HE, Mueller RA and Breese GR (1992) Pharmacologic evaluation of SCH-39166, A-69024, NO-0756, and SCH-23390 in neonatal-6-OHDA-lesioned rats. Further evidence that self-mutilatory behaviour induced by L-Dopa is related to D_1 dopamine receptors. *Neuropsychopharmacology*, **7**, 95-103.

Dalrymple-Alford JC, Jamieson CF, Donaldson I and Mac G (1995) Effects of selegiline on cognition in early Parkinson's disease. *Clinical Neuropharmacology*, **57**, 360-367.

Ellis C, Lemmens G, Parkes JD, Abbott RJ, Pye IF, Leigh PN and Ray Chaudhuri K (1997) Use of apomorphine in Parkinsonian patients with neuropsychiatric complications to oral treatment. *Parkinsonism and Related Disorders*, **3**, 103-107.

Hartikainen P, Helkala EL, Soininen H and Riekkinen P (1993) Cognitive and memory deficits in untreated Parkinson's disease and amyotropic lateral sclerosis patients: a comparative study. *Journal of Neural Transmission - Parkinson's Disease and Dementia Section*, **6**, 127-137.

Hubble JP, Cao T, Hassanein RES, Neuberger JS and Koller WC (1993) Risk factors for Parkinson's disease. *Neurology*, **43**, 1693-1697.

Hubble JP, Venkatesh R, Hassanein RES, Gray C and Koller WC (1993) Personality and depression in Parkinson's disease. *Journal of Nervous and Mental Disorders*, **181**, 657-662.

Lees AJ (1993) Dopamine agonists in Parkinson's disease: a look at apomorphine. *Fundamental and Clinical Pharmacology*, **7**, 121-128.

Lees AJ and Smith E (1983) Cognitive deficits in early stages of Parkinson's disease. *Brain*, **106**, 257-270.

Levin BE, Llabre MM and Weiner WJ (1989) Cognitive impairments associated with early Parkinson's disease. *Neurology*, **39**, 557-561.

Lieberman AN (1997) Point of view: Dementia in Parkinson's disease. *Parkinsonism and Related Disorders*, **3**, 151-158.

Louis ED, Marder K and Cote L (1997) Mortality from Parkinson's disease. *Archives of Neurology*, **54**, 260-264.

Luthman J, Fredriksson A, Sundström E, Jonsson G and Archer T (1989) Selective lesion of central dopamine or noradrenaline neuron systems in the neonatal rat: motor behaviour and monoamine alterations at adult stage. *Behavioural Brain Research*, **33**, 267-277.

Luthman J, Fredriksson A, Plaznik A and Archer T (1991) Ketanserin and mianserin treatment reverses hyperactivity in neonatally dopamine-lesioned rats. *Journal of Psychopharmacology*, **5**, 418-425.

Luthman J, Radesäter A-C, Bassen M and Archer T (1996) Functional and neurochemical responses to interventions in the developing dopamine system. In: *Dopamine Disease States* (Eds RJ Beninger, T Palomo and T Archer), pp. 337-358. Madrid University Press, Madrid.

Malapani C, Pillon B, Dubois B and Agid Y (1994) Impaired simultaneous cognitive task performance in Parkinson's disease: a dopamine related dysfunction. *Neurology*, **44**, 319-326.

Mayeux R, Stern Y, Rosen J and Leventhal J (1981) Depression, intellectual impairment, and Parkinson's disease. *Neurology*, **31**, 645-650.

Morrish PK, Piccini P, Burn DJ, Mark MH and Brooks DJ (1994) 18F-Dopa positron emission tomography scanning in a family with familial Lewy body disease. *Movement Disorders*, **9[Suppl. 1]**, 119.

Nyhan WL (1973) The Lesch-Nyhan syndrome. *Annual Review of Medicine*, **24**, 41-60.

Oh JD, Del Dotto P and Chase TN (1997) Protein kinase A inhibitor attenuates levodopa-induced motor response alterations in the hemi-parkinsonian rat. *Neuroscience Letters*, **228**, 5-8.

Poewe W, Gerstenbrand F, Ransmayr G and Plörer S (1983) Premorbid personality of Parkinson patients. *Journal of Neural Transmission*, **19[Suppl.]**, 215-224.

Ray Chaudhuri K, Abbott RJ and Millac PAC (1990) Subcutaneous apomorphine for Parkinsonian patients with psychiatric side effects on oral treatment. *Journal of Neurology, Neurosurgery and Psychiatry*, **54**, 372-373.

Robertson MM (1992) Self-injurious behaviour and Tourette syndrome. In: *Tourette syndrome: genetics, neurobiology, and treatment. Advances in Neurology, Vol. 58* (Eds TN Chase, Friedhoff and DJ Cohen), pp. 105-114. Raven Press, New York.

Robinson TE and Berridge KC (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Research Review*, **18**, 247-291.

Ruggieri S, Stocchi F, Carta A and Agnoli A (1989) Side effects of subcutaneous apomorphine in Parkinson's disease. *Lancet*, **i**, 566.

Sawle GV, Wroe SJ, Lees AJ, Brooks DJ and Frackowiak RSJ (1992) The identification of presymptomatic parkinsonism: clinical and (18F)Dopa positron emission tomography studies in an Irish kindred. *Neurology*, **32**, 609-617.

Stern Y, Tetrud JW, Martin WRW, Kutner SJ and Langston JW (1990) Cognitive change following MPTP exposure. *Neurology*, **40**, 261-264.

Stibe CMH, Kempster PA, Lees AJ and Stern GM (1988) Subcutaneous apomorphine in Parkinsonian on-off oscillations. *Lancet*, **i**, 403-406.

Schwarting RKW and Huston JP (1996) Unilateral 6-hydroxydopamine lesions of mesostriatal dopamine neurons and their physiological sequelae. *Progress in Neurobiology*, **49**, 215-266.

Taylor AE, Saint-Cyr JA and Lang AE (1987) Parkinson's disease: cognitive changes in relation to treatment response. *Brain*, **110**, 35-51.

Taylor AE, Saint-Cyr JA and Lang AE (1990) Memory and learning in early Parkinson's disease: evidence for a 'frontal lobe syndrome'. *Brain Cognition*, **13**, 211-232.

Todes CJ and Lees AJ (1985) The pre-morbid personality of patients with Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **48**, 97-100.

Tsai CH, Lu CS, Hua MS, Lo WL and Lo SK (1994) Cognitive dysfunction in early onset parkinsonism. *Acta Neurologica Scandinavica*, **89**, 9-14.

Vieregge P (1994) Genetic factors in the etiology of idiopathic Parkinson's disease. *Journal of Neural Transmission - Parkinson's Disease and Dementia Section*, **8**, 1-37.

Vieregge P, Heberlein I and Kömpf D (1997) Are neuropsychological tests useful in screening for the genetic risk of Parkinson's disease. *Parkinsonism and Related Disorders*, **3**, 141-150.

Wise RA, Mendrek A and Carlezon Jr WA (1996) MK-801 (Dizocilpine): synergist and conditioned stimulus in bromocriptine-induced psychomotor sensitization. *Synapse*, **22**, 362-368.