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 hypokinesia 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 Lösch 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., 1995; 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 D_1/D_3R 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; Vierregge, 1994). Retrospective analysis of personality-trait factors suggests less talkativeness and flexibility but more even-temperredness, 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, Vierregge 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), extraversion (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


