1 Dopamine disease states: From Parkinson's disease to schizophrenia

Tomás Palomo, Trevor Archer and Richard J. Beninger

The latter decades of the twentieth century have witnessed a massive proliferation of information about the structure and function of the central nervous system including the discovery of catecholaminergic cell bodies in the brainstem projecting widely to central targets. These include the dopaminergic neurons of the ventral mesencephalon that project to the telencephalon (see review by Lindvall, 1979). Of particular note is the finding that some of these cells are significantly reduced in number in the brains of patients suffering from Parkinson's disease and the great success in treating parkinsonian symptoms with dopamine (DA) replacement therapy (Birkmayer and Birkmayer, 1989). At the other end of the spectrum of dopaminergic function is the tenacious hypothesis that DA is overactive in schizophrenia. In spite of numerous failures to identify the nature of this putative dopaminergic hyperfunction, the DA hypothesis continues to find support in the relative success of DA receptor antagonists in the treatment of schizophrenia. Recently, neurodevelopmental theories of the etiology of schizophrenia have been found to account for more and more findings. These ideas have been linked by some investigators who have suggested that a cascade of events beginning with an insult in the second trimester may lead eventually at sexual maturity to hyperfunction of dopaminergic neurons especially during periods of stress (Lipska and Weinberger, 1993). These are interesting times in the study of DA disease states.

This edited book presents chapters written by leading basic and clinical researchers reporting their studies of various aspects of DA disease states. As the title of the present chapter suggests, the book is organized from Parkinson's disease to schizophrenia.

The book begins with a discussion by Portera-Sánchez (Chapter 2) of epidemiological studies of Parkinson's disease. This chapter provides a description of the incidence, prevalence and mortality of the disease and then analyses the significance of a number of risk factors. It provides a good background about Parkinson's disease and emphasizes the continuing need to understand the causes and mechanisms of dopaminergic cell loss in this disorder. Some later chapters (e.g., Fredriksson et al., Chapter 5; Lew et al., Chapter 9; Palomo et al., Chapter
29) discuss mechanisms of neurotoxic cell loss in animal models that are pointing to possible mechanisms for the development and progression of Parkinson's disease in humans.

While some investigators concentrate on the causes of Parkinson's disease, others explore treatment alternatives. These range from neurosurgery to pharmacotherapy. López-Lozano et al. (Chapter 3) report the results of grafting fetal mesencephalic tissue into the brains of ten Parkinson's patients. They present detailed data showing the progress of transplant patients following the surgery. Results reveal a reduction in Parkinson's symptoms in seven patients that persists for at least five years. Preclinical studies evaluate a new anti-Parkinson medication, cabergoline, in DA-denervated monkeys (McArthur et al., Chapter 4) and rats and mice (Fredriksson et al., Chapter 8). Results confirm the therapeutic effectiveness of cabergoline in treating the symptoms of Parkinson's disease and show cabergoline to be potent and long lasting.

Chapters 6 by Archer et al., 7 by Klint et al. and 11 by Broekkamp and Berendsen report the results of investigations of behavioural interactions of DA with other neurotransmitters including glutamate and serotonin. Chapter 6 reviews studies of the effects of glutamatergic agents on locomotor and other activities in DA-depleted rats and mice. In Chapter 7, the interactive effects of glutamatergic and serotonergic or dopaminergic antagonists on locomotor activity and water maze tasks are reviewed. Similarly, Chapter 11 discusses DA-serotonin interactions in behavioural tests. Results reveal an interaction of task with some drug combinations and differential effects of agents with a dopaminergic action versus those with primarily a serotonergic action. These data add to others that seek to identify the important aspects of the receptor profile of atypical neuroleptics for their antipsychotic action.

Chapter 10 by Sokoloff and Schwartz provides an up to date review of DA receptor subtypes and their localization. They review the currently available pharmacological agents for differentiating the function of DA receptor subtypes, concentrating on D₃-like receptors, as no current agents differentiate the two subtypes of D₂-like receptors. Finally, they review recent evidence exploring possible relationships between DA receptor genes and schizophrenia. This chapter provides some rationale upon which to base decisions about which DA receptors to pursue in drug discovery programs.

Continuing the investigation of interactions of other neurotransmitter systems with DA, Manzanares et al. (Chapter 12) look at the regulation of several DA systems by agents affecting kappa opiate receptors. They evaluate the nigrostriatal, mesolimbic, tuberoinfundibular and periventricular-hypophysial DA systems. Results show that stimulation of kappa receptors generally inhibits DA neurons; antagonism of kappa receptors, on the other hand, leads to activation of DA neurons but here the several DA systems studied are affected differently.
The next three chapters are concerned with the interesting atypical antipsychotic drug clozapine and related compounds. Ögren (Chapter 13) provides a clear overview of the types of tests that have been used traditionally to evaluate antipsychotic potential and their limitations when it comes to assessing clozapine and clozapine-like drugs. Goldstein (Chapter 14) discusses several newer behavioural tests that differentiate clozapine and haloperidol. He compares a number of agents thought to be clozapine-like to clozapine in these tests and concludes that quetiapine is the agent among these with the closest profile to that of clozapine. Finally, Jackson et al. (Chapter 15) present an elaborate series of biochemical and behavioural tests with clozapine and some provocative results. For example, they suggest that low doses of clozapine do not occupy D₁ or D₂ receptors. Furthermore, in some behavioural tests they showed that the action of clozapine was like that seen with a DA agonist. These data underscore the continuing challenge presented by atypical antipsychotic drugs like clozapine to discover the critical aspects of their mechanism of action for their therapeutic success.

Chapters 16 and 17 focus on the development of DA systems and the effects of perinatal insults. Luthman et al. (Chapter 16) discuss data showing that neonatal chronic DA depletions do not lead to Parkinson's disease-like symptoms in adulthood like those seen in adult rats receiving similar lesions. However, they identify a number of behavioural and biochemical changes in neonatally DA-depleted rats that may serve to compensate for the loss of DA. Fernández-Ruiz et al. (Chapter 17) provide a review of the effects of perinatal cannabinoid exposure on the function of DA neurons in adulthood and show that some significant changes occur. As anandamide, an endogenous ligand for cannabinoid receptors, has been discovered only recently (Devane et al., 1992), this work is particularly timely and adds to the other chapters reporting interactions of DA with various neurotransmitters. Chapters 16 and 17 show that chronic or acute alterations of dopaminergic function in neonates can have life-long consequences.

Five chapters deal with the role of DA and the circuitry associated with DA-innervated structures in cognitive processes such as learning, reward, memory and information processing. Izquierdo and Chaves (Chapter 18) focus on limbic structures -- the hippocampus, amygdala and entorhinal cortex -- and their role in memory. They review a number of procedures used to evaluate the role of glutamate, GABA, norepinephrine, acetylcholine and DA in memory. They identify intracellular molecules involved in memory and suggest possible mechanisms that may underlie the storage of information in the brain. Beninger and Nakonechny (Chapter 19) similarly implicate second messengers activated by DA D₁-like receptors in learning produced by rewarding stimuli, i.e., incentive learning. Their conclusion is consistent with that of Koob et al. (Chapter 20) who find that D₁ and D₃ receptors in the shell of the nucleus accumbens seem to play a
critical role in the rewarding effects of cocaine. Ellenbroek and Cools (Chapter 21) emphasize the importance of DA in information processing by showing that prepulse inhibition and latent inhibition are disrupted by apomorphine. They show further that animals bred for sensitivity to apomorphine are more easily disrupted in information processing tasks and suggest that these animals provide a good model of schizophrenia. Kalivas and Sorg (Chapter 22) then outline the circuitry that may underlie susceptibility to psychosis. They review two animal models of psychosis and suggest that in both a dysfunction in the hippocampal-cortical-mesencephalic (HCM) circuitry is involved. Their conclusion that schizophrenia cannot be understood as a single neurotransmitter disease but that a consideration of the HCM circuitry and the neurotransmitters therein is particularly supportive of the extensive attention paid to neurotransmitter interactions in this volume. Thus, although DA clearly is involved in learning and memory, it probably modulates the strength of synapses using other neurotransmitters.

In keeping with the idea of neurotransmitter interactions as a more fruitful approach to the study of disease states involving DA, the chapters by Deakin et al. (Chapter 23) and Moghaddam et al. (Chapter 24) emphasize excitatory amino acids. Deakin et al. present the glutamate deficiency theory of schizophrenia and data from responses to phencyclidine in humans and post mortem studies of regional changes in glutamatergic markers in the brains of schizophrenic patients that support it. They conclude, like Weinberger and his co-workers (Lipska and Weinberger, 1993), that a developmental structural abnormality may lead to a dysregulation of DA function. Moghaddam et al. review basic and clinical studies implicating frontal cortical glutamate, acting at the NMDA receptor, in the cognitive functions usually ascribed to the frontal cortex. They make the interesting observation that DA receptor antagonists reverse some of the deficits produced by NMDA receptor antagonists and point out that this suggests that antipsychotics work to overcome the deficit produced by reduced glutamatergic function. They end by emphasizing once again the importance of neurotransmitter interactions (in this case DA and glutamate) in schizophrenia.

Chapters 25 (Ebmeler and Ebert) and 26 (Andreasen et al.) present the results of imaging studies. Ebmeler and Ebert focus on the role of DA in depression, a topic that receives too little attention in this volume (cf. Palomo et al., Chapter 29). Altered D₂ and D₃ receptors are found in the basal ganglia in some studies of depressed patients and altered blood flow to the frontal cortex is reported but the implications for a role for DA in depression remain unclear. Andreasen et al. report the results of sophisticated PET and MRI studies implicating a number of regions in schizophrenia. One surprising finding indicated alterations in the cerebellum in schizophrenic patients. Like Kalivas and Sorg (Chapter 22), Andreasen et al. emphasize the usefulness of a more modern view of parallel circuits rather than
specific regions or neurotransmitters in a consideration of the neural deficits associated with schizophrenia.

The penultimate pair of chapters focuses on theories of schizophrenia. Davies and Murray (Chapter 27) review a wide range of studies (including neuroimaging) that point to an early neurodevelopmental impairment as a major contributing factor to the subsequent development of schizophrenia. Crow (Chapter 28) completes the picture by reviewing the failure of the DA hypothesis of schizophrenia to account for the types of structural and pre-morbid abnormalities discussed by Davies and Murray and many others. He suggests that a gene for hemispheric specialization may be responsible for schizophrenia and adduces arguments as to why such a gene should persist in the population. It is hard to avoid the shortcomings of the DA hypothesis of schizophrenia when reading Chapters 27 and 28. However, these chapters are consistent with and acknowledge the work of Weinberger and his associates (Lipska and Weinberger, 1993), bridging the neurodevelopmental hypothesis and the DA hypothesis of schizophrenia.

The final chapter (Chapter 29 by Palomo et al.) revisits many of the findings reported in the book organizing them around neurotoxicity as a central theme. The link is clear and well developed for Parkinson’s disease in this book and some of the neurotransmitter interactions that are discussed may provide a basis for understanding schizophrenia as arising from a mechanism involving neurotoxic insults. It is clear that much has been learned in recent years about the mechanisms of DA disease states and that much is to be done to continue this voyage of discovery.

References


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