

Interactive monoaminergic basis of schizophrenic disorders

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Two of the chapters in the section were aimed exclusively at an analysis of available antischizophrenic compounds, in particular olanzapine and ziprasidone. Zorn *et al.*, (Chapter 22) describe ziprasidone as a novel antipsychotic in late-stage clinical development, chemically unrelated to any available antipsychotic compound, and outlined its neuropharmacology and neurochemistry in the context of several other substances-of-reference. Moore and Bymaster (Chapter 21) first present a comprehensive account of the requirements to be filled by a late-generation antipsychotic: efficacy of action and lack of extrapyramidal side effects, a particular constellation of receptor-subreceptor properties, and sites of action like mesolimbic or prefrontal cortical interactions, before comparing olanzapine to other available compounds with similar pharmacological profiles, in particular clozapine. Zorn *et al.*, outline the *in vitro* receptor binding profile of ziprasidone in relation to olanzapine, clozapine, haloperidol and risperidone and in relation to human 5-HT_{2A} and D₂ high affinity receptors, but also 5-HT_{1A}, 5-HT_{1D} and 5-HT_{2D}, and the recently-described 5-HT₇ site; the comprehensive spectrum of neuropharmacological receptor profile and distinguishing characteristics are revealing, independently of allegiance. Note that the authors have sought to present the preclinical behavioural pharmacology, in parallel and *en masse*, including: locomotor response to d-amphetamine, apomorphine-stereotype, prepulse inhibition, conditioned avoidance behaviour and EPS-liability with tests of catalepsy. Microdialysis analysis of prefrontal cortex and striatum should be noted. The authors describe the serotonergic properties of these compounds at some length, which provides a reasonable footing for the eventual interactive discussion, as outlined by reduced adrenergic, histaminergic and absence of muscarinic properties of ziprasidone. Moore and Bymaster provide us with a state-of-the-art outline of clozapine effectiveness that ought to be compared with previous analyses (Goldstein, 1996; Jackson *et al.*, 1996; Ögren, 1996) for previous preclinical understandings. However, the

primary focus is directed upon several parallel issues: the receptor binding profile of the newer agents, their mesolimbic/prefrontal cortical interactions and the behavioural actions mediated by the dopaminergic, the serotonergic, the muscarinic cholinergic, and glutamatergic systems, to reach termination in a review of studies indicative of multiple transmitter interactions. It is recommended that these chapters (*i.e.*, Moore and Bymaster, Chapter 21; Zorn *et al.*, Chapter 22) be examined in association with one another.

The predominantly preclinical papers by Svensson *et al.*, (Chapter 24) and Sanger *et al.*, (Chapter 29) provide analyses and descriptions of etiologically likely modifications of the implicated monoamines due to the disease process: both star dopamine as the main neurochemical entity. Although D₂ antagonism is associated with an antipsychotic effect, Svensson *et al.*, discuss preclinical and clinical evidence of 5-HT_{2A} and alpha₁-adrenoceptor in the actions of currently relevant antipsychotics. Here, the alpha₂-adrenoceptor antagonistic action of compounds like clozapine and risperidone that may give a therapeutic contribution is also discussed. Sanger *et al.*, review some methodological and conceptual considerations of the dopamine 'multiple-receptor' that provide a necessary point-of-departure for an eventual standpoint on the disease state. Thus, this review is a useful text with a state-of-the-art description of higher-order applications of the drug discrimination/generalization methodology and the current understanding of the dopamine receptor-subtype story (refer to the chapter by Sokoloff *et al.*, in this volume and previously, 1996). This chapter urges a more comprehensive definition of DA-subreceptor agonistic/antagonistic actions through a greater conceptually-ocussed selection of pharmacological test batteries. If one accepts a cornerstone from Svensson *et al.*, namely that the intricate balance between 5-HT₂-antagonism (plus alpha₁-adrenoceptor antagonism) and a low level of D₂ receptor occupancy (Abi-Dargham *et al.*, 1997; Marcus *et al.*, 1996, 1997) in the treatment of schizophrenia, then the avoidance of conceptual-methodological pitfalls to be avoided (Sanger *et al.*) offers a necessary avenue.

Animal models of the disease state, reinforced by a clinical pathology analysis, provide the major theme in the chapters by Geyer and Swerdlow (Chapter 20) Johansson *et al.*, (Chapter 28) and Kalivas *et al.*, (Chapter 27). Geyer and Swerdlow address the phenomenon of sensory gating as both a preclinical and clinical means of dissecting the attentional deficits that accompany schizophrenia by investigating the prepulse inhibition (PPI) of startle responding, although as the authors indicate the effect is not limited to schizophrenia but seen in several other psychiatric-neurologic disorders. A review of procedural-conceptual dimensions is followed by an analysis of the involvement of multiple neurotransmitters in PPI: dopamine, glutamate, and serotonin. The role(s) of monoaminergic and non-monoaminergic mechanisms in PPI are outlined, with special regard to their interactions at limbic, striatal and brainstem sites. Here, we emphasize the clinical relevance in humans with clear regional indications (Waldo *et al.*, 1994). Johansson *et al.*, pursue a strategy of examining the neuropharmacological background of a representative group of available antipsychotics in relation to the neuropharmacology of drugs inducing a psychotic-like disease state. Thus, in the former com-

pounds such as haloperidol, clozapine and remoxipride were investigated in the 'psychotic context' of phencyclidine (PCP), and via this association the involvement of nitric oxide synthase (NOS) and inhibitors of NOS, in particular the non-selective NOS inhibitor NG-nitro-L-arginine methyl ester (L-NAME). The authors cite preclinical and clinical evidence (*e.g.*, Das *et al.*, 1996; Deutch *et al.*, 1996) for a disturbance of nitric oxide activity in schizophrenia. Their results indicated that the psychosis-type behaviours induced by PCP were selectively antagonized by blockade of nNOS. It should be noted also that this chapter demonstrates that PCP-induced behaviours bear similarities to 5-HT mediated behaviours; thus the putative relationship between NOS and 5-HT_{1A}/5-HT₂ receptors is discussed. The chapter by Kalivas presents a treatise on the phenomenon of psychostimulant-induced sensitization and discusses the case that stimulant-induced paranoia and psychosis represent sensitization phenomena. Their basic tenets, regarding amphetamine psychosis and sensitization, are clearly outlined: (1) progressiveness and greater sensitization in the addict, (2) lower dose requirement in the addict, (3) relapse psychosis inducible after long periods of abstinence. The authors then review the preclinical and clinical evidence to substantiate these standpoints.

Although attentional process disturbance has been analysed comprehensively the cognitive changes accompanying schizophrenia appear to some extent uncharted and the interactive monoaminergic substrate is rapidly proliferating (*cf.* Moghaddam *et al.*, 1997). The chapters by Moghaddam (Chapter 23), Izquierdo *et al.*, (Chapter 31) and Beninger (Chapter 30) address the role of monoamine disturbances in preclinical investigations of cognition modulation in schizophrenia. Moghaddam has administered noncompetitive NMDA antagonists, PCP and ketamine, to impair prefrontal cortical functions in rats, mimicking the clinical condition (but see also Moghaddam *et al.*, 1996). Both compounds increase glutamate outflow in the prefrontal cortex but also dopamine release in the same region. Functional changes included hyperlocomotion and impaired spatial delayed alternation implicating both disruption of dopaminergic neurotransmission and the cognitive functions associated with the prefrontal cortex and suggesting that compounds possessing a glutamatergic reducing action may provide therapeutic efficacy for the symptoms of schizophrenia and PCP psychosis (*cf.* Chapter 15 by Balster). Izquierdo *et al.*, have described at great detail the hippocampal processes in long-term memory formation, second messenger processes in the hippocampus (*i.e.*, the PKG cascade, protein kinase (PKC) cascade and Ca²⁺-calmodulin-dependent protein kinase II (CaMKII) cascade, the cyclic 3'5'-adenylyl monophosphate (cAMP)/protein kinase A (PKA)/CREB (cAMP) response element-binding protein) signalling pathway. Here we are presented descriptions of early modulatory influences and core mechanisms of long-term memory formation, the modulation of the late PKA-dependent phase of long-term memory formation in the hippocampus, the involvement of the amygdala, entorhinal cortex and posterior parietal cortex, respectively, in the consolidation of long-term memory, and the role of late post-training memory modulation. Much of the evidence provided by Izquierdo's chapter may be interpreted against the negative symptoms of the disorder, encompassing mood, emotion and memory, since as indicated DA D₁, beta- nora-

adrenergic and 5-HT_{1A} receptors are postulated to be critical for the modulation of mood and affect (*cf.* Heimer *et al.*, 1997). The regional implications of ontogenetic developmental factors (*e.g.*, environment) modulating hippocampal function are particularly emphasised (*cf.* Kempermann *et al.*, 1997). Finally, the events of long and short term memory in eventual formation of those entities referred to as memory are tentatively outlined. Beninger's chapter maintains the theme initiated by Izquierdo *et al.*, namely neurochemical events regulating second messenger cascade events in memory processing, in this case dopamine-second messenger interactions in reward-related learning. An important feature of this account is the attempt to relate findings from one arrangement of learning methodology with the neurochemical evidence of several other lines; yet more interesting are the obvious links indicated with several other papers, *e.g.*, Sokoloff *et al.*, (Chapter 38), Chase *et al.*, (Chapter 39) and Schmidt and Tschenkte (Chapter 40) in the section on Parkinson's disease. Once again the pivotal role of dopamine in these two major classes of the disease state is experienced.

Several of the above accounts address both preclinical and clinical aspects of schizophrenia though their main scope pertains to the laboratory examination of the disease process. It is somewhat unfortunate that a full-fledged clinical analysis was limited to the chapters by Nordström (Chapter 25) and Peralta and Cuesta (Chapter 26), worthy though most certainly are. Peralta and Cuesta have examined the global concept of the term 'schizophrenia' and its heterogeneity implications with regard to phenomenology, pathophysiology and etiology, but also the presence or absence of biological markers and the suitability of the available historical models, preliminary to presenting a 'basic symptoms model', the positive and negative symptoms model, and the multidimensional models. In their treatise of these models for developing techniques to understand and contain the disease state, the authors describe a categorical and a dimensional approach and finally present the recommendation of a polydiagnostic-multidimensional approach in attempting to guarantee both predictive and construct validity with acceptable model-utility. Nordström (Chapter 25) makes a comprehensive review of the application of positron emission tomography (PET) techniques in schizophrenic patients to examine the mechanism of action of antipsychotic compounds directly *in vivo*. Using selective radioligands the degree of receptor occupancy (dopamine and 5-HT₂) was determined and related to considerations of dose measurement, plasma drug concentration and putative clinical benefits. D₂ receptor occupancy and clinical effects, and thresholds for antipsychotic action and extrapyramidal side effects, as well as the effects of clozapine, DA subreceptor occupancy, serum concentration, combined D₂-5-HT₂ occupancy and selective 5-HT₂ receptor occupancy were determined for the classical and atypical antipsychotic compounds. In the study of the novel antipsychotic agents, compounds described include risperidone and olanzapine. This chapter offers an important review of clinical PET-scan implications to be compared with multivariate information provided in the chapters by Zorn *et al.*, and Moore and Bymaster (Chapters 22 and 21 respectively).

Recent reviews (Andreasen *et al.*, 1996; Crow, 1996; Davies and Murray, 1996; Wyatt, 1996) of neuroanatomical and neurobehavioural abnormalities in first-

episode schizophrenic patients have suggested the existence prior to clinical presentation (DeLisi *et al.*, 1995; Eaton *et al.*, 1995; Kareken *et al.*, 1995; Nopoulos *et al.*, 1994; Turetsky *et al.*, 1995). Accumulating evidence further suggests a disease progression by which anatomical alterations may modulate some of the pathological and biobehavioural features (Baldessarini *et al.*, 1997; Bilder *et al.*, 1992; Olney and Farber, 1995). Thus, Gur *et al.*, (1998) demonstrated that both first-episode and previously-treated patients had smaller brains and frontal and temporal lobes than controls at intake. Although the relationship between volume reduction and symptom alteration differed between patient groups, volume reduction was related to the decline in some neurobehavioural functions in both groups (*i.e.*, first-episode and previously-treated patients). Higher neuroleptic dosage providing improvements of thought disorder and delusions was associated with first-episode patients showing greater rate of reduction in frontal and temporal lobe volumes; however, these changes accompanied less improvement in affective flattening and alogia (Gur *et al.*, 1998). This pattern supports a neurodevelopmental in conjunction with progressive structural damage hypothesis (*cf* Davis and Murray, 1996).

An important property of the progressive degeneration observed in elderly patients is that Alzheimer's disease is only sparsely superimposed on symptoms defined by cognitive deficits in schizophrenia (Purohit *et al.*, 1993), nor were Alzheimer's disease development, increased senile plaques or neurofibrillary tangle formation in the brain associated with any susceptibility by elderly schizophrenia patients (Purohit *et al.*, 1998). Other mechanisms than Alzheimer's disease must account for the cognitive impairments. It has been discussed that a developmentally insufficient abnormal hippocampal formation may be rendered functionally defective in schizophrenic patients (Arnold *et al.*, 1994). Developmentally defective prefrontal and temporal lobe cortical circuitry, deficits in small interneurons, and increases in cingulate gyrus vertical axon numbers in schizophrenic patients' brains may underlie the cognitive deficits (Akbarian *et al.*, 1993, 1996; Benes *et al.*, 1991, 1992; Devinsky *et al.*, 1995). The findings of Purohit *et al.*, (1998) affirm that the cognitive decline was common to a clinical population of institutionalized, elderly schizophrenic patients. Further, in a recent study, no significant evidence of neurodegeneration or ongoing neural injury in the cerebral cortex was obtained in a sample of elderly schizophrenic patients (Arnold *et al.*, 1998); behavioural and cognitive deterioration was not correlated with age-related degenerative phenomena.

Schizophrenic patients suffer from memory dysfunction of considerable neuropsychological magnitude (McKenna *et al.*, 1990; Saykin *et al.*, 1991, 1994). Several postmortem studies have indicated cellular abnormalities on the hippocampal formation (Arnold *et al.*, 1995; Jeste and Löhr, 1989), whereas other postmortem studies have associated schizophrenia with hippocampus and parahippocampus gyrus overall volume reductions (Bogerts *et al.*, 1985, 1993; Colter *et al.*, 1987). The meta-analysis technique has provided an important method for structure-volumetric analysis in brain disease states (Elkis *et al.*, 1995; Hunter and Schmidt, 1990; Raz and Raz, 1990; Woodruff *et al.*, 1995). Recently, a comprehensive meta-analysis

sis by Nelson *et al.*, (1998) offered several interesting findings: (1) A significant association exists between schizophrenia and bilateral volumetric reduction of the hippocampus, (2) there were no differences in volumetric reduction in schizophrenics between right and left hippocampi, and (3) most of the studies included in the meta-analysis were either nonsignificant or else in the opposite direction so that solely positive findings are unlikely to provide a confounding variable. Given the critical nature of the negative symptomatology disease progression and prognosis, the documented cognitive deficiencies, and the structural abnormalities (above; Andreasen *et al.*, 1996) of foetal origin (Davies and Murray, 1996), several conclusions pertaining to direction ought to be considered: (1) Since structural abnormalities may exist at an early stage of development (Bilder *et al.*, 1995; Corey-Bloom *et al.*, 1995; DeLisi *et al.*, 1995; Lim *et al.*, 1996), there remains the need for longitudinal analyses of the effects of patient age and duration-of-illness on brain structure volumes (*e.g.*, hippocampus), (2) Volumetric differences should be related to gender differences and handedness of the patient sample, (3) the precise nature of relationship between symptoms-cognitive profile and structure volumes (*e.g.*, amygdala, prefrontal cortex, cingulate gyrus, *etc.*), (4) concurrent volumetric - functional MRI studies that analyse functional consequences of reduced volume and potential hippocampal laterality, (5) comparison of volumetric reductions of hippocampus with other gray matter structures, (6) relative involvement of anterior and posterior hippocampus in the context of afferent-efferent roles, (7) examinations of the anatomical hippocampus-amygdala boundaries in the disease state, (8) the consequences of neurogenesis, as reflected through psychosocial stress or environmental enrichment, to ascertain the underlying volume changes in an etiological perspective.

In keeping with the recent focus on negative symptomatology in schizophrenia, also emphatically concentrated upon by the present chapter, it has just been reported that olanzapine is proficient in the treatment of depressive signs and symptoms of schizophrenia (Tollefson *et al.*, 1998). The authors suggested that innovative agents hold promise for improved clinical outcome: this is a pleasing note to satisfy one of the major requirements of this volume, *i.e.*, to contribute to improved therapies for the relevant disorder.

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