

Introduction: schizophrenia, movement and cognitive disorders

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One of the major principles guiding the Madrid meeting, *Strategies for Studying Brain Disorders*, was to assemble neuroscientists and clinicians in order to disclose the utility of basic animal research as a strategy for understanding brain mechanisms underlying the therapeutic action of compounds with clinical or potential clinical application. To this second volume, *Strategies for Studying Brain Disorders*, 26 papers were contributed for the three sections: Schizophrenia, Movement and Cognitive Disorders. From the outset, it may be concluded that this volume achieves a healthy balance between preclinical and clinical papers, and of conceptual-methodological issues.

The principle of balance is well-reflected in the chapters dealing with the **Schizo-psychotic disorders**. Three largely preclinical papers (Ahlenius, Cools *et al.* and Sánchez) are interspersed with two clinical papers (Casas and Woggon) and four mixed clinical/preclinical papers that bridge the gap between predictions from animal research and the clinic (Lewander *et al.*, Ögren, Palomo and Wilson *et al.*). Of these, Lewander (chapter 4) and Wilson *et al.* (chapter 7) establish the preclinical lead from basic pharmacological investigations as a strategy for assessing the therapeutic potential of compounds in patients. These papers have demonstrated how clinical findings may be consistent with preclinical indications. The paper by Ögren (chapter 5) represents a basic research orientation that enjoys the continuous feedback from the emerging clinical picture (forwards) but at the same time benefits from the structure-activity information of newer compounds in the pipe-line (backwards). Palomo (chapter 6) emphasizes the need for better communication between basic researchers and clinicians, as illustrated by examples from preclinical studies designed on the basis of clinical observations.

Ahlenius (chapter 1) discusses the issue of how animal research may lead to a better understanding and thereby better treatment of brain disorders. Relying on the recent history of neurobiological progress and/or retrograde development, he traces the current therapeutic arsenal to animal research on brain mechanisms and pharmacodynamics and raises doubts regarding the extent to which the mechanisms may or may not be related to the disorder in question. Quite rightly, it is pointed out that commonsensical assumption, or anthropomorphism, breeds fallacy, e.g. the neglect of ethological principles. Obviously, there exists a wide

chasm from animal brain mechanisms (when these are understood) to human disease states and from human phenomenology to animal behaviour. To some extent the documented successes of the serendipity principle may confuse the issue. The three routes he advocates: models based on analogous behavioural functions, models based on brain mechanisms and models based on homologous relationships are followed up by the succeeding chapters. Thus, the examination of homologous structures known from neuroradiological techniques and post-mortem studies, for the more effective treatment of human psychosis to be relevant is pursued. The fundamental question of what constitutes an animal model of schizophrenic disorders is left unaddressed. The short answer: e.g. there is none, is pessimistic, so one long answer may be the application of selective attention in schizophrenic attention disorder (Crider *et al.*, 1982, 1986), e.g. in an attentional model utilizing the latent inhibition phenomenon in classical conditioning experiments (e.g. Weiner *et al.*, 1984; Lubow *et al.*, 1987; Weiner and Feldon, 1987). An eventual model of this type outlines a mechanism, "switching", originating in limbic DA regions and encompassing mesolimbic 5-HT – DA involvement for the functional processes necessary for the correct expression of behaviour (see Weiner, 1990; but also Cools *et al.*, 1990 for "control" processes).

The current importance placed upon drug development for the treatment of schizophrenia is reflected in the fact that 7 out of the 9 papers are related to research involving some aspect of atypical neuroleptics. The clinical lead is taken by Woggon (chapter 8) who defines atypical antipsychotic drugs as compounds that, in contrast to the classical neuroleptics: (1) produce the lowest incidence of extrapyramidal symptoms (EPS); (2) are effective for the treatment of negative symptoms, and (3) are effective in so-called "therapy-resistant" patients. To this end, the Woggon paper focuses attention on the initial atypical antipsychotic, clozapine, which has become established as the main reference drug for new antipsychotic compound derivation (see also Ögren and Archer, 1993; Ögren *et al.*, 1990). Preclinical observations suggest that atypical antipsychotics either do not cause motor effects (catalepsy and stereotyped behaviour), predictive of an EPS-producing disposition, at doses that block dopamine (DA) induced locomotion, or that have a regional affinity for mesolimbic and mesocortical structures (predictive of the antipsychotic effect) but not for striatal structures (predictive of EPS), or that share the clozapine mechanisms of action at receptor level.

Clozapine is a compound with a high affinity for 5-HT₂, 5-HT_{1C}, D₄, α_1 , α_2 , and muscarinic receptors, moderate activity for H₁, D₂, D₁ and 5-HT₃, and interacts with other receptors, such as sigma and NMDA. Understandably, it is difficult to decide which of its many receptor actions is responsible for its unique clinical effect. Ögren (chapter 5) examines the situation that a compound, remoxipride, which, unlike clozapine, is a selective D₂ antagonist and has the behavioural pharmacology profile of an atypical antipsychotic. Results of animal studies together with the clinical observation that remoxipride produces less EPS, leads Ögren to propose that the mechanism behind its atypical action may be determined by: (1) selectivity

for a subset of D_2 receptors, D_{2b} ; (2) differential effects on striatal DA subsystems acting preferentially on the matrix diffuse system, or (3) regional selectivity for extra-striatal areas, such as the olfactory tubercle, septum or substantia nigra. The potential importance of the olfactory tubercle in explaining differences between classical and atypical neuroleptics is examined by Cools *et al.* (chapter 2). These authors propose that the fundamental issue is that of regional specificity though not necessarily in the biochemical mechanisms. The olfactory tubercle and nucleus accumbens, both with DA and 5-HT innervations, are known sites of action for both classical and atypical neuroleptics. Using bilateral injections of DA or ergometrine into the olfactory tubercle or the nucleus accumbens, respectively, motor activity elicited is specific for DA and the particular area injected. Utilizing several different test models, different profiles are determined whereby atypical compounds are preferential for olfactory tubercle sites and classical compounds for accumbens sites, thereby underlining the importance of regional specificity.

In the chapter by Palomo (chapter 6) preclinical-clinical (and *vice versa*) lines of communication are considered with regard to basic research and what is understood from schizophrenia is interpreted as increasing responding to both DA over- and under-stimulation with a concomitance in the chosen animal model, amphetamine-induced exploratory and stereotyped behaviour. Accordingly, antipsychotics should prevent stereotypy (DA over-stimulation) and increase exploration (in preventing under-stimulation). This is quite opposite to what others have proposed as predictive of a low EPS capacity, which is not the issue. The issue concerns a widening of the limits of DA tolerance. The Casas *et al.* paper (chapter 3), clinically-oriented, would appear to provide a means by which Palomo may test clinically the altered DA-response hypothesis. Casas *et al.* have investigated the effects of low doses of apomorphine on yawning frequency as a test of DA reactivity in healthy volunteers and drug-abusers. It is remarkable that there is no overlap so that the test discriminates between abusers and non-abusers. In dealing with DA reactivity profiles this paper should be considered in the context of the Palomo paper which discusses DA responsiveness in the pathology of psychosis.

The remaining three, ostensibly clinical, chapters deal mainly with particular antipsychotic agents. Lewander *et al.* (chapter 4) unfold a preclinical story with predictions from the basic pharmacology pronouncing an antipsychotic efficacy with low EPS incidence, less prolactin and fewer autonomically-mediated side-effects. Remoxipride, with its selective D_2 affinity (unlike clozapine) and preference for limbic structures (like clozapine), as demonstrated by differential effects on regional c-fos expression, offers interesting preclinical-clinical-preclinical tactical approaches. The randomized double-blind multi-centre studies described indicate a comparable efficacy to haloperidol for positive and negative symptoms and lower EPS tendency. Be that as it may, studies with comparisons to other, classical, low potency neuroleptics (e.g. chlorpromazine, thioridazine, etc.) that produce less EPS than haloperidol are required. The few available do not show unrestricted advantages for remoxipride (McCreadie *et al.*, 1988; Chouinard,

1990). Wilson *et al.* (chapter 7) focus upon ondansetron, a potent and selective 5-HT₃ antagonist based on (1) the predictions about 5-HT₃ sites being highly localized to limbic regions modulating DA activity *in vitro* and inhibiting mesolimbic DA-induced activity in animals, and (2) the results from an open-trial showing efficacy and good tolerability. The results from a double-blind, multi-centre study showed no significant antipsychotic efficacy although there did appear some possible positive effects that may have been masked by methodological problems, which raises the cry for better controlled studies. The Sánchez paper (chapter 9) constitutes a preclinical study on sertindole, an interesting compound differing both from classical and atypical compounds. *In vitro* analyses showed high affinity for 5-HT₂, α_1 and D₂ > D₁, with a low affinity for α_2 , 5-HT_{1a}, 5-HT₃, muscarinic and β receptors. From *in vivo* analyses it appears that sertindole has a very potent anti-5-HT effect with selectivity for limbic areas and a behavioural preclinical profile predictive of low EPS potential. No clinical studies are currently available.

The search for new antipsychotic compounds continues apace. The enterprise is guided by several considerations: (1) absence of EPS; (2) regional specificity for mesolimbic and/or mesocortical areas; (3) effective in the treatment of negative symptoms, or (4) sharing the clozapine mechanism of action as a prototype with all three advantages. This search has led to a strategy involving the development of compounds with great variation in their receptor affinity profiles. Sadly, the receptor profiles described above remain incomplete as 5-HT₂/D₂ representatives are missing, e.g. risperidone (5-HT₂/D₂ > α_1 /H₁ > 5-HT₁), ICI 204 636 (α_1 /5-HT₂ > D₂), amperozide (5-HT₂ > α_1 > D₂), etc., all of which have undergone clinical examination (Claus *et al.*, 1992; Fabre *et al.*, 1990; Axelsson *et al.*, 1991). Compounds with still different profiles, such as SDZ HDC 912 (mixed agonist/antagonist D₂), SCH 23390 (mixed D₁/D₂ > 5-HT₂), have also been studied in the clinic (Gessa *et al.*, 1991; Naber *et al.*, 1992). Neither are other selective antipsychotics for DA sub-receptors, e.g. amisulpiride (D₂/D₃) (Boyer *et al.*, 1988), covered, nor are strategies involving glutamate, glycine, peptide, or GABA involvement addressed in the search for antipsychotics outlined in this volume, similarly lacking are studies on the antipsychotic action at gene regulation or transcription level (for review see Wetzel and Benkert, 1993).

One major problem pertaining to the schizophrenic disorders stems from the fact that, whereas in many neurological disorders the underlying neuropathological mechanisms are increasingly well-understood, in these disorders understanding and treatment fall a long way behind; this uncertainty is not least shown by the availability of preclinical models and their status. The main advances appear to be in the psychopathology and the "containment" of the disease, certainly not in curing it. Despite these limited objectives, one is still left with a large proportion (30%) of patients for whom the present treatments are ineffective (therapy resistant or non-responders). Obviously then, there remains a part area of schizophrenia psychopathology unaffected by the current therapies (primary negative symptoms

and deficit schizophrenia). Consequently, classical antipsychotic treatments riddled with problems of side-effects, primarily EPS, severely affect compliance such that a delineation between the genuine symptoms and those therapy-induced is not always possible.

The understanding of schizophrenia seems limited to the findings of regional brain alterations, mainly in limbic structures, the prefrontal cortex and the basal ganglia, as demonstrated by neuroradiological and postmortem techniques. It is unfortunate that the vast amount of highly exciting research into the neuropathology of the disorder represented to a limited extent at the Madrid meeting, failed to be contributed to this volume. Without this clinical evidence, this section on the Schizopsychotic Disorders must remain incomplete. It is also well-established that there is either a primary or secondary disturbance of the dopaminergic pathways, partially alleviated by existing antipsychotic medication, which possibly underlies the relationship of schizophrenia with drug abuse and sensitivity to stress, again subjects that miss coverage. In addition, it is broadly accepted that clozapine has a unique effect and that despite the side-effects incidence patients tolerate the compound strikingly well. Thus, these patients state that "they never felt so good" and they do not seem to bother about the autonomic and sedative side-effects. These clinical observations on the subjective feelings of patients, mentioned in the Woggon chapter and shared by all physicians of the disorder, were certainly worth description and research.

The important clinical consideration of negative symptoms is not addressed specifically in this section, an unfortunate omission since here exists some of the clearest clinical evidence defying explanation by a theory of schizophrenia. Most of the papers reviewed do refer to negative symptoms but the specific aspects are generally unclear. Negative symptoms may be classified as: (1) primary, genuinely schizophrenic; (2) secondary to the positive symptoms, which are alleviated by an antipsychotic medication that is effective for the positive symptoms; (3) negative symptoms induced by neuroleptics as a side-effect (particularly clear in relation to EPS, such as parkinsonisms and akinesia); and, (4) negative symptoms resulting from different etiologies (such as concurrent depression, etc.). This distinction is a fundamental one as the effectiveness of a particular drug on negative symptoms is construed as indicative of a novel action upon the "core of schizophrenia" that will divulge neurobiological mechanisms. The discrepancies between researchers, and more especially, the discrepancies between clinical expectations and reality, may arise from an improper usage of the term "negative". Möller (1993) has reviewed recently the results from papers claiming efficacy on negative symptoms for different compounds (classical neuroleptics, atypical antipsychotics selective for DA and atypical antipsychotics acting on the DA/5-HT balance). It is concluded that when these compounds are effective this comes about only during the acute phase of the illness when the positive symptoms are most prominent. Long term studies of chronic defectual schizophrenia patients seem essential if an eventual resolution of these fundamental issues is to be achieved.

The chapters included in section II on **Movement Disorders** address several issues including, the neuroanatomical consequences of exposure to psychostimulant drugs, an animal model of Parkinson's Disease, neurotrophic factors in Parkinson's disease, diagnostic factors and rehabilitation of Parkinsonian patients, the role of DA D_1 - D_2 interactions in movement disorders and animal models of Huntington's disease, essentially basic and clinical aspects of neurological disorders with measurable functional alterations. The paper by Groves *et al.* (chapter 10) addresses the potential risks to the brain following chronic use of psychostimulant drugs. For example, the treatment of animals with d-amphetamine causes drastic changes to the rat brain as well as reductions in DA neurotransmission. On the other hand, cocaine administration did not produce such severe histological effects but did lead to histological changes in the offspring of treated mothers that persisted into adulthood, indicating that the consequences of cocaine were more important for the developing brain. The effects of cocaine *in utero* are described in their neural complexity presenting both the damage and risk aspects of this type of abuse substance. Jackson (chapter 11) discusses the peculiar pharmacology of bromocriptine, a direct-acting DA D_2 receptor used for the treatment of various diseases, including hyperprolactinaemia and Parkinson's disease. Thus, both *in vivo* and *in vitro* D_1 - D_2 receptor interactions are described with regard to the behavioural and biochemical profiles of bromocriptine in the preclinical laboratory. Fredriksson and Archer (chapter 12) describe an animal model of parkinsonism that applies the DA neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), to mice on a long-term basis. The three cardinal symptoms of parkinsonism being rigidity, tremors and akinesia, the model, utilizing automated motor activity-measuring test chambers, aims at the consistent hypokinesia-producing effects of MPTP. These functional effects are long-lasting, beyond 12 weeks, and are dose-dependently reversed by L-Dopa. The role of D_1 - D_2 receptors interactions in MPTP-treated mice is indicated as well as the abolition between a low dose of L-Dopa and extremely low doses of the glutamate antagonist, CGP 40116, are described. The chapter by Emerich *et al.* (chapter 13), from the laboratory of Paul Sanberg, Functional effects and their concomitant neuropathology in animal models of Huntington's disease. This disorder is inherited and progressively neurodegenerative; a severe degeneration of the basal ganglia being characteristic. Thus, this paper attempts to mimic the behavioural and neurobiological consequences of the disorder by various treatment manipulations including intrastriatal injections of excitotoxins, e.g. kainic, ibotenic or quinolinic acid. Animals treated in this way show changes in spontaneous motor activity and in the performance of different tests of learning and memory. Finally, as in the case of the long-term MPTP model of parkinsonism, the possible involvement of NMDA receptors is examined through the application of the receptor antagonist, MK-801, but here the effects of striatal transplants are discussed also. These papers, described briefly above, pertain for the most part to the basic preclinical aspects of the movement disorders, but make suitable reference to the clinical situation to

compare the animal models to the clinical syndromes.

The three chapters dealing with aspects of the clinical reality of the Movement Disorders offer balance, albeit limited, to the preclinical ones described above. Chapter 14 by Aquilonius examines diagnostic aspects of the neuropathology of Parkinson's disease by the *in vivo* definition of dopaminergic mechanisms through use of 11-C-ligands in Positron Emission Tomography (PET) studies. Thus, DA receptor subtypes as well as presynaptic and postsynaptic mechanisms are examined and described. The role of the enzyme monoamine oxidase-B has gained much interest in the neurology of this disorder, following on the documented effects of the monoamine oxidase-B inhibitor, L-Deprenyl. In addition, the pharmacokinetics of L-Dopa maintenance and therapeutic considerations are outlined. The paper by Angeles Mena, José Casajeros and García de Yébenes (chapter 15) deal with the application of neurotrophic strategies for the treatment of neurodegenerative disorders. This class of compounds has been found to rescue specific types of neurons from "programmed" cell death, improving recovery/regeneration after lesioning of the target neuron, e.g. in the treatment of parkinsonian symptoms through *in vivo* and *in vitro* methods. Several nerve growth factors have been studied using lesioned DA models like MPTP of the disorder in rodents and primates. These nerve growth factors include brain derived neurotrophic factor (BDNF), epidermal growth factor (EGF) and basic fibroblast growth factors (bFGF) that affect DA neurochemistry and morphology in the damaged tissue. The chapter by Portera-Sánchez (chapter 16) suggests that the rehabilitation of patients suffering from neurological disorders can best be achieved through the application of the brain's regular repair mechanisms and thus follows suitably upon the preceding chapter. The problems and steps taken to ensure the rehabilitation of parkinsonian patients are discussed in an historical context outlining epidemiological studies from Spain. The cardinal symptoms of the disorder are defined together with other symptoms, such as altered postural reflexes, abnormal gait, depressive problems, dyskinesias and age-related disorders.

Presently, two general hypotheses are available for the neuropharmacological changes in tardive dyskinesia: (1) an imbalance between DA D_1/D_2 receptor function (Johansson *et al.*, 1987; Rosengarten *et al.*, 1986), and (2) the GABA hypothesis (Andersson *et al.*, 1989; Fibiger and Lloyd, 1984). It is unfortunate then that the involvement of brain GABAergic processes in Movement Disorders is conspicuously neglected in the papers included in this volume. Recently, Gunne and Andrén (1993) discussed evidence for the long-term malfunction of the involvement of GABAergic and glutamatergic pathways in a primate model of tardive dyskinesia and tardive parkinsonism. These models utilize the hyperkinetic states resulting from long-term chronic treatment with neuroleptic compounds that interfere with DA and/or GABA neurons (e.g. Lloyd and Hornykiewicz, 1977; Gunne *et al.*, 1984). From the point-of-view of the clinical it is important to note that dual occurrence of parkinsonian tremors and rigidity in conjunction with

dyskinetic and uncontrollable movements in patients who had partaken of neuroleptic compounds over several years (Wolf *et al.*, 1983; Jankovic and Casabona, 1987; Caligiuri *et al.*, 1991) has been remarkably neglected. Thus, Gunne and Andr  n (1993) have proposed the down-regulation of three GABA connections: i.e. the globus pallidus-subthalamic nuclei, caudate putamen-substantia nigra, and caudate putamen-globus pallidus connections, and in particular glutamate decarboxylase activity reductions, as a possible mechanism of tardive parkinsonism. Changes occurring in GABA neurons and excitatory glutamate neurons in parkinsonism (DeLong, 1990), where the subthalamic nuclei may constitute a major site (Crossman, 1987) implicate glutamatergic mechanisms (Smith and Parent, 1988). Glutamate neurons are up-regulated in the Parkinsonian brain (DeLong, 1990), in addition in brains subjected to chronic treatments with long-term neuroleptic administration (Gunne and Andr  n, 1993) and/or preclinical, neurotoxic (chapter 12) lesion. The review by Gunne and Andr  n (1993) offers therefore a model highlighting important DA-GABA-glutamate interactions at specific sites that is relevant to the clinical situation and confirms much evidence derived from laboratory models.

Section III, encompassing **Cognitive Disorders** related to the aging process, covers a wide range of behavioural paradigms for studying memory and an equally wide range of neuroactive peptides, focusing upon their roles in memory function. Collectively, these papers convey a taste of the intensive research interest which cognitive disorders have received in recent years. The ever-increasing importance of finding effective pharmacotherapies for the treatment of Alzheimer's disease and other dementing illnesses is underscored by the current prohibitive costs to national health care programmes of treating dementia and the demographic trends in most industrialized nations that guarantee an even greater health care burden from dementia patients in the future, as discussed by Cole and Growden in the final chapter (chapter 26).

Porsolt, Roux and Len  gre (chapter 17) make the point that one of the major problems faced by researchers interested in identifying possible pharmacotherapeutics for the treatment of dementia is the lack of a clinically effective reference compound. As a result, there is no animal model for predicting drug effectiveness. Researchers must validate animal models by identifying their similarities to the clinical condition. Thus, Porsolt *et al.* recommend the aged animal as a reasonable starting point, since aged animals can be shown to be impaired on a variety of tasks requiring the adequate functioning of *recent memory*. However, aged animals are expensive and cannot be used for routine drug screening. The cholinergic neurons of the basal forebrain have been shown consistently to be affected in the brains of patients dying with dementing illnesses (Coyle *et al.*, 1983) and in normal aging (Bartus *et al.*, 1982). Porsolt *et al.* therefore compare mnemonic performance in aged animals to young animals receiving the anticholinergic drug scopolamine, in an effort to identify aspects of cognition that are affected similarly by both conditions. Once validated for a particular task, the use of scopolamine-

treated young animals for screening potential anti-dementia (cognition-enhancing) compounds may become possible and economically viable. Russell (chapter 21) focuses on compounds affecting cholinergic neurotransmission and learning and memory in his review of the contemporary "search for the engram", following on the pioneering studies of Karl Lashley. He covers a number of topics, including selective breeding of rats for sensitivity to anticholinesterase agents (but see also Overstreet, 1992), the use of hemicholinium-3 to interfere with precursor transport and the role of nerve growth factor (NGF) in recovery from brain damage. The functional role of growth factors in "cognitive recovery" is especially interesting as studies reveal that the combination of brain transplants and NGF leads to significantly faster recovery of learning and memory deficits. As a strategic consideration, this approach offers great promise for the eventual treatment of the dementing illnesses.

Commenting on the cholinergic hypothesis, Danysz and Schmidt (chapter 19) enumerate recent unavoidable criticisms. They cite Fibiger's (1991) paper discussing the now well-documented lack of correlation between the loss of cortical choline acetyltransferase (ChAT), seen following basal forebrain excitotoxic lesions with different excitotoxins, and memory deficits. Thus, numerous investigators have found that quisqualic and ibotenic acid produce similar losses of cortical ChAT but that a much larger mnemonic deficit is seen following ibotenate (e.g. Dunnett *et al.*, 1987; Robbins, *et al.*, 1989; Wenk *et al.*, 1989). Danysz and Schmidt report one hypothesis that has been suggested to account for these findings: *the two excitotoxins may differentially affect noncholinergic neurons in the injected region*. This gives us the short answer, the long answer is: which. Boebman *et al.* (1992) have produced another hypothesis based on the finding that different excitotoxins, injected into the basal forebrain, differentially affected cholinergic efferents to the cortex and amygdala. Agents (e.g. quisqualate) producing a large decrease in cortical ChAT but a small decrease in amygdaloid ChAT have been reported in behavioural studies to induce smaller mnemonic effects than other agents (e.g. ibotenate) producing equally large decreases in cortical and amygdaloid ChAT. Post-mortem evidence has shown that amygdaloid cholinergic innervation is greatly reduced in the brains of Alzheimer patients and recent evidence has shown mnemonic impairments following intra-amygdaloid injections of scopolamine (Ingles *et al.*, 1993), supporting a role for amygdaloid acetylcholine in memory.

While not abandoning the cholinergic hypothesis, Danysz and Schmidt (chapter 19) and Izquierdo (chapter 20) shift the emphasis to the excitatory neurotransmitter glutamate. Izquierdo pursues the mnemonic role of glutamate acting at N-methyl-D-aspartate (NMDA) receptors in the amygdala, hippocampus and entorhinal cortex. He reviews data showing that the consolidation of memory in these forebrain areas involves the activation of NMDA receptors and is susceptible to modulation by GABA-A receptors and other neurotransmitter systems. Danysz and Schmidt review evidence that glutamate receptors are lost in the brains of

Alzheimer patients and discuss the possibility that this may result from the excitotoxic effects of glutamate, presumably due to endogenous metabolic processes. They integrate this concept with the cholinergic hypothesis by reviewing results suggesting that cholinergic neurons in the basal forebrain may be lost as a result of the excitotoxic actions of glutamate. Glutamate receptors are critically involved in long term potentiation, a neuronal model of cellular plasticity, and, possibly learning and memory. Further, glutamate antagonists have been reported to impair spatial learning in the Morris water maze and other learning procedures. All of which has led Danysz and Schmidt to suggest that agents affecting glutamatergic neurotransmission may eventually be useful in the treatment of dementia. One possibility is provided by the application of the glutamate antagonists, but to avoid iatrogenic impairments of memory, drugs that target a particular receptor subtype have to be sought. Another intriguing possibility is then presented by the use of agents that will protect against the neurotoxic effects of glutamate but at the same time will not antagonize the neuroexcitant effects. Partial agonists at the glutamate receptor may provide at least certain of these properties. One candidate substance is the endogenous tryptophan metabolite, picolinic acid (Cockhill *et al.*, 1992); this substance antagonizes the neurotoxic actions of high doses of quinolinic acid but in recent studies (Beninger *et al.*, 1994) has been found not to block the neuroexcitant effects of low doses. Continued study of the role of glutamate and its receptor subtypes, interacting with other receptor subtypes, e.g. D_1 and D_2 , in learning and memory and the search for pharmacotherapeutic agents that affect glutamatergic function may provide an increasingly realistic strategy for the treatment of dementia.

The role of neuropeptides in CNS function and recovery from tissue damage is given comprehensive treatment in the contributions by De Wied (chapter 22), Gispen (chapter 23) and Strand (chapter 24). The chapter by De Wied describes effects of peptides related to ACTH and MSH in facilitating compensatory mechanisms in frogs and monkeys, and functional recovery in rats, following brain damage. For the most part the damage induced was aimed at dopaminergic systems, although fimbria fornix lesions were also inflicted, by selective application of the catecholamine neurotoxin, 6-hydroxydopamine (6-OHDA), which maintains the strong thread of DA function throughout this volume. Gispen's chapter continues the description of nerve repair at cellular and tissue levels in monitoring the reinstatement of sensorimotor function. Animal models of neurological disease states are used to illustrate the recovery process. Strand (chapter 24) distinguishes between types of tissue and functional recovery in developmental and regenerative effects and in regeneration effects in the developing neuromuscular system. Taken together, in the context of brain disorder strategies, these three chapters provide an unexpected interface between the movement disorders and the cognitive disorders. On the other hand, López-Ibor (chapter 25) presents issues and descriptions pertaining to the diagnosis of the disorders, i.e. psychosis, neurology and memory, treated in this volume.

Further reflecting the diversity of brain regions and neurotransmitters that have been implicated in memory, White *et al.* (chapter 18) review the results of experiments concerning the role of striatal DA and ACh in mnemonic function. Using post-training drug treatments, they report that intrastriatal amphetamine enhances memory. The dopaminergic nature of this effect was shown by the finding that 6-OHDA lesions of the nigrostriatal dopaminergic pathway abolished the effect. Moreover, sulpiride but not SCH 23390, respectively D₂ and D₁ antagonists, abolished the effect of amphetamine, implicating the role of striatal D₂ receptors in memory. Anticholinergic agents injected into the striatum immediately following a training trial also enhanced memory, an effect that was also abolished by 6-OHDA lesions of the nigrostriatal pathway. One interpretation of these results may be that the memory-enhancing effects of anticholinergic agents may be mediated through an influence on the release of DA from terminals. The importance of modulation of DA release from terminals was further suggested by studies showing memory enhancement with post-trial injections of low doses of DA agonists that would act preferentially on DA receptors located on the terminals of DA-releasing neurons. Thus, these findings provide an important beginning to identifying possible synaptic mechanisms involved in the storage of memories in the brain.

It is certainly quite clear that the role of DA function receives much attention in this volume, from the schizophrenic through the movement to the cognitive disorders. Be that as it may, the functional role of DA, and its subreceptor types, is so rapidly emerging in the context of regional, and to some extent global, interactions with GABA, 5-HT, ACh, glutamate, neuropeptide, etc., receptors that revisions of preconceived notions on these disease states are becoming obsolete almost as fast as the descriptions themselves. In its inevitability the strategy of *rejection* (which presupposes the spice of *serendipity*) may offer us our only hope of consolation.

References

- Andersson, U., Häggström, J.E., Levin, E.D., Bondesson, U., Valverius, M. and Gunne, L.M. (1989). Reduced glutamate decarboxylase activity in the subthalamic nucleus in patients with tardive dyskinesia. *Movement Disorders*, 4, 37-46.
- Axelsson, R., Nilsson, A., Christensson, E. and Björk, A. (1991). Effects of amperozide in schizophrenia: an open study of a potent 5-HT₂ receptor antagonist. *Psychopharmacology*, 104, 287-292.
- Bartus, R.T., Dean, R.L., Beer, B. and Lippa, A.S. (1982). The cholinergic hypothesis of memory dysfunction. *Science*, 217, 408-416.
- Beninger, R.J., Colton, A.M., Ingles, I.L., Jhamandas, K. and Boebman, R.J. (1994). Picolinic acid blocks the neurotoxic but not the neuroexcitant properties of quinolinic acid in the rat brain: evidence from turning behavior and tyrosine hydroxylase immunohistochemistry. *Neuroscience*, in press.
- Boegman, R.J., Cockhill, J., Jhamandas, K. and Beninger, R.J. (1992). Excitotoxic lesions of the rat basal forebrain: differential effects on choline acetyltransferase in the cortex

- and amygdala. *Neuroscience*, **51**, 129-135.
- Boyer, P., Puech, A.J. and Lecrubier, Y. (1988). Etude en double insu contre placebo de l'amisulpride (Solian 50) à faible dose chez des schizophrènes purement déficitaires. *Annales de Psychiatrie*, **3**, 399-400.
- Caligiuri, M.P., Lohr, J.B., Bracha, H.S. and Jeste, D.V. (1991). Clinical and instrumental assessment of neuroleptic-induced parkinsonism in patients with tardive dyskinesia. *Biological Psychiatry*, **29**, 139-148.
- Chouinard, G. (1990). A placebo-controlled clinical trial of remoxipride and chlorpromazine in newly admitted schizophrenic patients with acute exacerbation. *Acta Psychiatrica Scandinavica*, **82**, (Suppl. 358), 111-119.
- Claus, A., Bollen, J., De Cuyper, H., Eneman, M., Malford, M., Peuskens, J. and Heylen, S. (1992). Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicentre double-blind comparative study. *Acta Psychiatrica Scandinavica*, **85**, 295-305.
- Cockhill, J., Jhamandas, K., Boegman, R.J. and Beninger, R.J. (1992). Action of picolinic acid and structurally-related pyridine carboxylic acids on quinolinic acid-induced cortical cholinergic damage. *Brain Research*, **599**, 57-63.
- Cools, A.R., van der Bos, R., Ploeger, G.E. and Ellenbroek, B. (1990). Control of behaviour by noradrenaline and dopamine in ventral striatum. In "The Mesolimbic Dopamine System: from Motivation to Action". (Eds P. Willner and J. Scheel-Kruger). John Wiley, Chichester.
- Coyle, J.T., Price, D.L. and DeLong, M.R. (1983). Alzheimer's disease: a disorder of cortical cholinergic innervation. *Science*, **219**, 1184-1190.
- Crider, A., Solomon, P.R. and McMahon, M.A. (1982). Disruption of selective attention in the rat following chronic d-amphetamine administration: relation to schizophrenic attention disorder. *Biological Psychiatry*, **17**, 351-361.
- Crider, A., Blockel, L. and Solomon, P.R. (1986). A selective attention deficit in the rat following induced dopamine receptor supersensitivity. *Behavioural Neuroscience*, **100**, 315-319.
- Crossman, A.R. (1987). Primate models of dyskinesia: the experimental approach to the study of basal ganglia-related involuntary movement disorders. *Neuroscience*, **21**, 1-40.
- DeLong, M.R. (1990). Primate models of movement disorders of basal ganglia origin. *Trends in Neurosciences*, **13**, 281-285.
- Dunnett, S.B., Whishaw, I.Q., Jones, G.H. and Bunch, S.T. (1987). Behavioural biochemical and histological effects of different neurotoxic amino acids injected into the nucleus basalis magnocellularis of rats. *Neuroscience*, **20**, 653-669.
- Fabre, L., Slotnick, V., Jones, V. *et al.* (1990). ICI 204.636: a novel atypical antipsychotic with early indications for safety and efficacy in man. Abstracts of the 17th CINP Congress, Vol. II, 223, Kyoto, Japan.
- Fibiger, H.C. (1991). Cholinergic mechanisms in learning, memory and dementia - a review of recent evidence. *Trends in Neurosciences*, **14**, 220-223.
- Fibiger, H.C. and Lloyd, K.D. (1984). Neurobiological substrates of tardive dyskinesia: the GABA hypothesis. *Trends in Neurosciences*, **8**, 462-464.
- Gessa, G.L., Canu, A., Del Zompo, M., Burrai, C. and Serra, G. (1991). Lack of acute antipsychotic effect of SCH 23390, a selective dopamine D1 receptor antagonist (letter). *Lancet*, **1**, 854-855.
- Gunne, L.M. and Andrén, P.E. (1993). An animal model for coexisting tardive dyskinesia and tardive parkinsonism: a glutamate hypothesis for tardive dyskinesia. *Clinical*

- Neuropharmacology*, **16**.
- Gunne, L.M., Häggström, J.E. and Sjöquist, B. (1984). Association with persistent neuroleptic-induced dyskinesia of regional changes in brain GABA synthesis. *Nature*, **309**, 347-349.
- Ingles, J.L., Beninger, R.J., Jhamandas, K. and Boegman, R.J. (1993). Scopolamine injected into the rat amygdala impairs working memory in the double Y-maze. *Brain Research Bulletin*, in press.
- Jankovic, J. and Casabona, J. (1987). Coexistent tardive dyskinesia and parkinsonism. *Clinical Neuropharmacology*, **10**, 511-527.
- Johansson, P., Levin, E.D., Gunne, L.M. and Ellison, G. (1987). Opposite effects of a D1 and a D2 agonist on oral movements in rats. *European Journal of Pharmacology*, **134**, 83-88.
- Lloyd, K.G. and Hornykiewicz, O. (1977). Effect of chronic neuroleptic or L-Dopa administration on GABA levels in the rat substantia nigra. *Life Sciences*, **21**, 1489-1496.
- Lubow, R.E., Weiner, I., Schlossberg, A. and Baruch, I. (1987). Latent inhibition and schizophrenia. *Bulletin of the Psychonomic Society*, **25**, 464-467.
- McCreadie, R.G., Todd, N., Livingstone, M., Eccleston, D., Watt, J.A., Tait, D., Crockett, G., Mitchell, M.J. and Huitfeldt, B. (1988). A double blind comparative study of remoxipride and thioridazine in the acute phase of schizophrenia. *Acta Psychiatrica Scandinavica*, **78**, 49-56.
- Möller, H.-J. (1993). Neuroleptic treatment of negative symptoms in schizophrenic patients. Efficacy problems and methodological difficulties. *European Neuropsychopharmacology*, **3**, 1-11.
- Naber, D., Gaussares, C., Moeglen, J.M. et al. and the SDZ HDC 912 Collaborative Study Group (1992). Efficacy and tolerability of SDZ HDC 912, a partial dopamine D2 agonist, in the treatment of schizophrenia. In "New Research Directions in the Development of Atypical and other Novel Antipsychotic Medications". (Ed. H.Y. Meltzer), pp. 99-107. Raven, New York.
- Ögren, S.O. and Archer, T. (1993). Effects of typical and atypical antipsychotic drugs on two-way active avoidance. Relationship to DA receptor blocking profile. *Psychopharmacology*, in press.
- Ögren, S.O., Florvall, L., Hall, H., Magnusson, O. and Angeby-Möller, K. (1990). Neuropharmacological and behavioural properties of remoxipride in the rat. *Acta Psychiatrica Scandinavica*, **82**, (Suppl. 358) 21-26.
- Overstreet, D.H. (1992). "Whole animal" inverse and positive line differences. *Behavior Genetics*, **22**, 15-17.
- Robbins, T.W., Everitt, B.J., Ryan, C.N., Marston, H.M., Jones, G. and Page, K.J. (1989). Comparative effects of quisqualic and ibotenic acid-induced lesions of the substantia innominata on the acquisition of a conditioned visual discrimination: differential effects on cholinergic mechanisms. *Neuroscience*, **28**, 337-352.
- Rosengarten, H., Schweitzer, J.W. and Friedhoff, A.J. (1986). Selective dopamine D₂ receptor reduction enhances a D₁ mediated oral dyskinesia in rats. *Life Sciences*, **39**, 29-35.
- Smith, Y. and Parent, A. (1988). Neurons of the subthalamic nucleus in primates display glutamate but not GABA immunoreactivity. *Brain Research*, **453**, 353-356.
- Weiner, I. and Feldon, J. (1987). Facilitation of latent inhibition by haloperidol in rats. *Psychopharmacology*, **91**, 248-253.
- Weiner, I., Lubow, R.E. and Feldon, J. (1984). Abolition of the expression but not the acquisition of latent inhibition by chronic amphetamine in rats. *Psychopharmacology*,

83, 194-199.

Wenk, G.L., Markowska, A.L. and Olton, D.S. (1989). Basal forebrain lesions and memory: alterations in neurotensin, not acetylcholine, may cause amnesia. *Behavioural Neuroscience*, 193, 765-769.

Wetzel, H. and Benkert, O. (1993). New psychotropic drugs for the acute treatment of schizophrenia. In "International Review of Psychiatry". (Eds J.A. Costa, E. Silva and C.C. Nadelson), 1, 185-228.

Wolf, M.E., Chevesich, J., Lehrer, E. and Mosnaim, A.D. (1983). The clinical association of tardive dyskinesia and drug-induced parkinsonism. *Biological Psychiatry*, 18, 1181-1188.