A glutamatergic deficiency model of schizophrenia

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Although the presence of hyperdopaminergia has been demonstrated in the brains of people with schizophrenia, at least in some circumstances, other neurotransmitters are important in this disorder, and a glutamatergic deficiency model of schizophrenia is proposed. It is suggested that the amount of sensory input allowed to reach the cerebral cortex is restricted by an inhibitory effect of the striatal complexes on the thalamus, thereby protecting it from being overwhelmed. Several strands of evidence are presented to support the concept that a weakened glutamatergic tone increases the risk of sensory overload and of exaggerated responses in the monoaminergic systems that could result in psychosis.

Any review of the pathogenesis and treatment of schizophrenia must include mention of the dopamine hypothesis. In 1963, Carlsson & Lindqvist first showed that major neuroleptic drugs such as chlorpromazine and haloperidol increase the turnover and synthesis of catecholamines in the mouse brain (Carlsson & Lindqvist, 1963). It was suggested that these effects are due to blockade of catecholamine receptors. It was subsequently shown that blockade of dopamine receptors is the common denominator of the available antipsychotic drugs (Andén *et al*, 1970; Nyback & Sedvall, 1970). Later, when binding techniques were developed, a correlation between clinical dosage and the affinity for dopamine receptors was also demonstrated (Creese *et al*, 1976; Seeman *et al*, 1976).

The dopamine hypothesis is still the subject of lively discussion, but two factors have since emerged that have an impact on it. The first factor is new data derived from imaging studies which tend to show that dopamine function and dopamine release are indeed elevated in the brains of people with schizophrenia, at least under certain conditions, thus strengthening the dopamine hypothesis (Hietala *et al*, 1995; Laruelle *et al*, 1996; Dao-Castellana *et al*, 1997; Breier *et al*, 1997). The second factor, however, tends to de-emphasise the role of dopamine in schizophrenia. Despite the existence of hyperdopaminergia in this disorder, it is becoming increasingly clear that other neurotransmitters must be taken into consideration, and that they may be at least as important as dopamine in schizophrenia.

This paper focuses on the striatal complexes of the cerebral hemispheres, which are composed of the caudate nucleus, the putamen, and several other structures. It will be suggested that the striatal complexes have an inhibitory effect on the thalamus, thereby restricting the amount of sensory input allowed to reach the cerebral cortex. In our hypothesis, schematically represented in Fig. 1, this action constitutes a highly selective filter mechanism that protects the cerebral cortex against overload and thus allows relevant information to

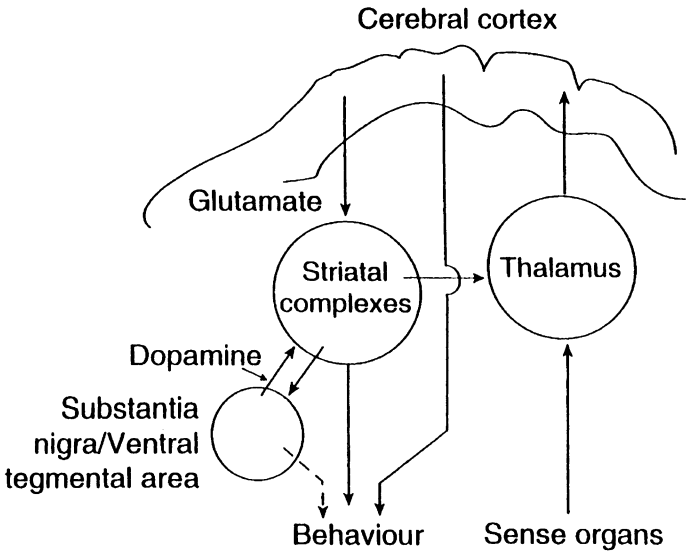

Fig. 1 Schematic representation of the hypothesis that the cerebral cortex can protect itself from an overload of information and from hyperarousal by means of feedback loops which engage the striatal complexes and the thalamus (as well as the mesencephalic reticular formation, not shown). The feedback loops are modulated by the mesencephalostriatal dopaminergic pathways (Carlsson, 1988). (Reproduced by kind permission of the American College of Neuropsychopharmacology.)

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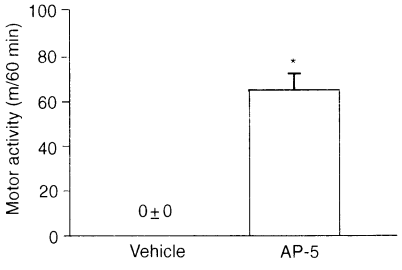
have precedence over irrelevant information. While this blocking action was originally demonstrated by the electrophysiological experiments of Gunther Stille (Stille, 1976), this article will be concerned with the role of neurotransmitters.

THE GLUTAMATE/DOPAMINE BALANCE

Two major factors counterbalance one another in the striatal complexes. First, there are pathways originating from glutamate in all parts of the cortex, both the limbic cortex and the neocortex, and then there are dopamine pathways coming from the substantia nigra and ventral tegmental area (VTA). Since dopamine is inhibitory, it can, if present in excess, open up the filter. The integrative capacity of the cerebral cortex may then be overwhelmed, a situation that could result in psychosis. It is known that dopaminergic agonists are indeed capable of psychostimulation and the induction of psychosis and that glutamate antagonists have a similar action.

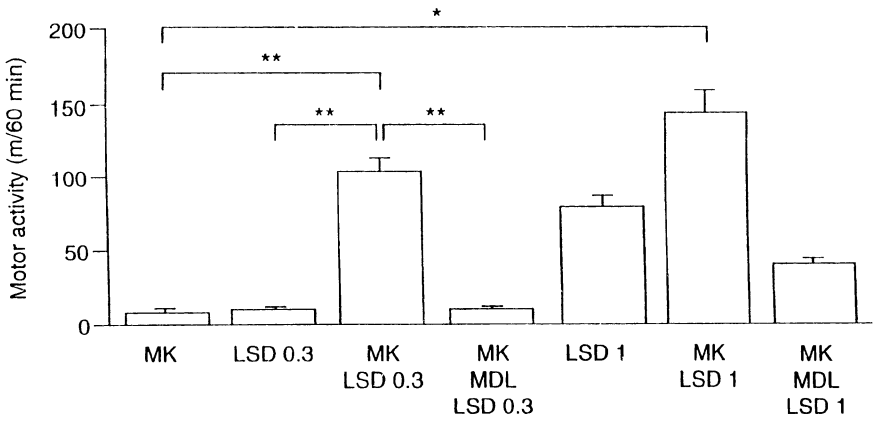
In order to test this hypothesis experimentally, we used inhibitors of one of the major glutamatergic receptors, the N-methyl-D-aspartate (NMDA) receptor (i.e. phencyclidine (PCP)), and other compounds that block the receptor by acting on a site in the ion channel or on other sites of the receptor, thus inducing schizophrenia-like symptoms.

It is well known, of course, that if dopamine is blocked, animals become immobile. According to our hypothesis, that may be due to an active effect of glutamate. In short, when an imbalance is created in favour of glutamate, it is the glutamatergic tone that actually induces immobility.



*P<0.01

Fig. 2 Locomotion-stimulating effect of the N-methyl-D-aspartate antagonist AP-5 (5 μg) or vehicle injected into the nucleus accumbens of monoamine-depleted mice. Locomotion is given as metres per 60 min measured in circular tracks (Svensson & Carlsson, 1992). (Reproduced by kind permission of Elsevier Science.)



*P<0.05; **P<0.01

Fig. 3 The 5-HT_{2A}-receptor antagonist MDL-100,907 antagonises the locomotor stimulation produced by a low dose of LSD in combination with MK-801 in monoamine-depleted mice. MK-801 (1 mg/kg) was administered for 60 min; MDL-100,907 (1 mg/kg) for 20 min; and LSD (0.3 or 1 mg/kg) was administered immediately prior to commencement of locomotor recording (Carlsson, 1995). (Reproduced by kind permission of Springer–Verlag.)

Blocking the NMDA receptor would then reduce glutamatergic tone, and the animal should start to move again, despite the complete absence of dopamine. In 1989 we demonstrated this experimentally (Carlsson & Carlsson, 1989).

We then showed that when a glutamatergic NMDA antagonist was administered systemically to these animals in increasing doses, mobility was again induced. The effects were even more dramatic when an antagonist, AP-5, was introduced locally into the nucleus accumbens of immobile, dopamine-free animals, and they too began to move again (Fig. 2) (Svensson & Carlsson, 1992).

In addition, the patterns of mobility induced were observed to be markedly different according to whether the NMDA receptor inhibitor was administered locally or systemically. When the animal was treated systemically, the movement was simple, direct, forward locomotion, and there was no ability to switch to another form of locomotion. When treated locally, more varied movement was observed, and the pattern of mobility was nearly, although not quite, normal.

INTERACTIONS OF GLUTAMATE WITH MONOAMINERGIC SYSTEMS

We also addressed the question of how glutamate interacts with the monoaminergic and other neurotransmitter systems, and found it to be unexpectedly dramatic. A mild glutaminergic deficiency was induced in monoamine-depleted animals with a subthreshold dose of the NMDA-receptor antagonist MK-801 that was insufficient to make them move. They were then treated with low-dose lysergic acid diethylamide (LSD) or dopaminergic or alpha-adrenergic agonists, in doses that by themselves had no activity. Combined with MK-801, however, they induced marked movement. The effect of LSD can be blocked very effectively by a highly selective 5-HT_{2A}-receptor antagonist, such as MDL-100,907 (MDL) as shown in Fig. 3 (Schmidt *et al*, 1995). The figure also shows that when this experiment is performed with higher doses of LSD, the effect is less dramatic since receptors in addition to the 5-HT_{2A} receptor are stimulated. At low doses of LSD, however, the situation is clear. Evidently, stimulation of 5-HT_2 receptors is then the major element inducing motility when glutamatergic tone is simultaneously reduced.

The action of MDL was further studied in animals with intact monoaminergic systems. In this experiment, glutamatergic tone was again lowered by means of the NMDA antagonist, thus strongly stimulating psychomotor activity, and the animals were then treated with MDL. In animals with normal glutamatergic function, the compound does not have much affect on motility, but in animals with elevated psychomotor activity, motility is reduced even with low doses of this powerful 5-HT_{2A}-receptor antagonist (Fig. 4).

Assuming that the glutamatergic deficiency model is an appropriate model for psychoses, these experimental outcomes

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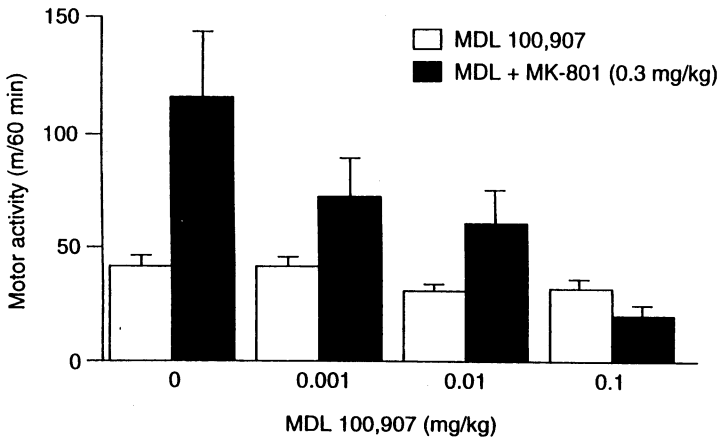

Fig. 4 Effect of various doses (mg/kg) of MDL-100,907 on MK-801 (0.3 mg/kg)-stimulated locomotor activity as well as on normal activity in monoamine-intact mice (Martin et *al*, 1997). (Reproduced by kind permission of Elsevier Science.)

are encouraging, since one would only want to reduce elevated activity. A strong effect on normal activity, such as occurs with conventional neuroleptic drugs, would not be desirable. Indeed, the interference with normal activity is the drawback of those drugs. This MDL compound is now in phase 3 trials, and we will hopefully learn more about its properties as an antipsychotic agent.

Thus, as schematically illustrated in Fig. 5, the cerebral cortex exerts a strong inhibitor effect through the glutamatergic pathways on monoaminergic pathways converging on GABA-ergic neurones in the striatum. If the effect of the glutamate is reduced, then these monoaminergic arousal mechanisms become uncontrolled and are followed by the problems of hyperarousal and psychosis.

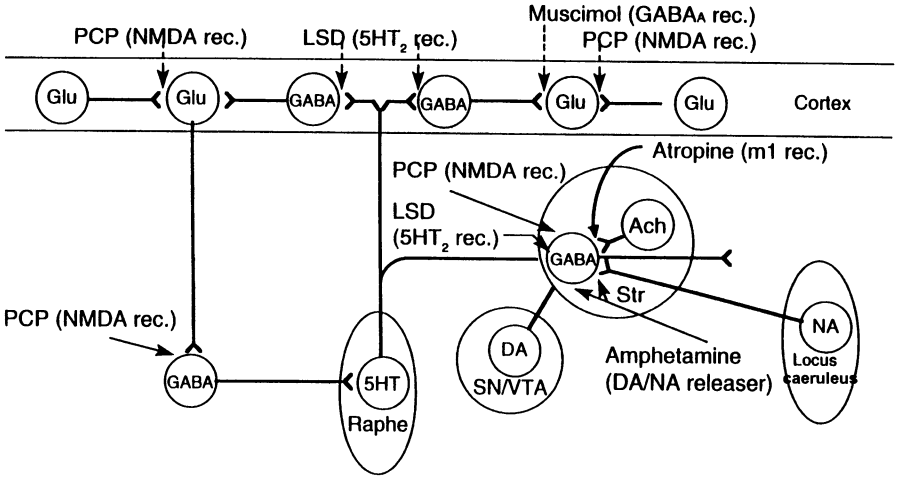

Fig. 5 Schematic diagram illustrating potential psychotogenic pathways and sites of action of psychotogenic and antipsychotic agents. The psychotogenic agents, amphetamine and phencyclidine (PCP), for example, may act on striatal dopamine release and N-methyl-D-aspartate (NMDA) receptors, respectively, in the (limbic) striatum, although other sites may be affected as well. As indicated in the figure, PCP may block cortical NMDA receptors (e.g. in the hippocampus), leading to reduced tone in corticostriatal glutamatergic pathways. The $5HT_2$-agonist LSD may act by stimulating cortical GABA-ergic interneurones, thereby reducing corticostriatal glutamatergic tone. LSD also seems to act on neurons in the striatum. The GABA-A receptor agonist, muscimol, which also appears to be psychotogenic (Tamminga et *al*, 1978), may likewise act by reducing corticostriatal glutamatergic tone. Anticholinergic agents appear to act by blocking predominantly muscarinic M_1 receptors (Carlsson et *al*, 1997) (Glu, glutamate; rec., receptors; SN, substantia nigra; VTA, ventral tegmental area; Str, striatum; Ach, acetylcholine; NA, noradrenaline).

Since acetylcholine operates together with glutamate in the striatum (Fig. 5), cholinergic mechanisms are also of considerable interest. It is known that anticholinergics are psychostimulants and can be psychotomimetic. None of these elements should therefore be singled out and none excluded in considering the induction of psychosis.

GLUTAMATERGIC DEFICIENCY: PRESYNAPTIC MONOAMINERGIC INTERACTIONS

While postsynaptic interactions can be demonstrated after removing the monoaminergic functions (see the previous section), the question arises as to how glutamatergic deficiency affects the monoaminergic systems at the presynaptic level. In our hypothesis, the dopaminergic, noradrenergic, or serotonergic neurones are controlled from the cortex by means of an 'accelerator', which is a direct glutamatergic fibre, and a 'brake', which is also glutamate but with an intermediary GABA-ergic interneuron (Fig. 6). Under normal conditions, it appears that the brake tends to be the stronger element in the balance. Consequently, if a deficiency is introduced in both systems by, for example, reducing NMDA-receptor function, the deficiency of the brake will be most apparent. In other words, where there is a glutamate

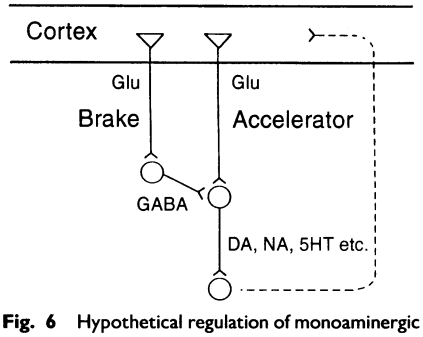

Fig. 6 Hypothetical regulation of monoaminergic neurons by cortical glutamatergic pathways at the presynaptic level. The monoaminergic neurons in the lower brainstem are regulated by cortical glutamate in two ways: (a) directly by means of fibres projecting to their somatodendritic areas ('accelerators') and (b) indirectly by fibres projecting to the GABA-ergic interneurons ('brakes'). The balance between accelerators and brakes is regulated in part by feedback loops, probably involving the thalamus. (cf. Figs 1 and 5) (Glu, glutamate; DA, dopamine; NA, noradrenaline).

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deficiency, the monoaminergic systems will be stimulated, especially if the animal is also subject to some other stimulant such as stress, or novelty, and then the brake cannot function.

Miller & Abercrombie (1996) have presented experimental data demonstrating that situation. If dopamine release is induced by means of amphetamine, there appears to be a feedback loop, which probably involves the thalamus, (Figs 1, 5) that strengthens the brake relative to the accelerator to counteract that release. Under these conditions, if the glutamatergic system is weakened by means of MK-801, there is an enormously enhanced release of dopamine and the full effect of amphetamine becomes apparent, unconstrained by the feedback system.

Laruelle *et al* have reported imaging data showing that if patients with schizophrenia are given a challenge dose of amphetamine, the release of dopamine induced by this drug can be measured using single-photon emission computed tomography (Laruelle *et al*, 1996). Interestingly, these patients were found to respond to amphetamine with a far stronger release of dopamine than did normal controls. A possible explanation of Laruelle's findings is that if a glutamatergic deficiency does, in fact, exist in schizophrenia, then the 'brake' that should counteract the evaluation of dopaminergic tone fails to function in this system, as it did in Miller and Abercrombie's experiment after treatment with MK-801.

Other animal experiments have demonstrated how a glutamatergic deficiency will change the pattern of monoaminergic indices. We treated rats with MK-801 to reduce glutamatergic tone, sacrificed the animals, and analysed the brains (Waters *et al*, 1994). Using a number of monoaminergic indices, a multivariate analysis was performed to define and describe the pattern of the monoaminergic systems. Figure 7 illustrates the dramatic change that occurs in the monoaminergic systems when glutamatergic tone was reduced. Briefly, the monoamine levels were reduced and the levels of their deaminated metabolites increased, a pattern indicative of enhanced monoaminergic activity.

The effect of different compounds, both typical and atypical antipsychotic medications, was examined in this model by treating rats with vehicle or MK-801, followed by haloperidol and clozapine. Ideally, the medications should have restored these 'psychotic' animals to the control state, but neither drug accomplished this task in an entirely satisfactory manner. The restoring action of haloperidol took place along the horizontal axis and that of clozapine along the vertical axis, involving dopaminergic and serotonergic indices, respectively (Fig. 8). When the rats were treated with haloperidol and MDL-100,907 after pretreatment with vehicle or MK-801, we found that the effect of MDL-100,907 was similar to that of clozapine, suggesting that 5-HT_{2A}-receptor antagonism may be an important component in the action of clozapine.

A number of postmortem studies have been performed on persons who had suffered from schizophrenia, using the same techniques as employed in the animal studies (Carlsson *et al*, 1997). These, too, demonstrated that the biochemical pattern of monoaminergic indices is different in patients with schizophrenia from that in controls.

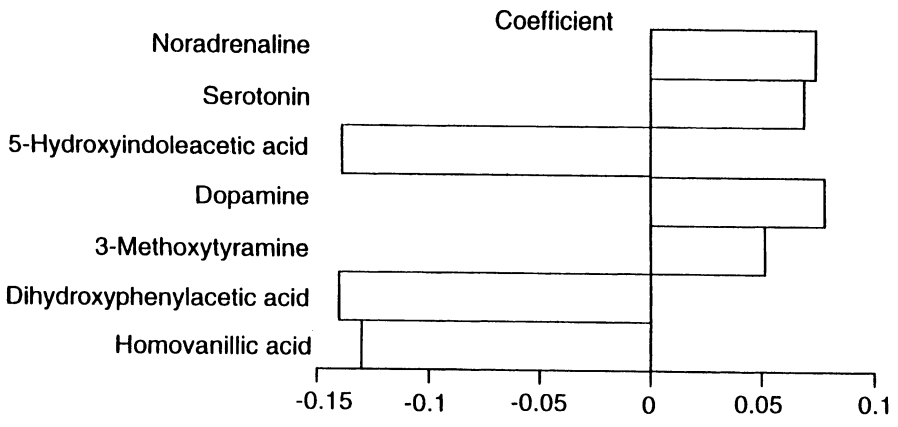

Fig. 7 The strongest discriminants in a multivariate analysis of the effect of MK-801 (0.7 mg/kg SC) on monoaminergic indices in the rat brain. Data derived from the limbic forebrain. Deviation to the left indicates a decrease compared with control; deviation to the right indicates an increase compared with control (see Waters *et al*, 1994).

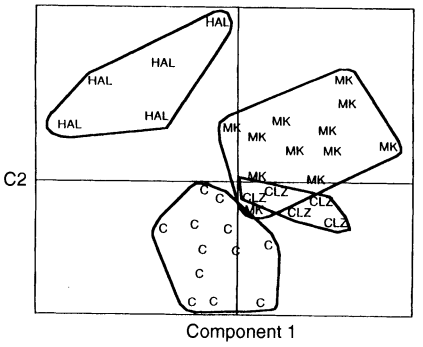

Fig. 8 Multivariate analysis of monoaminergic indices in the brains of rats pretreated with MK-801 (0.7 mg/kg SC(MK)) or vehicle (C) and subsequently treated with haloperidol (0.08 mg/kg SC (HAL)) or clozapine (10 mg/kg SC (CLZ)) (see Waters *et al*, 1995).

In conclusion, there is much evidence to suggest that schizophrenia involves a loss of stability due to a weakened glutamatergic tone, which increases the risk of sensory inputs, causing exaggerated responses in the monoaminergic systems that can lead to a psychotic episode. The future development of drugs capable of supporting the glutamatergic functions would be of great interest. The 5-HT_2-receptor antagonist, the MDL compound, could have such a supporting effect on glutamatergic functions (e.g. in the cortex) and it should soon be known whether or not it has antipsychotic properties. Other promising areas of drug development are the dopamine receptor subtype-selective ligands and drugs with multiple sites of action.

REFERENCES

Andén, N.-E., Butcher, S. G., Corrodi, H., *et al* (1970) Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. *European Journal of Pharmacology*, **11**, 303–314.

Breier, A., Sue, T.-P., Saunders, R., *et al* (1997) Schizophrenia is associated with elevated amphetamine-induced synaptic concentrations: evidence from a novel positron emission tomography method. *Proceedings of the National Academy of Sciences of the United States of America*, **94**, 2569–2574.

Carlsson, A. (1988) The current status of the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology*, **1**, 179–203.

— **& Lindqvist, M. (1963)** Effect of chlorpromazine or haloperidol on the formation of 3-methoxytyramine and normetanephrine on mouse brain. *Acta Pharmacologica et Toxicologica*, **20**, 140–144.

https://doi.org/10.1192/S0007125000293574 Published online by Cambridge University Press

—, Hansson, L. O., Waters, N., *et al* (1997) Neurotransmitter aberrations in schizophrenia: new perspectives and therapeutic applications. *Life Sciences*, **61**, 75–94.

Carlsson, M. L. (1995) The selective 5-HT_{2A} receptor antagonist MDL 100,907 counteracts the psychomotor stimulation ensuing manipulations with monoaminergic, glutamatergic or muscarinic neurotransmission in the mouse: implications for psychosis. *Journal of Neural Transmission*, **100**, 225–237.

— & Carlsson, A. (1989) The NMDA antagonist MK-801 causes marked locomotor stimulation in monoamine-depleted mice. *Journal of Neural Transmission*, **75**, 221–226.

Creese, I., Burt, D. R. & Snyder, S. (1976) Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science*, **192**, 481–483.

Dao-Castellana, M.-H., Paillère-Martinot, M.-L., Hantraye, P., *et al* (1997) Presynaptic dopaminergic function in the striatum of schizophrenic patients. *Schizophrenia Research*, **23**, 167–174.

Hietala, J., Syvalahti, E., Vuorio, K., *et al* (1995) Presynaptic dopamine function in striatum of neuroleptic-naïve schizophrenic patients. *Lancet*, **346**, 1130–1131.

Laruelle, M., Abi-Dargham, A., Gil, R., *et al* (1996) Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proceedings of the National Academy of Sciences of the United States of America*, **18**, 198.

Martin, P., Waters, N. R., Waters, S. E., *et al* (1997) MK-801-induced hyperlocomotion: differential effects of MDL 100,907, SDZ PSD 958 and raclopride. *European Journal of Pharmacology*, **335**, 107–116.

Miller, D. W. & Abercrombie, E. (1996) Effects of MK-801 on spontaneous and amphetamine-stimulated dopamine release in striatum measured with in vivo microdialysis in awake rats. *Brain Research Bulletin*, **40**, 57–62.

Nyback, H. & Sedvall, G. (1970) Further studies on the accumulation and disappearance of catecholamines formed from tyrosine-14-C in mouse brain. *European Journal of Pharmacology*, **10**, 193–205.

Schmidt, C., Sorensen, S. M., Kehne, J. H., *et al* (1995) The role of 5-HT_{2A} receptors in antipsychotic activity. *Life Sciences*, **56**, 2209–2222.

Seeman, P., Lee, T., Chau-Wong, M., *et al* (1976) Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature*, **261**, 717–719.

Stille, G. (1976) Neurophysiological correlates to antipsychotic effects of drug. In *Antipsychotic Drugs: Pharmacodynamics and Pharmacokinetics* (eds F. Sedvall, B. Uvnas & Y. Zotterman), pp. 51–62. Oxford: Pergamon Press.

Svensson, A. & Carlsson, M. L. (1992) Injection of the competitive NMDA receptor antagonist AP-5 into the nucleus accumbens of monoamine-depleted mice induces pronounced locomotor stimulation. *Neuropharmacology*, **31**, 513–518.

Tamminga, C. A., Crayton, J. C. & Chase, T. N. (1978) Muscimol: GABA agonist therapy in schizophrenia. *American Journal of Psychiatry*, **135**, 746–748.

Waters, N., Carlsson, A. & Hansson, L. (1994) An animal model of schizophrenia based on multivariate analysis of monoaminergic biochemistry and behaviour. *Society of Neuroscience Abstracts*, **20**, 1, 825.

—, — & — (1995) Evaluation of drug effects in a multivariate animal model of schizophrenia. *Society of Neuroscience Abstracts*, **21**, 1, 825.

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