S71. New therapeutic targets in schizophrenia

Chairman: R Kerwin

EFFECTS OF PHARMACOLOGICAL MANIPULATIONS OF 5-HT2A AND GLYCINE RECEPTORS IN A MOUSE MODEL OF HYPOGLUTAMATERGIA

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Since the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine, in contrast to d-amphetamine, mimics both positive and negative symptoms of schizophrenia, NMDA antagonist-induced behavioural aberrations in rodents may represent a better model of "core" schizophrenia than the d-amphetamine model. The aim of the present investigation was to investigate the ability of 5-HT2 receptor antagonists and glycine agonists to influence NMDA antagonist-induced hyperactivity in mice.

The 5-HT2A receptor antagonist MDL 100,907 attenuated NMDA antagonist-induced hyperactivity, while lacking clear-cut effects on spontaneous locomotion. The atypical neuroleptic clozapine also effectively counteracted NMDA antagonist-induced hyperactivity, but, in contrast to MDL 100,907, suppressed spontaneous locomotion. MDL 100,907 was also tested in models of dopamine agonist-induced hyperactivity, where it appeared less effective than in the hypoglutamatergia models. These results suggest that MDL 100,907 will lack sedative effects in moderate dosage in humans. It may be envisaged that MDL 100,907 will prove therapeutically useful preferably in hypoglutamatergic conditions.

The effects of the D- and L-forms of serine were also tested on NMDA antagonist-induced hyperactivity and spontaneous locomotion. D- and L-serine were administered systemically, ICV or into the nucleus accumbens. D-serine suppressed both spontaneous locomotion and MK-801-induced hyperactivity; preliminary evidence suggests that the L-form may be less effective. In this context the issues of use-dependency and the degree of saturation of the NMDA receptor-associated glycine site will be discussed.

REVIEW OF DOPAMINE D2/5HT2 BLOCKERS

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A 5HT2 antagonistic effect constitutes a significant part of many antipsychotics, both old drugs such as chlorprothixene and thioridazine, and newer drugs such as risperidone and olanzapine, but the significance of this 5HT2 component has never been significantly proven. Rodent studies indicate that 5HT2 antagonism may influence dopamine functions and reduce catalepsy, but studies in nonhuman primates have not been able to identify any effect of 5HT2 antagonists in haloperidol-induced extrapyramidal syndromes. In schizophrenic patients, 5HT2 antagonists given alone have mild, if any, antipsychotic effect, and in patients who have received 5HT2 antagonists in addition to a D2 receptor antagonist, inconsistent effects have been described, and studies showing positive effects have been less complete in their methodological architecture.

The new 5HT2-D2-alfa1 antagonists (risperidone, ziprazidone and sertindole) have all shown antipsychotic effect comparable with standard antipsychotics, but better effect in negative symptoms and relatively few EPS. However, in most cases these findings are better explained by a relatively high dose of the comparative drug, haloperidol, which has been used at an established EPS dose level (10–20 mg/day). By adding a cholinergic and histaminergic receptor blockade, more broad spectrum drugs (clozapine, olanzapine and seroquel) are created, and it is now totally impossible to evaluate the potential therapeutic contribution of the 5HT2 component. However, if a significant antipsychotic effect can be obtained with drugs causing a relatively low D2 receptor occupancy (as in the case of clozapine), these drugs will induce relatively few extrapyramidal syndromes and imply a substantial step forward.

ANTIPSYCHOTICS — THE NEXT GENERATION

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PCP, a non-competitive antagonist acting at the ion channel of the NMDA receptor induces a psychotic-like condition in humans. Attention has therefore focussed on the NMDA receptor as a novel site for pharmacological intervention in the treatment of schizophrenia. The NMDA receptor complex includes a gylcine sensitive binding site which modulates activation of the receptor via the agonist binding site. (+)-HA-966, a weak agonist at this glycine-binding site, has been demonstrated to exhibit NMDA-antagonist properties *in vitro*. In behavioural experiments in rodents this compound is able, also, to block the locomotor effects of amphetamine and of non-competitive NMDA antagonists. Work is needed to define the sites of functional interaction between dopamine and NMDA receptors in the forebrain, which may account for the "antipsychotic-like" profile of glycine site antagonists.

THE 5HT2 RECEPTOR AS A SITE FOR ANTIPSYCHOTICS

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The advent of newer antipsychotics such as clozapine and risperidone which have greater affinity for 5HT2 receptors has awakened interest in this site as a therapeutic target in schizophrenia. Studies on 5HT2 receptors post-mortem have consistently shown elevations in schizophrenia and selective 5HT2 receptor antagonists have properties overlapping atypical drugs which include a weak effect on negative symptoms and few extrapyramidal consequences. We have been testing whether the 5HT2 receptor mediates antipsychotic effect by correlating variation in clinical response to clozapine with polymorphic variation in polymorphisms for 5HT2a and 5HT2c receptors. So far we have studied a silent T to C change at position 106 of the 5HT2a receptor and a cystine to serine polymorphism at position 68 of the 5HT2c receptor. When analysed according to allotype or genotype in 174 patients the possession of a C allele in the 5HT2a receptors is more significantly associated with non response and possession of a serine allele in the 5HT2c is significantly associated with response. In addition a low frequency histidine to tyrosine variant close to the C terminus of 5HT2a is exclusively associated with non response. Although the mechanisms of these effects are not understood, taken together these results confirm the 5HT2 system as a mediator of antipsychotic effect and suggests that improving selectivity and affinity of drugs for these sites is a worthwhile strategy for drug discovery.

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