Pharmacology of New Antipsychotic Drugs: Are they Stabilizers of Schizophrenic Psychism?

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SUMMARY

In this article, pharmacology of new antipsychotic drugs are reviewed and discussed.

Key Words: Antipsychotic Drugs, atypical neuroleptics.

The utilization of chlorpromazine in early 1950's was the beginning of a new era in the treatment of schizophrenia. In the following thirty years numerous neuroleptics have been launched, most of them having the same fundamental mechanism i.e. the blockade of dopaminergic receptors, but some of their clinical properties were sometimes different inducing a classification based as well upon chemical structures as clinical features. The most important problem using these drugs was the dose equivalence as compared with chlorpromazine.

While these drugs have shown their efficacy in treating schizophrenia, they induce a wide range of side-effects. Yet psychiatrists tried to use minimal dosages and/or prescribe correctors even if there was not a strong consensus in that practice. On the other hand, classical neuroleptics are more efficient on positive than on negative symptoms, with 25% of patients as responders. Taking care of psychotic patients is an economic burden knowing that the epidemiology of schizophrenia comprise between 1 to 2% of the populations anywhere wide world. The global costs were estimated in France around 2.3 billion USD (1). Drug treatment makes up 5.6% of this cost with only 76% for neuroleptics. An analysis of lifetime resource use suggests that just 10% of patients incur nearly 80% of the total lifetime direct costs. These are the patients with episodes lasting more than 2.5 years and who require long-term care either in hospital or intensive community program. Thus, the failure of conventional therapies to improve the symptoms of a relatively small group of patients substantially increases the total burden of the disease. An improvement in treatment that halved the size of this group would reduce total lifetime direct costs by 37% (2).

The development of new drugs in the field of schizophrenia is orientated towards molecules having few side effects but as well an effect on negative symptoms (3). These new drugs may improve the quality of life of patients, their insertion into society and decrease the indirect costs linked to social burden. Ideally, the therapeutic strategies have to be compared between themselves to optimize the clinical results and costs.

The dopaminergic hypothesis of Carlsson and Crow, based on the fact that positive symptoms are linked to a hyperactivity of the dopaminergic system, and negative symptoms to a hypoactivity of that system, is now modulated by evidence concerning other neurotransmitters. Serotonin induces a negative feed back on dopamine release in some brain areas. Glutamate inhibits subcortical dopaminergic activity (4) and a primitive deficit of glutamate was suggested in schizophrenia. Other neuropeptides such as cholecystokinin and neurotensin are also proposed as modulators of dopaminergic transmission.

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The dopaminergic neurons with long axons, on which neuroleptics act include the following four pathways:

1) The nigro-striatal pathway implicated in producing extra pyramidal effects. In the striatum, dopaminergic neurons are linked with cholinergic neurons. The blockade of D_2 receptors induces a stimulation of the central cholinergic neurons.

2) The mesolimbic pathway, with anterior subcortical projections could be implicated in the initiation of the mobility as well as stabilization of mood. The hyperactivity in this area could be the main cause of positive symptoms of schizophrenia.

3) The meso-cortical pathway which projects to the frontal cortex. It participates in amnesic and cognitive processes. The hypoactivity of this pathway could be responsible for the negative symptoms.

4) The tubero-infundibular pathway, on which dopamine inhibits prolactin secretion of the anterior hypophysis by stimulating D_2 receptors.

The blockade of D_2 receptors by conventional neuroleptics induces amenorrhea-galactorrhea syndrome and decreases libido.

The present hypothesis of schizophrenia is based on a dopaminergic transmission deficit in nigrostriatal and mesocortical pathways, contrasting with an excess of dopaminergic transmission in mesolimbic area (5).

The development strategies in this field are not only focused on discovery of specific antagonists of one subtype of dopaminergic receptor (i.e. D_3 etc.) but on synthesis of molecules having different effects regarding the concerned brain areas.

Antipsychotic drugs with selective blockade of dopaminergic receptors

Up to a few years ago, two dopaminergic receptor subtypes, D_1 receptors activating adenylate cyclase and D_2 receptors inhibiting adenylate cyclase, were known. Stimulation D_1 receptors leads to an increase in cAMP production whereas, D_2 receptor stimulation inhibits cAMP production. Now, there are 5 dopaminergic subtypes: D_1 and D_5 linked to a Gs protein; D_2 and D_4 linked to a Gi protein; and the D_3 receptor, a presynaptic receptor playing a role on negative feed back (6). The dopaminergic receptor family is wide and there are numerous studies aimed at discovering selective blockers and agonists of each subtype of receptor and to correlate the selective binding to a special clinical profile.

Classical neuroleptics such as haloperidol block mainly D_2 receptors, whereas benzamides mainly block D_2 and D_3 receptors (7).

The D_4 receptor is selectively blocked by clozapine which could explain its better efficacy on refractory schizophrenia (8,9).

The wide distribution of D_2 receptors is an ubiquity expression particularly in neostriatum and hypophysis where its blockade explains motor as well as neuroendocrinological side effects of the conventional neuroleptics. Their blockade at limbic area explains their therapeutic effects on the positive symptoms, hallucinations and delusions. However, they block dopaminergic transmission in other brain areas, potentially increasing the negative symptoms and leading to tardive dyskinesia.

Blockers of D_2 and D_3 receptor subtypes

Various research has focused on development of D_2 receptor selective blockers with preferential actions at mesolimbic level compared to nigro-striatum system. The D_3 receptor subtype is located in limbic areas but not in the hypophysis or the striatum.

Benzamide compounds are able to selectively block enough D_2 and D_3 receptors (10). For example, sulpiride, preferentially blocks at low dosages presynaptic D_3 receptors, giving it a bipolar activity. Clinical trials have shown that sulpiride is an efficient antipsychotic, yet its side effect profile, particularly the extra-pyramidal symptoms and hyperprolactinemia, are not correlated with predictions based on dopaminergic selectivity at D_2 receptors (11). A possible explanation is that sulpiride is an hydrophilic drug so it does not easily cross the blood brain barrier. So, it is necessary to use high doses like 600 to 800 mg per day, and even up to 1 g which induce side effects.

Remoxipride is a weak D_2 blocker, but specific for the extrastriatal receptors. On the contrary of typical neuroleptics like haloperidol, animal studies in rats showed that there were wide differences between the doses of remoxipride in decreasing the locomotor activity induced by dopaminergic agonists and those inducing catalepsia. In vivo binding studies with D_2 receptors have shown, that remoxipride inhibits the binding of trotted spiperidone in some limbic areas more than in the striatum, compared to typical neuroleptics, which affect identically these two brain areas. Clinical extrapolation from its psychopharmacological profile seems to indicate that remoxipride can induce less extrapyramidal effects as well as lower prolactin secretion than classical neuroleptics. Recently, it was shown that remoxipride blocks D_2 as well as D_3 receptors as well as the sigma opioid receptor. Remoxipiride has been shown to antagonize amphetamine induced hyperlocomotor activity and demonstrate fewer stereotypic behaviors. The significance of these two effects is not yet very clear.

Nine multicentre controlled double blind studies compared remoxipride efficacy with haloperidol in treating acute schizophrenia. In a Canadian study (12) 242 schizophrenic patients and 242 patients presenting acute schizophrenia were treated with three dosages of remoxipride compared to placebo. In a range of 20 to 600 mg/day, remoxipride was comparable in efficacy with haloperidol used in a dose ranging from 15 to 45 mg/day. Remoxipride treated patients had better improvement of their negative symptoms as well as presenting with less extrapyramidal and neuroendocrinological side effects compared with haloperidol treated patients. On the other hand, more patients exhibited akathisia in the remoxipride group. Tardive dyskinesia risk seems to be less likely to develop with remoxipride compared to haloperidol. Eight cases of aplastic anemia out of 45000 remoxipride treated patients resulted in the withdrawal of remoxipride from the Swiss market which lead to withdraw..

Agonists of D_2 presynaptic receptors

These molecules, B-HT 920, EMD 49980, SND 919 and roxindole seem to decrease prolactinemia without inducing catalepsia. The actual evidence is poor and not conclusive (7).

D_2 post-synaptic partial agonists

D_2 partial agonists such as terguride and SDZ 208-911 could be effective agents in hypo and hyper dopaminergic activities. If evidence is found, these drugs could ameliorate positive and negative symptoms with few extrapyramidal side effects.

D_1 blockers

Interest in the D_1 receptor was raised when evidence accumulated about the interaction between D_1 and D_2 receptors (13). Derivatives of thioxanthene i.e. flupenthixol and zuclopenthixol as well as clozapine have higher affinity for D_1 receptor than do phenothiazines. Research in this field was dropped because there were no selective D_1 blockers available. Recently, several D1 blockers were developed i.e. SCH 23390 NO 756, SCH 39166 and A 69024. However studies with SCH 23390 were stopped because of toxicity. The other compounds are still studied in clinical trial.

D_4 antagonists

Distribution of mRNA that code for synthesis of D_4 receptors shows that it is mainly located in the limbic and mesocortical areas. Blockade of this receptor could explain the better activity of clozapine and olanzapine in refractory schizophrenia. Post mortem studies have shown that there was a high density of this receptor in schizophrenic patients. However, it has been found that recently, there is no link between D_4 receptor density and treatment response, and that it is not a predisposing factor of the illness (14).

Antipsychotic drugs with selective serotoninergic antagonism

Interest in the serotoninergic system is increasing in recent years because there is evidence that it plays a role in depression, anxiety and more recently in schizophrenia (15).

5-HT2 receptor blockers

It is known that thioridazine, clozapine and some other neuroleptics act as 5-HT2 antagonists beside their activities on the dopaminergic system. Recently 5-HT2 selective antagonists have been developed. Ritanserin is the most representative of these compounds. This drug was widely studied. It increases the activity of the dopaminergic neurons located in the mid-brain. This stimulating effect leads to the idea that 5-HT2 receptor blockers could improve negative symptoms in schizophrenia. However, there are few clinical trials of the antipsychotic activity of this compound.

5-HT3 blockers

Animal studies lead to evidence that 5-HT3 antagonists can reduce hyperactivity induced by dopaminergic agonists when directly injected in limbic structures. It was proven in open clinical trials that ondansetron which is a 5-HT3 selective blocker, had some antipsychotic properties at low but not at high doses. Several short term double blind studies confirmed some antipsychotic properties of the drug. Yet, the development of ondansetron in schizophrenia was kept aside in favor of other 5-HT3 blockers such granisetron, GR 68 756 C and BRL 46-470. Clinical studies of these compounds are promoted and evidence is waited upon to know if these kind of drugs have any efficacy in treatment of schizophrenia.

Antipsychotics with simultaneous blockade of D_2 and 5-HT$_2$ receptors :

Serotonergic neurons projecting from the raphe nuclei, have an inhibitory effect upon dopaminergic transmission inside the nigro-striatal and mesocortical areas leading to decreases in dopamine synthesis and release. In schizophrenic patients, this dopamine inhibition would be exaggerated, and may partly explain the nigro-striatal and mesocortical dopaminergic hypoactivity (4). This inhibition can be decreased by serotoninergic antagonists. So the most important fact explaining the superiority of new antipsychotics compared to conventional neuroleptics is their 5-HT$_2$ antagonism. The antago-

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nism of 5-HT action at the nigro-striatal and the frontal areas leads to an improvement of negative symptoms and a decrease of extrapyramidal symptoms with better tolerance. Some classical neuroleptics such as thioxanthene derivatives exhibit a weak 5-HT2 antagonism but very low compared to risperidone or clozapine. Considering this latest compound, its $5\text{-}HT_2$ blocking effect is more important than its D_2 receptor antagonism. Some authors suggested that there was a good correlation between $5\text{-}HT_2/D_2$ binding ratio and efficacy upon negative symptoms.

Developments of ziprasidone and sertrindole are now in phase III, those of other drugs like zotepine, melperone and R-79 598 are at an earlier stage.

Risperidone is a benzisoxazole derivative with $5\text{-}HT_2$ antagonist properties as well as D_2 antagonism. Several double blind controlled studies using haloperidol (20 mg/day) and placebo in chronic schizophrenics (16,17,18) showed that risperidone is a potent antipsychotic drug with an optimal efficacy in a range of 4 to 8 mg/day upon negative symptoms. Meta-analysis showed a better activity of risperidone upon negative symptoms comparative with haloperidol. Furthermore, risperidone induced few extrapyramidal effects. Some patients showed such effects as well as an increase of prolactin. Clinical trials comparing risperidone with clozapine, perphenezine and zuclopenthixol have not shown significant differences in their respective efficacy. On the other hand, efficacy of risperidone on refractory schizophrenia has not yet been demonstrated.

Alpha-adreno receptor blockers

Risperidone is also shown to exert blocking effects on alpha 1 and alpha 2-adreno receptors. The noradrenergic hypothesis in antipsychotic effect emerged ten years ago as a research pathway, but it was not possible to demonstrate that hypernoradrenergic activity increased in schizophrenic patients to exclude it. Numerous neuroleptics possess alpha 1 adreno-receptor blocking effects. This property leads to a sedative effect, orthostatic hypotension, tachycardia and vertigo and could potentiate an antihypertensive treatment. It is not known what are the clinical consequences of risperidone alpha 2 adreno-receptors blockade.

Seroquel exhibits an alpha 1 adreno-receptor blockade higher than its blockade of D_2 and $5\text{-}HT_2$ receptors. The only study yet published is a comparative study with chlorpromazine (385 mg/day). In that study using BPRS, CGI and PANSS, seroquel (400 mg/day) has not shown any superiority compared with chlorpromazine. In that clinical, trial extrapyramidal effects were not different in the three groups i.e. seroquel, chlorpromazine and placebo, leading to the idea of some bias. The main si-

de effects observed with risperidone were sedation, dry mouth and orthostatic hypotension (19).

ANTIPSYCHOTICS WITH ANTAGONISM OF NUMEROUS RECEPTORS, THE SO CALLED MIXED ANTIPSYCHOTICS

Active neuroleptics on refractory schizophrenia have antagonizing activity of numerous receptors: dopaminergic, alpha-adrenergic, muscarinic and histaminergic (H1). The ratio $5\text{-}HT_2/D_2$ is greater than 1 and dopaminergic binding is more important at limbic and mesocortical D_1 and D_4 receptor levels. The first drug showing this profile was clozapine but now olanzapine has a similar one.

Clozapine was developed in the beginning of the sixties as a derivative of the dibenzodiazepine family. It was shown that clozapine had antipsychotic properties equal or higher than neuroleptics used at that period but with few extra-pyramidal symptoms and no hyperprolactinemia (20). Clozapine does not induce tardive dyskinesia and could be active on tardive dyskinesia induced by classical neuroleptics. At the beginning of 1970's, clinical trials with clozapine were stopped in North America because it induced agranulocytosis. Clinical interest of clozapine was recovered because of its proved efficacy on refractory schizophrenia (around 30% of this kind of patients were improved). Recently, clozapine was registered in Europe than in North America with restrictive conditions because of its hematological toxicity and particularly agranulocytosis found in at least 0.8% of treated patients. So the only use now is in the treatment of refractory schizophrenia with a strict monitoring of the hematological parameters. Beside its efficacy in refractory schizophrenia, clozapine is interesting concerning its pharmacological profile which seems to be wider than that of classical neuroleptics. It is claimed to have an efficacy on cognitive defect, improvement of attention verbal fluency and recall memory of schizophrenics. On the other hand, it improves cognitive disorder in Parkinson disease. The major side effects of clozapine are hypersialorrhea (33% of patients), weight gain as well as convulsions which are dose-dependent (1 to 4,4%) (21).

Olanzapine is a new antipsychotic drug with a close psychopharmacological profile with clozapine. Its efficacy was shown to be better than haloperidol as well as on positive and negative symptoms. Clinical trials have shown that olanzapine had better efficacy than haloperidol and risperidone on depressive symptoms and suicidal ideas. It induces a better improvement of quality of life, already significant after some months of treatment. A potential anxiolytic effect of olanzapine is discussed because of the weak consumption of benzodiazepines, less drop out linked to anxiety in the olanzapine group

(22). Tolerance is good with few extra-pyramidal effects, no agranulocytosis and no tardive dyskinesia (23). It is too early to say if olanzapine could have an efficacy in patients refractory to clozapine treatment and if it could treat tardive dyskinesia.

Histaminergic H₁-receptor blockers

Clozapine and olanzapine block central histaminergic receptors inducing sedative effects as well as an orexigenic effect with an increase in weight (24).

Cholinergic receptor blockers

Cholinergic receptors are implicated in motor activity as well as in amnesic processes. It is not known at the moment if there is any relationship between clozapine and olanzapine blockade of cholinergic receptors and their superiority of action on negative symptoms. Long term treatment by neuroleptics induced an hypersensitivity of dopaminergic receptors and down-regulation of the cholinergic. Their implication in tardive dyskinesia is not clear as well as the anticholinergic effect to prevent them. On the other hand, blockade of cholinergic receptors decreased the extrapyramidal side effects but induced parasympatholytic side effects.

AMINOACID RECEPTOR BLOCKERS

Developments in this field are based on the fact that phencyclidine which is N-methyl-D-aspartate (NMDA) receptor blocker, induced psychotic features in healthy volunteers. Furthermore, glutamate is known to inhibit dopaminergic subcortical activity. These matters of evidence are linked to the fact that glutaminergic deficit could be implicated in pathophysiology of schizophrenia, corticolimbic neuronal neurodegeneration. Unfortunately, the first studies using glycine and micelamide gave negative results. On the other hand, it was proven in animals that clozapine, olanzapine and fluperlapine could prevent neurodegeneration observed when NMDA receptor activity was blocked.

SIGMA RECEPTOR ANTAGONISTS

Sigma receptors are mainly located in sub limbic area? The function of these receptors is not yet clarified but it is thought they could modulate some dopaminergic functions. Several neuroleptics, including haloperidol and remoxipride, bind to sigma receptors, but there is no evidence of any clinical feature. Recently studied sigma receptor antagonists such a rimcazole, cinuperone, BMY 14802 and BW 234 have shown very contradictory results.

CCK-B AND CCK-A RECEPTORS ANTAGONISTS

The relationship between cholecystokinin (CCK) and schizophrenia was the matter of numerous articles (for review see 25) and still is under research.

CCK-B receptors are linked with mesolimbic and nigrostriatal dopaminergic pathways, they modulate dopaminergic function (26). It was shown that acute and chronic administration of a selective CCK-B receptor blocker (LY 262691) decreases midbrain dopaminergic cells activity (27). The results are in favor that CCK-B antagonists could have an antipsychotic effect by modulating dopaminergic release. The effect seems to be more physiological than blockade of dopaminergic receptors (28). This regulation could avoid the long term side effects of neuroleptics such as tardive dyskinesia.

CONCLUSION

The research on antipsychotic drugs with more efficacy and tolerance was an important subject during the last years (29). Numerous drugs were studied. Some of them could be new treatment strategies compared with the classical dopaminergic antagonism. The limbic and frontal cortex specificity leads to a better tolerance as well as a better efficacy on negative symptoms with better quality of life for patients and at the end a decrease of the burden of schizophrenia. It was shown that new antipsychotic drugs decreased by 10% rehospitalisation of responders or non-responders (22). The profile of the new drugs leads to a better dopaminergic balance and decreases in spontaneous instability, and negative symptoms as well as limiting fluctuations between positive and negative symptoms. They seem to act as psychic stabilizers (30).

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