The New Generation of Anti-Psychotic Drugs: Pharmacological Mechanisms of Atypicality

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INTRODUCTION

The entire class of traditional anti-psychotics produces extrapyramidal signs (EPS) therefore, EPS and anti-psychotic activity were once thought to be closely linked. But with the discovery that Clozapine can produce anti-psychotic effect without producing EPS, this concept was no longer defensible. Clozapine thus, by this “atypical” behaviour became the arche-type for a new generation of anti-psychotic drugs that can have anti-psychotic effect without producing EPS and were termed atypical antipsychotics after the atypical behaviour of Clozapine. What makes these drugs behave atypically is still not yet clear. This article is a review of the most common theories explaining mechanisms of atypicality, and will discuss:

1. The definition of atypicality.
2. The four key dopamine pathways in the brain and their role.
3. The hypothesized theories of atypicality.
4. Conclusion.

DEFINITION OF ATYPICALITY

Most of the definitions agree that atypicality is principally low or no EPS, which is usually, but not always associated with other features which are:
Improved negative symptoms, improved mood and cognitive functions, reduced suicidal risk, and lack of sustained prolactin elevation.

THE FOUR KEY DOPAMINE PATHWAYS

1. **Meso-limbic tract**: from the ventral tegmentum of the brain stem to the limbic cortex. The increased dopamine activity in this tract is associated with occurrence of psychosis.
2. **Meso-cortical tract**: from the ventral tegmentum also to the cortical radiation. The decreased dopamine activity is associated with depression, decreased cognition and occurrence of negative symptoms.
3. **Nigro-striatal tract**: from the striatum of the midbrain to the substantia nigra. It is a part of the extrapyramidal system. The decreased dopamine in this tract is associated with the occurrence of EPS.
4. **Tubero-infundebular tract**: from the tuber cinereum of the hypothalamus to the infundibulum of the pituitary gland. Blocking dopamine in this tract abolishes the tonic inhibition of prolactin and increases its level in blood.

Effect of typical antipsychotics

They block D2 in the four pathways, with the following results:
- In the meso-limbic, it produces the antipsychotic effect.
- In the meso-cortical, it worsens negative symptoms, cognition and mood.
- In the nigro-striatal, it produces EPS.
- In the tubero-infundebular, it produces increased prolactin.

The first effect is the therapeutic effect, while the other three effects are side effects (The cost of doing business is too high!).

Theories of atypicality

A lot of theories were put forward to explain atypicality, the most famous are:

1. Limbic selectivity.
2. Other receptor involvement.
3. Fast dissociation from D2.
4. Partial agonism /antagonism of D2.
1- **limbic selectivity:**
This theory postulates that atypicals selectively block dopamine receptors in the mesolimbic tract only, so they produce the antipsychotic effect without producing the other side effects resulting from blocking D2 in the other dopamine tracts.

This theory is limited by being established only for Olanzapine, Quetiapine and Sertindole, but not for Risperidone and Ziprasidone.

2- **Other receptor involvement**
This theory was based on the finding that no antipsychotic effect can occur without D2 antagonism, which means that atypicality must occur through involvement of other receptors. According to this conclusion, two hypotheses were suggested:
1. D4 antagonism.
2. 5HT2A antagonism.

**A- D4 HYPOTHESIS:**
This theory postulates that antagonism at the D4 receptor is the basis of atypicality.

**Limitations:**
- Typical antipsychotics such as haloperidole and chlorpromazine are more potent than atypicals like clozapine or olanzapine at D4.
- Also some atypicals have no affinity for D4 e.g quetiapine & sertindole.
- Finally, clinical trials of drugs selective for D4 don’t show atypicality.

Thus high D4 affinity is neither necessary nor sufficient for producing atypical anti-psychotic activity.

**B- THE SEROTONIN–DOPAMINE HYPOTHESIS:**
This theory postulates that 5HT2 antagonism is critical for producing atypical effect, and assumes that:

**Effect of serotonin blockade on DA release in the 4 pathways**
1. Nigrostriatal → promote DA release → reversal of blockade → ↓ EPS.
3. Tubero-infundebular → reverses DA block → ↑ DA → ↓ prolactin.
4. Mesolimbic: blocking fails to reverse DA blockade → still psychotic improvement.

**Limitations of the theory**
- Some typical antipsychotics as Chlorpromazine have equally high 5HT2 and D2 occupancy.
- Some atypical antipsychotics as Amisulpride have no relevant affinity to 5HT2.
- The difference in affinity of the atypical drugs to 5HT2 and D2, may not be explained as higher affinity to 5HT2, but may be due to lower affinity to D2, as was more apparent in the following theory.

3- **The transient D2 occupancy (fast-off) hypothesis**
This theory postulates that 5-HT2 blockade is neither necessary nor-sufficient to produce atypicality, but it is assumed that the fast dissociation from D2 receptor is the critical factor for atypicality. This will be explained as follows:

The usual measure of affinity is only a relation of $K_{off} / K_{on}$. 

\[
\text{On rate constant} \quad K_{on} \\
\text{Off rate constant} \quad K_{off}
\]
**Drug-Receptor interaction**

The binding of an anti-psychotic to a receptor is a dynamic process with continuous association and dissociation and can be represented as follows:

All anti-psychotics (Typical or atypical) attach to D2 receptor with a similar rate constant, they differ only in how fast they come off of the receptor.

### Comparing 5HT&D2 affinities in the two groups:

<table>
<thead>
<tr>
<th></th>
<th>5 HT2</th>
<th>D2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical</td>
<td>8.37</td>
<td>8.88</td>
</tr>
<tr>
<td>Atypical</td>
<td>8.36</td>
<td>7.02</td>
</tr>
</tbody>
</table>

Atypical antipsychotics differ from typical ones by their lower affinity at D2 receptor and not by their higher affinity at 5HT.

### PET STUDIES OF D2 OCCUPANCY:

Pet studies of D2 occupancy in animal experiments have shown that there is a certain threshold for D2 occupancy to get the effect as shown in this order:

- Antipsychotic effect: 65% D2 occupancy.
- EPS: 78% of D2 occupancy.
- Prolactin elevation: 72% of D2 occupancy.

Since drugs like Clozapine and Quetiapine never exceed this threshold of D2 occupancy, they have placebo level of EPS.

Drugs like Risperidone and Olanzapine exceed this threshold in a dose dependent fashion, so they can give EPS at higher doses.

### D2 affinity and off rates for anti-psychotic agents

- **High D2 affinity, likely slow off rates:**
  - Haloperidol, Fluphenazine, Thiothixene, Chlorpromazine.
- **Intermediate D2 affinity:**
  - Atypical: Risperidone, Olanzapine, Ziprasidone, Amisulpride, Sertindole.
- **Low D2 affinity, likely fast off rates:**
  - Typicals: Thioridazine, Loxapine.
  - Atypicals: Clozapine, quetiapine.

Simulation performed by means of STELLA model-simulation software (High Performance Systems, Hanover, N. H.). Haloperidol occupancy is unchanged by physiological dopamine transmission. Clozapine occupancy decreases to allow physiological dopamine transmission.

### Implications of Fast Dissociation Theory:

Fast dissociation theory could explain some phenomena associated with the use of different types of the atypical antipsychotic drugs such as:

- **A- Responsiveness to endogenous competition:** Antipsychotics are always competing with endogenous dopamine, the faster the Koff, the more quickly the drug responds to dopamine surge, as shown in figure 2 below.

- **Figure (2). Effects on D2 Occupancy of a Surge of Dopamine After Achievement of Equal levels of Occupancy by Haloperidol and by Clozapine**

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D2 binding of conventional and atypical agents:  
- Slow Koff did not show significant impact to dopamine surge, thus disturbing physiological dopamine transmission.
- Fast Koff drug allowed physiological dopamine transmission to exert its effect.

B- Clozapine in refractory schizophrenia:  
Repeated transient blockade of D2 renders it more sensitive to the effect of dopamine blockade, but, continuous blockade produces tolerance and up-regulation of D2 receptor.

This explains why Clozapine is effective in refractory schizophrenia.

C- Quetiapine as monotherapy in Bipolar Depression:

Fast dissociation allows for better function of physiological dopamine, thus improves the mood and alleviates depression.

The fast dissociation hypothesis: Summary  
- Differences in the D2 affinity of anti-psychotics agents are determined by how fast they come off of the D2 receptor.
- Faster dissociation form D2 receptor, Koff explains the most important aspects of atypical anti-psychotic activity (Low potential for EPS).
- Faster dissociation allows more physiological dopamine signaling.

4- Partial D2 agonism/antagonism:  
The fourth theory attributes the occurrence of the atypical effect to partial D2 agonism/antagonism. This theory applies only to Aripiprazole and explains its function as acting differently on the receptor according to the status as follows:

With high D activity, it acts as antagonist, so it improves positive symptoms.

With low D activity, it acts as agonist, so it ameliorates negative symptoms and improves cognitive functions. It is also termed dopamine stabilizer due this differing effect.

Role of 5HT6 in explaining some factors associated with atypicality:
Sertindole is promoted as the atypical antipsychotic which is the least associated with cognitive impairment, and this was attributed to being acting on serotonin, besides the other atypicality factors.

CONCLUSION
- Atypical antipsychotics differ from the typicals in many clinical manifestations besides the low or non occurrence of EPS.
- Theories to explain atypicality include limbic selectivity, other receptor involvement as 5HT2A,D4, fast dissociation from D2 receptors and partial dopamine antagonism.
- 5HT2A blocking theory is the most accepted theory, but it has a lot of limitations.
- Other theories could not explain all phenomena associated with atypicality.
- Probably there isn’t one unitary pharmacological mechanism of atypicality.

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