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The Mechanisms of Action of Antipsychotic Drugs: Is Atypicality Superior in Schizophrenia Treatment?

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Abstract

This review presents the mechanisms of action of typical and atypical antipsychotic drugs, emphasizing the differences in the pharmacology of these drugs used in the treatment of schizophrenia. Initially, the concept of atypicality will be examined through the 2 most widely accepted hypotheses. Hypotheses concerning a high serotonin 5HT2A/dopamine D2 receptor antagonism ratio and a special interaction with D2 receptors via mesolimbic selectivity or a weaker blockade will be discussed. Next, the mechanisms of action of typical and atypical antipsychotics will be explored at the receptor level. Receptor activity of atypical antipsychotics other than D2 receptors at 5HT2A, 5HT2C, 5HT1A, and adrenergic α1 and α2, along with relevant, currently important, and consistent findings, and other mechanisms of action, such as glutamate modulation and increased prefrontal cortical acetylcholine release will be reviewed. In the final section, some specific mechanisms of action, which might be related to clozapine's superiority in schizophrenia treatment, will be examined. Atypical antipsychotics provide a variety of mechanisms of action as compared to typical antipsychotics, and they might be efficacious in treating symptom domains other than positive symptoms. In clinical practice, the superiority of atypical antipsychotics other than clozapine remains an issue that needs to be proven.

Key Words: *Schizophrenia, antipsychotics, mechanisms of action*

INTRODUCTION

After Delay and Deniker demonstrated the antipsychotic (AP) quality of chlorpromazine in 1952, the antipsychotics' mechanisms of action in the treatment of schizophrenia and other psychotic disorders became an area of interest to researchers. In the following years, with the introduction of clozapine and its clinical use, the concept of atypicality regarding antipsychotic action emerged. These new generation APs, referred to as atypical (AAP) due to their lower risk for extrapyramidal symptoms (EPS) compared to typical APs (TAP), have driven schizophrenia treatment since the early 1990s.

Today, the diversity of APs has increased and various classification systems have been introduced; in summary, the following classification might be appropriate:

I) Typical/First Generation Antipsychotics

Dopamine receptor antagonists

II) Atypical/New Generation Antipsychotics

Second generation: Serotonin dopamine antagonists: Benzamides

Third generation: Partial dopamine agonists (dopaminergic system modulators)

I) Typical/First Generation Antipsychotics

The common and basic mechanism of action of all TAPs is their high affinity for and antagonism of dopaminergic D2 receptors, and there is a very strong connection between the therapeutic doses of these drugs and their affinity for the D2 receptors. In vivo positron

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emission tomography (PET) and single photon emission computerized tomography (SPECT) studies have demonstrated the relationship of dopamine receptor involvement with AP response and side effects (Miyamoto et al., 2005). In these studies it was shown that the effect of APs is associated with 65%-70% striatal D2 receptor blockade, whereas D2 receptor blockade above 80% has been shown to increase the risk of EPS (Farde et al., 1992). Because imaging studies have shown that the therapeutic doses of TAPs block D2 receptors in the limbic cortical region and striatum equally and significantly, to minimize the risk of EPS, D2 blockade within the range of 65%-80% forms the therapeutic window and is therefore called the threshold. However, the model of receptor occupation has its limitations as well. Some patients respond to therapy at occupation levels that are below this value, whereas others do not respond to therapy at adequate levels of D2 blockade (Kapur et al., 2000). Although low-dose haloperidol (2-5 mg/day) is expected to create 60%-80% D2 blockade, in daily practice doses 5-20-fold higher can be used. It has been noted that this situation was associated with D2 hypersensitivity caused by long-term TAP use and dose increase could be needed to ensure the same effect on the dopaminergic connections in chronic patients (Kapur et al., 2000; Waddington et al., 2003; Miyamoto et al., 2005).

The fast striatal D2 blockade provided by APs does not match the slow and time-dependent emergence of the therapeutic response. These drugs block the postsynaptic dopamine receptors after which there is an increase in pre-synaptic dopamine action. This increase in dopamine metabolism and dopaminergic neuronal discharge is referred to as depolarization activation. The early response is followed by the inhibition of pre-synaptic dopamine activity. This process matches the time that is required for a clinical response. This spontaneous decrease in the active dopamine neurons within both the substantia nigra pars compacta (A9) and ventral tegmental region (A10) is described as depolarization inactivation (blockade) (Chiodo and Bunney, 1983; Miyamoto et al., 2005).

II) Atypical/New Generation Antipsychotics

Unlike TAPs, it is difficult to talk about a single mechanism of action that explains the effects of AAPs; however, a certain amount of D2 antagonism is still the prerequisite for AAP effect. It is debatable whether it is correct to classify these new generation AAPs, which are different from one another in terms of their side effect profiles, including EPS and receptor activities, under a single group; however, the concept of atypicality is still valid because it separates AAPs from TAPs and also carries an historical meaning. Although there are many hypotheses about the pharmacological basis for the differences between AAPs and TAPs, currently 2 hypotheses have attracted much attention (Abi-Dargham and Larulle, 2005).

II.1) Atypical APs interact both with dopamine (DA) and serotonin (5-hydroxytryptamine/5-HT) systems, and also have a higher rate of 5HT2A/D2 receptor antagonism.

II.2) It is suggested that AAPs demonstrate a different form of interaction with dopamine D2 receptors, observed in the form of 1) mesolimbic selectivity and 2) weaker inhibition. These 2 hypotheses are reviewed more thoroughly below.

The sections reviewing the hypotheses about atypicality will be followed by the sections about the various receptor activities of AAPs and their clinical meaning (II.3), other mechanisms associated with atypical qualities (II.4), and specific mechanisms associated with the superior effect of clozapine (II.5).

II.1) The Serotonin-Dopamine Antagonism Hypothesis

The serotonin-dopamine antagonism hypothesis (Meltzer et al., 1989) suggests that atypicality is determined by an antipsychotic drug's higher affinity for the 5HT2A receptor compared to the D2 receptor, and claims that it explains this group of APs' tendency for increased effect and decreased EPS. In the light of this hypothesis, after the first AAP, clozapine, other AAPs with serotonin-dopamine antagonism activity, such as quetiapine, olanzapine, risperidone, and ziprasidone were developed.

When the selective 5HT2A receptor M-100907 is compared to haloperidol, its ineffectiveness as a monotherapy in schizophrenia demonstrates that 5HT2A antagonism alone is not enough to explain the effects of AAPs (de Paulis, 2001). However, there is limited evidence obtained from animal studies pointing to the beneficial effects of combined 5HT2A and D2 receptor antagonism on positive, negative, and cognitive symptoms in the treatment of schizophrenia. For example, in an animal model, when ritanserin, a 5HT2A/2B72C receptor antagonist, and raclopride, a selective D2/D3 receptor antagonist, were administered together, it was shown that the inhibition of the conditioned avoidance

response, which is a classical test that demonstrates AP effect, increases (Wadenberg et al., 1996). Furthermore it has been shown that when ritanserin, which has no effect alone on DA secretion in the brain, is administered along with raclopride, DA secretion in the prefrontal cortex (PFC) increases, but striatal DA secretion is not effected (Andersson et al., 1995). In another rat study, simultaneous administration of M 100907 and low-dose, e.g. 0.1 mg/kg, haloperidol (less than 80% D2 occupation) provided a synergetic effect on cortical DA secretion, but when the haloperidol dose was increased no such effect was observed in cortical DA secretion (Liégeois et al., 2002). This study points to the importance of the presence of powerful 5HT2A antagonism together with weak D2 receptor inhibition. In terms of cortical DA secretion, it has been suggested that a clozapine-like effect can be achieved by concomitant use of haloperidol, at a dose that affects nigrostriatal functions at a low level, and 5HT2A receptor antagonists (Meltzer et al., 2003). In another double blind placebo controlled study conducted with schizophrenic patients, it was shown that the addition of ritanserin to low-dose haloperidol contributes to the improvement of negative symptoms (Duinkerke et al., 1993). In order to examine the potential role of 5HT2A antagonism, studies that investigate the concomitant use of dopamine D2 antagonists and selective 5HT2A antagonists, such as M 100907 are needed (Miyamoto et al. 2005).

The 5HT2A/D2 antagonism hypothesis has also been criticized. These criticisms, the most important of which are mentioned below, come mainly from researchers that have suggested the fast dissociation /hit and run hypothesis (Seeman, 2002):

1) Although APs, such as remoxipride and amisulpride, are APs with atypical characteristics, they do not occupy 5HT receptors and are distinguished from the others. 5HT inhibition is not required for AP effect.

2) There are clues in favor of the observation that selective 5HT2A inhibition by M 100907 increases catalepsy caused by D2 receptor inhibition (Wadenberg et al., 2001).

3) In the light of the 5HT2A/D2 hypothesis it is not possible to draw a precise line between TAPs and AAPs. With this hypothesis there are many more APs, which would have been described as atypical according to the D2 receptor loose binding theory that do not follow the rule.

4) A high 5HT2/D2 ratio does not annihilate EPS completely. For example, although a high level of 5HT2A receptor occupation (95%) is observed with risperidone (6 mg/d), in many cases it has not been possible to avoid EPS (Nyberg et al., 1996). Furthermore, although chlorpromazine inhibits 5HT2A receptors, it still can cause EPS (Trichard et al., 1998).

5) PET studies have shown that 5HT2A receptor inhibition does not change the D2 occupation level required for AP effect or D2 blockade causing EPS (Kapur et al., 1999).

6) Based on the 5HT2A/D2 ratio, atypical characteristics can be ensured or they can be removed through isomers created by increasing or decreasing D2 affinity. For example, by increasing the D2 receptor affinity of isoclozapine, a clozapine (AAP) isomer, the 5HT2A/D2 ratio can be decreased and atypical characteristics can be removed (Kapur et al. 2002). In contrast to this, by decreasing the D2 receptor affinity of isoloxapine, a loxapine (TAP) isomer, the 5HT2A/D2 ratio can be increased and atypical characteristics can be achieved (Natesan et al., 2005).

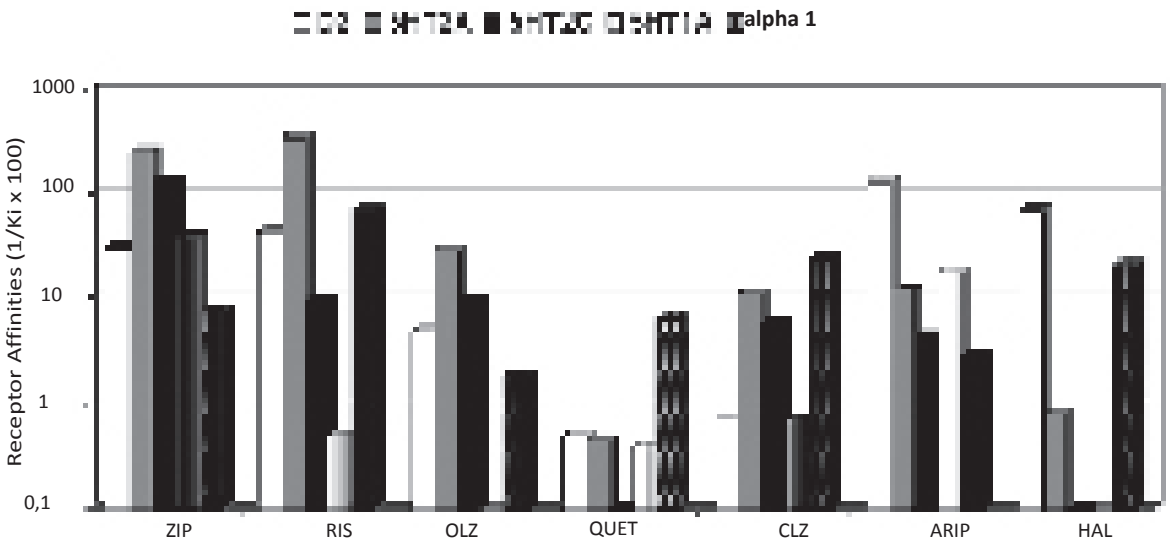
In summary, these criticisms demonstrate that a high 5HT/D2 ratio is neither necessary nor adequate for atypical characteristics and that the main determining factor in terms of AP effect is a drug's D2 affinity.

II.2) Different Interaction Modes of Atypical Antipsychotics with D2 Receptors

II.2.1) Mesolimbic Selectivity Hypothesis

It has been proposed that AAPs have a selective effect on the mesolimbic dopaminergic system, as compared to the nigrostriatal dopaminergic system, and that D2 receptor inhibition in the nucleus accumbens is responsible for the AP characteristics of the D2 receptor antagonists (Abi-Dargham and Laruelle, 2005). The dose-related selectivity of AAPs for triggering the A10 neurons, compared to the A9 neurons, and AAP initiation of gene expression at the level of the nucleus accumbens more than at the striatum have been regarded as important markers suggesting their mesolimbic selectivity (Chiodo and Bunney, 1983; Robertson et al., 1994). However, it is debatable whether or not this selectivity observed in animal studies at low doses is applicable to the clinical setting, where high doses are used in humans.

Benzamides are an example of AAPs whose fundamental mechanism of action is based on mesolimbic selectivity. Sulpride and its analogue amisulpride are selective, high affinity D2/D3 receptor antagonists with a low affinity for D1-like or non-dopaminergic receptors, and they do not



ZIP: Ziprasidone; RIS: Risperidon; OLZ: Olanzapine; QUET: Quetiapine' CLZ: Clozapine; ARİP: Aripiprazole; HAL:Haloperidol

Figure I. 5HT2A, 5HT2C, 5HT1A, α1, and D2 receptor binding affinities of various antipsychotics (Schmidt et al., 2001; Shapiro et al., 2003).

possess 5HT2A receptor antagonism. Laboratory studies have shown that low-dose amisulpride and sulpride inhibit D2 autoreceptors and increase dopaminergic secretion and transmission. Higher doses have been shown to be associated with post-synaptic dopamine receptors and laboratory tests have revealed that they cause behavioral changes that predict AP effect without causing catalepsy (i.e. low tendency to cause EPS) (Perrault et al., 1997). PET and SPECT studies have shown that amisulpride binds to the temporal cortical D2/D3 receptors in a dose-dependent manner, but that this non-striatal selectivity is lost at higher doses (due to increased striatal D2/D3 receptor occupation). It has been reported that amisulpride's medium affinity for the striatal D2 receptors and its selectivity for the limbic cortical D2/D3 receptors are responsible for both its therapeutic effect and its low level EPS characteristics (Xiberas et al., 2001; Bressan et al., 2003; la Fougere et al., 2005). Furthermore, amisulpride, similar to clozapine, has the ability to rapidly dissociate from D2 receptors (Seeman, 2002).

The mesolimbic selectivity of AAPs is supported by imaging studies. In SPECT studies, it has been shown that temporal cortical D2 receptor occupation of amisulpride, clozapine, olanzapine, quetiapine, risperidone, and sertindole are higher than striatal D2 occupation. The same finding has been reported in PET studies of amisulpride, clozapine, olanzapine, and risperidone. However, there are other studies in which this local difference in receptor occupation levels has not been demonstrated (Abi-Dargham and Laruelle, 2005).

II.2.2) Weaker Inhibition

The finding that AAPs cause a weaker and medium level blockade of the striatal D2 receptors compared to TAPs from the pioneering SPECT study of Pilowsky et al. (1992) has been repeated numerous times since then. Subsequently, 40%-60% striatal D2 occupation levels have been reported with therapeutic doses of amisulpride, clozapine, and quetiapine (Xiberas et al., 2001, Pilowsky et al., 1997, Stephenson et al., 2000). This observation obtained from imaging studies could have been due to the fact that AAP doses used in the clinical setting were lower than TAP doses (Abi-Dargham and Laruelle 2005).

II.2.2a) The Fast Dissociation/Hit and Run Hypothesis

An alternative approach to the concept that there is a difference in the interaction of AAPs with D2 receptors compared to TAPs would be the fast dissociation/hit and run hypothesis. According to the fast dissociation hypothesis, fast molecular dissociation (k_{off}) from D2 receptors is the only quality that determines the atypicality of a D2 antagonist. According to the fast dissociation hypothesis, low D2 receptor affinity is the most important characteristic that differentiates AAPs from TAPs (Kapur and Seeman, 2000; Abi-Dargham and Laruelle, 2005).

Recent in vitro studies have shown that APs dissociate from D2 receptors at different rates, described by the k_{off} value. Atypical APs have higher k_{off} values (i.e. dissociation

constants) compared to TAPs; however, this characteristic differs among AAPs (e.g. quetiapine > clozapine > olanzapine > ziprasidone > risperidone) (Seeman, 2002). According to this hypothesis, AAPs with low affinity and fast k_{off} allow for elasticity in increases and decreases and thus ensure a more physiologic dopamine transmission, fewer EPS, and an improvement in negative symptoms. At this point it is not possible to say precisely whether this situation is associated with the improvement of negative symptoms. In terms of clozapine, it has been suggested that the fast dissociation hypothesis is not adequate in explaining its superiority in treatment resistant schizophrenic patients. The potential role of the other receptors in the specific effect of clozapine cannot be excluded; however, it is thought that clozapine's fast dissociation quality increases the sensitivity of the dopamine system and, therefore, is of importance (Kapur and Seeman, 2001).

An important question about the fast dissociation hypothesis is whether the pharmacological effect of AAPs on the dopamine pathways is responsible for the therapeutic clinical effects as a whole. Another important question that remains to be answered is what the optimal k_{off} value is. In summary, the duration of D2 receptor occupation by an AAP that is required to increase the therapeutic effect and decrease D2-associated side effects is not known (Kapur and Seeman 2001).

The fast dissociation/hit and run hypothesis, an attempt to explain the concept of atypicality, has also been criticized and these criticisms can be listed as follows (Meltzer et al. 2003):

1) It has been suggested that measured or calculated k_{off} values (Kapur and Seeman, 2000) are questionable, in terms of atypicality. For example, Kapur and Seeman (2000) reported a slower k_{off} value for sertindole (k_{off}: 0.014) compared to haloperidol (k_{off}: 0.017), whereas they reported only a slightly faster k_{off} value for olanzapine (k_{off}: 0.039), compared to chlorpromazine (k_{off}: 0.020). Although it has been suggested that as the k_{off} value decreases the rate of dissociation from the receptor decreases and the quality of atypicality decreases, sertindole and olanzapine, as mentioned above, are regarded as AAPs in spite of this hypothesis.

2) Sertindole, risperidone, and ziprasidone show high affinity for D2 receptors. During their use severe EPS should have been observed; however, the lack of this observation suggests that additional pharmacological qualities, such as 5HT2A antagonism, might be creating a balance. Briefly, it is proposed that AAPs with high D2 receptor affinity cannot provide atypicality without an additional characteristic, such as 5HT2A antagonism.

II.2.2b) Partial Dopamine Agonist

Another distinct form of D2 interaction observed with AAPs, which sets them apart from TAPs, is partial dopamine agonism. Partial dopamine agonists show high affinity for D2 receptors and possess limited intrinsic activity. Aripiprazole is the first member of this group, which could also be called a third generation AP. It is thought that in aripiprazole's mechanism of action, in addition to its partial agonistic effect on D2 receptors, 5HT2A antagonism also plays a role. It has been reported that modulators of the dopamine system that show partial agonism provide AP effect through D2 inhibition of the mesolimbic pathway, do not cause EPS (because they do not simultaneously decrease dopamine activity on the mesocortical pathway), and can a improve negative and cognitive symptoms via an increase in mesocortical dopamine activity. The hypothesis of functional selectivity suggests that dopamine agonists might have various functional effects, such as milieu dependent (e.g. receptor and G protein concentration), cell specific, and agonist/partial agonist/antagonist activity (Shapiro et al., 2003; Monkul and Akdede, 2005).

II.3) Various Receptor Activities of Atypical Antipsychotics and Their Clinical Meaning

Atypical APs, apart from benzamides, act on many receptors other than D2 and 5HT2A, including dopamine (D1, D3, D4), serotonin (5HT1A, 5HT2C, 5HT6 and 5HT7), muscarinic cholinergic, α adrenergic, and histaminergic receptors.

Other receptor activities of AAPs can vary. It is thought that this variation might cause a difference in terms of treating the positive, negative, cognitive, and depressive symptoms of schizophrenia (Stahl, 2004). In the present review 5HT2A, 5HT2C, 5HT1A, and α1 and α2 adrenergic receptor activities and their clinical meaning will be addressed because of their frequent presence in the literature, and because of the importance and consistency of the current findings.

II.3.1) 5HT2A Receptors and 5HT2A Antagonism

The 5HT2A receptors are abundant in the brain and their highest concentration is in the cortex (Hoyer et al., 1986). They can be found in the cortical and hippocampal pyramidal glutamatergic neurons (Jakab and Goldman-Rakic, 1998), and GABAergic intermediary neurons (Willins et al., 1997). Through their activity on the GABAergic intermediary neurons, they can increase GABA secretion, but through their activity on the pyramidal neurons they can also decrease the effect of the GABA-A current. There are also 5HT2A receptors at the substantia and nigra ven-

tral tegmentum. Nigrostriatal and mesocorticolimbic DA neurons originate from and terminate in the substantia nigra and ventral tegmentum (Nocjar et al., 2002; Meltzer et al., 2003).

Serotoninergic stimulus via 5HT2A receptors decreases DA and noradrenalin (NA) secretion through DA and NA neurons, whereas 5HT2A antagonism increases DA and NA secretion by removing this indirect disinhibition (Stahl 2004). In numerous laboratory studies it has been shown that DA and NA secretion increases in the rat PFC after 5HT2A administration (Zhang et al., 2000). The quality of 5HT2A antagonism plus the prominent effect at PFC provided by AAPs are important in terms of the improvement in negative, cognitive, and depressive symptoms (Stahl, 2004). When analyzing the relationship between the 5HT2A antagonism and dopaminergic activity, it is important to study the interactions at the level of the 4 main dopaminergic systems, i.e. mesolimbic, nigrostriatal, mesocortical, and tuberoinfundibular, in order to understand the effect and side effect profiles of AAPs. Serotonin antagonism is not associated with mesolimbic D2 antagonism or AP activity. D2 receptors are more abundant in the striatum compared to 5HT2A receptors; however, because D2 inhibition caused by AAPs is less than 70%-80%, they reverse nigrostriatal D2 inhibition and, therefore, decrease EPS. In the cortex, 5HT2A receptors are more numerous than D2 receptors. Because AAPs induce strong cortical 5HT2A inhibition and because in the frontal cortex D1 receptors are more abundant than D2 receptors, AAPs can reverse mesocortical D2 inhibition. This contributes to the improvement of cognitive and negative symptoms. Atypical APs with 5HT2A antagonism can reverse tuberoinfundibular D2 inhibition to varying degrees and thus decrease the emergence of hyperprolactinemia (Leuner and Muler, 2006; Stahl, 2000).

Because the basic mechanism of action responsible for AAPs' effects on psychotic symptoms is dopamine D2 receptor inhibition, from this point on various AAPs' receptor affinities will be compared to their D2 receptor affinities. When 5HT2A and D2 receptor binding affinities of different AAPs are compared, it can be seen that ziprasidone, risperidone, olanzapine, quetiapine, and aripiprazole show higher affinity for the 5HT2A receptor compared to the D2 receptor (Figure I).

II.3.2) 5HT2C Receptors and 5HT2C Antagonism

The 5HT2C receptors are post-synaptic receptors, which are structurally similar to 5HT2A receptors. They are more abundant in the substantia nigra and VTA (Meltzer and al., 2003). Serotoninergic stimulus via 5HT2C receptors decreases DA and NA secretion through DA and NA neurons via the mediation of the GABA intermediary neurons, whereas in contrast to this 5HT2A antagonism increases DA and NA secretion (Stahl, 2004). Numerous laboratory studies conducted with 5HT2C antagonists have shown that DA and NA secretion increases in the rat PFC after 5HT2A administration, similar to the findings obtained with 5HT2A antagonists (Millan et al., 1998, Di Matteo et al., 1998). The 5HT2C antagonism plus the prominent effect in the PFC provided by AAPs are important in improving negative, cognitive, and depressive symptoms. It has been suggested that the summation of the similar effects of serotonin 5HT2A and 5HT2C antagonism on the PFC enhances the effect AAPs have on negative, cognitive, and depressive symptoms (Meltzer et al., 2003). When 5HT2C and D2 receptor binding affinities of different AAPs are compared it is seen that ziprasidone, olanzapine, and clozapine have higher affinity for the 5HT2C receptor compared to the D2 receptor (Figure I).

Some studies suggest a strong relationship between the 5HT2C receptors, and feeding behavior and obesity. In 5HT2C knockout mice, obesity and increased feeding behavior can be observed, whereas it has been shown in laboratory studies that the action of 5HT2C agonists (e.g. phenfluramine and mCPP) decreases weight gain and food intake. It is thought that 5HT2C agonism plays an important role in the weight gain associated with AAP use. The fact that ziprasidone demonstrates a significant advantage in terms of weight gain, despite its strong 5HT2C antagonism, might be explained through the lack of other pharmacological mechanisms (e.g. antihistaminic and anticholinergic) that play roles in weight gain (Schmidt, 2001).

II. 3. 3) 5HT1A Receptors and 5HT1A Partial Agonism

Agonistic activity on 5HT1A receptors has an effect functionally similar to an antagonistic effect on 5HT2A receptors, both at the pre-synaptic and post-synaptic level. The serotonin 5HT1A activity results in serotoninergic neuron inhibition, whether the activity is through somatodendritic autoreceptors that are located pre-synaptically within the raphe nucleus, or through cortical pyramidal neurons and hippocampal post-synaptic receptors. The partial 5HT1A agonism observed with AAPs is thought to contribute to their anxiolytic and antidepressant effects via filling 5HT stores pre-synaptically, desensitizing 5HT1A receptors, and increasing 5HT neuronal disinhibition. It

is proposed that AAPs, similar to 5HT2A antagonists, post-synaptically increase DA transmission at the PFC and contribute to the effects on negative and cognitive symptoms (Meltzer et al., 2003; Stahl, 2004). In a study that attempted to elucidate the effect of 5HT1A activity on DA transmission in the PFC, clozapine, risperidone, and olanzapine were administered to rats, along with WAY 100635, a 5HT1A antagonist. In that study, it was shown that 5HT2A receptor inhibition and D2 receptor inhibition provided by the AAPs increased DA secretion in the PFC. The researchers also showed that 5HT1A receptor inhibition provided by the addition of WAY 100635 further increased DA secretion. It was observed that the 5HT1A receptor inhibition of WAY 100635 removed this additional effect. As a result, it was shown that the combination of 5HT2A and D2 receptor inhibition caused prefrontal DA secretion partially via 5HT1A receptor activation (Ichikawa et al., 2001).

When the binding affinities of different AAPs to 5HT1A and D2 receptors are compared it is seen that ziprasidone, quetiapine, clozapine, and aripiprazole show higher affinity for 5HT1A receptors than D2 receptors (Figure I).

II.3.4) α1 and α2 Receptors, and α1 and α2 Antagonism

Clozapine's demonstrated high affinity for both α1 and α2 receptors has resulted in an interest on these receptors' role in AP effect.

It has been shown that neither prazosin, an adrenergic α1 antagonist, or idazoxan, an α2 antagonist, possess an AP effect on their own. Orthostatic hypertension and sedation are among the leading clinical side effects of α1 receptor antagonists. Prazosin causes inhibition of DA activity and it has been shown that systemic idazoxan administration in rats increases DA transmission in the PFC, which is thought to be of importance in terms of negative and cognitive symptoms. It has been proposed that presynaptic α1 receptor antagonism by clozapine and other AAPs might be controlling the excessive dopaminergic response and, therefore, might be contributing to AP activity (Svensson, 2003).

It has been suggested that adrenergic α1 receptor antagonism, together with D2 receptor antagonism, could enhance AP activity (Hertel et al., 1999). As a sign of a beneficial effect on the sensorimotor gating deficit, which is thought to be a basic disorder in schizophrenia, it has been shown that prazosin reverses pre-pulse inhibition (PPI) deficit (Bakshi and Geyer, 1997). Furthermore, it has been proposed that α1 receptor inhibition, together with 5HT2 receptor inhibition, could enhance AP activity (Svensson, 2003).

It has also been reported that α2-receptor antagonism, together with D2 receptor antagonism, could enhance AP activity. In rats, idazoxan, an α2 receptor antagonist, was added to raclopride, a D2/D3 dopamine receptor antagonist, and subsequently, dopamine transmission in the PFC was observed to increase and the inhibition of avoidance behavior, which is a predictor of AP response, was enhanced (Hertel et al., 1999).

In a recent microdialysis study conducted with rats, idazoxan therapy added to low-dose haloperidol and olanzapine was shown to enhance the inhibition of avoidance behavior. The researchers also observed an increase of DA in the PFC and they reported a reversal of catalepsy caused by haloperidol (Wadenberg et al., 2006).

When the α1 and D2 receptor binding affinities of various AAPs are compared, it is seen that clozapine, risperidone, and quetiapine show higher affinity for α1 receptors than for D2 receptors (Figure 1). However, when their binding affinities to adrenergic α2 and D2 receptors are compared, it is seen that only clozapine shows a higher affinity for α2 receptors than for D2 receptors. It is known that among TAPs, those with low potency show higher affinity for α1 receptors (Stahl, 2000).

II.4) Other Mechanisms

Various other mechanisms, such as increased acetylcholine (Ach) secretion and glutamate regulation, are among the action mechanisms of AAPs, which might be providing additional benefits as compared to TAPs. These two mechanisms will be summarized below.

In microdialysis studies conducted with rats it was reported that AAPs, such as clozapine, olanzapine, risperidone, and ziprasidone, provide an increase in Ach secretion in the PFC; however, with the administration of TAPs, such as haloperidol and thioridazine, an increase in Ach secretion was not observed. None of the AAPs used in the experiment had an effect on Ach secretion in the nucleus accumbens or striatum. This effect was reported to be unique for the PFC (Ichikawa et al., 2002). It is thought that the increase in Ach secretion in the PFC is especially important for the treatment of cognitive symptoms in schizophrenia.

Glutamatergic deficiency is considered to be just as important as dopaminergic imbalance in the etiopatho-

genesis of schizophrenia. Therefore, regulation of glutamate seems to be an important mechanism of action for treatment. Some AAPs have experimentally demonstrated a selective ability to improve decreased N-methyl D-aspartate (NMDA) receptor activity, both with acute and chronic administration, at the cellular and behavioral level (Abi-Dargham and Laruelle 2005). For example, when TAPs (haloperidol) showed no such effect, AAPs, such as clozapine and olanzapine, were observed to reverse the functional over-activity of NMDA receptors, which was triggered by the NMDA antagonist phencyclidine (PCP) (Ninan et al., 2003). It has also been noted that AAPs are able to antagonize the PPI deficit (Bakshi and Geyer 1995) and the social conduct disorder (Corbett et al., 1995) caused by NMDA antagonists and that they were able to inhibit metabolic activation associated with ketamine (Duncan et al., 2000). Clozapine is the most potent AAP to inhibit the effects of NMDA receptor antagonists (Olney and Farber, 1994). Clozapine's and other AAPs' mechanisms of action that underly this effect are not clear. Currently, researchers are conducting studies to determine if the molecular changes in glutamate receptors or the changes in neurotransmitter-receptor interactions are responsible for the inhibition of NMDA antagonist effects by AAPs. Improvement in positive, negative, and cognitive symptoms, and slowing down the disease course are among the possible clinical outcomes of glutamate modulation (Miyamoto et al., 2005).

II.5) Superior Activity of Clozapine: Clozapine-Specific Mechanisms

While analyzing schizophrenia treatment and AAPs' mechanisms of action, one should pay special attention to certain mechanisms that are specific to clozapine, which might be underlying its superiority in therapy.

It is thought that N-desmethylclozapine, a metabolite of clozapine, has an important place in the successful treatment response that is achieved by clozapine. N-desmethylclozapine is a strong allosteric M1 receptor agonist (Weiner et al., 2004) and there is positive data suggesting that it enhances hippocampal (CA1 pyramidal cells) NMDA receptor currents through M1 receptor activation (glutamatergic enhancement) (Sur et al., 2003). Furthermore, the partial D2-D3 receptor agonism demonstrated by N-desmethylclozapine is also regarded as one of the potentially important and specific mechanisms of action (Burstein et al., 2005).

Other than its metabolite, it is thought that clozapine itself has certain mechanisms that are different than those of other AAPs, which might be associated with its strong and specific effect. It is thought that clozapine's $\alpha 1$ and $\alpha 2$ adrenergic receptor antagonism (Svensson 2003), D4 receptor antagonism (Wong and Van Tol, 2003), its ability to increases plasma NA levels and peripheral noradrenergic activity (Elman et al., 1999), and its ability to inhibit dopaminergic neurons at the VTA through its interaction with the NMDA receptor complex (via interaction with the glycine region and temporary inhibition of the glycine transporter) are among these mechanisms (Schwieler et al., 2004).

It is not certain if clozapine is a D1 partial agonist or an antagonist; however, a higher D1/D2 receptor occupation ratio is observed with clozapine, in comparison to other AAPs (striatal D1/D2 occupation ratios: clozapine 0.88, olanzapine 0.54, quetiapine 0.41, risperidone 0.31), and this is another potentially important mechanism that has been attracting attention lately (Tauscher et al., 2004).

CONCLUSION

Today, it is not possible to predict which AP will be primarily beneficial to any particular schizophrenia patient. Through developments in the areas of pharmacogenetics and pharmacogenomics, such a prediction could be possible in the future. Although D2 antagonism provided by all AAPs is sin qua non for AP effect, within the context of the mechanisms reviewed above, it is possible for other mechanisms of action observed with AAPs to provide an additional benefit in treating the negative, cognitive, depressive, and anxiety symptoms. However, in current clinical practice it remains to be proven if AAPs, other than clozapine, are superior to TAPs. To what extent do the differences in their mechanisms of action manifest in the clinical setting and are they really superior? To date, these questions have not been fully answered. The superiority of AAPs over TAPS, apart from increased patient compliance due to fewer EPS and decreased secondary negative symptoms, has not found full support because of the contradictory results obtained from controlled clinical trials (e.g. CATIE) and meta analyses (Geddes et al., 2000; Davis et al., 2003; Lieberman et al., 2005). One of the important reasons behind the contradictions is the fact that the AAP and TAP doses that have been used in most of the studies were not really comparable. However, this problem has been addressed by new independent studies with large samples (e.g. CUtLASS) and it has been seen that no negative aspects have been detected with TAPs in

comparison to AAPs, clozapine excluded, in terms quality of life, patient preference, therapeutic effect, side effects, and cost (Jones et al., 2006). Although the superior aspects of AAPs compared to TAPs have found strong support from laboratory studies, in terms of therapeutic effect, whether or not this condition is valid in the clinical setting, apart from clozapine, remains to be elucidated by further studies.

REFERENCES

Abi-Dargham A, Laruelle M (2005). Mechanisms of action of second generation antipsychotic drugs in schizophrenia: insights from brain imaging studies. Eur Psychiatry, 20:15-27.

Andersson JL, Nomikos GG, Marcus M et al. (1995) Ritanserin potentiates the stimulatory effects of raclopride on neuronal activity and dopamine release selectivity in the mesolimbic dopaminergic system. Naunyn Schmiedebergs Arch Pharmacol, 352:374-85.

Bakshi VP, Geyer MA (1995) Antagonism of phencyclidine-induced deficits in prepulse inhibition by the putative atypical antipsychotic olanzapine. Psychopharmacology (Berl), 122:198-201.

Bakshi VP, Geyer MA (1997) Phencyclidine induced deficits in prepulse inhibition of startle are blocked by prazosin, an alpha-1 noradrenergic antagonist. J Pharmacol Exp Ther, 203: 666-674.

Bressan RA, Erlandsson K, Jones HM et al. (2003) Is regionally selective D2/D3 dopamine occupancy sufficient for atypical antipsychotic effect? An in vivo quantitative [123I]epidepride SPET study of amisulpride-treated patients. Am J Psychiatry, 160:1413-20.

Burstein ES, MA J, Wong S et al. (2005) Intrinsic efficacy of antipsychotics at human D2, D3, and D4 dopamine receptors: identification of the clozapine metabolite N-desmethylclozapine as a D2/D3 partial agonist. J Pharmacol Exp Ther, 315:1278-87.

Chiodo LA, Bunney BS (1983). Typical and atypical neuroleptics: differential effects of chronic administration on the activity of A9 and A10 midbrain dopaminergic neurons. J Neurosci, 3:1607-19.

Corbett R, Camacho F, Woods AT et al. (1995) Antipsychotic agents antagonize non-competitive N-methyl-D-aspartate antagonist-induced behaviors. Psychopharmacology (Berl), 120:67-74.

Davis JM, Chen N, Glick ID (2003). A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry, 60:553-64.

de Paulis T (2001). M-100907 (Aventis). Curr Opin Invest Drugs, 2:123-32.

Di Matteo V, Di Giovanni G, Di Mascio M et al. (1998) Selective blockade of serotonin2C/2B receptors enhances dopamine release in the rat nucleus accumbens. Neuropharmacology, 37:265-72.

Duinkerke SJ, Botter PA, Jansen AA et al. (1993) Ritanserin, a selective 5-HT2/1C antagonist, and negative symptoms in schizophrenia. A placebo-controlled double-blind trial. Br J Psychiatry, 163:451-5.

Duncan GE, Miyamoto S, Leipzig JN et al. (2000) Comparison of the effects of clozapine, risperidone, and olanzapine on ketamine-induced alterations in regional brain metabolism. J Pharmacol Exp Ther, 293:8-14.

Elman I, Goldstein DS, Eisenhofer G et al. (1999) Mechanism of peripheral noradrenergic stimulation by clozapine. Neuropsychopharmacology, 20:29-34.

Farde L, Nordstrom AL, Wiesel FA et al. (1992) Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. Arch Gen Psychiatry, 49:538-44.

Geddes J, Freemantle N, Harrison P et al. (2000) Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ, 321:1371-6.

Hertel P, Fagerquist MV, Svensson TH (1999) Enhanced cortical dopamine output and antipsychotic-like effects of raclopride by alpha2 adrenoceptor blockade. Science, 286:105-7.

Hoyer D, Pazos A, Probst A et al. (1986) Serotonin receptors in the human brain. I. Characterization and autoradiographic localization of 5-HT1A recognition sites. Apparent absence of 5-HT1B recognition sites. Brain Res, 376:85-96.

Ichikawa J, Ishii H, Bonaccorso S et al. (2001) 5-HT(2A) and D(2) receptor blockade increases cortical DA release via 5-HT(1A) receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. J Neurochem, 76:1521-31.

Ichikawa J, Dai J, O'Laughlin IA et al. (2002) Atypical, but not typical, antipsychotic drugs increase cortical acetylcholine release without an effect in the nucleus accumbens or striatum. Neuropsychopharmacology, 26:325-39.

Jakab RL, Goldman-Rakic PS (1998) 5-Hydroxytryptamine2A serotonin receptors in the primate cerebral cortex: possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. Proc Natl Acad Sci USA, 95:735-40.

Jones PB, Barnes TR, Davies L et al. (2006) Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry, 63:1079-87.

Kapur S, Zipursky, RB, Remington G (1999) Clinical and theoretical implications of 5-HT2 and D2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. Am J Psychiatry, 156:286-93.

Kapur S, Zipursky R, Jones C et al. (2000) Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry, 157:514-20.

Kapur S, Seeman P (2000) Antipsychotic agents differ in how fast they come off the dopamine D2 receptors. Implications for atypical antipsychotic action. J Psychiatry Neurosci, 25:161-6.

Kapur S, Seeman P (2001) Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: A new hypothesis. Am J Psychiatry, 158:360-9.

Kapur S, McClelland RA, VanderSpek SC et al. (2002) Increasing D2 affinity results in the loss of clozapine's atypical antipsychotic action. Neuroreport, 13:831-5.

la Fougere C, Meisenzahl E, Schmitt G et al. (2005) D2 receptor occupancy during high- and low-dose therapy with the atypical antipsychotic amisulpride: a 123I-iodobenzamide SPECT study. J Nucl Med, 46:1028-33.

Leuner K , Muller WE (2006) The complexity of the dopaminergic synapses and their modulation by antipsychotics. Pharmacopsychiatry, 39(Suppl 1):15-20.

Lieberman JA, Stroup TS, McEvoy JP et al. (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med, 353:1209-23.

Liégeois JF, Ichikawa J, Meltzer HY (2002) 5-HT(2A) receptor antagonism potentiates haloperidol-induced dopamine release in rat medial prefrontal cortex and inhibits that in the nucleus accumbens in a dose-dependent manner. Brain Res, 947:157-65.

Meltzer HY, Matsubara S, Lee JC (1989) Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. J Pharmacol Exp Ther, 251:238-46.

Meltzer HY, Li Z, Kaneda Y et al. (2003) Serotonin receptors: their

key role in drugs to treat schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry, 27:1159-72.

Millan MJ, Dekeyne A, Gobert A (1998) Serotonin (5-HT)2C receptors tonically inhibit dopamine (DA) and noradrenaline (NA), but not 5-HT, release in the frontal cortex in vivo. Neuropharmacology, 37:953-5.

Miyamoto S, Duncan GE, Marx CE et al. (2005) Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. Mol Psychiatry, 10:79-104.

Monkul ES, Akdede BB (2005). Yeni kuşak antipsikotiklerden aripiprazol:Bir gözden geçirme. Klinik Psikofarmakoloji Bülteni, 15:198-203.

Natesan S, VanderSpek S, Nobrega J et al. (2005) Contrasting loxapine to its isomer isoloxapine--the critical role of in vivo D2 blockade in determining atypicality. Schizophr Res, 77:189-99.

Ninan I, Jardemark KE, Wang RY (2003) Olanzapine and clozapine but not haloperidol reverse subchronic phencyclidine-induced functional hyperactivity of N-methyl-D-aspartate receptors in pyramidal cells of the rat medial prefrontal cortex. Neuropharmacology 2003; 44:462-72.

Nocjar C, Roth BL, Pehek EA (2002) Localization of 5-HT(2A) receptors on dopamine cells in subnuclei of the midbrain A10 cell group. Neuroscience, 111:163-76.

Nyberg S, Nakashima Y, Nordström AL et al. (1996) Positron emission tomography of in-vivo binding characteristics of atypical antipsychotic drugs. Review of D2 and 5-HT2 receptor occupancy studies and clinical response. Br J Psychiatry, 168(Suppl. 29):40-4.

Olney JW, Farber NB (1994) Efficacy of clozapine compared with other antipsychotics in preventing NMDA-antagonist neurotoxicity. J Clin Psychiatry, 55 (Suppl B):43-6.

Perrault G, Depoortere R, Morel E et al. (1997) Psychopharmacological profile of amisulpride: an antipsychotic drug with presynaptic D2/D3 dopamine receptor antagonist activity and limbic selectivity. J Pharmacol Exp Ther, 280:73-82.

Pilowsky LS, Costa DC, Ell PJ et al. (1992) Clozapine, single photon emission tomography, and the D2 dopamine receptor blockade hypothesis of schizophrenia. Lancet, 340:199-202.

Pilowsky LS, Mulligan RS, Acton PD et al. (1997) Limbic selectivity of clozapine. Lancet, 350:490-1.

Robertson GS, Matsumara H, Fibiger HC (1994) Induction patterns of Fos-like immunoreactivity in the forebrain as predictors of atypical antipsychotic activity. J Pharmacol Exp Ther, 271:1058-66.

Schmidt AW, Lebel LA, Howard HR Jr et al. (2001) Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. Eur J Pharmacol, 425:197-201.

Schwieler L, Engberg G, Erhardt S (2004) Clozapine modulates midbrain dopamine neuron firing via interaction with the NMDA receptor complex. Synapse, 52:114-22.

Seeman P (2002) Atypical antipsychotics: mechanism of action. Can J Psychiatry, 47:27-38.

Shapiro DA, Renock S, Arrington E et al. (2003) Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology, 28:1400-11.

Stahl SM (2000). Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 2. baskı, Cambridge, Cambridge University Pres: 365.

Stahl SM (2004). Symptoms and circuits, part 3: schizophrenia. J Clin Psychiatry, 65:8-9.

Stephenson CM, Bigliani V, Jones HM et al. (2000) Striatal and extra-striatal D(2)/D(3) dopamine receptor occupancy by quetiapine in vivo. [(123)I]-epidepride single photon emission tomography (SPET) study. Br J Psychiatry, 177:408-15.

Sur C, Mallorga PJ, Wittmann M et al. (2003) N-desmethylclozapine, an allosteric agonist at muscarinic 1 receptor, potentiates N-methyl-D-aspartate receptor activity. Proc Natl Acad Sci U S A, 100:13674-9.

Svensson T (2003) Alpha-adrenoceptor modulation hypothesis of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry, 27:1145-58.

Tauscher J, Hussain T, Agid O et al. (2004) Equivalent occupancy of dopamine D1 and D2 receptors with clozapine: differentiation from other atypical antipsychotics. Am J Psychiatry, 161:1620-5.

Trichard C, Paillere-Martinot ML, Attar-Levy D et al. (1998) Binding of antipsychotic drugs to cortical 5-HT2A receptors: a PET study of chlorpromazine, clozapine, and amisulpride in schizophrenic patients. Am J Psychiatry, 155:505-8.

Wadenberg ML, Salmi P, Jimenez P et al. (1996) Enhancement of antipsychotic-like properties of the dopamine D2 receptor antagonist, raclopride, by the additional treatment with the 5-HT2 receptor blocking agent, ritanserin, in the rat. Eur Neuropsychopharmacol, 6:305-10.

Wadenberg MG, Browning JL, Young KA et al. (2001) Antagonism at 5-HT(2A) receptors potentiates the effect of haloperidol in a conditioned avoidance response task in rats. Pharmacol Biochem Behav, 68:363-70.

Wadenberg ML, Wiker C, Svensson TH (2006) Enhanced efficacy of both typical and atypical antipsychotic drugs by adjunctive alpha 2 adrenoceptor blockade: experimental evidence. Int J Neuropsychopharmacol: 1-12.

Waddington JL, Kapur S, Remington GJ (2003). The neuroscience and clinical psychopharmacology of first- and second-generation antipsychotic drugs. Schizophrenia, 2. baskı, SR Hirsch, DR Weinberger (Ed), Oxford. Blackwell Science Ltd: 421-441.

Weiner DM, Meltzer HY, Veinbergs I et al. (2004) The role of M1 muscarinic receptor agonism of N-desmethylclozapine in the unique clinical effects of clozapine. Psychopharmacology (Berl), 177:207-16.

Willins DL, Deutch AY, Roth BL (1997) Serotonin 5-HT2A receptors are expressed on pyramidal cells and interneurons in the rat cortex. Synapse, 27:79-82.

Wong AH, Van Tol HH (2003) The dopamine D4 receptors and mechanisms of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry, 27:1091-9.

Xiberas X, Martinot JL, Mallet L et al. (2001) In vivo extrastriatal and striatal D2 dopamine receptor blockade by amisulpride in schizophrenia. J Clin Psychopharmacol, 21:207-14.

Zhang W, Perry KW, Wong DT et al. (2000) Synergistic effects of olanzapine and other antipsychotic agents in combination with fluoxetine on norepinephrine and dopamine release in rat prefrontal cortex. Neuropsychopharmacology, 23:250-62.