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Review

An Overview of Antipsychotics: Mechanisms of Action

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ABSTRACT

Antipsychotics are currently used in many disorders, especially schizophrenia and psychotic disorders. Due to extrapyramidal side effects including weight gain, sexual dysfunction, movement disorders, and development of tolerance, the production of new antipsychotic drugs is a subject that is still being studied. This process, which first started with the discovery of typical antipsychotics, has become widespread with the discovery of atypical antipsychotics after the 90s, and at the same time, the use of antipsychotics in diseases has expanded. This review aims to describe the types of antipsychotics, the physiological mechanisms by which antipsychotic drugs act on the brain, the different side effects of antipsychotic drugs on the brain, and the mechanisms of action of these drugs in various brain disorders as much as possible to express it clearly and understandably.

Keywords: Antipsychotics, atypical, extrapyramidal, schizophrenia, typical

Antipsychotics are currently used in psychiatric psychotic disorders, primarily schizophrenia, but there is also a study showing that their use in bipolar disorder (BD) is effective.[1-3] Although there are many categories of antipsychotics, the common classification can be defined as first (typical) and second (atypical) generation antipsychotics.[1]

MECHANISMS OF ACTION OF ANTIPSYCHOTICS

While typical antipsychotics (TAs) function as dopamine receptor antagonists, atypical antipsychotics (AAs), which started to be produced in the 90s, are differentiated in two different functions: serotonin-dopamine antagonists and partial dopamine agonism.[1,4]

Typical Antipsychotics

Typical antipsychotics are generally known that effective in the positive symptoms of schizophrenia.[5,6] They anatomically stop depolarization in dopamine cells in the mesolimbic, corticolimbic, and nigrostriatal systems of the brain.[7,8] Typical antipsychotics function by binding to the dopaminergic dopamine D2 receptor and there is a relationship between the drug's therapeutic effect and its D2 receptor binding action. They bind to postsynaptic D2 receptors and keep them.[9] Thus, they prevent the flow of extra dopamine into the brain. Since drug binding to the D2 receptor is associated with therapeutic effects, it can be predicted that this process may play a role in the alleviation of positive symptoms in schizophrenia. A dose range has been determined for the efficacy of TAs and to keep side effects under control. Since 65-70% D2 receptor blockade can provide the desired effect in patients, and there is a risk of increased side effects in the extrapyramidal system in the brain if it is above 80%, the threshold range for use of the drug has been determined as 65-80% D2 blockade.[1,10,11] However, there may be patients for whom this dose is not sufficient.[9] Prolonged suppression of dopamine during the treatment process leads to excessive dopamine sensitivity and an increase in dopamine receptors. In this case, the doses that patients receive after a certain period of time need to be increased

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further to achieve the same effect. In summary, patients develop tolerance to the drug.[1,9,12-14]

Atypical Antipsychotics

Research on AAs started with clozapine. According to an animal experiment, this drug was found to produce fewer extrapyramidal and other side effects and weaker D2 blockade in its mechanism of action.[15,16] The weaker D2 blockade may reduce the risk of dopamine sensitization and thereby the risk of tolerance. We mentioned that AAs act on the brain as serotonin dopamine antagonists or partially as dopamine agonists. Primarily, AA has a similar affinity for D2 receptors as TA but lower than TA. Atypical antipsychotics have differentially high levels of D3 and D4 receptor affinity.[17] There are several hypotheses regarding the effect of AAs on the dopaminergic system.[1]

The mechanism mentioned above is the hypothesis of a weaker D2 blockade, although there are several imaging studies on this blockade effect.[18-20] Another hypothesis is the rapid uncoupling hypothesis, which is thought to result from the low affinity of D2 partial agonists for D2 receptors in AAs.[1,21,13] The situation here is a rapid detachment of the agonist substance from D2 receptors.[21,13] The last hypothesis is that of partial dopamine agonists. According to this hypothesis, despite a high affinity for D2 receptors, there is also antagonism of the serotonin or 5-hydroxytryptamine (5-HT)2A receptors with limited efficacy. In this hypothesis, D2 partial agonism exists in the mesolimbic pathway.[1,22] In terms of serotonin-dopamine antagonism, the binding affinity of AAs to the 5HTA2 receptor is higher than the binding affinity to the D receptor. This is one of the conditions that lead to atypical effects, unlike TAs.[1,23,24] The 5HT2A receptors are serotonin receptors found in the brain, predominantly in the cortex.[25] These receptors are also located in brain areas where the terminals and sources of dopamine neurons in the nigrostriatal and mesocorticolimbic areas are located. In this connection, stimulation of 5HT2A receptors inhibits dopamine stimulation. However, suppression of 5HT2A receptors by AAs eliminates dopamine inhibition and increases dopamine excitation in these areas.[26-28] Negative effects in depressive states and psychotic disorders This 5HT2A antagonism may affect symptoms.[28] Similarly, suppression of the 5HT2C serotoninergic receptor, which antagonizes serotonin, can affect depressive states and negative symptoms. In combination with 5HT2A, the potency was increased.[27-29] In addition, there are studies in which increased dopamine activation in the prefrontal region was observed in rat experiments given 5HT2A and 5HT2C antagonists.[30-32] There is one research in which AAs can be evaluated as different from TA. According to the study, it is observed that some AAs cause an increase in acetylcholine in the prefrontal cortex. It has been observed that clozapine, olanzapine, risperidone, and ziprasidone can show this effect. Similar to 5HT2A receptors, it was observed that it can indirectly increase dopamine activation in the prefrontal cortex.[27,28] According to a study on this subject, the combination of 5HT2A and D2 antagonism is thought to be partially involved in dopamine release in the prefrontal cortex.[33,34] A mechanism of action first discovered with clozapine is adrenergic alpha 1 and alpha 2 receptor antagonism, which are epinephrine and norepinephrine receptors.[1] The combination of A1 receptor antagonism with 5HT2A antagonism or with D2 blockade increases the atypical effect of the drug.[35,36] Clozapine, risperidone and quetiapine were given examples of antipsychotics with high A1 affinity and low D2 affinity compared to A1. The difference between A1 and D2 affinity of risperidone is much less than clozapine and quetiapine.[37-40]

Clozapine

Clozapine is an antipsychotic with low D2 receptor affinity and high 5HT2 receptor affinity.[22,37] Low D2 affinity is thought to improve the positive symptoms of schizophrenia and reduce extrapyramidal side effects with high 5HT2 affinity.[38] Clozapine is a substance that acts against low D2 affinity. Its direct and indirect total D1 and D2 receptor occupancy is higher than other AAs. In addition to its antagonistic interference with D4 receptors, clozapine's metabolite N-desmethylclozapine also has D2 and D3 agonism.[41,42] In addition, this metabolite could indirectly increase glutamate activity by binding to muscarinic M1 receptors, one of the acetylcholine receptors.[43,44]

Risperidone

It is an antipsychotic that was introduced after clozapine and shows a high affinity for both D2 and 5HT2 receptors.[22,45] Thus, it is thought to be effective for both positive and negative schizophrenia symptoms. Additionally, BD is thought to be effective in short-term treatment for mania states and in long-term treatment to prevent relapse in schizophrenia.[38]

Quetiapine

Like clozapine, quetiapine is effective in

schizophrenia and acute mania. It has a high affinity for 5HT2A receptors and a low affinity for D2 receptors. Binding time to D2 receptors is short. For this reason, extrapyramidal side effects are also low. It can improve schizophrenia symptoms and manic episodes of BD.[45-47]

In a study on quetiapine, quetiapine in substance and related disorders usability has been reported. A few other studies that could contradict this study suggest that some antipsychotics with high antagonist properties administered to substance addicts may increase substance use in addicts. This risk was explained by the fact that due to the high dopamine antagonism of these antipsychotics, addicts may increase their substance use in order to reach satisfaction.[48-52] Regarding the therapeutic aspect of quetiapine, in a study on its effect on substance addicts, it was observed that addicts given quetiapine during the treatment process could alleviate anxiety, reduce pain and insomnia, and increase appetite.[53] However, quetiapine can also cause sedation in addicts.[54] The sedation effect is thought to be due to the blockade of histamine 1 (H1) receptors, the side of quetiapine that produces antihistamine effects.[48] Research on the abuse of quetiapine suggests that its ability to alleviate symptoms of anxiety and insomnia and its sedative effects lead to abuse.[48,55]

Ziprasidone

Ziprasidone shows high 5HT2 affinity and low D2 affinity in parallel with other AAs. In addition, it has greater 5HT1A agonism than other AAs. Results showed that ziprasidone may increase dopamine activation in the cortical area.[56-59] Another thing about ziprasidone that makes ziprasidone different from other AAs is that the 5HT2 and D2 affinity difference is much greater than other AAs.[59,60] There were found several studies on the clinical effects of ziprasidone on negative symptoms of schizophrenia and schizoaffective disorder. There were found several studies on the clinical effects of ziprasidone on negative symptoms of schizophrenia and schizoaffective disorder.[61-63]

Aripiprazole

Aripiprasole has high affinity partial agonism of D2 and 5HT1A.[63-65] Atypical antipsychotics While the difference in 5HT2 and D2 affinity is significant in others, this difference is quite low in aripiprazole.[27,65,66] In this situation, aripiprazole, interestingly, D2 full agonism and antagonism also to presynaptic D2 receptors. At this point can say that, the agonist effect of aripiprazole on presynaptic D2 receptors while showing antagonist effects on postsynaptic D2 receptors.[65,66]

Olanzapin

Olanzapine antagonizes 5HT2 and D2. The differences in 5HT2 and D2 affinity are greater than one. While D2 affinity is still higher than clozapine, it has an affinity for H1 receptors and 5HT2A, 5HT2C, and 5HT3 receptors.[67] At this point, we have discussed olanzapine's risk of weight gain and obesity. Since H1 receptors are also associated with the satiety center and there are studies that blockade of H1 may lead to weight gain.[68-70] At the same time, 5HT2C receptors are also associated with the satiety center and may further increase the risk of weight gain with H1 blockade. A second reason for 5HT2C affinity can also be shown according to this information.[71-73]

BIPOLAR DISORDER AND ANTIPSYCHOTICS

Lithium is known to be the most common and accepted treatment in BD, but antipsychotics can also be used.[74,75] Although haloperidol and chlorpromazine from TAs can be stabilizing in BD, there are studies showing that quetiapine, ziprasidone, aripiprazole, risperidone, and olanzapine from AAs can be effective.[76-80] However, two generations of antipsychotics Even though it can be used in BD, a comparative study on the treatment of BD with chlorpromazine and clozapine showed that clozapine was superior to chlorpromazine in the intervention of acute mania in BD.[81] Physiologically, BD has been found to be associated with over-arousal in the ventral limbic pathway and concomitant under-arousal in the cortical pathway in the left hemisphere.[82-86] There are studies showing that BD patients respond well to clozapine as an antipsychotic treatment.[87,88] In a study conducted on groups of BD patients who did not respond to gold-standard treatments or were unable to continue treatment, it was observed that clozapine use could regulate the mood of these patients.[89] Contrary to popular belief, clozapine is not a mood stabilizer It is more effective in patients with BD than in patients with schizophrenia.[87,89,90] Although the mood-regulating effect of clozapine has been established, it is more effective in manic episodes than depressive episodes.[91-93]

Although clozapine has similar effects to other AAs, it is not preferred due to certain side effects.[94] These side effects include sialorrhea leading to increased salivation, sedation and weight gain.[95-97]

Sialorrhea, which does not only lead to increased salivation, can indirectly disrupt daily life and patients may have to discontinue treatment.[97] Sedation, on the other hand, is most common with clozapine among AAs, but patients reported that they experienced this side effect only in the early stages of use and that it disappeared later.[98] In addition to habituation, it is also thought that the sedative effect disappears later since the metabolite produced by the action of clozapine has different affinities than clozapine.[99] Weight gain is another side effect, and again clozapine leads the way compared to AAs.[95] There is also a study showing that clozapine has no effect on weight gain in schizophrenia patients.[100]

ANTIPSYCHOTICS AND SEXUAL DYSFUNCTION

The common mechanism of antipsychotic D2 blockade is known to lead to problems with sexual function.[101] However, it is also possible that some diseases for which antipsychotics are used may lead to sexual dysfunction (SD) without drugs.[102] Many D2 affinity and its blockade in antipsychotics may indirectly affect prolactin levels and may alter sexual processes.[101] Increased prolactin, follicle-stimulating hormone, and luteinizing hormone inhibition, which may reduce sexual arousal and orgasm.[103] But this effect may be mediated by mesolimbic and is associated with dopamine blockade in the tuberoinfundibular pathway. Nevertheless, the increase in prolactin is not the only antipsychotic effect. Other than that, the dopamine effects of antipsychotic blockade may also affect sexual functioning by reducing sexual motivation. Similarly, H1 and A1, A2 receptor affinity can also cause SD. H1, for which many antipsychotics have an affinity, may cause sedation and prevent arousal.[101,104]

There is much information that M1, A1, and A2 blockade, which is one of the other mechanisms mentioned about antipsychotics, causes orgasm difficulties.[105,106] Considering the differences according to the drugs, although clozapine causes D2 blockade in the mesolimbic area, its blockade in the tuberoinfundibular pathway is not enough to lead to increased prolactin and SD.[106-108] The low D2 affinity of clozapine also plays a role here.[109] In addition, it can be said that D4 receptor antagonism by clozapine may also disrupt sexual functions, according to a study indicating that D4 receptor activity is associated with sexual functions.[110] Risperidone has a high affinity for D2 and 5HT2 receptors and a moderate affinity for A1 and A2 receptors.[111] The high D2 receptor affinity of risperidone may cause SD due to increased prolactin could be a trigger and this is supported in a comparative study with quetiapine.[104,112] There also appears to be research that risperidone causes erectile dysfunction.[113] Considering the differences according to the drugs, although clozapine causes D2 blockade in the mesolimbic area, its blockade in the tuberoinfundibular pathway is not enough to lead to increased prolactin and SD.[106,107] In addition, it can be said that D4 receptor antagonism by clozapine may also disrupt sexual functions, according to a study indicating that D4 receptor activity is associated with sexual functions.[110] Risperidone has a high affinity for D2 and 5HT2 receptors and a moderate affinity for A1 and A2 receptors.[111] The high D2 receptor affinity of risperidone may trigger SD due to increased prolactin and this is supported in a comparative study with quetiapine.[104,112] There is also research showing that risperidone causes erectile dysfunction.[113] Olanzapine has A1 and A2 affinity similar to risperidone and in addition, has affinity for M1 receptors and H1 receptors.[114] Although it does not cause erection problems as much as risperidone, it may cause sedation problems due to its H1 affinity. Sedation can be said to affect sexual functions.[104,115,116] In addition to what we have mentioned about quetiapine, it has A1 and A2 affinity. Quetiapine binds to D2 receptors with low affinity and does not cause an increase in prolactin.[109] There is even a study showing that it can bring increased prolactin to normal levels.[117] A similar study was done for aripiprazole and it was found that aripiprazole can also stabilize increased prolactin levels.[118]

In conclusion, antipsychotics are shown therapeutic in emotional and psychotic disorders in a variety of ways.The side effects of first-generation antipsychotics, mainly due to high D2 blockade, can be reduced with the development and widespread use of second-generation antipsychotics. In particular, it has been observed that side effects are reduced due to low D2 blockade and rapid dissociation from receptors. Its intense antagonism to 5HT receptors plays a role in the elimination of side effects.Different amounts of affinity according to AAs provide different effects of the drugs. Clozapine, despite its high success in schizophrenia and BD, is associated with SD sialorrhea weight gain and sedation for a certain period of time. Olanzapine differs in that its high affinity for both H1 and 5HT2C carries risks of weight gain. Sedation can be considered a common feature of AAs with H1 affinity. At this point, among the AAs that carry a risk in terms of SD, olanzapine causes sedation due to H1 affinity and risperidone

causes prolactin increase due to D2 affinity arousal problems can be mentioned. The difference between aripiprazole and quetiapine, which do not cause SD as much as these two AAs, is their ability to stabilize prolactin levels. An interesting difference that can be added to aripiprazole is that it can both fully agonize and antagonize. The fact that quetiapine relieves anxiety and insomnia in the treatment of addiction and that its sedation effect due to H1 affinity may be a risk factor in its use in addicts is also different from other AAs and should be taken into consideration. Differences such as these may be an opportunity to predict whether the use of AAs for the treatment of various disorders will be effective. In conclusion, Antipsychotics may still have unknown therapeutic effects despite the knowledge about their use and effects. Due to their side effects, their use should be appropriate. In therapeutic use, it is important to take precautions against dosage and tolerance.

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