Mechanism of Action of Risperidone

The video tutorial can be found here

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Risperidone is a second-generation antipsychotic that has affinity for D2, 5-HT2A, alpha 1, alpha 2 and H1 receptors.

The mechanism of action of risperidone is not fully understood, current theories focus mainly on its ability to block D2 and 5-HT2A receptors.

General Mechanism of Action of Antipsychotic Drugs

It has been observed that from a pharmacodynamic perspective, all antipsychotics share a common feature: they reduce dopaminergic neurotransmission.

According to the dopamine theory of schizophrenia, positive symptoms of schizophrenia might be explained through an overactivity of the mesolimbic pathway. Negative and cognitive symptoms of schizophrenia have been linked to a dysfunction of the mesocortical pathway [1].

Play the video below to learn more about the dopamine hypothesis of schizophrenia and the mechanism of action of antipsychotics.

Risperidone Pharmacodynamics and Binding Affinity

The table below shows Ki values for risperidone at different neurotransmitter receptors. Ki is inversely proportional to affinity. This means that high Ki numbers suggest low affinity at a given receptor, while low Ki numbers are associated with high affinity.

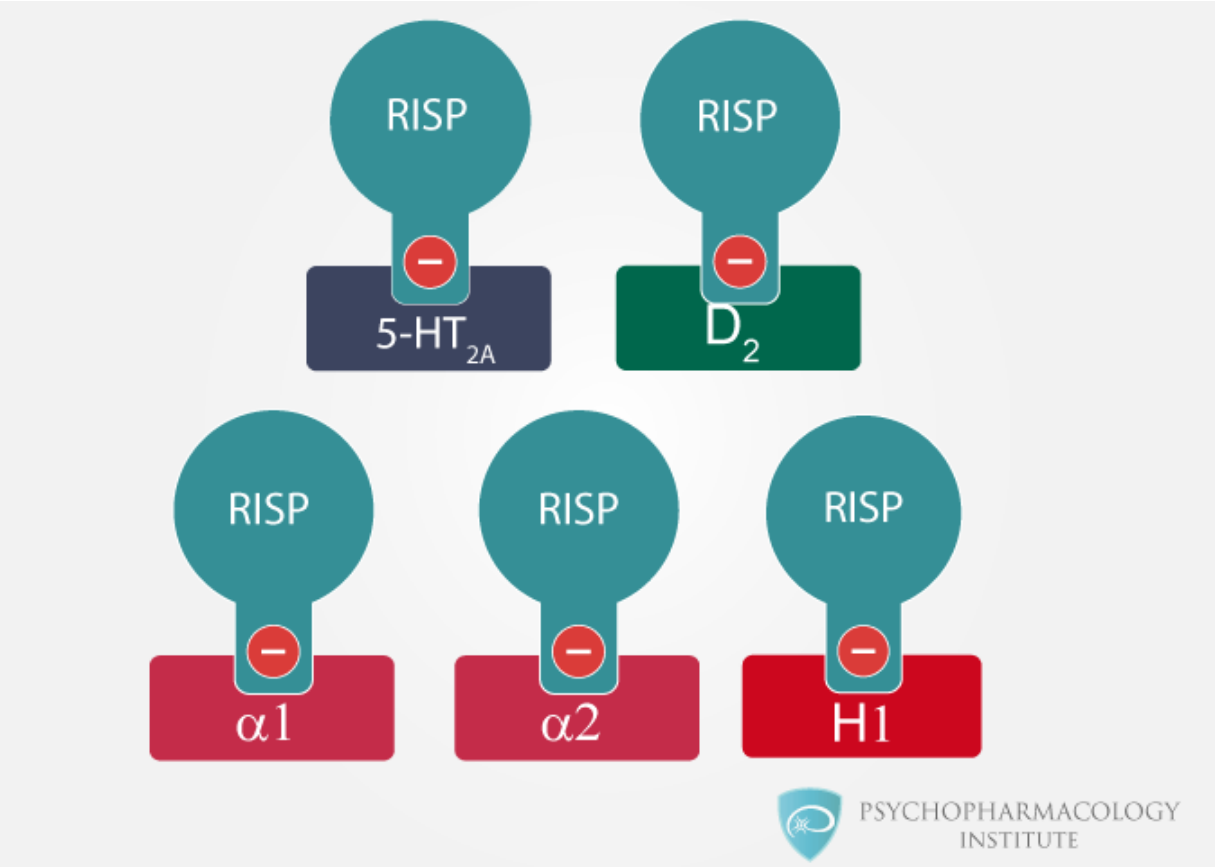
Receptor	Ki value (nM)
D2	3.2
5-HT1A	420
5-HT2A	0.2
5-HT2C	50
D1	240
D4	7.3
M1	>10,000
Alpha 1A	5
Alpha 2A	16
H1	20

Binding potency of risperidone at different receptors. Modified from [2]

Risperidone acts as antagonist at the following receptors:

- D2
- 5-HT2A
- Alpha 1
- Alpha 2
- H1 (moderate affinity)

The image below schematically illustrates the interaction of risperidone with different neurotransmitter receptors.



The 5-HT2A /D2 theory of atypicality

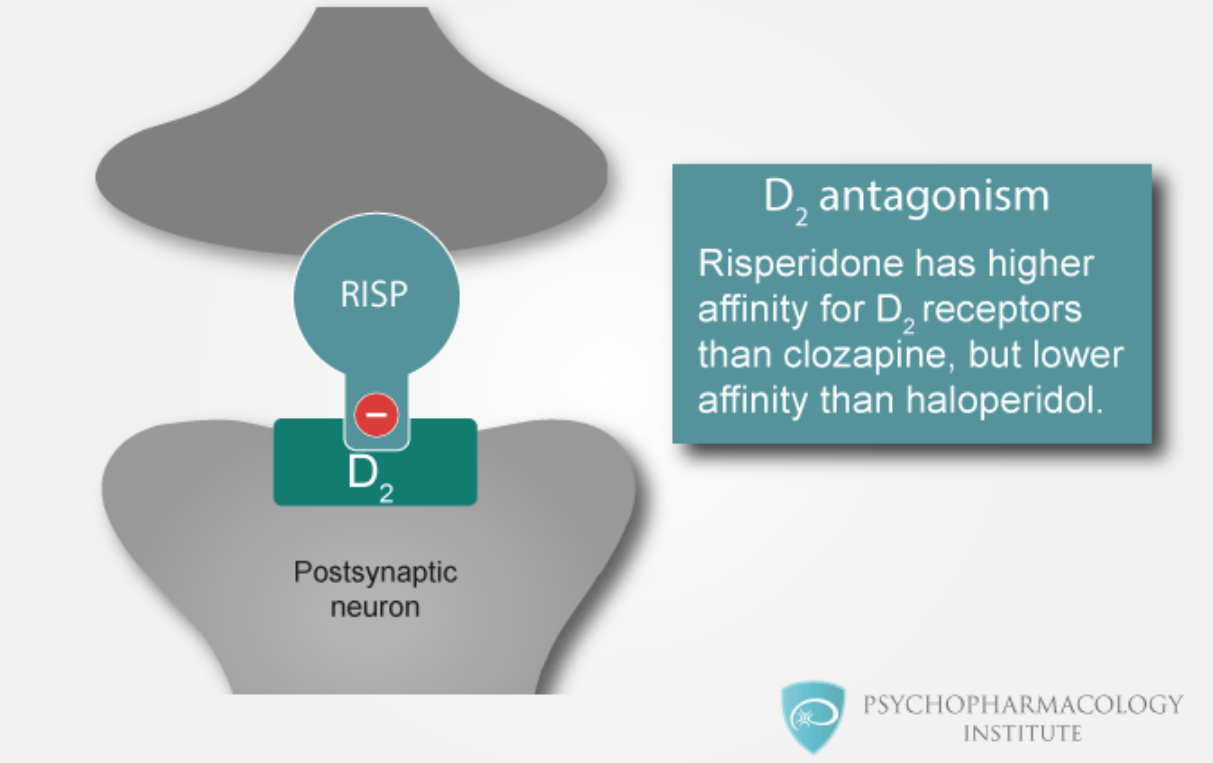
Risperidone was synthesized based on attempts to replicate clozapine effectiveness without its side effects profile. The goal was to develop a drug with low risk of extrapyramidal symptoms (EPS) based on the assumption that a high 5-HT2A/D2 ratio could confer this property [3].

However, when prescribed at higher doses, risperidone produces EPS consistently [4], indicating that 5-HT2A antagonism alone cannot eliminate EPS associated with substantial D2 receptor blockade.

D2 Antagonism

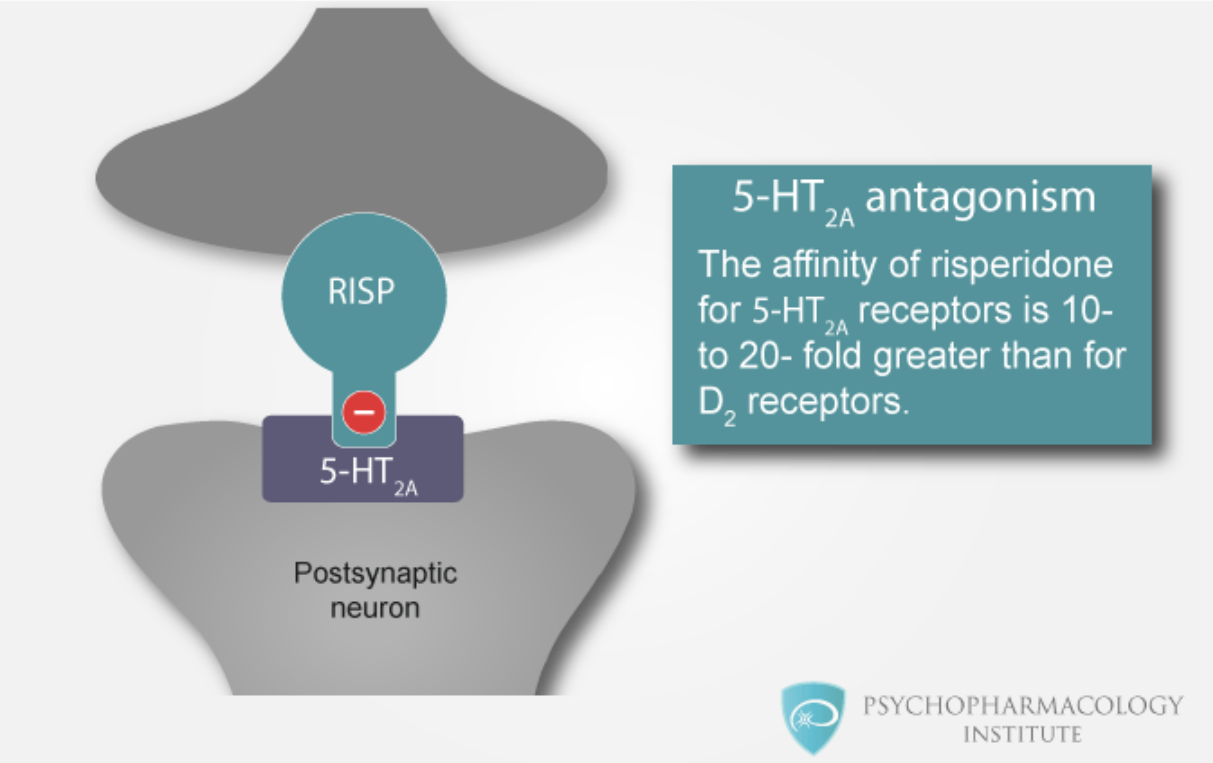
A PET study showed that risperidone occupies 75-80% of striatal D2 receptors when administered to patients suffering from schizophrenia at a dose of 6 mg/day [5]. Despite high levels of D2 receptor occupancy, moderate-dose risperidone treatment (4-6 mg/day) poses a somewhat lower EPS risk than treatment with some FGAs [6].

The affinity of risperidone for D2 receptors is approximately 50- fold greater than that of clozapine and approximately 20-50 % that of haloperidol [7].



5-HT2A Antagonism

Risperidone is characterized by a very high affinity for 5-HT2A receptors, and a moderately high affinity for D2, H1, and alpha 1 and alpha 2 adrenergic receptors. In vitro, the affinity of risperidone for 5-HT2A receptors is roughly 10- to 20-fold greater than for D2 receptors [3]



Summary – Key Points

- Risperidone is a SGA with a high 5-HT2A/D2 ratio (it has higher affinity for 5-HT2A receptors than for D2 receptors).
- According to the dopamine theory of schizophrenia, the mechanism of action of risperidone might involve reduction of dopaminergic neurotransmission in the mesolimbic pathway.
- The higher the risperidone daily dose, the higher the risk of EPS.

References

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