Partial Agonism: How Is It Thought to Work and What Is the Potential Clinical Relevance?

Pharmacologic management of psychiatric conditions involves not only knowing which medications are available, but also understanding the mechanisms that are hypothesized to underlie their activity. **Partial agonism** is one way of modulating receptor activity, distinct from both full agonism and antagonism, and it may offer an important perspective on how medications can potentially influence brain function.

For healthcare professionals (HCPs), familiarity with how partial agonism works can provide insight into how treatments are thought to help modulate neurotransmitter signaling in mental disorders, such as major depressive disorder (MDD), bipolar I disorder (BP-1), and schizophrenia. This understanding can help support decision-making and may provide an overview of how different pharmacologic mechanisms may play a role in patient care.[1]

Neurotransmission and Receptor Function

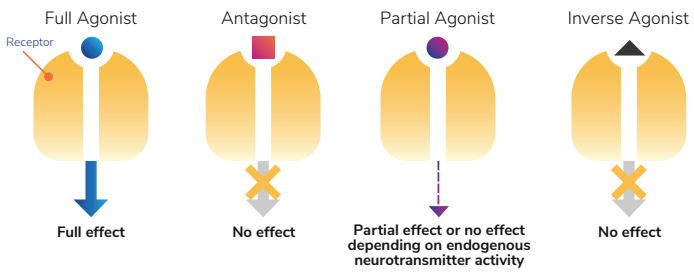
Neurotransmitters, such as dopamine, serotonin, norepinephrine, acetylcholine, glutamate, and gamma-aminobutyric acid (GABA), are thought to contribute to the regulation of diverse brain functions, including emotion, cognition, motivation, and motor functions.[1,2] These neurotransmitters are hypothesized to relay information across synaptic connections by binding to receptors on postsynaptic neurons.[1] Ligand binding is thought to induce conformational changes that regulate receptor activity.[3] Understanding how receptors are regulated through ligand binding provides the basis for how pharmacologic agents can activate or block signaling depending on their mechanism of action.[1]

The Agonist Spectrum

By mediating neurotransmitter signaling, receptors may act as molecular switches. The effect produced, however, depends on the **intrinsic activity** of the ligand. **Intrinsic activity** refers to the capacity of a ligand-receptor complex to trigger a cellular/biological response once bound.[3]

Agonist spectrum concept: Ligands, including psychotropic drugs, can range from full agonists to partial agonists, antagonists, and inverse agonists, according to their differences in intrinsic activity.[1]

Type	Effect on Signaling
Full agonist	Produces conformational changes that induce maximal receptor activation, leading to robust downstream effects.[1]
Antagonist	Produces conformational changes that result in no change in signal transduction, and it blocks receptor activity.[1]
Partial agonist	Induces a submaximal activation than a full agonist would, due to its lower intrinsic activity. Therefore, a partial agonist can act as a functional agonist or functional antagonist, depending on the levels of endogenous ligand in the surrounding region.[4]
Inverse agonist	Produces conformational changes that lead to a reduction in signal transduction to a level lower than that induced when there is no agonist present or by an antagonist.[1]



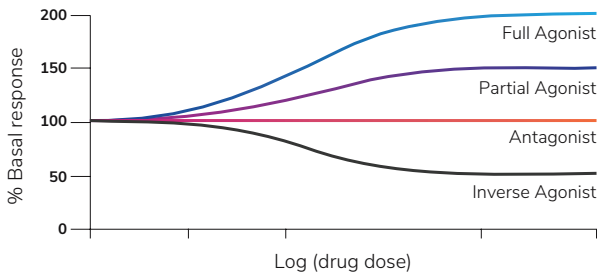


Figure 1. Neurotransmitter agonist and antagonist activity.[4,5]

Partial Agonism

Partial agonists are thought to demonstrate **context-dependent activity**, acting as either functional agonists or antagonists depending on neurotransmitter environment.[4]

- ***In high neurotransmitter states*** (when a full agonist is present)[4]: The partial agonist competes with endogenous full agonists, dampening overstimulation and functioning as a functional antagonist.
- ***In low neurotransmitter states*** (in the absence of a full agonist)[4]: The partial agonist binds to the receptor and produces a modest level of activation, acting as a functional agonist. This helps sustain signaling when neurotransmitter levels are deficient; however, the response is lower than that of a full agonist because of the partial agonist's reduced intrinsic activity.

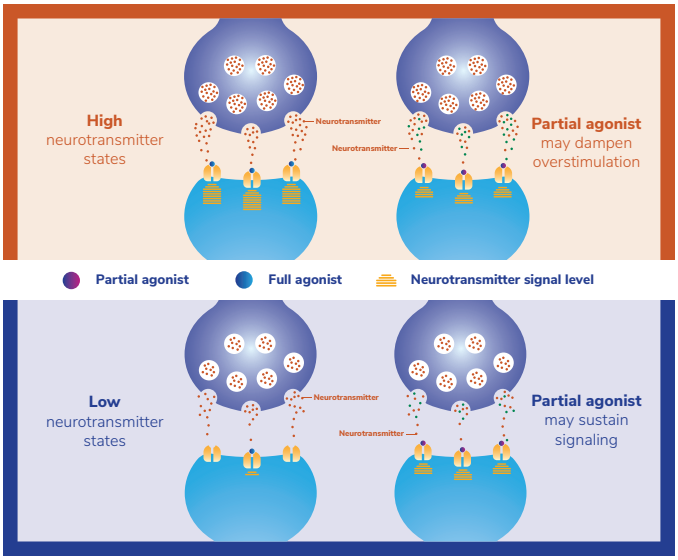


Figure 2. Context-dependent activity of partial agonists.[4]

Potential Clinical Relevance in Psychiatry

Partial agonists may help provide a **stabilization effect**, potentially able to modulate signaling instead of simply turning it on/off.[1] This may provide therapeutic benefit in disorders where neurotransmitter levels are hypothesized to fluctuate across brain region, such as in BP-1 and schizophrenia, by turning neurotransmission to more physiologic levels.[4]

- In the **dopamine mesolimbic pathway**, where excessive dopamine activity may contribute to positive symptoms of schizophrenia, a partial dopamine agonist can act as an antagonist.
- In the **dopamine mesocortical pathway**, where reduced dopamine activity may be associated with negative symptoms of schizophrenia, a partial dopamine agonist can act as an agonist. This can be helpful in maintaining dopaminergic tone in the nigrostriatal or tuberoinfundibular pathways, which may help reduce the risks of extrapyramidal symptoms and hyperprolactinemia.[1,4]

Therefore, partial agonists are sometimes called "**stabilizers**" because they can potentially buffer against over- or under-stimulation.[1]

Partial agonism represents a nuanced mechanism of receptor regulation that adapts signaling to the surrounding neurotransmitter environment.[1] Partial agonism is thought to buffer excessive or deficient neurotransmission. It may provide a therapeutic balance in some psychiatric disorders by adjusting neurotransmission to more physiological levels.[4] By understanding the mechanism of partial agonism, HCPs may be better able to interpret how receptor-level modulation may play a role in the management of mental disorders such as MDD, BP-1, and schizophrenia.[1]

References

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