

The 5-HT_{1A} Receptor in Psychopharmacology

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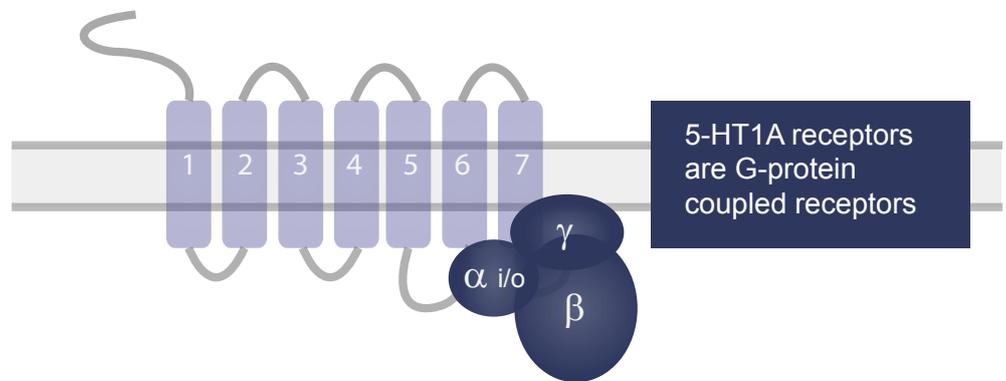
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The 5-HT_{1A} receptor is a subtype of serotonin receptor located in presynaptic and postsynaptic regions. Activation of this receptor has been involved in the mechanism of action of anxiolytic, antidepressant and antipsychotic medications.

General features

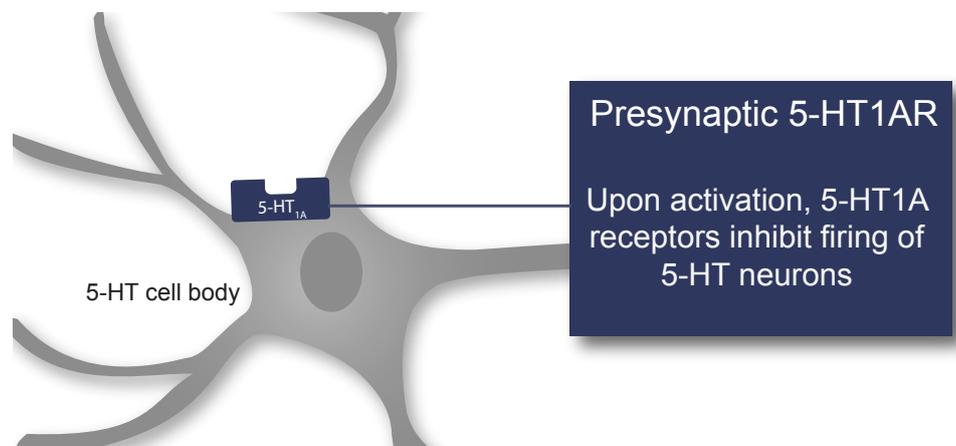
Serotonin is a monoamine neurotransmitter that interacts with 14 serotonin (5-HT) receptors that can be subdivided into 7 classes [1]. Specifically, the 5-HT_{1A} receptors are G-protein coupled receptors that exert their effects through Gi/o proteins to inhibit adenylyl cyclase, as well as other second messenger cascades such as MAPK pathways and NMDA receptor channels [2].



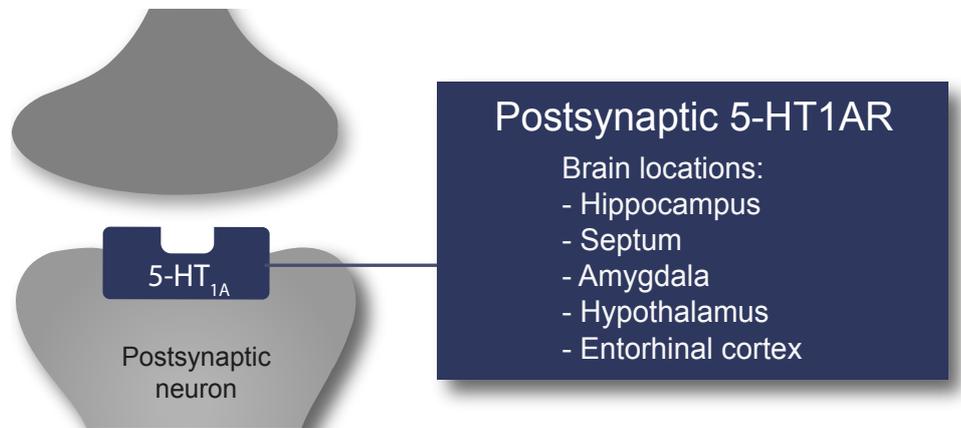
Location

5-HT_{1A} receptors can be found in the brain as:

Presynaptic autoreceptors on serotonergic cell bodies in the raphe nuclei. Upon stimulation, these receptors inhibit firing of 5-HT neurons [3,4].



Postsynaptic heteroreceptors in the limbic system, including the hippocampus, septum, amygdala and entorhinal cortex as well as the hypothalamus, cortex and dorsal horn [1,3,5]



Abundant 5-HT_{1A} receptors are also expressed on astrocytes and other glia where they are thought to be involved in mood control [1].

The 5-HT_{1A} receptor in psychiatric disorders

Postsynaptic 5-HT_{1A} receptors are found in those regions of the brain that are implicated in the control of mood, cognition and memory. It has become clear that these receptors can be a useful target in the management of various neuropsychiatric disorders [6].

The effect of drug molecules that act on 5-HT_{1A} receptors seems to vary with the location of the receptor, possibly due to a difference in regional receptor reserve [1]. It is therefore crucial to achieve the right balance of agonism at both pre and post synaptic 5HT_{1A} receptors in order to obtain the desired effect [1].

The Role of 5-HT_{1A} receptors in anxiety

The role of 5-HT in anxiety is well established. Recently, an animal study demonstrated increased anxiety behaviors in knockout mice bred without 5-HT_{1A} receptors in the cerebral cortex and limbic system, suggesting a key role specifically for 5-HT_{1A} in this respect [7].

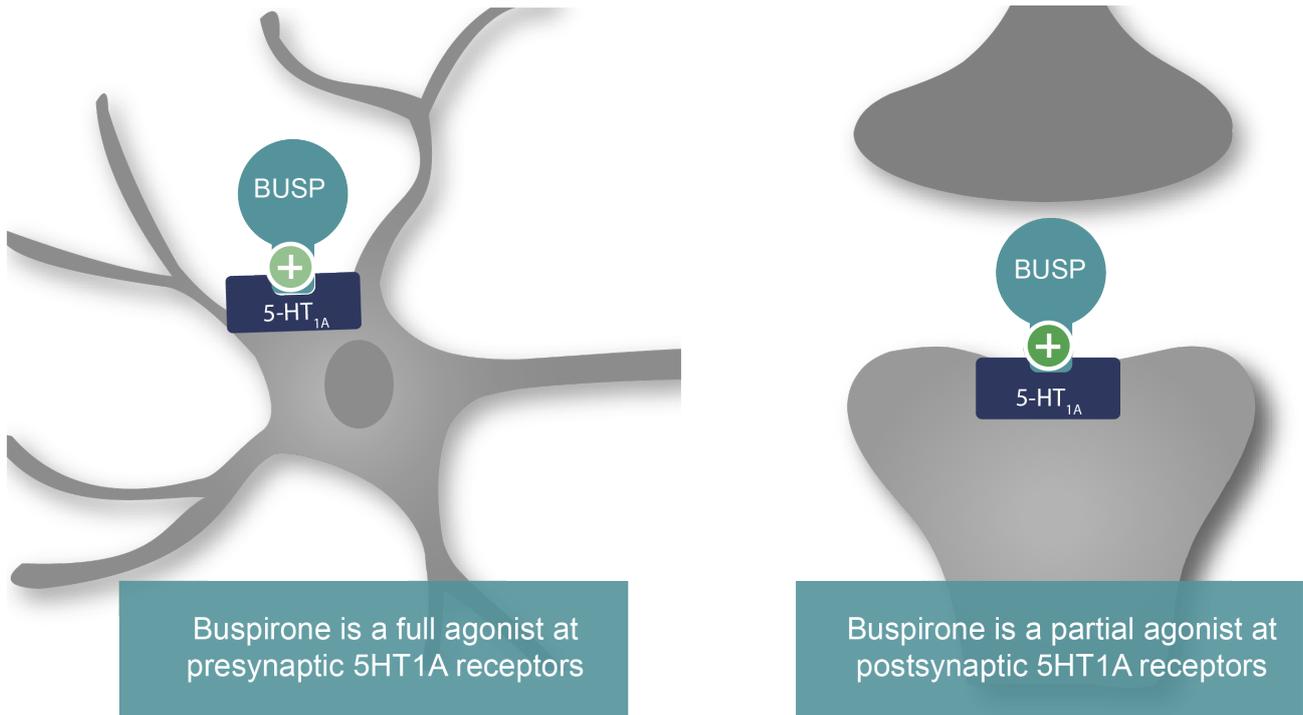
A study conducted on human subjects using neuroendocrine testing showed that panic disorder patients have impaired 5-HT_{1A} receptor function [8]. Furthermore, two functional imaging studies also conducted in humans revealed decreased 5-HT_{1A} binding in patients with untreated panic disorder [7,9].

The mechanism of action of buspirone

Buspirone is an azapirone that was originally thought to achieve its anxiolytic effects solely through D2 receptor antagonistic mechanisms. It was later discovered that buspirone specifically displaces 8- OH-DPAT from 5-HT_{1A} receptor binding sites, in addition to some D2 receptor antagonist activity [1].

Further investigation has revealed that buspirone acts at both:

- Presynaptic receptors (somatodendritic region) , where it behaves as a full agonist inhibiting the synthesis of neuronal 5-HT and firing.
- Postsynaptic receptors in the hippocampus and cortex as a partial agonist [1].



The role of 5-HT_{1A} receptors in antidepressant effects

The role of 5-HT_{1A} receptors in depression has been demonstrated through various studies.

Firstly, antidepressants such as MAOIs and TCAs, SSRIs, lithium, valproate, all increase postsynaptic 5-HT_{1A} signaling, either through direct or indirect mechanisms in humans [10].

Secondly, reduced numbers of 5-HT_{1A} receptors have been found in suicide patients following post mortem studies and a reduced binding affinity of 5-HT_{1A} receptors has been demonstrated using the same post mortem studies as well as PET scanning analysis [10].

Lastly, genetic studies on both humans and 5-HT_{1A} receptor knockout mice have led to the postulation that 5-HT_{1A} receptor dysfunction may be an underlying mechanism in depressive disorders [10]. These findings lead to the theory that 5-HT receptors may play a role in the alleviating depression, specifically through the desensitization of 5-HT_{1A} autoreceptors [1,2]

Proposed mechanism of action of vilazodone

Vilazodone is thought to exert its antidepressant effect through the combined effect of serotonin reuptake inhibition and partial agonism at 5-HT_{1A} receptors [4].

5-HT_{1A} receptors in schizophrenia

Schizophrenia is associated with positive symptoms including hallucinations and delusions, and negative symptoms such as flattened

affect, loss of sense or pleasure, loss of will or drive (avolition) and social withdrawal [6].

Recently it has been shown that compounds possessing balanced 5-HT_{1A} receptor agonism and D2 antagonism are efficacious antipsychotics that have a low propensity to elicit EPS or metabolic dysfunction. These agents, known as “selectively non-selective drugs”, might achieve the desired therapeutic benefit by targeting the sites responsible for the required effect but avoid the sites that are responsible for side effects [6].

Further research into this area has been prompted by a number of factors:

- 5-HT_{1A} receptor activation is required for the cortical DA release by antipsychotics- confirmed through studies on knockout mice; this effect is regionally selective and is only seen in frontocortical regions, but not the nucleus accumbens or striatum [6].
- 5-HT_{1A} receptor agonists such as 8-OH-DPAT eliminates catalepsy caused by typical antipsychotics in rats [11].
- 5-HT_{1A} receptors are upregulated in patients with schizophrenia.
- Buspirone and tandospirone that act as partial agonists at 5-HT_{1A} receptors reduce negative symptoms in patients with schizophrenia treated with haloperidol [6]

Clinically relevant 5-HT_{1A} partial agonists

Drug	Trade Name
Antianxiety agent	
Buspirone	Buspar
Second generation antipsychotic	
Clozapine	Clozaril
Ziprasidone	Geodon
Aripiprazole	Abilify
Antidepressant	
Vilazodone	Viibryd

It has been shown that optimal therapeutic benefit from targeting 5-HT_{1A} receptors can be obtained with the use of “biased agonists” or “functionally selective agonists”. These activate receptors that mediate therapeutic activity but avoid those that control other effects and result in unwanted effects. Biased agonists present a novel opportunity to manage psychiatric disorders that are associated with 5HT_{1A} receptor dysfunction [3].

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