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5-HT2A receptor's role as a modulator of salience in physiological...



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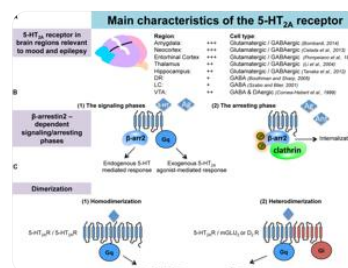
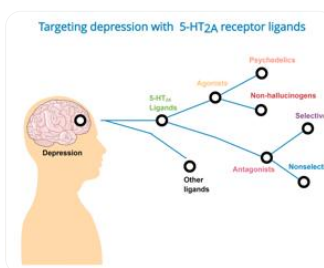
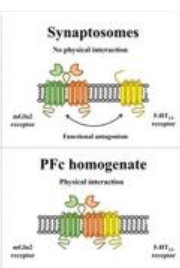
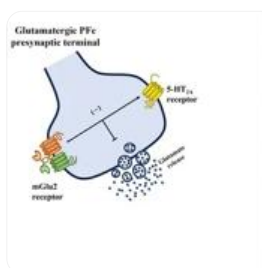
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The 5-HT2A receptor plays a critical role in modulating salience—the process of prioritizing biologically or contextually relevant stimuli—across neural circuits involved in cognition, emotion, and perception. Its influence spans synaptic plasticity, network connectivity, and neurotransmitter systems, with implications for both normal and altered states of consciousness.

Neural Circuit Modulation

- Prefrontal Cortex (PFC) and Thalamocortical Pathways:** 5-HT2A receptors are densely expressed in layer V pyramidal neurons of the PFC and presynaptically on thalamocortical fibers ^{2 9}. They enhance glutamatergic transmission by increasing spontaneous excitatory postsynaptic currents (sEPSCs) and NMDA receptor activity, which strengthens cortical network excitability ^{2 8}. This modulates attention and working memory, key components of salience detection ^{1 6}.
- Anterior Cingulate Cortex (ACC):** Activation here reduces anxious preoccupation by altering AMPA/NMDA receptor ratios and weakening maladaptive neuronal connections, promoting cognitive flexibility and fear extinction ⁴. Enhanced connectivity between the ACC/salience network and default mode network



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Neurotransmitter Interactions

- Glutamate Dynamics: 5-HT_{2A} receptors increase glutamate release from thalamocortical terminals, facilitating synaptic plasticity ^{2 8}. This is critical for updating salience assignments in response to new information.
- Dopamine Cross-Modulation: Indirect interactions with dopamine systems in the PFC influence reward prediction and motivational salience, though this is less directly studied in the provided sources.

Cognitive and Emotional Salience

- Fear and Emotional Processing: Blocking 5-HT_{2A} receptors alters the processing of fearful facial expressions, suggesting its role in prioritizing threat-related stimuli ⁵. Conversely, activation promotes fear extinction by disrupting entrenched fear memories ⁷.
- Hallucinations and Altered Perception: Psychedelics (5-HT_{2A} agonists) induce vivid sensory experiences by amplifying normally filtered stimuli, effectively "resetting" salience attribution ^{9 4}. This may explain their therapeutic potential in disorders like depression, where maladaptive salience patterns dominate ^{4 9}.

Clinical Implications

- Psychiatric Disorders: Dysregulated 5-HT_{2A} activity is linked to schizophrenia (aberrant salience attribution), depression (persistent negative bias), and addiction ^{3 7}. Antagonists (e.g., atypical antipsychotics) normalize hyper-salience of delusional stimuli, while agonists (e.g., psychedelics) disrupt rigid cognitive patterns ^{3 4}.
- Neurodegeneration: In Alzheimer's disease, 5-HT_{2A} loss correlates with impaired attention and memory consolidation, highlighting its role in maintaining cognitive salience ⁹.

Mechanistic Insights

- Structural Plasticity: Acute 5-HT2A activation rapidly enlarges dendritic spines in cortical neurons via PAK/kalirin-7 signaling, enabling dynamic reweighting of synaptic inputs ⁸.
- Network Reconfiguration: Psychedelics reduce DMN dominance over the central executive network (CEN), shifting focus from internal rumination to external stimuli ⁴. This aligns with Huxley's concept of perceptual "doors" opening to suppressed sensory details.

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In summary, the 5-HT2A receptor acts as a neuromodulatory pivot, balancing bottom-up sensory salience with top-down cognitive control. Its dual role in

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enhancing plasticity and resetting network hierarchies underscores its importance in both adaptive cognition and altered states of consciousness.

How do 5-HT2A receptors influence working memory



What role do 5-HT2A receptors play in associative memory



How does the activation of 5-HT2A receptors affect glutamatergic transmission in the PFC



What are the effects of 5-HT2A receptor antagonists on psychiatric disorders



How do 5-HT2A receptors contribute to hallucinations and spatial cognition

