5HT2a receptors on locus coeruleus and raphe

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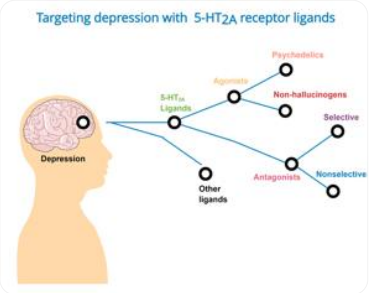

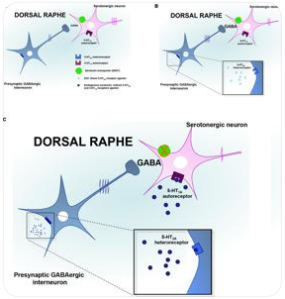

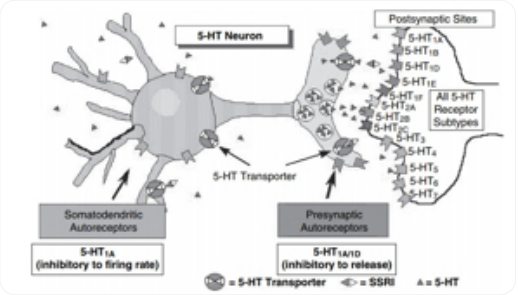

The 5-HT2A receptors in the locus coeruleus (LC) and raphe nuclei play distinct roles in modulating physiological and behavioral responses, particularly in fever, pain, and emotional states. These receptors are implicated in complex feedback mechanisms and network interactions between serotoninergic, noradrenergic, and GABAergic systems.

Locus Coeruleus (LC)

- Fever regulation: 5-HT2A receptors in the LC mediate the first phase of lipopolysaccharide (LPS)-induced fever. Antagonism with ketanserin abolishes this phase, while 5-HT1A receptors show no involvement [1] [3].
- Pain modulation: The LC's μ1-opioid receptors and 5-HT2A/2C receptors are critical for post-ictal hypoalgesia (reduced pain sensitivity after seizures). Synaptic inhibition in the LC or blockade of these receptors reduces hypoalgesia, indicating their role in descending pain control [5].
- Interaction with brainstem nuclei: The LC receives serotoninergic inputs from the dorsal raphe nucleus (DRN) and participates in feedback loops involving the periaqueductal gray matter (PAG) and DRN [5] [6].

- Panic and fear responses: 5-HT2A receptors in the DRN modulate panic-like behaviors and fear-induced antinociception. Their activation enhances GABAergic inhibition of DRN serotonin neurons, potentially regulating serotonin release [2] [4].

- Autoregulation of serotonin release: Systemic 5-HT2A agonists (e.g., DOI, DOB) inhibit DRN serotonin neuron activity via central (not peripheral) mechanisms. This involves postsynaptic 5-HT2A receptors on GABA interneurons, which dampen serotoninergic signaling [4].

- Cortical connectivity: Pyramidal neurons in the prefrontal cortex (PFC) projecting to the DRN and ventral tegmental area express 5-HT2A receptors, forming a regulatory loop between cortical and brainstem regions [6].

Functional Implications

- Network interactions: The LC and DRN are nodes in a broader circuit integrating arousal, pain, and emotional states. 5-HT2A receptors in these regions mediate cross-talk between serotonin, norepinephrine, and GABA systems [5] [6].

- Therapeutic targets: These receptors are potential targets for conditions involving fever, chronic pain, and anxiety disorders, though their dual roles in excitatory/inhibitory signaling complicate pharmacological modulation [1] [4] [5].

This interplay highlights the 5-HT2A receptor's role as a modulator of salience in physiological and cognitive processes, aligning with Huxley's exploration of consciousness through altered sensory perception.

Related

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