

Functional selectivity and antidepressant activity of serotonin 1A receptor ligands

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Serotonin (5-HT) is a monoamine neurotransmitter that plays an important roles in physiological functions as sleep, feeding, sexual behaviour, temperature regulation, pain, and cognition as well as in pathological states including mood disorders, anxiety disorders psychosis and pain disorders. Medications that increase levels of 5-HT, such as selective serotonin reuptake inhibitors, are effective treatments for depression and anxiety. While it is not known which of the at least 14 receptors for 5-HT mediate clinical response, an accumulation of data from both animal and clinical studies suggest a potentially important role for 5-HT_{1A} receptor. The receptor may be found in presynaptic as well as in postsynaptic part of the serotonergic tract. Presynaptically, the 5-HT_{1A} receptor is the major somatodendritic autoreceptor on the soma and dendrites of serotonergic neurons where it acts as a "brake" to inhibit the activity of the entire 5-HT system and is thought to delay antidepressant response.¹ The 5-HT_{1A} heteroreceptors are located on non-serotonergic neurons, primarily in the limbic areas, such as on the dendrites and soma of glutamatergic pyramidal neurons, and axon terminals of GABAergic and cholinergic neurons.

The primary coupling linkage of the 5-HT_{1A} receptor is to the inhibition of adenylyl cyclase (AC) and decrease protein kinase A activity.² However, the receptor has been found to inhibit and activate AC and phospholipase C, to stimulate nitric oxide synthase and an NAD(P)H oxidase-like enzyme, to activate K⁺ channels and high conductance anion channels, to inhibit Ca²⁺ conductances and inhibit or stimulate Ca²⁺ mobilization, and regulate a number of channels and transporters. The 5-HT_{1A} receptor can activate protein kinase C, Src kinase, and mitogen-activated protein kinases, activate or inhibit phosphatidyl inositol hydrolysis, and stimulate production of reactive oxygen species (both H₂O₂ and superoxide) and arachidonic acid.³

In the present paper we will discuss different biochemical pathways activated by 5-HT_{1A} receptor. The influence of the receptor ligands on the pathways and the implication on depressive like behaviour as well as on cytoprotective/cytotoxic activity will be discussed.

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