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REVIEW ARTICLE

A REVIEW ON FUNCTIONAL COMPARISON OF 5-HT1A AND 5-HT2C RECEPTORSDr P.R. Patil^{*}, M.A. Chaudhari¹, P.V. Sapkale¹, Dr Surajj Sarode², Md. Rageeb Md. Usman²^{*}JZMDS College of Pharmacy, Mamurabad, Jalgaon, Maharashtra, India²Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda, Maharashtra, India**ABSTRACT:**

5-HT neurotransmission system is targeted by drugs useful in behavioural disorders, including anxiety, depression, psychosis and eating disorders. 5-HT_{1A} autoreceptors, located on 5-HT neurones of the midbrain raphe nuclei, are coupled to K channels through a pertussis toxin-sensitive G-protein. 5-HT_{1A} receptor agonists inhibit adenylyl cyclase, while 5-HT_{2C} receptor agonists activate two signal transduction pathways coupled with these receptors. 5-HT_{1A} and 5-HT_{2C} receptors have lots potential in treating the disorders with less or no side effects.

Keywords: 5-HT_{1A}, 5-HT_{2C}, Receptor.**INTRODUCTION:**

The 5-HT neurotransmission system is targeted by drugs useful in behavioural disorders, including anxiety, depression, psychosis and eating disorders.

5-HT_{1A} autoreceptors, located on 5-HT neurones of the midbrain raphe nuclei, are coupled to K channels through a pertussis toxin-sensitive G-protein¹. Their activation hyperpolarizes 5-HT neurones and inhibits their firing activity². 5-HT_{1A} receptors are localised postsynaptically to 5-HT terminals, mainly in limbic and cortical structures³. The activation of postsynaptic 5-HT_{1A} receptors in cortical and hippocampus pyramidal neurones is also associated with hyperpolarization and reduction of their firing activity⁴, mediate the inhibition of forkolin-stimulated adenylyl cyclase activity; using the method of partial irreversible receptor activation⁵.

5-HT_{1A} receptor agonists exhibit anxiolytic and/or antidepressant activity in experimental models, and some members of the azapirone family, e.g., buspirone and gepirone, are used in the treatment of affective disorders^{6,7}. These drugs are also found to decrease feeding in food-deprived animals⁸.

In anxiety disorders, changes in the corticosteroid concentration and serotonergic transmission are observed, on which 5-HT_{1A} receptor agonists are clinically effective⁹, via the activation of glucocorticoid receptors by corticosterone, stressful stimuli enhance the activity of tryptophan hydroxylase and increase brain 5-HT turnover and extracellular 5-HT levels¹⁰. Reduction of 5-HT neurotransmission is thought to have an anxiolytic effect. The role of presynaptic 5-HT_{1A} receptors located in the raphe nuclei in mediating the anxiolytic effects of 5-HT_{1A} agonists has been demonstrated in animal models¹¹. It has been suggested that the anxiolytic effect of 5-HT_{1A} receptor agonists require action in the dorsal raphe nucleus through the

stimulation of somatodendritic 5-HT_{1A} autoreceptors, resulting in less firing of serotonergic neurones and a subsequent reduction in 5-HT release¹². Moreover, the glucocorticoid receptor antagonists like RU 38486 were shown to display anxiolytic-like activity in rats¹³. Thus, it can be hypothesised that the decreased density of glucocorticoid receptor binding sites in the raphe nuclei following 5-HT_{1A} receptor activation contributes to the anxiolytic action of 5-HT_{1A} agonists by restoring the efficiency of 5-HT_{1A} autoreceptor in the negative control of the electrical activity of serotonergic neurones¹⁴. The regulation of 5-HT_{1A} receptor is of considerable clinical importance as its adaptive changes appear to play an important role in the therapeutic effect of antidepressants.

The stimulation of 5-HT_{1A} receptor attenuates the extrapyramidal side effects of antipsychotic. For example, 5-HT_{1A} receptor agonists attenuate antipsychotic-induced extrapyramidal side effects in human¹⁵ and non-human primates¹⁶, and antipsychotic-induced catalepsy in rats¹⁷. The increased interest in 5-HT_{1A} receptors in antipsychotic research is evidenced by reports of novel antidopaminergic compound with affinity at 5-HT_{1A} receptors¹⁸.

5-HT_{1A} receptor may have a beneficial effect for treatment of schizophrenia, since the activation of postsynaptic 5-HT_{1A} receptors results in the activation of cortical dopaminergic system which may be important for ameliorating effect of atypical antipsychotic drugs on negative symptoms in schizophrenia^{19, 20}. Also it is known that 5-HT_{1A} receptors can induce the deficits passive avoidance retention, not 5-HT_{2A} receptors²¹.

5-HT_{1A} agonists induce multiple behavioural effects, e.g. modulate both general locomotor activity²², noniceptive thresholds²³ and elicit a characteristic

behavioural syndrome (5-HT syndrome)²⁴. These factors may interfere with learning performance by alteration of sensory input at the initial stage of information processing²⁵.

The stimulation of presynaptic 5-HT_{1A} receptor is involved in the ability of 8-OH-DPAT, a 5-HT_{1A} receptor agonist, to cause attentional dysfunction and enhance impulsivity while slowing of responding and increase in errors of omission mainly depend on stimulation of postsynaptic 5-HT_{1A} receptors²⁶.

The 5-HT is a major inhibitory agent of glutamatergic transmission in the human cerebral cortex. Not only serotonin inhibits the evoked release of glutamate from nerve terminals by acting at presynaptic 5-HT_{1D} receptors, it also can inhibit events triggered by glutamate release by acting at presynaptic receptors of the 5-HT_{1A} and of the 5-HT_{2C} subtype. Whatever the mechanisms, agonists at human 5-HT_{1D}, 5-HT_{2C} and 5-HT_{1A} receptors may be the potentially useful drugs in neuropathologies with underlying excessive glutamatergic transmission²⁷.

The human 5-HT_{2A} and 5-HT_{2C} receptor agonists differentially activate two signal transduction pathways independently coupled to these receptors²⁸ (Phospholipase C-mediated inositol phosphate accumulation and Phospholipase A₂-mediated arachidonic acid release). The transcript encoding the 5-HT_{2C} receptor undergo RNA editing events in which genomically encoded adenosine residues are converted to inosines by the action of double-stranded RNA deaminase²⁹. It has been suggested that this may affect receptor G-protein coupling efficiency, and hence the potency and efficacy of agonists may vary depending on the being studied.

Newton et al³⁰ (1998) expressed human 5-HT_{2A} and 5-HT_{2C} receptors in SHSY5Y cells. Both studies found 5-HT to be more potent at 5-HT_{2C} receptor than 5-HT_{2A} receptor.

Recently it is found that the selective 5-HT_{2C} receptor agonist Ro60-0175 can mimic many of the specific effects of the prototypical anorectic drug d-fenfluramine on feeding behaviour. In addition, the selective 5-HT_{2C} receptor antagonist SB 242084 either completely blocks,

or, substantially attenuates the behavioural effects on feeding of both d-fenfluramine and Ro60-0175 with the exception of meal size³¹. These results strongly support the investigation of 5-HT_{2C} receptor agonists as clinically effective anorectic drugs that avoid the peripheral cardiovascular side effects that may be associated with indirect agonist such as d-fenfluramine³².

Orexin-A-induced grooming is primary mediated by OX₁ receptors with involvement of downstream 5-HT_{2C} receptors. This study also suggested that orexin-A does not indirectly activate 5-HT_{2C} receptors throughout the rat CNS, but instead activates a neuroanatomically discrete population of 5-HT_{2C} receptors to increase rat grooming. In preliminary findings by Brown and Haas³⁴ (2000) demonstrated that orexin-A increases firing of neurones in the dorsal raphe nucleus. This suggests that antagonism of 5-HT_{2C} receptors can useful in anxiety and anxiety related disorders.

Lithium effectively controls manic-depressive illness³⁵. A possible explanation is that lithium modifies a downstream pathway to re-establish normal responses to the 5-HT_{2C} receptor, which is proposed to be one of the receptor responsible for manic-depressive illness, perhaps by interaction with phosphoinositide metabolic pathway. Lithium inhibits inositol signalling mainly by its specific effect on the 5-HT_{2C} receptor and acts as an inhibitor of inositol phosphate metabolism³⁶.

Like the 5-HT_{1A} receptor agonism, the 5-HT_{2C} receptor antagonism also decreases the extrapyramidal side effects of 'atypical' antipsychotic drugs³⁷.

CONCLUSION:

The 5-HT_{1A} receptor agonists inhibit adenylyl cyclase, while 5-HT_{2C} receptor agonists activate two signal transduction pathways coupled with these receptors. The above findings suggests that selective subtype drugs of 5-HT_{1A} and 5-HT_{2C} receptors have lots potential in treating the disorders with less or no side effects.

The 5-HT_{1A} receptors are potential target for anxiety, depression, eating disorders and for extrapyramidal side effects of atypical antipsychotics, the 5-HT_{2C} receptors for anxiety /panic, anxiety related disorders like OCD, maniac-depressive illness.

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