A REVIEW ON FUNCTIONAL COMPARISON OF 5-HT1A AND 5-HT2C RECEPTORS

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ABSTRACT:

5-HT neurotransmission system is targeted by drugs useful in behavioural disorders, including anxiety, depression, psychosis and eating disorders. 5-HT1A autoreceptors, located on 5-HT neurones of the midbrain raphe nuclei, are coupled to K channels through a pertusis toxin-sensitive G-protein. 5-HT1A receptor agonists inhibit adenylyl cyclase, while 5-HT2C receptor agonists activate two signal transduction pathways coupled with these receptors. 5-HT1A and 5-HT2C receptors have lots potential in treating the disorders with less or no side effects.

Keywords: 5-HT1A, 5-HT2C, Receptor.

INTRODUCTION:

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

5-HT1A autoreceptors, located on 5-HT neurones of the midbrain raphe nuclei, are coupled to K channels through a pertusis toxin-sensitive G-protein. Their activation hyperpolarizes 5-HT neurones and inhibits their firing activity. 5-HT1A receptors are localised postsynaptically to 5-HT terminals, mainly in limbic and cortical structures. The activation of postsynaptic 5-HT1A receptors in cortical and hippocampus pyramidal neurones is also associated with hyperpolarization and reduction of their firing activity, mediate the inhibition of forskolin-stimulated adenylyl cyclase activity; using the method of partial irreversible receptor activation.

5-HT1A 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. These drugs are also found to decrease feeding in food-deprived animals.

In anxiety disorders, changes in the corticosteroid concentration and serotonergic transmission are observed, on which 5-HT1A receptor agonists are clinically effective, via the activation of glucocorticoid receptors by corticosterone, stressful stimuli enhance the activity of tryptophan hydroxylase and increase brain 5-HT turnover and extracelluar 5-HT levels. Reduction of 5-HT neurotransmission is thought to have an anxiolytic effect. The role of presynaptic 5-HT1A receptors located in the raphe nuclei in mediating the anxiolytic effects of 5-HT1A agonists has been demonstrated in animal models. It has been suggested that the anxiolytic effect of 5-HT1A receptor agonists require action in the dorsal raphe nucleus through the stimulation of somatodendritic 5-HT1A autoreceptors, resulting in less firing of serotonergic neurones and a subsequent reduction in 5-HT release. Moreover, the glucocorticoid receptor antagonists like RU 38486 were shown to display anxiolytic-like activity in rats. Thus, it can be hypothesised that the decreased density of glucocorticoid receptor binding sites in the raphe nuclei following 5-HT1A receptor activation contributes to the anxiolytic action of 5-HT1A agonists by restoring the efficiency of 5-HT1A autoreceptor in the negative control of the electrical activity of serotonergic neurones. The regulation of 5-HT1A 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-HT1A receptor attenuates the extrapyramidal side effects of antipsychotic. For example, 5-HT1A receptor agonists attenuate antipsychotic-induced extrapyramidal side effects in human and non-human primates, and antipsychotic-induced catalepsy in rats. The increased interest in 5-HT1A receptors in antipsychotic research is evidenced by reports of novel antidepressinergic compound with affinity at 5-HT1A receptors.

5-HT1A receptor may have a beneficial effect for treatment of schizophrenia, since the activation of postsynaptic 5-HT1A 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. Also it is known that 5-HT1A receptors can induce the deficits passive avoidance retention, not 5-HT2A receptors.

5-HT1A agonists induce multiple behavioural effects, e.g. modulate both general locomotor activity, nonciceptive thresholds 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 processing\(^{25}\).

The stimulation of presynaptic 5-HT1A receptor is involved in the ability of 5-OH-DPAT, a 5-HT1A 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-HT1A receptors\(^{26}\).

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-HT1D receptors, it also can inhibit events triggered by glutamate release by acting at presynaptic receptors of the 5-HT1A and of the 5-HT2C subtype. Whatever the mechanisms, agonists at human 5-HT1D, 5-HT2C and 5-HT1A receptors may be the potentially useful drugs in neuropathologies with underlying excessive glutamatergic transmission\(^{27}\).

The human 5-HT2A and 5-HT2C receptor agonists differentially activate two signal transduction pathways independently coupled to these receptors\(^{28}\) (Phospholipase C-mediated inositol phosphate accumulation and Phospholipase A2-mediated arachidonic acid release). The transcript encoding the 5-HT2C receptor undergo RNA editing events in which genomically encoded adenosine residues are converted to inosines by the action of double-stranded RNA deaminase\(^{29}\). 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 al\(^{30}\) (1998) expressed human 5-HT2A and 5-HT2C receptors in SH-SY5Y cells. Both studies found 5-HT to be more potent at 5-HT2C receptor than 5-HT2A receptor.

Recently it is found that the selective 5-HT2C 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-HT2C 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 size\(^{31}\). These results strongly support the investigation of 5-HT2C receptor agonists as clinically effective anorectic drugs that avoid the peripheral cardiovascular side effects that may be associated with indirect agonist such as d-fenfluramine\(^{32}\).

Orexin-A-induced grooming is primary mediated by OX1 receptors with involvement of downstream 5-HT2C receptors. This study also suggested that orexin-A does not indirectly activate 5-HT2C receptors throughout the rat CNS, but instead activates a neuroanatomically discrete population of 5-HT2C receptors to increase rat grooming. In preliminary findings by Brown and Haas\(^{33}\) (2000) demonstrated that orexin-A increases firing of neurones in the dorsal raphe nucleus. This suggests that antagonism of 5-HT2C receptors can useful in anxiety and anxiety related disorders.

Lithium effectively controls manic-depressive illness\(^{34}\). A possible explanation is that lithium modifies a downstream pathway to re-establish normal responses to the 5-HT2C receptor, which is proposed to be one of the receptor responsible for manic-depressive illness, perhaps by interaction with phosphoinositol metabolic pathway. Lithium inhibits inositol signalling mainly by its specific effect on the 5-HT2C receptor and acts as an inhibitor of inositol phosphate metabolism\(^{35}\).

Like the 5-HT1A receptor agonism, the 5-HT2C receptor antagonism also decreases the extrapyramidal side effects of ‘atypical’ antipsychotic drugs\(^{36}\).

**CONCLUSION:**

The 5-HT1A receptor agonists inhibit adenylyl cyclase, while 5-HT2C receptor agonists activate two signal transduction pathways coupled with these receptors. The above findings suggests that selective subtype drugs of 5-HT1A and 5-HT2C receptors have lots potential in treating the disorders with less or no side effects.

The 5-HT1A receptors are potential target for anxiety, depression, eating disorders and for extrapyramidal side effects of atypical antipsychotics, the 5-HT2C receptors for anxiety /panic, anxiety related disorders like OCD, maniac-depressive illness.

**REFERENCES:**


