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REVIEW ARTICLE

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[1]. Their activation hyperpolarizes 5-HT neurones and inhibits their firing activity[2]. 5-HT1A receptors are localised postsynaptically to 5-HT terminals, mainly in limbic and cortical structures[3]. The activation of postsynaptic 5-HT1A receptors in cortical and hippocampus pyramidal neurones is also associated with hyperpolarization and reduction of their firing activity[4], mediate the inhibition of forkolin-stimulated adenylyl cyclase activity; using the method of partial irreversible receptor activation[5].

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[6,7]. These drugs are also found to decrease feeding in food-deprived animals[8].

In anxiety disorders, changes in the corticosteroid concentration and serotonergic transmission are observed, on which 5-HT1A receptor agonists are clinically effective[9], via the activation of glucocoticoid receptors by corticosterone, stressful stimuli enhance the activity of tryptophan hydroxylase and increase brain 5-HT turnover and extracellular 5-HT levels[10]. 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[11]. 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[12]. Moreover, the glucocorticoid receptor antagonists like RU 38486 were shown to display anxiolytic-like activity in rats[13]. 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[14]. 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[15] and non-human primates[16], and antipsychotic-induced catalepsy in rats[17]. The increased interest in 5-HT1A receptors in antipsychotic research is evidenced by reports of novel antidopaminergic compound with affinity at 5-HT1A receptors[18].

5-HT1A receptor may have a beneficial effect for treatment of schizophrenia, since the activation of postsynsptic 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[19, 20]. Also it is known that 5-HT1A receptors can induce the deficits passive avoidance retention, not 5-HT2A receptors[21].

5-HT1A agonists induce multiple behavioural effects, e.g. modulate both general locomotor activity[22], nonciceptive thresholds[23] 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 8-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 SHSY5Y 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[34] (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[35]. 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 phosphoinsitide 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[36].

Like the 5-HT1A receptor agonism, the 5-HT2C receptor antagonism also decreases the extrapyramidal side effects of 'atypical' antipsychotic drugs[37].

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.

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