Regulation of central 5-HT$_{2A}$ receptors: a review of in vivo studies

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Abstract

Numerous investigations have studied in vivo regulation of central 5-HT$_{2A}$ receptors. The majority of pharmacological studies point to non-classical regulation of this site. Serotonergic denervation does not modify 5-HT$_{2A}$ receptor density or second messenger responses (phosphoinositide hydrolysis). 5-HT$_{2A}$ receptor downregulation is produced by the chronic administration of 5-HT$_{2A}$ receptor agonists and uniquely among monoamine receptors by antagonists. Several classes of psychotherapeutic agents also downregulate 5-HT$_{2A}$ receptors with chronic administration including classical antidepressants and antipsychotics. 5-HT$_{2A}$ receptor downregulation produced by 5-HT$_{2A}$ antagonists and antidepressants occurs after presynaptic 5-HT denervation, suggesting that 5-HT$_{2A}$ receptors are postsynaptically localized and emphasizing that they are regulated differently than traditional monoaminergic receptors. Interestingly, the behavioral and biochemical effects of 5-HT$_{2A}$ receptor activation are modulated by activity at other 5-HT receptor subtypes (5-HT$_{1A}$), as well as by stimulation of receptors for other neurotransmitters and hormones such as norepinephrine (beta-adrenergic) and melatonin. It is suggested that these diverse modulatory influences on 5-HT$_{2A}$ receptor regulation and function may meaningfully impact the therapeutic actions of drugs, including pharmacologically distinct antidepressants.

Keywords: 5-HT$_{2A}$ receptor; Regulation; Antidepressant; Beta-adrenergic; Melatonin; Heterologous interaction

1. Introduction

Serotonin (5-HT) receptor nomenclature has recently undergone reclassification [31] reflecting increased understanding of the molecular basis of receptor heterogeneity, pharmacological specificity and functional correlates. The 5-HT$_2$ receptor class contains three distinct receptor subtypes: 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$. This discussion will focus on the 5-HT$_{2A}$ receptor which has been referred to as the 'classical' 5-HT$_2$ receptor [31]. In the central nervous system (CNS), highest densities of the 5-HT$_{2A}$ receptor are found in cortical regions with lower densities localized in the hippocampus and caudate nuclei [39]. 5-HT$_{2A}$ receptors are linked to the phosphoinositide (PI) hydrolysis pathway such that 5-HT$_{2A}$ agonists elicit phosphatidyl inositol metabolism and increases in inositol phosphate production [8].

Behavioral studies demonstrate that agonist action at 5-HT$_{2A}$ receptors evoke head shakes and wet dog shakes in rats, as well as head twitches in mice [3,27,29]. 5-HT$_{2A}$ receptors have been clinically implicated in mood disorders such as depression and schizophrenia. Increased densities of cortical 5-HT$_{2A}$ receptors are observed upon post-mortem examination in depressed patients [52] and suicide victims [30]. In contrast, the number of 5-HT$_{2A}$ receptors located in brain from post-mortem schizophrenic patients are reduced [36]. 5-HT$_{2A}$ receptors may also play a role in sleep regulation. 5-HT$_{2A}$ agonists decrease rapid eye movement sleep in rat [12] while 5-HT$_{2A}$ antagonists increase slow-wave sleep [22] in man. 5-HT$_{2A}$ receptors in rat brain have been shown to demonstrate circadian rhythms [50] and 5-HT$_{2A}$ antagonists have exhibited potential as a treatment for jet lag [21]. 5-HT$_{2A}$ receptors may also have some role in the action of hallucinogenic drugs [18] and in the mediation of sexual behavior [35].

2. Responses of 5-HT$_{2A}$ receptors to regulatory challenges

Chronic treatment of rats with 5-HT$_{2A}$ agonists such as DOI, DOB, DOM or quipazine reduces 5-HT$_{2A}$ receptor densities [6,14,26,34] with a corresponding
desensitization of 5-HT$_2A$-mediated behavior [14,26]. The same effect is also produced by chronic treatment with 5-HT$_2A$ antagonists. In studies where the 5-HT$_2A$ antagonists such as methysergide, mianserin, ritanserin, setoperone and ketanserin were chronically administered to rats, a decrease in 5-HT$_2A$ receptor density [14,25,32], a subsensitivity of the PI response [9], and an attenuation of the head-shake behavioral response were observed [14].

Chronic treatment with tricyclic antidepressants, atypical antidepressants such as mianserin, monoamine oxidase inhibitors, and lithium also down-regulates 5-HT$_2A$ receptors [4,15,40,49], desensitizes PI hydrolysis [9,23,38] and reduces 5-HT$_2A$-mediated behavior [14]. Conversely, electroconvulsive shock therapy increases 5-HT$_2A$ receptor densities and 5-HT$_2A$-mediated head-twitches with no change in second messenger activity [19,37,47] (Table 1).

Serotonergic denervation by 5,7-dihydroxytryptamine or raphe lesion does not affect binding parameters, signal transduction or behavioral responses mediated by 5-HT$_2A$ receptor stimulation [5,9,14,24]. In addition, noradrenergic (NE) denervation also has no effect on 5-HT$_2A$ receptor density [13]. Neither 5-HT nor NE lesions affect the 5-HT$_2A$ receptor downregulation seen with chronic 5-HT$_2A$ agonists, 5-HT$_2A$ antagonists or tricyclic antidepressants [14,15]. Taken together, these results suggest that 5-HT$_2A$ receptors are located postsynaptically and are regulated by a mechanism that is distinct from other monoaminergic receptors which reliably exhibit upregulation and hypersensitivity after denervation. It has been suggested that 5-HT$_2A$ receptors receive very low levels of stimulation under normal physiologic conditions. Because of this, the receptors may already exist in a supersensitized state and chronic blockade with antagonists would not produce further sensitization. Receptor downregulation and desensitization could thus be envisioned as a defense mechanism against excessive stimulation [26,44]. Alternatively, antagonist-induced downregulation of 5-HT$_2A$ receptors may reflect the ability of these agents to act as 'inverse agonists' as has been demonstrated with 5-HT$_2C$ receptors [45].

3. Modulatory influences on 5-HT$_2A$-mediated neurotransmission in vivo

Acute administration of 5-HT$_1A$ agonists inhibits 5-HT$_2A$-mediated behavior [2,53] suggesting a heterologous interaction between 5-HT$_1A$ and 5-HT$_2A$ receptors. Chronic administration of selective 5-HT$_1A$ agonists results in cortical 5-HT$_2A$ receptor downregulation [54]. This action of 5-HT$_1A$ agonists persists in the presence of 5-HT or NE denervation [54] suggesting a postsynaptic action for 5-HT$_1A$ agonists where stimulation of cortical 5-HT$_1A$ receptors may in turn influence the sensitivity of neighboring 5-HT$_2A$ receptors. Consistent with these findings, 5-HT$_1A$ and 5-HT$_2A$ receptors which coexist on prefrontal cortical neurons mediate opposing effects on membrane excitability [1].

Modification of 5-HT$_2A$-mediated behavioral responses may also be produced by changes in the NE system. In acute studies, beta-adrenergic receptor agonists are effective in potentiating the L-5-hydroxytryptophan-induced head-twitch in mice [20]. Increases in beta-adrenergic receptor densities following NE denervation or chronic treatment with directly acting beta-adrenergic antagonists enhance 5-HT$_2A$-mediated behavior while beta-adrenergic receptor downregulation results in reductions in 5-HT$_2A$-mediated responses independent of changes in 5-HT$_2A$ receptor number [13]. Similarly, the ability of chronic treatment with the antidepressant nomifensine to produce reductions in 5-HT$_2A$-mediated behavior is associated with a selective reduction in beta-adrenergic binding sites, in that nomifensine-induced reductions in the 5-HT$_2A$-mediated head shake and beta-adrenergic receptor downregulation were concomitantly blocked in NE-lesioned rats [15].

Recent evidence also suggests a heterologous interaction between 5-HT$_2A$ receptors and the neurohormone melatonin. Administration of melatonin counteracts the discrete effects upon sleep induced by 5-HT$_2A$ agonists such as DOM and antagonists such as ritanserin [11]. Further, acute administration of melatonin and related agonists inhibits both the DOI-induced head shake and

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<tr>
<th>Regulatory challenge</th>
<th>Receptor binding ($B_{max}$)</th>
<th>Second messenger</th>
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<tr>
<td>Chronic 5-HT$_2A$ agonist</td>
<td>↓</td>
<td>DOI, DOB, DOM, quipazine</td>
<td>↓ head shake</td>
<td>[6],[26],[14]</td>
</tr>
<tr>
<td>Chronic 5-HT$_2A$ antagonist</td>
<td>↓</td>
<td>methysergide ritanserin setoperone mianserin ketanserin</td>
<td>↓ PI hydrolysis</td>
<td>↓ head shake</td>
</tr>
<tr>
<td>Chronic antidepressant</td>
<td>↓ or no change</td>
<td>TCA's, MAOI's, atypicals, lithium SSRI's</td>
<td>↓ PI hydrolysis</td>
<td>↓ head shake, head twitch</td>
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<tr>
<td>Chronic ECS</td>
<td>↑</td>
<td>no change</td>
<td>↑ head twitch</td>
<td>[19],[37]</td>
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5-HT₂₄-mediated cortical PI hydrolysis but does not alter cortical 5-HT₂₄ receptor densities [16].

4. 5-HT₂₄ receptor sensitivity: a common substrate in the therapeutic actions of antidepressants

While upregulation of cortical 5-HT₂₄ receptors in post-mortem brains from depressed patients remains controversial [33], neurochemical studies nevertheless reveal that downregulation of 5-HT₂₄ receptors and desensitization of 5-HT₂₄-mediated neurotransmission are temporally correlated with the onset of clinical efficacy for pharmacologically distinct antidepressant drugs [23,28,48]. Further, clinical studies indicate that 5-HT₂₄ antagonists such as pizotifen, ritanserin, and nefazodone may be antidepressants in man [17,41,46]. Interestingly, 5-HT₁₄ agonists such as buspirone and gepirone have been shown to possess antidepressant properties [42,43] as have the more traditional agents which modify beta-adrenergic receptors upon chronic administration [48]. Further, melatonin hypofunction has been implicated in disorders of mood [7,51] and melatonin levels are reported to increase following administration of the antidepressant fluvoxamine [10].

It is tempting to speculate that these heterologous effects at 5-HT₁₄, β-adrenergic and melatonin receptors which result in reductions in 5-HT₂₄-mediated neurotransmission may play a role in the therapeutic actions of antidepressants. 5-HT₂₄ receptors may thus represent a highly redundant endogenous system which is sensitive to heterologous (monoaminergic, melatonin) as well as homologous (5-HT₂₄ antagonist/antidepressant) influences on receptor regulation and function (Fig. 1).

5. Future directions

The therapeutic action of antidepressant drugs that results from chronic treatment appears to involve slowly emerging neuroadaptive effects which implicate changes in regulation at the molecular level. Recent studies in cultured cells suggest that the 5-HT₂₄ receptor is regulated at both transcriptional and post-transcriptional levels. Reduction in 5-HT₂₄ receptor mRNA levels that occur following antidepressant treatment reflect a transcriptional change (see M. Toth, this volume), while changes in enzyme levels, intracellular messengers (e.g. protein kinase C) and heterologous receptor systems represent post-transcriptional processes that regulate 5-HT₂₄ receptor mRNA expression (see Ferry and Molinoff, this volume). To date, molecular techniques that reveal transcriptional and post-transcriptional events have principally been applied in cultured cell systems. Their application to in vivo systems will no doubt further illuminate aspects of the complex regulation of the 5-HT₂₄ receptor and the impact of antidepressant drugs.

References


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