A Novel Approach to the Identification of Psychiatric Drugs: Serotonin-Glutamate Interactions in the Prefrontal Cortex

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**ABSTRACT**

Activation of neocortical 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptors is thought to mediate the profound psychomimetic effects of hallucinogenic drugs such as LSD and mescaline. These effects include alteration in mood, perception, and cognition. Conversely, blockade of neocortical 5-HT$_{2A}$ receptor may be related to the thymoleptic effects of newly released antidepressant (e.g., mirtazepine, nefazodone) and atypical antipsychotic drugs (e.g., risperidone, olanzapine). Therefore, one strategy to develop novel antidepressant drugs might be to identify drugs which suppress the effects of 5-HT$_{2A}$ receptor activation in key neurocircuits. Electrophysiological experiments using *in vitro* rat slices of the medial prefrontal cortex have found that activation of 5-HT$_{2A}$ receptors results in glutamate release from thalamocortical terminals by a novel focal effect. A number of monoamine (5-HT$_{1A}$, $\beta_2$), metabotropic glutamate (mGlu2), and neuropeptide (µ-opioid) receptors suppress the glutamate release induced by 5-HT$_{2A}$ receptor activation. Clinical studies examining the effects of serotonin or catecholamine depletion suggest the activation of 5-HT or catecholamine receptors mediate the therapeutic effects of selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs), respectively. In addition, opiate agonists may have antidepressant properties. Therefore, it is suggested that elucidation of the specific receptors that suppress glutamate release induced by 5-HT$_{2A}$ receptor activation in the medial prefrontal cortex may have several effects. First, this might lead to a more complete understanding of the 5-HT receptor(s) that mediate the therapeutic effects of presently used drugs such as SSRIs. This site might be a therapeutic target free of side effects such as sexual dysfunction. Second, this strategy might lead to novel therapeutic targets for depression, such as metabotropic glutamate agonists which may not be efficacious in screening strategies primarily dependent on synaptic availability of monoaminergic neurotransmitters.
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