

# Neurotransmitter interactions in psychotropic drug action: beyond dopamine and serotonin

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A frequent topic of discussion among research clinicians and other scientists engaged in basic psychiatric research is the extent of real advances in approaches to drug therapy in psychiatry. After the serendipitous discovery of some major avenues of drug treatment for psychiatric disorders in the 1950s, a wide range of prescription drugs became available for treating mood disorders and schizophrenia. Nevertheless, it is difficult to deny that the most significant advances have been in reducing the unwanted side effects of these therapeutic agents. The provocative argument that we have really seen relatively little advance in therapeutic mechanisms for drug treatment is often based on the striking observation that many of the primary neural targets for treating depression and schizophrenia remain unchanged.

Soon after the introduction of monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants, noradrenaline and serotonin emerged as the primary candidates for the biochemicals that may be imbalanced and underlie depression. The MAOIs and tricyclics act primarily to increase functional availability of brain serotonin and catecholamines (particularly noradrenaline, in this context). Looking across the years, our approach appears to have turned full circle. This is clear from a comparison of early tricyclics such as imipramine with drugs such as venlafaxine. Imipramine is a strong inhibitor of serotonin and noradrenaline uptake into the presynaptic terminal, and the major primary metabolite, desmethylimipramine (desipramine), is a very potent inhibitor of synaptic

noradrenaline uptake, with less effect on serotonin. Venlafaxine blocks the synaptic uptake of both serotonin and noradrenaline and has a much "cleaner" spectrum of action in terms of improved side-effect profile compared with tricyclic antidepressants.<sup>1</sup> Some elegant studies indicate that serotonin plays a significant role in the regulation of mood.<sup>2</sup> For many drugs, antidepressant response appears to be related to increased serotonin neurotransmission. Although some antidepressants induce a primary increase in noradrenaline transmission, this effect may also lead to altered serotonin function.<sup>3,4</sup>

In the context of schizophrenia, since the extensive early drug design work of Paul Janssen and others, our principal focus for the neurochemicals to target in the treatment of psychosis has remained on dopamine and serotonin.<sup>5</sup> Some of the main neuroleptics that are still widely used today, such as haloperidol and chlorpromazine, were introduced at a very early stage. Although the precise therapeutic mechanisms of antipsychotic drugs remain to be established, the newer drugs that are considered "atypical" because of a reduced side-effect profile appear to block receptors for both dopamine and serotonin.

There was considerable interest in the atypical antipsychotic drug clozapine as a serotonin 5-HT<sub>2A/C</sub> receptor-blocking compound that appeared to have relatively little affinity for dopamine D<sub>2</sub> receptors. More recent work, however, has clearly placed this effective antipsychotic drug back in the lineup of atypical antipsychotic drugs that block both the D<sub>2</sub> and 5-HT<sub>2A/C</sub>

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receptors.<sup>6</sup> I expect that some readers who have an interest in this area will have attended at least 1 lecture at which a researcher has presented a brain imaging slide depicting positron emission tomographic (PET) scans of “atypical” antipsychotic occupancy of both dopamine D<sub>2</sub> receptors and serotonin 5-HT<sub>2A/C</sub> receptors, only to foil the audience with the announcement that they are looking at effects of the neuroleptic drug chlorpromazine. The point is well taken that, although the side-effect profile of the newer compounds may be much improved over the typical antipsychotics, the principal neural targets may still be the same.

From the broad perspective of behavioural neuroscience, there is tremendous interest in the role of monoamines such as serotonin and dopamine in the organization of behaviour. Looking at the literature, it may appear that dopamine systems have taken the lion's share of this interest. Considering the remarkable behavioural effects that alterations of dopamine transmission can have, as well as the early development of models for Parkinsonism and schizophrenia, this is not too surprising. The dopaminergic systems of the forebrain continue to provide a pivotal focus for models related to cognition, motivation and emotion.<sup>7</sup> Although there is also interest in noradrenaline and serotonin in this context, the relative subtlety of noradrenergic effects on behaviour<sup>8</sup> and the tremendous task of untying the Gordian knot presented by the plethora of serotonin receptors<sup>9</sup> has left dopamine at the forefront of many models. Cholinergic systems, often discussed in the context of unwanted side effects of drugs used in psychiatry, are of obvious importance in relation to cognition and the regulation of sleep. The list of players in the regulation of behaviour is increasingly lengthy and, of course, includes excitatory and inhibitory amino acids such as glutamate and gamma-aminobutyric acid (GABA), respectively. There is also extensive evidence for the involvement of neuroactive peptides such as cholecystokinin (CCK) in motivation and emotion.<sup>10</sup>

Current drug therapy for mood disorders and schizophrenia is effective, although not optimal, and the main neural targets for these psychiatric disorders have not changed radically in the last half-century. In view of this, could it be that early clinical researchers were lucky enough to point the way to the discovery of the basic root of these clinical problems, or are we missing something? When presented with an increasing and potentially overwhelming array of neuroactive mole-

cules, how can we begin to answer this question?

It is evident to most researchers in biological psychiatry that attempting to develop models of psychiatric disorders is a rather complex task. This is particularly true of attempts to use animals to model aspects of disease states or therapeutic drug action.<sup>11</sup> These endeavours continue to be useful in identifying relevant factors or for predicting therapeutic potential of novel drugs. Nevertheless, there remains considerable difficulty in bridging the gap between the laboratory and the clinic in attempts to identify the pathological changes in the neural circuitry underlying psychiatric disorders. This problem is exacerbated by the heterogeneity of psychiatric symptoms within a targeted diagnostic group and by the related problems of comorbidity. Clearly, these problems apply to the study of all psychiatric disorders, not simply mood disorders and schizophrenia.

It may be that we are in the midst of something of a paradigm shift in biological psychiatry in this decade — a shift that may allow us to use more effectively the vast and increasingly complex array of data that we have on neural function. Brain imaging technologies have provided us with a unique opportunity to observe changes in the brain activity of patients and healthy volunteers. We have seen very impressive applications of PET technology to examine the occupancy of receptors for dopamine, serotonin and other neuroactive molecules,<sup>12,13</sup> and magnetic resonance spectroscopy is now being used to study a variety of brain substrates in this context.<sup>14,15</sup> These techniques continue to provide useful insights into the functions of living brain, but relatively recent developments in functional magnetic resonance imaging (fMRI) indicate that it is also possible to look at *in vivo* functional changes in small brain nuclei in humans performing cognitive and behavioural tasks.<sup>16–19</sup> With the application of magnetic field strengths of 3T and above, the degree of spatial resolution for fMRI is obviously very promising in this context.<sup>20</sup>

The subtlety of this approach is apparent from studies such as that of Posse et al,<sup>21</sup> who reported amygdala activation during a single trial of self-induced sadness in healthy male and female subjects. With fMRI measurements of responses to negative versus neutral stimuli, Davidson et al<sup>22</sup> reported that patients exhibiting higher anterior cingulate activation at baseline showed the most robust treatment response to venlafaxine. The potential importance of such studies

is clearly evident, but it seems that we are just beginning to see the potential of this technology. fMRI data may play a unique role in generating models of brain function that may help to integrate the tremendous amount of data already provided by other approaches. For example, Keightley et al<sup>23</sup> recently provided evidence that patterns of activity in emotional circuits can be influenced by cognitive factors such as attention and suggested that such “top-down” regulation may have important implications for understanding disorders such as depression. Mayberg<sup>24</sup> has discussed the possibility of using fMRI to identify biomarkers for improving diagnosis of mood disorders and directing treatment strategies for patients. In a very interesting synthesis of recent imaging data, this clinical researcher described a testable limbic-cortical network model in which he proposed that characterization of adaptive and maladaptive functional interactions among limbic-cortical pathways will be critical for optimizing the diagnosis and treatment of individual depressed patients.

The potential of fMRI for advancing our understanding of the neural basis of psychiatric disorders is also illustrated by some recent schizophrenia studies from Weinberger and colleagues. Callicott et al<sup>25</sup> reported an abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. Although no group differences in performance on a working memory task were observed, the siblings showed an exaggerated response in the right dorsolateral prefrontal cortex that was similar to that seen in some earlier fMRI studies of patients with schizophrenia. The authors suggest that, in these cognitively intact individuals who are at greater genetic risk for schizophrenia, there may be inefficient information processing in prefrontal circuitry, and suggest that an inheritance of alleles that are related to inefficient prefrontal information processing may increase risk for schizophrenia. These results illustrate the possibility of identifying intermediate phenotypes that may be useful for identifying susceptibility genes in schizophrenia and other complex psychiatric disorders,<sup>25–27</sup> echoing to some extent Mayberg’s proposal related to depression.<sup>24</sup>

Returning to the question of whether we have a real lead on the basic roots of the neural pathophysiology underlying psychiatric disorders such as depression and schizophrenia, it is apparent that high-resolution fMRI studies may help to answer many questions. We

are presented with an increasing and potentially overwhelming array of neuroactive molecules. Nevertheless, from in vitro and in vivo non-human animal studies, we do have considerable data that allow us to consider the relations of these molecules to brain structure, drug action and behaviour. With the promise of greater insights into in vivo interactions between neurotransmitters and the elucidation of drug action in human brain with fMRI, perhaps it will be possible to begin to provide clearer answers to this question.

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