"Broad spectrum" antidepressants: Is more better for the treatment of depression?

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Abstract

The majority of antidepressants in current use selectively inhibit the reuptake of serotonin and/or norepinephrine. "Broad spectrum" antidepressants are compounds that inhibit the reuptake of norepinephrine, serotonin and dopamine, the three biogenic amines most closely linked to depression. The pharmacological profile of one such compound has recently been described (European Journal of Pharmacology, 461 (2003) 99). DOV 21,947, an azabicyclo[3.1.0]hexane, potently inhibits norepinephrine, serotonin and dopamine reuptake by the corresponding human transporter proteins. DOV 21,947 is orally active in the forced swim and tail suspension tests, preclinical procedures that are highly predictive of antidepressant action in patients. A closely related compound, DOV 216,303 is safe and well-tolerated in Phase I studies. The plasma concentrations of DOV 216,303 following both single and multiple doses appear sufficient to inhibit norepinephrine, serotonin, and dopamine reuptake. Based on the pivotal role proposed for dopamine in depression, it has been hypothesized that a broad spectrum antidepressant will produce a more rapid onset and/or higher efficacy than agents inhibiting the reuptake of serotonin and/or norepinephrine.

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Introduction

During the past four decades, inhibitors of biogenic amine reuptake have been the mainstay for the treatment of major depression. From a mechanistic perspective, the use of reuptake inhibitors has come full circle. The prototypical tricyclic antidepressant, imipramine, blocks the reuptake of both norepinephrine and serotonin. Modification of this tricyclic structure resulted in a family of dual uptake inhibitors (e.g., desmethylimipramine, nortryptiline, amitryptiline), albeit with different relative potencies at the serotonin and norepinephrine transporters (Briley and Moret, 1997; Eshleman et al., 1999). Selective reuptake inhibitors (e.g., serotonin specific reuptake inhibitors [SSRIs] such as fluoxetine, paroxetine and citalopram) have, in large part, supplanted tricyclic antidepressants as the standard of care because as a group, SSRIs are safer and easier to use than tricyclics. At present, a “second” generation of dual reuptake inhibitors (for example, venlafaxine, and duloxetine) with a “cleaner” side effect profile than tricyclics may soon replace SSRIs as the drugs of choice for major depression.

Decades of clinical experience with both single and dual uptake inhibitors indicate there are no remarkable differences among these compounds with respect to either onset of action or efficacy. Thus, in most double blind, placebo controlled studies, >3 weeks of treatment (the so-called “therapeutic lag”) are required to effect meaningful symptom improvement (Paul, 2001). Further, a significant proportion of patients (generally ranging from 30–40%) do not receive clinically meaningful relief from these agents (Paul, 2001). There are a number of experimental strategies to overcome these and other shortcomings of single and dual reuptake inhibitors. Some of these approaches circumvent the aminergic synapse, whilst others remain grounded in monoaminergic theories of depression (reviewed in Skolnick et al, 2001). Among monoaminergic strategies is the “broad spectrum” antidepressant (Skolnick, 2002) that inhibits the reuptake of norepinephrine, serotonin, and dopamine, the three biogenic amines most closely linked to depression. In this Current Topics article, the rationale for this approach is summarized, and the characteristics of DOV 216,303, a putative broad spectrum antidepressant, described.

Results and discussion

There are multiple lines of evidence that provide a compelling rationale for the “addition” of a dopamine component to a dual (norepinephrine and serotonin) uptake inhibitor. This evidence is outlined below:

1) Both clinical and pre-clinical findings link anhedonia, a core symptom of depression, to deficits in mesocorticolimbic dopaminergic function (reviewed in D’Aquila et al., 2000; Willner, 2000).
2) Homovanillic acid concentrations are lower in the cerebrospinal fluid of depressed patients compared to normal individuals (reviewed in Willner, 2000).
3) Imaging studies indicate a lower density of striatal dopamine transporters in depressed individuals than in controls (Meyer et al., 2001).
4) Clinical pharmacology, including the findings that dopamine reuptake blockers (e.g. buproprion) and dopamine agonists (e.g. pramipexole, bromocriptine) are antidepressant (Sitland-Marken et al., 1990; Corrigan et al., 2000). Further, adjunctive use of a dopamine agonist (e.g. pramipexole, pergolide) has been reported to augment the effect of “traditional” antidepressants in refractory patients (Izumi et al., 2000; Sporn et al., 2000).
5) In preclinical studies, an increased sensitivity of dopamine receptors is among the most consistent changes produced by chronic antidepressant treatments. These effects can be observed at the behavioral, cellular, and molecular levels (reviewed in: D’Aquila et al., 2000; Lammers et al., 2000). It has been hypothesized that the interval required to effect this increased sensitivity of dopamine receptors may contribute to the therapeutic lag common to biogenic-amine based antidepressants. These preclinical findings, together with the evidence that dopamine plays a key role in hedonic processes, indicate that a compound producing an immediate increase in synaptic dopamine concentrations will result in a more rapid onset of relief, shortening or eliminating the therapeutic lag.

Based on this body of evidence, it is hypothesized that a broad spectrum antidepressant will produce a faster onset of action and/or better efficacy than either single or dual uptake inhibitors. While the dopamine, serotonin, and norepinephrine transporters are all members of a twelve transmembrane domain gene superfamily (Povlock and Amara, 1997), the design and synthesis of orally available, safe, and well tolerated compounds active at all three amine transporters remains a synthetic challenge. Substituted azabicyclo[3.1.0]hexanes, such as DOV 21,947 (Skolnick et al., 2003) and a sibling molecule, DOV 216,303, appear to fulfill these criteria. As can be seen in Table 1, DOV 216,303 is about equipotent as an inhibitor of [3H]norepinephrine and [3H]serotonin uptake in HEK 293 cells expressing the corresponding recombinant human transporter proteins. DOV 216,303 is ~4-fold less potent at inhibiting [3H]dopamine uptake, albeit with a potency < 100 nM. The optimum potency ratios for a molecule at the three transporters are unknown. However, it is evident that serotonin selective (fluoxetine), norepinephrine selective (desmethylimipramine), and “balanced” dual (e.g. milnacipran) uptake inhibitors are active in the clinic (Table 1 and Briley and Moret, 1997). Nonetheless, in Phase I studies, plasma concentrations of DOV 216,303 are sufficient (based on in vitro IC50 values) to inhibit the reuptake of all three amine at doses that are safe and well tolerated (manuscript in preparation). Further, like many clinically effective antidepressants, DOV 21,947 (Skolnick et al., 2003) and DOV 216,303 are orally active (Fig. 1) in the forced swim test (Porsolt et al., 1977). This antidepressant-like activity does not appear to be due to motor stimulation since both molecules are active in the forced swim test at doses that do not increase motor activity (Skolnick et al., 2003 and data not shown). While the forced swim test is not generally considered a model of depression, it is highly predictive of clinically effective antidepressants (Borsini and Meli, 1988; Porsolt and Lenegre, 1992). The safety and tolerability of DOV 216,303 in normal volunteers indicates that this compound, or a closely related

Table 1
Inhibition of [3H]amine uptake by human recombinant neurotransmitter transporters with DOV 216,303: comparison with single and dual uptake inhibitors

<table>
<thead>
<tr>
<th>Transporter</th>
<th>[3H]5–HT (nM)</th>
<th>[3H]DA (nM)</th>
<th>[3H]NE (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOV 216,303</td>
<td>13.8 ± 1.5</td>
<td>78 ± 15</td>
<td>20.3 ± 6.1</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>7.3 ± 2.9</td>
<td>&gt;10^5</td>
<td>1020 ± 18</td>
</tr>
<tr>
<td>Imipramine</td>
<td>8.0 ± 2.3</td>
<td>&gt;10^5</td>
<td>70 ± 21</td>
</tr>
<tr>
<td>Desmethylimipramine</td>
<td>64 ± 17</td>
<td>&gt;10^5</td>
<td>4.2 ± 1.1</td>
</tr>
</tbody>
</table>

Transporters were expressed in HEK–293 cells exactly as described in Eshleman et al. (1999). [3H]Serotonin (5–HT), dopamine (DA) and norepinephrine (NE) were used to measure reuptake at the human serotonin, dopamine, and norepinephrine transporter, respectively. [3H]Amine uptake was measured exactly as described in Eshleman et al. (1999). Values (IC50, nM) represent the X ± SEM of at least three independent experiments for DOV 216,303. Values for the other compounds are from Eshleman et al. (1999).
molecule, may be used to test the hypothesis that a compound inhibiting the reuptake of the three biogenic amines most closely linked to depression will be superior to both single and dual uptake inhibitors, that is, “more is better” for the treatment of major depression.

References


