

# Possible directions for the discovery of new antidepressant treatments

Simon N. Young, PhD

Coeditor-in-Chief, *Journal of Psychiatry and Neuroscience*, and the Department of Psychiatry, McGill University, Montréal, Que.

In a recent editorial, Pierre Blier discussed some of the reasons that new antidepressants have become a rarity.<sup>1</sup> The situation is serious enough that GlaxoSmithKline and AstraZeneca have decreased work in many areas of psychiatry, and a recent article in *Science* asks, "Is pharma running out of brainy ideas?"<sup>2</sup> One of the problems is a lack of any clear understanding of the etiology of depression. As Krishnan and Nestler<sup>3</sup> have pointed out, "Unlike Parkinson's or Alzheimer's disease, depression lacks any clear consensus neuropathology, rare familial genetic causes, or highly penetrant vulnerability genes, providing no obvious starting points for molecular investigations." The important progress in understanding the etiology of Alzheimer disease has resulted recently in more than a dozen trials of experimental treatments, none of which has shown any therapeutic effect.<sup>4</sup> So, what hope is there for progress in treating depression?

Perhaps we have underestimated the complexity of the brain and, as a result, have unreasonable expectations of how fast research should translate into treatment. Although I believe that there is some truth in this statement, I also believe that there is hope for the development of new antidepressant treatments. The purpose of this editorial is to highlight potential targets for antidepressants that have recently been identified and strategies available for further progress in this area. By looking at the systems that known antidepressant treatments act on, it may be possible to develop new antidepressants without understanding the factors that lead to depression. In addition, greater understanding of the target systems of different antidepressant treatments may lead to more rational combination therapies.

Although this editorial is primarily about research on antidepressants, a recent study<sup>5</sup> demonstrates the power of modern techniques in identifying potential risk factors for depression. Whole-genome expression profiling in postmortem brains from patients with major depressive disorder and controls revealed a significant increase in the expression of mitogen activated protein kinase phosphatase-1 (MKP-1) in patients with depression.<sup>5</sup> Increased MKP-1 expression in

rodent models resulted in depression-related behaviour, and chronic antidepressant treatment reversed stress-induced MKP-1 expression and behaviour. Whereas MKP-1 may be a suitable target for the development of novel antidepressants, the experience with Alzheimer disease has shown that etiologically based strategies are not always successful. However, for depression, unlike Alzheimer disease, a number of very different treatments already exist. Focusing research on a variety of antidepressant treatments to examine their effects on the brain may provide new targets for novel antidepressants, even if the systems identified are not involved in the etiology of depression.

A problem with trying to discover how a treatment may act is that there is often little evidence to direct research in specific areas. However, researchers often seem able to overcome such limitations. The mechanisms of action of the first antidepressants, iproniazid and imipramine, followed relatively soon after the discovery of their antidepressant action.<sup>6</sup> Recently, a single dose of ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, was shown to have a rapid antidepressant effect in patients with treatment-resistant depression.<sup>7</sup> Given that side effects of ketamine, including perceptual disturbances, confusion, euphoria, dizziness and increased libido, may have compromised the blinding in that study, further study with a positive placebo is needed to establish the efficacy of ketamine. Nonetheless, the antidepressant action of NMDA antagonists recently was attributed to the rapid activation of the mammalian target of the rapamycin (mTOR) pathway, leading to increased synaptic signalling proteins and increased number and function of new spine synapses in the prefrontal cortex.<sup>8</sup> The examples given above illustrate that research into antidepressant treatments can point relatively quickly to pathways that are potentially important in antidepressant action. However, not all antidepressant treatments have been studied adequately.

In addition to the standard antidepressant drugs, there are a variety of other treatments for which there is reasonable evidence of efficacy. These include various forms of

**Correspondence to:** Dr. S.N. Young, Department of Psychiatry, McGill University, 1033 Pine Ave. W, Montréal QC H3A 1A1; fax 514 398-4370; Simon.Young@mcgill.ca

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psychotherapy; various types of direct brain stimulation, including electroconvulsive therapy, transcranial magnetic stimulation, direct current stimulation and deep brain stimulation; bright light, exercise and various other "alternative" treatments. There is no evidence that any of these treatments, except perhaps electroconvulsive therapy, are significantly better than the standard antidepressant drugs, which of course are not particularly effective. Therefore, there is an important need for new treatments. There are 2 potential advantages of the wide range of treatments available. First, given that no single treatment is very effective, a combination of treatments may be useful. However, given the number of potential combinations, insight into possible mechanisms may be a useful guide to determine which combinations to test first. It is reasonable to hypothesize that 2 treatments that act through different mechanisms are more likely to show an additive or synergistic effect than 2 treatments that act through the same mechanism. Second, if the mechanism of action of an antidepressant treatment is discovered, this may lead to better strategies for manipulating the relevant system for therapeutic purposes.

One alternative treatment, S-adenosylmethionine (SAME), is an important compound in mammalian metabolism. It is a major methyl donor and is involved in over 35 methylation reactions involving DNA, proteins and membrane constituents, as well as small molecules.<sup>9</sup> The antidepressant action of SAME was first demonstrated in a placebo-controlled study in 1978, and by 1994 a meta-analysis concluded that SAME was superior to placebo and had side effects that were not really different from placebo.<sup>10</sup> This conclusion is still valid, taking into account the 11 placebo-controlled studies done so far.<sup>11</sup> A recent study found that SAME augmented the action of serotonin reuptake inhibitors in patients who previously had not responded to those medications.<sup>12</sup> The relative lack of interest in SAME among biological psychiatry researchers is presumably owing to the lack of interest among drug companies, as SAME is sold over the counter as a dietary supplement in many countries. Nonetheless, I am astonished at the lack of interest in trying to discover how SAME may act as an antidepressant, given that biogenic amines are obviously not the initial target. For a methyl donor, the currently fashionable explanation would be an epigenetic effect. One possible target is the corticotropin-releasing factor gene, as methylation of this gene is associated with resilience to stress in rodents.<sup>13</sup> However, given the wide range of pathways involving SAME, there is a need to investigate possibilities other than epigenetic mechanisms. One obvious strategy for investigating pathways altered by a compound such as SAME is to use gene expression profiling in experimental animals after SAME administration. Whereas gene expression profiles are likely to produce a mass of data that are not all readily interpretable, they might provide clues about pathways that need further investigation. Another approach is to investigate the effects of SAME administration on the human brain.

Techniques for studying neurotransmitters in the human brain have advanced greatly over the past 2 decades and can potentially be applied to pathways of interest. Functional magnetic resonance imaging (fMRI) is probably the most

popular technique for studying the human brain, but is unlikely to point to neurotransmitter systems that may be involved in antidepressant response. Magnetic resonance spectroscopy (MRS) is more promising, as it gives information on glutamate and  $\gamma$ -aminobutyric acid, the major excitatory and inhibitory transmitters in the brain. Recent advances in this technique are providing more detailed information, for example enabling the resolution of the formerly overlapping resonances of glutamate and glutamine, and a recent review suggests MRS has the potential to help in the discovery of novel therapies for depression.<sup>14</sup> Advances in positron emission tomography (PET) make it possible to study an increasing number of neurotransmitter systems in greater detail. Any of these techniques could be applied to humans if animal models point to specific neurochemical pathways that SAME might alter.

Bright light is an established treatment for seasonal depression, but this treatment has also been investigated in non-seasonal depression. A Cochrane review concluded that the better-designed studies indicate efficacy in nonseasonal depression.<sup>15</sup> However, little research has been done on how bright light may work. Serotonin may be involved, as acute tryptophan depletion reverses the therapeutic effect of bright light in patients with winter depression.<sup>16</sup> Also, in euthymic women who exhibit mild seasonality, bright light prevents the lowering of mood due to acute tryptophan depletion.<sup>17</sup> Dopamine also may be involved, as bright light increases blood flow in the human striatum,<sup>18</sup> whereas dopamine synthesis in the human striatum is greater in summer than in winter.<sup>19</sup> The types of experimental approaches discussed in relation to SAME could also be applied to bright light.

A Cochrane review concluded that exercise has an antidepressant effect.<sup>20</sup> However, at least 1 other review concluded that the effectiveness of exercise in reducing symptoms of depression cannot be determined because of a lack of good quality research.<sup>21</sup> An ongoing trial funded by the National Institute of Mental Health expects to overcome sources of potential bias and threats to internal and external validity that have limited prior research in this area.<sup>22</sup> Exercise, unlike some other antidepressant treatments, has been studied extensively in animals. Reviewing those results is beyond the scope of this editorial, but effects on neurogenesis, on a variety of peptides and on the serotonergic system have been reported. Human research is much more limited. In humans, many studies have shown that exercise is associated with an increase in plasma tryptophan and a decrease in the plasma level of the branched chain amino acids, which compete with uptake of tryptophan into the brain, so an increase in brain serotonin synthesis would be expected.<sup>23</sup> The strong folklore that the runners' high is opioid-mediated is supported by the evidence from a PET study that showed the level of euphoria after running was related to opioid binding in prefrontal/orbitofrontal cortices,<sup>24</sup> whereas opioid receptor blockade with naltrexone blocked the improvement of mood after a 50-minute session of aerobic gymnastics.<sup>25</sup> More studies involving humans are needed to follow up some of the leads provided by research in animals.

The search for rapid antidepressant treatments has been

longstanding. One of the first to be identified was sleep deprivation. Unfortunately, the improvement in mood after missing sleep for 1 night does not persist beyond the next sleep. However, in comparison with medication alone, combining sleep deprivation and subsequent bright light and sleep phase advance treatments with medication produced a more rapid response that was maintained for 7 weeks.<sup>26</sup> In spite of these encouraging results, there is little information on the mechanism(s) by which sleep deprivation exerts its therapeutic effects, although the effect is probably not serotonergic as it is not reversed by acute tryptophan depletion.<sup>27</sup> There is scope for both animal and human studies on the effects of sleep deprivation.

For some treatments (e.g., psychotherapy and, because of the specificity of the brain area stimulated, transcranial magnetic stimulation), animal research is not possible. Studies of these therapies using PET and MRS would be interesting.

This editorial is not meant to be exhaustive, and there are other treatments (e.g., fish oils) that could also be considered. Nonetheless, the limiting factor in trying to elucidate the varied target systems for different antidepressant treatments is not the lack of treatments to investigate, but the interests of researchers. The overwhelming emphasis has been on commercial drug treatments, while other interesting treatments such as S-Adenosyl-L-methionine (SAMe) have been neglected. Whether this changes or not remains to be seen. The prospects for developing novel antidepressant treatments are good if researchers spread their interests more widely.

In addition to developing more treatments, there is scope for combining different treatments in a rational way based on mechanism. So, for example, the combination of scopolamine (which has recently been shown to have antidepressant activity and presumably works via muscarinic receptor blockade<sup>28</sup>) with exercise (which may act via serotonergic and opioid pathways) may target 3 different neurotransmitter systems. This would presumably be preferable to combining a selective serotonin reuptake inhibitor (SSRI) with exercise, which also may have an action on serotonin. Similarly, combining an SSRI with sleep deprivation (probably not serotonergic) might be better than combining an SSRI and bright light (which may have a serotonergic action). With increasing knowledge about the systems through which different antidepressant treatments work, it should be possible to select more combination treatments to test based on complementary actions.

The current pessimism of drug companies, based on their experiences over the past decade, must not blind researchers to the great opportunities for furthering our knowledge on how to treat patients with depression.

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