

## Zinc: The New Antidepressant?

Cathy W. Levenson, PhD

*Low serum zinc levels have been linked to major depression. Furthermore, zinc treatment has been shown to have an antidepressant effect. With the hope of understanding the role of zinc in mood disorders, recent work has begun to explore possible mechanisms of zinc action on serotonin uptake in the brain.*

**Key words:** depression, anxiety, serotonin, 5-HT, forced swim test, limbic

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The World Health Organization (WHO) has identified psychiatric illnesses such as depression and anxiety as a critical problem for the 21st century. Fifteen million people in the United States alone have been diagnosed with major depression, with an additional 15 million experiencing milder forms of depression at some point during their lifetime. Unfortunately, the development of new treatments for depression and depression-related illnesses has been hampered by the fact that we do not fully understand the neurobiological mechanisms that underlie the development of these disorders. Recently, there has been an increased interest in the possible role that nutrient deficiencies may play in the development of depression and how diet may be used as an adjunct to the treatment of mood disorders.

### ZINC DEFICIENCY AND DEPRESSION

Over the last two decades, there has been mounting evidence suggesting a link between zinc deficiency and clinical depression. One of the first reports to suggest this link was a case study that identified low serum zinc

levels in a patient with treatment-resistant depression.<sup>1</sup> Subsequent work showed that patients with major depression had serum zinc levels that were significantly (12%–16%) lower than those of controls, and that there was a relationship between serum zinc levels and the severity of the symptoms of depression.<sup>2–5</sup> For example, 80 patients with minor depression were found to have serum zinc levels approximately 7% lower than those of the controls, and those with major depression had serum zinc levels that were 12% lower.<sup>2</sup> Two separate studies have shown a significant negative correlation between the Hamilton Depression Rating Scale (HDRS) score and serum zinc levels in depressed individuals.<sup>2,5</sup> Additionally, treatment-resistant patients appear to have lower serum zinc levels than those who responded significantly to pharmacological intervention.<sup>3</sup>

There is some debate about the effect of antidepressive drug treatment on serum and brain zinc levels. Initial reports suggested that successful treatment increases serum zinc levels.<sup>6</sup> Later work did not confirm this finding, but was complicated by the fact that many of the subjects in the study were resistant to treatment.<sup>3</sup> There have also been reports suggesting that treatment increases hippocampal zinc concentrations relative to other regions of the brain.<sup>7</sup> These data, which suggest a shift in brain zinc concentrations after treatment with the tricyclic antidepressant imipramine, remain controversial and difficult to interpret because they do not take into account the high concentrations of free vesicular zinc found in the mossy fibers of the hippocampus.

### CAUSES OF ZINC DEFICIENCY IN DEPRESSION

While the above data clearly suggest a link between reduced serum zinc levels and clinical depression, they do not show that zinc deficiency is causative. While one interpretation of these data could be that low zinc levels lead to the development of depression, it is also possible that zinc deficiency is secondary to the development of depression-related reductions in food intake. Given that depression is frequently characterized by anorexia, this hypothesis is not unreasonable. However, several studies have found no relationship between serum zinc and food

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Dr. Levenson is with the Program in Neuroscience and the Department of Nutrition, Food and Exercise Sciences, Florida State University, Tallahassee, Florida, USA.

Please address all correspondence to: Dr. Cathy Levenson, Program in Neuroscience and the Department of Nutrition, Food and Exercise Sciences, Florida State University, 237 Biomedical Research Facility, Tallahassee, FL 32306-4340; Phone: 850-644-4122; Fax: 850-644-0989; E-mail: levenson@neuro.fsu.edu.

intake, anorexia, or body weight in depressed patients,<sup>2,3</sup> suggesting that reduced serum zinc levels are not simply a function of reduced food intake.

Another possible explanation for reduced serum zinc levels in depressed patients is altered cortisol production. Depressed patients have repeatedly been shown to have elevated cortisol levels that are not suppressed by dexamethasone. It has been hypothesized that increased glucocorticoid production induces the synthesis of the zinc-binding protein metallothionein, resulting in cellular sequestration of zinc and reduced serum zinc levels.<sup>8</sup> However, serum zinc levels do not appear to have any impact on the response to dexamethasone in depressed patients, suggesting that cortisol dysregulation is not responsible for the serum zinc abnormalities seen in depressed individuals.<sup>2</sup>

A third explanation for reduced serum zinc levels in depressed patients is stimulation of the immune system. There are a great deal of data showing that cytokine production, which is associated with activation of the immune system, can trigger the development of clinical depression.<sup>9</sup> Furthermore, activation of the immune system requires zinc and may contribute to its cellular sequestration. Thus, it has been hypothesized that activation of the immune system associated with depression may contribute to the observed reduction in serum zinc in depressed patients.<sup>3</sup> Consistent with this hypothesis, several studies reporting low serum zinc levels also found an increase in markers of immune activation.<sup>2,6</sup> Thus, the possibility remains that alterations in serum zinc may be the result of depression-related mechanisms such as cytokine production, rather than their cause.

## ANTIDEPRESSANT FUNCTIONS OF ZINC

The hypothesis that zinc deficiency plays a role in the development of depression has been strengthened by a number of reports showing that zinc has antidepressant effects in laboratory rodents.<sup>10-13</sup> While the human concept of depression, characterized by feelings of worthlessness and guilt and a loss of self-esteem, cannot be adequately studied in animals, there are many other depression-related behaviors that can be observed in both humans and animals, including anorexia and anhedonia. One of the best-characterized measures of depression-like behaviors in mice is the tail suspension test. Normally, when suspended by its tail for 5 minutes a mouse will move, exploring its immediate environment in an attempt to escape. Behavioral despair, an indicator of depression, is measured by the amount of time spent immobile in the tail suspension paradigm. Antidepressant drugs reduce immobility time in this test. Likewise, the forced swim test, used for both mice and rats, examines immobility time in a swim tank. Acute admin-

istration of antidepressant drugs such as the selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants are effective at reducing immobility time in the swim tank.

Using these measures of depression-like behaviors, several studies have shown that zinc, when injected at concentrations of 30 mg/kg body weight, significantly reduces immobility time.<sup>10,11,13</sup> In most studies, the antidepressant effects of zinc were comparable to those seen with similar doses of imipramine.<sup>10,11,13</sup> When low, ineffective doses of zinc (1 mg/kg) and imipramine (15 mg/kg) were combined, there was again a significant reduction in immobility,<sup>10</sup> suggesting that zinc is either acting via similar mechanisms as tricyclic antidepressants, or augmenting the mechanisms of imipramine action. It should be noted that caution is warranted when interpreting studies using the forced swim test because the outcome of this test for behavioral despair can be influenced by changes in locomotor activity. Specifically, hyperactivity, which would lead to increased locomotor activity, can be misinterpreted as reduced immobility. Similarly, decreased locomotor activity could be mistaken for increased behavioral despair. The effect of zinc administration on locomotor activity has been mixed and may be species specific, with some studies reporting decreased locomotor activity following zinc administration in mice (10–30 mg/kg),<sup>10,13</sup> and others finding no alterations in locomotor activity in rats.<sup>10</sup> Our recent data show that dietary zinc deficiency does not significantly alter locomotor activity compared with zinc-adequate controls.<sup>14</sup>

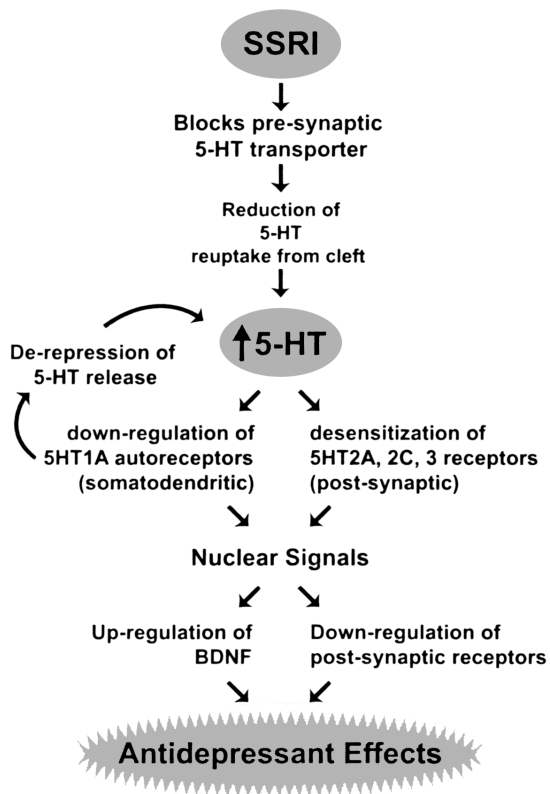
Human trials designed to test the efficacy of using zinc as an adjunct to antidepressant drug therapy have been consistent with the findings in rodents.<sup>15</sup> In a double-blind trial, 20 patients diagnosed with major depression using *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) criteria were given oral zinc supplementation (25 mg/d) or a placebo in addition to standard antidepressant drug therapy. Patients were assessed before zinc treatment and at 2, 6, and 12 weeks using the HDRS and the Beck Depression Inventory. These measures of depression status showed that 6 weeks of zinc supplementation augmented antidepressant drug therapy by over 50%. This difference was not only statistically significant, but was sustained through the full 12 weeks of the study.<sup>15</sup>

## MECHANISMS OF ZINC AND ANTIDEPRESSANT ACTION

SSRIs such as fluoxetine are widely used pharmacological agents for the treatment of major depression. These drugs increase the amount of the neurotransmitter serotonin (5-HT) in the synaptic cleft by inhibiting the

reuptake of 5-HT by pre-synaptic neurons (Figure 1). These acute increases in synaptic 5-HT, however, are not responsible for the antidepressant effects. In fact, these increases, which can occur within days of beginning SSRI treatment, are likely the cause of side effects of antidepressant drugs, including restlessness, irritability, and insomnia. The antidepressant effect results from the down-regulation of post-synaptic 5-HT receptors in response to elevated 5-HT concentrations in the cleft. This requires several weeks of treatment and explains why amelioration of depressive symptoms and the reduction in many of the side effects takes 3 to 8 weeks. In this same time frame, there is also evidence of downstream changes in gene expression, such as increases in brain-derived neurotrophic factor (BDNF) mRNA in the hippocampus, that may be linked to the antidepressant effects of SSRIs and other antidepressant drugs.<sup>16</sup>

Given the data in both humans and animals showing that zinc augments antidepressant drug efficacy, it was reasonable to hypothesize that zinc would augment the mechanisms that block 5-HT reuptake. However, a recent study has complicated our understanding of the role



**Figure 1.** Proposed mechanisms of selective serotonin reuptake inhibitor (SSRI) action. These pharmacological agents act on presynaptic serotonergic transporters, as well as on postsynaptic and somatodendritic receptors, to regulate synaptic concentrations of serotonin (5-HT) and the symptoms of depression. The role of zinc in the regulation of these mechanisms is currently under investigation.

of zinc in depression.<sup>17</sup> This study examined the effect of zinc and antidepressant drugs on 5-HT uptake in slice preparations of corpus collosum, cingulate cortex, and raphe nucleus taken from adult rat brain. As expected, 5-HT uptake in the corpus collosum was blocked by fluoxetine and imipramine. The SSRI fluoxetine and the tricyclic antidepressant imipramine both blocked uptake by approximately 50%. The addition of 1  $\mu$ M zinc as either ZnCl<sub>2</sub> or ZnSO<sub>4</sub> impaired the ability of these agents to block 5-HT uptake. In fact, zinc was so effective at blocking the action of these drugs that 5-HT uptake in zinc-treated slices was not different from untreated controls. Without drug treatment, zinc significantly increased 5-HT uptake in the corpus collosum (45%), cingulate cortex (58%), and raphe nucleus (65%). These curious observations, suggesting that zinc increases 5-HT uptake, are in apparent contradiction to the findings that zinc may act as an antidepressant.

There are a number of things that may explain this apparent contradiction. First, this work examined the effect of zinc on the uptake of 5-HT from the raphe nucleus. This region is the main location of serotonergic neuronal cell bodies that project to the frontal cortex, hypothalamus, and other limbic regions. It appears that the projections to the frontal cortex are primarily involved in the regulation of mood, while those to limbic areas control anxiety and panic. Although the best-known action of SSRIs on 5-HT reuptake appears to be the inhibition of the 5-HT transporters at the synapse, there is also evidence that they block 5-HT<sub>1A</sub> receptors on cell bodies. Blockage of these somatodendritic autoreceptors results in an increase in 5-HT release at the synapse. Thus, as illustrated in Figure 1, SSRIs increase synaptic 5-HT concentrations via two mechanisms: inhibition of reuptake and increased release. The role of 5-HT uptake in the raphe nucleus is not known, but if the zinc-mediated increases in uptake at the cell body block reuptake at the synapse or increase synaptic release, it would be consistent with the hypothesized antidepressant role of zinc.

While the study also shows zinc-enhanced uptake of 5-HT from the corpus collosum and cingulate cortex in the presence of SSRIs, the significance of this observation for the study of depression is not entirely clear. There have been some reports suggesting a possible link between size of parts of the corpus collosum and depression in young adult women, but these changes were not correlated to the severity of the depressive symptoms or duration of illness.<sup>18</sup> Another study found no alterations in corpus collosum size in patients with unipolar depression.<sup>19</sup> Furthermore, serotonin transporters have been identified in non-neuronal cell types in the brain, including astrocytes, so it is not yet possible to determine if the 5-HT uptake in this study was the result of zinc action on astrocytes in the raphe, corpus collosum, or cingulate cortex.

## CONCLUSIONS

Based on these data, it is clear that we do not yet fully understand the role of zinc in the regulation of mood. While reduced serum zinc levels have repeatedly been linked to depression, and zinc administration may have an antidepressant effect, the mechanisms for the action of zinc in the central nervous system that may control mood are completely unknown. The finding that zinc may increase 5-HT uptake in several brain regions complicates this picture even further. However, these studies do reveal several areas where future work could make a significant contribution. For example, much of the work on the function of zinc in the brain has focused on the role of zinc in neuronal transmitter and receptor activity. The current work suggesting that glial cells may also be involved in the zinc-regulated processing of transmitters is intriguing. Thus, the role of glial 5-HT uptake in depression and the effects of zinc on this process need to be explored. It would also be interesting to know the type of somatic mechanisms or receptors that are being regulated by zinc in the raphe. And finally, now that 5-HT uptake in the serotonergic cell bodies of the raphe nucleus has been measured, the next step would be to measure the effect of zinc on 5-HT reuptake in these neuronal projections in the frontal cortex and other limbic regions such as the amygdala and hippocampus. This would improve our understanding of the role of zinc on presynaptic 5-HT transporters, the main target of SSRIs, and provide clinicians with more information about the possible use of zinc as an adjunct to antidepressant therapy.

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