Role of zinc in the development and treatment of mood disorders

Elise C. Cope and Cathy W. Levenson

Department of Biomedical Sciences, Florida State University College of Medicine, Tallahassee, Florida, USA

Correspondence to Cathy W. Levenson, PhD, Department of Biomedical Sciences, Florida State University College of Medicine, 1115 West Call Street, Tallahassee, FL 32306-4300, USA
Tel: +1 850 644 4122;
e-mail: cathy.levenson@med.fsu.edu

Current Opinion in Clinical Nutrition and Metabolic Care 2010, 13:685–689

Purpose of review

The present review is a critical examination of the most recent published work on the role of zinc in the development and treatment of mood disorders.

Recent findings

Clinical studies and experimental work using animal models have both revealed a link between zinc status and neuropsychological disorders such as depression and anxiety. Not only has zinc deficiency been shown to induce depression-like and anxiety-like behaviors, supplementation has been used as a treatment for major depression. Zinc administration improves the efficacy of antidepressant drugs in depressed patients and may have a particular role to play in treatment-resistant patients. Recent investigations into the molecular mechanisms responsible for these observations suggest a role for zinc in the regulation of neurotransmitter systems, antioxidant mechanisms, neurotrophic factors, and neuronal precursor cells.

Summary

The data reviewed here not only indicate a role for zinc deficiency in the development of mood disorders, but also show that zinc may also be important in their treatment. Given the prevalence of zinc deficiency in human populations, this work has the potential to influence strategies to prevent and treat these disorders.

Keywords

anhedonia, anxiety, depression, hippocampus, zinc

Curr Opin Clin Nutr Metab Care 13:685–689

1363-1950

Introduction

It has been estimated that at least 10% of Americans consume less than half of the Recommended Dietary Allowance (RDA) of zinc. Worldwide the problem is even more severe, with as many as 50% of the population chronically receiving less than half of the RDA. Previous reviews have shown that zinc deficiency occurs in all age groups, nationalities, and sexes [1]. Given that zinc is needed for at least 100 cellular enzymes, as well as hundreds of transcription factors, it is not surprising that the effects of zinc deficiency can impact virtually every organ and biochemical system. The best characterized symptoms of zinc deficiency include immune insufficiency and infection, alopecia, skin eruptions and dermatitis, and diarrhea. Additionally, there is an increasing appreciation for the role that zinc deficiency may play in the development and treatment of depression and depression-related disorders. Thus, this review will evaluate the most recent data on the implications of zinc deficiency for mood disorders, including depression, anxiety, and anorexia, and explore the possible use of zinc as an adjunct to the pharmacological treatment of these disorders.

Role of zinc in clinical depression

We have known for some time that there is a relationship between low serum zinc levels and mood disorders. These observations have revealed an inverse relationship between serum zinc levels and the severity of depression [2]. Not only do patients with major depression have significantly lower levels of serum zinc compared to nondepressed controls, more importantly, it appears that the lower the serum zinc level, the more severe the symptoms of depression. For example, an 80-participant study showed that patients with minor depression had serum zinc levels that were approximately 93% of control, whereas patients with major depression had serum zinc levels that were 88% of control ($P < 0.001$) [3]. Recent work has not only confirmed these observations, but also linked the problem to dietary zinc deficiency. An examination of 23 young women with moderate-to-severe depression revealed significantly lower serum zinc levels in this population compared to healthy age-matched controls [4]. This is particularly disturbing, given a recent report showing that over a quarter of college-aged women may regularly consume less than the RDA for zinc [5].

DOI:10.1097/MCO.0b013e32833df61a

Thus, dietary intakes of zinc may play a role in eating behaviors in this population.

Unfortunately, 20–40% of patients with major depression do not adequately respond to antidepressant drug therapy [6]. Interestingly, treatment-resistant patients appear to have even lower levels of serum zinc compared to patients responsive to pharmacological treatment, making serum zinc a specific (93%) and sensitive (79%) marker for treatment resistance [2]. Thus, several investigators have attempted to use zinc in a clinical setting as part of the therapeutic approach for major depression. A recent pilot study showed that 15 women given a multivitamin supplement containing 7 mg of zinc for 10 weeks had increased serum zinc levels and a significant decrease in anger-hostility and depression-dejection scores compared to women given the same multivitamin without zinc [7•]. Other recent work has shown that zinc status may play a role in the ability of patients to respond to antidepressant drug therapy. A 12-week, double-blind placebo-controlled study showed that patients who were previously refractory to the antidepressant drug imipramine responded to drug therapy when their medication was supplemented with 25 mg zinc per day. In this study, imipramine-treated patients given the zinc supplement had significantly improved depression inventory scores compared to patients receiving drug therapy and a placebo [8••].

Experimental approaches to understanding behavioral effects of zinc deficiency

Although the inverse relationship between serum zinc and depression in humans has been repeatedly observed, there is no reliable way to determine whether or not zinc is a causative factor in the development of depression-related disorders. Thus, a number of recent experimental studies have been designed to determine the degree to which zinc deficiency causes depression. Depression-like behaviors such as anhedonia, behavioral despair, anorexia, and the appearance of comorbid anxiety-like behaviors, have all been studied in zinc-deficient rats.

Anhedonia

Anhedonia is associated with depression in humans. In experimental models, anhedonia is measured using a two-bottle test in which animals are provided with a choice between a dilute solution of sucrose or saccharin and deionized water. A reduced preference for the sweet solution is a standard marker for anhedonia in rodents. Tassabehji *et al.* [9] showed that after 2 weeks on a zinc-deficient diet, young adult rats significantly reduced their preference for saccharin. Anhedonia was present only after the introduction of the zinc-restricted diet, suggesting a causative role for zinc deficiency in development of the depression-like behavior of anhedonia.

Behavioral despair

Depression-like symptoms can also be monitored in rodents by the appearance of behavioral despair measured by increased immobility time in the forced swim test. Zinc-deficient rats exhibited symptoms of behavioral despair in the swim test that were reversed by addition of zinc to the diet [10,11•]. However, the swim test also revealed that zinc-deficient rats are resistant to treatment with the antidepressant drug fluoxetine. These data raise the possibility that resistance to pharmacological treatment in depressed patients may in part be the result of dietary zinc deficiency.

Anorexia

In humans, depression is frequently associated with changes in feeding behavior. In rodents, zinc deficiency leads to anorexia. Within 10 days of starting a severely zinc-deficient diet, adult rats exhibit a significant reduction in food intake that is characterized by a 4-day feeding cycle [9]. The resulting anorexia can be severe such that after 21 days of this diet, mean body weights of zinc-deficient rats fall to approximately 75% that of zinc adequate controls. This appears to be largely the result of carbohydrate avoidance [12]. Interestingly, more recent work has shown that zinc-deficient rats given intraperitoneal (i.p.) injections of zinc sulfate (0.5–2.0 μg Zn/g body weight) showed no alterations in food intake [13]. In contrast, oral zinc administration (19 μg/kg) significantly stimulated food intake [14•]. The mechanisms responsible for the role of oral zinc in food intake are not known, but may include the release of zinc-dependent hormones from the gastrointestinal tract.

Anxiety

It has been estimated that as many as 85% of patients with depression also exhibit symptoms of anxiety [15]. In addition to depressive behavior, zinc-deficient animals have also been shown to exhibit anxiety-like behaviors in both light-dark box and elevated plus maze tests [9,16]. They also show more aggressive behaviors such as biting attacks and wrestling, compared to pair-fed controls [17]. This increase in anxiety has been shown to develop within 2 weeks of beginning a zinc-deficient diet. In contrast to depression-like behaviors, however, anxiety-like behaviors may be reduced in zinc-deficient rats treated with fluoxetine [9]. It is well known that anxiety is related to stress. Furthermore, susceptibility to stress has been shown to be increased in zinc deficiency. For example, rats fed a zinc-deficient diet for a period of 2 weeks and then exposed to one of two mild stresses – water-immersion stress or forced swim test – were shown to have higher corticosterone levels following exposure to stress than zinc adequate controls. This suggests that zinc-deficient rats have a higher susceptibility to stress by activation of the hypothalamic–pituitary–adrenal axis [11•]. Furthermore, zinc levels may be altered by stress.

Both acute and chronic restraint stress have been shown to significantly decrease serum zinc levels in mice by 13 and 31% compared to controls, respectively [18].

Antidepressant effects of zinc

Zinc administration appears to have antidepressant activity in a variety of experimental models of depression. A study completed in 2008 in mice showed that a 30 mg/kg (i.p.) dose of zinc decreased immobility time in the forced swim test [19]. The same dose of zinc given orally in a single dose decreased behavioral despair in the tail suspension test [20]. Similar results were seen in the rat using the forced swim test when 15 mg/kg i.p. zinc was given daily for a 7-day period. Lower doses were not effective [21]. Chronic oral treatment for 30 days with 300 mg/l of zinc chloride also resulted in a robust antidepressant-like effect [21]. Zinc administration has also been shown to improve depression-like behaviors in the rat olfactory bulbectomy [22] and chronic mild stress models of depression [23]. Furthermore, the antidepressant drugs imipramine, citalopram, as well as electroconvulsive shock therapy, all appear to increase hippocampal zinc [24].

The combination of zinc and antidepressant drugs has also been recently investigated. Studies on chronic unpredictable stress-induced depression showed that though imipramine treatment alone does not reduce the number of fighting attacks in rats, the use of zinc supplementation in combination with imipramine reduced the aggressive behavior [25]. In other work, subeffective doses of zinc and antidepressants were used in combination and were shown to act synergistically to reduce immobility time in both rats and mice in the forced swim [26••] and in the tail suspension [20] tests without effecting locomotor activity. These data support clinical trials showing a positive role for zinc as an adjunct to antidepressant drug therapy, particularly in patients who are refractory to drug treatment [9].

Models and mechanisms: understanding neurobiology of zinc

Although the available data suggest a role for zinc in the development and treatment of mood disorders, the application of this information is dependent on our understanding of the mechanisms of zinc action in the brain. A number of recent studies have shed light on the possible role of zinc in neurotransmitter systems, particularly serotonergic and glutamatergic, as well as a role for zinc in antioxidant mechanisms, neurotrophic factors, and neuronal precursor cells that may participate in mood regulation.

Neurotransmitter activity

A recent experiment showed that the antidepressant action of zinc in the forced swim test can be blocked by pretreatment with inhibitors of serotonin synthesis or serotonin receptor antagonists [26••]. Chronic zinc administration increased the density of 5-HT_{1A} and 5-HT_{2A} serotonin receptors in the hippocampus and the frontal cortex, respectively [27•].

In addition to its possible role in serotonergic signaling, synaptic zinc is also a known modulator of glutamate signaling via *N*-methyl-D-aspartate (NMDA) and amino-3-hydroxyl-5-methyl-4-isoxazoleproprionate (AMPA)/kainate receptors [1]. Although NMDA receptor antagonists typically have antidepressant activity in experimental models, ineffectively low doses can become effective in the forced swim test when supplemented with zinc [28]. Zinc-induced decreases in behavioral despair were abolished when animals were co-treated with NMDA receptor agonists [29]. Furthermore, the binding affinity of glycine to the NMDA receptor was significantly reduced by chronic zinc treatment [26••]. Zinc enhanced the activity of AMPA receptors, and it has been hypothesized that AMPA/kainate glutamate receptors play a role in regulating zinc concentrations in the hippocampus [30], an important limbic structure associated with the regulation of mood. Subeffective doses of zinc co-administered with subeffective doses of AMPA receptor agonists reduced immobility time in forced swim test [28].

The relationship between zinc, glutamate and depression-like behaviors is complex and not fully understood. For example, examination of glutamate action under stressful conditions known to induce depression has been shown to increase extracellular glutamate concentration in the hippocampus while decreasing extracellular zinc concentrations [30,31]. Although the available data strongly implicate glutamate and the postsynaptic glutamate receptors in the antidepressant role of zinc, more work is clearly needed to understand the role of these mechanisms in the regulation of mood.

Oxidative stress

There is mounting evidence, that has recently been reviewed [32], suggesting that depressed patients have higher levels of reactive oxygen species (ROS). Furthermore, antidepressant drugs increase the activity of antioxidant enzymes such as superoxide dismutase. Zinc deficiency increases ROS that appears to be, at least in part, the result of mitochondrial ROS production [33]. Glutathione peroxidase mRNA is then upregulated, presumably as a protective response [34]. Consistent with this hypothesis, chronic oral zinc treatment with pharmacological doses of zinc (30 mg/ml provided in the drinking water) for 30 days increased glutathione levels in the rat hippocampus and cerebral cortex [21].

Neurotrophic factors

Whereas early work showed alterations in brain-derived neurotrophic factor (BDNF) and its tyrosine kinase

receptor B (TrkB) in the brains of patients with major depression resulting in suicide [34], more recent work has shown low serum BDNF in depressed patients with increased levels following chronic antidepressant therapy [35]. This has led to the hypothesis that zinc may be exerting its effects on mood via neurotrophic factors such as BDNF. Indeed, chronic zinc treatment in rats increased BDNF levels in the cortex and hippocampus [21,23]. It has been speculated that zinc-mediated increases in BDNF are due to the action of zinc on the serotonergic system [36]. Additionally, zinc has been shown to transactivate the downstream signaling pathways such as extracellular signal-regulated kinase (ERK1/2), cAMP response element binding protein (CREB), and phospholipase C-γ (PLC-γ) by increasing Src family kinase activity [37,38]. Furthermore, the activated downstream target ERK1/2 increased in the cerebral cortex following zinc treatment [21]. Lactational zinc deficiency in mice significantly reduced hippocampal phosphorylated ERK [39]. Thus, zinc may be working to not only stimulate BDNF production, but also aid in activating the downstream pathways independently of BDNF.

Neuronal precursor cells

Several lines of evidence implicate adult neuronal precursor cells in the cause of zinc deficiency-induced mood disorders. First, chronic use of antidepressant drugs stimulates neuronal precursor proliferation in the adult dentate gyrus. These cells not only proliferate, but can also differentiate into mature neurons and be integrated into the hippocampal circuitry [40]. Adult rats fed a zinc-deficient diet for 3 weeks not only developed depression-like behaviors, but also had an approximately 50% reduction in the number of proliferating cells in the subgranular zone of the dentate gyrus [33]. There was also an increase in the number of TUNEL-labeled cells in this region, as well as evidence of p53 and caspase involvement in the death mechanisms [33,41•]. Similar findings were reported in mice fed a zinc-deficient diet for 5 weeks [41•] as well as in lactational zinc deficiency [39]. These data are consistent with imaging studies of depressed patients showing reductions in hippocampal volume. Examination of post-mortem brains showed increased apoptosis in the dentate gyrus, CA1, and CA3 areas of the hippocampus [32]. Although future work will be needed to clarify the interactions between zinc and antidepressant drug action on neuronal precursor cells in the hippocampus and their role in the development and treatment of depression, these data raise the intriguing possibility that control of adult stem cells may be a target for the development of new pharmacological treatments for mood disorders.

Conclusion

Both clinical observations and experimental studies using animal models suggest a role for zinc deficiency in the cause of depression. Although not all depression is caused by zinc deficiency, and serum zinc levels are not a sensitive or accurate measure of zinc status, given that inadequate intakes of zinc are common, it is a factor that should be addressed in patients experiencing the symptoms of depression. Use of zinc as an adjunct to pharmacological intervention may increase drug efficacy and should be considered, particularly in patients who have not responded well to antidepressant therapy. Although supplemental zinc is generally not toxic, patients should be counseled not to supplement above the recommended upper limit of 40 mg/day as copper deficiency has been reported in several cases of extremely high zinc intakes. In conclusion, a better understanding of the role of zinc deficiency in the development of mood disorders and the possible role that supplemental zinc may play in their treatment is not only important for making clinical recommendations, but can also help identify new targets for intervention.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 754–755).

1 Takeda A, Tamano H. Insight into zinc signaling from dietary zinc deficiency. Brain Res Rev 2009; 62:33–44.

2 Maes M, Vandoolaeghe E, Neels H, *et al.* Lower serum zinc in major depression is a sensitive marker of treatment resistance and of the immune/inflammatory response in that illness. Biol Psychiatry 1997; 42:349–358.

3 Maes M, D'Haese PC, Scharpe S, *et al.* Hypozincemia in depression. J Affect Disord 1994; 31:135–140.

4 Amani R, Saeidi S, Nazari Z, Nematpour S. Correlation between dietary zinc intakes and its serum levels with depression scales in young female students. Biol Trace Elem Res 2009 [Epub ahead of print].

5 Lacey JM, Zotter DU. Zinc-specific Food Frequency Questionnaire to assess college women's eating habits. Can J Diet Pract Res 2009; 70:204–208.

6 Keitner GI, Ryan CE, Solomon DA. Realistic expectations and a disease management model for depressed patients with persistent symptoms. J Clin Psychiatry 2006; 67:1412–1421.

7 • Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study. Eur J Clin Nutr 2010; 64:331–333.
This pilot study supports the use of supplemental zinc (7 mg) once daily for 10 weeks in women between 18 and 21 years of age to significantly improve anger and depression scores measured by the Profile of Moods State (POMS) questionnaire.

8 •• Siwek M, Dudek D, Paul IA, *et al.* Zinc supplementation augments efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. J Affect Disord 2009; 118:187–195.
This study showed the effective use of 140 mg imipramine in addition to 25 mg of zinc once daily for 12 weeks in treatment-resistant patients with major depression between 18 and 55 years of age. Supplemental zinc decreased depression scores and improved treatment outcomes in patients who were previously nonresponsive to antidepressant therapy.

9 Tassabehji NM, Corniola RS, Alshingiti A, Levenson CW. Zinc deficiency induces depression-like symptoms in adult rats. Physiol Behav 2008; 95:365–369.

10 Tamano H, Kan F, Kawamura M, *et al.* Behavior in the forced swim test and neurochemical changes in the hippocampus in young rats after 2-week zinc deprivation. Neurochem Int 2009; 55:536–541.

11 • Watanabe M, Tamano H, Kikuchi T, Takeda A. Susceptibility to stress in young rats after 2-week zinc deprivation. Neurochem Int 2010; 56:410–416.
Rats fed a zinc-deficient diet for 2 weeks had increased levels of corticosterone following exposure to stress. Increased depressive-like behavior under zinc deficiency was restored to normal following 14 days of eating a control diet.

12 Rains TM, Shay NF. Zinc status specifically changes preferences for carbohydrate and protein in rats selecting from separate carbohydrate-, protein-, and fat-containing diets. J Nutr 1995; 125:2874–2879.

13 Jing MY, Sun JY, Wang JF. The effect of peripheral administration of zinc on food intake in rats fed Zn-adequate or Zn-deficient diets. Biol Trace Elem Res 2008; 124:144–156.

14 • Ohinata K, Takemoto M, Kawanago M, *et al.* Orally administered zinc increases food intake via vagal stimulation in rats. J Nutr 2009; 139:611–616.
Oral zinc administration of 19 μmol/kg but not i.p. zinc increases food intake in rats fed a zinc-deficient diet for 3 days. Additionally, neuropeptide Y and orexin significantly increased in the hypothalamus following oral zinc administration. Stimulation of food intake was abolished by vagatomy. Taken together, these data indicate that oral zinc administration stimulates food intake via orexigenic peptides and vagal stimulation.

15 Gorman JM. Comorbid depression and anxiety spectrum disorders. Depress Anxiety 1996; 4:160–168.

16 Takeda A, Tamano H, Kan F, *et al.* Anxiety-like behavior of young rats after 2-week zinc deprivation. Behav Brain Res 2007; 177:1–6.

17 Takeda A, Tamano H, Kan F, *et al.* Enhancement of social isolation-induced aggressive behavior of young mice by zinc deficiency. Life Sci 2008; 82:909–914.

18 Teng WF, Sun WM, Shi LF, *et al.* Effects of restraint stress on iron, zinc, calcium, and magnesium whole blood levels in mice. Biol Trace Elem Res 2008; 121:243–248.

19 Lobato KR, Binfare RW, Budni J, *et al.* Involvement of the adenosine A1 and A2 receptors in the antidepressant-like effect of zinc in the forced swimming test. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32:994–999.

20 Cunha MP, Machado DG, Bettio LE, *et al.* Interaction of zinc with antidepressants in the tail suspension test. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32:1913–1920.

21 Franco JL, Posser T, Brocardo PS, *et al.* Involvement of glutathione, ERK1/2 phosphorylation and BDNF expression in the antidepressant-like effect of zinc in rats. Behav Brain Res 2008; 188:316–323.

22 Nowak G, Szewczyk B, Wieronska JM, *et al.* Antidepressant-like effects of acute and chronic treatment with zinc in forced swim test and olfactory bulbectomy model in rats. Brain Res Bull 2003; 61:159–164.

23 Sowa-Kucma M, Legutko B, Szewczyk B, *et al.* Antidepressant-like activity of zinc: further behavioral and molecular evidence. J Neural Transm 2008; 115:1621–1628.

24 Nowak G, Schlegel-Zawadzka M. Alterations in serum and brain trace element levels after antidepressant treatment: Part I. Zinc. Biol Trace Elem Res 1999; 67:85–92.

25 Cieslik K, Klenk-Majewska B, Danilczuk Z, *et al.* Influence of zinc supplementation on imipramine effect in a chronic unpredictable stress (CUS) model in rats. Pharmacol Rep 2007; 59:46–52.

26 •• Szewczyk B, Poleszak E, Wlaz P, *et al.* The involvement of serotonergic system in the antidepressant effect of zinc in the forced swim test. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33:323–329.
Inhibition of the serotonergic system by the use of serotonin synthesis blockers or receptor antagonist abolishes the antidepressant effects of zinc as demonstrated in the forced swim test in rats.

27 • Cichy A, Sowa-Kucma M, Legutko B, *et al.* Zinc-induced adaptive changes in NMDA/glutamatergic and serotonergic receptors. Pharmacol Rep 2009; 61:1184–1191.
Antidepressant-effective doses of zinc alter the affinity of glycine to NMDA receptors and increase the density of the serotonin receptors in both the hippocampus and prefrontal cortex. These results are similar to the known action of antidepressant drugs.

28 Szewczyk B, Poleszak E, Sowa-Kucma M, *et al.* The involvement of NMDA and AMPA receptors in the mechanism of antidepressant-like action of zinc in the forced swim test. Amino Acids 2010; 39:205–217.

29 Poleszak E, Szewczyk B, Wlaz A, *et al.* D-serine, a selective glycine/N-methyl-D-aspartate receptor agonist, antagonizes the antidepressant-like effects of magnesium and zinc in mice. Pharmacol Rep 2008; 60:996–1000.

30 Takeda A, Sakurada N, Ando M, *et al.* Facilitation of zinc influx via AMPA/kainate receptor activation in the hippocampus. Neurochem Int 2009; 55:376–382.

31 Takeda A, Ando M, Kanno S, *et al.* Unique response of zinc in the hippocampus to behavioral stress and attenuation of subsequent mossy fiber long-term potentiation. Neurotoxicology 2009; 30:712–717.

32 Drzyzga LR, Marcinowska A, Obuchowicz E. Antiapoptotic and neurotrophic effects of antidepressants: a review of clinical and experimental studies. Brain Res Bull 2009; 79:248–257.

33 Corniola RS, Tassabehji NM, Hare J, *et al.* Zinc deficiency impairs neuronal precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain Res 2008; 1237:52–61.

34 Dwivedi Y, Rizavi HS, Conley RR, *et al.* Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. Arch Gen Psychiatry 2003; 60:804–815.

35 Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biol Psychiatry 2008; 64:527–532.

36 Szewczyk B, Poleszak E, Sowa-Kucma M, *et al.* Antidepressant activity of zinc and magnesium in view of the current hypotheses of antidepressant action. Pharmacol Rep 2008; 60:588–589.

37 Nagappan G, Woo NH, Lu B. Ama 'zinc' link between TrkB transactivation and synaptic plasticity. Neuron 2008; 57:477–479.

38 Huang YZ, Pan E, Xiong ZQ, McNamara JO. Zinc-mediated transactivation of TrkB potentiates the hippocampal mossy fiber-CA3 pyramid synapse. Neuron 2008; 57:546–558.

39 Xu H, Gao HL, Zheng W, *et al.* Lactational zinc deficiency-induced hippocampal neuronal apoptosis by a BDNF-independent TrkB signaling pathway. Hippocampus 2010.

40 Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 2000; 20:9104–9110.

41 • Gao HL, Zheng W, Xin N, *et al.* Zinc deficiency reduces neurogenesis accompanied by neuronal apoptosis through caspase-dependent and -independent signaling pathways. Neurotox Res 2009; 16:416–425.
Dietary zinc deficiency reduces the number of proliferating cells and the amount of neuronal differentiation in the dentate gyrus of weanling mice. Fas-medicated and caspase-dependent mechanisms were attenuated by zinc deficiency, leading to an increase in hippocampal TUNEL labeling.