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Disruption of calmodulin-dependent protein kinase II α/brain-derived neurotrophic factor (α-CaMKII/BDNF) signalling is associated with zinc deficiency-induced impairments in cognitive and synaptic plasticity

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Abstract

Maternal dietary Zn deficiency during fetal development induces substantial cognitive dysfunctions in the resultant offspring. The mechanism underlying this effect is unclear. The present study evaluated whether the impairments caused by gestational and lactational Zn deficiency are mediated by the hippocampal calmodulin-dependent protein kinase II α (α-CaMKII)/brain-derived neurotrophic factor (BDNF) signalling pathway as well as whether they can be restored by postnatal Zn supplementation. Rats were randomly divided into four groups on the first day of pregnancy (*n* 12): control (CO) group; pair-fed (PF) group; Zn-deprived (ZD) group; orally Zn-supplemented group. The spatial memory of the offspring was tested at postnatal day 35 using the Morris water maze. Long-term potentiation (LTP) in the rat hippocampal medial perforant path–dentate gyrus pathway was evaluated simultaneously, and α-CaMKII and BDNF protein levels were examined by Western blot analysis. The results demonstrated that the ZD group exhibited a significantly longer latency period in the Morris water maze as well as a significantly decreased LTP amplitude compared with the CO and PF groups. α-CaMKII and BDNF protein expression in the hippocampus was significantly reduced in the ZD group. Postnatal Zn supplementation restored the cognitive dysfunction induced by gestational Zn deficiency but could not completely reverse the decreased LTP and α-CaMKII/BDNF protein levels. Our findings suggest that the α-CaMKII/BDNF signalling pathway may be involved in Zn deficiency-induced cognitive and synaptic impairments.

Key words: Zinc deficiency and supplementation: Learning and memory: Synaptic plasticity: Calmodulin-dependent protein kinase II α/brain-derived neurotrophic factor signalling

An estimated 82 % of pregnant women worldwide consume a lower-than-recommended dietary dose of Zn; this rate may approach 100 % in developing countries[1]. Zn is one of the most abundant divalent metal ions in the central nervous system and is mainly stored in the hippocampus, which is important for maintaining cognitive function[2]. The developing nervous system is a prime target for the disruptive effects of Zn deficiency, as the brain undergoes its most rapid period of maturation during fetal life. Studies have shown a correlation between maternal Zn status and neonatal and infant behaviour and cognitive function[3].

Though many studies have shown that learning and memory dysfunction can be induced by Zn deficiency *in utero*, the mechanism underlying this effect is still obscure[4,5]. Recently, the relationships between changes in cell signalling pathways and long-term potentiation (LTP) in the nervous system as well as learning and memory function have become the focus of research. Neural plasticity, which is reflected by LTP, is considered to be the electrophysiological basis for learning and memory[6]. Notably, vesicular Zn is released as a neuromodulator into the synaptic cleft to modify different types of receptors during synaptic transmission. Studies involving dietary depletion of Zn or the Zn chelators dithizone[7] and Ca-EDTA[8,9] have suggested that endogenous Zn is required for the induction of LTP in CA1 and CA3 pathways. It is not known whether synaptic plasticity in the medial perforant path–dentate gyrus (MPP–DG) pathway is also affected by Zn deficiency.

Abbreviations: α-CaMKII, calmodulin-dependent protein kinase II α; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; CaM, calmodulin; CO, control; LTP, long-term potentiation; MPP–DG, medial perforant path–dentate gyrus; PF, pair-fed; ZD, Zn-deprived; ZS, Zn-supplemented.

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Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family that is activated by Ca/calmodulin-dependent protein kinase II α (α-CaMKII) and plays important roles in synaptic plasticity as well as learning and memory[10]. Interestingly, Zn has been shown to be an important modulator of this pathway, facilitating the maturation of BDNF from pro-BDNF through the activation of Zn-dependent matrix metalloproteinases[11].

α-CaMKII, one of the major CaMKII isoforms in the brain, also plays key roles in synaptic plasticity and learning and memory function[12]. Although several studies have shown that Zn can modulate the activity of CaMKII[13], to our knowledge, no studies have evaluated changes in α-CaMKII levels resulting from Zn deficiency. Hence, in the present study, we postulated that the cognitive deficits and synaptic obstacles observed in Zn-deficient rats result from a perturbation in α-CaMKII/BDNF signal transduction. In addition, little information is available regarding the effects of Zn supplementation on Zn deficiency-induced impairments in cognitive function and synaptic plasticity. Therefore, we investigated the possible mechanisms of learning and memory impairment in this context by analysing synaptic plasticity in the MPP–DG pathway and α-CaMKII/BDNF expression levels in the hippocampus in both Zn-deficient and Zn-supplemented rats.

Materials and methods

Animals, diets and tissue samples

The present study complied with the Guide for the Use and Care of Laboratory Rats and was administered under the auspices of the Animal Resource Services of Xinhua Hospital, affiliated with the Medical School of Shanghai Jiaotong University, which is accredited by the Chinese Association for the Accreditation of Laboratory Animal Care. A total of twenty-four virgin Sprague–Dawley rats (220–250 g) were obtained from a commercial source (Bikei Animal Company). After consumption of a standard, non-purified diet (Bikei Animal Dietary) for a 5 d acclimatisation period, the rats were impregnated. The pregnant rats were randomly divided into four groups on the first day of pregnancy: control (CO) group; pair-fed (PF) group; Zn-deprived (ZD) group; orally Zn-supplemented (ZS) group. Each group consisted of six pregnant rats. After birth, each dam's litter was culled to eight according to weight. The ZD and ZS groups received an AIN-93G-based diet containing 2 mg Zn/kg diet *ad libitum* throughout pregnancy and lactation. Both the CO and PF groups were fed the basal diet adequately supplemented with zinc sulphate at a dose of 25 mg Zn/kg, but each PF dam received only the daily average amount of food consumed by its ZD paired dam. After weaning (day 21), two male pups of similar weight were removed from each litter, so that each group contained twelve male pups. Pups in the CO and PF groups continued to receive the control diet, and pups in the ZD group continued to receive the Zn-deficient diet. However, the ZS pups were switched to the adequate-Zn diet (25 mg Zn/kg). All the four groups were supplied with deionised water *ad libitum*. The weight of the dams and offspring were monitored throughout the experiments. When the pups were 35 d old, they were tested using the Morris water maze and subsequently anaesthetised and decapitated. Serum samples were collected, and serum Zn levels were determined by atomic absorption spectrophotometry (Thermo M6). Resected hippocampal tissues were immediately frozen at −196°C and then stored at −80°C.

Morris water maze test

Beginning on postnatal day 35, the rats received 5 d of training to test their capacity for learning and memory acquisition using the Morris water maze. It is possible that Zn deficiency had led to a failure of the development of sensory systems[14]. Thus, an invisible platform was used in the Morris water maze. The rats were trained to swim to reach a platform in a circular pool (160 cm diameter × 50 cm height) located in a test room. The pool was filled with water (22–25 °C) to a depth of 16 cm. A movable circular platform, 12 cm diameter, was submerged 2 cm below the surface of water, which was opaque after being mixed with prepared Chinese ink (Shanghai Chinese Ink Factory) as described previously[15]. Briefly, for the place navigation test (spatial learning acquisition), each rat was subjected to two trials per d for four consecutive days. Each trial consisted of placing the rat in the water so that it faced the wall of the pool at one of the four starting locations (north, east, south and west) in a random order. The rat was allowed to search the platform for a maximum of 120 s. If the rat did not find the platform in 120 s, it was gently lifted up and placed onto the platform for 20 s before being returned to the cage. The escape latency (the duration before finding the platform) and swim paths were automatically recorded by a video/computer system. The escape latency, path length and swim speed were recorded as indices of learning and memory capacity.

Electrophysiological recordings and long-term potentiation induction

From each group, six pups were subjected to LTP induction. Hippocampal slices were prepared as described previously[16]. Briefly, the rats were anaesthetised with sodium pentobarbital (2 %) and decapitated. The brains were rapidly removed, and the hippocampi were dissected in ice-cold oxygenated (95 % O_2 and 5 % CO_2) artificial cerebrospinal fluid. Approximately 400 μm transverse slices were prepared on a tissue slicer and then incubated in a recovery chamber filled with oxygenated artificial cerebrospinal fluid. The slices were allowed to recover for at least 1·5 h before recordings were attempted. For electrophysiological recordings, the slices were transferred into a perfusion chamber continuously superfused with artificial cerebrospinal fluid at a rate of 2·5 ml/min and maintained at 30°C while recording. All the experiments were conducted on slices maintained *in vitro* for 2–8 h. For extracellular stimulation of the MPP–DG, a monopolar tungsten electrode was placed in the middle molecular layer of the dentate gyrus. Extracellular field excitatory postsynaptic potentials were recorded with a glass

Table 1. Effects of zinc deficiency and supplementation on serum zinc and body weight gain in rats

(Mean values and standard deviations; number of rats)

			Serum Zn (μg/l)		Gain in body weight (g)	
Rats	Groups	*n*	Mean	SD	Mean	SD
Maternal¶	CO	6	1038·50	68·87	70·50	5·96
	PF	6	998·67†	75·34	61·67‡	9·09
	ZD	6	657·83*§	60·83	12·26*§	1·45
	ZS	6	661·00*	61·88	10·83*	1·94
	F		57·85		194·43	
	P		<0·001		<0·001	
Offspring	CO	12	1427·50	155·38	105·50	9·74
	PF	12	1376·83†	156·67	85·35‡	8·38
	ZD	12	568·86*	57·93	35·75*‖	2·95
	ZS	12	1508·75†	157·13	82·42‡	9·27
	F		119·9		93·54	
	P		<0·001		<0·001	

CO, control group; PF, pair-fed group; ZD, Zn-deprived group; ZS, Zn-supplemented group.
* Mean value was significantly different from that of the CO and PF groups ($P<0·05$).
† Mean value was not significantly different from that of the CO group ($P>0·05$).
‡ Mean value was significantly different from that of the CO group ($P<0·05$).
§ Mean value was not significantly different from that of the ZS group ($P>0·05$).
‖ Mean value was significantly different from that of the ZS group ($P<0·05$).
¶ Maternal weight gain represents the period from conception to weaning. Offspring weight gain represents that from birth to 35 d.

microelectrode (2–10 MΩ resistance) filled with pontamine sky blue and situated in the middle molecular layer of the dentate gyrus. Responses were evoked using single-pulse stimuli of a fixed duration (0·1 ms), delivered at 30 s intervals. The optimal recording location for each rat was determined as the point at which the largest response could be obtained with a minimal amount of current. Only those slices that produced field excitatory postsynaptic potentials of 1 mV or higher in amplitude were selected for the experiments. Medial pathway responses were confirmed on the basis of a depression of field excitatory postsynaptic potentials elicited with paired pulses spaced 40–100 ms apart. The stimulation intensity that produced 30 % of the maximal evoked amplitude was chosen for the test pulse and tetanic stimulation. Test stimuli (0·1 ms pulse width) were delivered every 30 s before tetanisation. Once a stable baseline recording was obtained, LTP was induced by modifying a protocol (high-frequency stimulation: two trains, 500 ms each, 100 Hz within the train, repeated every 30 s).

Western blot analysis

At the end of the experiments, total protein was extracted from the rat hippocampi using a protein lysis kit (Beyotime). Using SDS–PAGE, 30 μg of protein were separated and then transferred onto polyvinylidene difluoride membranes. After blocking in 5 % fat-free milk for 3 h, the membranes were incubated with primary antibodies, including rabbit anti-BDNF (1:1500; Chemicon), rabbit anti-α-CaMKII (1:200; Santa Cruz) and mouse anti-actin (1:10 000; Kang Chen) overnight. On the next day, the membranes were washed and incubated with horseradish peroxidase-conjugated goat anti-rabbit (1:5000) or horseradish peroxidase-conjugated goat anti-mouse (1:5000) antibodies for 1 h. Immunolabelled protein bands were detected using an enhanced chemiluminescence system. Films were digitised using a scanner, and the relative optical density of the bands was determined with Scion Image software 4.03 (Scion Corp.).

Statistical analysis

All data were analysed using ANOVA. The level of significance was set at $P<0·05$. Statistical analysis was performed using

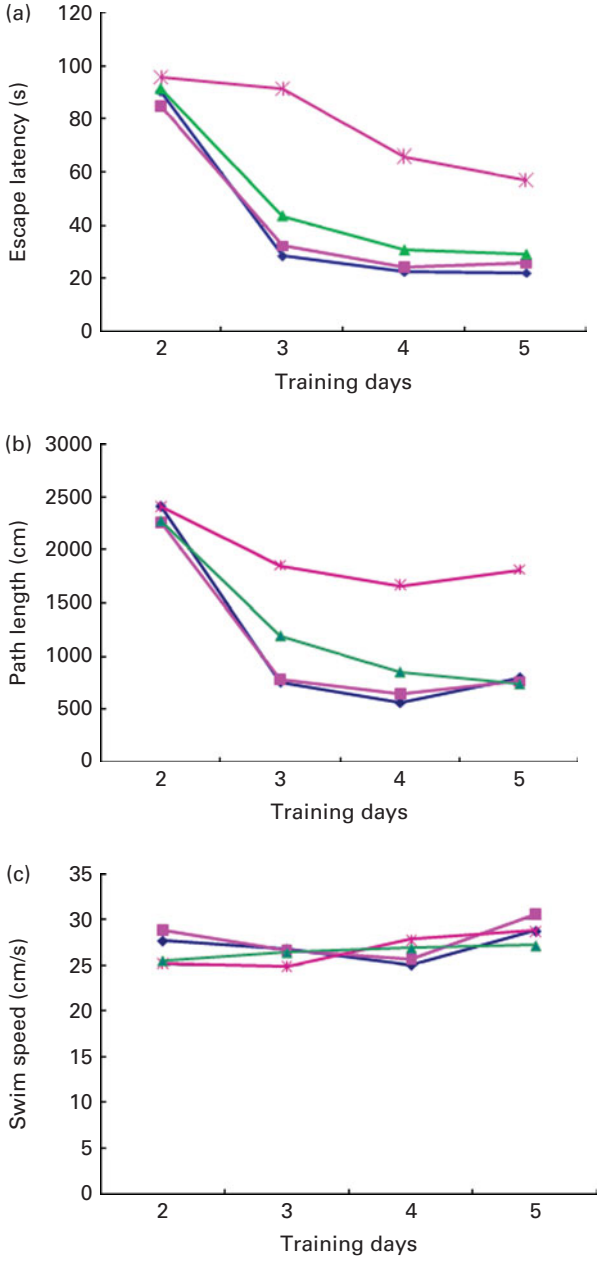

Fig. 1. Curve for (a) escape latency, (b) path length and (c) swim speed calculated for each rat on each training day. Values are means of twelve rats per group. CO (–◆–), control group; PF (–■–), pair-fed group; ZD (–✳–), zinc-deprived group; ZS (–▲–), orally zinc-supplemented group. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

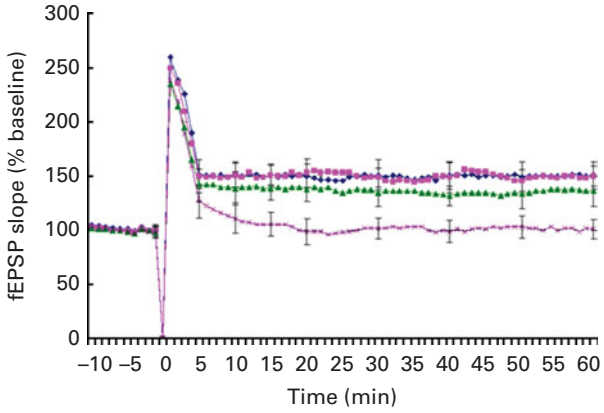

Fig. 2. Hippocampal long-term potentiation (LTP) in zinc-deprived (ZD, —✳—) and zinc-supplemented (ZS, —▲—) rats. The LTP induced by tetanic stimulations in the ZD slices was significantly smaller than that of the control (—◆—), pair-fed (—■—) and ZS slices ($P<0·05$). fEPSP, field excitatory postsynaptic potentials. (A colour version of this figure can be found online at (http://www.journals.cambridge.org/bjn).

SPSS for windows (version 13.0; SPSS, Inc.). All data are presented as the means and standard deviations.

Results

Zinc deficiency affected serum zinc concentrations and growth of the offspring

A general growth inhibition was observed in rats fed the Zn-deficient diet. In the ZD group, the dams had poor appetites after being fed the Zn-deficient diet for approximately 12–15 d and subsequently showed growth retardation. On the day of weaning (day 21), the final gain in body weight of the ZD dams (12·26 (SD 1·45) g) was significantly lower than that of the CO (70·50 (SD 5·96) g) and PF (61·67 (SD 9·09) g) dams. On day 35, the ZD pups exhibited a significantly lower weight gain than the CO and PF pups (ZD pups 35·75 (SD 2·95) g, CO pups 105·50 (SD 9·74) g and PF pups 85·35 (SD 8·38) g). These changes in growth, combined with the serum Zn status of these rats, indicated that we had successfully established a model of significant Zn deficiency. Pups in the ZS group had better appetites after 4–5 d of Zn supplementation and showed an accelerated weight gain. At the end of the experiments, serum Zn concentrations and body weight gain were similar between the ZS and PF pups ($P>0·05$; Table 1).

Learning and memory test

The swim speeds among the four groups were not significant ($P>0·05$), which meant that intact motor capability was not impaired by Zn deficiency. Compared with the rats in the CO and PF groups, those in the ZD group had poor orientation abilities. Their swimming traces were distracted, as they took more time to find the hidden platform (escape latency) and swam a longer distance to get there ($P<0·05$). The indices of the ZS group were similar to those of the CO and PF groups ($P>0·05$). With increased training, both the escape latency and path length gradually declined in all the groups. However, starting on the third training day, the improvements in the ZD group were not as apparent as those in the PF, CO and ZS groups ($P<0·05$) (Fig. 1).

Synaptic plasticity in the medial perforant path–dentate gyrus pathway

To detect changes in the hippocampal LTP, the LTP of the MPP–DG pathway was compared among the four groups. As shown in Fig. 2 and Table 2, the high-frequency stimulation evoked significantly larger LTP in the CO and PF slices than in the ZD slices, suggesting that Zn deficiency depressed LTP. In addition, there was a significant difference between the ZD and ZS samples, suggesting that Zn supplementation might improve the LTP depression caused by Zn deficiency during fetal life. However, the ZS samples showed significantly less LTP than the CO and PF samples, indicating that Zn supplementation did not completely restore the impaired LTP.

Zinc deficiency suppressed calmodulin-dependent protein kinase II α/brain-derived neurotrophic factor signalling in the hippocampus

Because α-CaMKII/BDNF signalling is closely involved in LTP formation, we decided to examine whether α-CaMKII or

Table 2. Effects of zinc deficiency and supplementation on long-term potentiation in offspring rats (Mean values and standard deviations)

	fEPSP slope (% baseline)													
	5 min		10 min		20 min		30 min		40 min		50 min		60 min	
Groups	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CO	152	13	152	12	150	11	151	14	151	13	149	15	151	13
PF	150	15	151	11	153	13	149	9	149	14	146	10	150	9
ZD	127*	15	111*	14	99*	12	102*	10	99*	10	103*	10	101*	9
ZS	142†‡	15	139†‡	15	138†‡	11	135†‡	13	132†‡	9	134†‡	14	136†‡	14
F	12·88		13·75		14·52		16·35		17·25		13·11		12·54	
P	<0·05		<0·05		<0·05		<0·05		<0·05		<0·05		<0·05	

fEPSP, field excitatory postsynaptic potentials; CO, control group; PF, pair-fed group; ZD, Zn-deprived group; ZS, Zn-supplemented group.
* Mean value was significantly different from that of the CO and PF groups ($P<0·05$).
† Mean value was significantly different from that of the CO and PF groups ($P<0·05$).
‡ Mean value was significantly different from that of the ZD group ($P<0·05$).

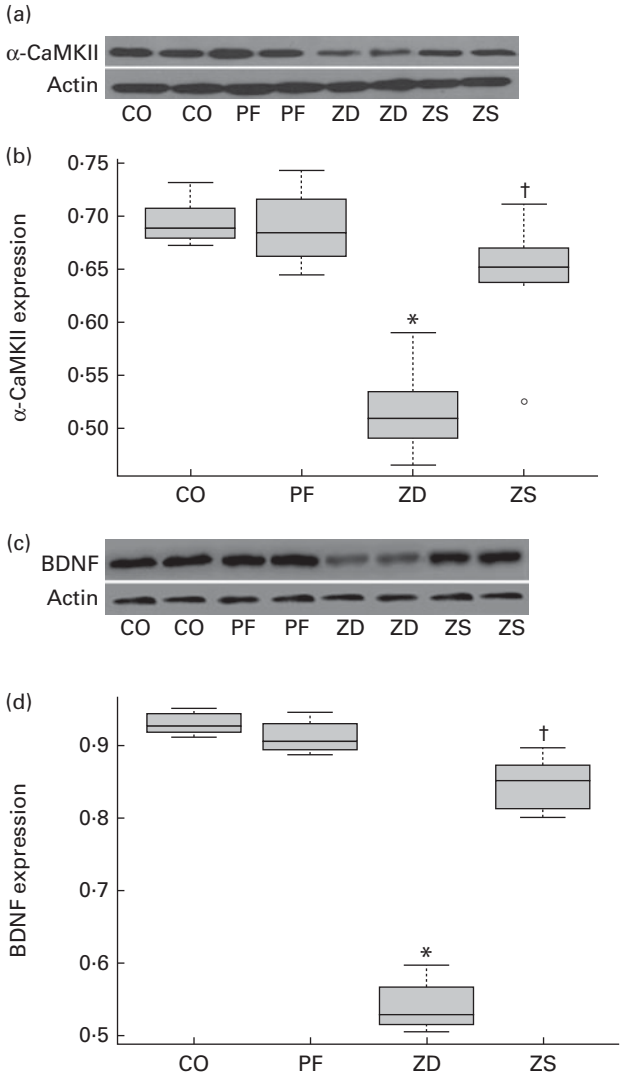

Fig. 3. Effect of zinc deficiency on the hippocampal expression of calmodulin-dependent protein kinase II α (α-CaMKII) and brain-derived neurotrophic factor (BDNF) in rats. (a) Western blot analysis of hippocampi obtained from the control (CO), pair-fed (PF), zinc-deficient (ZD) and zinc-supplemented (ZS) rats after incubation with antibodies against α-CaMKII and actin. (b) Densitometry of α-CaMKII expression was normalised to actin. Values are means (*n* 6), with standard deviations represented by vertical bars. * Mean value was significantly different from that of the CO, PF and ZS groups ($P<0·05$). † Mean value was significantly different from that of the CO and PF groups ($P<0·05$). (c) Western blot analysis of hippocampi obtained from the CO, PF, ZD and ZS rats after incubation with antibodies against BDNF and actin. (d) Densitometry of BDNF expression was normalised to actin. Values are means (*n* 6), with standard deviations represented by vertical bars. * Mean value was significantly different from that of the CO, PF and ZS groups ($P<0·05$). † Mean value was significantly different from that of the CO and PF groups ($P<0·05$).

BDNF in the hippocampus was affected by Zn nutrition status. As shown in Fig. 3, both α-CaMKII and BDNF levels were markedly decreased in the hippocampus of the ZD rats than in that of the CO and PF rats. Quantitative analysis revealed that α-CaMKII and BDNF protein levels in the ZD rats were significantly lower than those measured in the CO and PF rats ($P<0·05$). Rats that received Zn supplementation after weaning showed increased levels of α-CaMKII and BDNF relative to the ZD rats; however, their expression was still significantly reduced relative to the levels measured in the CO and PF rats ($P<0·05$), suggesting that Zn supplementation did not completely restore α-CaMKII and BDNF protein expression.

Discussion

In the present study, we used dietary Zn deficiency (2 mg Zn/kg diet) and Zn supplementation rat models to examine changes in learning and memory behaviour as well as LTP-related signalling pathways in the hippocampus. Because the effects of Zn deprivation could be ascribed to reduced food intake rather than to Zn deficiency, one group of controls (PF group) was pair-fed with the same amount of food consumed by the Zn-deprived group. The PF rats showed no changes in the parameters assessed, indicating that the effects were specific to Zn deficiency and not the consequence of a general reduction in food intake.

Growth retardation may be induced by the inhibition of protein synthesis and increased catabolic response to Zn deficiency[17]. After weaning, the pups were fed an oral Zn-abundant diet, and as a result serum Zn concentrations and body weight improved significantly and were similar to those of the PF group on day 35. These results are consistent with results reported by others[18,19], suggesting that oral supplementation with Zn after weaning could improve the growth of pups.

The results of the Morris water maze test revealed that the Zn-deficient rats exhibited defects in memory behaviour. This is consistent with previous reports showing that dietary Zn deficiency appears to damage learning and memory processes in the hippocampus[20]. Because intracellular Zn is necessary for many enzyme activities and protein functions associated with signal transduction and gene expression[21], it is reasonable to speculate that Zn deficiency-induced impairments of hippocampus-dependent learning and memory functions might be caused by disruptions in the LTP-related signalling cascade. With our rat model, we identified a new mechanism whereby dietary Zn deficiency impairs learning and memory function by disrupting the α-CaMKII/BDNF signalling pathway in the hippocampus. Furthermore, this is the first study to report LTP-related signalling pathway in rats subjected to Zn supplementation after experiencing Zn deficiency during gestation and lactation. The present results demonstrated that while body weight and memory behaviour were normal in the ZS rats, neither LTP nor α-CaMKII/BDNF protein levels had recovered to control levels by the end of the experiments.

α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors have been reported to elicit *N*-methyl-D-aspartic acid receptor activation and result in the influx of Zn (as well as Ca) into postsynaptic neurons, a process that is believed to be involved in LTP induction[20,22]. LTP in the hippocampus is considered to be an important tool for elucidating the molecular mechanisms of learning and memory[23,24]. Ca enters the postsynaptic neurons through AMPA and *N*-methyl-D-aspartic acid receptors and Ca channels and then binds with calmodulin (CaM) to form a Ca–CaM

complex[23,25]. The activated Ca–CaM complex combines with CaMKII, resulting in its autophosphorylation[25]. CaMKII activity is essential for normal *N*-methyl-D-aspartic acid receptor-dependent forms of LTP and spatial learning and memory[25] as well as for plasticity in other regions of the brain[26]. Interestingly, Zn can directly activate CaMKII, independently of Ca and CaM. Zn can also affect CaMKII activity by modulating the binding of the Ca–CaM complex to CaMKII[13]. There are four isoforms of CaMKII, α, β, γ and δ. Accumulating evidence suggests that different CaMKII isoforms are involved in different neural functions based on their characteristic cellular localisation patterns. The α-CaMKII protein is highly enriched at synapses, and a significant amount of *α-CaMKII* mRNA is localised in dendrites[27]. Recent experimental evidence indicates that almost 83% of α-CaMKII found in dendrites during normal brain function is synthesised locally[28]. α-CaMKII is known to play key roles in synaptic plasticity, hippocampal place cell stability and spatial learning. Mice with a mutation in the *α-CaMKII* gene show hippocampal LTP deficits and learning and memory abnormalities in hippocampal tasks[29]. The effect of Zn deficiency on α-CaMKII has not been explored previously. Our data showed that chronic Zn deficiency reduced α-CaMKII protein levels in the hippocampus.

BDNF, a member of the neurotrophin family, is highly expressed in neurons throughout the central nervous system[30]. BDNF promotes the survival of a wide variety of neurons and regulates axonal and dendritic growth, thereby accounting for synaptic plasticity in the central nervous system[31]. Previous studies have reported that membrane depolarisation-triggered Ca^{2+} influx through L-type voltage-dependent Ca^{2+} channels induces an increase in *BDNF* mRNA expression in cultured neurons and that this effect is blocked by the inhibitors of CaM[32]. These data suggested that BDNF lies downstream of the CaM/CaMKII signalling pathway and can be activated by CaMKII. Interestingly, the present study showed that the Zn deficiency-induced down-regulation of BDNF is mediated by an α-CaMKII-independent signalling pathway. Collectively, the down-regulation of both α-CaMKII and BDNF by Zn deficiency might in part explain the observed impairments in learning and memory.

The few studies on the effects of Zn supplementation on cognitive recovery in Zn-deprived animals have reported conflicting results. Halas *et al.*[18] showed that Zn nutritional insults during the critical period of cerebral growth were not reversed by subsequent Zn supplementation. However, the present study found that Zn supplementation restored the cognitive defects observed in the Zn-deficient rats, as reported by Piechal *et al.*[33]. The discrepancy in these results may be attributed to age differences in the offspring undergoing the cognitive tests. Importantly, Zn supplementation in children also confirmed the present results: Zn supplementation in undernourished children improves their developmental quotients, activity patterns and neuropsychological functions[34]. Our finding that Zn supplementation is beneficial for reversing hippocampal dysfunction seems to further substantiate the pivotal role played by synaptic Zn in shaping the physiological neurotransmission of the hippocampus, a crucial brain region. Notably, the fact that Zn supplementation only partially restored the protein expression of α-CaMKII and BDNF indicated that while the impairments in key molecules caused by *in utero* Zn deficiency may be irreversible, the cognitive symptoms can be restored.

In conclusion, the present study has shown that α-CaMKII/BDNF signalling is altered in a Zn-deprived model known to affect synaptic plasticity and cognitive function. Furthermore, Zn supplementation restored the cognitive dysfunctions induced by maternal Zn deficiency. Nevertheless, Zn supplementation could not completely restore LTP or α-CaMKII/BDNF expression to control levels. These findings will help to clarify the mechanism of Zn deficiency-induced cognitive impairments. In addition, the regulation of α-CaMKII/BDNF signalling pathway by Zn nutriture may represent an important new strategy for the prevention and treatment of neurodegenerative diseases.

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