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Zinc and Mossy Fiber LTP in the Mammalian Hippocampus: A Perspective

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Short Communication

The role of zinc, one of the most abundant metals present in mammalian central nervous system, in various synaptic transmission and plasticity processes has been widely studied. The main target is the free or loosely bound zinc that is present in zinc-enriched synapses, including the important the synaptic system mossy fibers-CA3 pyramidal cells of the hippocampus. It is generally considered that zinc has a neuro modulatory role of this system. However, the role of zinc in Long-Term Potentiation (LTP) remains controversial. Here we present the different views about zinc requirement for expression of mossy fiber LTP, taking into account the different theories for the loci of induction and expression of mossy fiber LTP. Zinc is one of the most common transition metals in the central nervous system, and a large quantity of chelatable zinc is sequestered in synaptic vesicles, especially in the glutamatergic vesicles of hippocampal mossy fibers [1-4] Zinc is released into the synaptic cleft in a calcium- dependent way, following high [5,6]of stimulation [4,7] and is taken up by zinc transport systems [2,8]. It has been shown that zinc is involved in several inhibitory and excitatory synaptic processes interacting with various neuro transmitter receptors and Voltage-Dependent Calcium Channels (VDCCs) [9-11]. Zinc may also enter postsynaptic neurons [12,13] and can have a neuro toxic effect when released at very high concentrations [14]. While most of the zinc present in the brain is contained in metallo proteins, a concentration of zinc of 10 - 300 μM may be obtained with the activation of the zinc-enriched mossy fiber synapses [15]. Several lines of evidence suggest that, at this concentrations, zinc plays a neuro modulatory role at hippocampal synapses, inhibiting glutamate release when acting at the pre synaptic site [4,16-18]. The pre synaptic action of vesicular zinc includes the inhibition of N- and P/Q types of VDCCs [19,20] and the activation of the potassium-activated ATP (KATP) channels [21,22]. The post synaptic actions of zinc include the inhibition of N-Methyl-D Aspartate (NMDA) [23], α-amino- 3-hydroxy-5-methyl-4-izoxazolepropionic acid (AMPA) receptors [24-29], GABAA [30] and kainaite [31] receptors (Figure 1). However, in previous observations, it was shown that zinc enhanced AMPA and kainaite receptor responses [10]. A possible explanation for this discrepancy is the difference between the kinetics of the zinc chelators used in the referred experiments. In the presence of ZX1, a fast zinc chelator, it was observed that zinc chelation enhanced the response of AMPA receptors, while Ca EDTA (a slower zinc chelator) did not have the same effect [24]. Thus, some unanimity exists about the neuro modulatory role of zinc in the hippocampus, even in the mossy fibers and the postsynaptic zinc-enriched CA3 hippocampal neurons. On the other hand, the role of zinc in Long-Term Potentiation (LTP) of the mossy fibers remains controversial. LTP is a form of synaptic plasticity that may underlie learning and memory [25]. Mossy fiber LTP is a form of LTP that is independent of the activation of NMDA receptors and that is common in zinc-enriched mossy fiber synapses [32,33]. Despite the large number of studies about mossy fiber LTP, some controversy remains about the role of zinc in its induction and expression (Figure 2). This controversy is sustained by different experimental observations that supports [34,7] or opposes [34,35] the idea that zinc is necessary for mossy fiber LTP induction. It was proposed that the physiological action of zinc may depend on its effective concentration and the distance from the release site, for example, at a specific synapse, zinc might facilitate local and depress surrounding synapses [21]. However, the main reason for these contradictory results is the difference between the experimental approaches used in these studies. For instance, the application of low concentrations of the impairment zinc chelator Ca-EDTA did not affect mossy fiber LTP, while highest Ca-EDTA concentrations blocked LTP induction [34,7]. The application of membrane-per meant chelators as TFL-Zn and TPEN also gave contradictory results [26,35]. It was observed that the application of ZX1, which rapidly sequesters zinc, inhibits the increase of NMDA receptor currents after LTP induction [36]. In contrast, the application of Ca-EDTA did not have the same effect. It was also shown that mossy fiber LTP induction with high-frequency stimulation was significantly impaired by ZX1, which seems to

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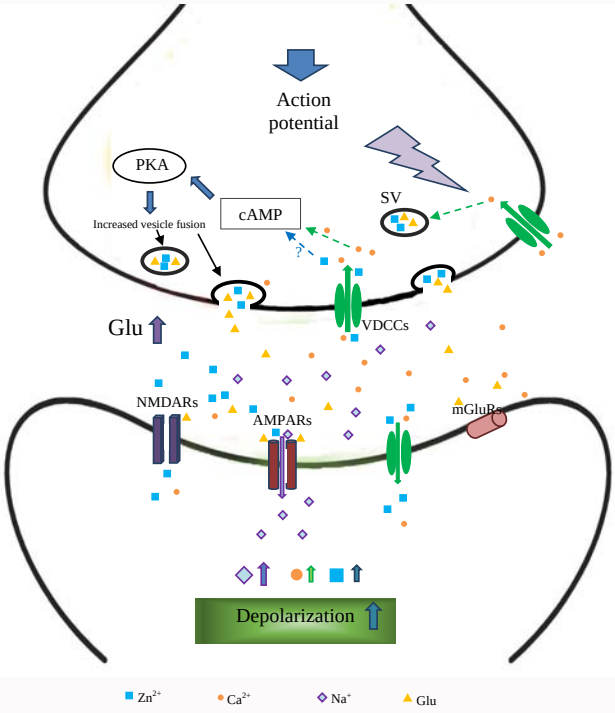

Figure 1: Mechanisms of LTP expression, considering a pre synaptic *locus*. The action potentials activate VDCCs and, subsequently, zinc and glutamate (Glu) release by the Synaptic Vesicles (SV). After the induction of LTP, calcium and eventually zinc may mediate the activation of PKA via cyclic AMP. The glutamate release rises for the same stimulation and the postsynaptic cell depolarizes, allowing the entry of higher quantity of sodium, calcium and zinc trough the receptor-activated channels (NMDARs, AMPARs).

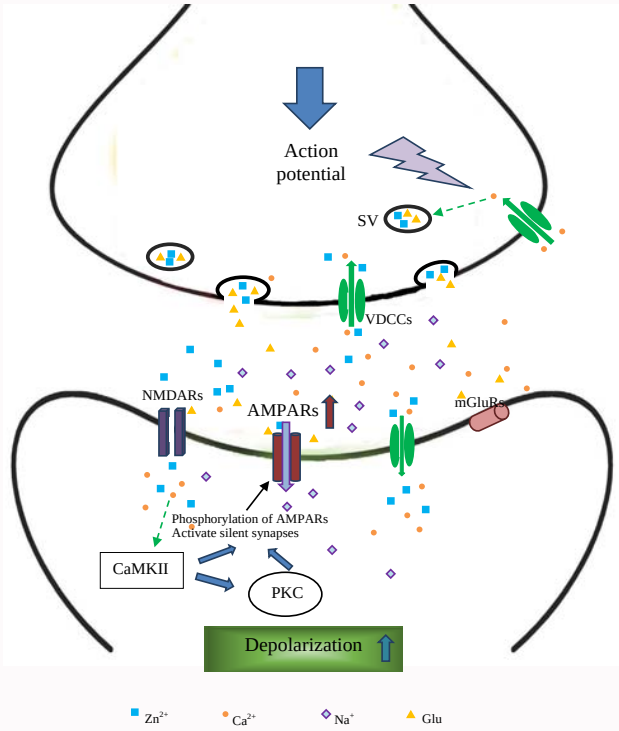

Figure 2: Mechanisms of LTP maintenance, considering a possibility of a postsynaptic *locus*. The action potentials activate VDCCs and, subsequently, zinc and glutamate (Glu) release by the Synaptic Vesicles (SV). The induction of LTP requires a rise in the calcium concentration and, subsequently, the activation of Ca MK II and PKC. The conductivity of the AMPA receptors rises due to the phosphorylation and/or the activation of silent synapses.

confirm that zinc is necessary for LTP induction. However, using transgenic mice lacking the zinc transporter ZnT3, which is necessary to sequester zinc in synaptic vesicles [8], the authors observed that high-frequency stimulation elicited LTP in those mice, confirming previous experimental results [34]. The difficulty in obtaining a clear answer about the role of zinc in LTP should be contextualized in the diversity of theories on induction and expression of mossy fiber LTP. A large number of studies characterize mossy fiber LTP as pre synaptically induced and expressed, being mediated by enhanced glutamate release [37,38]. However, some studies are in favor of the hypothesis of a postsynaptic locus for mossy fiber LTP induction [6,39,40]. The main argument in favor of the pre synaptic nature for mossy fiber LTP is the reduction of the paired-pulse facilitation, which is inversely correlated with the transmitter release probability [41]. However, changes in paired-pulse ratio could not be exclusively mediated by modifications of the pre synaptic release probability. For example, they can be influenced by postsynaptic receptor desensitization and lateral diffusion [27]. Further support for the pre synaptic locus of mossy fiber LTP comes from quantal analysis, since the failure rate is negatively correlated with the average release probability. Normally, a lower failure rate after LTP induction means a higher probability of glutamate release [42]. However, that conclusion can only be achieved assuming a constant number of synapses. The discovery of post synaptically silent synapses (i.e., synapses that do not include active AMPA receptors) provided a possible explanation for the mentioned lower failure rate after LTP [43]. Additional experimental evidence in favor of the pre synaptic hypothesis for the expression of mossy fiber LTP is the effect of cyclic AMP that mediates pre synaptic mossy fiber LTP processes [44]. Assuming a purely pre synaptic locus for mossy fiber LTP, the zinc released from mossy fibers should rise after electrically- or chemically-induced depolarization, since it is generally accepted that zinc is co-released with glutamate. However, there are experimental results showing that zinc release is not enhanced after the induction of LTP [6,26,45]. Thus, the lack of enhancement of zinc release after LTP induction may argue in favor of the contribution of postsynaptic mechanisms for the expression of mossy fiber LTP. In addition, it was shown that, in mice lacking the ZnT3 transporter, the locus of LTP expression is postsynaptic [36]. In conclusion, with this large number of conflictive interpretations it is difficult to build a model explaining the role of zinc in LTP induction and expression. Two different approaches can be used, assuming a pre synaptic and a postsynaptic locus for mossy fiber LTP. Considering the pre synaptic hypothesis, the existing models involve the activation of PKA via cyclic AMP. It was observed that zinc is necessary for PKA activation including the action of tyrosine kinase B [29]. In this case, the role of zinc in the induction of mossy fiber LTP seems uncontroversial. However, considering a possible postsynaptic locus, the molecular mechanisms involved in the maintenance of LTP, like the phosphorylation of AMPA receptors and the exocytosis of silent synapses, mediated by the activation of calmoduline-kinase II (Ca MK II) [46,47] may not require zinc entry through receptor-activated channels and/or VDCCs. However, it was shown that severe dietary deficiency of zinc causes an impairment of LTP expression [28], which allow us to conclude that, at least in part, zinc plays a role in LTP formation, namely in the in the construction of the multiple pathways related with learning and memory [28]. It should be noticed that severe dietary zinc deficiency might not reduce only the vesicular zinc. On

the other hand, vesicular zinc may not be required during the postsynaptic LTP induction and maintenance processes, since the main processes, such as the activation of Ca MK II, are mediated by calcium entry in the postsynaptic area [46,47]. In conclusion, zinc is, at least in some extent, always necessary for LTP formation and expression in mossy fiber LTP. Vesicular zinc is essential on the process of LTP expression if its locus is pre synaptic but is not required in the case of a postsynaptic locus of mossy fiber LTP maintenance. Further investigation should include the evaluation of a possible combination of pre-and postsynaptic loci of the expression of learning and memory in mammalian hippocampus.

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