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Chelators for investigating zinc metalloneurochemistry

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The physiology and pathology of mobile zinc signaling has become an important topic in metalloneurochemistry. To study the action of mobile zinc effectively, specialized tools are required that probe the temporal and positional changes of zinc ions within live tissue and cells. In the present article we describe the design and implementation of selective zinc chelators as antagonists to interrogate the function of mobile zinc, with an emphasis on the pools of vesicular zinc in the terminals of hippocampal mossy fiber buttons.

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Introduction

Divalent zinc (Zn^{2+}) is one of the most abundant trace elements in the human body, where it typically serves as a structural or catalytic component for numerous proteins [1]. Although the chemistry and biology of zinc metalloproteins have historically dominated the field of zinc biology, there is a growing appreciation for a role of mobile zinc (hereafter mZn) pools found in specialized secretory tissues such as the prostate, pancreas, and brain [2•,3,4]. Investigations of the function of mZn within these tissues have revealed that the biochemical action of mZn requires careful regulation of its concentration in order to ensure proper physiology without pathological consequences [5]. Of particular interest is the role of mZn within the central nervous system, where high concentrations of chelatable zinc occur in specific regions of the brain [6]. Understanding the biology of mZn requires the design and implementation of tools that specifically intercept and report on the location and concentration of mZn.

Among the most common agents used to investigate mZn in biology are zinc-responsive fluorescent probes. Recent reviews summarize the field of fluorescent zinc sensing and detail some challenges that remain [2•,7•]. Far less explored are zinc-specific chelators, which serve as antagonists for mZn [8]. With appropriately designed chelators one can apply fluorescent microscopy in conjunction with electrophysiology to unravel the molecular mechanisms of mZn. Unfortunately, the lack of an adequate variety of zinc-specific chelators has resulted in confusion and controversy within the field of metalloneurochemistry [8,9].

Here, we provide a brief background on zinc metalloneurochemistry [10], direct the reader to primary literature and reviews to outline the current status and challenges in the field, and detail how judiciously designed chemical tools can address complex biological questions involving mZn.

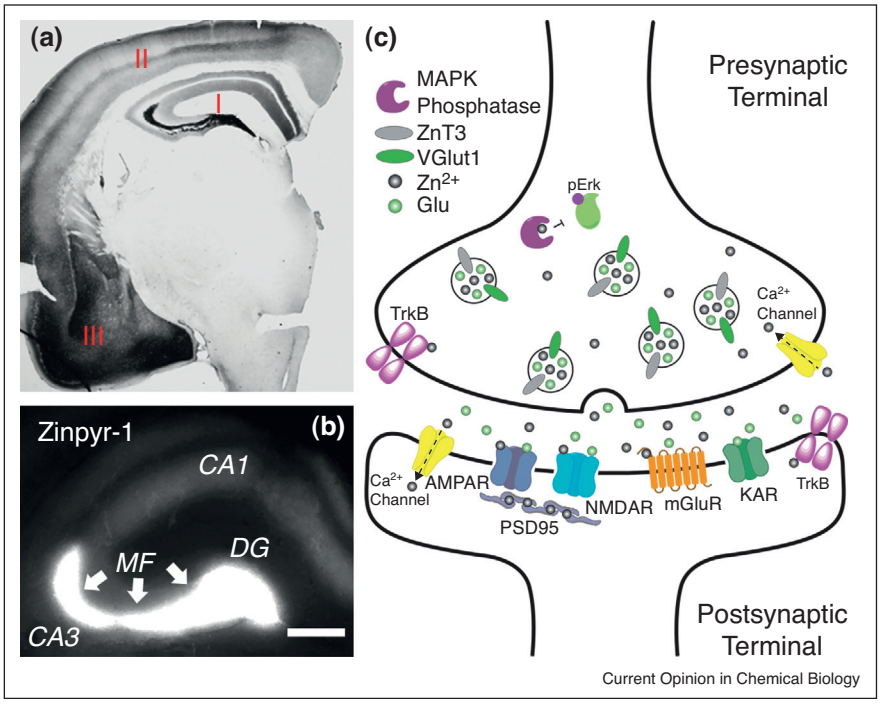
Anatomy of mZn in the brain

mZn is primarily restricted to the forebrain, where zinc-containing axons are particularly abundant in the hippocampus, cortex, and amygdala (Figure 1a) [11•]. Within these areas, the highest levels of mZn occur in the hippocampal mossy fibers (Figure 1b). Hippocampal mossy fiber axons project from granule cells of the dentate gyrus and are composed of two types of functionally specialized terminals, small filopodial extensions and large mossy fiber boutons [12]. Of the two, mZn is primarily localized to the mossy fiber boutons [13]. At the cellular level, mZn is loaded into presynaptic vesicles by the zinc transport protein ZnT3, which is expressed exclusively in neurological tissue and testis [14]. In mouse models, genetic deletion of ZnT3 (ZnT3 KO) abolishes vesicular zinc [15]. The glutamate transporter Vglut1 is also targeted to zinc-containing vesicles, and ZnT3 works in concert with Vglut1 to localize glutamate and zinc within the same vesicles [16].

The role of mZn in the hippocampus

The presynaptic location and high levels (>100 μM) of mZn within glutamatergic vesicles, in conjunction with the importance of glutamate as a neurotransmitter, led to the hypothesis that mZn may act as a neurotransmitter or neuromodulator [8]. The abundance of vesicles containing mZn within the hippocampus, the area of the brain associated with memory and learning [17], makes this idea particularly intriguing. Seminal work with ZnT3 KO mice, however, furnished enigmatic results that questioned the importance of hippocampal mZn [18]. Studies with 6–10-week-old ZnT3 KO mice revealed no change in synaptic excitability in the CA3 region of the hippocampus or impairment in spatial learning, memory, or sensorimotor function [18,19]. The only phenotypic consequences appeared to be an increased susceptibility to

Figure 1



(a) Timm staining of a coronal mouse brain section highlighting mobile zinc in the hippocampus (I), neocortex (II), and amygdala (III). **(b)** The fluorescent signal from Zinpyr-1 [59] exposes the high levels of mZn held within mossy-fiber terminals. **(c)** Diagram of a sampling of some presynaptic and postsynaptic targets of mZn.
(a) and (b) adapted from Ref. [38••].

limbic seizures [20]. The lack of an apparent phenotype in ZnT3 KO mice was perplexing because vesicular zinc is clearly localized to discrete regions of the brain (Figure 1a). These observations raised the question as to whether zinc was a neuromodulator or even released from vesicles upon stimulation [8,21,22•,23]. More recently, studies with older (≥3 months) ZnT3 KO mice revealed them to display impaired fear memory [24], accelerated age-dependent loss in cognitive ability [25••], and deficiencies in social and object recognition memory [26].

Despite the emergence of these mZn-dependent neurological phenotypes, their molecular mechanisms of action are poorly understood. The lack of a clear signal transduction mechanism can be attributed to the large number of potential targets of mZn (Figure 1c) [27]. For example, mZn is a potent inhibitor of protein-tyrosine phosphatases [28•]. It can also allosterically block NMDA receptors [29,30••], transactivate TrK B kinase [31,32], and modulate the function of AMPA and KAR receptors [11•,33]. mZn is also critical in the stabilization and formation of postsynaptic density [34,35•] and dictates the calcium sensitivity of glutamatergic vesicle release from presynaptic cells [36]. In addition, exogenously applied zinc activates a postsynaptic metabotropic zinc-sensing receptor, thereby inducing intracellular release of calcium via the ErK1/2-dependent pathway [37]. A subsequent study demonstrated that endogenous mZn could trigger ErK1/2-dependent signaling [38••]. In this study, a combination of *in vitro* and *in vivo* experiments revealed ZnT3 KO mice to have reduced levels of phosphorylated Erk in hippocampal mossy fiber terminals resulting from disinhibition of MAPK phosphatase [38••]. As a consequence, the ZnT3 KO mice were severely impaired in forms of memory that depend on hippocampal function, such as spatial working memory and contextual discrimination [38••]. One mechanism proposed by the authors entails mZn first being released into the synaptic cleft, only to reenter the presynaptic terminals where the temporary increase in cytosolic mZn concentrations inhibit MAPK phosphatase [38••]. Apart from the numerous protein targets, the complexity of mZn biology is underscored by a study that revealed both presynaptic and postsynaptic signal transduction mechanisms, a finding that may explain some of the controversies and apparent contradictions in the literature [39••]. Sorting out the activity of mZn will benefit from the answers to outstanding questions such as, how much mZn is released upon stimulation and how long does it remain in the synaptic cleft? Moreover, although several presynaptic and postsynaptic targets have been identified, details regarding downstream signal

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