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Review

Zinc and cortical plasticity

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ABSTRACT

The divalent cation zinc is an essential element, having both universal and specified functions throughout the body. In the mammalian telencephalon, zinc has extensive effects on neurotransmission, affecting receptor function and second messenger systems. Through these means, it is often postulated that zinc has a fundamental role in regulating cortical synaptic function. Given that plasticity, that is, the morphological and physiological alterations that occur within neurons, is a defining characteristic of the brain, it is of particular interest to examine the mechanisms by which zinc might be involved in this process. In this review, the neurobiological characteristics of zinc will be discussed, including its distribution and the processes by which its homeostasis is regulated. As well, the substantial effects zinc may have on neuronal functioning will be examined. Finally, evidence gathered from electrophysiological, behavioural, and anatomical experiments are utilized to argue for a role of zinc in cortical plasticity.

Contents

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Abbreviations: 5-HT, 5-hydroxytryptamine; ADP, adenosine diphosphate; AD, Alzheimer's disease; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; ATP, adenosine triphosphate; BDNF, brain derived neurotrophic factor; Ca-EDTA, calcium ethylenediaminetetraacetic acid; CaMKII, calcium/calmodulin-dependent protein kinases II; cAMP, cyclic adenosine monophosphate; CP94, 1,2-diethyl-3-hyrdocypyridin-4-one; DAG, diacylglycerol; DEDTC, diethyldithiocarbamate; EAAT, excitatory amino acid transporter; fEPSP, field excitatory postsynaptic potential; GABA, γ-aminobutyric acid; KA, kainic acid; IPSP, inhibitory postsynaptic potential; KO, knockout; LTD, long-term depression; LTP, long-term potentiation; MT, metallothionein; NMDA, N-methyl-D-aspartic acid; PKA, protein kinase A; PKC, protein kinase C; PMBSF, posteromedial barrel subfield; PPP, paired-pulse potentiation; SAMP10, senescence-accelerated-prone 10; SFK, Src family kinase; TFLZn, N-(6-methoxy-8-quinolyl)-p-carboxylbenzoylsulphonamide; TPEN, *N, N, N′, N′*-tetrakis(2-pyridylmethyl) ethylenediamine; Trk, tropomyosin-related kinase; TrkB, tropomyosin-related kinases B; UDP, uridine diphosphate; UTP, uridine triphosphate; VDCC, voltage-dependent calcium channel; ZnT, zinc transporter; ZIP, Zrt-Irt-like proteins

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1. Introduction

Throughout life, the structure and physiology of the mammalian cerebral cortex is in a state of constant flux. Although the relative magnitudes of the changes that occur vary depending on a number of factors, the propensity for these changes persists. The stimuli that regulate this malleability are similarly diverse, including processes that regulate development, damage and recovery mechanisms that are activated with injury, and the induction and maintenance of learning and memory. These changes are broadly labelled as plasticity and they govern the functioning of the brain, optimal or otherwise. Thus, in order to understand how the brain functions, it is of fundamental importance to understand how plasticity is induced and maintained. The factors that can regulate plasticity are numerous, dependent on the location, age, and stimuli, among others. Although some factors have been definitively shown to be integrally involved in the induction and/or maintenance of plasticity, evidence for some other factors is less clear. It is the intention of the present review, utilizing literature from anatomical, electrophysiological, and behavioural experiments, to clarify the role of the divalent cation zinc in plasticity.

2. The necessity of zinc

As an essential element, zinc is found in all cells and is necessary for life (Raulin, 1869; Prasad et al., 1963; King and Cousins, 2006). The ubiquity of zinc, along with the multitude of biological functions for which it is crucial, underlies the importance of this transitional metal. In addition to stabilizing hundreds of enzymes and other proteins, zinc also stabilizes the structure of DNA, RNA and ribosomes (MacDonald, 2000). Within the human genome, zinc-binding proteins account for nearly half of all proteins needed for transcription regulation (Tupler et al., 2001). In total, genes encoding proteins possessing binding sites for zinc account for approximately 8–10% of all genes in the human genome (Blasie and Berg, 2002; Cousins et al., 2006) Acting as a cofactor, zinc ensures the proper function of several hundred enzymes (Vallee and Falchuk, 1993). In these roles, zinc is able to potently regulate numerous processes within an organism, including but not limited to, DNA synthesis, wound healing, brain development, apoptosis, cell proliferation, and oxidative stress (Barceloux, 1999; Oteiza and Mackenzie, 2005; King and Cousins, 2006). While zinc performs essential functions that are present in nearly all cells, zinc also has specialized functions leading to its heterogenous distribution throughout the body.