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Zn^{2+} Modulates the Responses of Rat Dorsal Horn Neuron to C-Fiber Stimulation and Excitatory Amino Acids

Chang Hoon Ahn, Hong Kee Shin, and Jin Hyuk Kim

Department of Physiology, College of Medicine, Institute of Biomedical Sciences, Hanyang University, Seoul 133−791, Korea

Zinc contained in the neurons of central nervous system is activity-dependently released and then attenuates NMDA (N-methyl-D-aspartate)-induced neurotoxicity while augmenting non-NMDA-induced neurodegeneration. Zinc also has been reported to produce antinociceptive action on the inflammation- and nerve injury-induced hyperalgesia in the behavioral test. In this study, we investigated the effects of zinc on the responses of dorsal horn cells to NMDA, kainate and graded electrical stimulation of C-fibers. In the majority of WDR cells (70.6%), zinc current-dependently inhibited WDR cell responses to NMDA and in the remaining cells, produced biphasic responses; excitation followed by inhibition. Zinc augmented the responses of WDR cells to iontophoretical application of kainate. The dominant effect of Zn^{2+} on the responses of WDR cells to C-fiber stimulation was excitatory, but inhibition, excitation-inhibition and no change of the responses to C-fiber stimulation were induced. Ca^{2+}-EDTA antagonized the excitatory or inhibitory effects of Zn^{2+} on the WDR cell responses. These experimental findings suggest that Zn^{2+} modulates the transmission of sensory information in the rat spinal cord.

Key Words: Dorsal horn neuron, C-fiber stimulation, NMDA, Kainate, Zinc, Ca^{2+}-EDTA

INTRODUCTION

Zinc (Zn^{2+}) has been reported to be colocalized with excitatory amino acids in cerebellar granule neurons, amygdala, olfactory bulb, hippocampal, cortical and spinal neurons (Kozma et al, 1981; Frederickson & Danscher, 1990; Frederickson et al, 1992; Jo et al, 2000). Zinc stored in synaptic vesicles is released into synaptic cleft by high K^{+}, electrical stimulation, ischemia or epileptic discharges. The release of zinc is Ca^{2+}- and activity-dependent (Assaf & Chung, 1984; Aniksztejn et al, 1987; Takeda et al, 1999). In the specific disease-associated condition, zinc is known to selectively potentiate the neurodegeneration caused by kainate, AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) and ischemia, whereas NMDA (N-methyl-D-aspartate)-induced neurotoxicity is suppressed by zinc (Frederickson et al, 1989; Weiss et al, 1993; Freund & Reddig, 1994). Zinc released from the presynaptic vesicles is selectively concentrated in the degenerating postsynaptic neurons (Aniksztejn et al, 1987; Frederickson et al, 1989; Koh et al, 1996). Zinc influx into the degenerating neurons has been suggested to permeate voltage-dependent calcium channels (Weiss et al, 1991; Freund & Reddig, 1994) or calcium permeable AMPA/kainate channels (Yin & Weiss, 1995).

Zinc deficiency causes anorexia, slow wound healing, alopecia, dermatitis, growth retardation, hypogonadism (Prasad et al, 1963; Hesse, 1979), impairment of learning and memory (Halas et al, 1986), and also sensitizes nociceptive C-fibers (Izumi et al, 1995) which is caused by the increase in prostaglandin E_2 in the skin. In Zn^{2+}-deficient rats, field potentials evoked by stimulating mossy fibers was reduced and the depression of mossy fibers became severe in proportion to the degree of Zn^{2+} deficiency (Hesse, 1979).

Zinc has been reported to have antinociceptive

Corresponding to: Hong Kee Shin, Department of Physiology, College of Medicine, Hanyang University, 17 Haengdang-Dong, Sungdong-Gu, Seoul 133-791, Korea. (Tel) 82-2-2290-0612, (Fax) 82-2-2281-3603, (E-mail) shinhg@email.hanyang.ac.kr

action in the behavioral study. Zinc dose-dependently alleviates thermal and mechanical hyperalgesia induced by subcutaneous injection of complete Freund's adjuvant and lipopolysaccharide or partial injury of peripheral nerves, but do not have any effect on the thermal and mechanical sensitivity in the normal rat (Safieh-Garabedian et al, 1996; Liu et al, 1999). Zinc also has antinociceptive effect on acute pain model such as acetic acid writhing test, which is antagonized by zinc chelator, Ca^{2+}-EDTA (Larson & Kitto, 1997). In this study, the effects of iontophoretically applied zinc and zinc chelator on the dorsal horn cell responses to C-fiber stimulation and excitatory amino acids were investigated using the electrophysiological method.

METHODS

Sprague-Dawley male rats (300~450 gm) anesthetized with urethane (1.2 gm/kg i.p.) were used in this experiment. External jugular vein was cannulated with polyethylene tube (PE-60) through which pancuronium bromide (0.3 mg/kg/hr) was continuously infused to paralyze the musculature. The rats were artificially ventilated by a small animal ventilator (Model 683, Harvard Apparatus, USA) and end-tidal CO_2 level was maintained between 3.5 and 4.5% by adjusting respiratory rate and volume (End-tidal CO_2 analyzer, Capstar-100, IITC Inc.). Rectal temperature was maintained near 37°C with an electrical heating blanket (Harvard Apparatus, USA). A laminectomy was carried out to expose lumbar enlargement of spinal cord between T13 and L3. The common peroneal and tibial nerves were dissected from the surrounding tissues at popliteal fossa. Liquid paraffin pool was made around the exposed spinal cord and peripheral nerves to prevent drying. After finishing all these surgical procedures, the rats were placed in a stereotaxic apparatus.

The activities of dorsal horn neurons activated by electrical stimulation of the afferent nerves were extracellulary recorded with the central barrel of seven-barreled microelectrode that contained a low-impedance carbon filament. Once single unit activity of dorsal horn neuron was recorded, the type of neuron was classified according to the response pattern to mechanical stimuli applied to the receptive field. Wide dynamic range (WDR) cells, which responded to both innocuous and noxious mechanical stimuli were used in this experiment. One outer barrel of 7-barreled microelectrode was filled with 0.15 M NaCl and used for current balancing which makes the net current of all channels zero. The other barrels were used to apply the following substances by microiontophoresis; Zn^{2+} (0.2 M, Kanto Chemicals, Japan), Ca^{2+}-EDTA (ethylenediaminetetraacetic acid, disodium-calcium salt, 0.2 M, Sigma), NMDA (N-methyl-D-aspartate, 0.05 M, RBI) and kainate (0.015 M, RBI). pH of all solutions was 7.5~8.0. Retaining currents (5~10 nA) were used between drug applications to prevent drug leakage.

In each figure, the number next to, below or above the name of each drug applied shows the amount of ejection current (nA). The horizontal bars above each figure indicate the duration of iontophoretical applications. We first recorded the control responses of WDR cells to NMDA, kainate and graded electrical stimulation of afferent fibers and then investigated the changes in the control responses of WDR cells induced by a single or combined iontophoretical application of Zn^{2+} or Ca^{2+}-EDTA. NMDA or kainate was periodically ejected for 5 sec every 15 or 20 sec (Neurophore BH-2 System, Medical System Corp., USA). The C-fibers were activated by a train of three pulses (0.5 msec, 50 Hz) every 20 sec. The intensity of the stimuli was adjusted to activate all A- and C-fibers (200~300 T). T is times the threshold for activation of A fibers. The number of action potentials induced by an electrical stimulation of A- or C-fiber was differentially sampled according to the differences in the conduction velocity of A- and C-fibers (Chung et al, 1984).

All induced electrical activities were amplified (WPI DAM80), displayed on an oscilloscope and fed into a window discriminator (Frederic Haer & CO.) whose output was used by a computer to compile the poststimulus time histogram. Since the size of evoked responses varied from one unit to another, data were expressed as percentage of discharges in the control state before single or combined iontophoretic application of drugs. The data were expressed as mean ± SE. Statistical significance was determined by student's t test. P values less than 0.05 were considered significant.

RESULTS

In the 23 experiments, the responses of 63 WDR

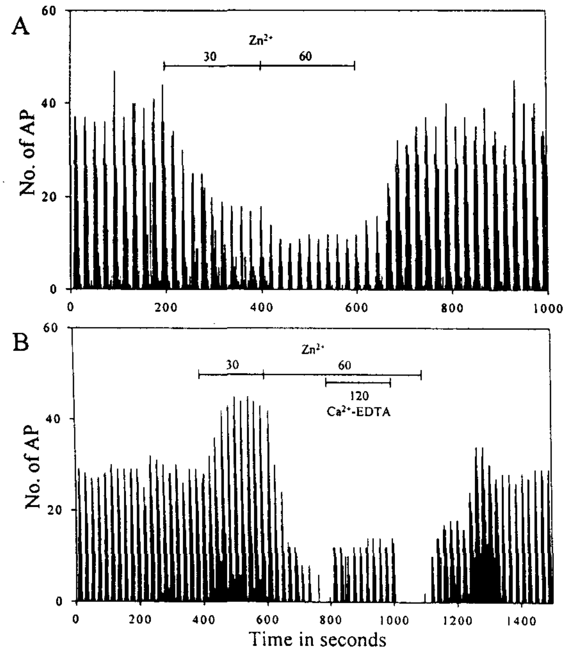

Fig. 1. Changes in the responses of WDR cells to NMDA (30 nA & 25 nA) following an iontophoretical application of zinc and the effect of Ca^{2+}-EDTA on the zinc-induced changes. The main effect of zinc on NMDA-induced responses was inhibitory (A). In other neurons, zinc induced biphasic responses: excitation followed by inhibition (B). The inhibitory effect of zinc was antagonized by Ca^{2+}-EDTA. No. of AP is number of action potentials induced by iontophoretical application of NMDA or other drugs. The number next to or below the name of each drug iontophoretically applied is the amount of ejection current.

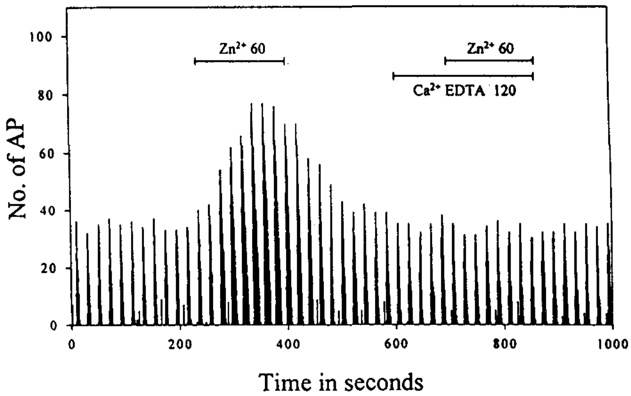

Fig. 2. Excitatory effect of zinc on the responses of WDR cells to kainate (20 nA) and the effect of Ca^{2+}-EDTA on the zinc-induced excitatory action. Ca^{2+}-EDTA strongly antagonized zinc-induced excitatory action.

cells were extracellulary recorded in the depth between 500 μm and 960 μm below the surface of lumbar enlargement of the rat spinal cord. Of the 3 responses of WDR cells to NMDA, kainate and electrical stimulation of C-fibers, 2 or 3 responses were recorded and tested in the same neurons in several cases. Iontophoretical application of zinc produced the inhibitory action on the NMDA-induced responses in 70.6% of WDR cells (N=14). In the remaining WDR cells (N=6), iontophoretical application of zinc ejected with low current produced the excitation, while zinc induced the inhibition of NMDA-induced responses at high ejection current. Zinc suppressed NMDA-induced responses to $48.9 \pm 7.3\%$ and $26.3 \pm 6.5\%$ of the control at the ejection current of 30 nA and 60 nA, respectively, and the inhibitory action was current-dependent (Fig. 1A). The inhibitory action of zinc was attenuated by zinc chelator, Ca^{2+}-EDTA ($P < 0.02$, Fig. 1B). Although the ejection current that produced the maximal excitation was different from one unit to another in the case of excitation-inhibition responses, the peak excitatory action ($136.0 \pm 8.3\%$ the control) was generally induced in the range of 30~60 nA (Fig. 1B).

The responses of WDR cells to kainate was strongly augmented by the iontophoretically applied zinc and this current-dependent excitatory action was also antagonized by Ca^{2+}-EDTA (N=6). Kainate-induced responses increased to $154.9 \pm 6.1\%$ and $214.2 \pm 13.5\%$ of the control after the application of zinc with the ejection current of 30 nA and 60 nA, respectively (Fig. 2).

The effects of zinc on the responses of WDR cells to electrical stimulation of C-fibers were variable. In 15 of 38 WDR cells tested, zinc induced the augmentations of C-fiber-induced responses, which were $126.0 \pm 3.6\%$ and $158.8 \pm 10.0\%$ of the control at an ejection current of 30 nA and 60 nA, respectively (Fig. 3A). Zinc also produced the inhibition (N=6) and excitation-inhibition (N=2) of C-fiber-induced responses (Fig. 3B & C). In the remaining 15 cells, zinc did not have any effect on the responses of WDR cells to C-fiber stimulation. Ca^{2+}-EDTA antagonized modulatory effects of zinc on the C-fiber responses ($P < 0.01 \sim 0.005$, Fig. 3).

Fig. 4 shows that zinc sometimes produced exceptionally strong inhibition of NMDA- (N=4), and C-fiber-induced (N=8) responses of WDR cells (Fig. 4). This inhibitory actions were not recovered for more than 20~30 min. The control responses to NMDA

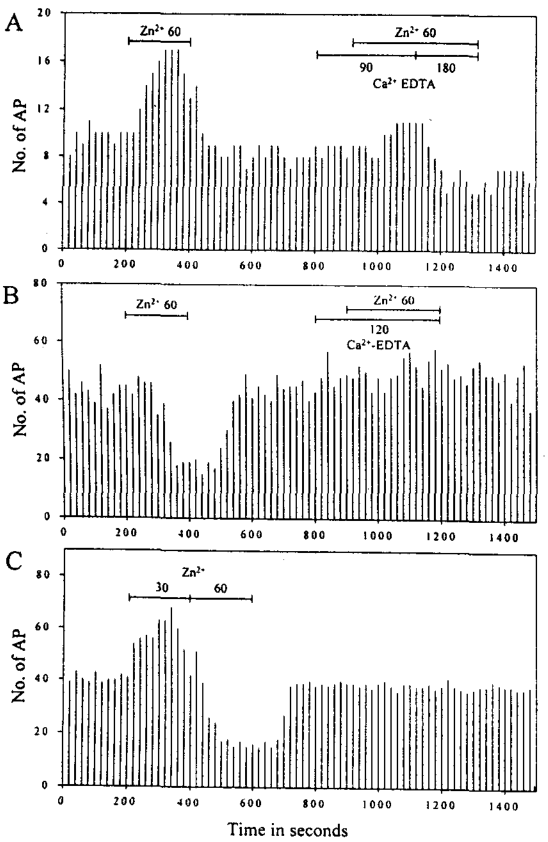

Fig. 3. Zinc produced the variable effects on the responses of WDR cells to C fiber stimulation. Zinc-induced excitatory (A), inhibitory (B) and excitatory-inhibitory effects (C) were strongly antagonized by Ca^{2+}-EDTA.

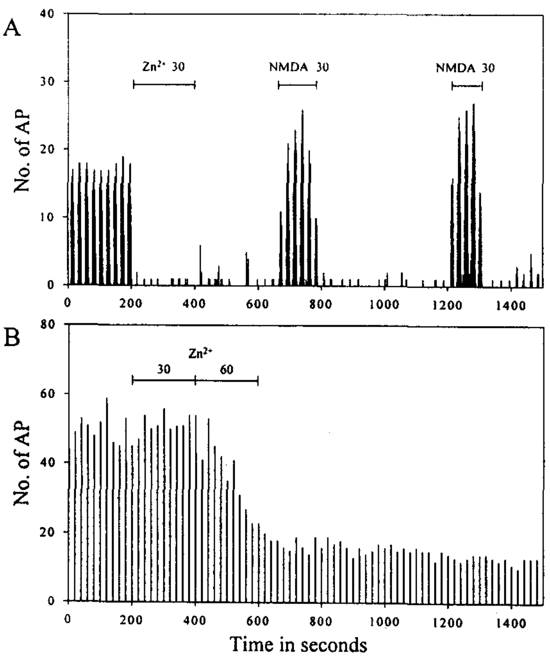

Fig. 4. Zinc-induced strong sustained inhibition of the responses of WDR cells to NMDA (A, 20 nA) and C fiber stimulation (B). In general, the zinc-induced suppressions were not recovered until 20 min after the termination of zinc application.

ejected with 20 nA were almost completely inhibited by zinc (30 nA), but the inhibited NMDA responses appeared again when the ejection current of NMDA increased to 30 nA (Fig. 4A). This strong inhibitory action of zinc seemed not to be attenuated by Ca^{2+}-EDTA.

DISCUSSION

Zinc is a divalent cation that is co-localized with excitatory amino acid in synaptic vesicles of central nervous system (Kozma et al, 1981; Frederickson & Danscher, 1990; Frederickson et al, 1992; Jo et al, 2000) and released in a Ca^{2+}- and activity-dependent manner (Assaf & Chung, 1984; Aniksztejn et al, 1987; Takeda et al, 1999). The concentration of zinc in synaptic vesicles was estimated to be 200 ~ 300 μM (Frederickson, 1989) and the limitation of zinc intake causes various deficiency symptoms including sensitization of nociceptive C-fibers, anorexia, dermatitis, slow wound healing, hypogonadism and growth retardation (Prasad et al, 1963; Hesse, 1979; Halas et al, 1986). Zinc has been reported to be implicated in many physiological functions, but its effect is a little different depending on its concentration and tissue preparation used. Although recent study reported that Zn^{2+}-containing nerve terminals were distributed in the spinal dorsal horn (Jo et al, 2000), the modulatory effect of zinc on the responses of dorsal horn neurons to afferent inputs has never been studied.

Zinc has been reported to have differential effects on the responses of neurons to NMDA and non-NMDA agonists. Zinc inhibits NMDA-induced excitation and neurotoxicity while dose-dependently potentiating the responses to AMPA and quisqualate (Peters et al, 1987; Frederickson et al, 1989; Christine & Choi, 1990; Rassendren et al, 1990; Freund & Reddig, 1994). In this study, zinc principally inhibited the responses of WDR cells to NMDA. However, in about 30% of WDR cells, zinc produced biphasic action on the NMDA-induced responses; potentiation at low ejection current and inhibition at high ejection current. This dual effect of zinc has never been reported. The potentiation by zinc of NMDA responses may be caused by zinc-induced increase in glycinergic current. Zinc of low concentration increases glycinergic current in the cultured rat spinal cord neurons (Bloomenthal et al, 1994; Laube & Betz, 1999). Glycine of nanomolar concentration has been reported to potentiate NMDA responses in neurons and *Xenopus* oocytes injected with rat brain messenger RNA (Kleckner & Dingledine, 1988). This potentiation is specific for the NMDA receptor because no effect was induced on kainate and quisqualate currents in neurons. The potentiating effect can also result from the reduction of inhibitory GABAergic current (disinhibition) that is induced by zinc (Dong & Werblin, 1995; Qian et al, 1997). However, it is not clear whether this disinhibitory mechanism is specific for NMDA response or not. Other inhibitory mechanisms for zinc-induced effect were reported. In the cultured rat hippocampal and cortical neurons, patch clamp recording of single channel revealed that zinc ions dose-dependently reduced opening frequency and mean open time of large conductance NMDA receptor without any effect on resting membrane potential (Christine & Choi, 1990; Legendre & Westbrook, 1990). Bath application of zinc strongly blocks voltage-activated Ca^{2+} current recorded from cultured rat dorsal root ganglion neurons and *Aplysia* abdominal ganglion neurons (Nishimura, 1987; Bsselberg et al, 1992), and inhibited in a concentration-dependent manner the NMDA-induced Ca^{2+} uptake in the cultured rat cerebellar granule cells (Eimerl & Schramm, 1993).

Kainate response of WDR cells was invariably potentiated by iontophoretical application of zinc in this experiment. However, there is no direct evidence showing what mechanism is implicated in the potentiating effect of zinc on kainate response. Experimental findings from kainate- and AMPA-induced neurotoxicity suggest that potentiation of kainate response may be mediated by Ca^{2+} and zinc influx through voltage-gated Ca^{2+} channel and/or Ca^{2+} permeable AMPA/kainate channels (Weiss et al, 1991; Freund & Reddig, 1994; Yin & Weiss, 1995). This suggestion is in sharp contrast with reported results that zinc dose-dependently inhibits Ca^{2+} current of neurons (Bsselberg et al, 1992). AMPA administered with zinc increases Ca^{2+} as well as zinc influx in cultured rat cortical neurons (Weiss et al, 1991), which contribute to the selective degeneration of neurons. The induced neurotoxicity is attenuated by CNQX (6-cyano-7-nitroquinoxaline-2,3-dione), EGTA (ethylene glycol tetraacetic acid) and Ca^{2+} channel blockers (Freund & Reddig, 1994). On the bases of these experimental findings, Freund & Reddig (1994) suggested that Ca^{2+} and zinc influxes through voltage-dependent Ca^{2+} channels triggered a series of responses leading to neuroexcitation and neurotoxicity. If this is the case, the increased intracellular calcium can activate PKC (protein kinase C) (Csermely et al, 1988) and zinc itself has been known to activate PKC. The increased PKC activity can induce a kind of excitatory responses in neurons.

The major effect of zinc on the C-fiber responses (N=15) was excitatory whereas the inhibitory action of zinc was also induced in 6 WDR cells. In general, zinc induced weaker effect on C-fiber responses than on the excitatory amino acid-induced responses. Since C-fiber responses recorded from WDR cells is induced, not by a single, but by multiple neurotransmitters released from primary afferent fibers, the mechanisms that are responsible for the action of zinc seems to be very complex. In addition to the excitatory and inhibitory mechanisms for NMDA and kainate responses discussed in previous section, these is no report on the effect of zinc on the responses of WDR cells to other neurotransmitters such as substance P and calcitonin gene-related peptide. An additional evidence responsible for the inhibitory action of zinc is that zinc inhibits neurotransmitter release at neuromuscular junction (Nishimura, 1987). This zinc-induced reduction of neurotransmitter release may contribute to the inhibitory action of zinc. On the other hand, Chung et al (2000) reported that zinc increased the excitability of dopaminergic neurons in rat substantia nigra by reducing 4-aminopyridine-sensitive outward current. If zinc also increases the excitability of dorsal horn neurons, this can be one of the factors responsible for the excitatory action of zinc.

Zinc sometimes induced exceptionally very strong and sustained inhibition of NMDA and C-fiber responses as seen in Fig. 4. At first, we took this strong inhibition for the wrong responses due to cell death, because we could not identify almost completely inhibited WDR cell activity for a very long time. However, we could confirm the inhibited cell activity by increasing ejection current in the later experiment as seen in Fig. 4A. Since the incidence of the exceptionally sustained inhibition was not so high, the systematic investigation on its mechanism was not carried out. So we could not explain the exact mechanism of this long-lasting inhibition, which needs further study.

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