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Commentary of "Copper Chaperone for Cu,Zn-SOD supplement potentiates the Cu,Zn- SOD function of neuroprotective effects against ischemic neuronal damage in the gerbil hippocampus"

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Reactive oxygen species (ROS), such as superoxide radicals, are known to cause oxidative stress contributing to the development of numerous pathological conditions including those in the central nervous system (CNS). Antioxidant enzymes, which are normal cellular defenses against ROS, scavenge these species to limit or prevent damage. The superoxide dismutases (SOD) are one family of antioxidant enzymes, which catalyzes the dismutation of superoxide radicals to oxygen and hydrogen peroxide [1]. This family of enzymes consists of cytoplasmic and nuclear CuZn-SOD [2], mitochondrial Mn-SOD [3], and extracellular SOD (EC-SOD) [4].

Among the SOD family, CuZn-SOD is the most abundant intracellular SOD, particularly in motor neurons [5]. The dysregulation of this SOD has been shown to lead to several diseases, such as amyotrophic lateral sclerosis [6–8], diabetes mellitus [9], Down Syndrome [10], and Parkinson's disease [11]. Similarly, studies have shown its ability to protect against neuronal cell death and oxidative injury following ischemia-reperfusion injury [12–14].

All three SOD enzymes require metal species at their active sites for full activity. Specifically, the activation of CuZn-SOD and EC-SOD require copper. Notably, the CNS has a limited capacity to bind free transition metals such as iron and copper [15]. These free transition metals are capable of participating in Fenton-like chemistry to produce the highly reactive hydroxyl radical. Thus, regulation of metal transfer to metal containing enzymes, such as the SODs is eminently important to inhibit Fenton-like chemistry. Importantly, the level of intracellular free copper is limited under physiological conditions due this reactivity and toxicity [16]. Therefore, copper chaperones are required to directly transfer copper to specific cellular targets [17,18]. Three copper chaperones have been identified to date [19]: Cox1, which delivers copper to cytochrome c oxidase in the mitochondria, copper chaperone for CuZn-SOD (CCS), and antioxidant-1 (Atox1), which delivers copper to secretory copper enzymes including EC-SOD [20].

Of these chaperones, the copper transfer and protein-protein interaction between CCS and CuZn-SOD is well characterized [18] and the regulation of CCS expression by cellular levels of copper has been noted [21]. Aside from its regulation, the activity of CCS has been shown to be necessary for CuZn-SOD activation *in vivo* [22] as well as its importation into the intermembrane space of the mitochondria [23].

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The manuscript by Hwang *et al.* [24] again highlights the importance of these copper chaperones. In this study, Hwang and colleagues used the Pep-1 peptide transduction domain [25] to show that ischemic neuronal damage could be attenuated by Pep-1-CuZn-SOD and that the protection was enhanced if CCS was given in addition to CuZn-SOD. These results were significant because they demonstrated that CuZn-SOD has a stronger neuroprotective effect when it is co-administered with its chaperone. This provides insight for potential novel therapies for ischemia-reperfusion injury as well as other oxidative injuries. Later, the importance of the copper chaperone CCS was confirmed *in vivo* in several CNS ischemia reperfusion injuries [24,26].

EC-SOD is another copper-containing SOD [4] that has been shown to have a wide variety of functions in the CNS including protection against ischemia reperfusion injury [27], vasogenic edema [28], and regulation of normal learning and memory [29–33]. Recently, Jeney *et al.* [20] showed that Atox1 was essential for the activity of EC-SOD and also positively regulates EC-SOD transcription illustrating its critical novel antioxidant function *in vivo*. Thus, targeting the copper chaperones that control the activity of EC-SOD may also be a beneficial approach for enhancing EC-SOD dependent responses in the brain

Overall, therapeutic approaches to limit oxidative stress and increase the activity of antioxidant enzymes, like SOD, may be beneficial in numerous neurological diseases. Targeting copper chaperones, which activate SOD enzymes and/or the SOD enzymes themselves, appears to be an effective mechanism for preventing oxidative damage and disease *in vivo*.

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