The human prion octarepeat fragment prevents and reverses the inhibitory action of copper in the $P2X_4$ receptor without modifying the zinc action

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Abstract

Human prion protein fragments ($PrP_{60–67}$ or $PrP_{59–91}$) prevented and reversed the inhibition elicited by 5 μM copper on the $P2X_4$ receptor expressed in *Xenopus laevis* oocytes. A 60-s pre-application of 5 μM copper caused a 69.2 ± 2.6% inhibition of the 10 μM adenosine triphosphate (ATP)-evoked currents, an effect that was prevented by mixing 5 μM copper with 0.01–10 μM of the PrP fragments 1-min prior to application. This interaction was selective, as $PrP_{59–91}$ did not alter the facilitatory action of zinc. The EC_{50} of $PrP_{60–67}$ and $PrP_{59–91}$ for the reduction of the copper inhibition were 4.6 ± 1 and 1.3 ± 0.4 μM, respectively. A synthetic $PrP_{59–91}$ variant in which all four His were replaced by Ala was inactive. However, the replacement of Trp in each of the four putative copper-binding domains by Ala slightly decreased its potency. Furthermore, the application of 10 μM $PrP_{59–91}$ reversed the copper-evoked inhibition, restoring the ATP concentration curve to the same level as the non-inhibited state. Fragment 139–157 of βA4 amyloid precursor protein also prevented the action of copper; its EC_{50} was 1.6 ± 0.1 μM; the metal chelator penicillamine was equipotent with $PrP_{60–67}$, but carnosine was significantly less potent. Our findings highlight the role of PrP in copper homeostasis and hint at its possible role as a modulator of synapses regulated by this trace metal.