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Title: Kaempferol protects against cadmium chloride-induced hippocampal damage and memory deficits by activation of silent information regulator1 and inhibition of poly (ADP-Ribose) polymerase-1

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ABSTRACT

The neuroprotective effect of Kaempferol against cadmium chloride (CdCl2) -induced neurotoxicity is well reported. The silent information regulator 1 (SIRT1) and poly (ADP-Ribose) polymerase-1 (PARP1) are two related cellular molecules that can negatively affect the activity of each other to promote or inhibit cell survival, respectively. It is still largely unknown if the neurotoxicity of CdCl2 or the neuroprotection of Kaempferol are mediated by modulating SIRT1 and/or PAPR1 activities. In this study,we tested the hypothesis that CdCl2-induced memory deficit and hippocampal damage are associatedwith downregulation/inhibition of SIRT1 and activation of PAPR1, an effect that can be reversed by co-treatmentwith Kaempferol. Rats (n=12/group) were divided into 4 groups as control, control+ Kaempferol (50 mg//kg), CdCl2 (0.5 mg/kg), and CdCl2 + Kaempferol. All treatments were administered orally for 30 days daily. As compared to control rats, CdCl2 reduced rat's final bodyweights (21.8%) and their food intake (30%), induced oxidative stress and apoptosis in their hippocampi, and impaired their short and long-term recognitionmemory functions. Besides, the hippocampi of CdCl2-treated rats had higher levels of TNF-α (197%), and IL-6 (190%) with a concomitant increase in nuclear activity and levels of NF-κB p65 (721% & 554%). Besides, they showed reduced nuclear activity (53%) and levels (74%) of SIRT1, higher nuclear activity and levels of PARP1 (292% & 138%), increased nuclear levels of p53 (870%), and higher acetylated levels of NF-κB p65 (513%), p53 (644%), PARP1 (696%), and FOXO-2 (149%). All these events were significantly reversed in the CdCl2 + Kaempferol-treated rats. Of note, Kaempferol also increased levels of MnSOD (73.5%), and GSH (40%), protein levels of Bcl-2 (350%), and nuclear activity (67%) and levels (46%) of SIRT1 in the hippocampi of the control rats. In conclusion, Kaempferol ameliorates CdCl2-induced memory deficits and hippocampal oxidative stress, inflammation, and apoptosis by increasing SIRT1 activity and inhibiting PARP1 activity.

Keywords: $CdCl_2$, Kaempferol, $SIRT_1$, $PARP_1$, Memory, Hippocampus, Rats