Newly Developed Oximes Reverse Malaoxon-Induced Mouse Cerebral Acetylcholinesterase Inhibition In Vitro

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Organophosphorus pesticides (e.g. malathion/malaoxon) are toxic compounds with strong inhibition potency toward acetylcholinesterase (AChE). The standard treatment to acute organophosphorus poisoning involves the administration of atropine as well as the use of oxime (commonly, pralidoxime) to reverse AChE inhibition. The objective of this study was to investigate the potency of newly developed oximes (K026, K027, K048, K074 and K075) to reactivate malaoxon-inhibited acetylcholinesterase in brain homogenates from Swiss male mice, comparing their effects with commonly used oximes (pralidoxima, HI-6, obidoxime, trimedoxime and metoxime). Homogenates were treated during 30 min with 3 µM malaoxon (IC50 of malaoxon on AChE) and with crescent oximes concentrations (0 – 200 µM) during 10 min. After incubation, aliquots were taken to measure AChE activity. The results demonstrated that trimedoxime (47%), obidoxime (34%), K075 (32%) and K074 (30%) displayed significant reactivation efficacy against malaoxon-induced AChE inhibition at the concentration of 200 µM. The other evaluated oximes displayed only modest reactivation effects (less than 20%). Dose-response studies showed that the observed reactivating effects were dependent on the oximes concentrations. Our results demonstrated that the newly developed oximes, K074 and K075, and commonly used oximes, obidoxime and trimedoxime, are able to significantly reverse malaoxon-induced acetylcholinesterase inhibition in mouse brain homogenates. Since these effects were higher when compared to the standard oxime pralidoxime, the newly developed oximes appear to be promising molecules for pharmacological in vivo studies on the antidotal treatment of acute malathion poisoning.

Keywords: acetylcholinesterase, Malaoxon, oximes.