A Toxidromic Approach for Chemical Medical Countermeasure Development

Soman-Induced Cell Death and Neuroinflammatory Response in Human Acetylcholinesterase Knock-in Carboxylesterase Knockout Mice

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Chemical warfare nerve agents (CWNAs) are acetylcholinesterase (AChE) inhibitors that lead to pharmacoresistant status epilepticus (SE) and severe neuropathology when treatment is delayed. Some organophosphorus CWNAs such as soman (GD) also inhibit carboxylesterase (CaE), which acts as a bioscavenger to reduce the toxicity of GD. Unlike humans, rodents have plasma CaE activity. A novel humanized mouse strain was used in this study in which the gene expressing serum CaE was interrupted and cross-bred with a mouse strain in which the gene expressing AChE was altered to express the amino acid sequence of the human form of the same protein. This AChE KI/ES1 KO (KIKO) mouse strain might better model human GD exposure compared to wildtype rodents. A model of treatment of soman exposed KIKO mice with standard medical countermeasures [atropine sulfate, an oxime (HI-6) and a benzodiazepine (midazolam)] was implemented to assess adjunct therapies for neuroprotective potential against soman exposure. Methods. KIKO mice implanted with telemetry transmitters for continuous EEG recording were exposed subcutaneously to a seizure-inducing dose of GD and treated with an admix (ip) of atropine sulfate and HI-6 at 1 min after exposure, and with midazolam at 15 min after onset of behavioral seizure. Mice euthanized at 24 h after GD exposure were evaluated for cell death using fluorojade B and activated microglia using Iba1. Additional measures include duration of GD-induced seizure activity and, at longer time points, the development of spontaneous recurrent seizures following administration of anticonvulsant treatments adjunct to midazolam. Results. Delayed midazolam treatment was unable to rapidly terminate EEG seizure activity but did not prevent cell death or neuroinflammatory responses following GD exposure. Conclusions. This study further demonstrates that midazolam shortly after onset of toxic signs is not fully protective against the GD-induced SE, neuropathology, and neuroinflammatory responses, exemplifying the need for adjunct antiepileptic treatment. Research was supported by DTRA-JSTO. The views expressed are solely those of the authors and do not necessarily represent the official views of the CCRP, NIAID, NIH, HHS, USAMRICD or DoD. The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense, and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended.