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Neuroinflammatory responses in a mouse model of acute organophosphate intoxication

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Abstract

Organophosphates are a class of synthetic, neurotoxic compounds that include nerve agents and pesticides that can cause convulsions, *status epilepticus* (SE), and death following acute intoxication. The current standard of care for OP intoxication can prevent mortality; however, survivors often exhibit persistent neuropathologic changes and cognitive deficits. These observations underscore the need for improved therapies. Currently available preclinical models of acute OP intoxication almost exclusively use rats or guinea pigs, two species for which there currently are limited numbers of available transgenic lines. To overcome this limitation, we have developed a mouse model of acute OP intoxication using the OP pesticide diisopropylfluorophosphate (DFP). Within minutes after a single injection of DFP, adult male C57BL/6 mice displayed robust behavioral seizures consistent with the induction SE. At 1, 7, 14, and 28 days post-intoxication, animals were euthanized, and the brains were removed for FluoroJade C labeling to quantify neurodegeneration, and GFAP/S100β or IBA1/CD68 immunohistochemistry to quantify reactive astrogliosis and microglial activation, respectively. A significant increase in neurodegeneration, reactive astrogliosis, and activation of microglia was observed in the somatosensory cortex, hippocampus, and piriform cortex of DFP mice relative to vehicle controls. These findings identify mice as a sensitive platform for the investigation of DFP-induced neurological consequences that recapitulate the patterns of injury observed in widely used preclinical models. The availability of genetically modified mouse strains will provide unique opportunities to elucidate the molecular mechanisms contributing to the pathophysiology of acute OP intoxication, which will provide insight regarding more effective targets for therapeutic intervention.

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