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Early Brain Transcriptional Signatures of Adult Male Rats with Differential Seizure Responses to Acute Organophosphate Intoxication

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Abstract: Acute organophosphate (OP) poisoning poses a significant public health risk through chemical warfare, accidental exposure, and suicide attempts. OPs inhibit acetylcholinesterase, triggering a cholinergic crisis marked by parasympathomimetic symptoms, respiratory distress, and seizures that may progress to status epilepticus (SE). Survivors often develop chronic neurological deficits despite treatment with atropine, an oxime, and midazolam (MDZ), which, while effective at controlling seizures, does not prevent long-term neurological damage. In a diisopropylfluorophosphate (DFP) rat model, approximately 13% of animals (low responders, LR) do not develop SE, whereas 87% (normal responders, NR) progress to SE. To elucidate seizure-independent mechanisms underlying chronic neurotoxicity, we performed RNA-sequencing on multiple brain regions—the hippocampus, piriform cortex, and cerebellum—in LRs, NRs, and MDZ-pretreated animals. Hierarchical clustering revealed distinct transcriptomic profiles, largely independent of sex. Notably, NR animals exhibited marked upregulation of TGF β signaling (e.g., *Tgfb1*, *Stat3*, *c-fos*, *Jak1*) and neuroinflammatory genes (e.g., *Cd11b*, *Gfap*, *Cd68*), suggesting a maladaptive immune response likely driven by severe seizure activity. In contrast, MDZ pretreatment attenuated these responses and reduced genes associated with protein stabilization and endoplasmic reticulum stress. These findings identify potential therapeutic targets for mitigating chronic OP-induced neuropathology and suggest seizure severity is a significant driver of neuroinflammation.

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