WG 1 (Chemical, Biological, Radiological and Nuclear materials)

Bridging the Gap: Utilizing Sarin Induced Brain Damage to Translate Proteomic Technologies into Clinical Applications

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Proteomics has emerged as a powerful tool for characterizing toxicant-induced pathologies, providing comprehensive datasets that include protein expression profiles, pathway alterations, and molecular interactions. However, the translation of these extensive datasets into practical clinical applications, such as diagnostic tools and targeted therapies, remains a major challenge. In this study, we employed a sarin exposure model to investigate long-term neurotoxic effects. Sarin is a highly toxic volatile AchE inhibitor that rapidly induces seizures, which result in prolonged abnormal brain activity and damage. Rats were exposed to sarin (1.2LD50. i.m.) and were treated with TA (TMB-4, atropine;1 min post exposure i.m.) resulting in acute seizures and abnormal behavior 2 weeks post-exposure. Three weeks post-exposure histological analysis revealed severe brain deficit. At that time point their brain tissues were dissected into cortical and hippocampal regions, followed by protein extraction and mass spectrometry-based proteomic analysis.
In an effort to decipher this long-term damage and establish novel therapeutic options, we focused on understanding proteomic alterations in the rat brain three weeks post-sarin exposure. Bioinformatics and artificial intelligence-driven computational tools were applied to process and interpret the data, enabling the identification of region-specific and shared proteomic signatures. Our analysis revealed 333 cortical proteins and 227 hippocampal proteins with elevated expression levels after sarin exposure compared to naïve. We delineated key molecular pathways involved in sarin-induced neurotoxicity and identified novel biomarkers for monitoring exposure-related damage. Furthermore, we leveraged these insights to map protein expression patterns to known pathologies, facilitating disease classification and prediction of clinical outcomes. Finally, we proposed therapeutic strategies, including broad-spectrum treatment approaches as well as targeted interventions aimed at specific dysregulated proteins.
This study demonstrates the potential of integrating advanced proteomics with computational analytics to bridge the gap between molecular research and clinical application, paving the way for improved diagnostics and precision medicine in sarin induced brain damage and neurological pathology.

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Improving Ocular Treatment Strategies for Organophosphate Nerve Agent-Induced Pathology

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Background and purpose:
Ocular exposure to organophosphate (OP) irreversible acetylcholinesterase inhibitors, results in long-term miosis and visual impairment. This study aims to improve an anti-cholinergic treatment that effectively mitigates miosis and visual impairment induced by the nerve agent's sarin and VX while minimizing adverse effects.
Experimental approach:
Rat pupil width and light reflex were measured from 15 min up to two weeks following whole-body or topical OP exposure. Treatments including topical atropine or tropicamide or an intramuscular administration of TMB-4 and atropine (TA) were evaluated using the topical OP model. Visual function following exposure and treatment was evaluated using a cued Morris water maze test.
Results:
Whole body exposure to sarin or VX induced a dose-dependent miosis, observed even at one-hundredth or one-fortieth of the LCt50, respectively. Similarly, topical exposure to sarin or VX presented a dose-dependent miosis and a significant visual impairment post exposure and thus was used as a model for treatment evaluation. Treatment with 0.1% and 0.5% (w/v) atropine effectively mitigated miosis and visual impairment in OP exposed eyes with minimal adverse effects of mydriasis on exposed and non-exposed eyes, outperforming 1% atropine which induced long term mydriasis. Intramuscular TA or 2 topical drops of tropicamide were sufficient to counteract sarin-induced ocular impairment. However, for VX exposure, additional topical treatment with 0.1 or 0.5% atropine was required.
Conclusions and complications:
Commercially available 0.5% atropine eye drops effectively mitigated ocular insult caused by VX or sarin exposure with minimal adverse effects and should be considered a universal treatment for such intoxication. The findings also emphasize the need for supplementary ocular treatment in addition to the systemic treatment in visually impaired casualties following VX exposure.