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## Quantitative proteomic analysis of the Guinea Pig Brainstem following exposure to Sarin

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**Background:** Sarin (O-isopropyl methylphosphonofluoridate; GB) is a toxic organophosphorus (OP) nerve agent developed during WWII. It has been used in both military andcivilian attacks, and reports suggest its use in the ongoing Syrian civil war. It is apotent inhibitor of acetylcholinesterase (AChE). The brainstem controls breathingand circulation, among other processes, and asphyxiation is typically the cause ofdeath from GB poisoning.

**Study Objective:** To analyze changes in the guinea pig brainstem proteome and corresponding biological reactome following acute sarin exposure, to gain insight into the distinct brain toxicological responses that impact respiratory and cardiovascular control.

**Methods:** A total of eight female guinea pigs (n=8) were divided into two groups: A) non-treated control group (n=4), and B) animals exposed to 2xLD50 sarin in 0.9% saline by subcutaneous injection (n=4). Analysis included observations of clinical parameters, blood pathology, and proteomic analysis of dissected brain stems upon death at 30 min exposure. Brainstem tissue was lysed and processed by tryptic digest and isobaric tags (iTRAQ) labeling. Sampleswere separated on a Waters NanoUPLC prior to ThermoLTQ Orbitrap Velosanalysis (LC-MS/MS). Western blotting was performed as a confirmation of the MS data.

**Results:** The iTRAQMSrelative peptide quantitation detected 198 proteins, of which 23.23% were upregulated and 18.18% were downregulated following sarin exposure. Direct gene ontology (GO) analysis of the MS-identified proteins using GO terms for "cellular compartments" and "biological processes", together with functional interaction (FI) network predictions using the Reactome FI application of Cytoscape 3.0.2. revealed novel and validated signaling pathway interconnections. The gained information will aid in understanding of the complex cellular proteomic responses following high dose sarin for development of higher efficiency therapeutics against sarin poisoning.

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