MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

Dose-dependent Effects Of Fentanyl In Mouse Cortex: An Integrative Mrna-mirna Profiling Approach

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Fentanyl exposure and overdose are growing concerns in public health and occupational safety. Overdose deaths from fentanyl has surpassed all other opioids combined and was the leading cause of mortality in individuals aged 18-45 in the United States in 2020 and 2021. The abuse of fentanyl and its potent derivatives impose severe risk to the exposed military combatants. Opioid-induced respiratory depression causes brain hypoxia that contributes significantly to the toxic effects associated with fentanyl. The overdose lethality of fentanyl could be explained by its ability to saturate μ-opioid receptors in the brain and showing high resistance to naloxone treatment, unlike classical opioids like morphine, codeine, and heroin. However, the molecular mechanisms driving such biological assault across the tissues, particularly in the brain are yet obscure. Research presented will include establishing the parameters for an integrative analysis of mRNA-miRNA profiles using fentanyl in an SKH1 mouse model to explore brain-specific transcriptomic changes. The objective of this study is to understand the longitudinal profile of cortical gene functions associated with increasing doses of fentanyl. Current work is focused on the cortex region of brain as it plays a vital role in regulating pain management and sensory functions.

To address this knowledge gap, SKH1 mice were subcutaneously administered fentanyl citrate in Ringer's solution at Lowest observe effect level (LOEL - 62 mg/kg), LD10 (110 mg/kg) or LD50 (135 mg/kg) doses before data collection at 40 mins, 6h, 24h and 7d post-exposure. A comprehensive PET and ICD imaging data of this model demonstrated that fentanyl exposure significantly affected the cortex region and showed a greater reduction in brain's activity at 6h post-exposure. Whole mouse genome microarray data was first probed by unsupervised Principal Component Analysis (PCA) and showed dose dependent separations among the mice at 40 mins, 6h and 24h post-exposure, respectively; but at 7d post-exposure, no clear separation was observed. Likewise, the longitudinal separations were evident in LD10 and LD50 cohorts, but not in LOEL. This observation corroborated with the fact that the fentanyl exposure is both time and dose dependent. Acute assaults of high doses of fentanyl differentially impacted the cortex gene profile. A 2-way ANOVA was computed to curate those gene profiles that were significantly altered by the co-factors, namely dose and time. Applying the cut-off at p| 1.5|, we curated 48, 313 and 530 differentially expressed genes (DEGs) due the effects of dose, time, and their cumulative effects (dose x time). Supervised analysis mined those gene sub-families that demonstrated shifts in expression values in sync with increasing dose or time delay. Functional analysis of DEGs identified networks linked to genotoxicity, necrotic and apoptotic cell death mechanisms, and myelination signaling pathway. Further analysis performed using mRNA-miRNA duplex revealed that fentanyl exposure induced a damage to the central and peripheral nervous system and led to neuronal myelin degeneration. A time- and dose-sensitive dynamics of gene functions threw light on fentanyl driven biomechanisms. Validation work and additional omics assay are underway to present a confirmatory holistic picture.