Kallikrein-Kinin System Modulation to Preserve Neurovascular Integrity After Organophosphate Exposure

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Organophosphate (OP) exposure affects millions worldwide due to life-threatening and possibly irreversible symptoms. Neurological injury often persists after treatment, suggesting non-cholinergic effects may contribute to endothelial dysfunction and blood-brain barrier (BBB) permeability. This research aimed to investigate how chlorpyrifos-oxon (CPF-oxon) disrupts brain endothelial cells (bEnd.3), and whether they are modulated by the kallikrein-kinin system (KKS). BEnd.3 cells were exposed to concentrations of CPF-oxon (1-100 μM), with or without kinin agonists (bradykinin, Lys-des-Arg?-bradykinin) and the bradykinin B2 antagonist HOE-140, with DMSO as a control. Cell viability was assessed using MTT assay, cytoskeletal integrity was evaluated via phalloidin staining assay, CPF-oxon bioactivity was assessed using enzymatic AChE assay, and mitochondrial respiration was evaluated via Seahorse assay. Pathway analysis and molecular docking were performed to explore off-target interactions along with ADMET to determine HOE-140's repurposing potential. CPF-oxon did not reduce viability under tested conditions, bioactivity of CPF-oxon was confirmed by AChE inhibition, and no detectable changes in F-actin fluorescence were observed. However, Seahorse assay revealed HOE-140 significantly decreased basal respiration, ATP production, and spare respiratory capacity. Computational analyses supported interactions between CPF-oxon and endothelial pathways. HOE-140 demonstrated repurposing potential according to ADMET and appears to behave as an inverse agonist. These findings suggest OP-induced BBB dysfunction may be driven by metabolic disruptions rather than cytoskeletal collapse, highlighting the KKS as a novel target for mitigating neurovascular injury upon OP exposure.

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