Apoptotic and necrotic basal forebrain cholinergic neuronal loss after acute and long-term chlorpyrifos exposure.

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INTRODUCTION

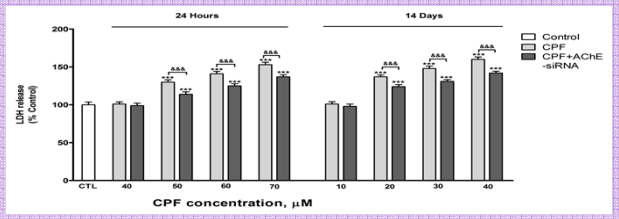
Chlorpyrifos (CPF) is an organophosphate insecticide reported to induce both after acute and repeated exposure learning and memory dysfunctions, although the mechanism is not completely known. CPF produces basal forebrain cholinergic neuronal loss, involved on learning and memory regulation, which could be the cause of such cognitive disorders. This effect was reported to be mediated through apoptotic process, although neuronal necrosis was also described after CPF exposure. Accordingly, we hypothesized that CPF induces basal forebrain cholinergic necrotic and apoptotic cell death.

METHODS

We evaluated in septal SN56 basal forebrain cholinergic neurons, the CPF effect after 24 h and 14 days exposure on the necrosis induction and the apoptotic and necrotic gene expression pathways.

RESULTS

This study shows that CPF induces after acute and long-term exposure necrotic cell death at higher concentrations than which induces apoptotic cell death and it was partially reverse by AChE silencing as apoptosis does. Evaluation of cell death pathways revealed that some of them are altered at lower concentrations than which produces the effects observed and below the No Observed Adverse Effect (NOAEL).



CONCLUSIONS

The present finding suggests that the use of gene expression profile could be a more sensitive and accurate way to determine the NOAEL.

Cell death pathways (24 h treatment)	
Genes disrupted (0.01µM)	**Genes disrupted (30 µM)**
PRO-APOPTOSIS ↑: TNF, TNFRSF1A, TNFRSF10A y TNFRSF11B.	PRO-APOPTOSIS ↑: CD40, CD40LG, FAS, FASLG, TNF, TNFRSF10A, TNFRSF1A, TNFRSF11B, GADD45A, TP53, BAX, BCL2L11, CASP1, CASP3, CASP7 y CASP9
ANTI-APOPTOSIS ↑: TRAF2, BICR2 y BIRC3.	ANTI-APOPTOSIS ↑: TRAF2 y BCL2Ll ↓: BICR2 y BIRC3,
NECROSIS ↑: MAG, S100A7A y KCN1P1	NECROSIS ↑: KCN1P1, MAG y S100A7A

Cell death pathways (14 treatment days)	
Genes disrupted (0.01µM)	**Genes disrupted (30 µM)**
PRO-APOPTOSIS ↑: TNF, TNFRSF1A, TNFRSF10A y TNFRSF11B	PRO-APOPTOSIS ↑: CD40, CD40LG, FAS, FASLG, TNF, TNFRSF10A, TNFRSF1A, TNFRSF11B, GADD45A, TP53, BAX, BCL2L11, CASP1, CASP3, CASP7 y_CASP9
ANTI-APOPTOSIS ↑: TRAF2, BICR2 y BIRC3	ANTI-APOPTOSIS ↑: TRAF2 y BCL2L1. ↓: BICR2 y BIRC3.
NECROSIS ↑: MAG, S100A7A y KCN1P1	NECROSIS ↑: ATP6VG2, BMF, CLORF159, CCDC103, COMMD4, CTSB, STSS, CYLD, DEFB1, DPYSL4, FOXIL1, GRB2, HSPBAP1, JPH3, PARP1, PARP2, PIK3C3, PVR y TXNL4B. ↓: GALNTL5, OR10J3, KCN1P1, MAG y S100A7A