SOCIÉTÉ FRANÇAISE DE MYOLOGIE
14èmes Journées de la Société Française de Myologie
23 - 25 NOV. 2016 BORDEAUX

MF23 : Induction of severe acute organophosphorus poisoning at the muscle level : what could we learn from zebrafish ?

Auteur présentateur : Patrick BABIN
p.babin@gpp.u-bordeaux1.fr

Co-auteurs : FARIA M, PRATS E, PADRÓS F , GARCIA-REYERO N, ARICK II M, RIAL E, SEBASTIÁN D, ZORZANO A, KNOLL-GELLIDA A, BABIN PJ, RALDÚA D

Adresse :
MRGM, Université de Bordeaux, INSERM U1211, - Allée Geoffroy St-Hilaire, Bat. B2, 2ème étage, CS 50023,
33615 Pessac cedex

Mots clés : organophosphorus, poisoning, muscle et animal model

Résumé :
Organophosphorus (OP) compounds are a class of acetylcholinesterase (AChE) inhibitors used not only as pesticides or in the industry, but also as chemical warfare nerve agents. In the present study we have generated and validated zebrafish models for mild, moderate and severe acute OP poisoning by exposing zebrafish larvae to different concentrations of the prototypic OP compound, chlorpyrifos-oxon (CPO). CPO induced concentration-dependent inhibition of AChE and the expression of three different phenotypes, mild (grade 1), moderate (grade 2) and severe (grade 3). Grade 2 was the most prevalent phenotype within the 0.75-1.50 µM range of CPO concentrations and larvae exhibited integrity impairment of axial muscle fibres. Grade 2 larvae were unable to swim and their touch motor response was fully abolished. AChE inhibition was an upstream event in the toxic pathways that resulted in hypercontracture of the axial muscles which was not related with calcium overload or ATP depletion. Grade 3 was the most prevalent phenotype at high CPO concentrations. It was characterized by an irreversible widespread necrosis of the axial muscle fibres. RNA-seq and pharmacological analyses supported the hypothesis that after initial cholinergic overstimulation, an influx of extracellular Ca2+ through NMDA receptors occurs and that the increase in the cytoplasmic levels of Ca2+ in animals with a compromised Ca2+ buffer capacity resulted in the uncontrolled activation of proteases, phospholipases and kinases. Our results show that zebrafish models mimic most of the pathophysiological mechanisms behind this toxidrome in humans. The suitability of the zebrafish larvae to in vivo high-throughput screenings of small molecule libraries makes these models a valuable tool for identifying new drugs for multifunctional drug therapy against acute organophosphorus poisoning.
Financial support: NATO Science for Peace and Security Programme (MD.SFPP 984777).