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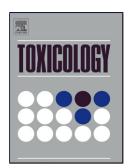
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ACCEPTED MANUSCRIPT

Cholinesterase and phenyl valerate-esterase activities sensitive to organophosphorus compounds in membranes of chicken brain

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Abstract

Some effects of organophosphorus compounds (OPs) esters cannot be explained by action on currently recognized targets acetylcholinesterase or neuropathy target esterase (NTE). In previous studies, in membrane chicken brain fractions, four components (EP α , EP β , EPy and EP δ) of phenyl valerate esterase activity (PVase) had been kinetically discriminated combining data of several inhibitors (paraoxon, mipafox, PMSF). EPy is belonging to NTE. The relationship of PVase components and acetylcholine-hydrolyzing activity (cholinesterase activity) is studied herein. Only EPα PVase activity showed inhibition in the presence of acetylthiocholine, similarly to a noncompetitive model. EP α is highly sensitive to mipafox and paraoxon, but is resistant to PMSF, and is spontaneously reactivated when inhibited with paraoxon. In this papers we shows that cholinesterase activities showed inhibition kinetic by PV, which does not fit with a competitive inhibition model when tested for the same experimental conditions used to discriminate the PVase components. Four enzymatic components (CP1, CP2, CP3 and CP4) were discriminated in cholinesterase activity in the membrane fraction according to their sensitivity to irreversible inhibitors mipafox, paraoxon, PMSF and iso-OMPA. Components CP1 and CP2 could be related to $EP\alpha$ as they showed interactions between substrates and similar inhibitory kinetic properties to the tested inhibitors.

Keywords: cholinesterase; phenyl valerate esterase; PMSF; mipafox; paraoxon; iso-OMPA

1. INTRODUCTION

Exposure to organophosphorus (OP) esters can cause several toxic effects, including acute cholinergic clinical episodes, intermediate syndrome, organophosphate-induced delayed neuropathy (OPIDN) and chronic neurological effects. The immediate effects of exposure to high levels of OPs involve inhibition of acetylcholinesterase, and they are well documented. Inhibition of acetylcholinesterase brings about changes in functions in central and peripheral nervous systems. However, the effects of long-term low doses exposure are controversial and not well known. (Sogorb et al., 2010).

Some OPs induce OPIDN after acute exposure associated with neuropathy target esterase (NTE) inhibition, followed by the so-called "aging reaction" (Williams and Johnson, 1981; Johnson, 1982). NTE is a membrane protein and chicken is the animal model, and extensive studies have been conducted into chicken brain and peripheral nerve that have used OPs compounds. NTE have been operationally measured as the PVase activity that resistant to paraoxon and sensitive to mipafox. The test involves assaying PVase activity in 2 conditions: (B) 20/30 min preincubation with 40 μ M paraoxon; (C) preincubation with 40 μ M paraoxon and 50 μ M mipafox, being NTE activity the difference B-C.

A neurotoxic syndrome called "Intermediate syndrome" has been described after acute cholinergic crisis, which has been interpreted as the result of pre- and postsynaptic disruptions of

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