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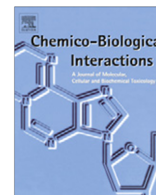

Interactions of neuropathy inducers and potentiators/promoters with soluble esterases

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ABSTRACT

Organophosphorus compounds (OPs) cause neurotoxic disorders through interactions with well-known target esterases, such as acetylcholinesterase and neuropathy target esterase (NTE). However, the OPs can potentially interact with other esterases of unknown significance. Therefore, identifying, characterizing and elucidating the nature and functional significance of the OP-sensitive pool of esterases in the central and peripheral nervous systems need to be investigated. Kinetic models have been developed and applied by considering multi-enzymatic systems, inhibition, spontaneous reactivation, the chemical hydrolysis of the inhibitor and "ongoing inhibition" (inhibition during the substrate reaction time). These models have been applied to discriminate enzymatic components among the esterases in nerve tissues of adult chicken, this being the experimental model for delayed neuropathy and to identify different modes of interactions between OPs and soluble brain esterases. The covalent interaction with the substrate catalytic site has been demonstrated by time-progressive inhibition during ongoing inhibition. The interaction of sequential exposure to an esterase inhibitor has been tested in brain soluble fraction where exposure to one inhibitor at a non inhibitory concentration has been seen to modify sensitivity to further exposure to others. The effect has been suggested to be caused by interaction with sites other than the inhibition site at the substrate catalytic site. This kind of interaction among esterase inhibitors should be considered to study the potentiation/promotion phenomenon, which is observed when some esterase inhibitors enhance the severity of the OP induced neuropathy if they are dosed after a non neuropathic low dose of a neuropathy inducer.

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1. Introduction

1.1. Esterases as targets of organophosphorus toxicity

Organophosphorus compounds (OPs) cause several neurotoxic disorders in humans [1]. Acute cholinergic toxicity is caused by covalent organophosphorylation on serine at the acetylcholinesterase catalytic center. Organophosphate-induced delayed neuropathy (OPIDN) is a neurodegeneration observed in humans, for which adult chicken is the most sensitive experimental species, and it is caused by the inhibition and subsequent aging (e.g., net dealkylation) of the membrane protein called neuropathy target esterase (NTE) [2]. Esterase inhibitors such as phenylmethylsulfonyl fluoride (PMSF) have proven capable of enhancing the severity of the OPIDN when animals are dosed after a low non neuropathic dose of a neuropathy inducer. This phenomenon is known as potentiation or promotion of neuropathy [3,4]. The term "promotion" has been suggested for this special class of potentiators because in this case the potentiation effect needs a sequential interaction, first with the substance causing the first chemical insult (the "inducer") and then with the second one ("the promoter"), using a similar nomenclature to that used in carcinogenesis. Changing the order of dosing does not cause potentiation; on the contrary, PMSF protects, thus avoiding a severe degeneration when PMSF if it is used before a high neuropathic dose of an inducer. The target of the potentiation/promotion effect remains unknown, although a soluble fraction of esterases described in our laboratory [5] has been suggested to be implicated [6].

Actions on currently recognized targets cannot explain the neurological and neurobehavioral effects reported in animals and humans caused by low-level long-term OP exposure [7–9]. Many proteins showing esterase activity other than cholinesterases and NTE have the potential for interaction with OPs. Therefore, identifying, characterizing and elucidating the nature and functional significance of the OP-sensitive pool of esterases in the central and peripheral nervous systems is an important research task to not only understand how low levels might affect cognitive effects, but to also design prevention and therapy strategies, which need investigating [10,11,12–14].

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Kinetic models have been developed and applied to study complex biological preparations by considering multi-enzymatic systems, inhibition, spontaneous reactivation, the chemical hydrolysis of the inhibitor and ongoing inhibition (inhibition during the substrate reaction time) [15,16,17–20]. A summary of the mathematical models is provided in Supplementary material.

1.2. Antecedents of discrimination of enzymatic components in several tissues

The developed kinetic models have been applied in our lab to discriminate enzymatic components among esterases in nerve tissues of adult chicken (Tables 1 and 2). The interest in esterases of the adult chicken nervous system using phenyl valerate as a substrate stems from studies of OPIDN and promotion [4]. The main findings are as follows: In peripheral nerve soluble fraction, three enzymatic components (EI, EII and EIII) have been discriminated by interaction with mipafox [21], paraoxon [17], 1-(saligenin cyclic phospho)-9-biotinyldiaminononane (S9B) [16] and PMSF [19]: EII and EIIII are sensitive to all the tested inhibitors but both are spontaneously reactivated when pre-inhibited with paraoxon, EIIII is also spontaneously reactivated when it is pre-inhibited with S9B while EIII is sensitive only to S9B (Table 1).

In serum, three enzymatic components have been discriminated with mipafox [22] and paraoxon [17,22]; E1 and E2, which are sensitive to paraoxon and mipafox and are spontaneously reactivated when pre-inhibited with paraoxon; and E3, which is resistant.

In the brain, membrane enzymatic components have been discriminated according to their interaction with mipafox and paraoxon [20]: EPα is sensitive to mipafox and paraoxon, and is spontaneously reactivated when pre-inhibited with paraoxon; EPβ is sensitive to paraoxon; EPγ, identified as NTE, is sensitive to mipafox, but is resistant to paraoxon. Finally component EPδ, is resistant to mipafox and paraoxon.

In brain soluble fractions, three enzymatic components have been discriminated with mipafox, paraoxon [18] and PMSF [23] (Table 2): Eα, which is highly sensitive to mipafox and paraoxon, but resistant to PMSF, is spontaneously reactivated when pre-inhibited with paraoxon; Eβ, which is sensitive to paraoxon and PMSF, but is resistant to mipafox; Eγ, which is resistant to paraoxon, and is sensitive to mipafox and PMSF, and is the fraction named "soluble NTE" or S-NTE [24].

In this work, we present additional *in vitro* data showing examples of interactions of esterase inhibitors with the substrate (PV) and how pre-exposure of a non inhibitory concentration of one inhibitor may modify sensitivity to time-progressive inhibition by further exposure to other inhibitors. The data have been compared with previous data of the esterase components obtained in our laboratory according to kinetic criteria. The biological material used as example is the soluble fraction of chicken nerve tissue as this is the animal experimental model employed for assaying OP-delayed neuropathy and the model in which the neuropathy promotion phenomenon is usually studied.

Table 1
Enzymatic components in chicken nerve tissues. Components were discriminated using kinetic analysis of the time-progressive inhibition at several inhibitor concentrations. The kinetic models applied are described in the specific publications and are based on the approaches described by [15,19]. The proportions of the components and their corresponding I50 at 30 min are indicated. In some cases, a range is indicated in which several experiments are considered. R is the component resistant to the highest tested concentration. (r) The component is spontaneously reactivated.

Tissue Component	Proportion	Paraoxon I50 (30 min)	Mipafox I50 (30 min)	PMSF I50 (30 min)	S9B I50 (30 min)
Peripheral nerve soluble fraction[a]					
EI	41–52%	6–12 nM (r)	11–12 nM	0.58–0.77 µM	5 nM
EII	33–41%	0.24–0.26 nM (r)	69–71 nM	6.8–17 µM	0.20 nM(r)
EIII	15–22%	R	R	R	83 nM
Serum[b]					
E1	21–22%	0.43 nM (r)	>100 nM		
E2	72–75%	13.7 nM (r)	3.6–4 nM		
E3	5.0–5.6%	R	R		
Membrane fraction of brain[c]					
EPα	4–8%	15–43 nM (r)	29 nM		
EPβ	38%	1540 nM	R		
EPγ (NTE)	39–48%	R	6601 nM		
EPδ	10–11%	R	R		

[a] Extracted from [19].
[b] Extracted from [17] and [22].
[c] Extracted from [20].

Table 2
Enzymatic components in the soluble brain fraction discriminated with different inhibitors. The corresponding I50 values (30 min) are shown. For mipafox, the I50 values in the sample pre-incubated with PMSF at the indicated concentration are also provided. R is the component that is resistant to the highest tested concentration.

	Proportion (%)[a]	PMSF I50 (20 min)[a]	Paraoxon I50 (30 min)[a]	Mipafox I50 (30 min)[a]	MIPAFOX[a] I50 (30 min) pre-incubated with PMSF 20 min			
					5 µM	50 µM	150 µM	4000 µM
Eα	11–28%	R	9–11 nM (r)	4 nM	26 nM	43 nM	72 nM	222 nM
Eβ	61–84%	70 µM	1216 nM	R	R	R	*	*
Eγ	5–11%	447 µM	R	3398 nM	25.7 nM	R	R	*

(r) The component is spontaneously reactivated.
[a] Extracted from the data in [23].
* Preinhibited by PMSF.

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