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Organophosphate-sensitive lipases modulate brain lysophospholipids, ether lipids and endocannabinoids

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ABSTRACT

Lipases play key roles in nearly all cells and organisms. Potent and selective inhibitors help to elucidate their physiological functions and associated metabolic pathways. Organophosphorus (OP) compounds are best known for their anticholinesterase properties but selectivity for lipases and other targets can also be achieved through structural optimization. This review considers several lipid systems in brain modulated by highly OP-sensitive lipases. Neuropathy target esterase (NTE) hydrolyzes lysophosphatidylcholine (lysoPC) as a preferred substrate. Gene deletion of NTE in mice is embryo lethal and the heterozygotes are hyperactive. NTE is very sensitive *in vitro* and *in vivo* to direct-acting OP delayed neurotoxicants and the related NTE-related esterase (NTE-R) is also inhibited *in vivo*. KIAA1363 hydrolyzes acetyl monoalkylglycerol ether (AcMAGE) of the platelet-activating factor (PAF) de novo biosynthetic pathway and is a marker of cancer cell invasiveness. It is also a detoxifying enzyme that hydrolyzes chlorpyrifos oxon (CPO) and some other potent insecticide metabolites. Monoacylglycerol lipase and fatty acid amide hydrolase regulate endocannabinoid levels with roles in motility, pain and memory. Inhibition of these enzymes in mice by OPs, such as isopropyl dodecylfluorophosphonate (IDFP), leads to dramatic elevation of brain endocannabinoids and distinct cannabinoid-dependent behavior. Hormone-sensitive lipase that hydrolyzes cholesteryl esters and diacylglycerols is a newly recognized *in vivo* CPO- and IDFP-target in brain. The OP chemotype can therefore be used in proteomic and metabolomic studies to further elucidate the biological function and toxicological significance of lipases in lipid metabolism. Only the first steps have been taken to achieve appropriate selective action for OP therapeutic agents.

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1. Introduction

1.1. OP (organophosphorus)-sensitive lipases

The serine hydrolase superfamily is one of the largest and most diverse enzyme classes in mammalian proteomes with key roles in all cells and organisms. The lipase subfamily hydrolyzes a myriad of lipid substrates important in cellular structure and as signaling molecules. Disruption of lipid homeostasis is implicated in neurodegeneration [1], cancer [2], obesity [3], and atherosclerosis [4]. Despite their physiological, toxicological and clinical significance, there are gaps in our knowledge of lipases and the lipids they regulate. The human genome encodes more than 1000 serine hydrolases, including lipases, most of which are unannotated or poorly characterized in terms of their physiological functions [5].

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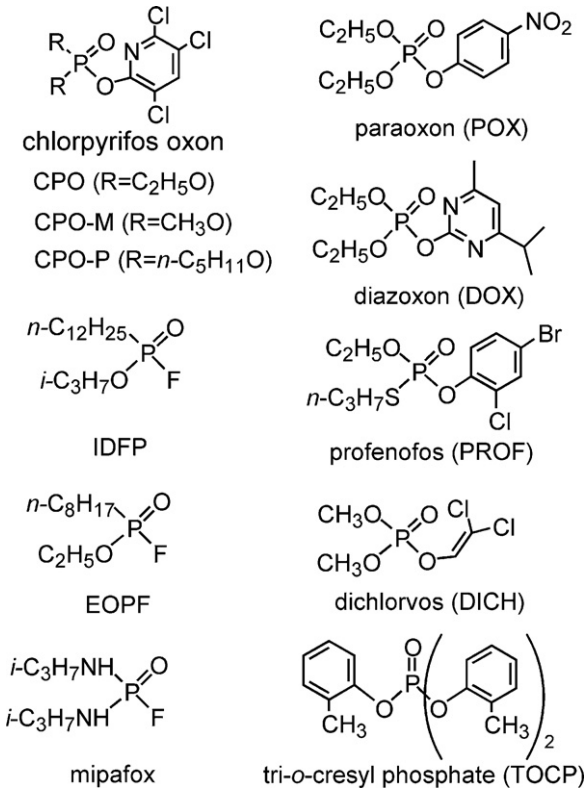

Fig. 1. Structures of OP insecticides and analogs. CPO, POX and DOX are metabolites of the important insecticides chlorpyrifos (CPF), parathion (PT) and diazinon, respectively. Profenofos and dichlorvos are insecticides while most of the others are compounds designed to achieve potency or selectivity. TOCP, mipafox, EOPF and IDFP are delayed neurotoxicants.

1.2. OP chemotype

The OP chemotype (Fig. 1) contains important insecticides and chemical warfare agents all of which act as acetylcholinesterase (AChE) inhibitors [6]. OP research for the past seven decades emphasized AChE inhibition and disruptions in the cholinergic system on acute or chronic exposure. During this time, several billion pounds of OP pesticides were used to protect crops and livestock from pests. Hundreds of thousands of OPs were screened for potency and selective toxicity to develop the 100 or so currently used insecticides. OPs account for about 25% of the insecticide world market value and there are also important OP herbicides and fungicides. The OP chemical scaffold allows the study of all serine hydrolases including lipases due to their unique reactivity with the active site serine [7]. Structurally diverse OP inhibitors optimized for potency and selectivity can be used to study the physiological, toxicological and therapeutic relevance of lipases and their associated systems.

1.3. Functional proteomics and metabolomics

OPs have been extensively used to profile serine hydrolases through functional proteomic and metabolomic platforms. Activity-based protein profiling (ABPP) [7–9] examines their functional state using a fluorophosphonate (FP) reactive group conjugated to a spacer arm and analytical handle (e.g. rhodamine or biotin). ABPP in a competitive mode helps discover potent and selective probes and elucidate toxicological secondary targets. Gel-based ABPP with FP-rhodamine is illustrated in Fig. 2A for several OP insecticides (i.e. DOX, CPO (chlorpyrifos oxon), CPO-M, POX, PROF and DICH) and designer compounds [ethyl octylphosphonofluoridate (EOPF) and isopropyl dodecylfluorophosphonate (IDFP)] as *in vitro* inhibitors of the mouse brain proteome. Each serine hydrolase has a different OP inhibition profile. Neuropathy target esterase (NTE) and fatty acid amide hydrolase (FAAH) are most sensitive to EOPF and IDFP; KIAA1363 to DOX, CPO, POX, EOPF and CPO-P; monoacylglycerol lipase (MAGL) to CPO, CPO-M, EOPF and IDFP; and ABHD6 to EOPF. ABPP coupled to mass spectrometry (MS) [(Multidimensional Protein Identification Technology (MudPIT)] (ABPP/MudPIT) [9,10] with FP-biotin allows increased resolution and sensitivity and thereby more comprehensive selectivity profiles. For example, assays of mouse brain membranes 4 h after CPO and IDFP are administered ip to mice reveals major *in vivo* disruptions in the serine hydrolase activity profiles (Fig. 2B). CPO inhibits not only AChE, but also MAGL, FAAH, KIAA1363, and other serine hydrolases considered later. IDFP inhibits NTE, NTE-related esterase (NTE-R), MAGL, FAAH, KIAA1363, and several additional targets. The physiological functions of the new OP-sensitive target enzymes discovered by ABPP can be elucidated with metabolomic liquid chromatography (LC)-MS and gas chromatography (GC)-MS platforms.

This review considers six OP-sensitive lipases, i.e. NTE, NTE-R, KIAA1363, MAGL, FAAH and hormone-sensitive lipase (HSL) (Fig. 3) (Table 1). The endogenous substrates are known in most cases. Structures of these enzymes are defined by crystallography (FAAH) or deduced from models (except NTE-R). They vary in molecular weight from 37 to 150 kDa (without glycosylation) and in number of amino acids from 339 to 1352. The GXSXG motif is evident (except for FAAH) with variations in the catalytic dyad or triad. Knockout mouse models are developed other than for NTE-R and MAGL. All six lipases are highly OP-sensitive *in vitro* or *in vivo* prompting detailed analysis of their recognition, structure, function and toxicology or pharmacology.

2. NTE and lysophospholipids

2.1. Recognition

TOCP added to drinks as a substitute for ginger extract in “ginger jake” in the prohibition-era 1930s induced a delayed neurotoxicity in thousands of people. Recurring incidents with TOCP, used as a cooking oil, high pressure lubricant, and in the manufacture of plastics or hydraulic oils, and a few with insecticides during manufacturing (mipafox) or application led to a total of at least 75,000 victims in the past 75 years. Research in the Medical Research Council Toxicology Unit in England defined the target protein in brain associated with this toxicological problem and designated it NTE; phosphorylation of NTE

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