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Conference Paper

Classification and Catalytic Properties of Esterases Reacting with Organophosphorus Compounds*

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The classification, molecular structure and substrate specificity of serine esterases and phosphoric triester hydrolases is described. Human serum cholinesterase (EC 3.1.1.8) and paraoxonase (EC 3.1.8.1) are described in more detail. The clinical significance of these two esterases is also discussed.

INTRODUCTION

This paper deals, in general terms, with the properties of enzymes interacting with organophosphorus compounds and, more specifically, with human serum cholinesterases and paraoxonases.

Two groups of esterases react with organophosphorus compounds: serine esterases and phosphoric triester hydrolases. Both groups react only with fully substituted phosphoric, phosphonic and phosphinic acids, and both groups react on the same ester bond. The leaving goups on the phosphorus vary widely and cleavage occurs on P-O, P-S, P-F, P-CN or other bonds.

The group of serine esterases includes enzymes with a broad substrate specificity for esters and peptides. These enzymes have no common classification number given by the Nomenclature Committee of IUBMB; the group includes carboxylic ester hydrolases (such as acetylcholinesterase EC 3.1.1.7, butyrylcholinesterase EC 3.1.1.8, carboxylesterase EC 3.1.1.1) and serine endopeptidases (such as trypsin EC 3.4.21.4 and chymotrypsin EC 3.4.21.1).[1] Organophosphorus compounds are progressive inhibitors of serine esterases.

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The reaction mechanism is analogous to substrate hydrolysis (*cf.* 2). It consists of acylating (phosphorylating) the active site serine which is then no longer catalytically active. Contrary to acylation by substrates, the phosphorylated serine reacts only slowly with water, rendering a long-lasting inhibited enzyme. The time course of phosphorylation and dephosphorylation is usually measurable, and the potency of an organophosphorus compound as inhibitor is therefore expressed in terms of two rate constants: the rate constant of phosphorylation and the rate constant of dephosphorylation. The same reaction mechanism applies to carbamates and organosulphur compounds. Inhibition of serine esterases by organophopshorus compounds is stereospecific, particularly around the phosphorus atom and less so around the attached groups.

Phosphoric triester hydrolases (EC 3.1.8) are divided into two subgroups: aryldialkylphosphatase (EC 3.1.8.1) and diisopropyl-fluorophosphatase (EC 3.1.8.2).[1] Their characteristic substrates are paraoxon and DFP, and therefore the enzymes are also termed paraoxonase and DFPase, respectively. Phosphoric triester hydrolases require divalent cations for activity and are inhibited by chelating agents. However, Hg^{2+} and Cu^{2+} are inhibitors of these enzymes, and so are 5,5'-dithiobis-2-nitrobenzoic acid and 4-chloromercury benzoic acid, suggesting that -SH groups play a role in the mechanism of catalysis. The mechanism of catalysis is still unknown and no intermediate steps in the hydrolysis have been identified so far. The reaction with organophosphorus compounds is therefore expressed in terms of the Michaelis constant and k_{cat} or V_{max}. Phosphoric triester hydrolases are stereoselective in their reaction with substrates, which applies both to the phosphorus atom and the attached groups. The present data on these enzymes have been summarized in two symposia.[3,4]

CHOLINESTERASES

The first two cholinesterases whose primary structure was solved were acetylcholinesterase from *Torpedo californica*[5] and butyrylcholinesterase from human serum.[6] The enzymes contain 575 and 574 amino acids per subunit, respectively, and their sequence similarity is 54%. The active site serine is the 200th and 198th residue, respectively. Recently, the primary structures of cholinesterases from other sources have also been resolved. The three-dimensional structure of the *T. californica* enzyme was determined by X-ray analysis in 1991.[7] The crystal structure established that the catalytic triad of the active centre (Ser 200, Glu 327, His 440) is at the base of a narrow gorge about 20 Å deep. Several reviews on cholinesterase structure and gene organization have been published.[8,9,10]

Cholinesterases hydrolyse choline and thiocholine esters, and a wide range of compounds without a quaternary nitrogen atom such as oxyesters,

thioesters, carbamoylesters and phosphorylesters. Acetylcholine is the physiological substrate of acetylcholinesterase; its rate of hydrolysis (k_{cat}/K_m) is about 10^{10} M^{-1} min^{-1}.[2,10] The high efficiency of this reaction suggests that the rate limiting step is diffusion of the substrate to the enzyme active site. When the substrates are carbamates or organophosphates, deacylation of the serine is the rate limiting step, and the over-all rate of hydrolysis becomes many orders of magnitude slower than the rate of acetylcholine hydrolysis. Thus, for instance, the rate constant of dephosphorylation of acetylcholinesterase phosphorylated by paraoxon amounts to 10^{-4} min^{-1}.[2,10] When the organophosphorus compound is DFP, the rate of dephosphorylation approaches zero and is no longer measurable.

Certain substrates cause cholinesterase inhibition at concentrations higher than their K_m constants. Acetylcholine is an inhibitor of acetylcholinesterase, while benzoylcholine is an inhibitor of butyrylcholinesterase. The mechanism of substrate inhibition in butyrylcholinesterase has not been explained so far.

The mechanism of substrate inhibition of acetylcholinesterase consists of binding of the substrate to an allosteric site, termed the substrate inhibition site or peripheral anionic site (*cf.* 2, 10). Ligands other than substrates can also bind to the substrate inhibition site: coumarin derivatives,[2,11,12,13] the fluorescent inhibitor propidium,[13,14,15] peptide snake toxins of the fasciculine group[16] and several bis- and tris-quaternary compounds.[14,15] Kinetic evidence of the substrate inhibition site was obtained from competition studies between substrates and inhibitors. It was shown that inhibition by coumarin derivatives can be prevented only with substrate concentrations (acetylcholine and acetylthiocholine) in the order of their K_{ss} constants. This indicated that inhibition by coumarin and substrate inhibition occur at the same site.

Titration of acetylcholinesterase with the fluorescent inhibitor propidium showed that binding to the allosteric site occurred both in the catalytically active enzyme and the phosphorylated enzyme.[13] Recent studies have shown that the allosteric site of acetylcholinesterase is probably located at the rim of the active site gorge; binding of a ligand to the allosteric site may therefore prevent access of the substrate to the gorge and/or alter the active site conformation.[10] Kinetic studies with substrates and inhibitors have suggested that butyrylcholinesterase has no peripheral anionic site. Mutations involving the peripheral anionic site in acetylcholinesterase and modelling of the conversion of acetylcholinesterase to butyrylcholinesterase have supported this assumption.[17]

Genetic variants are known for human serum cholinesterase. In addition to the usual cholinesterase (U), the atypical (A), fluoride resistant (F), silent (S), J-variant and K-variant have also been described.[9,18,19] Homozygous and heterozygous cholinesterase forms have been found. They differ in their catalytic properties. Distribution studies of human serum cholinesterase activities in Caucasian population groups have shown that 95–96% individuals

belong to the usual phenotype.[18] In a population group of 245 individuals from Zagreb (Croatia), 91% were of the usual phenotype.[20] The other individuals belonged to the UA, UF, AK and AF phenotypes. Because the occurrence of phenotypes other than the usual once is small, the activity distribution profiles appear unimodal and symmetrical. Phenotyping of human serum cholinesterases is done with acetyl(thio)choline, propionyl(thio)choline and benzoylcholine as substrates, and dibucaine, fluoride and the dimethylcarbamate Ro 02-0683 as inhibitors.[18–21]

The primary structures of several cholinesterase variants are known and they differ from one another in only one amino acid residue.[9,22–25] Thus, for instance, the U variant has aspartic acid at position 70 in the sequence and the A variant glycine. Phenotypes differ in their reaction with positively charged compounds, but it is still not clear whether this is due to different affinities or different rates of catalysis. It was shown that, for a given substrate (positively charged or neutral), the U cholinesterase has lower K_m values than the A variant, but both variants have the same k_{cat} (*cf.* 9, 18). Further, the reaction of U, A and FS phenotypes was studied with two positively charged substrates, two pyridinium oximes, the neutral 4,4'-bipyridine, and with five neutral and one charged organophosphorus compound (paraoxon, sarin, soman, tabun, VX and phosphostigmine).[26] Binding of a compound (expressed in terms of the K_m or enzyme/inhibitor dissociation constants) was about the same for the studied phenotypes irrespective of whether the compound had a positive charge or was neutral. However, rate constants of phosphorylation by charged compounds and V_{max} for the charged substrates were higher for the U than A phenotype. It was further shown that the enzyme/substrate reaction deviated from the Michaelis- Menten kinetics.

PARAOXONASES

Phosphoric triester hydrolases are widely distributed, but so far their physiological role is still unknown. They were detected in many mammalian tissues, in aquatic animals and microorganisms. Paraoxonases and DFPases overlap in their catalytic properties and substrate specificities. Mammalian sera are a rich and widely used source for studies on paraoxonases, while the enzyme in squid has been widely used as a source for the DFPase.[3,4,27–29]

Extensive studies on human serum paraoxonases in different population groups have revealed a polymodal distribution profile.[27,29,30] One well defined mode of low activity was shown to correspond to phenotype A, and two less defined modes of high activity to the heterozygote AB and phenotype B. Frequencies of the phenotypes differ depending on the ethnic group.[27] In European populations between 45–61% individuals belong to phenotype A, in Japan only 10%, while phenotype A has not been detected in the Australian aborigines.

Both phenotypes have been sequenced. LaDu *et al.*[31] found 354 residues and Furlong[32] found 355. Phenotypes A and B differ in residue 191 (or 192) having Glu and Arg, respectively; residue 54 is Met or Leu according to LaDu.[31] The k_{cat} for paraoxon in phenotypes A and B was reported to be 300 and 700 min^{-1}, respectively, and their corresponding K_m values 0.5 and 0.3 mM.[33] Paraoxon is a better substrate for some microorganisms than for human sera; the enzyme from *Pseudomonas diminuta* has been reported to have a k_{cat} of 126000 min^{-1} and K_m of 0.09 mM.[34]

Human sera contain two paraoxonases: one sensitive and the other insensitive to EDTA (cf. 27). The effect of EDTA is reversible and the enzyme activity is restored by addition of Ca^{2+}. There are speculations that the EDTA-insensitive activity might be attributed to albumin. The pH profile of the two enzymes is different and the contribution of each activity to the total activity will, therefore, depend upon the experimental conditions. For instance, in a population group of 273 individuals from Zagreb (Croatia), the activity of the EDTA-insensitive enzyme amounted, on average, to 7% of the total activity when measured at pH 7.4.[30] The distribution profile of the EDTA-insensitive activity in human sera is unimodal, but asymmetric.[27,30]

Other sources of phosphoric triester hydrolases also seem to contain EDTA-sensitive and EDTA-insensitive enzymes. For instance, the DFPase from squid and from thermophilic bacteria retain 10% of their activity in the presence of EDTA.[28]

Monovalent, divalent and trivalent cations are either activators or inhibitors of human serum paraoxonases. Eckerson *et al.*[36,37] used the effect of cations to better differentiate between the paraoxonase phenotypes A and B. The A phenotype was not activated by 1.0 M NaCl, while the activity of the B phenotype increased 3-fold. The activity modes, corresponding to A, AB and B phenotypes in the distribution profile of human serum paraoxonases, were therefore better separated in the presence of molar Na^+ concentrations.

Many studies have been undertaken on the substrate specificity of paraoxonases concerning their reaction with carboxylic acid esters, but no conclusive evidence has been obtained so far. The most widely studied compound is phenylacetate (PA), which is the characteristic substrate of arylesterase (EC 3.1.1.2).[1] The hydrolysis of carboxylic esters in human sera is inhibited by EDTA. Results obtained on 183 individuals have shown[38] that the activity of beta-naphthylacetate (BNA) in the presence of EDTA (at pH 7.4) amounts, on average, to 23% and of PA to 1% of the total activity. This points to the conclusion that each substrate is hydrolysed by an EDTA-sensitive and an EDTA-insensitive enzyme, and this is analogous to the hydrolysis of paraoxon. The EDTA-insensitive hydrolysis of PA and BNA was, however, shown to have properties of a serine esterase, and not of a paraoxonase. The EDTA-sensitive hydrolysis of paraoxon and BNA revealed a high correlation coefficient (0.85) pointing to the same enzyme hydrolysing the

two substrates.[38] However, there is controversy as to the correlation coefficients between paraoxon and PA hydrolysis. Eckerson *et al.*[37] concluded that paraoxon and PA are hydrolysed by the same enzyme, having obtained a correlation coefficient of 0.9 (on 348 individuals) between their rates of hydrolysis. Contrary to that, Geldmacher and Diepgen[27] and Reiner *et al.*[38] found no correlation between the EDTA-sensitive hydrolysis of paraoxon and PA, indicating that different enzymes hydrolyse paraoxon and PA. A low correlation (r = 0.6) was also found between BNA and PA activities[38] The time course of heat inactivation measured with paraoxon is different from that measured with PA, indicating that different enzymes hydrolyse these substrates; the inactivation kinetics corresponded to two or more enzymes hydrolysing each substrate.[39]

CLINICAL SIGNIFICANCE OF CHOLINESTERASES AND PARAOXONASES

Organophosphorus compounds are used as pesticides, as chemical warfare agents (nerve gases) and also as drugs. Activities of human blood cholinesterases (acetylcholinesterase and butyrylcholinesterase) are indicators of the absorption of organophosphorus compounds or other cholinesterase inhibitors (such as carbamates). To confirm absorption, it has been suggested to detect the compound, or its metabolite, in the blood or urine since it was shown that metabolites in the urine are a more sensitive index of absorption than inhibition of blood cholinesterases.[40] It has been further suggested that individuals with a high activity of phosphoric triester hydrolases will metabolise organophosphorus compounds faster and would, therefore, be better protected against possible poisoning. So far, no correlation has been observed between inhibition of serum cholinesterase, the activity of serum paraoxonases and levels of organophosphorus metabolites detected in blood or urine of exposed individuals.

The therapy of organophosphate poisoning consists of administration of atropine, as an antagonist to acetylcholine on the receptor, and oximes, as reactivators of phosphorylated cholinesterases. However, recent studies have brought up new possibilities concerning the use of enzymes as therapeutic and/or protective agents against organophosphate intoxication. Fetal bovine serum acetylcholinesterase was shown to protect non-human primates against intoxication by soman, an organophosphorus nerve gas.[41] Protection is based upon phosphorylation of the exogenous enzyme by soman, whereby the enzyme served as a scavenger of soman. Large quantities of enzyme would be required if the same treatment was to be applied in humans, because cholinesterases and organophosphorus compounds react on a 1:1 molar basis. An alternative approach is the use of phoshoric triester hydrolases, for which organophosphorus compounds are substrates. It was shown

that a purified recombinant DFPase protected mice against lethal doses of soman.[42] Studies along the same lines are likely to lead towards developing enzyme agents suitable for the protection/therapy against poisoning by organophosphorus compounds.

Human serum paraoxonases seem to be markers of certain diseases.[43–46] Studies in various population groups have shown that individuals with lipid and glucose metabolism disorders have lower paraoxonase activities than non-diseased individuals. There is evidence of a relationship between paraoxonase activities and atherosclerosis. Patients after infarction and patients with the Fish eye disease have low paraoxonase activities. So far, measurements of paraoxonase activities have not been used for diagnostic purposes, but their possible clinical significance is under discussion. It has been suggested that paraoxonase might be involved in the protection of low-density lipoprotein against oxidative modification.[47,48]

Human serum cholinesterases are also markers of certain diseases.[18,19] Low serum cholinesterase activities were found in patients with liver metabolism disorders and in some infectious diseases. Serum cholinesterase activities decrease during pregnancy. Phenotyping of cholinesterases is conducted for diagnosing genetic variants unable to hydrolyse short acting muscular relaxants used in anesthesia (such as Suxamethonium).[9,18,19]

Some inhibitors of cholinesterases (organophosphates and carbamates) are used as drugs (*cf.* 49). The organophosphorus compound metrifonate (trichlorphon) is used as an antiparasitic drug in the treatment of *Schistosoma haematobium* infections. The carbamates neostigmine and pyridostigmine are used in the treatment of myasthenia gravis. DFP, ecothiopate and physostigmine (eserine) are used in the therapy of glaucoma and some neurological disorders. Metrifonate has been suggested as a possible drug for the treatment of the Alzheimer disease.[50]

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SAŽETAK

Klasifikacija i katalitička svojstva esteraza koje reagiraju sa organofosfornim spojevima

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Opisana je klasifikacija, molekulska struktura i substratna specifičnost serinskih esteraza i fosfor-triester-hidrolaza. Podrobnije su opisane ljudska serumska kolinesteraza (EC 3.1.1.8) i paraoksonaza (EC 3.1.8.1). Prikazano je i kliničko značenje tih dviju esteraza.