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Review article

Slow-binding inhibition of cholinesterases, pharmacological and toxicological relevance

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ABSTRACT

Slow-binding inhibition (SBI) of enzymes is characterized by slow establishment of enzyme-inhibitor equilibrium. Cholinesterases (ChEs) display slow onset of inhibition with certain inhibitors. After a survey of SBI mechanisms, SBI of ChEs is examined. SBI results either from simple slow interaction, induced-fit, or slow conformational selection. In some cases, the slow equilibrium is followed by an irreversible chemical step. This later was observed for the interaction of ChEs with certain irreversible inhibitors. Because slow-binding inhibitors present pharmacological advantages over classical reversible inhibitors (e.g. long target-residence times, resulting in prolonged efficacy with minimal unwanted side effects), slow-binding inhibitors of ChEs are promising new drugs for treatment of Alzheimer disease, myasthenia, and neuroprotection. SBI is also of toxicological importance; it may play a role in mechanisms of resistance and protection against poisoning by irreversible agents.

Contents

Abbreviations: AChE, acetylcholinesterase; BChE, butyrylcholinesterase; ChE, cholinesterase; CSP, cresyl saligenin phosphate; DFP, diisopropylfluorophosphate; DTI, delay time for inhibition; PAS, peripheral anionic site; PD, pharmacodynamics; PK, pharmacokinetics; OP, organophosphorus compound; SBI, slow-binding inhibition; TBI, tight-binding inhibition; TMTFA, *m*-(N,N,N-trimethylammonio)trifluoroacetophenone.

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