EuroSciCon

EuroSciCon Congress on

Enzymology and Molecular Biology

August 13-14, 2018
Paris, France

Rona R Ramsay, Insights Enzyme Res 2018, Volume 2
DOI: 10.21767/2573-4466-C1-001

KINETICS, INHIBITION AND DRUG DESIGN FOR MONOAMINE OXIDASES

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Monoamine oxidase (MAO) has been a drug target for 60 years, particularly to treat neuropsychiatric disorders. The flavin-containing monoamine oxidases (MAO A and MAO B) located on the outer membrane of mitochondria oxidise neurotransmitter amines and generates hydrogen peroxide. In the brain, inhibition of MAO increases neurotransmitter levels, alleviating depression or helping compensate for cell loss in neurodegeneration. In the periphery, MAO activity is essential for protection against biogenic amines. MAO also metabolizes many amine drugs, an important factor in pharmacokinetics. Kinetic studies of the two forms of MAO (MAO A and MAO B) have revealed that ligands bind differently to the oxidized and reduced forms, and have facilitated design of selective inhibitors. This presentation will summarize the structure and function of MAO and its inhibition by current drugs. Most successful drugs are irreversible inhibitors that inactivate MAO by forming a flavin adduct, so that activity *in vivo* is recovered only by new protein synthesis. Recent data that resolves the controversial structure of adduct will be presented, along with steady-state and stopped-flow kinetics of adduct formation. Going forward, computational methodologies, medicinal chemistry, and enzymology facilitate structure-based drug design for new multi-target compounds that inhibit not only MAO, but also other targets where binding might prevent neurodegeneration in one multi-target compound.

Biography

Rona R Ramsay has pursued her Research in Enzymology in Cambridge, California and St Andrews (where she has lectured for 23 years), focusing on mitochondrial enzymes, investigating how these enzymes work and how they are regulated, techniques of kinetic analysis, spectroscopy, structural determination, inhibitor studies, and molecular biology are combined with molecular modelling to elucidate mechanism and guide drug discovery. Her historic works include the discovery of the carnitine carrier and the regulation of carnitine acyltranferases in fatty acid metabolism; the metabolism of the neurotoxin MPTP and identification of Complex I in the respiratory chain as the target of MPP+ toxicity; and the kinetics of iron-sulfur proteins and of flavoenzymes. Her Current research focusses on monoamine oxidases involves collaborations with medicinal chemists and neuropharmacologists to identify new multi-target molecules against neurodegenerative diseases. ORCHID ID: orcid.org/0000-0003-1535-4904.

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