Institut Ruđer Bošković

CIX. Kolokvij Zavoda za organsku kemiju i biokemiju i

Sekcije za organsku kemiju Hrvatskog kemijskog društva

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predavaonica **III.** krila IRB
15:00-16:00 sati

Monoamine oxidase kinetics and drug design

Monoamine oxidase (MAO) is a target in the design of drugs for the treatment of depression, attention deficit disorders, Parkinson's disease and Alzheimer's disease in order to elevate the levels of depleted neurotransmitters. Increases in MAO A activity in heart and MAO B activity in brain with age have been linked with increased oxidative damage, providing another rationale for inhibiting these enzymes. MAO A and MAO B share 70% sequence identity and the same FAD cofactor covalently attached at a conserved cysteine residue. Their deep active site cavities are different in volume and shape conferring very different substrate and inhibitor specificities. The majority of MAOI drugs in current use are mechanism-based irreversible inhibitors such as L-deprenyl (selegiline) which is selective for MAO B. Restoration of the activity is slow because human MAO turnover in brain has a half-life of 30 days. The irreversible inhibition of MAO A in the gut results in tyramine in the blood and cardiovascular side-effects, so there are many series of new reversible inhibitors being published. In all this research, a key technique is experimental kinetic analysis. This lecture will cover kinetic experiments from the last 20 years that have lead to our current understanding of the functional aspects including mechanism and inhibition of this important drug target.

RELEVANT ARTICLES:

Ramsay RR. (2012) Monoamine oxidases: the biochemistry of the proteins as targets in medicinal chemistry and drug discovery. *Curr Top Med Chem* 12: 2189–2209.

Juárez-Jiménez J, Mendes E, Galdeano C, Martins C, Silva DB, Marco-Contelles J, Carreiras MC, Luque FJ, Ramsay RR. (2013) Exploring the structural basis of the selective inhibition of monoamine oxidase A by dicarbonitrile aminoheterocycles: Role of Asn181 and Ile335 validated by spectroscopic and computational studies. *Biochim Biophys Acta (Proteins and Proteomics)*; in press; DOI: 10.1016/j.bbapap.2013.11.003

McDonald GR, Olivieri A, Ramsay RR, Holt A. (2010) On the formation and nature of the imidazoline I(2) binding site on human monoamine oxidase-B. *Pharmacol Res* 62: 475–488.

Tan AK, Ramsay RR. (1993) Substrate-specific enhancement of the oxidative half-reaction of monoamines oxidase, *Biochemistry* 32: 2137–2143.

Vianello R, Repič M, Mavri J. (2012) How are biogenic amines metabolized by monoamine oxidases? *Eur J Org Chem* 36: 7057–7065.

Edmondson DE, Binda C, Wang J, Upadhyay AK, Mattevi A. (2009) Molecular and mechanistic properties of the membrane-bound mitochondrial monoamine oxidases. *Biochemistry* 48: 4220–4230.