Serum uric acid and oxidative stress activity of XOR

G. Massimo[1], C. Borghi[2], P. Hrelia[3], A. Ahluwalia[1]

[1]Dept.of Clinical Pharmacology, Queen Mary University of London, Charterhouse Square, London
[2]Dept. of Medical and Surgical Science, University of Bologna, Via Massarenti 9, Bologna
[3]Dept. of Pharmacy and Biotechnology, University of Bologna, Via Irnerio 48, Bologna

Background to the study: Xanthine Oxidoreductase (XOR) belongs to the molybdenum-containing hydroxylase enzymes along with Aldehyde Oxidase (AO), Sulphite Oxidase (SO), and mitochondrial Amidoxime Reductase. XOR exists as a homodimer, with a single monomer having two N-terminal *Iron-Sulphur sites* (Fe_2-S_2), a *FAD site*, and a C-terminal *Molybdenum-binding domain*. To date, the Molybdenum domain is well recognized as the most important site of the enzyme, where the two final steps of oxidative metabolism of purine occur, with two oxidization reactions of hypoxanthine to xanthine, and then xanthine to the final product uric acid. Furthermore, the molybdopterin site is also important for its reductase activity, through which inorganic nitrite is reduced to the important antihypertensive agent, nitric oxide (NO). It is well known that XOR can exist in two interconvertible states, as reduced form XDH, and as oxidative form XO, and XDH can be reversibly and irreversibly converted to XO. Both isoforms catalyse catabolise of purines. The primary difference between the isoforms is at the FAD site where NAD^+ is used as an electron acceptor by XDH (although O_2 can be used in case of NAD^+ deficiency), and an O_2 molecule by XO. This difference is thought to play an important role in pathology, since the reduction of O_2 leads to the production of the reactive oxygen species, the superoxide anion (O_2^-). Even though uric acid (UA)**,** the end product of purine metabolism, has been described as an oxygen radical scavenger, in the recent past evidence has indicated that an increased risk of total cardiovascular morbidity and mortality is associated with elevated levels of serum uric acid. This observation along with acquired knowledge about the prominent role of the XOR system in the development of an oxidative stress condition, warranted in the last decade a huge number of *in vivo* and *in vitro* studies to investigate the beneficial effects of the XOR inhibition through allopurinol administration.

Hypothesis of the study: We wish to revaluate XOR activity with respect to its role in uric acid generation relative to its superoxide generating activity. We will determine whether in environments reflecting cardiovascular disease scenarios whether there might be a reciprocal relationship between the activities at the molybdenum and FAD domains to ascertain the impact of uric acid on superoxide generation and vice versa. In addition we will assess the impact of specific single site mutations on the relationship between the two products.