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ORIGINAL ARTICLE

Chemoprotective role of molybdo-flavoenzymes against xenobiotic compounds

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KEYWORDS

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Abstract Aldehyde oxidase (AO) and xanthine oxidoreductase (XOR) are molybdo-flavoenzymes (MFEs) involved in the oxidation of hundreds of many xenobiotic compounds of which are drugs and environmental pollutants. Mutations in the XOR and molybdenum cofactor sulfurase (MCS) genes result in a deficiency of XOR or dual AO/XOR deficiency respectively. At present despite AO and XOR being classed as detoxification enzymes the definitive experimental proof of this has not been assessed in any animal thus far. The aim of this project was to evaluate *ry* and *ma-l* strains of *Drosophila melanogaster* as experimental models for XOR and dual AO/XOR deficiencies respectively and to determine if MFEs have a role in the protection against chemicals. In order to test the role of the enzymes in chemoprotection, MFE substrates were administered to *Drosophila* in media and survivorship was monitored. It was demonstrated that several methylated xanthines were toxic to XOR-deficient strains. In addition a range of AO substrates including N-heterocyclic pollutants and drugs were significantly more toxic to *ma-l* AO-null strains. This study therefore provides definitive proof that both AO and XOR are involved in detoxification.
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1. Introduction

Xenobiotics are compounds that are foreign to the body, which include drugs, pollutants and other substances that are not normally present in the body that are potentially toxic. Xenobiotic metabolism is the series of metabolic reactions that change the chemical structure of xenobiotics; generally acting to detoxify the toxic chemical compounds. Sometimes, however, the product of xenobiotic metabolism can be the cause of toxic effects (Hodgson and Smart, 2001). This study is concerned with detoxification role for two of these enzymes aldehyde oxidase (AO; EC 1.2.3.1) and xanthine oxidoreductase (XOR; EC 1.2.3.2) against effects of xenobiotics. Those are molybdo-flavoenzymes (MFEs) found in nearly every organism from bacteria to human (Garattini et al., 2009; Garattini and Terao, 2011). Aldehyde oxidase (AO) and xanthine oxidoreductase (XOR) are molybdo-flavoenzymes (MFEs) involved in the oxidation of hundreds of endogenous, exogenous and N-heterocyclic compounds many of which are drugs and environmental pollutants (Garattini and Terao, 2011; Hille et al., 2014; Catarina et al., 2015; Dalvie and Zientek, 2015). Mutations in the XOR and molybdenum cofactor sulfurase (MCS) genes result in a deficiency of XOR or dual AO/XOR deficiency respectively (Amrani et al., 2000; Ichida et al., 2001). Xanthinuria is an inherited deficiency of XOR, which results in the inability to convert

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xanthine and hypoxanthine to uric acid (Holmes and Wyngaarden, 1989). Hereditary xanthinuria can be subdivided into two types. Hereditary xanthinuria type I is characterised by a lack of XOR whereas the type II disease is characterised by a dual deficiency of AO and XOR due to a MCS deficiency genes (Levartovsky et al., 2000; Yamamoto et al., 1991). *Drosophila melanogaster* have been investigated for a number of years and first mutant that lacked both molybdoflavoenzymes were discovered in 1956 (Forrest et al., 1956). These mutants lack both XOR and AO activity and retain SO activity (Wahl and Rajagopalan, 1982). Maroon-like locus (*ma-l*) homozygotes are completely deficient in XDH and AO activities (Kamdar et al., 1997) and display a maroon eye colour compared to the bright red seen in wild type *Drosophila* (Amrani et al., 2000; Wahl and Rajagopalan, 1982). The *rosy* gene encodes the XDH apoprotein and *rosy* mutants show a normal AO activity (Kidd et al., 1999). The complex and versatile role of XOR, particularly in the mammalian could be linked to the unique rapid post-translational conversion from the XDH to the XO form. Only mammalian XOR, but not XOR from chicken and *Drosophila*, can be converted from the XDH to the XO form (Hille and Nishino, 1995; Kooij et al., 1992). AO and pyridoxal oxidase (PO) enzymes in *D. melanogaster* are encoded by *aldox* and *lpo* structural loci (Keller and Glassman, 1964) and were identified in many adult *Drosophila* tissues (Cypher et al., 1982) using heptaldehyde and 2,4,5-trimethoxybenzaldehyde as specific substrates for AO and PO, respectively (Cypher et al., 1982). As well as in addition to studies in *Drosophila*, AO has been found in antennae of tobacco hawk *moth* (*Manduca sexta*), cabbage armyworm (*Mamestra brassicae*), polyphemus silkmoth (*Antheraea polyphemus*) and domestic silkworm (*Bombyx mori*) (Maibeche-Coisne et al., 2004; Merlin et al., 2005; Rybczynski et al., 1989, 1990). In addition to enzyme activities XOR and AO genes have been investigated in several insects. *D. melanogaster* has one XDH and four AO (AOX 1–4) genes were identified on chromosome 3 (Garattini et al., 2003; Marelja et al., 2014). The evolution of the AOX genes was determined and phylogenetic analysis showed that the AOX gene cluster evolved via independent duplication events in the vertebrate and invertebrate lineages (Marelja et al., 2014). Recently, Marelja et al., 2014 have reported that pyridoxal oxidase is the product of the *Drosophila* AOX1 gene. Uric acid has been shown to be an effective *in vitro* scavenger of singlet oxygen, peroxyl radical and hydroxyl radical (Chow, 1988). As *ry* and *ma-l* strains cannot produce uric acid as they are deficient in XDH activity these strains provide a means for critical *in vivo* analysis of the role of uric acid in oxygen defence (Phillips and Hilliker, 1990). Biological models proposing an important antioxidant role of uric acid predict that urate-null mutants should be more susceptible to oxygen radicals. Hilliker et al. (1992) reported an investigation of the role of uric acid in oxygen defence in ry^{506} urate-null mutants. Hilliker et al. (1992) measured the toxic response of these mutants to oxygen stress imposed by exposure to radical generating redox cycling agents, ionising radiation, and increased oxygen tension. The results clearly demonstrated the *in vivo* radical-scavenging role of urate and revealed a critical metabolic role of this classical molybdoenzyme-genetic system in *Drosophila*. Hilliker et al. reported that ry^{506} mutants are demonstrably impaired in their capacity to detoxify the active oxygen generated by such diverse agents as paraquat, hyperoxia, and ionising radiation (Hilliker et al., 1992). In addition, Humphreys et al. found *ma-l* strain had paraquat hypersensitivity due to the lack of XDH activity, which leads to the absence of uric acid (Humphreys et al., 1993). In this role, uric acid can act either by directly scavenging active oxygen species, in which case it is oxidised into a variety of products including allantoin, oxaluric acid and parabanic acid (Kaur and Halliwell, 1990) or by binding radical-generating transition metals into poorly reactive complexes (Davies et al., 1986). Hamatake et al. also demonstrated that the urate-null strain was more sensitive to environmental cigarette smoke (ECS) toxicity than wild type strains (Oregon-R) as assayed by survival and fecundity. They hypothesised that oxidative damage seems to be involved in the toxicity of ECS as uric acid plays a role as an important antioxidant in *Drosophila* (Hamatake et al., 2009). It has been proposed that uric acid has an important role as an antioxidant *in vivo* and singlet oxygen scavenger properties and it is important in determining species longevity (Ames, 1983). AOX is important in xenobiotic metabolism. Recent focus has been mainly on *in vitro* metabolism of pharmaceuticals containing aldehyde or N-heterocyclic compounds (Kitamura et al., 2006; Pryde et al., 2010). Recently, results from toxicological research have shown the toxicological importance role of AOX *in vivo* in xenobiotic metabolism in mammals (Swenson et al., 2013).

2. Materials and methods

2.1. *D. melanogaster* strains used for research

D. melanogaster strains were obtained from the Bloomington *Drosophila* Stock Centre, Indiana University (USA). All these strains and mutations were those as described by (Lindsley and Zimm, 1992).

The following strains were obtained from Bloomington *Drosophila* Stock Centre:

Bloomington stock numbers are in parentheses

- Canton-S (1): Normal wild type *D. melanogaster* (parental strain).
- ry^{506} (225): Strain deficient in XOR activity.
- *mal-1* (3973) and *mal-f1* (180): Strains deficient in MCS activity.
- Transgenic T1 and T2 strains: ry^{506} mutant strain transformed with a normal *Drosophila* XDH gene in Carnegie 20 vector.

2.2. *D. melanogaster* toxicity tests

All toxicity experiments were carried out at 25 °C in a 12 h light/dark cycle with 3 day old flies being used (Ashburner, 1989). The flies were collected and transferred to the medium containing different concentrations of the AO and XOR substrates used to evaluate chemoprotection by XOR and AO. All these substrates were made up in concentrations from 0 mM to 100 mM in distilled water or in appropriate solvents (Table 1). As the higher concentrations were close to the saturation point of some of the compounds the solutions were placed in a sonicating bath to increase dissolution of the compound. All the final concentrations of these xenobiotics were

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