An investigation into the possible sources of free radical generation in synthetic hormone metabolism

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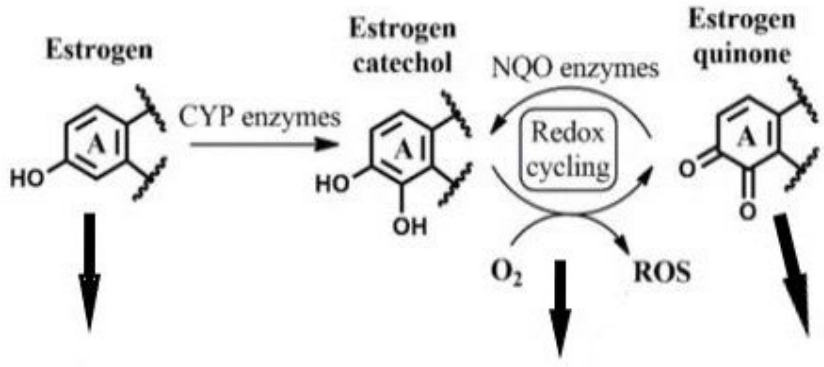

Figure: Possible carcinogenic effects originating from estrogen hormones (adapted from Benedek et al., 2021)

It is now well known that estrogens which includes the natural hormones estradiol (E2) and estrone(E1) can induce tumors in various organs of several laboratory animal species. In humans exogenous estrogen-containing medications or elevated concentrations of circulatingendogenous estrogens increase the risk of breast cancer. Two possible mechanisms of tumor induction by estrogens were initially suspected: 1) estrogen receptor-based proliferation of cells carrying spontaneous replication errors and 2) disruption of spindle formation and subsequent numeric chromosomal changes. More recently it has been established that catechol estrogens (CE) may be involved in tumor initiation. This is supported by a large body of evidence which shows that estrogens induce various types of DNA damage *in vitro* and *in vivo.* The biotransformation reactions involved in the metabolism of estrogens include phase II enzyme-initiated conjugation to sulfates and glucuronides. The phase I reactions which include Cytochrome P450 conversion of estrogens to catechol estrogens and subsequent formation of semi-quinones and quinones, is important from a cancer research viewpoint as the reaction of these reactive intermediates with DNA may produce adducts which can be either stable or depurinating.

Our research focusses on comprehensive profiling of estrogen biotransformation. This is doneby monitoring levels of 39 hormone-related metabolites with electrospray-tandem mass spectrometry (ESI-MSMS). The outcome of biotransformation investigations in the eBOSS- study by our group where results from combined oral contraceptive (COC) users were compared to that of control cases revealed increased levels of reactive oxygen species (ROS)in the user group. Our initial hypothesis was that redox cycling by cellular quinone reductasemay be responsible for the ROS formation. This was however contradicted by further investigation into estrogen DNA-adduct formation in the COC-user group where no corresponding increase in DNA-adduct formation was associated with high ROS production. Here we want to present our approach to further investigations regarding the origin of high free radical production associated with the use of COC's.

Keywords: Estrogen biotransformation; Catechol estrogens; DNA-adducts; Reactive OxygenSpecies (ROS)

References: Benedek, Z.; Girnt, P.; Olah, J. The Reactivity of Human and Equine EstrogenQuinones towards Purine Nucleosides. *Symmetry* **2021**, *13*, 1641. https://doi.org/10.3390/sym13091641