BIOMIMETIC ELECTROCHEMICAL SYNTHESIS OF QUINOL-THIOETHER CONJUGATES : THEIR IMPLICATION IN THE SEROTONERGIC NEUROTOXICITY OF AMPHETAMINE DERIVATIVES

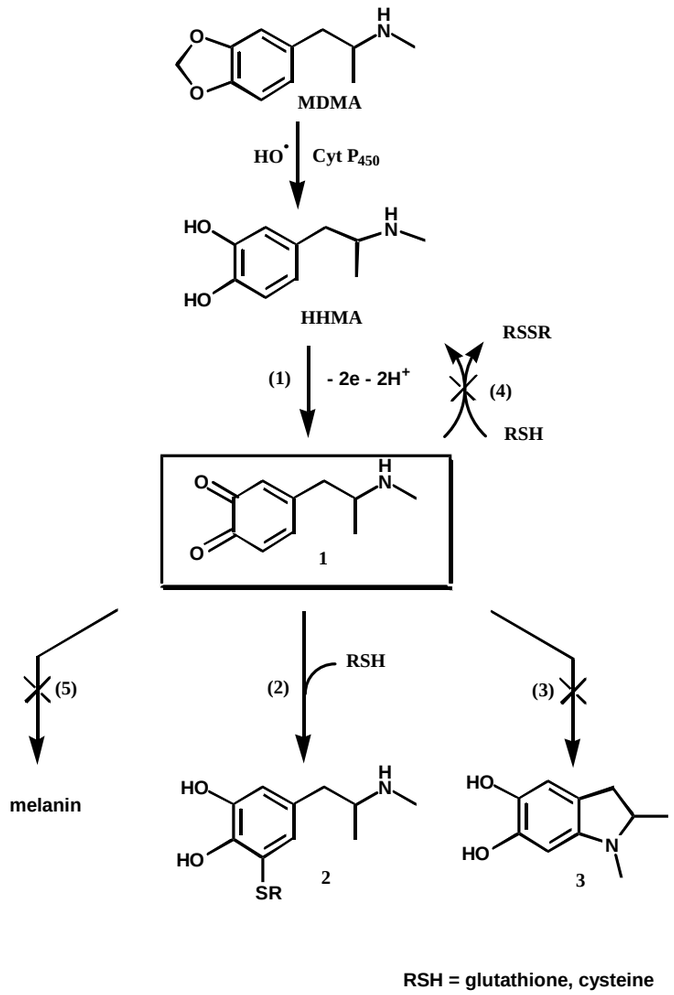
ANNE NEUDORFFER, JEAN-PIERRE GRAMOND, CYRINE SLIM, MAURICE-BERNARD FLEURY AND MARTINE LARGERON

Laboratoire de Chimie Analytique et Electrochimie, UMR 8638 CNRS – Université René Descartes, Faculté des Sciences Pharmaceutiques et Biologiques, 4 Avenue de l'Observatoire, 75270 Paris Cedex 06, France.

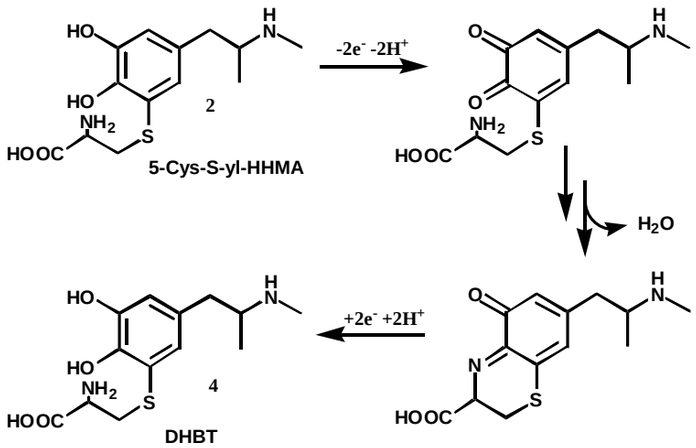
3,4-methylenedioxymethamphetamine (MDMA, or *ecstasy*), a popular recreational drug, is a selective serotonergic neurotoxin[1] in humans and in animals (rats, mice). However, injection of *ecstasy* directly into the brain fails to reproduce the long-term effects observed after peripheral administration, implying an essential role for systemic metabolites in the development of toxicity, though the precise identity of the neurotoxic metabolites remains unclear. *In vivo,* these metabolites are oxidized to the corresponding *ortho*quinones, that readily react with protein and non-protein sulfhydryls, leading to quinol-thioether conjugates **2** (Scheme **1**), which subsequently can cyclize to afford DiHydroBenzothiazine derivatives (DHBT, Scheme **2**)[2-6].

The aim of this study is to evaluate the respective contribution of both quinol-thioether adducts and DHBT to the neurotoxicity of MDMA. For this purpose, the biomimetic electrochemical synthesis of quinol-thioether adduct **2** (R=glutathione) is reported: 3,4-quinone species **1** was generated from 3,4-dihydroxymethamphetamine (HHMA), using controlled potential electrolysis, at a platinum electrode (eqn. 1, Scheme **1**). First, to prevent intramolecular subsequent cyclisation into 5,6-dihydroxyindole **3** (eqn. 3), the reaction was performed in HCl 0.2 mol.L^{-1} aqueous solution. Second, to rule out possible redox interchange (eqn. 4) in the course of the electrolysis, glutathione was added to the exhaustively oxidized solution (eqn. 2). After high performance liquid chromatography, compound **2** was isolated as the major product in 45% yield (98-99% purity grade). These preliminary results provide a basis for further *in vivo* biological investigations.

1. T.J. Monks, S.S. Lau, *Ann. Rev. Pharmacol. Toxicol.*, **1998**, *38*, 229.
2. R.T. Miller, S.S. Lau, T.J. Monks, *Eur. J. Pharmacol.*, **1997**, *323*, 173.
3. R.T. Miller, S.S. Lau, T.J. Monks, *Chem. Res. Toxicol.*, **1995**, *8*, 634.
4. F. Zhang, G. Dryhurst, *J. Electroanal. Chem.*, **1995**, *398*, 117.
5. X.M. Shen, F. Zhang, G. Dryhurst, *Chem. Res. Toxicol.*, **1997**, *10*, 147.
6. H. Li, G. Dryhurst, *J. Neurochem.*, **1997**, *69*, 1530.



Scheme **1**



Scheme **2**