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ROLE OF DDT AND DDE ON MDR1 INDUCTION AND STABILITY

Arsalan Shabbir¹, Susan Distasio¹, Jiangbo Zhang², Christopher Cardozo² and Avrom J. Caplan¹
¹Department of Pharmacology and Biological Chemistry, Mount Sinai School of Medicine, New York NY 10029, ² Rehabilitation and Research Development Center of Excellence for the Secondary Consequences of Spinal Cord Injury, VA Medical Center Bronx, NY

DDT and DDE are persistent organochlorine compounds that are associated with endocrine disruption in animals. Since both compounds are known to accumulate in cells, we analyzed whether they were substrates for xenobiotic efflux pumps such as p-glycoprotein, the product of the MDR1 gene. Using a human hepatocarcinoma cell line (HepG2), we tested for the ability of DDE and DDT to inhibit the efflux of a fluorescent pump substrate, Rhodamine 123. The results of these experiments showed that DDT was a weak pump substrate, and that DDE had almost no ability to affect Rhodamine transport. Thus, DDT and DDE accumulate in cells because they are poor substrates for efflux pumps. Subsequent studies addressed whether DDT or DDE induced MDR1 gene expression as part of the human response to xenobiotic exposure. We observed that both compounds induced MDR1, but only to 2-3 fold above background at exposures in the 1-10 μ Molar range. However, Western blot analysis revealed that the levels of p-glycoprotein were reduced substantially in cells exposed to micromolar amounts of DDE or DDT. Current studies investigating the mechanism underlying this reduction will be presented.