INTRODUCTION

- Arsenic is a ubiquitous occupational and environmental contaminant that imposes threat to humans through its toxicity and carcinogenicity. Thiocarbamates, such as monomethylarnihoarsenic acid (MMMTA), have been detected in the urine of arsenic-exposed humans and animals suggesting their involvement in arsenic toxicity.
- Both inorganic arsenic and its methylated metabolites have been shown to modulate aryl hydrocarbon receptor (AhR)-regulated phase I (such as Cyp1a1) and phase II (such as Nqo1) xenobiotic metabolizing enzymes. Cyp1a1 is involved in carcinogenesis through activating procarcinogens, while Nqo1 contributes to cytoprotection as a member of the antioxidant defense system.

OBJECTIVES

Examining the effect of MMMTA on constitutive and inducible expression of cytochrome P450 1a1 (Cyp1a1) and NADPH:quinone oxidoreductase (Nqo1) at mRNA, protein, and enzymatic activity levels using murine hepatoma (Hepa1c1c7) cells.

MATERIALS & METHODS

Murine hepatoma (Hepa1c1c7) cells were treated with increasing concentrations of MMMTA (0, 1, 5, and 10 µM) in the absence and presence of 1 nM TCDD at mRNA, protein, and enzymatic activity levels using murine hepatoma (Hepa1c1c7) cells.

SUMMARY AND CONCLUSIONS

- MMMTA does not affect Hepa1c1c7 cells viability at all concentrations tested.
- MMMTA decreases Cyp1a1 mRNA without effect its protein or catalytic activity.
- MMMTA only induces Nqo1 in the presence of TCDD at mRNA and protein levels.
- MMMTA has a differential modulatory effect on Cyp1a1 and Nqo1 that entails diminishing carcinogenic risk and eliciting antioxidant cytoprotection.

RESULTS

Figure 2. Effect of MMMTA on constitutive and TCDD-induced Cyp1a1 (A) and Nqo1 (B) mRNA in Hepa1c1c7 cells. Cells were treated with increasing concentrations of MMMTA in the absence and presence of 1 nM TCDD for 6 h. Results are presented as mean ± SEM (n=6). (*) P < 0.05, compared to control (concentration 0 µM); (¶) P < 0.05, compared to TCDD.

Figure 3. Effect of MMMTA on constitutive and TCDD-induced Cyp1a1 (C) and Nqo1 (D) mRNA in Hepa1c1c7 cells. Cells were treated with 10 µM of MMMTA in the absence and presence of 1 nM TCDD for 3, 6, 12, and 24 h. Results are presented as mean ± SEM (n=6). (*) P < 0.05, compared to control (concentration 0 µM); (¶) P < 0.05, compared to TCDD.

Figure 4. Effect of MMMTA on constitutive and TCDD-induced Cyp1a1 (E) and Nqo1 (F) protein in Hepa1c1c7 cells. Cells were incubated for 24 h with increasing concentrations of MMMTA in the absence and presence of 1 nM TCDD. Results are presented as mean ± SEM (n=3). (*) P < 0.05, compared to control (concentration 0 µM); (¶) P < 0.05, compared to TCDD.

Figure 5. Effect of MMMTA on constitutive and TCDD-induced Cyp1a1 catalytic activity in Hepa1c1c7 cells. Cells were incubated for 24 h with MMMTA in the absence and presence of 1 nM TCDD. Data from EROD assay are presented as mean ± SEM (n=6). (*) P < 0.05, compared to control; (¶) P < 0.05, compared to TCDD.

Figure 6. Effect of MMMTA on cell viability. Hepa1c1c7 cells were treated for 24 h with MMMTA (0, 1, 5, and 10 µM) in the presence of 1 nM TCDD. Cell cytotoxicity was determined using the MTT reduction assay. Data are expressed as the percentage of untreated control (100%) ± SEM (n=6).

ACKNOWLEDGEMENT

This work was supported by Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant RGPIN 250139 to A.O.S.E., M.A.E. is the recipient of Pharmacy PhD Alumni Graduate Student Scholarship.

The authors declare that they have no known conflicting interests.

Modulation of aryl hydrocarbon receptor (AhR)-regulated genes expression by monomethylarnihoarsenic acid (MMMTA) in Hepa1c1c7 cells

Mahmoud A. El-Ghiaty, Mohammed A. Alqahtani, and Ayman O.S. El-Kadi
Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada