Modulation of androgen receptor function by brominated flame retardants

av

Joubert Banjop Kharlyngdoh

Akademisk avhandling

Avhandling för filosofie doktorsexamen i biologi, som kommer att försvaras offentligt
Fredag den 05 juni 2015 kl. 10.00,
HSM, Örebro Universitet

Opponent: Prof. Peter Pärt
European Commission, Joint Research Centre,
Institute for Environment and Sustainability, Italy

Örebro universitet
Institutionen för naturvetenskap och teknik
Fakultetsgatan 1
701 82 ÖREBRO
Abstract


Sex steroids play a vital role in the development of gonads, secondary sexual characteristics as well as in reproduction. Alterations in the balance of sex steroids can bring about disturbances in the male to female ratio in a population. The presence of environmental pollutants has resulted in feminization and masculinization of animals, through activation of sex-related signaling pathways and interactions with receptors. In the first part of the study, using a combination of in silico and in vitro approach, we identified the brominated flame retardants (BFRs) allyl 2,4,6-tribromophenyl ether (TBP-AE), and 2,3-dibromopropyl-2,4,6-tribromophenyl ether (TBP-DBPE) and its metabolite 2-bromoallyl 2,4,6-tribromophenyl ether (TBP-BAE) as potent antagonists to the human androgen receptor. Due to their ability to alter the L-type amino acid transporter encoding genes, these compounds are also potential neuronal disruptors. The second study showed that the BFR 1, 2-dibromo-4-(1, 2-dibromoethyl) cyclohexane (DBE-DBCH) was able to bind and activate the zebrafish androgen receptor but at a lower potency when compared to that of the natural ligand 11-ketotestosterone. In vivo studies, further showed that DBE-DBCH affected early development in zebrafish. The third study was focused on the promiscuity of androgen receptor resulting from W741C and T877A mutations associated with prostate cancer and resulting in enhanced activation potency by the non-androgenic substances DBE-DBCH diastereomers. The fourth study was aimed at determining the effect of mixed exposures to the AR agonist DBE-DBCH and the AR antagonists TBP-AE, TBP-BAE and TBP-DBPE, a condition normally found in environmental and house dust sample exposures. TBP-AE, TBP-BAE and TBP-DBPE when present at higher concentrations inhibited DBE-DBCH-induced AR activity and the inhibition of AR function occurred at the nucleus level. DBE-DBCH and TBP-DBPE, counteracted each other on the expression of steroidogenic genes, and the results indicate an involvement in prostate growth and reproductive function.

Keywords: DBE-DBCH, TBP-AE, TBP-BAE, TBP-DBPE, androgen receptor, endocrine disrupters, brominated flame retardant

Joubert Banjop Kharlyngdoh, School of Science and Technology, Örebro University, SE-701 82 Örebro, Sweden, e-mail: joubert.banjop-kharlyngdoh@oru.se