Organizational Effects of Early-Life Exposure to Low-Dose Bisphenol-A (BPA) and Diethylstilbestrol (DES) on Hypothalamic Circuits Regulating Energy Balance

H. MacKay, Z. Patterson, R. Khazall, A. Abizaid
Department of Neuroscience, Carleton University. Ottawa, ON.

Introduction

Bisphenol-A (BPA) is a ubiquitous chemical plasticizer that is used in the production of polycarbonate plastics and epoxy resins. Because of its structural similarity with endogenous estrogen such as 17β-estradiol, as well as a potent androgen receptor (e.g. dihydrotestosterone (DHT)), it has been suggested as an endocrine disruptor. In addition to estrogen and androgen receptors, BPA binds to the estrogen receptor α (ERα) and the estrogen receptor β (ERβ) of the hypothalamic arcuate nucleus (ARC). This region is the site of origin for the anorexigenic POMCexpressing neurons that regulate energy balance and maintain body weight and composition. The hypothalamic POMC-expressing neurons are critical for the proper maintenance of energy balance and are likely to be affected by a wide range of environmental factors, including low-dose BPA exposure. The ARC of the hypothalamus is comprised of five main nuclei: PVN, VMN, DMN, AHA, and VMN. The PVN contains the majority of POMC-expressing neurons, which are responsible for the regulation of appetite and energy balance. The VMN contains the majority of agouti-related protein (AgRP)-expressing neurons, which are responsible for the regulation of energy balance and are antagonistic to the POMC-expressing neurons. The results of this study show that perinatal exposure to environmentally relevant doses of BPA leads to sexually dimorphic adverse effects on the hypothalamic POMC and AgRP-expressing neurons, as well as on the expression of key downstream genes and the regulation of energy balance.

Method

Material and Methods: Male Sprague-Dawley rats (4-6 weeks old) were obtained from a local supplier and were housed in a reverse cycle, 12:12 h light:dark cycle with ad libitum access to food and water. The animals were randomly assigned to one of the following four groups: control (CON), low BPA (LBPA), high BPA (HBPA), and DES. The animals were exposed to these treatments postnatally, and at 3 months of age, they were placed on a high-fat diet (60% kcals from fat, 5.24kcal/g) for 2 months. The experimental procedures were approved by the institutional animal care and use committee.

Histology: The ARC was rapidly dissected from brains in the control (CON) and the experimental (HFD) groups. Tissue sections were collected using a protocol that prevents apoptosis from occurring during tissue processing and analysis. The tissue sections were then analyzed using unbiased stereology techniques.

Hypothalamic mRNA Expression: Tissue samples were collected from the ARC of the control (CON) and the experimental (HFD) groups. The tissue samples were then analyzed using qRT-PCR and MilliPlex Mouse Adipokine kits.

Conclusions

We have demonstrated that perinatal exposure to environmentally relevant doses of BPA and DES leads to insulin and glucose intolerance in males. The adverse effects of BPA exposure are more pronounced in males, and the effects of DES exposure are more pronounced in females. The results of this study suggest that perinatal exposure to environmentally relevant doses of BPA and DES leads to sexually dimorphic adverse effects on the hypothalamic POMC and AgRP-expressing neurons, as well as on the expression of key downstream genes and the regulation of energy balance.

Acknowledgements

This study was supported by the Canadian Institutes of Health Research (CIHR). The authors would like to thank the CIHR for their support. We would also like to thank the reviewers for their helpful comments.