Modulation of Hormone Signaling by Cadmium: From Molecular Mechanisms to Health Implications

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet officiellt försvaras i Samuelssonsalen

Fredagen den 18 Oktober, 2013, kl 09.30

av

Imran Ali
M.Sc.

Huvudhandledare:
Dr. Krister Halldin
Karolinska Institutet
Institutet för miljömedicin

Bidhandledare:
Professor Helen Håkansson
Karolinska Institutet
Institutet för miljömedicin
Enheden för miljömedicinsk riskbedömning

Docent Agneta Åkesson
Karolinska Institutet
Institutet för miljömedicin
Enheden för nutritionsepidemiologi

Dr. Pauliina Damdimopoulou
Karolinska Institutet
Institutionen för klinisk vetenskap, intervention och teknik

Fakultetsopponent:
Professor Mats Olovsson
Uppsala Universitet
Institutionen för kvinners och barns hälsa
Obstetrik/Gynekologi

Betygsnämnd:
Docent Lena Sahlin
Karolinska Institutet
Institutionen för kvinners och barns hälsa
Enheden för reproduktionsendokrinologi

Professor Jonas Tallkvist
Sveriges lantbruksuniversitet, SLU
Institutionen för biomedicin och veterinär folkhälsovetskap
Sektionen för farmakologi och toxikologi

Docent Erika Gustafsson
Läkemedelsverket
Tillstånd, effekt och säkerhet

Stockholm 2013
ABSTRACT

Cadmium is a toxic metal classified as human carcinogen and ubiquitously found in our environment mainly from anthropogenic activities. Exposure to cadmium has been associated with increased risk of certain hormone-dependent cancers in humans, and the metal has been proposed to possess endocrine disruptive properties by mimicking the physiological actions of estrogens. However, the mechanisms behind these effects are unclear. The overall aim of this thesis was to provide mechanistic insights into the estrogenicity of cadmium that may have implications for the human health. To achieve this aim, investigations on the estrogen-like effects of cadmium as well as possible involvement of classical/non-classical estrogen receptor signaling was studied in mice, and these mechanisms were further scrutinized in cell-based models. Furthermore, associations of biomarker of cadmium exposure with endogenous circulating sex hormones were evaluated in a population-based study of women.

Results presented here indicate that exposure to cadmium does not affect the genomic estrogen response in vivo in mice, suggesting that classical estrogen signaling is not targeted by cadmium. However, some estrogen-like effects were observed in cadmium exposed mice, i.e. significant thickening of uterine epithelia, in the absence of uterine weight increase, and activation of ERK1/2 MAPKs in the liver. This suggests the existence of alternative signaling pathways modulated by cadmium. In addition, exposure to a wide dose range of cadmium, dose-dependently increased the expression of the endogenous genes Mti1, Mti2, p53, c-fos, and Mdm2 in mouse liver, with p53 being the most sensitive gene. However, phosphorylation of ERK1/2 was already induced at the lowest exposure level (0.5µg/kg body weight), rendering ERK1/2 a more sensitive marker of exposure than any change in gene expression. Furthermore, in vivo findings suggest that cadmium-induced effects are markedly concentration dependent: low-level exposure activates protein-kinases whereas high-level exposure turns on cellular stress responses. The data from in vitro studies indicate that cadmium at regular human exposure levels activates protein-kinase signaling through Raf-MEK-ERK/MAPKs, and we identified EGFR and GPR30 as the mediating receptors. This cadmium-induced activation of protein-kinases further leads to a disturbance in Mdm2/p53 balance, with a significant increase in the Mdm2/p53 ratio in the presence of genotoxic compounds, which in turn suggest that cadmium may disrupt stress response to genotoxins. In 438 postmenopausal women, a positive association was observed between the concentrations of cadmium in blood and testosterone in serum, while an inverse association was observed with estradiol. This may suggest that cadmium affects steroidogenesis.

In conclusion, data presented in this thesis collectively suggests that cadmium-induced estrogen-like effects do not involve classical estrogen receptor signaling but rather appear to be mediated via membrane-associated signaling. The activation/ transactivation of GPR30/EGFR-Raf-MEK-ERK/MAPKs and Mdm2 represent a general mechanism by which cadmium may exert its effects. Since EGFR, ERK and Mdm2 are all known key players in cancer promotion, cadmium-induced activation of these and disturbance in the estradiol/testosterone balance in women may have implications for the promotion/development of hormone-related cancers.