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Endocrine Disruption in the Omics *Era*: New Views, New Hazards, New Approaches

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Supplementry Material Table S1. Summary of laboratory controlled and field studies that have utilized transcriptomic techniques in Ecotoxicological research of Endocrine disruption chemicals.

Species	Compounds	MoA	Effects	Study	References
Xenopus laevis	Bisphenol A	TH-signaling pathway	Inhibitory on metamorphosis	T	[1]
Danio rerio	17-ethinylestradiol Flutamide	Estrogenic action Anti-androgenic action	Induced terpenoid backbone pathways Induce neurotransmitter and hormone activity	T	[2]
Danio rerio	17β-estradiol 17α-ethynyestradiol Permethrin Atrazine Nonylphenol	Inflammation and infection	Induce innate immune system	T	[3]
Danio rerio	Atrazine	Neuroendocrine and reproductive system development Cell cycle control Carcinogenesis	Disruption in the release of LH and stimulation of aromatase activity	T	[4]
small fish	17-ethynyl estradiol Fadrozole 17-trenbolone Fipronil Prochloraz Flutamide Muscimol Ketoconazole Trilostane Vinclozolin	Stress response Apoptosis Cell cycle	HPG-axis compiled, p53 and TGF-beta signaling pathways	T	[5]
Danio rerio	Fadrozole	Neurodegenerative stress in brain tissue	Differentiation, development, DNA replication, and cell cycle	T	[6]
Pimephales promelas		Reproductive disorders	Induced the one-carbon pool by folate pathway Induce cholesterol synthesis	T	[7]

(Supplementry Material Table 1) contd.....

Species	Compounds	MoA	Effects	Study	References
SH-SY5Y cells	2,3,7,8-tetrachlorodibenzo-p-dioxin Polychlorinated biphenyls Propylthiouracil Iodoacetic acid Methylmercury β-estradiol Methimazole 3-methylcholanthrene Aminotriazole Amiodarone Cadmium chloride Dimethoate Fenvalerate Iopanoic acid Methoxychlor 4-methylbenzylidene-camphor Octylmethoxycinnamate	Thyroid hormone production	Detection deiodinase deficiency	T	[8]
Peripheral blood cells of Flemish adults	Lead Benzene PAHs PCBs Dioxin Hexachlorobenzene p,p'-DDE Cadmium	Estrogen and STAT5 signaling		T	[9]
Zebrafish Medaka	Genistein	Apoptosis Estrogenic response Hox gene expression Steroid hormone synthesis	Thyroidal mode of action Disruption of the nervous system development	T	[10]
Nucella lapillus	TBT Rosiglitazone	Fertility Energy metabolism Reproduction Fat deposition Carbohydrate	Steroid dysfunction Neuroendocrine peptide hormone dysfunction Retinoid mechanisms Peroxisome proliferator–activated receptor (PPAR) pathways	T	[11]
Gasterosteus aculeatus	Ethinyl-estradiol	EE2-responsive genes	Hepatic vitellogenins and choriogenins Choriogenins showed the more sensitive responses Phosvitinless vitellogenin C transcripts were highly expressed	T	[12]
Danio rerio	Bisphenol-A	Ephrin receptor Clathrin-mediated endocytosis Synaptic long-term potentiation Integrin Tight junction Vascular endothelial growth factor Those processes were deregulated Axonal guidance	Nervous Cardiovascular Skeletal-muscular Blood and reproductive systems	T	[13]
Rainbow trout	PCBs Resveratrol β -naphthoflavone	Aryl hydrocarbon receptor dependent signaling Aryl hydrocarbon receptor independent signaling	Disrupts steroid production Sex steroid biosynthesis Molecular regulation of neuroendocrine pathways that are also AhR-independent Neuroendocrine function of stress	T	[14]
Scrobicularia plana			Cell signaling Microtubule assembly Cell cycle control Sperm physiology Energy production/metabolism	T	[15]

(Supplementry Material Table 1) contd.....

Species	Compounds	MoA	Effects	Study	References
Fundulus heteroclitus	17-α-ethinylestradiol	Caspase 8 Cyclin B (Cycb) Cyclin-dependent kinase 1 (Cdk1) Histone acetlytransferase Apoptosis-related cysteine peptidase (Casp1)	Cell processes associated with lipids were affected	T	[16]
Mouse liver in vivo	di-(2-ethylhexyl)-phthalate (DEHP)	PPARα targets Heme synthesis Rev-erbα pathway cellular clock energy metabolism Constitutive Androstane Receptor (CAR)	Hepatic expression of Alas1	T	[17]
Oncorhynchus mykiss	17-α-ethinylestradiol 2,3,7,8-tetrachloro-di-benzodioxin (TCDD) Paraquat (PQ) 4-nitroquinoline-1-oxide (NQO) Mixture of the 4 contaminants	Activation of ER-dependent pathways Phase I and II biotransformation enzymes may be induced Redox cycling creating cellular oxidative stress	Vitellogenin and vitelline envelope protein Cytochrome p4501A and UDP-glucuronosyl transferase Glutathione reductase and gammaglutamyl cysteine synthetase	T	[18]
Oncorhynchus kisutch	17-α-ethinylestradiol	Circadian rhythm signaling Calcium signaling Peroxisome proliferator-activated receptor (PPAR) signaling PPAR/retinoid x receptor activation Netrin signaling	Luteinizing hormone subunit Follicle-stimulating hormone subunit Gonadotropin releasing hormone (GNRH) Transforming growth factor-signaling	T	[19]
Goldfish	Bisphenol A DEHP Nonylphenol	AMPK and cAMP signaling	Stress response	T	[20]

T- transcriptomics

Table S2. Summary of laboratory controlled studies that have utilized proteomics techniques in Ecotoxicological research of Endocrine disruption chemicals.

Species	Compounds	Disease associated	Techniques	Protein identification	Study	Role	References
Human pituitary tumors		Oncogenic GsαProtein (GSP)–activating mutations Pituitary tumor–derived fibroblast growth factor receptor-4 (ptd-FGFR4) GADD45 Tumor suppressor gene mutations associated with multiple endocrine neoplasia type 1 (MEN1) bone morphogenic protein (BMP)4 pituitary tumor–transforming gene (PTTG)	Immunohistochemistry epigenetic reductions in p27		P		[21]

(Supplementry Material Table 2) contd.....

Species	Compounds	Disease associated	Techniques	Protein identification	Study	Role	References
Sperm proteins frozen epididymides of rats	Vinclozolin		Two-dimensional fluorescence difference gel electrophoresis	Mass spectrometry	P	Sperm fertilizing ability Malate dehydrogenase 2 Aldehyde dehydrogenase Two mitochondrial enzymes	[22]
Zebrafish	Prochloraz		Two-dimensional electrophoresis	LC–MS/MS	P	Metabolism Learning Neuroprotection Calcium regulation	[23]
Cell model H295R	Zearalenone (mycotoxin)	Endocrine dysfunction Several oncogenes	Stable-isotope labeling by amino acids in cell culture (SILAC)		P	Oxidative phosphorylation pathway Mitochondrial dysfunction pathway	[24]
Artery smooth muscle cells (PASMC)	Exposed to TGF-β1 Cells pretreated with vehicle or cGMP		Mass spectroscopy Two-dimensional differentiaL in-gel electrophoresis coimmunoprecipitation and immunostaining		P		[25]
Serum proteins of pediatric population		Systemic inflammation Endocrine disruption in humans	Spectral count shotgun proteomics		P	Atheroprotective lipid profiles Acute-phase proteins Reduced diurnal cortisol in children	[26]
Rana catesbeiana	T3	Thyroid hormone disruption	cDNA array Mass spectrometry Isobaric tags for relative and absolute protein quantitation; (iTRAQ)		T P M		[27]
Reptiles Amphibians Fish	Endocrine disruptors estrogens estrogenic chemicals	Changes in reproductive Changes in nonreproductive organs	cDNA microarrays		T P M		[28]
Mytilus galloprovincialis	BDE 47	Hepatotoxicity Carcinogenecity Neurotoxicity	Two-dimensional gel electrophoresis MS analysis 1H NMR spectroscopy		PM	Disturbance in energy metabolism in males Disruption in both osmotic regulation and energy metabolism in females Cell apoptosis Reduced reactive oxygen species (ROS) production Protein homeostasis in male mussels Disturbance in female mussel proteolysis	[29]

(Supplementry Material Table 2) contd.....

Species	Compounds	Disease associated	Techniques	Protein identification	Study	Role	References
fetus of Pregnant sheep	Mixture of PCB153 and PCB118	Affected developing fetal testis proteome	Two-dimensional (2D) gel-based proteomics	Liquid chromatography (LC)–mass spectroscopy (MS)/MS	P	Protein synthesis Cytoskeleton regulation Cellular processes as stress response	[30]
Hyalella azteca Diporeia spp.	Desethylatrazine Atrazine	Non-specific stress response	Two-dimensional gel electrophoresis		P	Mitochondrial function hormesis Energy production	[31]
SGBS cells		aAdipokines	2D-MS/MS nLC-MALDIMS/MS		P		[32]
Rainbow trout	β-estradiol	Stress response	Two-dimensional gel electrophoresis		P	Induce vitelogenin synthesis	[33]
Stimulated weanling rat	Linuron (LIN) Flutamide (FM) 1,1-dichloro-2,2-bis(4 chlorophenyl)-ethane (DDE)		Two-dimensional gel electrophoresis	Mass spectrometry	P	Identification of three isoforms of L-amino Acid Oxidase (LAO)	[34]
Cell line cultures (H295R)	PCB 153 PCB 126 PCB 118	Elevated estradiol secretion increasing estradiol, cortisol, progesterone secretion Increased estradiol and cortisol secretion	Two-dimensional (2D) gel-based	Liquid chromatography with mass spectroscopy (LC-MS/MS)	P	Protein synthesis Stress response Apoptosis Perturbed steroidogenesis and protein expression Cellular processes	[35]
Immune organs of mouse	Bisphenol A	Immune interaction pathways	2D gel analyses	Mass fingerprinting	P	Proteins apo-AI, DPPIII, and VAT1 associated with endocrine disorders	[36]

M- Metabolomics
P- Proteomics
T- Transcriptomics

Table S3. Summary of laboratory controlled studies that have utilized metabolomics techniques in Ecotoxicological research of Endocrine disruption chemicals.

Species	Compounds	Techniques	Study	Role	Effects	References
Pregnant rats	Butylbenzyl phthalate (BBP)	NMR	M	Amino acid metabolism Purine metabolism TCA cycle Phospholipid metabolism	Anti-androgenic activity of BBP	[37]
Rutilus rutilus	17-α-ethinylestradiol	Mass spectrometry Metabolite profiling Tandem GC-MSMS analysis	M	Sex steroid pathway Glucocorticoid pathway		[38]
Gasterosteus aculeatus	Ethinyl-estradiol (EE2)	cDNA microarrays 1H NMR ELISA methods	T M		Induced serum vitellogenin protein Induced Phosvitinless vitellogenin c transcripts	[12]

(Supplementry Material Table 3) contd.....

Species	Compounds	Techniques	Study	Role	Effects	References
yeast human cell H295R	Ethanol Fenarimol Genistein Ketoconazole Tamoxifen Trenbolone Triton X-100 Vinclozolin Zearalenone Methyltestosterone Ethinylestradiol Dimethyl formamide Diethylstilbestrol dipropionate Bisphenol A Caffeine Colchicine	YES- yeast estrogen screening YAS- yeast androgen screening GC–MS LC–MS/MS	M	Corticosteroid synthesis inhibition in the adrenal cortex		[39]
Lampsilis fasciola	17-ethinylestradiol (EE2)	Liquid chromatography (LC) Gas chromatography(GC) Tandem mass spectrometry (MS2) Tandem mass spectrometry sequencing	M	Signal transduction Immune response Neuromodulation	Glycogen metabolism end products Glucose Several essentialfatty acids in females Reductions in energy reserves	[40]
Hyalella azteca	atrazine desethylatrazin (DEA)	GC x GC/TOF-MS LC/TOF-MS	M	By-products of b-oxidation of fatty acids Disruption in energy metabolism Perturbations in neuropeptide hormonal systems		[41]
H295R cells	Vinclozolin	Gas chromatography–mass spectrometry(GC–MS) Liquid chromatography–MS/MS (LC–MS/MS)	M			[42]

M- Metabomics

T- Transcriptomics