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The developmental neurotoxicity of lead in rat primary aggregating brain cell cultures using transcriptomics and metabolomics approaches

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Tox-21c proposed a paradigm shift in the field of toxicology. Instead of relying on traditional animal experiments, the report proposes the application of the latest advances in science and technology to develop more relevant test strategies. The concept is that pathways of toxicity (PoT) can be identified using *in vitro* cell systems, high throughput testing, 'omics' approaches, systems biology and computational modeling. The so-called "pathways of toxicity" are defined as changes in normal biological processes, e.g. cell function, communication and adaptation to environmental changes, which are expected to result in adverse health effects. An area of toxicology where Tox-21c could have a significant impact is developmental neurotoxicity (DNT). There is concern that exposures to environmental chemicals contribute to the increasing incidence of neurodevelopmental disorders in children. However, due to lack of DNT studies only very few substances have been identified as developmental neurotoxicants. This study aimed to develop an *in vitro* approach using metabolomics and transcriptomics for DNT assessment. A 3D rat primary neuronal organotypic model was exposed to lead chloride (0.1, 1, 10μM) from day 7 up to 21. Quantitative measurement of genes expressed in different cell types (nestin in neural precursor cells, neurofilament-200 (NF-200) in neurons, S100β in astrocytes and myelin basic protein (MBP) in oligodendrocytes) and mass spectrometry based metabolomics measurements were performed.

Treatment with lead chloride significantly down-regulated the mRNA levels of NF-200, S100β and MBP. In contrast the mRNA levels of nestin were significantly increased. The obtained data indicates different effects by lead chloride exposure on all cell types present. Moreover, the mass spectrometry analysis showed differences in metabolite levels between control and treated cells in a concentration dependent manner. Further analysis of the altered metabolites should give mechanistic insight into the DNT of lead. This study demonstrates that gene expression and metabolomic analysis can be sensitive endpoints for DNT assessment.

Biography

Dr. Helena Hogberg obtained a bachelor degree in Biology and a master degree in Molecular biology from Stockholm University in 2004 and 2005. She gained her PhD degree from the Physiology Department, Stockholm University in Sweden in 2009. The scientific work during her Ph.D. was performed at the European Centre for the Validation of Alternative Methods (ECVAM), European Commission, Ispra, Italy and aimed to develop new in vitro approaches to detect chemicals with developmental neurotoxicity (DNT) potential. Since 1st of April 2010 Dr. Helena Hogberg is a postdoctoral fellow at Johns Hopkins University, Bloomberg School of Public Heath, Center for Alternatives to Animal Testing, Baltimore, MD, US. Her research aims to use transcriptomics and metabolomics for the detection of pathways of toxicity as proposed by the NAS report Toxicology of the 21st century from 2007. Her main focus is in the area of developmental neurotoxicity (DNT).

She was recently in the Scientific Steering Committee of the Third International Conference on Alternatives for Developmental Neurotoxicity testing hosted in Italy in May 2011 by the Joint Research Centre, European Commission. She has several peer-reviewed publications including a book chapter in the field of DNT.