that exposure to CS_2 may be considered a risk factor in disturbances of arterial blood pressure regulation.

341 MICROARRAY ANALYSIS REVEALS COMPLEX DEREGULATION OF GENE EXPRESSION IN HEART TISSUE UPON AROCLOR 1254 TREATMENT – IMPLICATIONS FOR CARDIOTOXICITY

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Polychlorinated biphenyls (PCBs) are well known environmental pollutants and several reports are available to implicate PCBs in cardiovascular disease. Little is known about the effects of PCBs on gene expression in the heart. We investigated the effects of Aroclor 1254 (20mg/kg), a well known mixture of PCB isomers and congeners on gene expression in rat hearts by employing a microarray. Its design enabled a survey of gene expression and included gene coding for basic biological functions, such as detoxification, cell proliferation, tumor development, heat shock response, signal transduction, apoptosis, cell cycle regulation, metabolism and so forth.We found 10 genes to be increased >1.5-fold and 25 genes to be repressed <70% of controls. The transcription factors c-jun and serum response factor were significantly repressed upon Aroclor 1254 treatment. Further, gene expression of the vascular endothelial growth factor and the early growth response protein were repressed to 65% and 24% of controls. In contrast, genes coding for the catecholamine-degrading enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) were significantly upregulated (1,9 and 2,3-fold). Similar, transcript level of the aldehyde dehydrogenase ALDH1A1 was strongly increased upon Aroclor 1254 treatment. We additionally investigated promoters of regulated genes and identified several Ahr binding sites in basically all genes deregulated by Aroclor 1254. We suggest Ahr-ARNT to play a role in the transcriptional activation of heart specific genes upon PCB treatment and found PCBs to modulate expression of genes coding for programs of cellular differentiation and stress. Our findings in rat heart may be of importance in understanding the increase of cardiovascular disease in polluted areas.

342 CARDIOVASCULAR TOXIC EFFECTS OF ACUTE EXPOSURE TO HIGH GLUCOSE CONCENTRATIONS IN RATS

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Chronic hyperglycemia leads to cellular dysfunction that may become irreversible over time, a process that is termed glucose toxicity. This is mainly due to excessive intracellular glucose concentration which induces damage by increasing the production of free radicals. Cardiovascular toxic effects induced by hyperglycemia occur following acute exposure of cardiovascular specimens to high glucose concentrations (HGC). Our study showed that HGC (33.3 mmol/l) increase iNOS gene expression and nitric oxide levels in isolated rat hearts. Up-regulation of iNOS was accompanied by a marked concomitant increase of superoxide (O_2^-) production, a condition favouring the production of peroxynitrite, a powerful pro-oxidant that mediates the toxic effects of high glucose on heart, as suggested by the detection of cell apoptosis. Increased cardiac malondialdehyde (MDA) and poly(ADP-ribose) synthetase (PARS) activity were found. Cardiovascular consequences of these biochemical alterations were QT interval prolongation, coronary perfusion pressure (CPP) increase, and heart dysfunction. Glutathione, a powerful antioxidant capable of quenching both O_2^- and peroxynitrite, when infused along with high glucose, normalized CPP and reverses cardiac QT interval prolongation, induced by high glucose. Glutathione also reduced formation of peroxynitrites into cardiac cells as evidenced by reduced levels of nitrotyrosine immunostaining into the hearts subjected to HGC. Similarly, increase PARS levels and MDA activity induced by high glucose concentration were reduced by addition of glutathione to the medium. Therefore, therapeutic interventions against glucose toxicity are warranted because of the elevated markers of damage following hyperglycemia.

343 OXIDIZED LDL IS A MAJOR REGULATOR OF METABOLIC PATHWAYS IN HUMAN ENDOTHELIAL CELLS

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Enhanced oxidation of low density lipoprotein particles (oxLDL) is an important risk factor for vascular disease and atherosclerotic plaque formation. Upon intracellular availability oxLDL causes vascular toxicity and is considered to be responsible for an altered expression of adhesion molecules, production of radical oxygen species (ROS), scavenging of nitric oxide (NO) and formation of peroxynitrates. Overall, these events impair endothelial function and regulation of vascular tonus. To further our understanding of oxLDL induced endothelial toxicity, cultures of human endothelial cells (EAhy926) were treated with ascending doses of oxLDL (10 – 100μg/ml). We used an oligonucleotide microarray to study the expression of 9614 genes (Nimblegen). The design of the microarray enabled a survey of gene expressions and included genes coding for detoxification, cell proliferation, tumor development, heat shock response, signal transduction, apoptosis, cell cycle regulation, metabolism and so forth. We found oxLDL treatment to result in >2-fold induction of 130 highly abundant expressed genes and repression of 119 genes (<30% of control). Further, 69 genes were only expressed in oxLDL treated cells, whereas 78 gene were present in controls only. We employed gene ontology to interrogate metabolic networks and found glycolytic, lipid and steroid hormone metabolism to be altered. Specifically, oxLDL treatment of cultured endothelial cells resulted in increased transcript levels of palmotyl-protein thioesterase 2, sterol O-acetyl transferase, phospholipase C and A2, pyrroline-5-carboxylase amongst others. Likewise, oxLDL treatment resulted in altered arachidonic acid metabolism based on expression analysis of the cytochrome P450 monooxygenases 2C8, 2C9, CYP17 and others. This treatment also repressed gene expression of transcription factors nuclear factor 1 and HNF3alpha. Some of the altered gene expression findings were correlated with metabolic functions of the coded proteins. For instance, CYP2C mediated production of epoxyeicosatrienoic acids was repressed, as was the transcript level of the coded gene.

We thus demonstrate gene expression in cultured human endothelial cells to be dramatically altered upon treatment with oxLDL. We show oxLDL to be a powerful regulator of genes coding for metabolic pathways, and particular vascular cytochrome P450 monooxygenases. Our study contributes towards an understanding of endothelial toxicity brought about by oxLDL.

344 MODULATION OF PLASMA LIPID LEVELS AFFECTS B[A]P-INDUCED DNA DAMAGE IN TISSUES OF TWO HYPERLIPIDEMIC MOUSE MODELS

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To which extent modulation of plasma lipids plays a role in the uptake, transportation and distribution of lipophilic carcinogens like benzo[a]pyrene (B[a]P) is not yet clear. Therefore, we have investigated the effects of dietary modulated plasma lipids on B[a]P-induced DNA adducts after a single oral dose of B[a]P in several organs of two hyperlipidemic mouse models.

Male apoE*3-Leiden (n=22) and apoE-KO mice (n=20) were fed a high fat diet (HFC) or normal mouse chow (SRM-A) for three weeks, after which the animals were exposed to a single oral dose of 5 mg/kg.bw B[a]P and killed 4 days later. Plasma lipids were