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The Impact of Alcohol on the blood Pressure of Adolescents

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Introduction

As part of the sixteen-year follow-up of the Raine study participants filled in "Alcohol Diaries" assessing quantity and drinking patterns. Participants' blood pressure was also measured. This project assesses whether the established link between alcohol intake and blood pressure manifests as early as adolescence

Methods

1250 16-year old Raine study participants completed alcohol diaries asking about alcohol consumption; type, quantity and days they consumed it. Blood pressure was measured by trained nurses using a calibrated electronic sphygmomanometer (DINAMAP). Participants were supine and six readings were taken at two minute intervals over a ten minute period.

Results

Cohort was stratified based on number of standard drinks consumed: of the 1250, 651 had consumed 0 standard drinks, 355 consumed 0 to 10, 127 consumed 10.1 to 20 and 117 consumed >20. Mean was 6.9 standard drinks with Std Dev 10.1. In terms of prehypertension (systolic BP >120 mm Hg), 20% of the "0 std drinks" group suffered from prehypertension, 24.6% of the "0 to 10 std drinks" group, 27.1% of the "10-20 std drinks" group and 29.1% of the "20+ std drinks" group.

Discussion

Since alcohol-intake has been established as a contributor to hypertension in adulthood, these findings have public health implications. They constitute another reason to reduce alcohol intake in adolescents and may attract further preventative health funds to this cause. Further it may influence government policy e.g. the "alco-pops" tax. Ultimately, given causality cannot be established without randomised control trials, further research is required on this topic.

Effects of omega-3 fatty acids and their derivatives on inflammation and oxidative stress in human placenta

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Introduction

Intrauterine inflammation and oxidative stress are implicated in the pathogenesis of common obstetric complications including preterm labour and preeclampsia. The aim of the present project was to assess the effects of fish oil-derived ω-3 PUFAs, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), on placental inflammation and oxidative stress.

Methods

Placental explants and decidual cells were cultured from term placentae *in vitro* and pre-incubated with lipid controls (linoleic acid; LA, gamma linolenic acid; GLA, oleic acid; OA, arachidonic acid; AA) or ω-3 PUFAs (20 μM) for 48-96 h. An inflammatory stimulus (LPS 1ug/mL) was provided following pre-incubation and qRT-PCR, cytokine ELISAs (TNF-α, IL-6) and oxidative stress assays were performed at 4- and 12-h. Data from multiple experiments were pooled and analysed by ANOVA and *post hoc* Dunnett test.

Results

Placental and decidual cell IL-6 production was significantly inhibited by DHA and EPA supplementation by 34% and 47%, respectively ($P < 0.01$), although surprisingly mRNA expression was not altered. Interestingly, OA and AA also inhibited IL-6 production to a comparable extent. Ω-3 PUFAs had no effect on TNF-α production, expression or markers of oxidative stress.

Discussion

These findings indicate that ω-3 PUFAs may exert protective effects in pregnancy through selective suppression of IL-6 production. The apparent lack of effect on IL-6 mRNA expression, TNF-α production and oxidative stress is at odds with the understood mechanisms of action of ω-3 PUFAs and their putative protective role in pregnancy.

The Role of Copy Number Variations in the Pathogenesis of Neuropsychiatric Disorders

Laura Florez

Introduction

Copy number variations (CNVs) and their role in human health and disease are becoming of increasing research interest. Within the past year, several studies reported association of rare 15q13.3 CNVs with a range of neuropsychiatric conditions. Limited data on penetrance and expressivity of these variants, hence their diagnostic and prognostic value, call for further studies. We have addressed the emerging need for standardized reliable methodology for CNV detection and validation in the context of 15q13.3 CNVs and neuropsychiatric disorders.

Methods

We have analysed 15q13.3 microaberrations, targeting the best candidate gene in the region (*CHRNA7*) in a phenotypically well characterized sample of ~600 cases and relatives with autism, schizophrenia and focal epilepsies.

Results

We show that the widely used TaqMan assays require rigid optimization and quality control for reliable results. 15q13.3 duplications were detected at frequencies, higher than previously reported, in schizophrenia and autism. Deletions were detected at the expected frequency (0.2%) in schizophrenia but not in the autism sample.

Discussion

Additional confirmatory analyses are needed for validation of detected CNVs. While initial results suggest reduced penetrance of duplications for clinically diagnosable illness, variable expressivity with milder neurocognitive and psychiatric manifestations should be examined in detail, to reveal the full spectrum of 15q13.3 phenotypes.

The effect of donor age on the remyelination potential of transplanted olfactory ensheathing cells in the demyelinated CNS

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Introduction

Olfactory ensheathing cell (OEC) transplantation is a promising approach to restore myelin in demyelinating conditions of the CNS. This study aimed to investigate the effect of donor age on the remyelination ability of transplanted OECs.

Methods

Highly purified populations of OECs extracted from embryonic (OEC_E), postnatal (OEC_P) and adult (OEC_A) rats were transduced with a GFP-labelled lentivirus and transplanted into X-irradiated ethidium bromide demyelinating lesions in adult rat spinal cords; control animals were injected with media only. After 21 days, histological analysis was performed using fluorescent, light and electron microscopy.

Results

Peripheral-type remyelination was seen after transplantation of OEC_A, OEC_P and, for the first time *in vivo*, OEC_E. In all ages OECs were directly associated with the majority of peripheral-type myelin labelled with P_0 or periaxin. OEC_E resulted in significantly more extensive remyelination than either OEC_P or OEC_A ($p<0.05$), which remyelinated axons to a similar extent.

Discussion

This study suggests that the myelination potential of OECs after transplantation into focal areas of demyelination is age-dependent until a point between E18 and P7, whereafter myelination potential is not affected by donor age. Therefore, we conclude that OEC_E are the optimal age for transplant-mediated CNS remyelination and repair, and transplantation studies assessing remyelination using OEC_A and OEC_P may be compared without donor age becoming a confounding factor.

The Role of SLIRP, A Nuclear Receptor Corepressor in Human Colorectal Cancer

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Introduction

Colorectal cancer (CRC) is a major cause of morbidity and mortality globally. Recent data implicates key roles for specific nuclear receptors (NRs) in CRC (e.g. the vitamin D receptor (VDR) and the peroxisome proliferator activated receptor γ (PPARγ)). A novel NR coregulator, steroid receptor RNA activator stem-loop interacting RNA-binding protein (SLIRP) is a potent repressor of VDR and PPARγ activity that has been shown to influence apoptosis and chemotherapeutic resistance (eg. Cisplatin), which has not been studied in CRC.

Methods

SLIRP levels in the SLIRP over-expressing SW620 CRC cell line were depleted using siRNA. Luciferase reporter assays were used to measure VDR/PPARγ activity. Cisplatin-induced apoptosis was measured using caspase assays and PARP cleavage analysis. cDNA microarray analysis was used to identify SLIRP regulated genes in CRC models.

Results

SLIRP depletion augments VDR/PPARγ reporter activity and significantly increases cisplatin-induced apoptosis in SW620 cells. cDNA microarray analysis of SLIRP depleted SW620 cells identified a range of genes, validated by RT-PCR.

Discussion

SLIRP is a potent regulator of VDR/PPARγ signalling and its depletion from CRC cells can enhance sensitivity to chemotherapeutic agents, this having a potential impact clinically (therapeutic strategies to reduce SLIRP's activity in CRC). Array data suggests SLIRP regulates a range of genes involved in CRC.

In UTERO exposure to arsenic via drinking water causes an early life deficit in post-natal lung development

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Background

Arsenic exposure via drinking water is a significant global health issue. While arsenic is a well recognised carcinogen, epidemiological data suggest a relationship between *in utero* arsenic exposure and non-malignant lung disease. We investigated the effect of *in utero* arsenic exposure on postnatal lung function using a mouse model.

Methods

Pregnant C57BL/6 mice were given drinking water containing 0 (control) or 100 ppb arsenic from gestational day 8 to birth. Lung volume and lung mechanics of offspring at 2 weeks of age were measured using plethysmography and the forced oscillation technique which partitions lung mechanics into parameters representing the conducting airways (R_{aw} = airway resistance) and lung parenchyma (G = tissue damping; H = tissue elastance).

Results

Arsenic exposed offspring were smaller ($p < 0.001$) than controls and had significantly higher lung parenchymal mechanics (G, $p < 0.001$; H, $p < 0.001$) for a given lung volume at 2 weeks of age indicating altered tissue structure. There was no difference in R_{aw} between arsenic exposed mice and controls.

Conclusions

The combination of delayed growth and mechanical evidence for altered tissue structure provide a mechanistic explanation for the epidemiological link between early life arsenic exposure and obstructive lung disease.

Modulating excitability of the human motor cortex during voluntary movement with transcranial magnetic stimulation

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Introduction

Non-invasive transcranial magnetic stimulation (TMS) interventions are available that target cortical plasticity and have potential to promote restoration of function after brain injury. Most promising is the combination of these interventions with physical therapy; however it is not known how effective these interventions are during movement. In this study we tested the efficacy of paired-pulse TMS intervention delivered during performance of a motor task.

Methods

Ten healthy subjects received 15 minutes of paired-pulse TMS intervention (1.5ms interpulse interval; IPI), in which pulse pairs were delivered during a 10%-of-maximum contraction of the first dorsal interosseous muscle. The effects of the intervention were assessed by measuring the level of facilitation at IPIs of 0.8-4.8ms in 0.2-0.3ms steps. Fifteen minutes of single-pulse TMS delivered during contraction served as a control.

Results

During the paired-pulse intervention MEP amplitude increased steadily to 137% of the initial value by the end of 15mins ($r=0.93$, $p<0.001$). There was no change in amplitude for the control experiment ($r=0.02$, $p=0.951$). Following intervention, MEP amplitude was increased at all IPIs, with the greatest increase (26%) at 1.5ms ($p=0.013$).

Discussion

A paired-pulse TMS intervention is effective during voluntary contraction, and may be a promising approach for combining TMS with physical therapy in neuro-rehabilitation.

Cerebral sequelae of ventilator induced haemodynamic disturbance exacerbated by antenatal inflammation

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Introduction

Preterm birth (PTB) is the greatest problem facing contemporary obstetrics in the developed world, being associated with life-long problems including cerebral palsy, cognitive impairment and respiratory disease. An ovine model was developed to investigate the relationship

between *in-utero* inflammation, PTB, resuscitation/ventilation, and cerebral injury. This study aims to characterise the relationship between ventilation-induced changes in neonatal cardiopulmonary haemodynamics and brain injury in the presence of antenatal inflammation.

Methods

Singleton Merino fetuses (n=24) were randomised to receive a saline or lipopolysaccharide (10mg, E.coli; LPS) intra-amniotic injection (Figure One) 2 or 4 days prior to PTB (128 days gestation). Fetuses were instrumented with catheters and transonic flowprobes, and ventilated using an injurious strategy associated with haemodynamic disturbance. Real-time systemic/cerebral blood flow and pressure monitoring were conducted throughout. Cerebral tissue was examined using histological, immunohistochemical and molecular techniques.

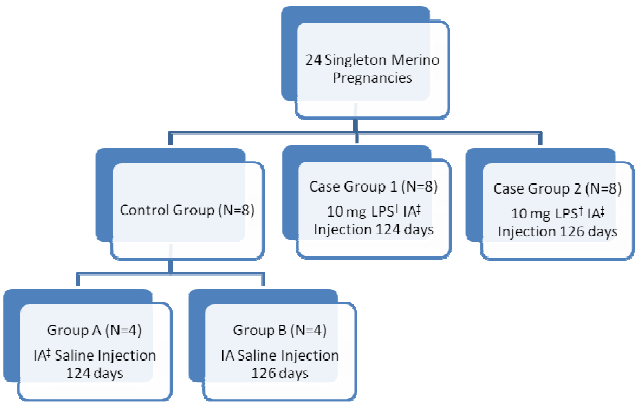
Results

Preliminary results suggest that the antenatal environment may predispose the preterm neonate to cerebral injury and subsequent long-term adverse neurodevelopmental outcomes resultant from ventilation.

Discussion

It has been hypothesised that cardiopulmonary haemodynamic disturbance, moderated by fetal/neonatal inflammation and neonatal ventilation, correlate with cerebrovascular/cerebral injury. If supported, this has potential implications for neonatal resuscitation and ventilation, and the need to balance immediate resuscitative success with long-term neurodevelopmental outcomes.

Figure One. Randomisation of Study Subjects



Note: † lipopolysaccharide endotoxin derived from Escherichia coli 0.55:B5 produces a transient effect consistent with human chorioamnionitis; ‡ Intra-amniotic injection at either 124 or 126 days gestation (term ovine gestation 150 days)

Stem cells endogenous to human breastmilk form milk-secreting ductal-alveolar structures in three-dimensional culture

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Introduction

Human breastmilk contains cells that generate differentiated epithelial lineages in primary culture. When cultivated in a three-dimensional biomatrix these cells form differentiated spherical milk protein-secreting structures resembling the *in vivo* secretory alveoli. These are distinct properties of multipotent stem cells.

Methods

Cells isolated from milk expressed from 20 lactating women were immunofluorescently labelled for stem and differentiated epithelial cell markers prior to cultivation then at three day intervals for 21 days of growth in monolayer culture and in differentiated three-dimensional cultures.

Results

All breast milk samples possessed a population of cells with a stem cell phenotype. Expansion of the stem cell population in culture occurred in the first five days of growth and depleted reciprocally with emergence of adherent cells expressing differentiated mammary epithelial markers. When grown in three-dimensional culture tissue architecture was highly dependant on cell plating density. Cultivation at high density results in rapid (<12 hours growth) self-assembly into ductal structures that later developed terminal alveolar structures.

Discussion

This verifies that human milk is a robust and non-invasive source of multipotent cells from lactating tissue that provide a novel platform for studying stem cell differentiation and mammary gland biology.