Diabetes Conference 2017

International Conference on

DIABETES, NUTRITION, METABOLISM & MEDICARE

July 24-26, 2017 Vancouver, Canada

Keynote Forum | Day 1

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Chris R Triggle

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Metformin: A drug for all reasons?

Metformin is the most frequently administered drug for the treatment of type 2 diabetes wherein it has vasculoprotective benefits and is also used for PCOS. Furthermore, trials are underway to assess its anti-ageing properties. Over the past ten years and based on evidence from the retrospective analysis of patient data it has also emerged that metformin may reduce the risk of various types of cancer. In addition, the data from a number of *in vitro* studies indicate that high (mM) concentrations of metformin may have anti-proliferative actions, but the relevance to clinical use is unclear and the cellular basis for the putative anti-cancer effect of metformin remains unknown. Our previous work with metformin indicates that within the concentration range that it is effective as an anti-hyperglycaemic drug metformin also protects the endothelium against the pro-senescence effects of hyperglycaemia (HG) and reverses HG-induced endothelial dysfunction (1,2). In the current study we examined the concentration-dependent effects of metformin on markers of angiogenesis and also markers of the pro-survival endoplasmic reticulum (ER) stress and autophagy pathways in micro-vascular endothelial cells (MECs) in culture.

Methods: Mouse MECs (MMECs) were exposed for 24h to a low concentration (50 µM), or a high concentration (2 mM) of metformin in normal glucose (NG), high glucose (HG), or a glucose-starved (GS) culture media. Markers of senescence (β-galactosidase) and ageing (Sirt1), ER stress, (GRP78, ATF4, CHOP), autophagy (LC3A & LC3B) and angiogenesis (antiangiogenic thrombospondin 1 (TSP1) were quantified by western blotting.

Results and Discussion: Exposure of MMECs to 50 µM metformin reduced HG-senescence as determined by the β-galactosidase assay ($P < 0.05$) and also protected against HG-induced reduction in Sirt1 expression ($P < 0.05$); however 50 µM metformin had no effect on GS-induced increases in the protein markers of ER Stress or autophagy. In contrast, exposure to 2 mM, but not 50 µM, metformin markedly reversed the effect of GS on ER stress proteins as evidenced by the significant decrease in the levels of GRP78 (~ 4 fold, $p<0.05$) ATF4 (~ 2 fold, $p<0.05$ and CHOP (~ 3 fold, $p<0.05$), similarly for autophagy (LC3A-I to LC3A-II ~ 5.5 fold, $p<0.05$; LC3B-I to LC3B-II ~ 4.3 fold, $p<0.05$) and in contrast to 50 µM, metformin raised TSP1 (~ 4.0 fold, $p<0.05$) and in both NG and GS reduced expression of the anti-ageing deacetylase, Sirt1, by ~ 25% ($p<0.05$). These data demonstrate concentration-dependent effects of metformin on endothelial function with pro-survival, pro-angiogenesis effects at 50 µM and anti-angiogenic and anti-survival effects at 2 mM. Whether anti-angiogenic effects of metformin can be achieved during clinical use will depend on the ability of endothelial cells in the blood vessels supplying solid tumours to accumulate metformin – a drug that is not metabolised in humans

Biography

Chris R. Triggle, PhD, FBPhS (Fellow of the British Pharmacology Society) joined Weill Cornell Medicine - Qatar in 2007 as Professor of Pharmacology and was the Assistant Dean Admissions 2009-2014. He was born in Hackney, London, UK, and obtained a B.Sc. (Honours) in Biological Sciences, University of East Anglia and Ph.D. in Pharmacology, University of Alberta in Edmonton with postdoctoral studies completed in the Department of Biochemical Pharmacology, S.U.N.Y. in Buffalo. He has held academic appointments in both Australia & Canada including the first Director of the Biotechnology Institute and Innovation Professor at RMIT University in Melbourne; Head of the Department of Pharmacology & Therapeutics, Chair in Cardiovascular Research - Alberta Heart and Stroke Foundation, Associate Dean Research Medicine at the University of Calgary, as well as research advisory positions with Ciba and Novartis Canada and chaired numerous peer review grant panels.

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Omorogieva Ojo

University of Greenwich, London, UK

Exploration of the effect of diabetes training in primary health care

Background: Despite the increasing prevalence of diabetes in the UK and worldwide and its effect on patients' morbidity and mortality, evaluation of the impact of diabetes training that should sustain the quality of diabetes care provision is limited1. Therefore, the aim of this study was to explore the effect of diabetes training on the provision of diabetes care and service among healthcare professionals.

Method: This was a qualitative research study involving healthcare professionals (doctors, nurses) who attended the diabetes training programme which consisted of a 3-day Foundation level course and/or the 2.5 day programme for injectable therapy (Pitstop) course. Participants attended four focus group sessions in health centres in East Kent, UK. Ethical approval for the study was obtained and all participants consented before taking part in the study. The focus group sessions were recorded using audiotapes which were then transcribed.

Data Analysis: Four researchers carried out thematic analyses of the data separately and these were then integrated into six themes. The themes were; the benefits of the diabetes training, areas for improvement of the training, impact on health services, healthcare professionals and patients, and barriers to its implementation.

Results: The benefits of the training included the resources provided, promotion of participants' knowledge, ongoing support and the environment for inter-professional learning. On the other hand, the effect of the diabetes training was evident in terms of its positive impact on the practices or service delivery (such as improved team working), the healthcare professionals (improved knowledge and skills) and the patients (improved quality and continuity of care). Although there were merits in the training programme, there were also areas for improvement. Barriers to implementing the training programme included patients not attending appointments, volume of patients, not able to prescribe and conflicting sources of information.

Discussion: The findings of this study are in line with previous research which suggest that diabetes training can promote the knowledge and skills of nurses and other health care professionals to empower patients to manage their conditions effectively.

Conclusion: The Foundation and Pitstop diabetes training programme is useful in promoting the delivery of diabetes service in East Kent in terms of promoting improvement in team working. In addition, it has enhanced the confidence, knowledge and practice of health care professionals while ensuring early diagnosis, better education and tighter control of patients' blood glucose levels. Despite the advantages of the diabetes training programme, there are areas for improvement. Acknowledgement: The authors wish to acknowledge the support of Paula Carr Diabetes Trust in funding this study.

Biography

Omorogieva Ojo has a PhD in nutrition from the University of Greenwich, London, a post graduate diploma in diabetes from University of Surrey, Roehampton and a graduate certificate in Higher Education from University of Greenwich. Prior to these qualifications. He had his BSc and MSc in animal science from University of Ibadan, Nigeria. He has been a Senior Lecturer in Primary Care for nearly seven years and he teaches across a range of courses and programmes in the Faculty of Education and Health, University of Greenwich. His key interest and areas of expertise are diabetes and nutrition which form the focus of his research and teaching activities. He leads the school Diabetes Specialist Interest Group and co-ordinates the Diabetes Care and Management course for post registration nurses and Patient Pathways of Care for pre-registration participants.

He supervises both undergraduate and postgraduate research students including PhD students. His research interests are reflected in his 35 publications in reputable journals and 12 conference presentations. His work is recognised both nationally and internationally and he has been a keynote speaker at the NNNG conference in Manchester, UK and Global Diabetes Conference and Medicare Expo, in Birmingham, UK. Dr Ojo is a reviewer for a range of journals and he sits on the Editorial Board on a number of International Journals.

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Yoram Oron

Tel Aviv University, Israel

Subtle traps: Lessons from transplantation of pancreatic beta-precursor MSC

Transplantation of stem cells-derived beta cells has been a target of diabetes research for many years, but has yet to mature into a therapeutic option. We showed previously that proliferating human islet-derived de-differentiated cells (DIDs) exhibit many characteristics of mesenchymal stem cells (MSC). Dispersed DIDs, induced by serum deprivation to undergo mesenchymal-to-epithelial transition, aggregate into epithelial cell clusters (ECCs). ECCs implanted under kidney capsules of SKID mice tend to differentiate into β-cell colony. Albeit in a large proportion of mice implanted cells de-differentiate back to stem-like phenotype. As ECCs disperse and undergo epithelial-to-mesenchymal transition by re-addition of sera, we postulated that the differentiation failure in vivo may have been due to an agent in the host serum. We found that PDGF-BB alone mimics serum-induced ECCs' dispersal accompanied by accumulation of cytoplasmic b-catenin and a decrease in the levels of insulin and glucagon mRNAs. Moreover, PDGF-BB-induced dispersal of ECCs was a more general phenomenon that occurred with bone marrow MSC and dermal fibroblasts (DFs). In DIDs, BM-MSC, and DFs, PDGF decreased the levels of DKK1 mRNA, suggesting involvement of the Wnt signaling pathway. PDGF-BB stimulated a significant increase in S473 phosphorylation of Akt and the PI3K specific inhibitor (PIP828) partially inhibited PDGF-BB-induced ECC dispersal. Lastly, the PDGF-receptor (PDGF-R) antagonist JNJ-10198409 inhibited both PDGF-BB and serum-induced ECC dispersal. Epidermal growth factor (EGF), which shares most of the PDGF signaling pathway, did not induce dispersal and only weakly stimulated Akt phosphorylation. Hence, PDGF-BB mediated serum-induced DIDs dispersal correlated with the activation of the PI3K-Akt pathway. In conclusion, although we may manipulate cells to change their physiology, the ultimate result depends on many uncontrolled and/or unknown factors. Our understandings of the complexity of inter and an intracellular interaction *in vitro* and in vivo is still too sketchy to allow prediction of therapeutic outcomes.

Biography

Yoram Oron is currently a Professor Emeritus at the Department of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel Aviv University, Israel. He received his BSc in Chemistry and his MSc and PhD in Biochemistry from the Hebrew University in Jerusalem. He further trained in diabetes research at the University of Virginia in the laboratory of Professor Joseph Larner and continued to study signal transduction pathways at Tel Aviv University, utilizing mainly the Xenopus oocyte system and electrophysiology and microscopic imaging techniques as read-outs. In the last 12 years he has changed the focus of his research to studying the biology of diabetes and pancreatic adenocarcinoma. In the past he served as Department Chair and as a Head of the Office of International Academic Relations at Tel Aviv University. He has authored and co-authored more than 110 peer-reviewed publications in quality journals, including Nature, Science, PNAS, and J Physiol.

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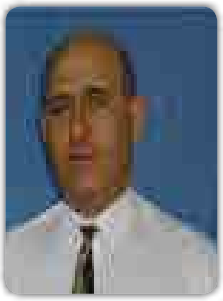

Fuad A Iraqi

Tel-Aviv University, Israel

Dissection the complexity of host susceptibility to type 2 diabetes development and the pharmacogenetics dilemma

Type-2 diabetes (T2D) is a complex metabolic disease characterized by impaired glucose tolerance. Despite environmental high risk factors, host genetic background is a strong component of T2D development. Identifying these genetic factors could contribute to developing new medical treatments and tools to identify most at risk individuals. Recently, a novel highly genetically diverse mouse resource population, named the Collaborative Cross (CC), was developed and aimed for studying complex traits, including T2D. The CC mice have more genetic diversity than human population. Here, we used this mouse population of mapping Quantitative Trait Loci (QTL) underlying impaired glucose tolerance phenotypic variations and associated diseases including liver fat accumulation in CC mice. Furthermore, we used Next generation RNA-sequencing (RNAseq) for studying gene expression variations and alternative splicing observation to identify genes that may underline the disease development. Our results have shown significant variations between the recorded phenotypes between the different CC lines and a sex was observed. QTL mapping results have identified number of small genomic regions associated with the tested traits.

Methods: A Cohort of 683 mice of 68 CC lines maintained on high-fat (42% fat) diet (HFD) for 12 weeks followed by biweekly body weight (BW), body length (BL), waist circumstance (WC), and body mass index (BMI) were measured. Subsequently, assessed by intraperitoneal glucose tolerance test (IPGTT), and liver weight (electronic balance) and fattiness (DEXA scanner) was assessed. Genomic DNA of the CC lines was genotyped with high-density single nucleotide polymorphic (SNP) markers and finally QTL mapping was conducted. Next generation RNA-sequencing (RNAseq) was performed for livers of diabetic and non-diabetic mice of CC lines following 12 weeks HFD, and DNA methylation assessed on blood for testing epigenetic effect of HFD.

Results & Discussion: Genome wide search for QTL analysis has revealed number of significant QTL associated with glucose tolerance test, which was defined as area under curve (AUC), as well QTL underline fatty liver accumulation as a results of T2D development. RNAseq approach of hepatic gene expression analysis has identified significant gene variations between the diabetic and no-diabetic mice, as well between both sexes.

Biography

Fuad A Iraqi is a Molecular Geneticist and world leader in the area of dissecting complex traits including hosts susceptibility to infection and chronic diseases. His current research is focused on understanding diseases etiology and host susceptibility to infectious and chronic diseases including type 2 diabetes and cardiovascular diseases (CVD) associated with obesity, Klebsiella pneumonia, Aspergillus fumigatus, dental infection (Periodontitis), and mapping modifiers for colon cancer development. His research projects are important for better understanding the host susceptibility to variety of infectious and chronic diseases, which will serve a step towards improving our knowledge of specific and general pathways and network systems, which can lead to establish better disease prevention and control strategies. He has studied for his BSc (Biology), MSc (Biochemistry) and PhD (Molecular Genetics) at the Hebrew University at Jerusalem. He worked as a Postdoctoral for two years at the Hospital for Sick Children at Toronto, Canada, and two more years at the USDA, ARS- East Lansing, MI, before joining the International Livestock Research Institute (ILRI), based in Nairobi, Kenya as Scientist. In 2007, he moved to his current position as Professor and Chairman of the Department of Clinical Microbiology and Immunology, at the Faculty of Medicine at Tel-Aviv University. He has more than 135 publications on per reviewed journals, and more than 25 book chapters. His current H-Index is 27.

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