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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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