MON-LB82

Introduction.: There is no effective and reliable biomarker to distinguish benign thyroid nodules (BTN) from papillary thyroid carcinomas (PTC). In this study we analyzed a set of four miRNA molecules in plasma of patients with papillary thyroid cancer, benign nodules and healthy controls to identify miRNA molecules that may be markers of PTC.**Aim.:** We aimed to investigate the dysregulation of plasma miRNAs in PTC and evaluate the diagnostic value for differentiation of PTC from BTN. **Methods.:** The expression levels of 4 miRNAs (miR-221, miR-222, miR-146b, miR-21) were measured in 48 PTC patients before thyroidectomy and again after thyroidectomy in a subgroup of 36 patients. Preoperative and postoperative plasma miRNA expression levels were compared with baseline levels established in plasma from the heathy controls group (N=57) and patients with BTN (N=22). MicroRNA-222 and miR-146b, miR-221, miR-21 were included in a panel because they all reportedly were overexpressed in PTC compared to benign nodules or normal thyroid tissue.**Results.:** Compared with baseline levels in the healthy controls group, miR-221, miR-222, miR-146b, miR-21 levels were significantly higher in the preoperative PTC group (P <0.0001, P=0.002, P=0.028, P =0.021, respectively). A significant reduction in miR-21 expression was observed in postoperative PTC patients. MiR-21 decreased by 5.98-fold (P=0.046) in post- operative samples compared with preoperative samples in the PTC patients. In comparison MiRNRs expression levels in BTN group with healthy controls, miR-221, miR-21 expression levels were significantly higher in the BTN group (P=0.003, P=0.048, respectively). No significant difference was observed between the preoperative PTC group and the preoperative BTN group with regard to the expression of these four miRNA's. **Conclusions:** The expression levels of miR-222, miR-146b in plasma were significantly higher in patients who had PTC than in healthy volunteers, whereas levels of miR-221, miR-21 in plasma were significantly higher in patients who had either PTC or BTN before thyroidectomy than in healthy volunteers. Furthermore, miR-21 showed a significant reduction of expression levels after thyroidectomy in PTC patients. However, value of these four miRNAs is still limited in differential diagnosis of PTC and benign nodules.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY

Metabolic and Brown Adipose Tissue-Specific Effects of the Novel Non-Steroidal Mineralocorticoid Receptor Antagonist Finerenone in a Mouse Model of Diet-Induced Obesity

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SAT-LB106

In this work we studied the metabolic effects of the novel non-steroidal MR antagonist Finerenone (FIN) in mice fed a high-fat diet (HFD, 60% kcal as fat). We also investigated the signaling pathways underlying the beneficial metabolic effects of MR antagonism. After 3 months of HFD, mice treated with FIN showed an improvement of glucose tolerance compared to control mice as shown by intraperitoneal glucose tolerance tests. Despite this metabolic improvement, FIN-treated mice did not show a reduction in body weight compared to control mice. In order to elucidate the favourable effect of FIN on glucose tolerance we performed histological and molecular analyses at level of different adipose depots. We did not observe significant differences in classical white adipose depots (subcutaneous and visceral) between control and FIN-treated mice. Interestingly, interscapular brown adipose tissue (iBAT) of FIN-treated mice showed an increased multilocularity and a reduced size of lipid droplets, suggesting an iBAT-specific effect of FIN. We than analyzed mRNA and protein expression of uncoupling protein 1 (UCP-1) and peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PCG1-alpha), showing a significant increase of both markers at iBAT level in FIN-treated mice. Furthermore, leptin and adenylate cyclase 5 (Adyc5) (specific white adipose tissue markers) mRNA expression was reduced at level of iBAT in FIN-treated mice. Finally, we demonstrated that FIN-induced MR antagonism determined an increased activation of AMP-activated protein kinase (AMPK) which, in turn, stimulated adipose triglyceride lipase (ATGL) activity, with subsequent up-regulation of genes involved in fatty acids oxidation, tricarboxylic acid cycle and thermogenesis, in iBAT. In summary, our study shows that FIN protects from iBAT dysfunction and improves glucose tolerance in HFD-fed mice. Importantly, FIN effects on iBAT are mediated by a MR-AMPK-ATGL-UCP-1 signaling cascade. Therefore, MR antagonism by FIN in clinical settings might offer metabolic advantages, on top of its anti-fibrotic action, in multi-morbid cardiorenal patients.

Diabetes Mellitus and Glucose Metabolism

METABOLIC INTERACTIONS IN DIABETES

Real-World Safety and Effectiveness of Insulin Glargine 300 U/ML (Gla-300) in People With Type 2 Diabetes Who Fast During Ramadan

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SUN-LB126

ORION was a prospective, observational study evaluating the safety and effectiveness of the second-generation basal insulin analog Gla-300 in people with type 2 diabetes (T2DM) who fast during Ramadan. Adults with T2DM who intended to fast for ≥15 days during Ramadan, had taken

Gla-300 for ≥8 weeks prior to inclusion, and intended to continue its use during Ramadan were enrolled in 11 countries. During Ramadan, Gla-300 treatment was adjusted as per routine practice by the treating physician. Overall, the majority of people (402 [85%]) fasted for the entire Ramadan period and 10.8% fasted for ≥25 days but with at least one missed day. Mean (SD) age was 54.4 (11.0) years, 51.7% were male, BMI was 29.7 (5.3) kg/m^2, and duration of diabetes was 10.7 (7.0) years. Risks of diabetes-related complications associated with fasting were assessed by physicians according to IDF-DAR fasting risk category; risk was low/moderate in 82.8%, high in 14.3%, and very high in 2.9% of people. The proportion of people with ≥1 severe and/or documented symptomatic (SMPG ≤70 mg/dL) hypoglycemia event was low (2.2% [event rate: 0.021 per participant-month (PPM)] in pre-Ramadan, 2.6% [0.039 PPM] in Ramadan and 0.2% in post-Ramadan [0.003 PPM]). Overall, 0.8% (0.005 PPM) of participants experienced severe and/or documented symptomatic hypoglycemia at SMPG <54 mg/dL, and only during pre-Ramadan. No participants had severe hypoglycemia during Ramadan or post-Ramadan; 1 participant had severe hypoglycemia pre-Ramadan. Most of those who experienced symptomatic hypoglycemia during Ramadan did so during fasting hours (11/13 people). Reductions were shown pre- to post-Ramadan for mean (SD) HbA_{1c} (8.10 % [1.29] pre-Ramadan to 7.64 % [1.05] post-Ramadan; change of −0.44 % [0.97]), FPG (144.3 [45.8] mg/dL pre-Ramadan to 128.5 [37.8] mg/dL post-Ramadan; change of −13.5 [44.1] mg/dL), and fasting SMPG (130.7 [32.9] mg/dL pre-Ramadan to 126.8 [28.5] mg/dL post-Ramadan; change of −3.3 [26.6] mg/dL). Mean Gla-300 dose was reduced slightly between pre-Ramadan and Ramadan (25.6 [11.9] U/0.32 [0.14] U/kg pre-Ramadan to 24.4 [11.5] U/0.30 [0.13] U/kg in Ramadan) and returned to 26.0 (12.2) U/0.32 (0.14) U/kg in the post-Ramadan period. AE incidence was low (5.5%); 3 (0.6%) participants had an AE of hyperglycemia, 2 (0.4%) during Ramadan. In this study, performed in a real-world setting, incidence of hypoglycemia was low in people with T2DM treated with Gla-300 who fasted for Ramadan, with no incidence of severe hypoglycemia during the Ramadan period; HbA_{1c}, FPG and fasting SMPG reductions were also observed. Supported By: Sanofi

Thyroid

NO LONGER A PAIN IN THE NECK — RECENT INSIGHT INTO THYROID GROWTH, DEVELOPMENT, AND PATHOLOGY

Drug Repurposing Identifies Inhibitors of the Proteostasis Network to Augment Radioiodine Uptake in Combinatorial Approaches Targeting Thyroid Cancer

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OR28-03

New combinatorial drug strategies are urgently needed to improve radioiodine (RAI) uptake and efficiently ablate thyroid cancer cells, thereby reducing the risk of recurrent disease. Drug repurposing offers the promise of identifying already approved compounds capable of inducing sodium iodide symporter (NIS) function to enhance iodide uptake. However, a lack of thyroid cell-based assays amenable to high-throughput screening has limited progress. We utilised the mutated yellow fluorescent protein (YFP) as a surrogate biosensor of intracellular iodide and screened the Prestwick Chemical Library (1200 drugs; 95% approved) for quenching of YFP fluorescence. This allowed us to identify putative candidate drugs which increased iodide uptake >2 SD above mean. Categorisation of these revealed a high proportion of drugs that modulate the proteostasis network (19/48; ~40%), including key processes in protein homeostasis such as endoplasmic reticulum-associated protein degradation (ERAD) and autophagy. Secondary screening validated the activity of proteostasis modulators in enhancing iodide uptake after ranking 73 leading compounds based on their pharmacologic (AUC, E_{MAX} and EC_{50}) and specificity of response (NIS+ve vs NIS-ve YFP-thyroid cells) at ten different drug doses (0.1 to 50 μM). Of importance, several repurposed drugs (e.g. ebastine, Prestwick N, Prestwick C and clotrimazole) in combination with the HDAC inhibitor vorinostat induced a robust enhancement in RAI uptake in thyroid cancer cells (TPC-1 and 8505C NIS+ve cells, up to 11-fold vs DMSO, P<0.001), which was significantly greater than using vorinostat alone (up to 3-fold, P<0.01). For clotrimazole, we designed 7 new chemical derivatives, 3 of which showed enhanced aqueous solubility and retained the ability to significantly enhance RAI uptake. TaqMan RT-PCR revealed that, in contrast to vorinostat, our repurposed drugs failed to alter NIS mRNA expression, highlighting post-transcriptional mechanisms. Critically, 11 repurposed drugs induced significant gains in RAI uptake in human primary thyroid cells (up to 4.1-fold; P<0.05), the most physiological setting for NIS function. In conclusion, we performed high-throughput screening and identified proteostasis modulators, as well as other repurposed drugs, that markedly enhance radioiodine uptake. Further clinical investigation of these drugs might offer new combinatorial approaches, especially with existing therapies, to improve the treatment of thyroid cancer.

Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS II

MODY3 With Insulin Coding Gene Mutation and Craniofacial Microsomia: A Case Report

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