

Drug repurposing identifies inhibitors of the proteostasis network to augment radioiodine uptake in combinatorial approaches targeting thyroid cancer

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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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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; $\sim 40\%$), 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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