in the SR detected with Fluo-5N, a specific SR calcium indicator, and caused VSMC relaxation. These effects were blocked by cyclopiazonic acid (CPA, a SERCA inhibitor), suggesting that SERCA plays a critical role in P4 induction of VSMC relaxation. Similarly, the effects of P4 and OD 02-0 on relaxation of umbilical artery rings measured with a myograph were significantly attenuated by CPA, which confirms the critical role of SERCA in the rapid action of P4 and 02-0 on vascular muscle relaxation. P4 has previously been shown to activate MAPK and Akt signaling pathways to induce VSMC relaxation. The P4- and OD 02-0-induced increases in calcium in the SR were blocked by MAPK and Akt/P3k signaling inhibitors, AZD6244 and wortmannin. Taken together, these results suggest that the direct, rapid effects of P4 on relaxation of VSMCs through mPRα involves regulation of the expression and function of the SR proteins SERCA and PLB through MAPK and Akt signaling pathways.

Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS II

Dulaglutide Commonly Known as Trulicity; An Anti-Diabetic Medication Causing Small Bowel Obstruction

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MON-681

Introduction Small bowel obstruction is a common and life threatening surgical emergency. The general causes are intra and extra-intestinal mechanical obstruction, such as from post-operative adhesions, malignancy, hernias, Crohn's disease, and volvulus. Less frequently neurologic, metabolic, and medications interfere with intestinal motility and lead to obstructive features. Here, we present a rare case of small intestinal obstruction caused by the anti-diabetic glucagon-like peptide 1 (GLP-1) agonist, Dulaglutide (Trulicity). Case A 52-year-old male with Diabetes Mellitus, presented with two weeks of severe nausea and vomiting, accompanied by four days of diffused abdominal pain. CT scan of the abdomen showed multiple mildly distended dilated loops of the proximal jejunum. The results led to suspect the presence of fecal stasis with an apparent transition zone of a normal caliber bowel. This is strongly indicative of partial or evolving small bowel obstruction. The patient was treated with conservative management of bowel rest and NG tube per the surgery on board. However, patient deteriorated too quickly and the partial bowel obstruction lead to full obstruction and eventually taken for an emergent surgery. With careful investigation to identify underlying causes of small bowel obstruction revealed no mechanical, structural, or metabolic explanation. However, a review of patient’s medication list disclosed a daily consumption of Dulaglutide (Trulicity). The medication was started 3 weeks prior to admission. He started developing partial bowel obstruction symptoms within one week of starting the medications. Unfortunately, surgeon ended up performing a partial resection a small bowel due to severe ischemia. Patient improved clinically in four to five days and was discharged home with an alternative anti-diabetic medications. He follows up with us in the clinic and has no signs of bowel obstructions with the other anti-diabetic medications. Discussion: Dulaglutide (Trulicity) is associated with small bowel obstruction. The side effect is more common in males and in patients who are using the medication for less than one month. A total of 8 cases were reported in 2017 with majority of them requiring surgical intervention for the small bowel obstruction. In our patient, it also required a surgical intervention and was life threatening. Unfortunately, the actual mechanism Trulicity causing the small bowel obstruction is unknown; however the moderate side effect of Trulicity is constipation. In this case, our patient was not constipated. He had normal bowel movements on a regular basis. Also, he never had any history of abdominal surgeries which can cause adhesion and lead to small bowel obstruction. All the other caused of small bowel obstructions had been ruled out and finally concluded Trulicity was the culprit of this unfortunate case.

Bone and Mineral Metabolism

PARATHYROID HORMONE TRANSLATIONAL AND CLINICAL ASPECTS

The Role of β-arrestin2 in Bone Catabolic Response to Hyperparathyroidism In Vivo

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SAT-392

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by elevated parathyroid hormone (PTH) levels and hypercalcemia caused by the overactive parathyroid glands, resulting in negative impacts on the skeleton including bone loss and increased bone fragility1. PTH binds and activates parathyroid hormone type 1 receptor (PTH1R) which primary couples to Gαs, stimulating the downstream effectors that mediate bone remodeling processes2. PTH1R activity is regulated by arrestins, specially β-arrestin2 (β-ar2), through signal termination and receptor internalization2. Previously, we have seen anabolic effects of hyperparathyroidism (ePTH) on trabecular bone in mice overexpressing Gαs2. We hypothesized that increased Gαs protein levels in osteoblasts outcompete β-ar2 binding to PTH1R, leading to reduced signal termination and increased bone formation. To test this hypothesis, we are testing if the deletion of β-ar2 will also result in an anabolic response to cPTH in this study. The response of β-ar2 knockout (KO) mice to cPTH have yet to be documented. The hypothesis of this study is that β-ar2 KO mice treated with cPTH will exhibit anabolic effects on the trabecular bone. Nine-week-old wild-type (WT) C57BL/6 and β-ar2 KO mice were treated for 14 days with either rPTH1-34 (80ng/g/day) or saline (PBS) using micro-osmotic pumps to simulate hyperparathyroidism. There are 8 groups (n=10 per group) including both sexes, 2 genotypes (WT and KO), and 2 treatment groups (PTH and PBS). Two 30 mg/kg doses of 0.6% calcein green were administered subcutaneously to
mice at 7 and 2 days prior to euthanasia to label bones. Decalcified tibiae were embedded in paraffin for histological analysis. Undecalcified tibiae were embedded in plastic for dynamic histomorphometry. Micro-computed tomography (μCT) was used to access bone microarchitecture of femurs and vertebrae followed by biomechanical testing of bone strength. The μCT data of distal femurs show that cPTH treatment increased bone volume in female KO mice (6.864 ± 2.318 vs 4.690 ± 1.555 %; P= 0.0328; n=9 per group) and maintained bone in male KO mice (13.37 ± 2.860 vs 13.38 ± 3.135; P= 0.9968, n= 10) compared to control. Histological analysis show higher osteoclastic activity in both sexes and genotypes when treated with cPTH, suggesting that the anabolic response may be at the level of osteoblasts and osteocytes. These promising results support our hypothesis that arrestin-mediated PTH receptor downregulation plays an important role in bone weakness associated with hyperparathyroidism. These studies are important for understanding the clinical phenotype of PHPT patients and suggest that inhibition of β-arrest2 in PHPT could be a path for drug therapy.

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Adipose Tissue, Appetite, and Obesity
RARE CAUSES AND CONDITIONS OF OBESITY: PRADER WILLI SYNDROME, LIPODYSTROPHY
Weight Loss After Glucagon-Like Peptide-1 Receptor Agonist Treatment in Childhood Obesity with Diabetes and Cirrhosis Associated with a Homozygous MC4R Mutation
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SUN-602
Background
Mutations in the melanocortin-4 receptor (MC4R) represent the most common cause of monogenic obesity. Treatment options are limited but glucagon-like peptide-1 receptor agonists (GLP-1 RA) may be of use to induce weight loss. Methods
Exome of the patient was captured using the Agilent SureSelect QXT Human All Exon V5 kit and sequenced on Illumina.
Clinical findings and results
We report obesity-associated diabetes and cirrhosis in a 13-year girl born from consanguineous parents of Afghan origin. Past medical history revealed mild mental retardation and excessive weight gain since infancy. Linear growth was normal. Her father was obese and no diabetes was found in the family. The girl was initially investigated for hoarseness and found to have pulmonary hypertension, later accepted to be secondary to cirrhosis and portal hypertension. Physical examination revealed obesity (BMI 34.9kg/m2) and acanthosis nigricans. Blood exams showed leucopenia and thrombocytopenia without anemia, compatible with portal hypertension. Chest CT revealed important dilatation of the pulmonary arteries, a nodular liver and splenomegaly. Liver biopsy confirmed cirrhosis. An extensive workup including whole exome sequencing identified a homozygous MC4R variant [NM_005912.2 (MC4R): c.63_64del, p.(Tyr21*)], classified as pathogenic according to the ACMG guidelines. Both parents were heterozygous for this variant. An endocrinological workup showed insulin resistance with a HOMA-IR index of 7.27 and diabetes with peak blood glucose of 11.5mmol/l. HbA1c was 5.1% (32mmol/mol). Thyroid tests, leptin, proinsulin levels (3.5pmol/l, n <11.0pmol/l) were normal.
The mutation being homozygous with a predicted complete loss of function (https://www.mc4r.org.uk/), no treatment with a MC4R agonist was tried. At the age of 15 years (BMI 36.0kg/m2), the patient underwent liver transplantation because of progressive portal hypertension and to halt the progression of pulmonary hypertension. At the age of 16 years (BMI 33.2kg/m2, HbA1c 4.9% (30.0 mmol/mol), HOMA-IR 5.3) a treatment with GLP-1 RA (liraglutide) was started at a dosage of 0.6mg and progressively increased to 3mg, in an attempt to induce weight loss, avoid the accumulation of liver fat and to protect the graft. GLP-1 RA is supposed to exerts its effects on appetite independently of the MC4R pathway. 2 months after liraglutide introduction, no side effects, a weight loss of 4kg and a decrease of appetite were observed (BMI 31.6kg/m2, HbA1c 4.5% (26mmol/mol), HOMA-IR 3.14).
Conclusion
Obesity-associated MC4R mutations, in homozygous state, may lead to diabetes, liver cirrhosis and portal-pulmonary hypertension. Treatment options are scarce, but GLP-1 RA seem to have a rapid, positive effect on weight and metabolic control. Would earlier treatment have prevented progression to end-stage-liver disease and need for liver transplantation?

Diabetes Mellitus and Glucose Metabolism
DIABETES COMPLICATIONS II
Euglycemic Diabetic Ketoacidosis Associated with SGLT-2 Inhibitors - an Under-recognized Diagnosis
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MON-690
Euglycemic Diabetic Ketoacidosis Associated With SGLT-2 Inhibitors - An Under- recognized Diagnosis
Background
Sodium glucose cotransporter-2 inhibitors (SGLT-2i) are a promising class of oral anti-hyperglycemic agents with mounting evidence of reduced cardiovascular risk and renal failure, in patients with type 2 diabetes mellitus. Recent increase in their use has led to identification of hitherto unknown side effects of these drugs. Euglycemic Diabetic Ketoacidosis (eDKA), found to be associated with SGLT-2i use, is a life-threatening condition and commonly goes unrecognized due to absence of the cardinal sign of hyperglycemia.
Clinical Case