in view of the rapid exchange between protein-bound and free cortisol compartments and evidence that metabolic elimination is restricted to the free cortisol compartment. In the present study, we sought to explore potential limitations of the descriptive, single-compartment model for cortisol elimination by assessing the influence of CBG concentration ([CBG]) on cortisol half-life estimates obtained using the descriptive model. We studied the influence of [CBG] and other variables on descriptive cortisol half-life using a Monte Carlo simulation of cortisol concentration decay curves developed using data from healthy controls (1). Total cortisol concentration ([TF]) curves were generated on the basis of 4 predictor variables: (i) [CBG], (ii) albumin concentration, (iii) [TF] at time zero following iv bolus (total cortisol at time 0, y-intercept), and (iv) free cortisol half-life central to a *mechanistic* (dynamic, 3-compartment) model (2). Simulations used a multivariable normal distribution and selected means, SDs, and correlation structure among these 4 variables in healthy controls. After generation of a series of cortisol decay curves (n=1000), half-lives for total and free cortisol were solved using the conventional (descriptive, single-compartment) model. The influence of predictor variables on conventional half-life estimates were assessed using standardized beta (STB) coefficients, which represent change in the SD of the outcome (numerator, i.e. total or free cortisol half-life obtained by descriptive model) for each SD change in a predictor (denominator) in a multivariable context (3). For total cortisol half-life (descriptive model) STBs were 0.91 ([CBG]), 0.73 (free cortisol half-life), -0.37 (y-intercept), and 0.04 ([albumin]) (all P<0.001). For free cortisol half-life (descriptive model), STBs were 0.98 ([CBG]), 0.73 (free cortisol half-life), -0.78 (y-intercept), and 0.11 [albumin]) (all P<0.001). We conclude that the conventional descriptive model for estimation of cortisol has significant limitations, including inaccuracy and systematic bias related to the influence of CBG concentration on half-life estimates. By inference, a similar bias confounds interpretation of the half-life obtained using conventional single-compartment model of other hormones associated with high-affinity serum binding proteins. **References:** (1) Perogamvros et al. Clin Endo 2011;74:30-36, (2) Keenan et al. *Am J Physiol Endocrinol Metab* 2004;287:E652-E661 (3) Dorin et al., J Endocrinol Soc 2017 July;1(7):945-56.

Diabetes Mellitus and Glucose Metabolism

METABOLIC INTERACTIONS IN DIABETES

The G209R Mutant Mouse as a Model for Human PCSK1 Polyendocrinopathy

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SUN-669

A striking number of SNPs and rare mutations have been identified in *PCSK1*, the gene that codes for the enzyme proprotein convertase 1/3 (PC1/3) which proteolytically activates prohormones within the secretory pathway. All infants bearing two copies of catalytically inactivating mutations, including G209R, exhibit severe neonatal malabsorption requiring parenteral nutrition for months and subsequently develop additional endocrinopathies, often including diabetes and obesity. In order to create a mouse model to explore the underlying mechanism of the malabsorption phenomenon and the endocrinopathies, a G209R point mutation was introduced into exon 6 of mouse *Pcsk1* using CRISPR-Cas9 genome editing. Fifty-six live pups were collected at postnatal days one or two; however, most homozygous G209R mutant pups succumbed by day 2, and surviving pups were severely dwarfed. In homozygous, but not heterozygous pups, blood glucose levels were significantly lower with elevated plasma insulin-like immunoreactivity and accumulation of unprocessed proinsulin in G209R pancreas compared to the wild type pups from the same litters. The POMC product α-MSH (produced by PC2 from PC1/3-generated ACTH) has been strongly implicated in obesity mechanisms. We found pituitary POMC processing to ACTH was also affected by the G209R mutation in combined anterior and intermediate pituitary lobes. ACTH was markedly reduced in homozygote pituitary, with significant accumulation of POMC. Using Western blotting, we observed a significant reduction in PC1/3 protein in homozygote brains, while PC2 protein levels remained unaffected. Most likely due to the continued presence of PC2, pituitary and brain levels of α-MSH were not impaired, suggesting that α-MSH itself is not involved in the phenotype. Prior studies have shown that G209R PC1/3 is not efficiently trafficked out of the ER; further studies will examine the contribution of misfolded G209R PC1/3 to possible cellular ER stress, as well as determine peptide hormone levels in brain and peripheral tissues.

Adrenal

ADRENAL CASE REPORTS I

Are Pet Scans Needed in Evaluating Lipid Rich Adrenal Adenomas?

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SAT-190

Introduction Adrenal glands are highly vascularized organs and can be the foci of metastatic disease. Incidentally discovered adrenal nodules should be evaluated with CT or MRI imaging and biochemical testing. Metastatic lesions do not have a specific clinical presentation or imaging features but are suspected when there is attenuation greater than 10 HU, presence of calcification, hemorrhage, or abnormal enhancement signals in CT scan or MRI. However, malignant lesions can be present along with benign ones as described here. **Clinical Case** A 74-year-old female initially presented with uncontrolled hypertension in 2002, at which time she was found to have a left