Steroid Hormones and Receptors

**STEROID BIOLOGY AND ACTION**

**Spiral Steroid Lactones Are Synthesized by Condensation of a Steroid Precursor with Coenzyme a Derivatives**

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SAT-744

**Background:** Szent-Gyorgyi proposed that digoxin wasn’t really a drug but was a substitute for an endogenous cardiotonic steroid (ECS). Endogenous ouabain and marinobufagenin have been proposed as ECS.

**Hypothesis:** Ionotropin, our first candidate for the ECS, is unique among steroids because it is the phosphocholine ester of a steroid with 23 carbon atoms. Logically, either there must be a novel mechanism for adding carbon atoms to a pregnenolone-like precursor or a novel mechanism for side-chain cleavage from a cholesterol-like precursor.

**Experimental design:** Serum samples were extracted with acetonitrile, filtered and analyzed by MS-N on an LTQ-XL ion trap mass spectrometer. The instrument permits multiple rounds of fragmentation and identification of the parent ion and each fragment ion. This process permitted recognition of ions that were phosphocholine esters and of the mass of the steroid fragments. The chemical formula of each steroid fragment was determined by trial and error analysis. Although not every mass ion has a unique chemical formula, in fact, each of the steroid ions had a unique formula. Possible isomers were resolved by consideration of knowledge of steroid biosynthetic pathways.

**Major results:** In brief, human serum samples had steroid fragment ions consistent with 23 (354 Da) and 25 (398 Da) carbon atoms. This provides an additional constraint as the synthetic mechanism must account for both products. These mass ions were consistent with condensation of either acetyl-CoA or acetoacetyl-CoA with the phosphocholine ester of pregna-5,7-diene-3β,17α-diol-20-one. After condensation, the steroid adduct would be dehydrated and cyclized to form the corresponding spiral steroid phosphocholine ester. This pathway is similar to the mechanism of addition of 2 carbon fragments to a long chain fatty acid. This is the first explanation for the biosynthesis of endogenous mammalian ECS. Spiral lactones would be expected to cross react with many antibodies specific for digoxin, ouabain or marinobufagenin. Either one of the spiral lactones would satisfy Szent-Gyorgyi’s suggestion as the endogenous digoxin-like material.

**Conclusions:** In summary, we have isolated 2 spiral steroid lactones from mammals and identified the mechanism of their biosynthesis. We propose, as the spiral steroids share structural features with the spironolactone class of potassium sparing diuretics, that they also share functions. Nicholls proposed that a candidate for ECS should not be accepted without [a] isolation, [b] precursors, and [c] a biosynthetic path. As there has been no satisfaction of these requirements for ouabain or marinobufagenin, their existence as ECS in mammals needs to be reconsidered.

**Cardiovascular Endocrinology**

**PATHOPHYSIOLOGY OF CARDIOMETABOLIC DISEASE**

**The Effect of Leptin Treatment on Blood Pressure and Autonomic Nervous System Function in Patients with Lipodystrophy.**

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**SUN-565**

Leptin is an adipokine that reflects energy storage levels. Patients with obesity have high leptin, hypertension, and increased cardiovascular disease (CVD) risk. In rodents, leptin increases blood pressure (BP), by increasing sympathetic nervous system (SNS) activity, suggesting high leptin may cause hypertension and CVD. Studies of leptin administration in 2 human models of leptin deficiency (weight reduced and congenital leptin deficiency) showed decreased SNS activity in the leptin-deficient state, which increased after leptin replacement. This has clinical relevance as high SNS and low parasympathetic nervous system (PNS) activity correlate with increased risk of hypertension and CVD. In lipodystrophy syndromes adipose tissue is deficient thus leptin is low. We hypothesized that leptin treatment in patients with lipodystrophy would increase SNS activity and BP. SNS and PNS activity in the heart can be assessed using heart rate variability (HRV). The high frequency (HF) component of HRV is directly related to PNS activity whereas the low frequency (LF) component reflects both SNS and PNS. The LF/HF ratio reflects sympathetic-vagal balance. Lower standard deviation of the beat to beat interval (SDNN) inversely correlates with CVD risk. Leptin-naive patients with lipodystrophy (N=17, 5 generalized, 12 partial) were housed on an inpatient unit for 19 days. Patients were studied without leptin for the first five days. Leptin was administered for the next 14 days. At the end of the OFF-leptin and ON-leptin periods, 24-hr EKG recordings were used to derive HRV parameters and an automated BP monitor measured BP every 30 minutes during the day and every 60 minutes at night. 5 patients had generalized lipodystrophy (median 75th percentile) endogenous leptin [0.5 [0.4, 0.6] ng/mL]; 12 had partial lipodystrophy (leptin 7.5 [3.9, 20.3]). In the combined cohort with generalized and partial lipodystrophy, leptin treatment did not alter BP or any measure of autonomic nervous system function after 24 hours, 2 weeks, or 6 months. In exploratory subgroup analyses of generalized vs partial lipodystrophy, those with generalized lipodystrophy had an increase in LF after 2 weeks of leptin and a 4.5 mm Hg increase in systolic BP after 6 months; no changes were observed in those with partial lipodystrophy. Unlike previous human and rodent studies, we did not see increased SNS tone or BP after leptin treatment in patients with lipodystrophy. However, exploratory analyses in patients with generalized lipodystrophy and very low endogenous leptin
levels showed small increases in systolic BP and increased LF component of HRV after 2 weeks, which is regulated by both SNS and PNS. This suggests that leptin may alter autonomic function in the transition from very low to normal plasma leptin levels.

Diabetes Mellitus and Glucose Metabolism

TYPE 2 DIABETES MELLITUS

The Warburg Effect: A Case of Persistent Hypoglycemia and Lactic Acidosis

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SUN-677 Background: It is well established that malignant cells are able to metabolize glucose to lactate in the presence of oxygen, known as the Warburg effect (WE) · a rare metabolic complication of malignancies, presenting with lactic acidosis & hypoglycemia. It signifies a poor prognosis with high mortality rates. We present the case of a woman with malignancy who presented with persistent hypoglycemia requiring a dextrose drip and type B lactic acidosis.

Clinical case: A 63-year-old female was referred to our institution for persistent hypoglycemia and lactic acidosis after being admitted to another hospital for a urinary tract infection. Her history was notable for generalized fatigue & weight loss. She had lactic acidosis (18-25mEq/L; Normal: 0.5–2.2mEq/L) despite stable hemodynamics that did not improve with resuscitation & antibiotics. Her hospital course was complicated by worsening mental status & non-hypoxic respiratory distress due to profound acidosis, requiring intubation. She required a dextrose infusion of up to 40g/hour to maintain normoglycemia and with the infusion, an increase in lactate level was noted. Workup to rule out insulin-dependent hypoglycemia, adrenal insufficiency, GH deficiency, MELAS, mesenteric ischemia & drug-related lactic acidosis was unremarkable. EEG was not suggestive of seizure activity. Initial labs were notable for elevated levels of CA-125 430U/mL (normal: 0–34) which were attributed for elevated levels of CA-19-9 408U/mL, &rosthe patient was felt to be not severe enough to her newly diagnosed cirrhosis. However, the degree of her liver dysfunction was felt to be not severe enough to cause hypoglycemia. Imaging studies looking for tumors were unrevealing. A bone marrow biopsy done to rule out occult malignancy showed metastatic carcinoma with neuroendocrine features. Further treatment was not pursued by her family. Based on the diagnosis of metastatic cancer, it was felt that her persistent hypoglycemia was due to the Warburg effect. Conclusion: The Warburg effect (WE) is observed in cancers when the malignant cells utilize glycolysis over oxidative phosphorylation, regardless of oxygen content, for energy production. This involves aerobic glycolysis & lactic acid is its by-product. Cancer cells use more glucose via the glycolysis pathway to meet their demands leading to hypoglycemia & concurrent lactic acidosis despite normal oxygen levels. WE is a rare but severe complication of malignancies that signifies a poor prognosis.

Patients with this complication need to be monitored closely until definitive treatment can be implemented. This case highlights the importance of maintaining a high clinical index of suspicion for diagnosing WE. Reference Elhomsy G. C., Eranki V., Albert S. G., et al. “Hyperwarburgism,” a cause of asymptomatic hypoglycemia with lactic acidosis in a patient with non-Hodgkin’s lymphoma. The Journal of Clinical Endocrinology & Metabolism. 2012;97(12):4311–4316.

Adrenal

ADRENAL CASE REPORTS I

The Diagnosis and Management of a Functional Paravertebral Paraganglioma

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SAT-195

A 32-year-old male presented with a 4-year history of palpitations, diaphoresis, and orthostatic hypotension. One year prior to presentation, he began experiencing severe, episodic headaches and neck pressure. Neurological work-up included an MRI head, neck, and spine, identifying a left posterior mediastinal lesion adjacent to the T5 vertebral body, approximately 2.4 x 2.0 cm. A community surgical center attempted mass resection via Video-assisted (VATS) approach. Resection was aborted intraoperatively due to a hypertensive crisis following lesion manipulation, with his systolic blood pressure increasing above 325 mmHg. Subsequent evaluation revealed a 24-hour urine norepinephrine of 6117 nmol/d (normal <575) and normetanephrines of 16.6 umol/d (normal <3.4). An MIBG study showed intense tracer avidity in the left paraspinal lesion and minimal uptake in the adrenal glands. A functional paravertebral paraganglioma was diagnosed and the patient was initiated on alpha and beta-blockade in preparation for staged combined treatment. Spinal angiography was performed to define the arterial supply of spinal cord and tumor, which confirmed a hypervascular left thoracic paraspinal tumor. Arterial supply emanated from the left T4 intercostal and left supraventricular arteries and a prominent draining vein was present. Transarterial particle embolization was performed via both arteries with minimal residual tumor blush present post procedure. Successful VATS excision of the tumor was completed one week after arterial embolization with minimal blood loss. Pathology of the resected tumor revealed an overall intact tumor that stained diffusely positive with synaptophysin and sustentacular cells highlighted by S100 protein with a few foci of coagulative necrosis. Episodes of hypertension (maximum BP 210/80) occurred during embolization and surgical resection with vascular manipulation. These were managed with intraoperative nitroprusside and phentolamine. Peri-procedural plasma