OII-A-3

SOLUBLE GUANYLYL CYCLASE IS AN ATP SENSOR COUPLING NITRIC OXIDE SIGNALING TO CELL METABOLISM. S. R. Tiyyagura, MD, I. Ruiz-Stewart, PhD, S. Kazerounian, PhD, E. Lin, G. M. Pitari, MD, PhD, S. Schulz, PhD, E. Martin, PhD, F. Murad, MD, PhD, S. A. Waldman, MD, PhD, Thomas Jefferson University, Philadelphia, PA.

Defending cellular integrity against disturbances in intracellular concentrations of ATP ($[ATP]_i$) is predicated upon coordinating the selection of substrates and their flux through metabolic pathways (metabolic signaling), ATP transfer from sites of production to utilization (energetic signaling), and the regulation of processes consuming energy (cell signaling). Nitric oxide (NO) and its receptor soluble guanylyl cyclase (sGC) are key mediators of cellular energetics and can regulate ATP supply and demand. However, mechanisms coordinating NO/sGC and energetic signaling remain undefined. Here, we demonstrate that sGC is a nucleotide sensor whose responsiveness to NO is regulated by intracellular ATP ($[ATP]_i$). ATP inhibits purified sGC with a K_i predicting >60% inhibition of NO signaling in cells maintaining physiological $[ATP]_i$. ATP inhibits sGC by interacting with an allosteric site that prefers ATP>GTP. Moreover, in RFL-6 cells, alterations in $[ATP]_i$ are coupled to NO/sGC signaling. Indeed, oligomycin, an inhibitor of mitochondrial ATP synthase, reduced $[ATP]_i$ 48%, from 1.25 nmol to 0.65 nmol of ATP/mg protein, but increased $[cGMP]_i$ 45%, from 42 to 61 pmol/mg protein. Thus, $[ATP]_i$ serves as a "gain control" for NO signaling by sGC. At physiological $[ATP]_i$, NO signaling by sGC is repressed, while insults that reduce $[ATP]_i$, such as ischemia, de-repress sGC and amplify responses to NO.

OII-A-4

MALADAPTIVE CARDIAC REMODELING AND MORTALITY UNDER MINERALOCORTICOID INDUCED HYPERTENSION FOLLOWING KATP CHANNEL KNOCKOUT. G. C. Kane, MD, F. O'Coclain, MD, D. M. Hodgson, MD, S. Reyes, T. Miki, MD, S. Seino, MD PhD, A. Terzic, MD PhD, Mayo Clinic, Chiba University, Rochester, MN.

Chronic hemodynamic load predisposes to cardiac dysfunction, yet the molecular components of myocardial adaptation are not completely understood. Kir6.2 is the pore-forming subunit of cardiac ATP-sensitive potassium (KATP) channels implicated in the cardiac stress response. Here, following unilateral nephrectomy, Kir6.2 knockout (KO) & C57BL/6 wild-type (WT) mice, were challenged with deoxycorticosterone acetate-salt (DOCA/salt) loading for 21 days. DOCA/salt induced similar extent of hypertension & contralateral renal hypertrophy with fibrosis in KO and WT. However, in KO, DOCA/salt challenge produced left ventricular dysfunction, pulmonary congestion, reduced exercise performance, & catecholamine-induced cardiac failure with more severe increase in left ventricular mass & more extensive interstitial fibrosis. Indeed, cyclosporine, the inhibitor of Ca2+ mediated calcineurin-dependent hypertrophic reprogramming, reversed the exaggerated cardiac restructuring in the KO. Overall, DOCA/salt-KO mice displayed significant mortality compared to DOCA/salt-WT. Treatment with the Ca2+ channel antagonist verapamil rescued the KO with prevention of cardiac pathology & associated mortality. Thus, suggesting an essential homeostatic role for cardiac KATP channels in the setting of mineralocorticoid induced hypertension. This work has implications for hypertensive diabetic patients treated with KATP channel antagonists sulfonylureas & a potential therapeutic role for KATP channel openers.

OII-B-1

POPULATION PHARMACOKINETIC ANALYSIS OF ATOMOXETINE IN PEDIATRIC PATIENTS. J. Witcher, PhD, D. Kurtz, MS, M. Heathman, MS, J. Sauer, PhD, B. Smith, PhD, Eli Lilly and Company, Indianapolis, IN.

Atomoxetine is a novel treatment of ADHD in children, adolescents, and adults. The purpose of this analysis was to characterize atomoxetine pharmacokinetics and the potential influence of patient factors in pediatric patients. A population pharmacokinetic model was developed using the combined sparse and serial plasma data of 420 patients with 2354 observations from 5 pediatric studies. Patient factors with clinical and demographic significance were identified a priori and evaluated on model parameters. The final model was a 1-compartment model and was validated using several methods. Covariates retained in the final model included CYP2D6 genotype, body weight, and food consumption. The results demonstrate linear pharmacokinetics across the dose range evaluated of 5 to 45 mg twice-daily. CYP2D6 poor metabolizers had a 9-fold lower clearance compared to extensive metabolizers. Clearance and volume of distribution increased nearly proportional to increased body weight, indicating dosing based on body weight is appropriate. Simulations showed that weight-based dosing provides a more narrow and predictable range of exposures in patients. Food consumption decreased the rate of atomoxetine absorption, however the decrease (9% lower Cmax) was deemed clinically insignificant. Age, gender, ethnic origin, and caffeine consumption did not influence atomoxetine disposition. This analysis provided valuable data concerning these patient factors in the target patient population.

OII-B-2

EFFICACY, SAFETY AND PHARMACOKINETICS OF LEVOCETIRIZINE IN ALLERGIC CHILDREN AGED 1-2 YEARS. N. E. Cranswick, MD, M. Fuchs, MD, J. Turzikova, MD, Royal Children's Hospital, Bulovka Hospital, Parkville, Australia.

Purpose: This was a pilot study to assess the efficacy, safety and pharmacokinetics of levocetirizine in children aged 1-2 years treated for recurrent cough associated with other allergic symptoms.

Methods: This was a 90 day, open-label, non-controlled study of levocetirizine oral drops, 0.125 mg/kg twice daily in 15 children aged 1-2 years. Cough symptom scores were recorded daily. Serial plasma samples were obtained until 12 h after the first dose, 3-6 days and 90 days of treatment. Histamine-induced wheal and flare reactions were recorded before initiation of therapy, and on days 3-6 and 90. Study visits took place every month.

Results: The study population included 11 M and 4 F children, aged 1.1 - 2.1 years and weighing 9 - 15 kg. Mean weekly cough score decreased over time. Median wheal and flare inhibition at 12 h post-dose was almost 100%. Safety and tolerability were good. Eleven full PK profiles were available on day 1. C_{max} and AUC were similar to those in adults receiving 5 mg daily, however the elimination half-life of 4 h, was 2-fold shorter. Steady-state trough concentrations were within the expected range.

Conclusion: The observations indicate that levocetirizine has good efficacy and safety profile that needs to be confirmed. The exposure in children was similar to adults and demonstrates that the current dosing regimen is appropriate for further studies in children aged 1 to 2 years.