

**STUDENT RESEARCH SYMPOSIUM****Abstracts from the 39th Annual National  
Student Research Forum**

Galveston, Texas, USA \*

**CHARACTERIZATION, CHOLINERGIC  
REGULATION, AND FUNCTIONAL  
SIGNIFICANCE OF LARGE CONDUCTANCE  
CA<sup>2+</sup>-DEPENDENT K<sup>+</sup> CHANNELS IN HUMAN  
ESOPHAGEAL SMOOTH MUSCLE CELLS**

B. Hurley, H.G. Preiksaitis, S.M. Sims

Department of Physiology, University of Western Ontario, London,  
Ontario, Canada

Investigations were undertaken to examine cholinergic regulation of ion channels in human esophageal smooth muscle cells. Measurements of channel activity were made in the cell-attached patch configuration. Acetylcholine (ACh) was shown to cause contraction and a transient increase in activity of a channel whose properties were consistent with the large conductance calcium activated potassium channel (KCa). Addition of caffeine also led to activation of this K<sup>+</sup> channel, and effects of both ACh and caffeine persisted in Ca<sup>2+</sup> free solution. It is concluded that effects of ACh were mediated by the release of Ca<sup>2+</sup> from intracellular stores and that entry of extracellular calcium is not required to activate KCa channels. Simultaneous patch-clamp and calcium fluorescence recording allowed quantification of the calcium sensitivity of this KCa channel. Studies using tetra-ethyl ammonium (TEA), a blocker of the KCa channel, demonstrated that inhibition of this channel increased the magnitude and duration of muscle contraction in response to ACh. These studies are the first to characterize KCa channels in human esophageal muscle

and to demonstrate the role of KCa channels in limiting depolarization of smooth muscle.

**Bernard Hurley** was awarded the Sigma Xi Award for Overall Excellence of Research and the Mason Guest Memorial Award.

**INCREASED VASCULAR ALPHA2-RECEPTOR  
RESPONSIVENESS WITH INDOMETHACIN: IN  
VIVO EVIDENCE FOR DECREASED  
VASODILATOR PROSTAGLANDIN RELEASE  
IN PATIENTS WITH MILD TO MODERATE  
CONGESTIVE HEART FAILURE**

I.D. Callow, N. Dzeka, J. Malcolm, O. Arnold

Departments of Medicine and Dentistry and of Pharmacology and  
Toxicology, University of Western Ontario, London, Ontario, Canada

In patients with mild to moderate congestive heart failure (CHF), the current authors have previously demonstrated that venous  $\alpha$ -receptor responsiveness is increased compared with normal controls. This finding was unexpected. It was subsequently demonstrated in young normal subjects that endothelial vasodilator prostaglandins (PG's) are released secondary to venous  $\alpha$ 2-receptor activation and decrease the net venoconstriction. Since endothelial function is impaired in CHF, it was hypothesized that the prostaglandin synthesis inhibitor, indomethacin, would increase venoconstriction to clonidine in age-similar normals but would have no effect on venoconstriction to clonidine in patients with CHF. Patients ( $64.0 \pm 3.7$  yrs,

\* Held by the University of Texas Medical Branch at Galveston on April 16-18, 1998.

mean  $\pm$  sem) with mild to moderate CHF (left ventricular ejection fraction:  $23.8 \pm 3.5\%$ ) and 7 age-similar ( $65.3 \pm 2.6$  yrs) normal subjects were each studied on two separate days. Graded local infusions of the  $\alpha_2$ -noradrenergic receptor agonist clonidine (3 to 7000 ng/min) were administered into a dorsal hand vein in conjunction with either indomethacin (3 mg/min) or saline placebo. Venous distention at 45 mmHg was measured using a hand vein tonometry technique. Dose-response curves to clonidine were constructed and the maximum hand vein constriction calculated. No systemic effects of clonidine or indomethacin were observed. The dose-response curve to clonidine was shifted to the left in CHF patients compared to normals ( $p = 0.05$ ) consistent with our previous findings. However, with indomethacin co-infusion, the clonidine curve in normals was displaced up and to the left ( $p < 0.01$ ) (to the level seen in CHF patients during saline co-infusion) but remained unchanged in CHF patients. Maximum venoconstriction to clonidine was increased with indomethacin compared to saline ( $44.1 \pm 5.8\%$  vs.  $17.8 \pm 3.7\%$ ,  $p < 0.01$ ) in normal controls but remained unaltered in patients with CHF ( $40.5 \pm 7.6\%$  vs.  $39.0 \pm 6.0\%$ ). These results are consistent with our hypothesis that  $\alpha_2$ -receptor stimulation normally releases endothelial vasodilatory PG's which antagonize the vasoconstrictor response to clonidine and modulate the sympathetic vascular response. Increased alpha receptor mediated constriction may contribute to progression of CHF and may also be relevant in other diseases with endothelial dysfunction.

**Ian D. Callow** was awarded the George I. Ellis Memorial Award.

**PERSISTENCE OF INFECTIOUS  
HEPADNAVIRUS IN OFFSPRING BORN TO  
MOTHERS CONVALESCENT FROM  
HEPATITIS IN THE WOODCHUCK  
MODEL OF HEPATITIS B**

C.S. Coffin, T.I. Michalak

Faculty of Medicine, Memorial University of Newfoundland,  
St. John's, Newfoundland, Canada

Hepatitis B virus (HBV) is a hepatotropic virus, but it can also replicate in lymphoid cells. The virus induces life-threatening liver diseases, such as cirrhosis and hepatocellular carcinoma, and there are more than

300 million chronic HBV carriers worldwide. Transmission of HBV from mothers to babies is the most important route for virus spread within the population. Recent findings have established the existence of a serologically silent HBV persistence in healthy individuals convalescent from acute hepatitis B. In these patients, traces of HBV genomes were documented years after recovery. Similar data has been obtained in a woodchuck model of hepatitis B in this laboratory. Woodchuck hepatitis virus (WHV) is closely related to HBV and provides an excellent model for the study of HBV pathogenicity. This study was undertaken: (i) to determine whether hepadnaviral genomes can be transmitted from maternal woodchucks with a past episode of acute WHV hepatitis to their offspring; (ii) if so, to identify reservoirs of hepadnavirus replication during long-term follow-up of these newborn animals; (iii) to characterize physicochemical properties of molecules carrying WHV DNA in sera of these offspring; (iv) to test whether silent carriage of WHV genomes acquired after vertical transmission reflects the existence of biologically competent virus infectious to WHV-naive woodchucks. In this work, 11 offspring born to four woodchuck mothers were investigated. The results have shown that serologically silent WHV carriage acquired after recovery from an episode of viral hepatitis is transmittable to newborns as an asymptomatic chronic infection. Importantly, all of the offspring tested carried WHV DNA through the entire follow-up, lasting for more than three years after birth, and remained nonreactive for serological markers of WHV infection. WHV DNA and RNA specific sequences were detectable both in the liver and lymphoid cells in the majority of the animals, although in some offspring WHV persisted exclusively at an extrahepatic location in the lymphatic system. Particles carrying WHV DNA in sera of offspring with WHV genomes in both the liver and lymphoid cells or the lymphatic system alone had physicochemical properties comparable to those of complete WHV virions. In addition, virus contained in offspring sera with or without WHV DNA expression in the liver, as well as culture supernatant from mitogen-stimulated peripheral blood mononuclear cells, were infectious to WHV-naive woodchucks. Since there are significant pathobiological similarities between HBV and WHV, it is possible that a comparable situation may exist in babies born from mothers with a past history of hepatitis B.

**Carla S. Coffin** was awarded the McLaughlin Award in Infectious Disease.