BIOGRAPHICAL SKETCH

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INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Kearney State College, Kearney, Nebraska	B.S.	1984	Biology
University of South Dakota School of Medicine Vermillion, South Dakota	Ph.D.	1993	Biochemistry
Thomas Jefferson University	Postdoctoral	1997	Physiology

A. Personal Statement

I am an Associate Professor in the Department of Pharmacology, Physiology and Neuroscience. The board interest of my laboratory focuses on Ca^{2+}-dependent regulation of mitochondrial physiology and liver metabolism and how adaptations in receptor-coupled Ca^{2+} signaling contribute to the onset and development of liver diseases. Our studies have proved insight into the decoding mitochondrial Ca^{2+} increases into changes in oxidative energy metabolism and more recently how mitochondrial Ca^{2+} regulates the formation of ROS. Current studies are examining the hypothesis that alcohol intoxication triggers “adaptive” changes in phosphoinositide-dependent Ca^{2+} signaling pathways that results in mitochondrial dysfunction and liver injury. Our data indicate that chronic alcohol intake enhances the liver’s sensitivity to a group of hormones that control hepatic metabolism by increasing cytosolic calcium. Normally, calcium-mobilizing hormones stimulate mitochondrial metabolism to increase ATP production. However, the addition of hormone to liver cells from alcohol-fed animals induces prolonged and more sustained increases in mitochondrial calcium levels and stimulates the production of reactive oxygen species (ROS).

My laboratory has hands on experience investigating receptor-coupled phospholipase C activity, measurement of second messengers (e.g. $InsP_3$) and determining the mRNA and protein levels of signaling molecules (e.g. G-proteins) within the phosphoinositide-dependent signaling cascade. My staff and I also have expertise in carrying out wide-field fluorescence imaging and confocal microscopy studies to measure receptor-mediated increases in cytosolic Ca^{2+} and the resultant changes in mitochondrial metabolism and bioenergetics in isolated hepatocytes and liver endothelial cells. As a postdoctoral fellow at Thomas Jefferson University, I developed the confocal imaging techniques to monitor hormone-induced increases in cytosolic Ca^{2+} at the cellular and subcellular level in the intact perfused tissues. I have expanded these techniques to the 2-photon confocal microscope system which allows us to measure fluorescence intensity changes in Ca^{2+}-sensitive fluorescent dyes or genetically encoded Ca^{2+} indictors in thick tissues. We have successfully adapted these confocal techniques to *ex vivo* perfused rat and mouse livers. Moreover, we have recently used these methods to identify Ca^{2+} signaling events in specific liver cells interacting with circulating cancer cells while they are trafficking through the liver microcirculation in the *ex vivo* perfused liver. These studies are part of a NCI funded R03 grant and expected to yield novel information about the Ca^{2+} signaling pathways involved in tumor cell adhesion.

B. Positions and Honors

Positions and Employment:

1993-1996 **Postdoctoral Research Fellow** - Department of Pathology, Anatomy & Cell Biology, Thomas Jefferson University, Philadelphia, PA. Supervisors: Drs. Andrew P. Thomas & Jan B. Hoek.

1993-1996	**Research Assistant** - Department of Pathology, Anatomy & Cell Biology, Thomas Jefferson University, Philadelphia, PA. Supervisor: Dr. Andrew P. Thomas.
1998-2009	**Assistant Professor**- Department of Pharmacology & Physiology, UMDNJ-New Jersey Medical School. Newark, NJ.
2009-present	**Associate Professor**- Department of Pharmacology & Physiology, Rutgers-New Jersey Medical School. Newark, NJ..

Experience and Professional Memberships:

1999-present	**Member**- Biophysical Society.
2010-present	**Member**- Research Society on Alcoholism
2011	**Reviewer** NIH Special Emphasis Panel (ZAA1 JJ (01)) "Alcohol-Induced Metabolic and Hepatic Injury."
2012	**Ad hoc reviewer** AA-1 Biomedical Research Study Section.
2013-2015	**Ad hoc reviewer** NIDDK DDK-C Grant Review Subcommittee.
2015	**Reviewer** NIH Special Emphasis Panel (ZDK1 GRB-8 (J1)) "Program project on liver."
2016	**Ad hoc reviewer** The Veterans Affairs Oncology C panel study section.

Honors:

1987-1993	**Research Assistantship** - Department of Biochemistry and Molecular Biology, University of South Dakota, School of Medicine, Vermillion, SD. John A. Thomas, advisor.
1993-1996	**Postdoctoral NRSA Training Fellowship**- Department of Pathology, Anatomy & Cell Biology,Thomas Jefferson University, Philadelphia, PA. Supervisors: Drs. Andrew P. Thomas & Jan B. Hoek.
2000	**Burroughs Wellcome Fund Research Travel Grant-** King's College London, London, UK.
2005	**Invited Professor**- Department of Biology, l'Université Paris-Sud, Orsay, France.

C. Contribution to Science

1. The role of calcium signaling in the development of alcoholic liver disease. "Adaptive" responses to the toxic effects of chronic alcohol consumption may contribute to the onset and progression of alcoholic liver disease (ALD). Alcohol administration can perturb multiple signaling pathways including inositol 1,4,5-trisphosphate ($InsP_3$)-dependent cytosolic calcium ($[Ca^{2+}]_i$) signaling, which can adversely affect mitochondrial Ca^{2+} levels, reactive oxygen species production and energy metabolism. We have shown that chronic alcohol feeding induces adaptive molecular changes in receptor-coupled phosphoinositide-specific phospholipase C (PI-PLC) activity resulting in enhanced $InsP_3$ accumulation and potentiation of Ca^{2+} release from internal stores. Submaximal concentrations of Ca^{2+}-mobilizing hormones evoked more sustained and prolonged $[Ca^{2+}]_i$ increases after alcohol feeding. This increase in hormone efficacy was recorded in hepatocytes within the intact perfused liver and hepatocytes cultured overnight in the absence of ethanol. Chronic alcohol feeding also increased the protein levels of the voltage-sensitive anion channel (VDAC) and mitochondrial Ca^{2+} uniporter (MCU); two key mitochondrial proteins involved in Ca^{2+} transport across the outer and inner mitochondrial membranes. The molecular changes in mitochondrial Ca^{2+} handling were associated with higher levels of mitochondrial Ca^{2+} under basal conditions and more prolonged elevations in matrix Ca^{2+} after hormone stimulation. Importantly, hormone challenge selectively increased mitochondrial ROS levels in the alcohol-group compared to controls suggesting that the chronic alcohol dependent shift in hormone-evoked Ca^{2+} increases could lead to oxidative damage and cell injury. Hormone-induced $[Ca^{2+}]_i$ oscillations are an essential signaling pathway to coordinate many physiological functions of the liver including regulation of glucose homeostasis, mitochondrial oxidative phosphorylation, stress responses and tissue regeneration. However, alterations in cellular Ca^{2+} homeostasis and aberrant and sustained increases in cytosolic Ca^{2+} increases has also been implicated in numerous diseases states. Our data indicate that the alcohol-induced changes in receptor-coupled PLCß activity coupled with the enhanced capacity to accumulate and retain Ca^{2+} in the mitochondrial matrix leads to mitochondrial Ca^{2+} overload, increased ROS production, oxidative damage and degradation of mitochondrial proteins, such as the respiratory chain complexes. Our data have led to the hypothesis that

attenuating receptor-coupled PLC activity may be a novel therapeutic intervention to treat alcoholic liver diseases.

Wang, G., Memin, E., Murali, I., and **Gaspers, L. D.** (2016) The effect of chronic alcohol consumption on mitochondrial calcium handling in hepatocytes. Biochem J 473, 3903-3921.

Bartlett, P. J., Antony, A. N., Agarwal, A., Hilly, M., Prince, V. L., Combettes, L., Hoek, J. B., and **Gaspers, L. D.** (2017) Chronic alcohol feeding potentiates hormone-induced calcium signalling in hepatocytes. Chronic alcohol feeding potentiates hormone-induced calcium signalling in hepatocytes. J Physiol 595, 3143-3164.

2. Mechanisms underlying hormone-induced calcium spiking and the propagation of intracellular and intercellular Ca^{2+} waves. Calcium mobilization from intracellular stores and Ca^{2+}-influx from the extracellular space are involved in regulating numerous intracellular metabolic processes in both electrically excitable and non-excitable tissues. In hepatocytes, physiological levels of hormones such as, cathecholamines and vasopressin, evoke periodic increases in the concentration of cytosolic free calcium ($[Ca^{2+}]_i$) by activating the phosphoinositide-specific phospholipase C (PI-PLC) signaling cascade. These Ca^{2+} spikes propagate across the entire hepatocyte as regenerative intracellular Ca^{2+} waves ensuring that the entire cell receives the maximal signal during each $[Ca^{2+}]_i$ oscillation. Studies during my post-doctoral career at Thomas Jefferson University and current work are focused on delineating the dynamic regulation and feedback loops controlling the generation of 1,4,5-trisphosphate-dependent Ca^{2+} increases and propagation of Ca^{2+} waves. Moreover, I have developed and continue to refine of laser scanning confocal imaging techniques to monitor in real-time hormone-induced cytosolic Ca^{2+} increases in the intact perfused liver. These techniques are capable of resolving the organization of Ca^{2+} responses at the cellular and subcellular in individual hepatocytes within the intact liver tissue. Our studies were the first to demonstrate that the hormone-evoked Ca^{2+} increases propagate across entire lobules as coordinated intercellular Ca^{2+} waves, starting in the periportal and ending in the pericentral zones. The intercellular Ca^{2+} waves initiate from a small number of periportal hepatocytes that act like pacemakers determining the frequency and spatial pattern of $[Ca^{2+}]_i$ oscillations for the entire lobule, thus synchronizing the metabolic output of the liver.

Robb-Gaspers, L.D. and Thomas, A.P. (1995) Coordination of Ca^{2+} signaling by intercellular propagation of Ca^{2+} waves in the intact liver. J. Biol. Chem. 270 8102-8107.

Patel, S. **Robb-Gaspers**, L.D., Shon, M. and Thomas, A.P. (1999) Coordination of Ca2+ signalling by endothelial-derived nitric oxide in the intact liver. Nature Cell Biology 1 467-471. (**Joint first author**).
PMID: 10587641

Smaili, S.S., Stellato, K.A., Burnett, P., Thomas, A.P. and **Gaspers, L.D.** (2001) Cyclosporin A inhibits inositol 1,4,5-trisphosphate-dependent Ca^{2+} signals by enhancing Ca^{2+} uptake into the endoplasmic reticulum and mitochondria. J. Biol. Chem. 276 23329-40

Gaspers, L. D. and Thomas, A. P. (2005) Calcium signaling in liver. Cell Calcium 38, 329-342. (**Corresponding author**) **PMID: 16139354**

Politi, A., **Gaspers, L. D.**, Thomas, A. P., and Hofer, T. (2006) Models of IP3 and Ca^{2+} oscillations: frequency encoding and identification of underlying feedbacks. Biophys. J 90, 3120-3133. (**Joint first author**).
PMCID: PMC1432125

Gaspers, L.D., Bartlett, P.J., Politi, A., Burnett, P., Metzger, W., Johnston, J., Joseph, S.K., Hofer, T., and Thomas, A.P. (2014). Hormone-induced calcium oscillations depend on cross-coupling with inositol 1,4,5-trisphosphate oscillations. Cell Reports 9, 1209-1218.
PMID: 25456123

Bartlett, P.J., Metzger, W., **Gaspers, L.D.** and Thomas, A.P. (2015) Differential regulation of multiple steps in inositol 1,4,5- trisphosphate signaling by protein kinase C shapes hormone-stimulated Ca^{2+} oscillations. J. Biol. Chem. 290, 18519-33.

PMCID: PMC4513112

3. Calcium-Dependent Regulation of Mitochondrial Metabolism.
A recurrent paradigm in Ca^{2+} signal transduction is the coordination of calcium stimulus with the activation of metabolic energy production in the target tissue. During my postdoctoral studies, I was part of a research group that first described how mitochondrial Ca^{2+} signals are translated into activation of mitochondrial metabolism. Stimulus-metabolic coupled occurs in many tissues, including cardiac and skeletal muscle where contractile activity and ATP production are coordinately regulated by the frequency and amplitude of calcium transients and in non-excitable cells, such as hepatocytes, where the downstream targets of calcium include both catabolic and anabolic processes. The primary mechanism by which calcium enhances the capacity for energy production is through calcium-dependent stimulation of mitochondrial oxidative metabolism, achieved by increasing NADH production and respiratory chain flux. Although this mechanism enhances energy production, it also has the potential for deleterious consequences resulting from increased generation of reactive oxygen species (ROS). I continue to work on this topic and now am investigating the relationship between mitochondrial Ca^{2+} increases, ATP production and the dysregulation of ROS formation.

Hajnóczky, G., **Robb-Gaspers**, L.D., Seitz, M.B. and Thomas, A.P. (1995) Decoding of cytosolic calcium oscillations in the mitochondria. Cell 82, 415-424.
PMID: 7634331

Robb-Gaspers, L.D., Burnett, P., Rutter, G.A., Denton, D.M., Rizzuto, R. And Thomas, A.P. (1998) Integrating cytosolic calcium signals into mitochondrial metabolic responses. EMBO J. 17, (17) 4987-5000.
PMCID: PMC1170827

Turner, J.D., **Gaspers**, L.D., Wang, G. and Thomas, A.P. (2010) Uncoupling Protein-2 Modulates Myocardial Excitation-Contraction Coupling. Circ. Res. 106(4):730-738.
PMID: 20056920

Gaspers, L.D. Mémin, E. and Thomas, A.P. (2012) Calcium-dependent physiologic and pathologic stimulus-metabolic response coupling in hepatocytes. Cell Calcium 52, 93-102. (**Corresponding author**).
PMCID: PMC 3391328

5. Calcium signaling and the integrated regulation of liver metabolism. We have extended our initial studies on the calcium-dependent regulation of hepatocyte metabolism in the intact liver to include other liver cell types. We have examined the interactions between hepatocytes and liver sinusoidal endothelial cells, hepatocytes and Kupffer cells. These studies are increasingly focused on nutrient signaling and the genesis of nonalcoholic fatty liver disease.

Patel, S., **Gaspers, L. D.**, Boucherie, S., Memin, E., Stellato, K. A., Guillon, G., Combettes, L., and Thomas, A. P. (2002) Inducible nitric oxide synthase attenuates vasopressin-dependent Ca^{2+} signaling in rat hepatocytes. J. Biol. Chem. 277, 33776-33782
PMID: 12097323

Gaspers, L.D. and Thomas, A.P. (2008) Calcium-dependent activation of mitochondrial metabolism in mammalian cells. Methods 46, 224-232. (**Corresponding author**).
PMCID: PMC2640951

Gulati, P., **Gaspers, L.D.**, Dann, S.G., Joaquin, M., Nobukuni, T., Natt, F., Kozma, S.C. Thomas, A.P. and Thomas, G. (2008) Amino acids activate mTOR complex 1 via Ca^{2+}/CaM signaling to hVps34. Cell Metab. 7, 456-465.
PMCID: PMC2587347

Bartlett, P.J., **Gaspers, L.D.**, Pierobon, N. and Thomas, A.P. (2014) Calcium-dependent regulation of glucose homeostasis in the liver. Cell Calcium 55, 306-316.
PMID: 24630174

Complete List of Published Work in MyBibliography:http://www.ncbi.nlm.nih.gov/sites/myncbi/lawrence.gaspers.1/bibliography/40323273/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

1R03CA182132-01A1 Period: 1Jan2016-31Dec2017
NIH/NCI

Inositol-trisphosphate 3-kinase and colorectal cancer cell adhesion.

The project will test hypothesis that the down-regulation of ItpkC provides an advantage for microvascular adhesion to circulating colon cancer cells and therefore for metastasizing to liver.

Role: Principal Investigator
No scientific or budgetary overlap with current application.

Completed Research Support

R01-AA017752 Period: 10Aug 2008-31July 2014
NIH/NIAAA

The role of hormone-evoked mitochondrial calcium increases in the pathogenesis of alcoholic liver disease.

This project investigated the effects of chronic alcohol intoxication on mitochondrial function and the role mitochondrial dysfunction plays in the progression of alcoholic liver disease.

Role: Principal Investigator

R01 Subcontract Period: 1Oct 2009-30September 2011
NIH/NIAAA

ER-mitochondrial signaling and alcoholic tissue injury. (G. Hajnóczky, PI)
This project tested the hypothesis that chronic alcohol intoxication disrupts the interactions between the mitochondrial and endoplasmic reticulum leading to tissue injury.

Role: Co-investigator/Subcontract PI