A. Personal Statement

I have spent the last 21 years investigating the cellular and molecular mechanisms by which general anesthetic agents alter regulation of intracellular free Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]) in cardiac myocytes and pulmonary artery smooth muscle cells. Functional studies examining the ramifications of the anesthetic-induced alterations in [Ca\(^{2+}\)] were evaluated simultaneously by assessing alterations in contractility of the cardiomyocytes using video edge detection whereas isolated pulmonary arterial rings were used to simultaneously assess concomitant changes in [Ca\(^{2+}\)] and isometric tension (vascular reactivity). My laboratory has also assessed the extent to which anesthetic agents alter \(\alpha\) and \(\beta\) adrenergic signal transduction pathways important for the regulation and modulation of myocardial contractility and vascular tone. Over the past 8 years, I have extended my studies of anesthetic actions on cardiomyocyte Ca\(^{2+}\) and contractility, to anesthetic interactions with TRP ion channels that allow for passage of Ca\(^{2+}\) into DRG sensory neurons and signaling pathways regulating these sensitivities to agonist activation. TRPV1 and TRPA1 channels have emerged as key players in sensing tissue damage and it is proposed that these channels communicate with each other in the cross regulation of each other’s function. Not only do they contribute to numerous pathophysiological and chronic pain syndromes in the nervous system but have recently emerged as key regulators of vasomotor tone in the vascular system and mediators of cardiac protection from ischemic insult. Hence, we have recently extended our studies to examine the extent to which TRPA1 and TRPV1 ion channels may mediate hypotensive responses observed in vivo and depressor responses observed in coronary microvessels in vitro. Finally, we have extended our studies by returning back to the heart to study the role of TRP ion channels in providing cardiac protection in the setting of ischemic insult. We are the first to have identified the presence of TRPA1 functional protein in the heart, a potential role for this channel in mediating cardioprotection following ischemic insult and the potential signal transduction pathways activated by TRPA1 agonists that afford cardioprotection. Having set this stage, the long-term research objective of my laboratory is to elucidate the cellular and molecular mechanisms regulating TRP ion channel function, the
signaling pathways and mechanisms associated with TRP ion channel cross-talk important in pain sensation, regulation of vasmotor tone and cardioprotection as well as to elucidate the direct molecular interactions that occur between TRPA1 and TRPV1 ion channels. The physiology of nociceptive neurons and cross-talk between TRPA1 and TRPV1 receptors lay at the core of understanding peripheral hypersensitivity and chronic pain syndromes. Moreover, the role of TRP ion channels in regulating vascular tone and providing cardioprotection from ischemic insult will provide important fundamental insight into mechanisms of a variety of pathophysiological conditions in the cardiovascular system. Such information is vital to the design and synthesis of novel agents that can directly target these TRP ion channels thereby defining a new and logical strategy in pain relief, management of blood pressure disorders and cardioprotection from ischemic injury. I have a broad background in cellular and molecular signal transduction in the cardiovascular system and associated physiological function, which is absolutely necessary for the challenging projects I have planned for the future.

In addition, I have included undergraduates in research throughout my entire career as noted in the research plan and Facilities and Environment sections of the current application, as well as focusing on teaching. Over the past 5 years while serving as the Assistant Chair of the Department of Biological Sciences at Kent State University, I have assisted faculty conceptually and financially in the development of two new courses designed to prepare students for careers in science as well as provide hands-on training in cellular and molecular techniques (Advanced Cell Biology Lab and Molecular Biology Lab). These courses include training for undergraduates in using fluorescence microscopy, DNA and protein analyses, PCR-cloning and expression on recombinant proteins, and other techniques that prepare students for work in research laboratories. Many of the students who have worked in my research lab have completed these two laboratory courses. In addition, I collaborated on developing a research based course entitled Biophotonics with colleagues in Physics and Chemistry. In this course, students learned the underlying chemical and physical principles of fluorescence and then synthesize fluorescent dyes which they introduced into cells and examined with confocal microscopy. We have a strong history in our department of involving undergraduate students in research and providing courses that prepare students for research.

B. Positions and Honors

Employment
1991-1994 Research Fellow, Molecular Cardiology, Cleveland Clinic
1994-2002 Project Scientist, Division of Anesthesiology and Critical Care Medicine, Cleveland Clinic
2002-2007 Assistant Professor, Division of Anesthesiology and Critical Care Medicine, Cleveland Clinic
2007-2009 Associate Professor, Dept. of Biological Sciences, Kent State University
2009-present Professor, Dept. of Biological Sciences, Kent State University

Honors
1992 Robert C. Tazari Award for Cardiovascular Research, Cleveland Clinic
1992 Bernardine Healy Chairman's Research Award, Cleveland Clinic
1994 William F. Lowry Award for Basic Research, Cleveland Clinic
2004 "Best of the Meeting Finalist" International Anesthesia Research Society Annual Meeting
2009 "Best of the Meeting Finalist" International Anesthesia Research Society Annual Meeting

C. Contribution to Science

Graduate Studies (1988-1991; Kent State University)
My early publications as a graduate student directly addressed the role of calcium influx on trauma-induced alterations of brain lipid metabolism. Specifically, we utilized rat brain cerebral minces to labeled with 3H-arachidonic acid to assess phospholipid metabolism in response to ischemic insult and isolated hippocampal mossy fiber nerve terminals to assess the role of arachidonic acid and its metabolites (eicosanoids) in mediating both changes in intracellular free Ca2+ concentration and release of the excitatory neurotransmitter, glutamate. The cerebral mince publications provide important information regarding brain lipid metabolism following ischemia and the isolated nerve terminal studies provided important fundamental information regarding the modulation of depolarization-, Ca2+-dependent release of glutamate by arachidonic acid and/or eicosanoids. The latter studies provided implications into cellular and molecular mechanisms related to long term potentiation, a biochemical correlate to learning and memory in the mammalian brain.
**Post-doctoral work (1991-1994; Cleveland Clinic)**

My post-doctoral studies in the department of Molecular Cardiology at Cleveland Clinic were an extension of my graduate studies except I moved into the area of Ca^{2+}-dependent and Ca^{2+} independent regulation of myocardial contractility. It is believed that inotropic agents exert their effect in cardiac muscle via modulation of Ca^{2+} cycling and/or alterations in myofilament Ca^{2+} sensitivity, however the involvement of phospholipase activation and the biochemical pathways participating in inotropic responses remain unclear. The aim of these studies was to determine whether arachidonic acid and/or eicosanoids participate in modulating Ca^{2+} cycling and/or myofilament Ca^{2+} sensitivity of contractile proteins as cellular mechanisms to alter cardiomyocyte contractility. Freshly isolated cardiomyocytes loaded with the Ca^{2+} sensitive probe fura 2 was the model system. Experiments were performed in field-stimulated myocytes where changes in amplitude of the Ca^{2+} transients could be monitored in real time. Biochemical assessment of post translational modifications of contractile proteins were also performed. These studies were funded by a F32 NIH NRSA post-doctoral fellowship to Derek Damron. Arachidonic acid was found to potentiate Ca^{2+} transients; even in the presence of inhibitors of eicosanoid production but severely attenuated in the presence of PKC inhibitors and involves changes in both Ca^{2+} influx and release of Ca^{2+} from the sarcoplasmic reticulum. Moreover, arachidonic acid also stimulated PKC-dependent phosphorylation of troponin I and myosin light chain 2 leading to increase in myofilament Ca^{2+} sensitivity. Together, these alterations identified novel pathways by which arachidonic acid potentiates Ca^{2+} availability and enhances myofilament Ca^{2+} sensitivity to increase cardiomyocyte contractility.


**Project Scientist (1994-2001; Cleveland Clinic)**

As a project scientist under the direction of Dr. Paul A. Murray (Director) in the Center for Anesthesiology Research at Cleveland Clinic, my role as Co-I on his NIH RO1 (HL38291-18) was to oversee and coordinate in vitro studies to complement his in vivo studies examining the extent to which anesthetic agents modify pulmonary artery (PA) vascular reactivity in response to α-adrenergic stimulation. This way I could extend his studies to the cellular and molecular level while beginning to sort out my own research interests and collect preliminary data for an NIH RO1. Our studies in isolated PA smooth muscle cells demonstrated that α-adrenergic stimulation with phenylephrine (PE) induced Ca^{2+} oscillations that were attenuated dose-dependently by propofol and ketamine. Interestingly, benzodiazepines differentially alter either the amplitude and/or the frequency of the PE-induced Ca^{2+} oscillations. We also demonstrated a role for capacitative Ca^{2+} entry in PA smooth muscles to regulate vasomotor tone and that propofol attenuates this effect. In addition, we identified fundamental mechanisms regulating intracellular free Ca^{2+} concentration in PA smooth muscle including roles for tyrosine kinase, rho kinase and K^{+} channels. These data all provided important fundamental information regarding the effects of anesthetic agents on cellular mechanisms regulating pulmonary vascular reactivity.


**First-Independent step (2001-2007)**

Studies as an independent investigator (Assistant Professor) following my time as a project scientist under Dr. Paul A. Murray also occurred in the Division of Anesthesiology Research at Cleveland Clinic. It is well established that anesthetic agents often have deleterious effects on the cardiovascular system. In fact, surgery is very often avoided in patients with limited cardiovascular reserve due to the high risk for poor patient outcomes including morbidity or even mortality. The focus of my studies was to delineate the extent to which intravenous anesthetics (IVA) modify the Ca²⁺ transients and contractile properties of individual cardiomyocytes and to determine the cellular and molecular mechanisms mediating these effects. We initially examined a number of different IVA on baseline parameters and selected propofol as our anesthetic of choice due to its extensive use by clinicians because of the beneficial physical properties of the compound. **These studies were funded by an NIH RO1 HL65701 (2001-2006) to Derek Damron.** We were the first to determine that propofol alters a number of parameters that regulate overall cardiomyocyte contractility including intracellular Ca²⁺ handling (influx through L-type channels, Ca²⁺ release and reuptake from sarcoplasmic reticulum stores and efflux through Na+/Ca²⁺ exchange. We also determined that propofol increased myofilament Ca²⁺ sensitivity and intracellular pH via activation of Na+/H⁺ exchange. In addition, propofol stimulated phosphorylation of the contractile proteins troponin I and myosin light chain 2 resulting in an increase in myofilament Ca²⁺ sensitivity. Finally, propofol had differential effects on inotropic stimulation of cardiomyocytes resulting in decreased β-adrenergic responsiveness but increased α-adrenergic responsiveness. Virtually all of these effects pointed towards a role for PKC isofoms (primarily PKCε) as the mediator(s) of altered cardiomyocyte Ca²⁺ handling, myofilament Ca²⁺ sensitivity and overall contractility. Our data indicated to clinicians that propofol may not necessarily always be the anesthetic of choice due to its predominant negative inotropic effects. However, the data provide important fundamental information for the design and synthesis of novel anesthetic agents which lack these adverse side effects.


**Established Investigator (2007-present; Kent State University)**

In addition to the contributions described above, with a team of collaborators we have begun to investigate interactions between the IVA propofol and TRP ion channels in sensory neurons (nociception) and the coronary vasculature. We have identified that propofol is a TRPA1 agonist and is capable of resensitizing previously desensitized TRPV1 via a PKCα- nitric oxide synthase dependent pathway in sensory neurons. These data are the first to show crosstalk between the two channels via intracellular signaling pathways that are likely important in mediating both acute and chronic pain syndromes. In addition, we have determined that TRPA1 channels in the vasculature are also targets for the IVA propofol causing vasodilation through a nitric oxide and BKα channel pathway. These data imply that TRPA1 agonists in the vasculature may be potential targets for anti-hypertensive drugs in the future.


Complete List of Published Work in My Bibliography:
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D. Research Support (last 5 years)

**Current Research Support:**

N/A

**Completed Research Support**

**Title:** Prevention of Reperfusion Injury in Ischemic Stroke: Role of High Molecular Weight Kininogen and PKCδ

**Type:** Intramural  Wen-hai Chou (PI), Derek S. Damron (Co-I)  Period 9/1/2013-8/31/2015

**Agency:** Kent State University/Cleveland Clinic

The major goal of the project is to determine the link between kininogen and PKCδ in the prevention of reperfusion injury in ischemic stroke.

The major goal of the project is to identify the role of TRPV1 ion channels in mediating oxidative stress-induced uncoupling of myocardial blood flow.

**Title:** Propofol and Protein Kinase C: Molecular Interactions in Cardiomyocytes

**Type:** RO1 HL65701-12  Derek S. Damron (PI)  Period: 07/01/2007-05/31/2014

**Agency:** NIH/NHLBI

The major goal of the project is to identify the cellular signaling pathways by which the intravenous anesthetic, propofol, acts as a ligand to activate PKCs, and to delineate the molecular mechanism by which interaction and activation of the enzyme occurs.