Graduate School of Arts & Sciences

Final Examination of

Christopher Lee Schaich

For the Degree of

Doctor of Philosophy

Physiology and Pharmacology
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Committee in Charge
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Piedmont Triad Community Research Center
115 S. Chestnut Street
Auditorium
Monday, April 21, 2014
2:00 p.m.
PROFESSOR IN CHARGE OF RESEARCH
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FIELDS OF GRADUATE STUDY
Major Subject: Physiology and Pharmacology

SUMMARY OF DISSERTATION

BLOOD PRESSURE REGULATION BY THE ENDOCANNABINOID SYSTEM IN CONDITIONS ASSOCIATED WITH HYPERTENSION

Hypertension is associated with various conditions including obesity, type II diabetes and aging. Despite decades of research, the mechanisms involved in the development of hypertension are still poorly understood. Emerging evidence suggests hypertension is mediated by an imbalance in autonomic nervous system activity. Baroreflex sensitivity for control of heart rate, an important index of vagus nerve function as well as general morbidity and mortality, is often impaired in conditions associated with hypertension. Restoration of baroreflex function is now recognized as a therapeutic strategy for prevention of cardiovascular diseases. Therefore, it is crucial to identify key factors that regulate brainstem regions controlling autonomic outflow in conditions associated with baroreflex dysfunction. Mounting evidence suggests a functional role for the endocannabinoid system in the impairment of baroreflex sensitivity during hypertension, which may be related to interactions with the renin-angiotensin system (RAS). Our goal is to determine if the brain endocannabinoid system contributes to baroreflex dysfunction and elevated blood pressure in conditions associated with altered RAS activity.

Specifically, we determine whether CB1 cannabinoid receptor tone is present at the level of the brainstem solitary tract nucleus (NTS) in transgenic rats with high or low brain RAS activity. Data from these studies demonstrate that blockade of NTS CB1 receptors in anesthetized hypertensive (mRen2)27 rats with high brain RAS expression dose-dependently improves the blunted baroreflex sensitivity in this strain. However, blockade of CB1 receptors in the NTS of anesthetized ASTROGEN rats with low brain RAS expression has opposite effects, dose-dependently reducing the enhanced baroreflex sensitivity in this strain. In contrast, there is no effect of NTS CB1 blockade in normotensive Sprague-Dawley rats. Biochemical data indicate higher medullary production of the endocannabinoid 2-arachidonoylglycerol (2-AG) in (mRen2)27 rats compared to lower 2-AG production in ASTROGEN rats. Together, these observations suggest a differential role for the endocannabinoid system in the modulation of baroreflex sensitivity in conditions associated with altered brain RAS activity.

We then determine whether altered endocannabinoid tone is present at the level of the NTS of aged Sprague-Dawley rats. Microinjection studies in older animals demonstrate that blockade of NTS CB1 receptors normalizes baroreflex sensitivity only in animals that exhibit age-related impaired baseline baroreflex function. However, biochemical data indicate significantly higher 2-AG content in the dorsal medulla of aged relative to young adult Sprague-Dawley rats, and also show altered expression of CB1 and CB2 receptor mRNA expression with age in this region. These studies suggest a role for the endocannabinoid system in the impairment of baroreflex sensitivity associated with aging.

Finally, we evaluate the hemodynamic and metabolic effects of systemic administration of a CB1 receptor antagonist in (mRen2)27 rats, which feature increased body weight and insulin resistance in addition to Ang II-dependent hypertension. Results from these studies indicate that systemic blockade of CB1 receptors significantly reduces blood pressure in this strain while having no effect on blood pressure in normotensive control rats. The blood pressure-lowering effect is associated with significant improvement in indices of conscious autonomic outflow following chronic treatment with the CB1 antagonist. Furthermore, animals receiving chronic systemic CB1 blockade exhibit an improved metabolic profile compared to animals treated with the vehicle.

In summary, the present studies suggest that upregulation of the endocannabinoid system contributes to the maintenance of hypertension, impaired baroreflex sensitivity, and symptoms of metabolic syndrome associated with overactivity of the RAS. These results are consistent with an interaction between the endocannabinoid system and RAS that may promote the development of hypertension associated with aging and obesity. Therefore, we conclude that targeting the endocannabinoid system for blockade may confer therapeutic benefits during hypertension associated with an activated RAS.
SCHOLASTIC VITAE

EDUCATION
2014  Ph.D., Integrative Physiology and Pharmacology
      Wake Forest University, Winston-Salem, North Carolina
2006  B.A., Psychology, Magna Cum Laude, With Distinction
      University of Connecticut, Storrs, CT
      Minors in Neuroscience and Ecology & Evolutionary Biology

PROFESSIONAL MEMBERSHIPS
2012 – Present  American Society for Pharmacology and Experimental Therapeutics
2011 – Present  Society for Neuroscience – Western North Carolina Chapter
2011 – Present  International Cannabinoid Research Society
2010 – Present  American Heart Association
2010 – Present  American Physiological Society

AWARDS
2014  Finalist, 3 Minute Thesis (3MT) competition, Wake Forest University
2014  ASPET Graduate Student Travel Award
      To attend Experimental Biology 2014, San Diego, CA
2013  Onsite Poster Competition Award: Council for High Blood Pressure Research
      High Blood Pressure Research 2013, New Orleans, LA
2013  ICRS Travel Award
      To attend the 23rd Annual Symposium of the International Cannabinoid Research Society, Vancouver, BC
2013  Finalist, Nature Careers Columnist Competition
2013  Mary A. Bell Award, Systems Neuroscience. Western North Carolina Society for Neuroscience Research Day
2012  Finalist, Sixth Annual Graduate Student Poster Competition, Charlotte Life Sciences Conference
2012  Runner-Up Award, Integrative Sciences. Twelfth Annual Graduate Student and Postdoctoral Fellow Research Day, Wake Forest University
2011  Wake Forest University Alumni Travel Award
      To attend the 21st Annual Symposium of the International Cannabinoid Research Society conference, St. Charles, IL
2010  Wake Forest University Alumni Travel Award
      To attend the High Blood Pressure Research Council 2010 Scientific Sessions, Washington, DC
PUBLICATIONS

Manuscripts


Schaich CL, Shaltout HA, Brosnihan KB, Howlett AC, Diz DI. Acute and Chronic Systemic CB₁ Cannabinoid Receptor Blockade Improves Blood Pressure Regulation and Metabolic Profile in Hypertensive (mRen2)27 Rats. Submitted to American Journal of Physiology – Regulatory, Integrative and Comparative Physiology. (Under review).


Selected Abstracts


Chris L., Schaich, Hossam A. Shaltout, Allyn C. Howlett, Debra I. Diz; Chronic Systemic CB₁ Receptor Blockade Reduces Blood Pressure and Weight Gain and Improves Baroreflex Function and Heart Rate Variability in Hypertensive (mRen2)27 Rats. Hypertension 62:A183, 2013.