Final Examination of

Swapnil V. Shewale

For the Degree of

DOCTOR OF PHILOSOPHY

COMMITTEE IN CHARGE

Martha Alexander-Miller, PhD, Chairperson

John S. Parks, PhD, Advisor

Michael C. Seeds, PhD

Kylie Kavanagh, VMS, MS, MPH

Ann Tallant, PhD

WF Bio-Tech Place – Auditorium
575 N. Patterson Avenue
June 11, 2015
9:00 a.m.
PROFESSOR(S) IN CHARGE OF RESEARCH
John S. Parks, PhD

FIELDS OF GRADUATE STUDY
Major Subject:
Physiology and Pharmacology

SUMMARY OF DISSERTATION
THE ROLE OF BOTANICAL OILS ENRICHED IN FADS2-DERIVED N-3 VS. N-6 POLYUNSATURATED FATTY ACIDS IN PREVENTION OF ATHEROSCLEROSIS

Dietary polyunsaturated fatty acids (PUFAs) reduce atherosclerosis in animal models and humans relative to dietary saturated and monounsaturated fatty acids. Although some of the atheroprotection of dietary PUFAs is due to plasma lipid lowering, in vivo conversion of 18 carbon PUFAs through the rate-limiting fatty acid desaturase-2 (FADS2, delta-6 desaturase) step of fatty acid desaturation and elongation results in 18 and ≥ 20 carbon PUFAs that are substrates for pro-inflammatory and anti-inflammatory eicosanoid production, which affect atherosclerosis progression and inflammation. We previously showed that an atherogenic diet containing echium oil (EO), which is relatively enriched in stearidonic acid (18:4 n-3), the immediate product of FADS2-mediated desaturation of 18:3 n-3, effectively enriches plasma and tissue lipids in the anti-inflammatory PUFA 20:5 n-3 and was as atheroprotective as dietary fish oil (FO) compared to palm oil (PO), which is enriched in saturated and monounsaturated fatty acids. However, whether a similar strategy of dietary enrichment in FADS-2 n-6 products would lead to atheroprotective is unknown. To address this gap in knowledge, we tested the hypothesis that dietary borage oil (BO), enriched in the FADS-2 product 18:3 n-6, would not be as atheroprotective as EO, due to in vivo conversion to 20:4 n-6, a pro-inflammatory eicosanoid precursor. We also investigated the role of an anti-inflammatory protein G-protein coupled receptor 120 (GPR120) that is activated by PUFAs, in atheroprotection and hypothesized that dietary n-3 PUFAs would lead to greater activation of GPR120 and less inflammation than n-6 PUFAs.

Three studies were performed using: 1) LDL receptor knockout (LDLrKO) mice, 2) irradiated LDLrKO mice transplanted with wild type (WT) or GPR120 knockout (KO) bone marrow, or 3) irradiated LDLrKO mice transplanted with WT or macrophage-specific PPARγ KO bone marrow. Mice were fed one of four atherogenic diets containing 0.2% cholesterol and 10% fat as PO + an additional 10% of fat as PO, FO, EO or BO for 8-16 weeks. Measurements of lipid metabolism, atherosclerosis, and inflammation were made to test out hypotheses.

In study 1, mice fed BO, EO and FO vs. PO had significantly lower plasma total and VLDL cholesterol concentrations, hepatic neutral lipid content and inflammation, aortic CE content, aortic root intimal area and macrophage content, and peritoneal macrophage inflammation, CE content, and ex vivo chemotaxis. We conclude that botanical oils enriched in 18:3 n-6 and 18:4 n-3 PUFAs beyond the rate-limiting FADS2 enzyme are equally effective in preventing atherosclerosis and hepatosteatosis compared to saturated/monounsaturated fat due to cellular enrichment of ≥20 PUFAs, reduced plasma VLDL, and attenuated macrophage inflammation.

In study 2, mice fed BO, EO and FO vs. PO had significantly reduced plasma cholesterol, triglycerides, VLDL cholesterol, hepatic steatosis, and atherosclerosis that were equivalent for mice transplanted with WT and GPR120 KO mouse bone marrow, demonstrating that leukocyte GPR120 expression did not affect these outcomes. In BO, EO and FO, but not PO-fed mice, lack of leukocyte GPR120 resulted in neutrophilia, pro-inflammatory Ly6Chi monocytes, increased monocyte recruitment into aortic roots, and increased hepatic inflammatory gene expression. We conclude that leukocyte GPR120 expression has minimal effect on dietary PUFA-induced plasma lipid/lipoprotein reduction and atheroprotection, and that there is no distinction between n-3 vs. n-6 PUFAs in activating anti-inflammatory effects of leukocyte GPR120 in vivo.
SCHOLASTIC VITAE

EDUCATION

2015  Ph.D., Integrated Physiology and Pharmacology, Wake Forest University, Winston-Salem, NC

2010  M.S., Boonshoft School of Medicine, Dayton, OH

2007  B.S., Pharmacy and Pharmaceutical Sciences, Pune University, India

AWARDS

2014  Team Leader, Wake Forest Team, 5th Annual Biotech Case Competition

2013  Member, Wake Forest Team, 4th Annual Biotech Case Competition (runner up team)

2013 - 2014  Chair, Graduate Student’s Association, Wake Forest School of Medicine

2012  Treasurer and Departmental Representative, Graduate Student’s Association, Wake Forest University

2011  Best Poster, Integrative Category, Annual Research Retreat, Wake Forest Univ.

2010  Graduate Student Excellence Award, Wright State University, Dayton, OH

2008 - 2010  Fellowship, Graduate Research Assistant, Department of Pharmacology and Toxicology, Boonshoft School of Medicine, Dayton, OH

Professional Memberships

2015  Member, Association of University Technology Transfer Managers (AUTM)

2013 – Current  Member, American Physiological Society (APS)

2013 – Current  Member, American Society for Pharmacology and Experimental Therapeutics (ASPET)

2012  Poster presentation, ATVB Scientific Sessions

2009 – Current  Member, American Heart Association
PUBLICATIONS

Manuscripts
1. Swapnil V. Shewale, Elena Boudyguina, Xuewei Zhu, Lulu Shen, Patrick M. Hutchins, Robert M. Barkley, Robert C. Murphy, John S. Parks. Botanical oils enriched in n-6 and n-3 fatty acid products of FADS2 are equally effective in preventing atherosclerosis and hepatosteatosis in mice. J Lipid Res. 2015 Apr 28. pii: jlr.M059170


Abstracts
1. Swapnil V Shewale; Elena Boudyguina; Xin Bi; Xuewei Zhu; Nilamadhab Mishra; Da Young Oh; Jerrold Olefsky; John S. Parks. Role of Leukocyte GPR120 in Atherosclerosis Development in Polyunsaturated Fatty Acid Diet Induced Atheroprotection in LDLrKO Mice. Arterioscler Thromb Vasc Biol. 33: A121, 2013

2. Swapnil V Shewale, Elena Boudyguina, Patrick M Hutchins, Robert C Murphy, John S Parks. Echium and Borage Oil Are as Atheroprotective as Fish Oil in Mice. Arterioscler Thromb Vasc Biol. 32: A190, 2012
