Final Examination of

Eric Edward Ewan

B.A., University of Wisconsin-Eau Claire
Eau Claire, WI

For the Degree of

DOCTOR OF PHILOSOPHY

COMMITTEE IN CHARGE

James C. Eisenach, M.D., Chairman
Anesthesiology

Thomas J. Martin, Ph.D., Advisor
Anesthesiology

Steven R. Childers, Ph.D.
Physiology and Pharmacology

Robert C. Coghill, Ph.D.
Neurobiology and Anatomy

Richard L. Rauch, M.D.
Anesthesiology

David C. Roberts, Ph.D.
Physiology and Pharmacology

Piedmont Triad Community Research Center Auditorium
August 15, 2011
9:00 a.m.
PROFESSOR IN CHARGE OF RESEARCH

Thomas J. Martin, Ph.D.
Associate Professor
Anesthesiology
Wake Forest University School of Medicine

FIELDS OF GRADUATE STUDY
Major Subject: Physiology and Pharmacology

Cell and Molecular Pharmacology
Basic Physiology and Pharmacology
Systems Pharmacology
Integrated Physiology and Pharmacology
Quantitative Methods Behavioral Sciences

SUMMARY OF DISSERTATION

BEHAVIORAL PHARMACOLOGICAL ANALYSIS OF DEEP BRAIN STIMULATION FOLLOWING NERVE INJURY

Treatment of neuropathic pain remains a major unmet public health problem. Serious concerns arise over misuse of prescription opioids in chronic pain patients, a drug class representing the fastest growing substance abuse problem in the United States. Ascending pain pathways overlap significantly with limbic regions involved in reward and reinforcement, therefore pain and reward systems substantially interact and modulate one another. The extent to which pain modulates mesolimbic dopamine systems and thereby alters the reinforcing and abuse-related effects of opioids is not fully understood. The ability of pain relief to produce reinforcement in and of itself through modulation of this circuitry is also unknown.

To address these concerns the current work employed intracranial self-stimulation (ICSS), an operant paradigm pairing lever presses with electrical stimulation of discrete brain regions. Studies employing ventral tegmental area (VTA) ICSS in normal and neuropathic rats suggest that mesolimbic dopamine neurons function normally after nerve injury, yet stimulation of these pathways by opioids appears to be selectively diminished. In addition, alleviation of hypersensitivity (and possibly spontaneous pain) with spinal analgesics does not stimulate this circuitry following neuropathy. In contrast, acute pain induced by paw incision produces brief suppression of mesolimbic dopamine pathways, suggesting that intense spontaneous pain in the postoperative period, but not pain following neuropathy, inhibits limbic reward pathways in rats.

Stimulation of the hypothalamic paraventricular nucleus (PVN) and periaqueductal gray (PAG) reversed mechanical hypersensitivity induced by spinal nerve ligation, though only PVN stimulation produced reinforcing effects in neuropathic rats. PVN stimulation also produced reinforcing effects in normal rats, and the reinforcing effects of PVN ICSS in neuropathic rats were not altered by spinal analgesics. These studies suggest that alleviation of hypersensitivity is unlikely to be the primary stimulus mediating ICSS in the PVN.

Collectively, these studies provide some insights into the interactions between pain and reward systems, and how each is altered under neuropathic states. These studies also highlight the difficulties in assessing spontaneous pain in laboratory animals. Given the results from these studies, it is unclear if nerve-injured rats experience significant spontaneous pain after peripheral nerve injury, or if the ICSS paradigm as it is typically used is not sensitive enough to detect subtle manifestations of ongoing pain in neuropathic rats. Future studies utilizing different approaches in performing ICSS studies, as well as studying the effects of different nerve injury models or other chronic pain models may be useful in addressing these issues.
SCHOLASTIC VITAE

EDUCATION

Ph.D. Physiology and Pharmacology, 2011
Wake Forest University School of Medicine
Winston-Salem, North Carolina

B.A. Psychology, 2006
Summa Cum Laude
University of Wisconsin-Eau Claire

PROFESSIONAL MEMBERSHIPS

2007- Present American Pain Society
2007- Present Society for Neuroscience
2004 – 2006 Ronald E. McNair Postbaccalaureate Achievement Program
2003 – 2006 Phi Eta Sigma honor society
2003 – 2006 Alpha Lambda Delta honor society

AWARDS

2010 Travel Award to American Pain Society Annual Meeting
2006 Outstanding Student Research Award – Dept of Physiology and Pharmacology
          UW-Eau Claire
PUBLICATIONS

Ewan, E.E. and Martin, T.J. (accepted). Rewarding electrical brain stimulation in rats following peripheral nerve injury: Decreased facilitation by commonly abused prescription opioids. *Anesthesiology*


