BIOGRAPHICAL SKETCH

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NAME: Koerber, H Richard

eRA COMMONS USER NAME (agency login): koerber

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Marietta College, Marietta, Ohio	BS	05/1975	Biology
West Virginia University, Morgantown, WV	MS	09/1977	Physiology and Biophysics
West Virginia University, Morgantown, WV	PHD	10/1981	Physiology and Biophysics

A. Personal Statement

I have over 40 years of experience in recording from spinal and sensory neurons. During the early years of my career I was involved with developing novel physiological approaches for the recording and stimulation of specific primary sensory neurons in cats. In addition, these techniques also allowed for the simultaneous recording of neuronal response to individual afferent stimulation inputs in the spinal cord. Subsequently, I developed a novel *ex vivo* spinal cord/DRG/skin preparation to allow similar studies to be carried out in mice. We are now using this preparation to investigate the function of specific spinal neural networks while employing optogenetics to stimulate specific populations of sensory neurons. Thus, I am highly qualified to provide expert assistance in the experiments in this proposal.

1. Brown AG, **Koerber HR**, Noble R. An intracellular study of spinocervical tract cell responses to natural stimuli and single hair afferent fibres in cats. **J Physiol**. 1987 Jan; 382:331-54. PMID: 3625552; PMCID: PMC1183027.
2. **Koerber HR**, Seymour AW, Mendell LM. Tuning of spinal networks to frequency components of spike trains in individual afferents. **J Neurosci**. 1991 Oct;11(10):3178-87. PMID: 1941079.
3. Kardon AP, Polgár E, Hachisuka J, Snyder LM, Cameron D, Savage S, Cai X, Karnup S, Fan CR, Hemenway GM, Bernard CS, Schwartz ES, Nagase H, Schwarzer C, Watanabe M, Furuta T, Kaneko T, **Koerber HR**, Todd AJ, Ross SE. Dynorphin acts as a neuromodulator to inhibit itch in the dorsal horn of the spinal cord. **Neuron**. 2014 May 7;82(3):573-86. PMID: 24726382; PMCID: PMC4022838.
4. Hachisuka J, Omori Y, Chaing MC, Gold MS, **Koerber HR**, Ross SE. Wind-up in lamina I spinoparabrachial neurons: a role for reverberatory circuits. **Pain**. 2018 Aug 159(8):1484-1493. PMID: 29578943 PMCID: PMC6053328.

B. Positions and Honors

Positions and Employment

1981 - 1982	Postdoctoral Fellow, University of Utah, School of Medicine, Salt Lake City, UT
1982 - 1984	Postdoctoral Fellow, University of Edinburgh, Edinburgh
1984 - 1986	Research Associate, SUNY at Stony Brook, Stony Brook, NY
1986 - 1989	Research Assistant Professor, SUNY at Stony Brook, Stony Brook, NY
1989 - 1993	Assistant Professor, Department of Neurobiology, Anatomy and Cell Science, University of Pittsburgh School of Medicine, Pittsburgh, PA
1993 - 1996	Assistant Professor, Department of Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, PA

1996 - 2007	Associate Professor, Department of Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, PA
2007 -	Professor, Department of Neurobiology, University of Pittsburgh, School of Medicine, Pittsburgh, PA

Other Experience and Professional Memberships

1977 -	Member, Society for Neuroscience
2005 -	Member, IASP
2007 -	Member, APS

C. Contributions to Science

1. Over the past 40+ years I have made several significant contributions to our understanding of the organization, function and plasticity in the somatosensory system. The first seminal contributions come from my work as an NIH (NRSA) funded postdoctoral fellow at the University of Edinburgh in the lab of Dr. Alan G. Brown. One of the historic difficulties in understanding the integration of sensory information in the spinal cord is the fact that cutaneous stimulation activates a wide range of sensory fibers. During the two years of this fellowship I developed a method for establishing dual recordings from in vivo cat preparations. First, I established an intracellular recording from an identified cutaneous sensory neuron located in the dorsal root ganglia. While maintaining this recording, a second was established from an identified spinocervical tract cell in the spinal dorsal horn. Using this approach, we were able to stimulate individual primary afferent fibers while recording the evoked responses in the identified spinal projection neuron. These studies resulted in a series of three manuscripts describing the functional properties of these specific spinal networks. I extended these findings as a Research Associate and later as an Assistant Professor at SUNY Stony Brook working with Dr. Lorne Mendell describing how spinal networks receiving input from different fiber types were tuned to respond to differently to frequency modulated inputs.

    a. Brown AG, Koerber HR, Noble R. An intracellular study of spinocervical tract cell responses to natural stimuli and single hair afferent fibres in cats. J Physiol. 1987 Jan;382:331-54. PubMed PMID: 3625552; PubMed Central PMCID: PMC1183027.
    b. Brown AG, Koerber HR, Noble R. Actions of trains and pairs of impulses from single primary afferent fibres on single spinocervical tract cells in cat. J Physiol. 1987 Jan;382:313-29. PubMed PMID: 3625551; PubMed Central PMCID: PMC1183026.
    c. Koerber HR, Mendell LM. Functional specialization of central projections from identified primary afferent fibers. J Neurophysiol. 1988 Nov;60(5):1597-614. PubMed PMID: 3199174.
    d. Koerber HR, Seymour AW, Mendell LM. Tuning of spinal networks to frequency components of spike trains in individual afferents. J Neurosci. 1991 Oct;11(10):3178-87. PubMed PMID: 1941079.

2. While at Stony Brook I began my first independently funded NIH research project examining the anatomical and functional plasticity in the spinal cord following peripheral nerve injury and regeneration. I continued this project in my next position as an Assistant Professor at the University of Pittsburgh. The rationale for these studies stemmed from the clinical observation that following nerve injury and regeneration, patients initially loose the ability to localize stimuli applied to the reinnervated skin. However, with time the ability to localize the stimulus is frequently restored. I hypothesized that the recovery in function was due to spinal plasticity. Over the course of these studies we made two major findings. First, we found that following regeneration some primary afferent fibers appeared to sprout into the superficial laminae of the dorsal horn apparently confirming the results of earlier studies by Clifford Woolf and colleagues. Second, we found that immediately following regeneration, dorsal horn cells had very large cutaneous receptive fields and with time these receptive fields became smaller and more concise. Finally, we determined that this process involved the establishment of new functional synapses in the spinal dorsal horn.

    a. Koerber HR, Mirnics K, Brown PB, Mendell LM. Central sprouting and functional plasticity of regenerated primary afferents. J Neurosci. 1994 Jun;14(6):3655-71. PubMed PMID: 8207480.

b. Koerber HR, Mirnics K, Mendell LM. Properties of regenerated primary afferents and their functional connections. J Neurophysiol. 1995 Feb;73(2):693-702. PubMed PMID: 7760128.

c. Koerber HR, Mirnics K. Plasticity of dorsal horn cell receptive fields after peripheral nerve regeneration. J Neurophysiol. 1996 Jun;75(6):2255-67. PubMed PMID: 8793739.

d. Koerber HR, Mirnics K, Lawson JJ. Synaptic plasticity in the adult spinal dorsal horn: the appearance of new functional connections following peripheral nerve regeneration. Exp Neurol. 2006 Aug;200(2):468-79. PubMed PMID: 16696973.

3. Subsequently, I was intrigued by two widely accepted findings. First was the suggestion that during development large diameter low threshold mechanoreceptors initially project into the superficial laminae of the dorsal horn and with time retract into their adult locations in deeper laminae. The second was the suggestion that following injury these large diameter fibers could sprout and reenter the superficial laminae. This sprouting was considered to be the possible anatomical substrate for the appearance of mechanical allodynia in chronic pain patients. In order to study the possible mechanisms involved in this extensive plasticity of the afferent fiber projections, we developed an ex vivo mouse somatosensory preparation consisting of spinal cord, DRGs, nerves and innervated skin. Using this preparation we were able to determine that large low threshold mechanoreceptive afferent fibers did not initially project into the superficial laminae of the dorsal horn nor did they sprout into these laminae following injury. In addition, we identified a group of fast conducting high threshold mechanoreceptive fibers that projected into these and deeper laminae that were probably the source of the prior findings suggesting sprouting. These studies demonstrated that the spinal plasticity resulting in mechanical allodynia did not require anatomical reorganization, but rather plasticity in existing spinal circuits.

   a. Woodbury CJ, Ritter AM, Koerber HR. Central anatomy of individual rapidly adapting low-threshold mechanoreceptors innervating the "hairy" skin of newborn mice: early maturation of hair follicle afferents. J Comp Neurol. 2001 Jul 30;436(3):304-23. PubMed PMID: 11438932.

   b. Koerber HR, Woodbury CJ. Comprehensive phenotyping of sensory neurons using an ex vivo somatosensory system. Physiol Behav. 2002 Dec;77(4-5):589-94. PubMed PMID: 12527004.

   c. Woodbury CJ, Koerber HR. Widespread projections from myelinated nociceptors throughout the substantia gelatinosa provide novel insights into neonatal hypersensitivity. J Neurosci. 2003 Jan 15;23(2):601-10. PubMed PMID: 12533620.

   d. Woodbury CJ, Kullmann FA, McIlwrath SL, Koerber HR. Identity of myelinated cutaneous sensory neurons projecting to nocireceptive laminae following nerve injury in adult mice. J Comp Neurol. 2008 May 20;508(3):500-9. PubMed PMID: 18335545; PubMed Central PMCID: PMC2664515.

4. The advent of novel mouse genetic techniques and our ex vivo mouse preparation has also allowed us to make a number of other important contributions to the field. While other recording methods allow for recording from primary afferents, our preparation allows for comprehensive phenotyping of sensory neurons. This approach, in collaboration with different groups producing novel transgenic and knock-out mouse lines, has allowed us to address many fundamental questions concerning the roles of specific receptor and channels in the development and function of cutaneous sensory neurons. The first of these studies addressed the roles of neurotrophic factors during development. Drs. Kathryn Albers and Brian Davis had developed transgenic mice that overexpressed different neurotrophic factors in the skin. We found that in addition to being required for survival of particular afferent types, these neurotrophic factors play profound roles in the functional properties of different subsets of afferent fibers including both nociceptive fibers as well as low threshold tactile afferents. These collaborations have lead to additional studies examining the roles of specific receptors and channels in primary afferent function. Examples of these studies are referenced below.

   a. Albers KM, Woodbury CJ, Ritter AM, Davis BM, Koerber HR. Glial cell-line-derived neurotrophic factor expression in skin alters the mechanical sensitivity of cutaneous nociceptors. J Neurosci. 2006 Mar 15;26(11):2981-90. PubMed PMID: 16540576.

   b. McIlwrath SL, Lawson JJ, Anderson CE, Albers KM, Koerber HR. Overexpression of neurotrophin-3 enhances the mechanical response properties of slowly adapting type 1 afferents and myelinated nociceptors. Eur J Neurosci. 2007 Oct;26(7):1801-12. PubMed PMID: 17897394.

c. Rau KK, McIlwrath SL, Wang H, Lawson JJ, Jankowski MP, Zylka MJ, Anderson DJ, Koerber HR. Mrgprd enhances excitability in specific populations of cutaneous murine polymodal nociceptors. J Neurosci. 2009 Jul 1;29(26):8612-9. PubMed PMID: 19571152; PubMed Central PMCID: PMC2756673.

d. Molliver DC, Rau KK, McIlwrath SL, Jankowski MP, Koerber HR. The ADP receptor P2Y1 is necessary for normal thermal sensitivity in cutaneous polymodal nociceptors. Mol Pain. 2011 Feb 10;7:13. PubMed PMID: 21310055; PubMed Central PMCID: PMC3049184.

5. Our studies of the effects peripheral nerve injury and regeneration demonstrated that many different types of nociceptive fibers reinnervating the skin were either sensitized or had undergone phenotypic change. In order to investigate potential mechanism for this injury induced plasticity we examined expression changes in the DRG as well as in the skin following injury and during regeneration. We found a number of changes in expression in both skin and DRG that were correlated with the changes in nociceptor function. In order to determine any causal relationships between these expression and functional changes we developed a novel method for in vivo siRNA knockdown of expression of specific gene products. The results from these studies have identified specific molecular mechanisms underlying the functional and phenotypic changes observed following peripheral injury.

   a. Jankowski MP, Lawson JJ, McIlwrath SL, Rau KK, Anderson CE, Albers KM, Koerber HR. Sensitization of cutaneous nociceptors after nerve transection and regeneration: possible role of target-derived neurotrophic factor signaling. J Neurosci. 2009 Feb 11;29(6):1636-47. PubMed PMID: 19211871; PubMed Central PMCID: PMC2768416.

   b. Jankowski MP, Rau KK, Soneji DJ, Anderson CE, Koerber HR. Enhanced artemin/GFRα3 levels regulate mechanically insensitive, heat-sensitive C-fiber recruitment after axotomy and regeneration. J Neurosci. 2010 Dec 1;30(48):16272-83. PubMed PMID: 21123573; PubMed Central PMCID: PMC3018779.

   c. Jankowski MP, Rau KK, Soneji DJ, Ekmann KM, Anderson CE, Molliver DC, Koerber HR. Purinergic receptor P2Y1 regulates polymodal C-fiber thermal thresholds and sensory neuron phenotypic switching during peripheral inflammation. Pain. 2012 Feb;153(2):410-9. PubMed PMID: 22137295; PubMed Central PMCID: PMC3264839.

   d. Jankowski MP, Soneji DJ, Ekmann KM, Anderson CE, Koerber HR. Dynamic changes in heat transducing channel TRPV1 expression regulate mechanically insensitive, heat sensitive C-fiber recruitment after axotomy and regeneration. J Neurosci. 2012 Dec 5;32(49):17869-73. PubMed PMID: 23223305; PubMed Central PMCID: PMC3533441.

Complete List of Published Work available at: http://www.ncbi.nlm.nih.gov/pubmed/?term=koerber+hr

D. Research Support

Ongoing Research Support

R01 AR069951-01 Koerber, H Richard (MPI) 04/01/16-03/31/21
Characterization of Epithelial-Neural Communication
This study will determine how ChR2-mediated activation of skin keratinocytes impacts activation of different functional classes of cutaneous sensory afferents under normal and inflamed conditions.
Role: **MPI**

R01 NS096705 Koerber, H Richard (PD/PI) 09/01/16-08/31/21
Molecular Genetic Dissection of the Spinal Microcircuits of Wind-up
Chronic pain is a serious health concern effecting millions of American annually. In this project, we are using use innovative genetic tools together with a novel somatosensory preparation to dissect the spinal circuitry involved in processing nociceptive information. These studies will provide new knowledge about how specific spinal networks process peripheral sensory information under normal and inflamed conditions. This knowledge should provide targets for new pharmaceutical therapies for the treatment of chronic pain.
Role: **PD/PI**

Completed Research Support (past 7 years)

R01 NS023725-28 Koerber, H Richard (PI) 09/01/89-06/30/19

Peripheral Nerve Regeneration and Sensory Neuron Plasticity

The goal of this project is to understand the molecular mechanisms underlying nociceptor sensitization following peripheral nerve injury and regeneration.

Role: **PI**

R01NS050758 Davis, Brian M (PI) 01/15/05-02/28/13

Characterization and Plasticity of Visceral Nociceptors

The goal of this project was to determine the distribution and comprehensive phenotype of visceral nociceptors and to determine the effects of inflammation of these properties.

Role: **Co-Investigator**

R01NS059003 Albers, Kathy M (PI) 12/01/08-11/30/12

Sox11 and Functional Recovery of Sensory Neurons

The goal of these experiments was to determine the role of the transcription factor Sox11 in sensory neuron survival and response to injury. In addition, we also identified factors downstream of Sox11 and their potential roles in survival and regeneration.

Role: **Co-Investigator**

R01NS031826 Davis, Brian M (PI) 02/01/07-01/31/12

Role of Growth Factors in Persistent Pain

The goal of this project was to further determine the cellular mechanisms that mediate the persistent alterations in pain observed following injury and inflammation, by studying both the peripheral nerve and the spinal cord mechanisms initiated by persistent nociception.

Role: **Co-Investigator**

R01 NS052848 Koerber, H Richard (PI) 04/17/06-03/31/11

Primary and Secondary Nociceptors in Persistent Pain

In this project we used our ex vivo spinal cord/skin/nerve preparation and a combination of behavioral, anatomical (both LM and EM) and electrophysiological techniques to determine the time course of post-injury changes in cutaneous sensory neurons and superficial dorsal horn cells in both wild type and transgenic mice following the induction of persistent pain states.

Role: **PI**