

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: WEBER, STEPHEN G

eRA COMMONS USER NAME (credential, e.g., agency login): sweber

POSITION TITLE: Professor of Chemistry

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
Case Western Reserve University, Cleveland, OH	BA	06/1970	Biology and Chemistry
McGill University, Montreal, Quebec	PHD	05/1979	Chemistry

A. Personal Statement

We want to understand chemical events related to normal and pathological brain. Our laboratory develops, refines, and applies new and quantitative methods to learn more about biological systems. The primary goals are (1) the determination of neurotransmitters by microdialysis with fast, capillary, online liquid chromatography (2) the investigation of neuropeptide processing in the extracellular space and (3) to empower others to make better measurements using our methods. We are experienced in capillary chromatography, electrochemical detection, chromatographic theory, mass transport phenomena, electroosmotic flow in brain, small sample handling, peptide chemistry, and live animal experiments. We also have experience in microscopy, organotypic culturing as well as chemical synthesis and purification, statistical methods, and standard biochemical techniques. Our emphasis is on critical assessment of what information can be obtained from a measurement, and how to obtain more accurate information. We have collaborated with the Michael group for several years in the pursuit of better understanding of the limitations of microdialysis. We use that information to develop ideas of how to avoid the limitations. The best of those ideas become new methodological improvements providing more and better information about the brain.

We are excited to collaborate with Josh to help him probe the chemical changes in myocardial hypoxia-reperfusion and the efficacy of his treatment approach. My group has been dissecting the chemical details of redox biology in the brain tissue subjected to ischemia-reperfusion injury for over a decade. We recently developed a system that rapidly changes oxygen tension in tissue culture models. This system more accurately models the quick changes that take place in ischemia-reperfusion. We look forward to expanding the scope of our approach from modeling ischemic stroke to modeling myocardial infarction through this collaboration.

1. Gu H, Varner EL, Groskreutz SR, Michael AC, Weber SG. In Vivo Monitoring of Dopamine by Microdialysis with 1 min Temporal Resolution Using Online Capillary Liquid Chromatography with Electrochemical Detection. *Anal Chem.* 2015 Jun 16;87(12):6088-94. PubMed PMID: [25970591](#); PubMed Central PMCID: [PMC4835028](#).
2. Zhang J, Jaquins-Gerstl A, Nesbitt KM, Rutan SC, Michael AC, Weber SG. In vivo monitoring of serotonin in the striatum of freely moving rats with one minute temporal resolution by online microdialysis-capillary high-performance liquid chromatography at elevated temperature and pressure. *Anal Chem.* 2013 Oct 15;85(20):9889-97. PubMed PMID: [24020786](#); PubMed Central PMCID: [PMC3899587](#).web
3. Zhang J, Liu Y, Jaquins-Gerstl A, Shu Z, Michael AC, Weber SG. Optimization for speed and sensitivity in capillary high performance liquid chromatography. The importance of column diameter in online monitoring of serotonin by microdialysis. *J Chromatogr A.* 2012 Aug 17;1251:54-62. PubMed PMID: [22771067](#); PubMed Central PMCID: [PMC3419010](#).

- Liu Y, Zhang J, Xu X, Zhao MK, Andrews AM, Weber SG. Capillary ultrahigh performance liquid chromatography with elevated temperature for sub-one minute separations of basal serotonin in submicroliter brain microdialysate samples. *Anal Chem.* 2010 Dec 1;82(23):9611-6. PubMed PMID: [21062014](#); PubMed Central PMCID: [PMC3008768](#).

B. Positions and Honors

Positions and Employment

1970 - 1974	Hospital Corpsman (E5), United States Navy, Great Lakes, IL
1979 - 1985	Assistant Professor, University of Pittsburgh, Pittsburgh, PA
1985 - 1994	Associate Professor, University of Pittsburgh, Pittsburgh, PA
1991 - 1992	Visiting Scientist Fellow, Swedish Medical Research Foundation, Goteborg
1994 -	Professor of Chemistry, University of Pittsburgh, Pittsburgh, PA
1999 - 2001	Associate Chair, University of Pittsburgh, Pittsburgh, PA
2001 -	Director of Graduate Studies, University of Pittsburgh, Pittsburgh, PA
2009 -	Professor, Clinical and Translational Science, University of Pittsburgh, Pittsburgh, PA

Other Experience and Professional Memberships

1989 -	Contributing Editor, Trends in Analytical Chemistry
1989 - 2004	Editorial Board, Journal of Pharmaceutical and Biomedical Analysis
1991 - 1997	Editor, Comprehensive Analytical Chemistry
2001 - 2004	Editorial Advisory Board, Analytical Chemistry
2001 - 2004	Editorial Board, Talanta
2010 -	Editorial Board, Journal of Chromatography A
2011 -	Editorial Board, Chemical Analysis
2016 - 2019	Editorial Advisory Board, Analytical Chemistry

Honors

1991	Visiting Scientist Fellowship, Swedish Medical Research Council
1998	Fisher Lectureship, Bucknell University
2005	Gold Medal of Assiut University, Assiut University
2008	Frontiers Lectureship, Wayne State University
2008	Pittsburgh Award of the American Chemical Society, American Chemical Society
2012	Excellence in Mentoring, University of Pittsburgh
2015	Palmer Award, Minnesota Chromatography Forum
2016	Dal Nogare Award, Chromatography Forum of the Delaware Valley

C. Contribution to Science

- Recent work has focused on the development and application of techniques to understand neurochemical function in vitro (organotypic hippocampal slice cultures, OHSCs) and in vivo. We have developed the idea that electroosmotic flow is a better and more controllable method for tissue perfusion than pressure flow. We are applying that to the determination of ectopeptidase activity and thiol metabolism in OHSCs.
 - Guy Y, Muha RJ, Sandberg M, Weber SG. Determination of zeta-potential and tortuosity in rat organotypic hippocampal cultures from electroosmotic velocity measurements under feedback control. *Anal Chem.* 2009 Apr 15;81(8):3001-7. PubMed PMID: [19298057](#); PubMed Central PMCID: [PMC2736137](#).
 - Xu H, Guy Y, Hamsher A, Shi G, Sandberg M, Weber SG. Electroosmotic sampling. Application to determination of ectopeptidase activity in organotypic hippocampal slice cultures. *Anal Chem.* 2010 Aug 1;82(15):6377-83. PubMed PMID: [20669992](#); PubMed Central PMCID: [PMC2920223](#).

- c. Wu J, Sandberg M, Weber SG. Integrated electroosmotic perfusion of tissue with online microfluidic analysis to track the metabolism of cystamine, pantethine, and coenzyme A. *Anal Chem.* 2013 Dec 17;85(24):12020-7. PubMed PMID: [24215585](#); PubMed Central PMCID: [PMC3899583](#).
 - d. Ou Y, Wu J, Sandberg M, Weber SG. Electroosmotic perfusion of tissue: sampling the extracellular space and quantitative assessment of membrane-bound enzyme activity in organotypic hippocampal slice cultures. *Anal Bioanal Chem.* 2014 Oct;406(26):6455-68. PubMed PMID: [25168111](#); PubMed Central PMCID: [PMC4184924](#).
2. Capillary liquid chromatography, cLC, is ideally suited to the small, complex samples obtained from tissue culture perfusion or microdialysis *in vivo*. However, improvements can make it operate faster, with higher sensitivity and greater flexibility.
 - a. Groskreutz SR, Horner AR, Weber SG. Temperature-based on-column solute focusing in capillary liquid chromatography reduces peak broadening from pre-column dispersion and volume overload when used alone or with solvent-based focusing. *J Chromatogr A.* 2015 Jul 31;1405:133-9. PubMed PMID: [26091787](#); PubMed Central PMCID: [PMC4488902](#).
 - b. Liu Y, Zhang J, Xu X, Zhao MK, Andrews AM, Weber SG. Capillary ultrahigh performance liquid chromatography with elevated temperature for sub-one minute separations of basal serotonin in submicroliter brain microdialysate samples. *Anal Chem.* 2010 Dec 1;82(23):9611-6. PubMed PMID: [21062014](#); PubMed Central PMCID: [PMC3008768](#).
 - c. Zhang J, Liu Y, Jaquins-Gerstl A, Shu Z, Michael AC, Weber SG. Optimization for speed and sensitivity in capillary high performance liquid chromatography. The importance of column diameter in online monitoring of serotonin by microdialysis. *J Chromatogr A.* 2012 Aug 17;1251:54-62. PubMed PMID: [22771067](#); PubMed Central PMCID: [PMC3419010](#).
 - d. Groskreutz SR, Weber SG. Temperature-assisted on-column solute focusing: a general method to reduce pre-column dispersion in capillary high performance liquid chromatography. *J Chromatogr A.* 2014 Aug 8;1354:65-74. PubMed PMID: [24973805](#); PubMed Central PMCID: [PMC4100596](#).
3. Collaboration with Prof. Adrian Michael, who is working on minimizing the impact of microdialysis-induced probe damage on microdialysis determinations of neurotransmitter concentrations *in vivo* in combination with our development of fast and sensitive capillary liquid chromatography will lead to better, more informative neurochemical investigations.
 - a. Jung MC, Shi G, Borland L, Michael AC, Weber SG. Simultaneous determination of biogenic monoamines in rat brain dialysates using capillary high-performance liquid chromatography with photoluminescence following electron transfer. *Anal Chem.* 2006 Mar 15;78(6):1755-60. PubMed PMID: [16536408](#); PubMed Central PMCID: [PMC1488825](#).
 - b. Jaquins-Gerstl A, Shu Z, Zhang J, Liu Y, Weber SG, Michael AC. Effect of dexamethasone on gliosis, ischemia, and dopamine extraction during microdialysis sampling in brain tissue. *Anal Chem.* 2011 Oct 15;83(20):7662-7. PubMed PMID: [21859125](#); PubMed Central PMCID: [PMC3193568](#).
 - c. Zhang J, Jaquins-Gerstl A, Nesbitt KM, Rutan SC, Michael AC, Weber SG. *In vivo* monitoring of serotonin in the striatum of freely moving rats with one minute temporal resolution by online microdialysis-capillary high-performance liquid chromatography at elevated temperature and pressure. *Anal Chem.* 2013 Oct 15;85(20):9889-97. PubMed PMID: [24020786](#); PubMed Central PMCID: [PMC3899587](#).
 - d. Gu H, Varner EL, Groskreutz SR, Michael AC, Weber SG. *In Vivo* Monitoring of Dopamine by Microdialysis with 1 min Temporal Resolution Using Online Capillary Liquid Chromatography with Electrochemical Detection. *Anal Chem.* 2015 Jun 16;87(12):6088-94. PubMed PMID: [25970591](#); PubMed Central PMCID: [PMC4835028](#).
4. Much of my work over the years has probed the effects of ischemia-reperfusion injury on the rat brain using both *in vivo* models and OHSCs. Recently, we developed a new apparatus that induces

rapid changes in oxygen tensions in OHSCs, more realistically recapitulating ischemic stroke. Using this system, readouts with genetically-encoded redox probes uncovered new insights about the mitochondrial GSH/GSSG redox couple and the mechanism for differential sensitivity of hippocampal regions to ischemic injury.

- a. Li X, Wallin C, Weber SG, Sandberg M. Net efflux of cysteine, glutathione and related metabolites from rat hippocampal slices during oxygen/glucose deprivation: dependence on gamma-glutamyl transpeptidase. *Brain Res.* 1999 Jan 2;815(1):81-8. PubMed PMID: [9974125](#).
- b. Wallin C, Puka-Sundvall M, Hagberg H, Weber SG, Sandberg M. Alterations in glutathione and amino acid concentrations after hypoxia-ischemia in the immature rat brain. *Brain Res Dev Brain Res.* 2000 Dec 29;125(1-2):51-60. PubMed PMID: [11154760](#).
- c. Yin B, Barrionuevo G, Weber SG. Optimized real-time monitoring of glutathione redox status in single pyramidal neurons in organotypic hippocampal slices during oxygen-glucose deprivation and reperfusion. *ACS Chem Neurosci.* 2015 Nov 18;6(11):1838-48. PubMed PMID: [26291433](#).
- d. Yin B, Barrionuevo G, Batinic-Haberle I, Sandberg M, Weber SG. Differences in Reperfusion-Induced Mitochondrial Oxidative Stress and Cell Death Between Hippocampal CA1 and CA3 Subfields Are Due to the Mitochondrial Thioredoxin System. *Antioxid Redox Signal.* 2017 Sep 20;27(9):534-49. PubMed PMID: [28129719](#); PubMed Central PMCID: [PMC5567420](#).

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01 GM044842-25 WEBER, STEPHEN G. (PI) 05/01/91-04/30/19

Sensitive and Selective Detection of Peptides

Role: PI

R01 MH104386-02 WEBER, STEPHEN G. (PI) 08/15/14-05/31/18

Fast Online Microdialysis/Liquid Chromatography for Monoamine Neurotransmitters

Role: PI

1608757, National Science Foundation WEBER, STEPHEN G (PI) 08/01/16-07/31/19

Expanding the Use of Liquid Chromatography Through Active Temperature Control

This project is funded by the Chemical Measurement and Imaging Program of the Division of Chemistry at the National Science Foundation. Professor Stephen Weber and colleagues at the University of Pittsburgh address limitations of liquid chromatography. The team is improving the ability of liquid chromatography techniques to distinguish one substance from another, as well as improving the ability to measure trace concentrations in a variety of samples. Chromatography is based on the principle of partitioning, the tendency of a substance to prefer an oily substance to water-based solution. The outcomes of this project include obtaining more and better information from samples with lower cost and lower environmental burden than has been previously realized. Collaborations with scientists in the fields of proteomics (for example, health, pharmaceuticals, and biochemistry research) and two-dimensional liquid chromatography (for example, pharmaceuticals, chemical industry, agriculture, and the environment) demonstrate the effectiveness of the project goals. The broader impacts are evidenced in that improvements in chromatographic processes that are useful across many fields and applications. Liquid chromatography is used in virtually every industry, for example, environmental, pharmaceutical, nutritional, forensic, toxicology, polymers, chemicals, and cosmetics. A Girl Scout merit badge project is also being developed by Dr. Weber to explore chromatography methods and its uses. The project uses temperature control of the column to achieve greater solute focusing and to control retention in a predictable way. Retention enthalpies, which control the sensitivity of a particular compound to changes in temperature,

are determined for a number of related organic compounds. These data are used to determine molecular fragment enthalpies. The temperature dependence of the retention of novel compounds are then predicted. Software to predict chromatographic behavior in the face of changing column temperature aids in chromatographic method development. The temperature control, when used to aid solute focusing, significantly improves concentration detection limits.

Role: PI

Completed Research Support

R01 GM066018-12 WEBER, STEPHEN G. (PI) 07/01/03-07/31/16

Single Cell Electroporation

Role: PI

R21 MH083134-02 WEBER, STEPHEN G. (PI) 04/01/08-02/28/11

Serotonin Transporter Kinetics In Vivo by Microdialysis/Capillary UPLC

Role: PI

R41 GM067325-01 WEBER, STEPHEN G. (PI) 02/03/03-02/02/06

Supported Fluorous Lipids for Triphasic Reactions

Role: PI