

C U R I C U L U M V I T A E

DONALD W. HILGEMANN

Place of Birth Postville, Iowa
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Research Overview.

We study the function and regulation of Na transporters in the surface membrane of mammalian cells, recently with a focus on the regulation of transporters by surface membrane turnover via exo- and endocytosis. To so do, we employ innovative electrical and optical methods. Three Na transporters have been of most interest to us; Na/Ca exchangers, Na/K pumps, and Na/H exchangers, all of which can determine the fate of cardiac cells in pathological settings such as ischemia. To improve biophysical and regulatory studies of these mechanisms, we developed 'giant' patch clamp methods and analyzed conformational changes of transport proteins with 1 microsecond resolution. Recently, we refined ion selective electrode methods to measure ion fluxes independent of electrical activity. Along the way, we discovered that phosphatidylinositides are powerful direct regulators of ion transporters and channels. We are now studying nonconventional endocytic processes that become highly activated in response to metabolic stress. We recently discovered that these domain-driven endocytic processes become activated during ischemia/reperfusion of the heart and can rapidly internalize >30% of the sarcolemma. These studies open new pathways to elucidate the dynamics of cell membrane turnover with a high relevance to disease states that involve metabolic stress.

Education

University of Iowa

General Education, 1970-1972.

University of Tuebingen, F.R.G.

Diplom (M.S.) 1977, Biology

Physikum (Preclinical Medical Studies), 1977, Medicine.

Dr.rer.nat. (Ph.D.) 1980, Pharmacology & Physiology.

Positions

1977-1980 Research and Teaching Assistant, Department of Pharmacology,
University of Tingen, F.R.G.

1980-1981 Research Associate, Merrell International, Strasbourg, France.

1981-1987 Assistant Research Physiologist, Department of Physiology, UCLA School
of Medicine, Los Angeles, CA.

1982-1987 Assistant Clinical Professor of Nursing, UCLA School of Nursing.

1985-1988 Visiting Research Fellow, Oxford University, G.B.

1988-1991 Assistant Professor, Dept. of Physiology, UTSouthwestern.

1991-1996 Associate Professor, Dept. of Physiology, UTSouthwestern

1996- Professor, Dept of Physiology, UTSouthwestern.

Scientific Societies *Biophysical Society*
American Physiological Society

Awards

1979-81: Graduate student research award, German Scientific Society (DFG)

1983: Lievre Research Award, Greater Los Angeles AHA

1989-1992: Established Investigatorship, AHA

1997 Young Investigator Award: International Biophysical Society

2004: Roy & Christine Sturgis Chair in Biomedical Research

Services & Teaching

Editorial Boards:

Journal of General Physiology

American Journal of Physiology – Cell

Physiology (formerly NIPS)

Molecular Pharmacology

Advisory Boards:

Max Planck Gesellschaft & MPI for Biophysical Chemistry

UTSW Department of Bioengineering

Review Panels

1996-99 Member: AHA, Cardiovascular Pharmacology
1994-98 Ad hoc: NIH Pharmacology & Physiology Study Sections.
1998-2004 Member: NIH NMD3 Study Section
2004- Ad hoc reviewer for NIH Study Sections & Review Panels
2004- Member: UTSW Promotion & Tenure Committee

Department Affiliations

Physiology, Internal Medicine, and Bioengineering

Teaching

Organizer –Membrane Section: UTSW Graduate Core Curriculum (1990-95).
"High Exposure" Lecturer – UTSW Medical Physiology (1990-present).
Teacher and Organizer (1988-94) - The Molecular Basis of Excitability, UTSW
Teacher and Lecturer - Diverse graduate school courses

Chair & Organizer

Third International Meeting on Sodium-Calcium Exchange, sponsored by the New York Academy of Sciences, Woods Hole, MA, April, 1995.

Symposium: Phosphoinositides in Cell Signaling – Biophysical Society, 2001.

Gordon Conference on Membrane Transport Mechanisms, 2001.

Symposium: Lipid Signals – Biophysical Society, 2004.

Lipid Signaling in Physiology, Society of General Physiology, 2004.

Symposia: UTMETROPLEX DAYS: A 4-day scientific program to promote scientific interactions in the Dallas-Fort Worth Metroplex, 2006.

Fellow

Binational Israeli-USA Foundation (Tel Aviv University), 1995-1997.
Japan Society for the Promotion of Science (University of Kyoto), 1993.

Council Member

Society of General Physiologists, 1999-2003
International Biophysical Society, 2007-

Publications

Investigative reports in reviewed journals

Hilgemann, D.W., Englert, R., and Mensing, J., The opposed influences of adrenergic stimulation and adenosine on the frequency-force relationship of isolated left atria of guinea pigs. *Experientia*, 33: 1629-1630, 1978.

Hilgemann, D.W., Delay, M. and Langer, G.A. Activation-related cumulative depletions of free extracellular calcium in guinea pig atrium measured with Antipyrylazo III and tetramethylmurexide. *Circ. Res.* 53:779-793, 1983.

Hilgemann, D.W. and Langer, G.A. Transsarcolemmal calcium movements in arterially perfused right ventricle of rabbit measured with calcium-sensitive dyes. *Circ. Res.* 54:461-467, 1984.

Hilgemann, D.W. Extracellular calcium transients and action potential configuration changes related to post-stimulatory potentiation in rabbit atrium. *J. Gen. Physiol.* 87:675-706, 1986.

Hilgemann, D.W. Extracellular calcium transients at single excitations in rabbit atrium. *J. Gen. Physiol.* 87:707-735, 1986.

Hilgemann, D.W. and Noble, D. Excitation-contraction coupling and extracellular calcium transients in rabbit atrium: Reconstruction of basic cellular mechanisms. *Proc. R. Soc. Lond. B* 230:163-205, 1987.

Hilgemann, D.W. Numerical approximations of sodium-calcium exchange. *Prog. Biophys. Molec. Biol.* 51: 1-45, 1988.

Hilgemann, D.W., Roos, K.P. and Brady, A.J. Slowly relaxing caffeine responses in rat ventricle: relationships of ryanodine and caffeine actions. *Am. J. Physiol.* 256: H1100-H1109, 1989.

Hilgemann, D.W. Giant excised cardiac sarcolemmal membrane patches: Sodium and sodium-calcium exchange currents. *Pfl ers Arch.* 415:247-249, 1989.

Hilgemann, D.W. Regulation and deregulation of cardiac sodium-calcium exchange in giant excised sarcolemmal patches. *Nature* 334: 242-245, 1990.

Zhaoping, L., Nicoll, D.A., Hilgemann, D.W., Collins, A. Penniston, J.T., Tomich, J., Weiss, J.N., & Philipson, K.D. Identification of a peptide inhibitor of the cardiac sarcolemmal Na/Ca Exchanger. *J. Biol. Chem.* 266: 1014-1020, 1991.

Hilgemann, D.W., Nicoll, D.A., & Philipson, K.D. Charge movement during sodium translocation by native and cloned cardiac Na/Ca exchanger in giant excised membrane patches. *Nature*, 352: 715-719, 1991.

Collins, A., Somlyo A., & Hilgemann, D.W. The giant cardiac membrane patch method: Stimulation of outward Na/Ca exchange current by MgATP. *J. Physiol.* 454: 37-57, 1992

Hilgemann, D.W. & Collins, A. The mechanism of sodium-calcium exchange stimulation by ATP in giant cardiac membrane patches: Possible role of aminophospholipid translocase. *J. Physiol.* 454: 59-82, 1992.

Hilgemann, D.W., Matsuoka, S. & Collins, A. Dynamic and steady state properties of cardiac sodium-calcium exchange: Sodium-dependent inactivation. *J. Gen. Physiol.* 100:905-932, 1992.

Hilgemann, D.W., Collins, A., and Matsuoka, S. Dynamic and steady state properties of cardiac sodium-calcium exchange: Calcium- and ATP-dependent activation. *J. Gen. Physiol.* 100:933-961, 1992.

Matsuoka, S. and Hilgemann, D.W. Dynamic and steady state properties of cardiac sodium-calcium exchange: Ion- and voltage dependencies of transport cycle. *J. Gen. Physiol.* 100:962-1001, 1992.

Collins, A. and Hilgemann, D.W. A novel method for direct application of phospholipids to giant excised membrane patches in the study of sodium-calcium exchange and sodium channel currents. *Pfl ers Archives* 423: 347-355, 1993.

Matsuoka, S., Nicoll, D.A., Reilly, R.F., Hilgemann, D.W. and Philipson, K.D. Identification of regulatory regions of the cardiac sarcolemmal Na⁺-Ca²⁺ exchanger. *PNAS (USA)* 90: 3870-3874, 1993.

Matsuoka, S. & Hilgemann, D.W. Inactivation of outward Na/Ca exchange current in guinea pig ventricular myocytes. *J. Physiol.* 476: 443-458, 1994.

Hilgemann, D.W. Channel-like function of the Na,K pump probed at microsecond resolution in giant membrane patches. *Science* 263: 1429-1432, 1994.

Lu, C.-C., Kabakov, A., Mager S., Markin, V., Frazier, G., & Hilgemann, D.W. Membrane transport mechanisms probed by capacitance measurements with megahertz voltage clamp. *PNAS*, 92, 11220-11224, 1994.

Kabakov, A.Y. and Hilgemann, D.W. Modulation of Na,Ca exchange current by EGTA calcium buffering in giant cardiac membrane patches. *Biochimica et Biophysica Acta.* 1240:142-8, 1995.

Hilgemann, D.W. Unitary cardiac Na⁺, Ca²⁺ exchange current magnitudes determined from channel-like noise and charge movements of ion transport. *Biophysical Journal.* 71: 759-68, 1996.

Hilgemann, D.W. and Ball, R. Regulation of cardiac Na^+ , Ca^{2+} exchange and KATP potassium channels by PIP₂. *Science*. 273(5277):956-9, 1996.

Linck, B., Qiu, Z, He, Z., Tong, Q., Hilgemann, D.W., and Philipson K.D. Functional comparison of the three isoforms of the Na/Ca exchanger (NCX1, NCX2, NCX3). *Am. J. Physiol.* 274:C415-23, 1998.

Hwang, C.L., Feng, S., and Hilgemann, D.W. Direct interaction of PIP₂ with inward rectifier potassium channels and its enhancement by G-beta-gamma. *Nature* 391:803-806, 1998.

He, X., Tong, Q, Quednau, B.D., Philipson, K.D. and Hilgemann, D.W. Cloning, Expression, and Characterization of the Squid Na^+ - Ca^{2+} Exchanger (NCX-SQ1). *J.Gen. Physiol.* 111: 857-873, 1998.

Lu, C. and Hilgemann, D.W. GAT1 (GABA:Na:Cl) Cotransport Function: Steady state studies in giant *Xenopus* oocyte membrane patches. *J. Gen. Physiol.* 114:429-444, 1999.

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D. W. Hilgemann and C. Lu, GAT1 (GABA:Na:Cl) Cotransport Function: Data base reconstruction with an alternating access model. *Gen. Physiol.* 114, 459-476, 1999.

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K. B. Womack, S.E. Gordon, F. He, T.G. Wensel, C.-C. Lu and D.W. Hilgemann. Do Phosphatidylinositides Modulate Vertebrate Phototransduction? *The Journal of Neuroscience*, 20: 2792-9, 2000.

Yamamoto M, Hilgemann DW, Feng S, Bito H, Ishihara H, Shibasaki Y, and Yin HL. Phosphatidylinositol 4,5-Bisphosphate Induces Actin Stress Fiber Formation and Inhibits Membrane Ruffling in CV1 Cells. *J.Cell Biol.*152:867-76, 2001.

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Nasuhoglu C, Feng S, Mao Y, Shammatt I, Yamamoto M, Earnest S, Lemmon M, Hilgemann DW. Modulation of cardiac PIP2 by cardioactive hormones and other physiologically relevant interventions. *American Journal of Physiology – Cell Physiology* 283:C223-34, 2002.

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J Biol Chem. 2003 278:16852-6.

Kang TM, and Hilgemann DW. Multiple transport modes of the cardiac Na/Ca exchanger.

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Fuster D, Moe OW, and Hilgemann DW. Lipid- and Mechano-sensitivities of Sodium-Hydrogen Exchangers Analyzed by Electrical Methods. Proc Natl Acad Sci U S A.

101(28):10482-10487, 2004.

Horowitz LF, Hirdes W, Suh BC, Hilgemann DW, Mackie K, Hille B.

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Li Y, Gamper N, Hilgemann DW, Shapiro MS. Regulation of Kv7 (KCNQ) K⁺ channel open probability by phosphatidylinositol 4,5-bisphosphate. J Neurosci. 2005 Oct 26;25(43):9825-35.

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Hilgemann DW, Yaradanakul A, Wang Y, Fuster D. Molecular control of cardiac sodium homeostasis in health and disease. J Cardiovasc Electrophysiol. 2006 May;17 Suppl 1:S47-S56.

Yaradanakul A, Feng S, Shen C, Lariccia V, Lin MJ, Yang J, Kang T M, Dong P, Yin HL, Albanesi JP, Hilgemann DW. Dual control of cardiac Na⁺ Ca²⁺ exchange by PIP(2): electrophysiological analysis of direct and indirect mechanisms. *J Physiol.* 2007, 582 (Pt 3):991-1010.

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Hilgemann DW. Local PIP(2) signals: when, where, and how? *Pflugers Arch.* 2007 455(1):55-67.

Hilgemann DW. On the physiological roles of PIP(2) at cardiac Na⁺ Ca²⁺ exchangers and K(ATP) channels: a long journey from membrane biophysics into cell biology. *J Physiol.* 2007 Aug 1;582(Pt 3):903-9.

Fuster D, Moe OW, Hilgemann DW. Steady-state function of the ubiquitous mammalian Na/H exchanger (NHE1) in relation to dimer coupling models with 2Na/2H stoichiometry. *J Gen Physiol.* 2008 132:465-80.

Wang TM, Hilgemann DW Ca-dependent nonsecretory vesicle fusion in a secretory cell.. *J Gen Physiol.* 2008 132:51-65.

Yaradanakul A, Wang TM, Lariccia V, Lin MJ, Shen C, Liu X, Hilgemann DW. Massive Ca-induced membrane fusion and phospholipid changes triggered by reverse Na/Ca exchange in BHK fibroblasts. *J Gen Physiol.* 2008 132:29-50.

Yaradanakul A, Hilgemann DW. Unrestricted diffusion of exogenous and endogenous PIP(2)in baby hamster kidney and Chinese hamster ovary cell plasmalemma. . J Membr Biol. 2007 220(1-3):53-67.

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Fine M, Llaguno MC, Lariccia V, Lin MJ, Yaradanakul A, Hilgemann DW. Massive endocytosis driven by lipidic forces originating in the outer plasmalemmal monolayer: a new approach to membrane recycling and lipid domains. J Gen Physiol. J Gen Physiol. 2011 137:137-54.

Hilgemann DW, Fine M. Mechanistic analysis of massive endocytosis in relation to functionally defined surface membrane domains. J Gen Physiol. 2011 137:155-72. *With Commentary: Cells on the MEND: exploring the role of lipidic forces in membrane trafficking. J Gen Physiol. 2011 137:133-6. Cohen FS, Andersen OS.*

Hilgemann DW, Lin MJ, Fine M, Frazier G, Wang HR. Toward an understanding of the complete NCX1 lifetime in the cardiac sarcolemma. Adv Exp Med Biol. 2013;961:345-52. doi:10.1007/978-1-4614-4756-6_29. PMID:23224893

Fine, M., F.M. Lu, M.J. Lin, O. Moe, H.R. Wang, and D.W. Hilgemann. 2013. Human-induced pluripotent stem cell-derived cardiomyocytes for studies of cardiac ion transporters. American journal of physiology. Cell physiology. 305:C481-491. doi:10.1152/ajpcell.00143.2013.

Hilgemann, D.W., M. Fine, M.E. Linder, B.C. Jennings, and M.J. Lin. 2013. Massive endocytosis triggered by surface membrane palmitoylation under mitochondrial control in BHK fibroblasts. eLife. 2:e01293. doi:10.7554/eLife.01293.

Lin, M.J., M. Fine, J.Y. Lu, S.L. Hofmann, G. Frazier, and D.W. Hilgemann. 2013. Massive palmitoylation-dependent endocytosis during reoxygenation of anoxic cardiac muscle. *eLife*. 2:e01295. doi:10.7554/eLife.01295.

Reilly L, Howie J, Wypijewski K, Ashford ML, Hilgemann DW, Fuller W. Palmitoylation of the Na/Ca exchanger cytoplasmic loop controls its inactivation and internalization during stress signaling. *FASEB J*. 2015 Nov;29(11):4532-43. doi: 10.1096/fj.15-276493.

Invited Articles, Book Chapters and Dissertations

Hilgemann, D.W. Experiments with a new automated method for 'driving' frequency-force relations in guinea pig atrium. M.S. Thesis. University of Tuebingen, 1977.

Hilgemann, D.W. New perspectives on the interval-strength relationship of guinea pig atrium: Toward an understanding of mechanisms coupling membrane excitation and contraction in heart. Ph.D. Dissertation, Faculty of Biology. University of Tuebingen. 1980.

Mensing, H.J. and Hilgemann, D.W. Inotropic effects of activation and pharmacological mechanisms in cardiac muscle. *Trends in Pharmacological Sciences*. 2: 303-307, 1981.

Hilgemann, D.W. Numerical Probes of sodium-calcium exchange. In, *Sodium-Calcium Exchange*. Edited by H. Reuter, T.J.A. Allen and D. Noble. Oxford University Press. 1989.

Hilgemann, D.W. Calcium homeostasis and the cardiac electrical cycle: The function of sodium-calcium exchange. In: *Cardiac Electrophysiology from Cell to Bedside*. Saunders & Co. Edited by J.Jalife. pp. 55-61, 1990.

Hilgemann, D.W. Mechanism and regulation of the sodium-calcium exchange system in giant cardiac membrane patches. *Annals of the New York Academy of Sciences* 639: 126-139, 1991.

Hilgemann, D.W., Nagel, G.A., and Gadsby, D.C. Na/K pump current in giant membrane patches excised from ventricular myocytes. In: *The Sodium Pump: Recent Developments*. Edited by P. DeWeer, P. & J.H. Kaplan pp. 543-547. Rockefeller University Press, 1991.

Hilgemann, D.W. The giant excised-patch method. *Axobits*. 9: 5-6, 1992.

Hilgemann, D.W. Flexibility and constraint in the Interpretation of Na,K Pump Electrogenicity: What is an Access Channel? In: *The Sodium Pump*. Edited by E. Bamberg and W. Schoner pp.507-516, Steinkopff, Darmstadt, 1994.

Hilgemann, D.W. Electrostatic measurement of extracellular sodium binding by the Na/K pump and the cardiac Na/Ca exchanger in giant membrane patches. *Heart and Vessels* 9, 155-158, 1995.

Hilgemann, D.W. The Giant Membrane Patch. In: *Single Channel Recording* by B. Sakmann and E. Neher. pp. 307-327, Plenum Press, New York, 1995.

Hilgemann, D.W. The cardiac sodium-calcium exchanger in giant membrane patches. *Annals of the New York Academy of Sciences*. 779:136-58, 1996

Matsuoka, S., and Hilgemann, D.W. Multiple functional states of the cardiac Na,Ca exchanger: Whole-cell, native-excised and cloned-excised properties. *Annals of the New York Academy of Sciences*. *Annals of the New York Academy of Sciences*. 779:159-70, 1996 .

Hilgemann, D.W., Philipson, K.D., and Vassort, G., Editors, Proceedings of the Third International Conference on Sodium-Calcium Exchange. Annals of the New York Academy of Sciences Vol. 779, 1996.

Gonzalez-Serratos H. Hilgemann DW. Rozycka M. Gauthier A. Rasgado-Flores H. Na-Ca exchange studies in sarcolemmal skeletal muscle. Ann. New York Acad. Sci.. 779:556-60, 1996

Hilgemann, D.W. Cytoplasmic ATP-dependent regulation of ion transporters and channels: Mechanisms and Messengers. Ann. Rev. Physiol. 59, 193-220, 1997.

Hilgemann, D.W. Recent electrical snapshots of the cardiac Na,K pump. N. Y. Ac. Sci., 834: 260-269, 1997.

Hilgemann, D.W. and Lu., C.-C. Giant membrane patches: improvements and applications. Methods in Enzymology, 293: 267-280, 1998.

Hilgemann, D.W., Nasuholglu, C., and Feng, S., The complex and intriguing lives of PIP₂ with ion channels and transporters. Science-Web 111:RE19 2001.

Kang TM, Steciuk M, and Hilgemann DW. Sodium-calcium exchange stoichiometry: Is the noose tightening? New York Academy of Sciences 2002; 976:142-51

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Hilgemann DW. New insights into the molecular and cellular workings of cardiac Na/Ca exchange. *Am J Physiol Cell Physiol*. 2004 287(5):C1167-72.

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Hilgemann DW. Fitting K(V) potassium channels into the PIP₂ puzzle: Hille group connects dots between illustrious HH groups. *J Gen Physiol*. 2012 Sep;140(3):245-8. doi: 10.1085/jgp.201210874. PMID:22930801

Hilgemann DW. Fishing for holes in transporters: How protons breach the security gates of the Na/K pump. *J Gen Physiol*. 2014 Apr;143(4):437-41. doi: 10.1085/jgp.201411189.

Hilgemann DW. Cardiac electrophysiology delivered a "grand slam" by angiotensin II: the third explanation of transmural cardiac electrical activity gradients. *Biophys J*. 2014 Jun 3;106(11):2288-90. doi: 10.1016/j.bpj.2014.04.043.

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