

Stanford



Richard Tsien

George D. Smith Professor, Emeritus

Molecular & Cellular Physiology

 NIH Biosketch available Online

 Curriculum Vitae available Online

CONTACT INFORMATION

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Bio

ACADEMIC APPOINTMENTS

- Emeritus Faculty, Acad Council, Molecular & Cellular Physiology
- Member, Bio-X
- Member, Wu Tsai Neurosciences Institute

HONORS AND AWARDS

- Charter Member, Biophysical Society (1999)
- Alan C. Beering Award, University of Indiana (2000)
- Kaiser Award for Outstanding and Innovative Teaching, Stanford University (1991, 1995, 1999)
- Member, Institute of Medicine of the National Academy of Sciences (1994)
- MERIT Award, National Institutes of Mental Health (July 2004)
- Bauer Lectureship, Brandeis University (March 2007)
- Member, National Academy of Sciences (1997)

LINKS

- My Lab Site: <http://www-leland.stanford.edu/group/MCP>

Research & Scholarship

CURRENT RESEARCH AND SCHOLARLY INTERESTS

We are studying how the location and identity of presynaptic calcium channels is regulated. Voltage-gated Ca²⁺ channels provide the critical link between the firing of a presynaptic nerve terminal and its release of neurotransmitter. The Ca²⁺ channels must be positioned very close to sites of vesicle fusion, and come in diverse forms with distinct activity-dependence, responsiveness to GABA, dopamine, acetylcholine and other neuromodulators, and susceptibility to neurological disorders such as migraine, ataxia or dystonia. Our working hypothesis involves molecular “slots” for particular types of channels. Slots regulate the mix of channel types and also help explain how defective channels might displace normal ones in genetically dominant disorders.

Our lab is particularly interested in studying multiple modes of synaptic vesicle fusion. The opening of Ca²⁺ channels drives at least two distinct forms of fusion.

In the classical mode, the vesicle membrane fully merges with and flattens into the presynaptic membrane (“full collapse fusion”). In a newly characterized mode, termed “kiss-and-run” the connection between the vesicle interior and the external medium lasts long enough to allow passage of neurotransmitter, but the connection is severed before the identity of the vesicle is lost. We study the dynamic properties and functional implications of both fusion modes by loading single synaptic vesicles with single photoluminescent reporter particles#quantum dots. Sharp distinctions between full collapse fusion and kiss-and-run are now in hand. Experiments are underway to monitor the same fusion event optically and electrophysiologically.

One area of intense attention in our lab is the fundamental unit of cell-cell communication between brain neurons: quantal synaptic transmission. Presynaptic release of a packet of neurotransmitter, for example, glutamate, causes activation of postsynaptic receptors and a brief flow of current that promotes firing of the postsynaptic cell. We work on neuronal mechanisms that allow synapses to adapt to a sudden or long-lasting change in their level of activity. For example, blockade of impulses or of postsynaptic glutamate receptors causes a cascade of biochemical events that eventually leads to readjustment of critical molecular players on both sides of the synapse. We use state-of-the art methods to pin down the cell biology of changes in synaptic strength, of importance for adaptation of brain networks in learning and memory. Ongoing work in cultures of isolated neurons and brain slices

We study how synaptic transmission and depolarization cause changes in neuronal gene expression. Despite its importance, signaling from synapse or surface membrane to nucleus is only partly understood. One example of such signaling involves a local increase in Ca²⁺ concentration near a class of Ca²⁺ channels (L-type) different from those that trigger presynaptic transmitter release, subsequently leading to activation of an exemplar transcription factor, CREB, a regulator of transcription of many important neuronal genes. Our approach is to combine physiological approaches (how fast, how steeply voltage-dependent, how is signal transduced) and biochemical experiments using cDNA microarrays (which genes, in what context, what relationship to learning and memory).

Teaching

GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Molecular and Cellular Physiology (Phd Program)

Publications

PUBLICATIONS

- **Comprehensive behavioral phenotyping of Ts65Dn mouse model of Down Syndrome: Activation of pradrenergic receptor by xamoterol as a potential cognitive enhancer** *NEUROBIOLOGY OF DISEASE*
Faizi, M., Bader, P. L., Tun, C., Encarnacion, A., Kleschnevnikov, A., Belichenko, P., Saw, N., Priestley, M., Tsien, R. W., Mobley, W. C., Shamloo, M.
2011; 43 (2): 397-413
- **Excitation-transcription coupling in sympathetic neurons and the molecular mechanism of its initiation** *NEUROSCIENCE RESEARCH*
Ma, H., Groth, R. D., Wheeler, D. G., Barrett, C. F., Tsien, R. W.
2011; 70 (1): 2-8
- **beta Ca²⁺/CaM-dependent kinase type II triggers upregulation of GluA1 to coordinate adaptation to synaptic inactivity in hippocampal neurons** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Groth, R. D., Lindskog, M., Thiagarajan, T. C., Li, L., Tsien, R. W.
2011; 108 (2): 828-833
- **Postsynaptic GluA1 enables acute retrograde enhancement of presynaptic function to coordinate adaptation to synaptic inactivity** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Lindskog, M., Li, L., Groth, R. D., Poburko, D., Thiagarajan, T. C., Han, X., Tsien, R. W.
2010; 107 (50): 21806-21811
- **Inhibitory Neurons Hear Themselves during Development** *NEURON*
Owen, S. F., Tsien, R. W.

2010; 66 (2): 164-166

- **Different Relationship of N- and P/Q-Type Ca₂₊ Channels to Channel- Interacting Slots in Controlling Neurotransmission at Cultured Hippocampal Synapses** *JOURNAL OF NEUROSCIENCE*

Cao, Y., Tsien, R. W.

2010; 30 (13): 4536-4546

- **Inhibitory role for GABA in autoimmune inflammation** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*

Bhat, R., Axtell, R., Mitra, A., Miranda, M., Lock, C., Tsien, R. W., Steinman, L.

2010; 107 (6): 2580-2585

- **Uncoupling Dendrite Growth and Patterning: Single-Cell Knockout Analysis of NMDA Receptor 2B** *NEURON*

Espinosa, J. S., Wheeler, D. G., Tsien, R. W., Luo, L.

2009; 62 (2): 205-217

- **The Dynamic Control of Kiss-And-Run and Vesicular Reuse Probed with Single Nanoparticles** *SCIENCE*

Zhang, Q., Li, Y., Tsien, R. W.

2009; 323 (5920): 1448-1453

- **CaMKII locally encodes L-type channel activity to signal to nuclear CREB in excitation-transcription coupling** *JOURNAL OF CELL BIOLOGY*

Wheeler, D. G., Barrett, C. F., Groth, R. D., Safa, P., Tsien, R. W.

2008; 183 (5): 849-863

- **A Role for Retinoic Acid in Homeostatic Plasticity** *NEURON*

Groth, R. D., Tsien, R. W.

2008; 60 (2): 192-194

- **Synapse-specific adaptations to inactivity in hippocampal circuits achieve homeostatic gain control while dampening network reverberation** *NEURON*

Kim, J., Tsien, R. W.

2008; 58 (6): 925-937

- **The Timothy syndrome mutation differentially affects voltage- and calcium-dependent inactivation of Ca(V)1.2 L-type calcium channels** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*

Barrett, C. F., Tsien, R. W.

2008; 105 (6): 2157-2162

- **Quantum dots provide an optical signal specific to full collapse fusion of synaptic vesicles** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*

Zhang, Q., Cao, Y., Tsien, R. W.

2007; 104 (45): 17843-17848

- **Organization of beta-adrenoceptor signaling compartments by sympathetic innervation of cardiac myocytes** *JOURNAL OF CELL BIOLOGY*

Shcherbakova, O. G., Hurt, C. M., Xiang, Y., Dell'Acqua, M. L., Zhang, Q., Tsien, R. W., Kobilka, B. K.

2007; 176 (4): 521-533

- **LTP and adaptation to inactivity: Overlapping mechanisms and implications for metaplasticity** *NEUROPHARMACOLOGY*

Thiagarajan, T. C., Lindskog, M., Malgaroli, A., Tsien, R. W.

2007; 52 (1): 156-175

- **Selective engagement of plasticity mechanisms for motor memory storage** *NEURON*

Boyden, E. S., Katoh, A., Pyle, J. L., Chatila, T. A., Tsien, R. W., Raymond, J. L.

2006; 51 (6): 823-834

- **L-type calcium channel ligands block nicotine-induced signaling to CREB by inhibiting nicotinic receptors** *NEUROPHARMACOLOGY*

Wheeler, D. G., Barrett, C. F., Tsien, R. W.

2006; 51 (1): 27-36

- **Kiss-and-run and full-collapse fusion as modes of exo-endocytosis in neurosecretion** *JOURNAL OF NEUROCHEMISTRY*

Harata, N. C., Aravanis, A. M., Tsien, R. W.

2006; 97 (6): 1546-1570

- Frequency-dependent kinetics and prevalence of kiss-and-run and reuse at hippocampal synapses studied with novel quenching methods *NEURON*
Harata, N. C., Choi, S., Pyle, J. L., Aravanis, A. M., Tsien, R. W.
2006; 49 (2): 243-256
- CaMKII tethers to L-type Ca²⁺ channels, establishing a local and dedicated integrator of Ca²⁺ signals for facilitation *JOURNAL OF CELL BIOLOGY*
Hudmon, A., Schulman, H., Kim, J., Maltez, J. M., Tsien, R. W., Pitt, G. S.
2005; 171 (3): 537-547
- Adaptation to synaptic inactivity in hippocampal neurons *NEURON*
Thiagarajan, T. C., Lindskog, M., Tsien, R. W.
2005; 47 (5): 725-737
- Gating deficiency in a familial hemiplegic migraine type 1 mutant P/Q-type calcium channel *JOURNAL OF BIOLOGICAL CHEMISTRY*
Barrett, C. F., Cao, Y. Q., Tsien, R. W.
2005; 280 (25): 24064-24071
- Effects of familial hemiplegic migraine type 1 mutations on neuronal P/Q-type Ca²⁺ channel activity and inhibitory synaptic transmission *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Cao, Y. Q., Tsien, R. W.
2005; 102 (7): 2590-2595
- Presynaptic Ca²⁺ channels compete for channel type-preferring slots in altered neurotransmission arising from Ca²⁺ channelopathy *NEURON*
Cao, Y. Q., Piedras-Renteria, E. S., Smith, G. B., Chen, G., Harata, N. C., Tsien, R. W.
2004; 43 (3): 387-400
- Presynaptic homeostasis at CNS nerve terminals compensates for lack of a key Ca²⁺ entry pathway *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Piedras-Renteria, E. S., Pyle, J. L., Diehn, M., Glickfeld, L. L., Harata, N. C., Cao, Y. Q., Kavalali, E. T., Brown, P. O., Tsien, R. W.
2004; 101 (10): 3609-3614
- Paired-pulse depression of unitary quantal amplitude at single hippocampal synapses *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Chen, G., Harata, N. C., Tsien, R. W.
2004; 101 (4): 1063-1068
- Recordings from single neocortical nerve terminals reveal a nonselective cation channel activated by decreases in extracellular calcium *NEURON*
Smith, S. M., Bergsman, J. B., Harata, N. C., Scheller, R. H., Tsien, R. W.
2004; 41 (2): 243-256
- Imaging single synaptic vesicles undergoing repeated fusion events: kissing, running, and kissing again *NEUROPHARMACOLOGY*
Aravanis, A. M., Pyle, J. L., Harata, N. C., Tsien, R. W.
2003; 45 (6): 797-813
- Single synaptic vesicles fusing transiently and successively without loss of identity *NATURE*
Aravanis, A. M., Pyle, J. L., Tsien, R. W.
2003; 423 (6940): 643-647
- Signaling from synapse to nucleus: the logic behind the mechanisms *CURRENT OPINION IN NEUROBIOLOGY*
Deisseroth, K., Mermelstein, P. G., Xia, H. H., Tsien, R. W.
2003; 13 (3): 354-365
- Altered properties of quantal neurotransmitter release at endplates of mice lacking P/Q-type Ca²⁺ channels *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Urbano, F. J., Piedras-Renteria, E. S., Jun, K. S., Shin, H. S., Uchitel, O. D., Tsien, R. W.
2003; 100 (6): 3491-3496
- alpha- and beta CaMKII: Inverse regulation by neuronal activity and opposing effects on synaptic strength *NEURON*
Thiagarajan, T. C., Piedras-Renteria, E. S., Tsien, R. W.
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- **Differences in apparent pore sizes of low and high voltage-activated Ca₂₊ channels** *JOURNAL OF BIOLOGICAL CHEMISTRY*
Cataldi, M., Perez-Reyes, E., Tsien, R. W.
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- **Dynamic multiphosphorylation passwords for activity-dependent gene expression** *NEURON*
Deisseroth, K., Tsien, R. W.
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- **Calmodulin priming: Nuclear translocation of a calmodulin complex and the memory of prior neuronal activity** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Mermelstein, P. G., Deisseroth, K., Dasgupta, N., Isaksen, A. L., Tsien, R. W.
2001; 98 (26): 15342-15347
- **Increased expression of alpha(1A) Ca₂₊ channel currents arising from expanded trinucleotide repeats in spinocerebellar ataxia type 6** *JOURNAL OF NEUROSCIENCE*
Piedras-Renteria, E. S., Watase, K., Harata, N., Zhuchenko, O., Zoghbi, H. Y., Lee, C. C., Tsien, R. W.
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- **Limited numbers of recycling vesicles in small CNS nerve terminals: implications for neural signaling and vesicular cycling** *TRENDS IN NEUROSCIENCES*
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- **Visualizing recycling synaptic vesicles in hippocampal neurons by FM 1-43 photoconversion** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
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- **Molecular basis of calmodulin tethering and Ca₂₊-dependent inactivation of L-type Ca₂₊ channels** *JOURNAL OF BIOLOGICAL CHEMISTRY*
Pitt, G. S., Zuhlike, R. D., Hudmon, A., Schulman, H., Reuter, H., Tsien, R. W.
2001; 276 (33): 30794-30802
- **Activity-dependent CREB phosphorylation: Convergence of a fast, sensitive calmodulin kinase pathway and a slow, less sensitive mitogen-activated protein kinase pathway** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Wu, G. Y., Deisseroth, K., Tsien, R. W.
2001; 98 (5): 2808-2813
- **Spaced stimuli stabilize MAPK pathway activation and its effects on dendritic morphology** *NATURE NEUROSCIENCE*
Wu, G. Y., Deisseroth, K., Tsien, R. W.
2001; 4 (2): 151-158
- **Rapid reuse of readily releasable pool vesicles at hippocampal synapses** *NEURON*
Pyle, J. L., Kavalali, E. T., Piedras-Renteria, E. S., Tsien, R. W.
2000; 28 (1): 221-231
- **Syntaxin modulation of slow inactivation of N-type calcium channels** *JOURNAL OF NEUROSCIENCE*
Degtar, V. E., Scheller, R. H., Tsien, R. W.
2000; 20 (12): 4355-4367
- **Syntaxin modulation of calcium channels in cortical synaptosomes as revealed by botulinum toxin C1** *JOURNAL OF NEUROSCIENCE*
Bergsman, J. B., Tsien, R. W.
2000; 20 (12): 4368-4378
- **Postfusional regulation of cleft glutamate concentration during LTP at 'silent synapses'** *NATURE NEUROSCIENCE*
Choi, S., Klingauf, J., Tsien, R. W.
2000; 3 (4): 330-336
- **Critical dependence of cAMP response element-binding protein phosphorylation on L-type calcium channels supports a selective response to EPSPs in preference to action potentials** *JOURNAL OF NEUROSCIENCE*
Mermelstein, P. G., Bito, H., Deisseroth, K., Tsien, R. W.

2000; 20 (1): 266-273

● **Visualization of synaptic activity in hippocampal slices with FM1-43 enabled by fluorescence quenching** *NEURON*

Pyle, J. L., Kavalali, E. T., Choi, S., Tsien, R. W.
1999; 24 (4): 803-808

● **Activity-dependent regulation of synaptic clustering in a hippocampal culture system** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*

Kavalali, E. T., Klingauf, J., Tsien, R. W.
1999; 96 (22): 12893-12900

● **L-type calcium channels and GSK-3 regulate the activity of NF-ATc4 in hippocampal neurons** *NATURE*

Graef, I. A., Mermelstein, P. G., Stankunas, K., Neilson, J. R., Deisseroth, K., Tsien, R. W., Crabtree, G. R.
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● **Properties of fast endocytosis at hippocampal synapses** *Symposium on Molecular and Cellular Aspects of Exocytosis*

Kavalali, E. T., Klingauf, J., Tsien, R. W.
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● **Neuronal voltage-activated calcium channels: On the roles of the alpha(1E) and beta(3) subunits** *Conference on Molecular and Functional Diversity of Ion Channels and Receptors*

Smith, S. M., Piedras-Renteria, E. S., Namkung, Y., Shin, H. S., Tsien, R. W.
NEW YORK ACAD SCIENCES.1999: 175-198

● **Kinetics and regulation of fast endocytosis at hippocampal synapses** *NATURE*

Klingauf, J., Kavalali, E. T., Tsien, R. W.
1998; 394 (6693): 581-585

● **Antisense oligonucleotides against alpha(1E) reduce R-type calcium currents in cerebellar granule cells** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*

Piedras-Renteria, E. S., Tsien, R. W.
1998; 95 (13): 7760-7765

● **Translocation of calmodulin to the nucleus supports CREB phosphorylation in hippocampal neurons** *NATURE*

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1998; 392 (6672): 198-202

● **Aspartate substitutions establish the concerted action of P-region glutamates in repeats I and III in forming the protonation site of L-type Ca₂₊ channels** *JOURNAL OF BIOLOGICAL CHEMISTRY*

Chen, X. H., Tsien, R. W.
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● **Dendritic Ca₂₊ channels characterized by recordings from isolated hippocampal dendritic segments** *NEURON*

Kavalali, E. T., Zhuo, M., Bito, H., Tsien, R. W.
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● **CREB phosphorylation and dephosphorylation: A Ca₂(+)- and stimulus duration-dependent switch for hippocampal gene expression** *CELL*

Bito, H., Deisseroth, K., Tsien, R. W.
1996; 87 (7): 1203-1214

● **Multiple structural elements in voltage-dependent Ca₂₊ channels support their inhibition by G proteins** *NEURON*

Zhang, J. F., Ellinor, P. T., Aldrich, R. W., Tsien, R. W.
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- **Changes in action potential duration alter reliance of excitatory synaptic transmission on multiple types of Ca₂₊ channels in rat hippocampus** *JOURNAL OF NEUROSCIENCE*
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- **Signaling from synapse to nucleus: Postsynaptic CREB phosphorylation during multiple forms of hippocampal synaptic plasticity** *NEURON*
Deisseroth, K., Bito, H., Tsien, R. W.
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Liu, G. S., Tsien, R. W.
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Randall, A., Tsien, R. W.
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- **MOLECULAR DETERMINANTS OF VOLTAGE-DEPENDENT INACTIVATION IN CALCIUM CHANNELS** *NATURE*
Zhang, J. F., Ellinor, P. T., Aldrich, R. W., Tsien, R. W.
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- **NITRIC-OXIDE SYNTHASE EXPRESSION IN SINGLE HIPPOCAMPAL-NEURONS** *MOLECULAR BRAIN RESEARCH*
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NEW YORK ACAD SCIENCES.1994: 294-301
- **DISTINCTIVE PROPERTIES OF A NEURONAL CALCIUM-CHANNEL AND ITS CONTRIBUTION TO EXCITATORY SYNAPTIC TRANSMISSION IN THE CENTRAL-NERVOUS-SYSTEM** *Wenner-Gren International Symposium on Molecular and Cellular Mechanisms of Neurotransmitter Release*
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Zhang, J. F., Randall, A. D., Ellinor, P. T., Horne, W. A., Sather, W. A., Tanabe, T., Schwarz, T. L., Tsien, R. W.
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