Stanford

Richard Tsien

George D. Smith Professor, Emeritus

Molecular and Cellular Physiology

NIH Biosketch available Online Curriculum Vitae available Online

CONTACT INFORMATION

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Bio

ACADEMIC APPOINTMENTS

- Emeritus Faculty, Acad Council, Molecular and 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 particlesquantum 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., Kleschevnikov, 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.
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- **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.
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- **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.
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- **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.
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- **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.
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- **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.
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- **LTP and adaptation to inactivity: Overlapping mechanisms and implications for metaplasticity** *NEUROPHARMACOLOGY*
  Thiagarajan, T. C., Lindskog, M., Malgaroli, A., Tsien, R. W.
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- **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.
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- **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*
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- **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*
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- **Adaptation to synaptic inactivity in hippocampal neurons** *NEURON*
  Thiagarajan, T. C., Lindskog, M., Tsien, R. W.
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- **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.
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- **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.
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  Chen, G., Harata, N. C., Tsien, R. W.
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  Smith, S. M., Bergsman, J. B., Harata, N. C., Scheller, R. H., Tsien, R. W.
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  Aravanis, A. M., Pyle, J. L., Tsien, R. W.
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- **Signaling from synapse to nucleus: the logic behind the mechanisms** *CURRENT OPINION IN NEUROBIOLOGY*
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  Wu, G. Y., Deisseroth, K., Tsien, R. W.
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- **Rapid reuse of readily releasable pool vesicles at hippocampal synapses** *NEURON*
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  Degtiar, V. E., Scheller, R. H., Tsien, R. W.
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  Bergsman, J. B., Tsien, R. W.

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- **Postfusional regulation of cleft glutamate concentration during LTP at 'silent synapses'** *NATURE NEUROSCIENCE*
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- **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.
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  Pyle, J. L., Kavalali, E. T., Choi, S., Tsien, R. W.
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