Daniela Pietrobon
Curriculum vitae

Education and training

1979, University of Padova, Degree (Laurea) in Chemistry, Magna cum Laude.
1979-1982, Research Fellow, Institute of General Pathology, University of Padova:
Energy transduction in mitochondria.
1984-1985, Postdoctoral Fellow (two EMBO Short Term Fellowships), Dept of Membrane Research, Weizmann Institute of Science, Israel:
Non-equilibrium thermodynamics of oxidative phosphorylation and kinetic modelling of mitochondrial H+ pumps.
1987-1990, Postdoctoral Fellow (EMBO Long Term Fellowship and Fogarty International Fellowship), Dept of Cellular and Molecular Physiology, Harvard Medical School, U.S.A.:
Biophysics of voltage-gated Ca^{2+} channels.

Employment and Research experience

1983-1991, CNR Researcher, CNR Unit Physiology of Mitochondria, Institute of General Pathology, University of Padova:
Energy transduction in mitochondria.
1991-1993, CNR Director of Research, CNR Unit Physiology of Mitochondria, Dept. of Biomedical Sciences, Univ. of Padova:
Biophysics and physiology of neuronal Ca^{2+} channels.
1993-2000 Associate Professor of General Physiology (Faculty of Sciences), Dept. of Biomedical Sciences, Univ. of Padova:
Biophysics and physiology of neuronal Ca^{2+} channels.
2000-, Professor of Physiology, Dept. of Biomedical Sciences, Univ. of Padova:
Calcium channelopathies of the central nervous system; in particular familial hemiplegic migraine; migraine pathophysiology

Honors and Professional Memberships and Committees

1985, Luigi Galvani Prize of the Bioelectrochemical Society.
1996-2000 Member of Council of the Italian Society of Pure and Applied Biophysics
1996-2002 Member of Council of IUPAB (Int. Union of Pure and Applied Biophysics)
2000-2003, Coordinator of the PhD Program in Molecular and Cellular Biology and Pathology of the Univ. of Padova.
2001, National Prize "President of the Republic" in Mathematical, Physical and Natural Sciences awarded by the Accademia dei Lincei
2005-2015, Coordinator of the PhD Program in Neurobiology within the PhD School of Biosciences of the Univ of Padova
2006-2011 Editorial Board of "The Journal of Physiology"
2007- Editorial Board of "Channels".
2010-2017 Member of Faculty of 1000
2011- Member of the Venetian Institute of Letters, Arts and Sciences
2016- Editorial Board of "Neuroscience"

2017- Editorial Board of "European Journal of Physiology"
2018- Editorial Board of "Current Opinion in Neurobiology"
2019-Associate Editor of "The Journal of Headache and Pain"
2020-Associate Editor of "Frontiers in Cellular Neuroscience"

Selected **invited talks** (since 2013):

-FASEB Conference on Ion Channel regulation (2013)
-International Union of Physiological Societies Congress (IUPS) (Keynote Lecture, 2013)
-9th FENS Forum of Neuroscience (2014)
-15th World Congress on Pain (2014)
-Symposium on Migraine Disorders (2015)
-Winter Conference on Neural Plasticity (2015)
-2nd European Calcium Channel Conference (2015)
-COSBID 2016 (2016) Keynote lecture
-Conference "More than neurons: towards a less neurocentric view of brain disorders" (2016)
-Mediterranean Neuroscience Meeting (2017)
-17th SINS National Congress (Plenary lecture, 2017)
-SBF-F44 Symposium Physiology and Pathophysiology of Voltage-Gated Ca2+ Channels: Recent Insights (2018)
-12th European Headache Federation Congress (2018)
-Quantitative Biomedicine for health and disease (QBio2019) Workshop (2019)
-Symposium: Ion Channels in Brain diseases (2020)
-Gordon Research Conference on Membrane Transport Proteins (2020)

Acts as **referee** for many prestigious scientific journals (including Science, Neuron, Nature Communications, PNAS, eLife, Ann Neurol, Cereb Cortex, J Neurosci, J Physiol) and international granting agencies (including: Human Frontier Science Program, Wellcome Trust Foundation, NIH, ANR, Israel Science Foundation, Austrian Science Foundation).

Contribution to Science (and selected publications)

1. **Functional consequences of mutations causing familial hemiplegic migraine and migraine pathophysiology**

Familial Hemiplegic Migraine type 1 (FHM1). We characterized the effect of several FHM1 mutations on the biophysical properties of human recombinant $Ca_V2.1$ channels expressed in both heterologous systems and neurons. We demonstrated that the mutations increase the open probability and shift the activation of the calcium channel to lower voltages and hence produce gain-of-function of the human $Ca_V2.1$ channel (1-3). Later, we characterized the functional consequences of FHM1 mutations on neuronal calcium channels, cortical synaptic transmission and cortical spreading depression in FHM1 knockin mice. We confirmed the gain-of-function of the calcium current in several neurons of FHM1 mice including cortical pyramidal neurons (4-7), but also showed that in specific types of neurons, including cortical fast-spiking interneurons, the calcium current was barely affected (7-8). We showed that cortical excitatory synaptic transmission and glutamate release at cortical pyramidal cell synapses were enhanced in FHM1 mice, whereas, in striking contrast, inhibitory synaptic transmission and GABA release were unaltered at fast-spiking

and other multipolar interneuron synapses (5, 8-9). We also showed enhanced thalamocortical synaptic transmission and dysregulation of the excitatory-inhibitory balance at the thalamocortical feedforward inhibitory circuit (10). We demonstrated a lower threshold for induction of cortical spreading depression (CSD) and a higher rate of CSD propagation in FHM1 mice both in vivo and in cortical slices (4-6), and showed that the facilitation of CSD in these mice is due to the excessive release of glutamate from cortical excitatory synapses (5).

Familial Hemiplegic Migraine type 2 (FHM2). We characterized the functional consequences of a FHM2 mutation on glutamate and K+ clearance by cortical astrocytes in heterozygous FHM2 knockin mice with reduced expression of the α2 Na, K ATPase and revealed that i) the reduced expression of the α2 Na, K ATPase leads to a similar reduction in the membrane expression of the glutamate transporter GLT1 in perisynaptic astrocytic processes surrounding cortical glutamatergic synapses and ii) the rates of glutamate and K+ clearance by cortical astrocytes are both reduced in FHM2 mice (11). We demonstrated a lower threshold for CSD induction and a higher rate of CSD propagation in FHM2 knockin mice both in vivo and in cortical slices (11, 12), and showed that the reduced rate of glutamate clearance by astrocytes can account for a large fraction of the facilitation of CSD induction and propagation in these mice (11). Recently, we have shown that the reduced rate of glutamate clearance in FHM2 mice results in increased amplitude and slowing of the NMDAR EPSC elicited in L2/3 pyramidal cells; these alterations as well as the faciliation of CSD were rescued by inhibition of diheteromeric GluN1-N2B NMDARs, which hardly affected the NMDAR EPSC and CSD in WT mice, suggesting that the enhanced susceptibility to CSD in FHM2 is mainly due to specific activation of extrasynaptic GluN1-N2B NMDARs (13). Using fluorescent glutamate imaging in awake mice, we have confirmed slower glutamate clearance in FHM2 mice during sensory processing and revealed previously undescribed spontaneous "plumes" of glutamate under basal conditions in layer 1 of somatosensory cortex not present in wild-type mice; interestingly, a rise in plume frequency and extracellular glutamate preceded the onset of CSD, which was prevented by inhibition of the plumes and glutamate rise (14).

1. M. Hans, S. Luvisetto, M.E. Williams, M. Spagnolo, A. Urrutia, A. Tottene, P.F. Brust, E.C. Johnson, M.M. Harpold, K.A. Stauderman and **D. Pietrobon**. Functional consequences of mutations in the human α1A calcium channel subunit linked to familial hemiplegic migraine. **J Neurosci** (1999) 19, 1610-1619.

2. A. Tottene, T. Fellin, S. Pagnutti, S. Luvisetto, J. Striessnig, C. Fletcher and **D. Pietrobon.** Familial hemiplegic migraine mutations increase Ca2+ influx through single human $Ca_V2.1$ channels and decrease maximal $Ca_V2.1$ current density in neurons. **Proc Natl Acad Sci** (2002) 99, 13284-13289.

3. A. Tottene, F. Pivotto, T. Fellin, T. Cesetti, A.M.J.M. van den Maagdenberg and **D. Pietrobon.** Specific kinetic alterations of human $Ca_V2.1$ calcium channels produced by mutation S218L causing familiar hemiplegic migraine and delayed cerebral edema and coma after minor head trauma. **J Biol Chem** (2005) 280, 17678-17686.

4. A.M.J.M. van den Maagdenberg*, **D. Pietrobon***, T. Pizzorusso, S. Kaja, L.A.M. Broos, T. Cesetti, R.A.G. van de Ven, A. Tottene, J. van der Kaa, J.J. Plomp, R.R. Frants, M.D. Ferrari. A cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression. **Neuron** (2004) 41, 701-710
*Shared first authorship and shared corresponding authorship.

5. Tottene A., Conti R., Fabbro A, Vecchia D, Shapovalova M, Santello M, van den Maagdenberg AMJM, Ferrari M and **Pietrobon D** Enhanced excitatory transmission at cortical synapses as the basis for facilitated spreading depression in CaV2.1 knockin migraine mice. **Neuron** (2009) 61: 762-773

6. Van den Maagdenberg AMJM*, Pizzorusso T, Kaja S, Terpolilli N, Shapovalova M, Hoebeek FE, Barrett CF, Gherardini L, van de Ven RC, Todorov B, Broos LAM, Tottene A, Gao Z, Fodor M, De Zeeuw CI, Frants RR, Plesnila N, Plomp JJ, **Pietrobon D*** and Ferrari MD. High cortical spreading depression susceptibility and migraine-associated symptoms in $Ca_V2.1$ S218L mice. **Ann. Neurol.** (2010) 67:85-98.
* Shared corresponding authorship

7. Fioretti B, Catacuzzeno L, Sforna L, Gerke-Duncan MB, van den Maagdenberg AM, Franciolini F, Connor M, **Pietrobon D**. Trigeminal ganglion neuron subtype-specific alterations of Ca(V)2.1 calcium current and excitability in a Cacna1a mouse model of migraine. **J Physiol** (2011) 589: 5879-5895

8. Vecchia D, Tottene A, van den Maagdenberg AM, **Pietrobon D**. Mechanism underlying unaltered cortical inhibitory synaptic transmission in contrast with enhanced excitatory transmission in $Ca_V2.1$ knockin migraine mice. **Neurobiol Dis** (2014) 69:225-34

9. Vecchia D, Tottene A, van den Maagdenberg AM, **Pietrobon D**. Abnormal cortical synaptic transmission in CaV2.1 knockin mice with the S218L missense mutation which causes a severe familial hemiplegic migraine syndrome in humans. **Front. Cell. Neurosci.** (2015) 9:8; doi: 10.3389

10. Tottene A., Favero M, **Pietrobon D.** Enhanced thalamocortical synaptic transmission and dysregulation of the excitatory-inhibitory balance at the thalamocortical feedforward inhibitory microcircuit in a genetic mouse model of migraine. **J. Neurosci.** (2019) 39:9841-51

11. Capuani C, Melone M, Tottene A, Bragina L, Crivellaro G, Santello M, Casari G, Conti F, **Pietrobon D**. Defective glutamate and K+ clearance by cortical astrocytes in familial hemiplegic migraine type 2. **EMBO Mol Med.** (2016) 8:967-86

12. Leo L, Gherardini L, Barone V, De Fusco M, **Pietrobon D**, Pizzorusso T, Casari G. Increased susceptibility to cortical spreading depression in the mouse model of familial hemiplegic migraine type 2. **PLoS Genet** (2011) 7(6):e1002129

13. Crivellaro G, Tottene A, Vitale M, Melone M, Casari G, Conti F, Santello M, **Pietrobon D.** Specific activation of GluN1-N2B NMDA receptors underlies facilitation of cortical spreading depression in a genetic mouse model of migraine with reduced astrocytic glutamate clearance. **Neurobiol Dis.** (2021) 156:105419**.**

14. Parker PD, Suryavanshi P, Melone M, Sawant-Pokam PA, Reinhart KM, Kaufmann D, Theriot JJ, Pugliese A, Conti F, Shuttleworth CW, Pietrobon D, Brennan KC. Non-canonical glutamate signaling in a genetic model of migraine with aura. **Neuron** (2021) 109(4):611-628.

We were asked to write several **reviews on familial hemiplegic migraine and migraine mechanisms** (15-21, 23-25), and a review on **cortical spreading depression** (22).

15. **D. Pietrobon** and J. Striessnig. Neurobiology of Migraine. **Nature Rev Neurosci** (2003) 4, 386-398

16. **D. Pietrobon.** Migraine: New Molecular Mechanisms. **Neuroscientist** (2005) 11, 373-386.

17. **D. Pietrobon.** Familial Hemiplegic Migraine**. Neurotherapeutics** (2007) 4, 274-284

18. **D. Pietrobon.** Insights into migraine mechanisms and $Ca_V2.1$ channel function from animal models of familial hemiplegic migraine. **J Physiol** (2010) 588: 1871-1878

19. Vecchia D and **Pietrobon D**. Migraine: a disorder of brain excitatory-inhibitory balance? **Trends Neurosci.** (2012) 35:507-520

20. **Pietrobon D.** Calcium channels and migraine. **Biochim Biophys Acta** (2013) 1828:1655-65.

21. **Pietrobon D** and Moskowitz M. Pathophysiology of migraine. **Ann Rev Physiol** (2013) 75:365-91

22. **Pietrobon D** and Moskowitz M. Propagation of chaos and commotion in the wake of cortical spreading depression and spreading depolarizations. **Nature Rev. Neurosci.** (2014) 15:379-93

23. **Pietrobon D.** Ion channels in migraine disorders. **Curr Opin Physiol** (2018) 2:98-108

24. Brennan KC and **Pietrobon D**. A systems neuroscience approach to migraine. **Neuron** (2018) 97:1004-21

25. **Pietrobon D** and Brennan KC Genetic mouse models of migraine. **J Head Pain** (2019) 20:79

2. $Ca_V2.1$ channelopathies

Before concentrating on FHM we studied the functional consequences of mutations in the CACNA1A gene causing episodic ataxia type 2 (EA2) and the functional consequences of knocking out the $Ca_V2.1$ channel in mice. We demonstrated that EA2 mutations cause loss-of-function of $Ca_V2.1$ channels (26). In $Ca_V2.1$-/- mice, we showed dystonia and cerebellar atrophy in a highly specific pattern (27), and by analyzing pain-related behavioral responses we revealed a pronociceptive role of $Ca_V2.1$ channels in inflammatory and neuropathic pain states (26). We wrote several reviews on $Ca_V2.1$ channelopathies (29-32).

26. S. Guida, F. Trettel, S. Pagnutti, E. Mantuano, A. Tottene, L. Veneziano, T. Fellin, M. Spadaro, K. Stauderman, M.E. Williams, S. Volsen, R.A. Ophoff, R.R. Frants, C. Jodice, M. Frontali and **D. Pietrobon** Complete loss of P/Q calcium channel activity caused by a CACNA1A missense mutation carried by patients with episodic ataxia type 2. **Am J Hum Genet** (2001), 68, 759-764

27. C. Fletcher*, A. Tottene*, V.A. Lennon, S.M. Wilson, S.J. Dubel, R. Paylor, D.A. Hosford, L. Tessarollo, M.W. McEnery, **D. Pietrobon**, N.G. Copeland and N. A. Jenkins Dystonia and cerebellar atrophy in Cacna1a null mice lacking P/Q calcium channel activity. **FASEB J** (2001), 15, 1288-1290
* Shared first authorship

28. S. Luvisetto, S. Marinelli, M.S. Panasiti, F.R. D'Amato, C.F. Fletcher, F. Pavone and **D. Pietrobon**. Pain sensitivity in mice lacking the Ca(v)2.1alpha1 subunit of P/Q-type Ca2+ channels. **Neuroscience** (2006) 142, 823-32.

29. **D. Pietrobon.** Calcium channels and channelopathies of the central nervous system. **Mol Neurobiol** (2002) 25, 13-32.

30. **D. Pietrobon.** Function and dysfunction of synaptic calcium channels: insights from mouse models**. Curr Opin Neurobiol** (2005) 15, 257-269

31. Catterall WA, Dib-Hajj S, Meisler MH and **Pietrobon D.** Inherited Neuronal Ion Channelopathies: New Windows on Complex Neurological Diseases. **J. Neurosci**. (2008) 28:11768-11777

32. **Pietrobon D.** $Ca_V2.1$ channelopathies. **Pfluegers Arch**. (2010) 460:375-393.

3. Biophysical properties of voltage-gated Ca^{2+} channels and the molecular and functional diversity of neuronal Ca2+ channels

Before getting interested in $Ca_V2.1$ channelopathies, we used single channel current recordings to characterize i) the biophysical properties of cardiac voltage-gated L-type Ca^{2+} channels and of recombinant human $Ca_V2.1$ channels and ii) the functional diversity of neuronal Ca^{2+} channels. We discovered a new mechanism of regulation of the conductance of L-type Ca^{2+} channels by protons (33-36) and a new mechanism of voltage-dependent gating of L-type Ca^{2+} channels (37). Moreover we revealed different gating modes of human $Ca_V2.1$ channels (38-39). We discovered a new "anomalous" neuronal voltage-gated L-type Ca^{2+} channel and characterized its biophysical and molecular properties (40-42). We also revealed a novel neuronal P-type and two novel neuronal R-type Ca2+ channels (43-45).

33. B. Prod'hom, **D. Pietrobon** and P. Hess. Direct measurement of proton transfer rates to a group controlling the dihydropyridine-sensitive Ca2+ channel. **Nature** (1987) 329, 243-246

34. **D. Pietrobon**, B. Prod'hom and P. Hess. Conformational changes associated with ion permeation in L-type calcium channels. **Nature** (1988) 333, 373-376

35. **D. Pietrobon**, B. Prod'hom and P. Hess. Interactions of protons with single open L-type calcium channels. pH dependence of proton induced current fluctuations with Cs+, K+ and Na+ as permeant ions". **J Gen Physiol** (1989) 94, 1-21

36. B. Prod'hom, **D. Pietrobon** and P. Hess. Interactions of protons with single open L-type calcium channels. Location of protonation site and dependence of proton-induced current fluctuations on concentration and species of permeant ion. **J Gen Physiol** (1989) 94, 23-42

37. **D. Pietrobon** and P. Hess. Novel mechanism of voltage-dependent gating in L-type calcium channels. **Nature** (1990) 346, 651-655

38. S. Luvisetto, T. Fellin, M. Spagnolo, B. Hivert, PF Brust, M.M. Harpold, K.A. Stauderman, M.E. Williams and **D. Pietrobon.** Modal Gating of Human CaV2.1 (P/Q-type) Calcium Channels: I. The Slow and the Fast Gating Modes and their Modulation by {beta} Subunits. **J Gen Physiol**. (2004) 124, 445-461.

39. T. Fellin, S. Luvisetto, M. Spagnolo, and **D. Pietrobon.** Modal Gating of Human CaV2.1 (P/Q-type) Calcium Channels: II. The b Mode and Reversible Uncoupling of Inactivation. **J Gen Physiol.** (2004) 124, 463-74.

40. L. Forti and **D. Pietrobon.** Functional diversity of L-type calcium channels in rat cerebellar neurons. **Neuron** (1993) 10, 437-450

41. B. Hivert, S. Luvisetto, A. Navangione, A. Tottene and **D. Pietrobon.** Anomalous L-type calcium channels of rat spinal motoneurons**. J Gen Physiol** (1999) 113, 679-693

42. Koschak A, Obermair GJ, Pivotto F, Sinneger-Brauns MJ, Striessnig J and **Pietrobon D.** Molecular nature of anomalous L-type calcium channels in mouse cerebellar granule cells. **J. Neurosci.** (2007) 27:3855-3863

43. L. Forti, A. Tottene, A. Moretti and **D. Pietrobon.** Three novel types of voltage-dependent calcium channels in rat cerebellar neurons. **J Neurosci** (1994) 14, 5243-5256

44. A. Tottene, A. Moretti and **D. Pietrobon.** Functional diversity of P-type and R-type calcium channels in rat cerebellar neurons. **J Neurosci** (1996) 16, 6353-6363.

45. **A. Tottene, S. Volsen and** D. Pietrobon**.** α1E subunits form the pore of three cerebellar R-type calcium channels with different pharmacological and permeation properties. **J. Neurosci.** (2000) 20, 171-178

4. Biophysical properties of mitochondrial proton pumps and energy transduction in mitochondria.

At the beginning of my scientific career I combined experiments and modelling to investigate the biophysical mechanisms of coupling between electron transfer and proton translocation in mitochondrial redox-driven proton pumps and between ATP synthesis-hydrolysis and proton translocation in mitochondrial proton ATPases, and the role of the H+ electrochemical gradient across the inner mitochondrial membrane in mitochondrial energy transduction. We revealed that the mitochondrial proton pumps are incompletely coupled (46-48) and that classical mitochondrial uncouplers induce pump "slippage" besides acting as protonophores (49), and developed detailed kinetic models of the mitochondrial H+ pumps and their chemiosmotic coupling (50-55)

46. **D. Pietrobon**, G.F. Azzone and D. Walz. Effect of funicolosin and antimycin A on the redox-driven H^+-pumps in mitochondria: on the nature of leaks. **Eur J Biochem** (1981) 117, 389-394

47. **D. Pietrobon**, M. Zoratti, G.F. Azzone, J.W. Stucki and D. Walz. Non equilibrium thermodynamic assesment of redox-driven H+ pumps in mitochondria. **Eur J Biochem** (1982) 127, 483-494

48. **D. Pietrobon**, M. Zoratti and G.F. Azzone. Molecular slipping in redox and ATPase H^+-pumps. **Biochim Biophys Acta** (1983) 723, 317-321

49. **D. Pietrobon**, S. Luvisetto and G.F. Azzone. Uncoupling of oxidative phosphorylation. 2) Alternative mechanisms: intrinsic uncoupling or decoupling?. **Biochemistry** (1987) 26, 7339-7347

50. **D. Pietrobon** and S.R. Caplan. Flow-force relationships for a six-state proton pump model: intrinsic uncoupling, kinetic equivalence of input and output forces, and domain of approximate linearity. **Biochemistry** (1985) 24, 5764-5776

51. **D. Pietrobon.** A non linear kinetic model of chemiosmotic energy coupling. **Bioelectrochem Bioenerg** (1986) 15, 193-209

52. **D. Pietrobon**, M. Zoratti, G.F. Azzone and S.R. Caplan. Intrinsic uncoupling of mitochondrial proton pumps. II. Modelling studies. **Biochemistry** (1986) 25, 767-775

53. **D. Pietrobon** and S.R. Caplan. Double inhibitor and uncoupler-inhibitor titrations. I. Analysis with a linear model of chemiosmotic energy coupling. **Biochemistry** (1986) 25, 7682-7690

54. **D. Pietrobon** and S.R. Caplan. Double inhibitor and uncoupler-inhibitor titrations. II. Analysis with a nonlinear model of chemiosmotic energy coupling. **Biochemistry** (1986) 25, 7690-7696

55. S.R. Caplan and **D. Pietrobon**. Theoretical analysis of double-titrations experiments. **Biochim Biophys Acta** (1987) 895, 241-258

Bibliometric indicators

h index: 49 (Google Scholars); 44 (Scopus)
total citations: 9743 (Google Scholars); 6523 (Scopus)
Total IF 643 (av IF per publication 7.9)

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