Enrico Cherubini
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Trained as a Child Neurologist at La Sapienza University in Roma, Enrico Cherubini is an internationally recognized expert in synaptic transmission and activity-dependent synaptic plasticity processes during postnatal development. Over the years, he provided a series of fundamental studies aimed at understanding the functional role of GABAergic signaling in the hippocampus at early developmental stages in both physiological and pathological conditions.

In 1971, he obtained a fellowship to work in the Service d'Exploration Fonctionelle du Système Nerveux (Marseille) directed by Prof. H. Gastaut, a leading figure in the field of Epilepsy. In 1973, he was appointed assistant professor at the Institute of Child Neurology in Rome where he contributed to build up the Clinical Neurophysiology Unit, conducting basic and clinical research in the field of Epilepsy. In 1976-78 as a Post Doc at the Brain Research Institute (UCLA), he characterized, under the supervision of Dr. NA Buchwald, the functional connections of basal ganglia in developing kittens using electrophysiological recordings from single neurons *in vivo*. Back to Rome, he realized that it was almost impossible to share the time between clinical and basic research. Thus, in 1981 he resigned from the University of Rome and took the opportunity of joining RA North's lab at MIT (Cambridge, USA). This lab represented an ideal environment to gain more expertise on synaptic signalling using *in vitro* preparations. In 1984, he obtained the position of "Directeur de Recherche" at INSERM in Paris. Here, he set up an *in vitro* electrophysiology laboratory devoted to the study of the hippocampus at early developmental stages. In 1991, he came back to Italy as full Professor of Physiology first at the of University of Siena and then at the International School for Advanced Studies (SISSA) in Trieste where, together with Antonino Cattaneo, he contributed to build up the Department of Neurosciences. During that period he actively collaborated with Prof. Jean-Pierre Changeux (Collège de France and Institut Pasteur, Paris), a leading Figure in the field of nicotinic acetylcholine receptors. In the last years, his studies have been focused on Autism Spectrum Disorders working on several animal models: $NL3^{R451C}$ knock-in, NL3 knock-out and BTBR T+tf/J mice.

After retiring from SISSA, in 2014 he joined as Scientific Director the European Brain Research Institute in Rome, where he coordinates the joint EBRI-Bambin Gesù Pediatric Hospital (OPBG) laboratory on drug-resistant forms of epilepsies in children.
He published over 250 peer-reviewed articles in prestigious scientific journals.
Number of citations: 13155; h-index: 56; i10-index: 183 (Google Scholar).

Main achievements

1. First electrophysiological evidence that GABA regulates transmitter release *via* $GABA_B$ receptors, just discovered by Hill and Bowery. In myenteric neurons of the guinea pig ileum, GABA has two distinct actions: i. it opens bicuculline-sensitive, rapidly desensitising $GABA_A$ receptor channels permeable to anions. ii. It reduces *via* $GABA_B$ receptors acetylcholine release through a bicuculline-insensitive non-desensitising action, mimicked by baclofen
2. Discovery that in myenteric neurons of the guinea pig ileum, activation of μ and k subtypes of opioid receptors inhibits transmitter release *via* different mechanisms: μ receptors reduces acetylcholine release through an increase in potassium conductance, whereas k receptors through a direct reduction of calcium entry into nerve terminals. These pieces of work have become a reference in the field, often cited in textbooks.
3. Effects of anoxia on synaptic transmission in the neonatal and in the adult hippocampus. The immature hippocampus exhibits excitatory postsynaptic potentials (EPSPs) that, in comparison to adulthood, are more resistant to anoxia. A greater resistance to anoxia has been also found for L-type calcium currents: while in adults these currents are virtually eliminated by 2-3 min of anoxia, during the first postnatal week these are only partially depressed. The exceptional resistance of immature brain to anoxia favors newborn's survival after parturition.
4. Discovery that γ-aminobutyric acid (GABA), the main inhibitory transmitter in the adult brain, early in postnatal development exerts depolarizing and excitatory effects on targeted cells *via* an outwardly directed flux of chloride. The interplay between the depolarizing action of GABA and glutamate generate a primordial form of synchrony, the so-called Giant Depolarizing Potentials or GDPs crucial for synaptic wiring and refinement of local neuronal circuits.
5. Calcium transients associated with network-driven GDPs act as coincident detectors for enhancing synaptic efficacy at emerging GABAergic and glutamatergic synapses. This effect disappears towards the end of the first postnatal week when GABA shifts from the depolarizing to the hyperpolarizing direction. GDPs are also instrumental for shifting silent synapses, abundantly expressed in the immature brain, into conductive ones.
6. Immediately after birth, mossy fibers, the axons of dentate gyrus granule cells which convey information from the entorhinal cortex to the hippocampus proper, release into CA3 principal cells and local GABAergic interneurons instead of glutamate GABA, which exerts on its targets a depolarizing and excitatory action. Downregulation of GABA release *via* activation of $GABA_B$, kainate and CB1 receptors localized on MF terminals, would limit the excessive activation of the auto-

associative CA3 network by the excitatory action of GABA, thus preventing membrane hyper-excitability and the development of seizures.

7. Overall, changes in GABAergic signaling have important implications in neurodevelopmental disorders such as schizophrenia, autism and epilepsy.

Education

1968	MD (cum laude) University of Rome
1972	Specialization in Child Neurology, University of Rome
1972	Attestation d'Etude d'Electroencephalographie Clinique, Univ Aix-Marseille

Positions held

1971	Bourse Assistant Etranger, CNRS, Marseille
1973-80	Assistant Professor, Institute of Child Neurology, University of Rome
1976-78	Post Doc, UCLA, Los Angeles
1980-83	Research Scientist, MIT, Cambridge, USA
1983-91	Directeur de Recherche, INSERM, Parigi
1987	Visiting Scientist, Vollum Institute, Portland, USA
1990	Visiting Scientist, Hebrew University, Jerusalem
1991-1993	Full Professor (Physiology), University of Siena
1994-1997	Head of the Biophysics Sector, SISSA, Trieste
2002-2013	Head of the Neurobiology Sector, SISSA, Trieste
2014-present	Scientific Director EBRI

International and National Scientific Committee's member

1998-2001	Grant Committee Human Frontiers Science Program
1998-present	Evaluation Committee for: INSERM, CNRS, ANR, Ministere de la Recherche (Francia), Austrian Science Foundation, Poland Academy of Science
2004-2008	European Commission
2006-present	Evaluation Committee MIUR
2007	Medical Research Council (UK)
2007	Riken Institute (Tokyo)
2009-2016	Advisory Board of Institut Pasteur, Montevideo
2011, 2019	President evaluation committees, CNR
2018-2020	Chair ATIP-Avenir grant committee for Neurosciences (Paris)

Honors

2012-2013	President of the Italian Neuroscience Society

Editorial Activity

2002-2009	Editorial Board, The Journal of Physiology, London
2009-2018	Associate Editor, Frontiers in Cellular Neuroscience. He edited two special topic 1. building up the inhibitory synapses 2. The CA3 region of the hippocampus: how is it? What is it for? How does it do? (in collaboration with R Miles, Paris)

2019-present Chief Editor of Frontiers in Cellular Neuroscience, Neurophysiology Section

Symposia and workshops organization

GABA and glycine in the developing brain (Munich, 1992)
Intracellular Channels, Organelles and Cell Function (Trieste, 1993)
Transduction Mechanisms and Synaptic Function (Erice, 1997)
New insights into the Hebbian synapse (Berlin, 1998)
Electrical signaling in the CNS (Trieste 1999)
Globalizzazione e Scienza: profitto ed etica nelle nuove frontiere della Biologia (Trieste, 2002)
Regulation of Neuronal and Synaptic Function (Eilat, 2003)
Mute, whispering or deaf silent synapses (Prague, 2003)
Emerging Aspects in synaptic Physiology (Ischia, 2005)
FISV, Riva del Garda (2008) Molecular regulation of synaptic plasticity
New insights into gephyrin function (IBRO, Florence, July 2011)
Best practices for early diagnosis and intervention in ASD, (Jerusalem April 2013)
Satellite symposium FENS Forum 2014: Synapses as therapeutic targets for Autism Spectrum Disorders (Pavia, 2014)

IBRO Schools

Montevideo (Uruguay, 1993, 1995, 1996, 2001)
Wroclaw (Poland, 2002)
Ho-Chi Min City (Vietnam, 2005)
Belgrade (Serbia, 2005)
Nagpur (India, 2008)
FENS –IBRO-Hertie Winter School, Obergugl, Austria (2010)
Tehran 2016

Selected publications

Cherubini E, North RA (1984) Actions of gamma-aminobutyric acid on neurones of guinea-pig myenteric plexus. Br J Pharmacol 82: 93-100

Cherubini E, North RA (1984) Inhibition of calcium spikes and transmitter release by γ-aminobutyric acid in the guinea-pig myenteric plexus. Br J Pharmacol 82:101-105.

Cherubini E, North RA (1985) Mu and kappa opioids inhibit transmitter release by different mechanisms. Proc Natl Acad Sci U S A 82:1860-1863.

Cherubini E, Ben Ari Y, Gho M, Bidard JN, Lazdunski M (1987) Long-term potentiation of synaptic transmission in the hippocampus induced by a bee venom peptide. Nature 328:70-73.

Cherubini E, Herrling PL, Lanfumey L, Stanzione P (1988) Excitatory amino acids in synaptic excitation of rat striatal neurones in vitro. J Physiol 400:677-690.

Cherubini E, Ben-Ari Y, Krnjevic K (1989) Anoxia produces smaller changes in synaptic transmission, membrane potential, and input resistance in immature rat hippocampus. J Neurophysiol 62:882-895.

Ben-Ari Y, Cherubini E, Corradetti R, Gaiarsa JL (1989) Giant synaptic potentials in immature rat CA3 hippocampal neurones. J Physiol 416:303-325.

Cherubini E, Gaiarsa JL, Ben-Ari Y (1991) GABA: an excitatory transmitter in early postnatal life. Trends Neurosci 14:515-519.

Ito S, Cherubini E (1991) Strychnine-sensitive glycine responses of neonatal rat hippocampal neurones. J Physiol 440:67-83.

Strata F, Atzori M, Molnar M, Ugolini G, Tempia F, Cherubini E (1997) A pacemaker current in dye-coupled hilar interneurons contributes to the generation of giant GABAergic potentials in developing hippocampus. J Neurosci 17:1435-1446.

Domenici MR, Berretta N, Cherubini E (1998) Two distinct forms of long-term depression coexist at the mossy fiber-CA3 synapse in the hippocampus during development. Proc Natl Acad Sci U S A 95:8310-8315.

Mozrzymas JW, Barberis A, Michalak K, Cherubini E (1999) Chlorpromazine inhibits miniature GABAergic currents by reducing the binding and by increasing the unbinding rate of $GABA_A$ receptors. J Neurosci 19:2474-2488.

Gasparini S, Saviane C, Voronin LL, Cherubini E (2000) Silent synapses in the developing hippocampus: lack of functional AMPA receptors or low probability of glutamate release? Proc Natl Acad Sci U S A 97:9741-9746.

Saviane C, Savtchenko LP, Raffaelli G, Voronin LL, Cherubini E (2002) Frequency-dependent shift from paired-pulse facilitation to paired-pulse depression at unitary CA3-CA3 synapses in the rat hippocampus. J Physiol 544: 469-476.

Maggi L, Le Magueresse C, Changeux J-P, Cherubini E (2003) Nicotine activates immature silent connections in the developing hippocampus. Proc Natl Acad Sci USA 100: 2059-2064.

Barberis A, Petrini EM and Cherubini E (2004) Presynaptic source of quantal size variability at GABAergic synapses in rat hippocampal neurons in culture. Eur J Neurosci 20: 1803-1810.

Voronin LL, Cherubini E (2004) "Deaf, mute and whispering" silent synapses: their role in synaptic plasticity. J Physiol 557: 3-12.

Kasyanov AM, Safiulina VF, Voronin LL, Cherubini E (2004) GABA-mediated giant depolarizing potentials as coincidence detectors for enhancing synaptic efficacy in the developing hippocampus. Proc Natl Acad Sci USA 101: 3967-3972.

Safiulina VF, Fattorini G, Conti F and Cherubini E (2006) GABAergic signaling at mossy fiber synapses in neonatal rat hippocampus. J Neurosci 26: 597-608.

Mohajerani MH, Sivakumaran S, Zacchi P, Aguilera P, Cherubini E (2007) Correlated network activity enhances synaptic efficacy *via* BDNF and the ERK pathway at immatureCA3-CA1 connections in the hippocampus. Proc Natl Acad Sci USA 104: 13176–13181.

Moretto Zita M, Marchionni I, Bottos E, Righi M, Del Sal G, Cherubini E, Zacchi P (2007) Post-phosphorylation prolyl-isomerisation of gephyrin represents a mechanism to modulate glycine receptors function. EMBO J 26: 1761-1771.

Safiulina VF, Zacchi P, Taglialatela M, Yaari Y, Cherubini E (2008) Low expression of Kv7/M channels facilitates intrinsic and network bursting in the developing rat hippocampus. J Physiol 586:5437-5453.

Sivakumaran S, Mohajerani MH, Cherubini E (2009) At immature mossy fiber-CA3 synapses correlated pre and postsynaptic activity persistently enhances GABA release and network excitability *via* BDNF and cAMP-dependent PKA. J Neurosci 29:2637-2647

Kasap Varley Z, Pizzarelli R, Antonelli R, Stancheva SH, Kneussel M, Cherubini E, Zacchi P (2011) Gephyrin regulates GABAergic and glutamatergic synaptic transmission in hippocampal cell cultures. Journal Biological Chemistry 286:20942-20951.

Caiati MD, Safiulina VF, Fattorini G, Sivakumaran S, Legname G, Cherubini E (2013) PrP^C controls via PKA the direction of synaptic plasticity in the immature hippocampus. J Neurosci 33:2973-2983 (Highlighted in Nature News).

Griguoli M, Cellot G, Cherubini E (2013) In hippocampal oriens interneurons anti-Hebbian Long-Term Potentiation requires cholinergic signalling via α7 nicotinic acetylcholine receptors. J. Neurosci 33: 1044-1049.

Antonelli R, Pizzarelli R, Pedroni A Fritschy J-M, Del Sal G, Cherubini E, Zacchi P (2014) Pin1-dependent signaling negatively affects GABAergic transmission by modulating neuroligin2/gephyrin interaction. Nat Commun 5:5066 doi:10.1038/ncomms6066 (2014).

Cellot G, Cherubini E (2014) GABAergic signaling as therapeutic target for Autism Spectrum Disorders. Frontiers in Pediatrics, DOI: 10.3389/fped.2014.00070.

Cherubini E, Griguoli M (2019) GABAergic Signaling at Newborn Mossy Fiber–CA3 Synapses Short and Long-Term Activity-Dependent Synaptic Plasticity Processes. In "Comprehensive Developmental Neuroscience", Rakic and Rubenstein Eds, in press

Badurek S, Griguoli M, Malik A-S, Zonta B, Fei G, Middei S, Lagostena L, Jurado-Parras MT, Gillingwater TH, Gruart A, Delgado-García JM, Cherubini E, Minichiello L (2020) Immature dentate granule cells require Ntrk2/Trkb for the formation of functional hippocampal circuitry. iScience 2020 Apr 18;23(5):101078. doi: 10.1016/j.isci.2020.101078.