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Obituary

A career that transformed neuroscience

What defines the best of science, the paradigmatic experiments that change a discipline? This is a complex topic, but we can look for answers in the familiar ground of our own fields. Many of our colleagues agree that the work of Rousoudan Bourtchouladze (Fig. 1), who passed away on August 6, 2011 in New York City, played an important role in starting a new field and catalyzing a change in neuroscience that continues to transform the discipline to this day.

Rusiko, as she was known to her friends, was born in 1952 in Tbilisi, Georgia. Her father was carrier military and her mother a doctor. From an early age, she showed an interest in science and music. She could have been a concert pianist, but the pull to science was simply too strong. Rusiko graduated from Tbilisi State University with a Physiology major in 1977. In 1984 she received her Ph.D. in Physiology and Behavioral Neuroscience from the Anokhin Institute of Normal Physiology and the Sechenov First Medical Institute, in Moscow, Russia. Following her Ph.D., she became a Senior Staff Investigator in the Beritashvili Institute of Physiology in Tbilisi. It was there that her life-long love affair with memory research started. Her colleagues remember her as a creative, confident, and beautiful woman with a big courageous heart. I remember a story she shared with our laboratory about her first week in a primate laboratory. She was asked to handle a particularly aggressive monkey, and she was simply terrified. How did you possibly manage it, I asked her. She told me that she knew that animals sense fear, and therefore before entering the vivarium each day, she simply made sure that she controlled her fear! This type of courage, determination, and pragmatism defines Rusiko's unfortunately short but brilliant career.

Rusiko realized early on in her career that integrated molecular, electrophysiological, and behavioral studies were key to neuroscience. This view has become popular in the last 10 years, but in the late seventies, there were very few examples of multilevel cross-disciplinary studies in neuroscience. Not only was there a paucity of appropriate integrative tools, many neuroscientists believed that it was impossible to appropriately master multiple approaches, and consequently multidisciplinary efforts were in general regarded as foolhardy and superficial. Rusiko's earlier work combined pharmacological tools, hypothalamic electrophysiology, and behavioral analysis in rabbits to implicate specific receptor systems in behavioral responses triggered by hypothalamic stimulation [9].

Rusiko emerged as a young pre-eminent neuroscientists in Georgia, and in 1991 she published a very thoughtful and prescient analysis of Georgian neuroscience [6]. She argued for the importance of international collaboration for Georgian neuroscience in the aftermath of the fall of the Soviet Empire. Her work was recognized internationally and she won a series of fellowships and awards from the Netherlands Academy of Sciences, European Science Foundation, Royal Society and Wellcome Trust.

Rusiko fell in love with the new wave of biochemical studies of memory coming from Europe and the United States in the late eighties, and between 1989 and 1992, already a mother married to a successful heart surgeon, she defied conservative Georgian traditions and made extended visits to research groups in Western Europe, most notably Steven Rose's laboratory at the Open University in the UK. Because the mkhedruli alphabet of her native language is so different from that of English, in the years that followed her papers would be written under a number of variants of her last name (Burchuladze, Bourtchouladze, and Bourtchuladze). As a visiting scientist in the Rose laboratory, she carried out influential studies on the role signaling mechanisms, in including NMDA receptors and kinase C on memory [7,8]. And this is how our paths crossed in 1992. She had heard about novel transgenic approaches that I had used to manipulate calmodulin kinase II in studies of plasticity and learning in mice [15]. She contacted me about a visit to our newly minted group in Cold Spring Harbor Laboratories (CSHL), and within a few months she had moved with her family to the United States for a Visiting Scientist position at CSHL. In the years that followed in our laboratory at CSHL and then in Eric Kandel's laboratory at Columbia University, she carried out a series of studies that had a critical role in the emergence of molecular and cellular cognition as a new field in neuroscience. This field now has its own society (Molecular and Cellular Cognition Society; www.molcelcog.org) with more than 4000 members and regular meetings in America, Europe, and Asia.

The first wave of transgenic studies of memory focused on molecular processes required for triggering hippocampal plasticity and learning. Unfortunately, it was not always easy to ascertain whether learning per se was affected in the mutant mice or some other behavior required for learning (e.g., sensory perception, motivation, etc.). Similar problems had plagued earlier Drosophila genetic studies of memory [12], and Rusiko was determined to find a way around this issue. The solution came in the form of mice with mutations in the transcription factor CREB. Earlier studies in Aplysia had suggested that this transcription factor was involved in synaptic plasticity, and Rusiko's elegant studies in our laboratory showed that CREB was critical for long-term memory [5]. Importantly, Rusiko showed that CREB mutant mice had intact short-term memory, thus allaying concerns that the memory deficits were due to behavioral abnormalities unrelated to memory [5]! Remarkably, the same CREB mutant mice showed clear deficits in late, but not early, stages of long-term potentiation (LTP), a mechanism suspected to underlie learning and memory[5]. Rusiko's 1994 Cell paper reporting these results is one of the most highly sited papers in learning and memory. Beyond providing a clear example of how information at the molecular, electrophysiological and behavioral levels could be integrated into a seamless and compelling story, Rusiko's 1994 CREB paper laid

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Fig. 1. Rusiko Bourtchouladze.

down many of the integrated cross-disciplinary strategies that would be used in many other papers that that studied the role of transcription in memory. She would follow up that work with a paper that provided the first electrophysiological and behavioral evidence that mechanisms of short-term plasticity have a role in hippocampal dependent learning and memory [14].

To continue her CREB experiments, Rusiko teamed up with Ted Abel in the Kandel Laboratory. There, she showed that animals with a transgene that disrupted the function of a kinase (protein kinase A) that activates CREB also showed late-LTP and long-term memory deficits, although early LTP and short-term memory were unaffected [1]. This was the first convergent and compelling series of studies that specifically implicated a signaling pathway in mammalian long-term plasticity and long-term memory. It was an elegant illustration of the power of integrating molecular mechanisms (in this case, transcriptional activation), cellular physiology (late phases of LTP), and specific memory processes (long-, but not, short-term memory). It is difficult to underestimate the importance and impact of these pioneering studies: they were extensively discussed both in the scientific and public press, and they played an important part in catalyzing the rapid expansion of the field of molecular and cellular cognition. There are now many hundreds of published studies similar to the ones that Rusiko carried out, and PKA/CREB signaling is one of the most extensively explored molecular mechanisms of memory. Her experiments represent early examples of the new brand of multi-level explanations of behavior that literally integrate across disciplinary boundaries, from molecular mechanisms to complex behavior, and that over the last 20 years have overcome the many disciplinary silos that previously fragmented neuroscience.

Rusiko continued to work on the role of the PKA/CREB pathway in learning and memory [2,3,10,11] and once again surprised all of us by announcing that she was accepting a leadership position in a biotech company built around her findings with PKA and CREB. She became entranced by the idea of finding small molecules that could be used to boost CREB activation and hopefully memory performance in patients with cognitive problems. Indeed, two of her papers focused on mouse models of cognitive disorders. For example, she published the first mouse model of a learning disability (Neurofibromatosis type I) [13], and she reported that inhibitors of PDE4 improved the memory deficits of a mouse model of Rubinstein Taybi syndrome [4].

She also took the time to write a book for the general public on molecular mechanisms of memory (memories are made of this) [13]. It is a personal and engaging account of some of the very roads she took in her life-long quest for molecular and cellular mechanisms of memory. Even though our ways parted after Cold Spring Harbor, our friendship remained strong. Rusiko was a creative, resourceful, and brilliant scientist, and she had a big heart. Science will never forget her contributions and her friends will always remember the big personality, incredible generosity and passion of the woman behind the experiments that catalyzed a field an.

Conflict of interest

No conflicts of interest.

References

[1] T. Abel, P.V. Nguyen, M. Barad, T.A. Deuel, E.R. Kandel, R. Bourtchouladze, Genetic demonstration of a role for PKA in the late phase of LTP and in hippocampus-based long-term memory, Cell 88 (1997) 615–626.

[2] M. Barad, R. Bourtchouladze, D.G. Winder, H. Golan, E. Kandel, Rolipram, a type IV-specific phosphodiesterase inhibitor, facilitates the establishment of long-lasting long-term potentiation and improves memory [In Process Citation], Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 15020–15025.

[3] R. Bourtchouladze, T. Abel, N. Berman, R. Gordon, K. Lapidus, E.R. Kandel, Different training procedures recruit either one or two critical periods for contextual memory consolidation, each of which requires protein synthesis and PKA, Learn. Mem. 5 (1998) 365–374.

[4] R. Bourtchouladze, R. Lidge, R. Catapano, J. Stanley, S. Gossweiler, D. Romashko, R. Scott, T. Tully, A mouse model of Rubinstein-Taybi syndrome: defective long-term memory is ameliorated by inhibitors of phosphodiesterase 4, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 10518–10522.

[5] R. Bourtchuladze, B. Frenguelli, J. Blendy, D. Cioffi, G. Schutz, A.J. Silva, Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein, Cell 79 (1994) 59–68.

[6] R. Burchuladze, Neuroscience in the Republic of Georgia, Trends Neurosci. 14 (1991) 131–132.

[7] R. Burchuladze, J. Potter, S.P. Rose, Memory formation in the chick depends on membrane-bound protein kinase C, Brain Res. 535 (1990) 131–138.

[8] R. Burchuladze, S.P. Rose, Memory formation in day-old chicks requires NMDA but not non-NMDA glutamate receptors, Eur. J. Neurosci. 4 (1992) 533–538.

[9] R.A. Burchuladze, Analysis of the effect of increasing electrodermal stimulation on the somatovegetative reactions evoked by stimulation of the ventromedial hypothalamus, Biull. eksperimental noi biologii i meditsiny 96 (1983) 7–9.

[10] Y.Y. Huang, E.R. Kandel, L. Varshavsky, E.P. Brandon, M. Qi, R.L. Idzerda, G.S. McKnight, R. Bourtchouladze, A genetic test of the effects of mutations in PKA on mossy fiber LTP and its relation to spatial and contextual learning, Cell 83 (1995) 1211–1222.

[11] C. Pittenger, Y.Y. Huang, R.F. Paletzki, R. Bourtchouladze, H. Scanlin, S. Vronskaya, E.R. Kandel, Reversible inhibition of CREB/ATF transcription factors in region CA1 of the dorsal hippocampus disrupts hippocampus-dependent spatial memory, Neuron 34 (2002) 447–462.

[12] W.G. Quinn, W.A. Harris, S. Benzer, Conditioned behavior in *Drosophila melanogaster*, in: Proceedings of the National Academy of Sciences of the United States of America, 71, 1974, pp. 708–712.

[13] A.J. Silva, P.W. Frankland, Z. Marowitz, E. Friedman, G.S. Laszlo, D. Cioffi, T. Jacks, R. Bourtchuladze, A mouse model for the learning and memory deficits associated with neurofibromatosis type I, Nat. Genet. 15 (1997) 281–284.

[14] A.J. Silva, T.W. Rosahl, P.F. Chapman, Z. Marowitz, E. Friedman, P.W. Frankland, V. Cestari, D. Cioffi, T.C. Südhof, R. Bourtchuladze, Impaired learning in mice with abnormal short-lived plasticity, Curr. Biol. 6 (1996) 1509–1518.

[15] A.J. Silva, C.F. Stevens, S. Tonegawa, Y. Wang, Deficient hippocampal long-term potentiation in alpha-calcium-calmodulin kinase II mutant mice, Science 257 (1992) 201–206.

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