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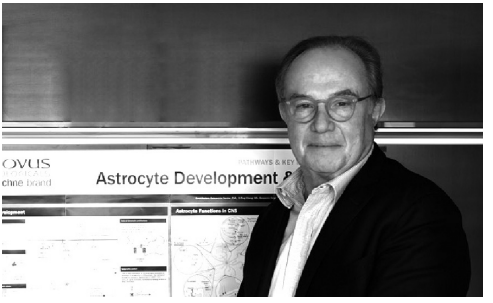
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Astrocyte Development

Pierre J. Magistretti

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Milano, Italy
September 30, 1952

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University of Geneva Medical School, Diploma (1977)
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Maître Assistant, Department of Pharmacology, University of Geneva (1982–1987)
Professor, Department of Physiology, University of Lausanne Medical School (1988–2004)
Chairman, Department of Physiology, University of Lausanne Medical School (2001–2004)
Director, Brain Mind Institute, EPFL (2008–2012), Co-Director (2005–2008)
Founding Director, Center for Psychiatric Neuroscience, University of Lausanne (2004–2012)
Director, National Center for Competence SynaPsy (2010–2016)
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President, Swiss Society for Neuroscience (1997–1999)
President, Federation of European Neuroscience Societies (FESN) (2002–2004)
President, International Brain Research Organization (IBRO) (2014–2019)
Member: Board of Trustees, Human Frontier Science Program (2003–2018)
Vice Chairman, European Dana Alliance for the Brain (EDAB) (2002–)
IPSEN Foundation Prize, Co-recipient with David Attwell and Marcus Raichle (2016)
Honorary member of the Chinese Association for Physiological Sciences (2014)
Camillo Golgi Medal Award, Golgi Foundation (2011)
Goethe Award for Psychoanalytic Scholarship, Canadian Psychological Association (2009)
International Chair Professor, Collège de France (2007–2008)
Emil Kraepelin Guest Professorship, Max Planck Institute für Psychiatrie (2002)
Member of the Swiss Academy of Medical Sciences, ad personam (2001)
Member of Academia Europaea (2001)

Pierre Magistretti has made important contributions to the study of brain energy metabolism and has pioneered the field of glia biology. His laboratory has discovered some of the cellular and molecular mechanisms that underlie the coupling between neuronal activity and energy consumption by revealing the key role that glial cells, in particular astrocytes, play in this physiological process. Pierre Magistretti has unraveled the role of lactate produced by astrocytes through the Astrocyte Neuron Lactate Shuttle not only as an energy substrate for neurons but also as a signaling molecule in the brain. These findings are particularly relevant for understanding the origin of the signals detected by functional brain imaging and have revealed the role of astrocytes and lactate in neuronal plasticity, memory and neuroprotection. Over the past decade, he has engaged in translational research in psychiatry focusing on the role of glia in psychiatric diseases.

Pierre J. Magistretti

I was surprised and honored to receive the request by Tom Albright and Larry Squire asking me to contribute a chapter for the Society for Neuroscience series *History of Neuroscience in Autobiography*. Over the preceding 20 years, I had made cursory readings of some of the chapters written by neuroscientists I knew. Two things had struck me: first, the personal side of the narrative and, second, the path to their original observations and successful careers, including the scientific aspects and also, and maybe more so, the personal choices and anecdotes that guided them. In fact, I am not certain that the term "guided" is the appropriate one: indeed, when one reads a biography, life events often appear to the reader as representing an orderly sequence of logical steps based on mostly rational decisions. Granted, an unexpected event may pepper here and there the narrative and be given appropriate importance in determining life's course, but the logical sequence stands strong. The evolutionary value of such mental process is obvious, in that our brains are geared to make predictions that guide decisions ensuring survival. This process, however, also may intrude when one looks back into one's past life. One tends to remember life events mostly as following a master plan, even when the unexpected occurred. A friend psychoanalyst with a great sense of humor once told me that psychoanalysts tend to be great specialists in making predictions of the past! It is the challenge of the narrator to capture the unpredictability of life and the infinite opportunities that it had offered in the course of one's existence.

Early Years in Milano

I was born in Milano, Italy, on September 30, 1952, to two young doctors: Massimiliano, known as Max, Magistretti and Carla Giuliana, known as Liana, née Bolis. They had met during medical school in Milano, my mother Liana being one of five women out of a class of 80 or so. Things have fortunately changed since then. My father Max was the second son of a successful architect, Pier Giulio Magistretti, who had designed among other important buildings in Milano, the Arengario,[1] an edifice tainted by the grandiosity of the architectural style current in Italy in the 1920s and 1930s, which sits next to the Duomo, the magnificent Gothic cathedral. It hosts now a very interesting museum featuring Italian art of the 20th century. I remember the outings with my grandmother from my mother's side, Francine, and one of her daughters who lived with her, my beloved Aunt Giovanna, to

[1]Pier Giulio Magistretti, https://it.wikipedia.org/wiki/Pier_Giulio_Magistretti.

the Duomo square to feed the pigeons and the inevitable comments, mostly negative, they made about Pier Giulio's building. This obviously biased for a long time my appreciation of the building, but I now find it nice and harmoniously fitting the large Duomo square. One should appreciate the challenge that my grandfather faced: to design a building that could sit next to a cathedral built five centuries earlier.

My father had an older brother, Vico, who followed his father's path, becoming one of the great Italian architects and designers of the 20th century (Pasca, 1991; Irace and Pasca, 1999). He was one of the founding fathers of the cultural movement that was born in Milano after World War II and made the city one of the capitals of design. Several of his pieces are displayed in design museums, including the MOMA. He died in 2006. A street has been recently named after him in Milano and in 2020 a large retrospective takes place at the Triennale museum in Milano to celebrate his centennial. Still now, I am asked, mostly in Europe, if I am related to Vico Magistretti. This is fine with me, but I know that it was something that tended to bother my dad when he was asked. He had somehow suffered being in the shadow of his older brother during his short life. My father died at age 48 while on vacation in the Eolian Islands.

Vico and Max had a younger sister, Luisa, a child psychologist who married a surgeon, Sergio Pliteri, who specialized in abdominal surgery. When I was eight, he operated on me for an appendicitis. He published two books: one about his life experience as a surgeon and another on his specialty, exocrine pancreas surgery (Pliteri 2003; Pliteri and Sironi 2005).

My mother was from a larger family: she had five siblings born to Pietro Bolis, an engineer who specialized in the design and construction of hydroelectric power plants, and Françine, née Grassi, a housewife. My grandmother brought some French heritage, as she was born near Nice in the South of France close to the Italian border. I keep very fond memories of my grandmother Françine as I spent a good part of my childhood years, between three and nine, with her in her apartment in Milano or, during the summers, in Sospel a small village near Nice where she kept the house where she was born. My mother was very busy with her professional life, and she would drop me with grandma Françine for entire days; sometimes I even stayed for sleepovers. Her love and attention for me have been a priceless gift: she told me stories of her family and she taught me geography, which I loved. We would spend time in the kitchen watching the maid cook, as I was eager to learn and "help." I still love cooking, an activity that I think is akin to biochemistry, which eventually became my trade. I think I owe much to the unlimited love that my grandmother gave me, including the strength and serenity that helped me go through some difficult periods in my life. Two of my mother's sisters married Frenchmen and lived in France. The summers in Sospel gave me the opportunity to see my French cousins and to become fluent in French.

Soon after I was born, my parents moved to a small village in the Alps, North of Milano, known as Sondalo, where my father was hired as a resident in a sanatorium. This type of hospital, which is usually located in sunny places where the air is pristine, had become popular for the management of patients with tuberculosis, before the advent of antibiotics. In fact, my father had spent several months during medical school as a patient in that very sanatorium. My mother worked there in the laboratory medicine unit running blood tests of the patients. I have no recollection of the year I spent there: my mother later told me that it had been the happiest year in her married life.

After one year as a resident, my father became interested in cardiology and obtained a fellowship to enroll in a program at the University of Brussels. My mother adjusted to this novel situation and managed to obtain another fellowship, in the Department of Physiology in the same university. Her research project was about the emerging field of transport of ions and solutes across cell membranes, in particular red blood cells, a topic that she would pursue over the next 50 years.

In the fall of 1955, we came back to Milano where my father joined the Department of Cardiology as a senior clinical fellow with the intent to pursue an academic career. He was in fact following one of the family traditions, clinical medicine (the other one being architecture) that dated back to the 18th century. Indeed, the Magistretti emigrated to Milano from Torricella, a small village near Lugano in the Italian-speaking part of Switzerland, in the mid-1700s (Locatelli, 2012). Over the following 200 years, several Magistretti engaged in the medical profession. The most prominent physician of my family was probably Pietro Magistretti (Figure 1), who enrolled in 1786 in the faculty of medicine at the University of Pavia. He was trained by the then-famous surgeon Antonio Scarpa, who found talent in the young Magistretti and sent him in 1790 to Vienna, for further training in ophthalmology with Joseph Barth (Giulietti, 2008). Pietro Magistretti had a distinguished career as a professor of anatomy and an ophthalmologist in Milano during the 19th century, his claim for fame being to have successfully operated, in 1811, on the eye of the prominent Italian literate, Ugo Foscolo (Giulietti, 2008). A small street is named after Pietro Magistretti in Milano.

While my father was pursuing his academic career, which however did not bring great revenues, my mother took a well-remunerated job as scientific director of a small pharmaceutical company in Milano that belonged to the father of one of her childhood friends. Her job ensured a good financial situation that even improved the following year. We then moved from the small apartment we had been renting upon our return from Brussels into a nice and large apartment that my father inherited. The apartment was located in a building in the center of Milano, Via Conservatorio 20, that grandfather Pier Giulio had designed. The whole Magistretti "clan" lived there: Uncle Vico and Aunt Luisa with their family, grandmother Cina

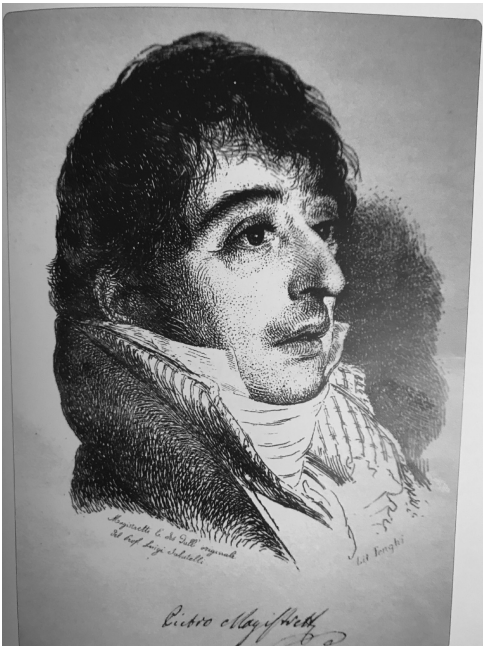

Fig. 1. Portrait of Pietro Magistretti, Professor of Anatomy and distinguished ophthalmologist. Circa 1810, by Luigi Sabatelli.

(her husband Pier Giulio had died at the end of the war) and now Max with his family, which had welcomed a new arrival: Filippo, born in July 1956. Other apartments had been sold or rented to a few tenants. The offices of my grandfather's firm were now occupied by Vico. Since the demise of Vico in 2006, the offices are now home to a foundation, where the works of Vico are on display.[2]

The building faced a square surrounded on the other three sides by the baroque church Santa Maria della Passione, the Verdi music conservatory, and Palazzo Archinto, a 19th-century building, home of a private school for girls, which had been designed by my great-great grandfather, the architect Gaetano Besia. I would spend long afternoons playing football (soccer) with my older cousin Stefano and friends in the square facing our building and the church, to the great displeasure of the priests. I remember as a torture being called in from the balcony of my apartment to stop immediately playing football and run home for my piano lesson.

I soon joined a public primary school nearby, Scuola Corridoni: we had to wear a black overall with a white collar and a large blue tuft, an outfit I found quite unaesthetic. I was a disciplined pupil pleasing my teachers and

[2]Fondzaione Vico Magistretti, V1CO: 1920/2020 Magistretti [digital archive], http://www.vicomagistretti.it/en/.

parents and receiving good marks. When I reached fourth grade in 1961, Italy celebrated the centennial of its reunification. Until 1861, several independent states had occupied the Italian Peninsula, not the least the Vatican State in the center. Giuseppe Garibaldi conquered Sicily and the Southern part of Italy and handed them to King Victor Emmanuel II of Savoy, who eventually became the first King of Italy. Thus, 1961 was a year of patriotic enthusiasm: we learned the names of all the battles and heroes that contributed to the reunification. Now, almost six decades after I left Italy, I still feel deep inside myself a patriotic fiber, in particular when the Italian football team wins a match.

Life continued uneventfully until 1963. A quiet and protected life of a boy from the Milanese bourgeoise: first Communion after several months of instruction by the priests of Santa Maria della Passione, frequent weekend outings with my parents to Lake Como and Lake Maggiore, skiing in Courmayeur during winter, football matches at San Siro stadium with my father to watch Inter—the favored team of the Magistretti—summers at my grandmother's place in Sospel. In August 1963, I received a call from my mother while my brother and I were staying with one of our French aunts. I will never forget that conversation: it meant the end of the world, at least of my world. My mother announced to me that our parents were getting separated and that we would be sent to a boarding school in the Swiss Alps. She said that it would be best for us to be removed from the turmoil of the new family situation. I was asked to explain this to my younger brother. I had noticed during the preceding months that my mother looked sad, occasionally I caught her crying; my father was less present, and I had registered some hints that our lifestyle might change for the upcoming new school year, but I couldn't see the catastrophe that was to come.

The Unexpected Move to Switzerland

On September 19, 1963, we arrived in Crans-Montana, a tourist resort in the French speaking region of Switzerland, which was rather popular with Milanese families since by train it was only a few hours away from the city. My mother accompanied us with the intent to spend a couple of months to recover from what was most likely a breakdown. A great aunt from my father's side joined for a week to help us settle. We arrived on a Thursday: Monday morning I was sitting in a fifth-grade classroom, with people I had never met who spoke only French. Actually I had no problem to communicate with them, but I was completely incompetent in writing as, unlike Italian, written French is not phonetic and its orthography rules are rather challenging. For my first dictation, I made almost as many errors as there were words. My mother had insisted that I join secondary school, as I had completed my elementary studies in Milano. The director of the school argued that the change in language and culture would be challenging enough and that secondary school would be above my competencies. Despite

my weaknesses in writing, it soon became clear that my level of knowledge was above that of my classmates and that I should join the first year of secondary school. There, I definitely found many challenges, as it was my first exposure to several branches of knowledge: Latin, German, English, algebra, French literature (all taught in French, of course). My father had insisted that we attended a public school, as he considered that international private boarding schools were academically insufficient. So, once my mother left in early January 1964, my brother and I were placed in a boarding school for food and lodging, but were attending the local public school.

The first few months were destabilizing. While academically I caught up relatively quickly, I missed my family life; the cultural and social environment presented new challenges every day, with the local classmates and teachers on one side and the international crowd of the boarding school on the other. I had to constantly adapt: fortunately, I had my brother Philippe, as he was now being called, the only reference point I had from my previous life. The bond we created helped us go through these difficult times and still persists strongly today. Like my brother, I also converted my Italian first name, Pier Giulio (my grandfather's name), into its French and shorter version, Pierre. We felt that by changing our names, we were helping our integration. My classmates were mostly born in 1949 or 1950: two to three years at that age make a big difference. The boys were strong, most of them sports oriented and not particularly motivated academically; the girls were naturally more mature and were proficient. I was struggling physically, in fact once while playing rough, two of my buddies threw me into a ravine breaking my leg. Discipline was strictly enforced by the teachers: being grounded for peccadilloes was the rule; physical punishments (hands hit with a wooden stick) were not rare. Quite a change from my pampered life in Milano! My safe place was learning: I was performing well in school, had good marks, and was able to achieve some sort of consideration from my classmates. By the third year in secondary school, I had physically grown and was able to follow down the ski slopes the "big guys" in the class.

Despite what had undoubtedly been a hardship, I am very fond of those years in Crans-Montana. It was a life-changing experience that influenced the ways I have approached new situations later in life. I learned to adapt, to understand other cultural backgrounds, and to organize my work to achieve a goal, and probably most of all, it has given me an assurance that with persistence one finds light at the end of a tunnel. Fifty-six years since I first landed in Crans-Montana, I still regularly spend time there, where we have an apartment. I am friends with many former classmates who now work in or own hotels, restaurants, bakeries, sports stores, real estate companies, or garages. Crans-Montana brought me another gift that has had some importance in my life: golf. Indeed, Crans-Montana is the site a magnificent 27-hole course where the Swiss Open has been played since the 1930s. Over the past decade, the Swiss Open has become the European Masters,

at which world class professionals compete. Golf and Crans-Montana are synonymous: every local plays or is somehow involved in golf. It is a small Scottish oasis in the middle of the Alps. I started playing golf just before the first snowflakes began to fall in the winter of 1963. Over the years, I became quite good, reaching a handicap of one and eventually playing for the Swiss National team during the better part of the 1970s.

Upon her return to Milano in January 1964, after the convalescence period in Crans-Montana, my mother decided to try an academic career. Not an easy decision for a forty-year-old woman. She reconnected with colleagues in the Department of Pharmacology at the University of Milano, where she had done some internships during medical school and managed to obtain a part-time fellowship to work on transport properties of red blood cell membranes. She also kept some consultancies in the pharmaceutical industry. These activities kept her quite busy, while she was also trying to rebuild a personal life. We would not see her much during those years, nor our father for that matter.

The Roman Experience

In 1966, my mother obtained the equivalent of an assistant professorship at the University of Rome, in the Department of General Physiology. The decision was made for us to join her in Rome and enroll in school there. My father was a bit hesitant about us living in the capital. As a man from the North of Italy he was wary about the Roman lifestyle: he felt that the Roman "Dolce vita" would not be conducive for serious academic studies. We moved into a small apartment in a calm residential area near Villa Borghese, with a nice garden and many trees around the building. Now back to Italian, I enrolled in a curriculum of classical studies with the main emphasis on Latin, ancient Greek, philosophy, history, and Italian literature. French was my foreign language (I got a break there); science teaching was on the light side. I realize now what a privilege it was to study classics in Rome: the heritage of the ancient Romans is before one's eyes. You read a speech by Cicero one day and you can visit the next day where he pronounced it two millennia earlier. But thanks to an exceptional teacher, my passion soon became studying ancient Greek literature. I was in particular, fascinated by the ancient Greek lyric poets. They were active between 600 and 300 B.C. and described the depth of human emotions so vividly, in a timeless manner that makes them very contemporary. Here is a poem about love, written more than 2,500 years ago by the lyric poet Sappho (D'Angour, 2013):

> *He seems to me, that man, almost a god—*
> *the man, who is face to face with you,*
> *sitting close enough to you to hear*

your sweet whispering
And your laughter, glistening, which
the heart in my breast beats for.
For when on you I glance, I do not,
not one sound, emit.
But my tongue snaps, lightly
runs beneath my flesh a flame,
and from my eyes no light, and rumbling
comes into my ears,
And my skin grows damp, and trembling
all over racks me, and greener than the grass
am I, and one step short of dying
I seem to myself.

The fact that those poems and other productions of ancient Greek literature were placing human sentiments at center stage in ways that were still moving readers in the 20th century gave me the first hint that there may be some sort of universality of emotions and feelings that transcended cultures, times, and geographic locations. This intuition was reinforced by readings that were rather *en vogue* at the time, including those of structuralists such as Claude Lévi-Strauss and Roland Barthes, which emphasized the existence of constant laws of abstract structure for how humans perceive, analyze, and organize systems, such as natural and social environments, as well as how they develop systems like language. My possibly naïve and certainly simplistic take from these readings was that there must be a biological basis for these mental processes and that to understand the human mind, I should study the brain. Several years later, I was telling my brother that this was how I thought I decided to become a neuroscientist. He argued instead, with his dry sense of humor, that I chose this path because I realized that our parents were emotionally unstable and I decided to try and understand them by studying the organ of behavior.

The late 1960s were years of social unrest in Europe, sparked by the student revolts of May 1968 in Paris. Rome, like many other cities, followed: our school was regularly occupied by the students. We would debate for hours about political issues, challenging the capitalistic and patriarchal organization of society, down to what was thought to by its most dysfunctional unit: the family. These were intellectually stimulating times, but clearly quite disruptive for the academic curriculum. Likewise, universities were often closed because of violent confrontations between the students and police. I had two years left before graduating from high school and entering university. (In Europe, the high school curriculum is eight years, the last two being equivalent to the first two years of college in the United States.) It was pretty clear that studying in Italy during the next couple of years would be disrupted. I was torn between the attraction that I had for the political

and social issues that were debated, and my determination to move ahead with my studies. I was hesitating between psychology, biology, and at some point even architecture with the idealistic view to build cities for a more just society. My parents were telling me, as they later told my brother: "study medicine, then you can chose what you really want." By default, I eventually decided that I would enroll in medical school. Given the unstable situation in Italian universities, I thought that returning to Switzerland was the way to go. The problem, however, was that one needed a Swiss high school diploma to enroll in a Swiss medical school.

The solution was to take, as a private student, an exam called Maturité Fédérale, which is administered twice a year in select academic venues in one of the three linguistic regions of Switzerland. I checked the requirements for the exam in the Italian-speaking Ticino region. I concluded that, in view of the strong training I had received in Rome in classics, the relative ease with which I was handling the scientific subjects, and the fact that French would be my foreign language, I should have no problem passing that exam when I graduated from high school two years later. As I was thinking about this solution, I considered that spending two more years in Rome while being subjected to a bumpy academic curriculum was a loss of time. I could take the Swiss Maturité Fédérale exam within a year! I would retire from school, study alone at home, and take the exam the next summer session. Looking back on this decision now seems to me completely crazy. I was taking a monumental risk for an uncertain future. My father thought that it was a good idea; he had done the same thing during the war.

I moved back to Crans-Montana in September 1969, as I thought it would be impossible to focus on my studies in Rome. I prepared a weekly plan of work for the ten or so branches of knowledge on which I would be examined nine months later. That program required on my part a very strong discipline: I had received from the examination authority the textbooks that I should complete, and was moving along one chapter after the other, week after week. I arranged some tutoring in math, because this was, and still is, a weak point. I think that being back in Crans-Montana where I had studied a few years earlier in a disciplinarian school somehow put me in the right frame of mind for the challenge I had put on myself. Fortunately, during those months, I was living with a very nice and warm family, the Rey-Barras. Angèle, the mother, ran a small, family-style boarding school. She radiated an incredible positive energy that I found very reassuring. I became very attached to her, and in fact I consider her as my second mother. In July 1970, I successfully passed the Maturité Fédérale exam in Locarno, Ticino; I had my passport to the University of Geneva Medical School, where I had decided to enroll. Three years later, my brother Philippe followed exactly the same path.

Medical School in Geneva

Those months of self-imposed hardship spent preparing for the Maturité Fédérale exam took a toll on me. I had some bouts of anxiety and felt emotionally and physically drained. My reaction to this condition was, I think, a healthy one: I played a lot of golf. My handicap went down dramatically, reaching two by the end of the summer. The lazy mood persisted through the fall of 1970: I was spending time in Rome catching up with my friends and hardly went to class in Geneva. Early December, I eventually moved to Geneva into a small studio in the Old Town. My main motivation had been that Geneva was close to Crans-Montana, and it would be easier to spend the Christmas vacation there, where a French girl I had met during the summer, and of whom I was fond, would be. During the second part of the academic year, I was more assiduous in attending lectures and labs. The program mostly consisted of physics, chemistry, and biology, all branches I had no major problem with. I passed the whole series of propedeutical exams, as they are called, and was ready to enter the second year when the "real stuff" would start: anatomy, histology, physiology, and biochemistry.

Biochemistry and physiology of the nervous system were my favorite subjects: I remember the excitement at the beginning of lectures, realizing that by the end of that day, I would know something new about those two topics. As the end of the second academic year was approaching, I arranged to spend the summer of 1972 at Duke University. I had a connection there, Daniel Tosteson, the chair of the Department of Physiology. My mother knew him through their common research interest in red blood cell membrane transport. A few years later, he became dean of Harvard Medical School, where he pioneered problem-based learning in the teaching curriculum. Dan was in fact much more than a professional acquaintance of my mother: he had become a close family friend and was very attentive to the academic and personal development of myself and my brother. He accepted very positively my request of spending a summer internship in his department. I learned there some theoretical biophysics of ionic transport and did experiments on transport across artificial membranes and red blood cells, some of which were carried out at the Marine Station in Beaufort, where Duke University had a laboratory. Most important, my summer internship at Duke represented a full immersion into the "American way of life," including the culture and social life of a university campus. I also realized how political bipartisanism could exist in the same country or state, a consideration that is particularly relevant to today's political landscape. For example, during the 1972 U.S. presidential race between McGovern and Nixon, the progressive, antiwar, and socially driven platform of the South Dakota senator was largely supported by the students and the academic personnel. Yet, when I left Duke's campus and drove from Durham to Beaufort, I could

read on a billboard on the side of the state highway a welcome message from the local Ku Klux Klan.

Thanks to my mother, Dan Tosteson was not the only prominent scientist whom I had the privilege to become acquainted with over the years. Soon after she started her appointment at the University of Rome, she set out to organize what she called "The international conference on biological membranes." The field was burgeoning; she had a knack for convincing leaders in the field to attend and she established an atmosphere of camaraderie among them. Her biennial conferences took place in beautiful spots in Italy, and became a sort of salon, where high-quality science was presented and discussed in a relaxed atmosphere, with excellent Italian meals between the sessions. The proceedings of the conferences were published shortly after (e.g., see Karnovsky and Bolis, 1982). Attendance was limited to at most 40 participants. This is how I got to know Joseph Hoffmann, like Tosteson, a leader in red blood cell physiology; David Robertson, a pioneer of electron microscopy who developed the concept of the "unit membrane"; Richard Keynes, a major figure of the distinguished school of electrophysiology at Cambridge; and the Nobel Laureates Carl Cori, Feodor Lynen, Konrad Bloch, Carleton Gajdusek, Julius Axelrod, and Torsten Wiesel. I still have regular email exchanges with Torsten, and my wife and I occasionally have dinner with Torsten and his wife Mu. Over the years, I have often relied on Torsten's wisdom for advice and guidance.

During my third year of medical school I enrolled in a new optional lab course called "Introduction to Medical Research" given by a recently appointed professor at the University of Geneva Medical School, Bernard Jeanrenaud, who was developing research projects in what we would call today "translational endocrinology." His focus was on diabetes and his course was mostly hands on. The first experiment I did was to measure the activity of glycolytic enzymes in adipose tissue. Looking back to that year I spent working after hours and on weekends in his lab, I realize that in an amusing turn of fate (is it really fate?), the identification of glycolysis in astrocytes, as a main mechanism of metabolic cooperation between neurons and glial cells, has been one of the main research lines in my lab since the early 1980s.

Moving into the clinical years of medical school, my attraction for the study of the nervous system became even stronger, as I was following the lectures and bedside tutorials in neurology and psychiatry. As part of the required clinical internships, I spent several months in these two clinical services.

During the first months of 1977, with my colleagues, I was taking almost fortnightly an exam in clinical medicine branches, as part of what was called "Examen Final." One week dermatology, two weeks later ophthalmology, followed by neurology, and so on for five months. This was a sort of marathon during which you review a given specialty, forget everything the moment you

took the exam and switch to the next review. Prior to starting the Examen Final, I had arranged a position in the Department of Pharmacology at the University of Geneva Medical School, to work upon graduation with a junior faculty who had recently joined the department, Michel Schorderet. He had completed postdoctoral training in Paul Greengard's lab at Yale, contributing to the demonstration that synaptic transmission in the superior cervical ganglion is associated with increases in cyclic adenosine 3′,5′-monophosphate (cAMP) in postsynaptic neurons (McAfee et al., 1971). As he did for the other few students who had enrolled in his course, Bernard Jeanrenaud facilitated my acceptance into a lab that would take medical graduates for experimental thesis work.

The Examen Final was successfully passed and I was ready, and very excited, to work in the lab for real. In fact, I had enjoyed working in the clinical services: I liked the contact with patients in all disciplines where I did an internship, with a fascination for obstetrics, since to see the birth of a new life, as I would experience much more intensely later for my children, is a unique, very strong, and moving experience. But since my interest was in the brain and in reconnecting with my early considerations about the mind and emotions, my clinical choice was definitely psychiatry. Yet, to use a sweeping formula, I thought that before becoming a psychiatrist, I should understand how the brain worked. Neuropharmacology, the kind of work I could do with Michel Schorderet, seemed like a good start.

Since his arrival in Geneva, Michel had moved from the rat superior cervical ganglion to the rabbit retina as a model for neurotransmission. Building upon the work of John Kebabian in Greengard's lab, which revealed the existence of dopamine-stimulated cAMP formation in the caudate nucleus (Kebabian et al., 1972), and upon the discovery that dopamine was present in amacrine cells of the retina (for review, see Djamgoz and Wagner, 1992), Schorderet had just published an article showing dopamine-stimulated cAMP formation in the rabbit retina (Bucher and Schorderet, 1975). Greengard and his associates had just proposed that antipsychotics such as haloperidol were acting as antagonists at putative dopamine receptors coupled with the formation of cAMP in nervous tissue (Clement-Cormier et al., 1974). This connection with psychiatry immediately caught my attention. As I was digging into the literature on neurotransmission and signaling in the nervous system, I realized that novel neurochemical techniques were being developed to identify and characterize neurotransmitter receptors, using radiolabeled ligands. The name of one neuropharmacologist was standing out in the field, as far as I could judge: Solomon Snyder from Johns Hopkins. Using ligand-binding assays, his lab was publishing, almost weekly, the characterization and distribution of a given receptor (Enna et al., 1977), including the dopamine receptor (Burt et al., 1975). With Michel Schorderet, we decided that characterizing dopamine receptors (DR) in the retina would be a good project for me to start. These receptors had not

been identified yet in the retina and the ligand-binding study also could contribute to the characterization of their pharmacological properties, as the evidence was emerging for the existence of two types of DR, DR1 and DR2, with the former thought to be positively coupled to cAMP formation (Garau et al., 1978).

After a few months, it became clear that rabbit retinas would not provide sufficient tissues to carry out the project. I was also struggling with highly nonspecific binding. Michel arranged a visit to the lab of a colleague who had set up the technique at Sandoz in Basel. The protocol that was used helped me clarify some of the methodological steps that could explain my lack of success, and the decision was made to use the much larger bovine retina. So, here I was, showing up early in the morning at the local slaughterhouse to collect eye bulbs of cows immediately after they had been put to death. The general ambiance was rather rough and exchanges were direct. One morning I arrived late: the first batch of animals had been slaughtered. One of the workers told me that I could grab some eye bulbs that had been thrown into a large bucket. I told him that I needed them when they were still warm and that I would wait for the next batch to be processed. As the first pair of eye bulbs was cut off from the head, I placed them into a Styrofoam box filled with ice. Several workers looked at me with surprise; one of them shouted "Hey young man, make up your mind: you just said that you wanted them warm, and the first thing you do, you put them on ice!" There was a big laugh. I felt quite embarrassed, made a big smile, and left without trying to explain my awkward behavior. Finally, after several months, experiments were starting to work. I could establish kinetic curves from the binding data and quantitatively determine the properties of the DRs using a variety of analytical tools, and I presented posters at a couple of local meetings.

On a personal level, I was going through a difficult time, a time of great doubts. First, my relationship with my wife Anna was falling apart. She was from a well-to-do family in Milano. We had met in Crans-Montana early during my studies at the medical school in Geneva, while she was finishing high school in Milano. We found the long-distance relationship unsatisfactory and decided that she would come to the Geneva to study sociology at the university. Given the social and cultural background in which we lived, it was unimaginable for two young people to live together without being married, which we did, obviously at a much too young age. After three years, we divorced in an amiable way. We had no children. Despite the nonconflictual nature of our separation, I was left with a feeling of failure. I also started to have doubts about my professional choice: what was I doing early in the morning in a slaughterhouse to collect bovine eye bulbs while my classmates were doing something useful like relieving the suffering of patients? I was also having doubts about the direction my research project was taking me: as much as I liked working with Michel, after a while, I was finding the receptor-binding experiments rather tedious and not intellectually

challenging. Where was the biological question? Would this project help me understand how the brain worked? I felt so far from the exciting questions about the mind that had driven me where I was now.

Some difficult months during the spring of 1978 went by until I read an article published in *Science* two years earlier entitled "Endorphins: Profound behavioral effects in rats suggest new etiological factors in mental illness." The first author was a scientist named Floyd E. Bloom from the Salk Institute in La Jolla, California (Bloom et al., 1976). I felt an incredible sense of relief and excitation at the same time. There, before my eyes, was the evidence that a chemical recently discovered in the brain could affect behavior and be related to a mental illness. There was an answer to my doubts; there was the lab that I wanted to be part of and the scientist with whom I wanted to work. The next day I wrote him a letter (no emails at the time) with my meager curriculum vitae that featured, in terms of publications, a couple of abstracts and an article in preparation. I received Floyd's reply a couple of weeks later indicating that he would soon be in Milano for a conference and that we could meet there. I still am a very good sleeper, but the night before I met Floyd was sleepless. I was anxious and excited. We met in the cafeteria of the congress center: I was immediately struck by Floyd's energy, quick mind, and charm. My English was average, yet sufficient to explain my previous work and my motivations. I could sense his impatience at my laborious discourse, but he listened very gently, smiling often. Floyd mentioned that he was aware of the work that Schorderet had done in Greengard's lab, asked me if I was familiar with cAMP determinations, and did not seem particularly interested in receptor-binding experiments. He told me that we should reconnect a month later in Paris where he would be attending the International Union of Pharmacology meeting, and he would let me know at that time if he had positions available for the fall 1979. Our initial meeting in Milano lasted 15 minutes, but it felt much longer to me. In Paris, in a two-minute exchange, Floyd confirmed that I could join his lab. I hardly realized what he said and was left with the impression that the exchange might have been a fantasy. Shortly after I received a confirmation letter from Floyd, I applied for a fellowship from the Swiss National Science Foundation. Within a few months, I was awarded the fellowship. I had submitted the main findings on DRs in the retina (Magistretti and Schorderet, 1979) and presented my medical doctorate thesis to the University of Geneva Medical School. Such medical theses are in no way comparable to a doctoral thesis and, in fact, have been suppressed since. I wished I could have enrolled in a neuroscience graduate program, as I realized that the neuroscience education I had received during medical school was rather superficial. But there were no such programs in Switzerland. I mentioned this wish to Floyd, and he suggested that I explore possibilities at the University of California, San Diego (UCSD) campus once I was in San Diego.

On the personal level, things also looked on the bright side. In February 1979, I met a lovely girl, Christine, full of energy and with a great positive attitude toward life. She was finishing nursing school and was planning to continue her studies in the United States. Luckily, she eventually joined me in San Diego and enrolled in a bachelor program in psychology at Muir College at UCSD. In the meantime, I had been accepted in the biology graduate program in the same university. We both received some credits for our previous education in Switzerland and graduated with our respective degrees within three years.

The Salk Institute Years

I joined Floyd's lab at the Salk in September 1979. The A.V. Davis Center for Behavioral Neurobiology, as the lab was named, was remarkable for the variety of experimental approaches that it comprised, electrophysiology, neuroanatomy, immunocytochemistry, electron microscopy, neurochemistry, and behavior, each component being overseen by a senior scientist. It was in fact a small neuroscience department. My direct supervisor was William (Bill) Shoemaker—a fine neurochemist trained at MIT in the lab of Richard Wurtman—who, like some of the other staff scientists, had followed Floyd to La Jolla from the Bloom lab in St. Elizabeth's hospital at the National Institute of Mental Health. The lab atmosphere was very open, reflecting Floyd's personality, with considerable exchanges and collaborations among its members. The role of noradrenaline (NA) as a neurotransmitter in the brain was still a strong research theme developed by several units of the lab, following up on the seminal observations made by Floyd and his associates at St. Elizabeth's, George (Bob) Siggins and Barry Hoffer (Hoffer et al., 1971; Siggins et al., 1971). Despite the strong evidence of a neurotransmitter role for NA, based notably on iontophoresis studies showing that the application of NA affected the excitability of the Purkinje cells of the cerebellum (Siggins et al., 1971), it remained unclear which were the behavioral instances during which NA-containing locus coeruleus neurons would fire. Contrasting with the view from the Bloom lab that NA was a synaptically released neurotransmitter in its own right, Alain Beaudet and Laurent Descarries, two Canadian neuroscientists, suggested that NA was only marginally released at synapses but mostly from varicosities along noradrenergic axons, a modality of release that was questioning the nature of NA as a classical neurotransmitter. Their conclusions were based on the visualization by electron microscopy autoradiography of radioactively labeled NA in the cerebral cortex (Beaudet and Descarries, 1978). In Floyd's lab, Steve Foote and Gary Aston-Jones were recording *in vivo* from the locus coeruleus of squirrel monkeys and rats. They showed that in awake behaviorally responsive animals, these neurons responded to non-noxious sensory stimuli from any modality, decreased their activity when animals were

inattentive, and eventually became silent during rapid-eye movement sleep (Foote et al., 1980, 1983). These observations were taken as reinforcing the view that NA acted as a neurotransmitter in the brain.

The other main line of research in Floyd's lab was the localization and function of newly discovered neuropeptides, such as somatostatin, opioid peptides, vasoactive intestinal peptide (VIP), neuropeptide Y, cholecystokinin, and corticotropin-releasing factor, as putative brain neurotransmitters. The lab next door was Roger Guillemin's, who recently had shared the Nobel Prize with Andrew Schally for the discovery of hypothalamic-releasing factors. Guillemin's lab, as well as that of Wylie Vale who had been Guillemin's student before starting his own lab at the Salk, were providing peptides and their antibodies to Floyd and his associates to study their localization by immunocytochemistry and their actions on neuronal excitability. Although the immunocytochemical studies significantly contributed to mapping the field of several peptides' cellular localization in extrahypothalamic areas of the brain (Chavkin et al., 1983; Morrison et al., 1983), the actions of the newly discovered peptides on neuronal excitability produced pleiotropic results, with few exceptions, such as for example for opioid peptides and somatostatin (Siggins et al., 1986; Pittman and Siggins, 1981). The scientific focus of Floyd's lab being the role of NA and peptides, it is not surprising that the projects that I eventually developed in his lab would be concerned with the interactions between NA and a particular peptide, VIP.

Floyd's lab had just been awarded a large grant to study the mode of action of lithium as a mood stabilizer in bipolar disorder, with a focus on noradrenergic transmission (Bloom, 2012). Floyd was looking for an assay to probe noradrenergic signaling after chronic lithium administration, that would be more sensitive than those available in the lab, which were responses to iontophoretically applied NA in hippocampal or cerebellar neurons, noradrenergic receptor sensitivity tested by ligand-binding assays, and the formation of the downstream second-messenger cAMP. None of these assays had provided any evidence for changes in noradrenergic signaling efficiency. Shortly after I joined the lab, Floyd visited the lab of Jean-Charles Schwartz in Paris where he became interested in an original assay for noradrenergic signaling in the central nervous system: NA-evoked glycogenolysis (Quach et al., 1978). What had caught Floyd's attention was the sensitivity of the assay, which revealed an EC50 (the concentration of NA necessary to elicit 50% of the maximal effect) of NA that was 10 to 50 times lower than that observed for cAMP generation. This phenomenon had been described for the glycogenolytic effect of adrenaline acting at beta-adrenergic receptors in liver and muscle and was thought to result from the amplification of the signal at each step of the signaling cascade, from the receptor to cAMP formation, to phosphorylation of enzymes for glycogen metabolism, and eventually to glycogenolysis. Earl Sutherland had been awarded

the 1971 Nobel Prize for the elucidation of this signaling cascade (Rall and Sutherland, 1958; Sutherland and Robinson, 1966).

The higher sensitivity of NA-evoked glycogenolysis suggested to Floyd that this assay could be useful to reveal a potential change in noradrenergic transmission in the brain of animals chronically treated with lithium. Upon his return, Floyd asked me to set up this assay, which looked relatively simple. It consisted of preparing, with a McIlwain tissue chopper, 350 um slices of the neocortex and incubating them in a standard Krebs-Ringer bicarbonate buffer in the presence of tritiated glucose. The energy crisis elicited by the decapitation-induced anoxia and the subsequent dissection of the neocortex, completely degrades endogenous glycogen stores. Consequently, incubation of the slices with tritiated glucose results in the resynthesis of tritiated glycogen with high specific activity. A steady state between synthesis and degradation usually is reached within 30 minutes at which point molecules can be applied to test their potential glycogenolytic effect. After inactivating the tissue by sonication followed by microcentrifugation, the supernatant is pipetted onto filters and tritiated glucose and glycogen are separated by ethanol precipitation, since glycogen precipitates on the filter while glucose is solubilized in ethanol. Filters containing the precipitated tritiated glycogen are then placed into vials and radioactivity determined by liquid scintillation (Quach et al., 1978). The assay turned out to be more difficult than it looked, possibly also because of my limited lab experience. Week after week I would do experiments with limited and inconsistent results. I became quite frustrated and felt awful because I knew I was disappointing Floyd who had so graciously accepted me in his lab.

My dismay became even greater one day, when Steve Foote, who was obviously strongly biased toward *in vivo* experiments, passed by while I was preparing slices and said with his baritone voice and sharp sense of humor: "Pierre do you really think that you will understand how the brain works by chopping it up like you do?" I didn't know what to say: maybe Steve was right; and while I admired Steve's intellectual depth, I trusted Floyd's acumen and intuition and kept working on the assay. Eventually, some encouraging results were coming, but not reproducible enough to apply them to test on a large-scale *ex vivo* experiment like the one Floyd had in mind. Floyd was being patient and empathic: as I told him that I was returning back to Switzerland for a short break in June, nine months after my arrival in San Diego, he suggested that I visit Jean-Charles Schwartz's lab in Paris to perform the assay there. Tham Quack, the postdoctoral fellow who had set up the assay in Schwartz's lab was very welcoming and helpful. Within a few days at the bench with him, I had identified the critical steps to improve the reproducibility and was able to implement it successfully in Floyd's lab.

The role of the newly discovered peptides was increasingly becoming a central question in Floyd's lab, and for that matter, for neuroscientists

around the world who were interested in chemical neurotransmission. For example, Harvey Karten a specialist of the visual system, who was visiting the lab from SUNY had come to the Salk to study the localization of peptides in the retina, mostly the avian retina. His hypothesis was that specific subtypes of retinal cells would contain a specific peptide. This sort of code for neurotransmission was not confirmed, neither in the retina nor in other parts of the nervous system. What turned out to be the case, as shown by Tomas Hökfelt at the Karolinska Institute in Stockholm, was the co-localization within the same neuron of a peptide and a "classical" neurotransmitter, for example, NA and somatostatin (Hökfelt, 1977; Hökfelt, 1991). In terms of physiology, many open questions remained concerning the actions of neuropeptides in the brain. Within less than five years, the vocabulary of neurotransmission had expanded from a handful of molecules, such the amino acids gamma amino butyric acid, glycine, and glutamate (paradoxically questions about the actual role of the latter as a neurotransmitter remained until the early 1980s), acetylcholine, and the monoamines NA, serotonin, and dopamine, to a plethora of peptides, approaching two to three dozen (Bloom, 1977)! The notion of neuromodulators emerged, meaning that some of these peptides were somehow adjusting the actions of the classical neurotransmitters (Bloom, 1977; Siggins et al., 1982). This was an issue often debated during "Startrek," the thought provoking weekly meetings of the lab. Francis Crick, who had recently joined the Salk Institute, was an active participant in these meetings, relentlessly chasing to the limit any hypothesis formulated about the role of neuropeptides. For all lab members, his was an intimidating yet stimulating presence.

Although I was quite satisfied that the glycogenolysis assay was working, the prospect of spending the next few months feeding lithium to dozens of rats to then probe their noradrenergic transmission seemed to me only moderately exciting compared with the challenge of revealing the role of neuropeptides in the brain. One day, as I was looking in the library for articles about neurotransmitter-evoked cAMP formation in neural tissues (no PubMed available at the time) I stepped on an article from Leslie Iversen's lab, one of the towering figures in neuropharmacology at the time and a good friend of Floyd, showing that VIP induced cAMP formation in homogenates of the cerebral cortex (Quik et al., 1978). This observation sparked the following reasoning in my mind: NA stimulated both cAMP formation and glycogenolysis in the cerebral cortex. Why shouldn't VIP do the same? This thought really excited me because, unlike cAMP formation, glycogenolysis served a physiological function, namely—by analogy with its role in liver and muscle—a mechanism to provide energy substrates. Possibly VIP would be glycogenolytic in the cortex. I decided to test this hypothesis with the assay that I had just implemented in the lab for NA. I admit that I was very optimistic: it seemed so logical. One day in November 1980, I came home and told Christine: "I just found out that VIP mobilizes energy stores in the

brain. I think that this is a really important observation because it means that within the brain there are neurons that exert a metabolic function rather than directly modulate neuronal excitability." Christine looked at me with her usual sweet and supporting smile and said, "Yes, I am sure that this is very important. Let's celebrate." We cooked "risotto alla Milanese" and opened a good bottle of red wine. I was euphoric.

I spent the next few days in the library to collect articles about glycogen metabolism in the brain. The literature search was scarce on this topic. I eventually found what is probably the first convincing demonstration of the presence of glycogen in the brain: a 1938 article in the *Journal of Biological Chemistry* by Kerr from the American University of Beirut (Kerr, 1938). More recent articles were from the lab of Oliver Lowry and Janet Passoneau from Washington University (Nelson et al., 1968) and some electron microscopy observations (Sotelo and Palay, 1968; Phelps, 1972). Two main features emerged from this search: (1) there is very little glycogen in the brain and (2) it is almost exclusively localized in a type of glial cell, the astrocyte, not in neurons! This came as a great surprise to me; I hardly knew what glial cells were, possibly a sort of inert connective tissue that kept neurons together. Had I known this information I probably would have never tested the glycogenolytic effect of VIP in the cortex. Why bother studying a molecule that was present in low amounts, ten to a hundred times less than in muscle or liver respectively, and in addition that was localized in a kind of inert cell type that likely was not active in information processing in the brain. Yet, as it turns out, my serendipitous encounter with glycogen and glial cells was going to determine the research field that I would develop over the next 40 years. Paradoxically, some degree of ignorance actually may be healthy. It prevents us from having preconceived notions and enables us to keep an open mind to explore uncharted paths.

Once I had a clearer view about glycogen in the brain, I presented the results to Floyd, stressing how a pharmacological assay developed to explore noradrenergic function led to an observation that could provide some insights for the study of cell-cell signaling in the brain. First, the glycogenolytic effect of VIP indicated that certain neurotransmitters could exert their effects on glial cells, which provided an opening to further studies of neuron-glia interactions. Second, this interaction implied the existence of a mechanism to couple neuronal activity to energy metabolism. Third, at least as far as VIP was concerned, there was now evidence for a physiological action of a newly discovered neuropeptide. The results and their discussion definitely caught Floyd's attention: he was smiling and nodding his head as I was reciting these ideas. He said, "Fantastic," and asked me if I needed more resources to move the project forward. Over the next few months, I worked relentlessly to complete the characterization of this metabolic effect of VIP and wrote up the results in an article published in October 1981 in

the *Proceedings of the National Academy of Sciences*, entitled "Vasoactive intestinal polypeptide induced glycogenolysis in mouse cortical slices: a possible regulatory mechanism for the local control of energy metabolism." I was particularly happy with the concluding sentence I had written:

> A final observation can be made: VIP and norepinephrine display similar glycogenolytic actions in peripheral tissues. This action may indicate that certain substances with specific hormonal roles in several cell systems may exert similar homeostatic functions at the cellular level within the central nervous system, which are constrained by the spatiotemporal functional precision inherent to neural transmission. (Magistretti et al., 1981)

Indeed, the results suggested that certain neurotransmitters, such as VIP and NA, could exert hormone-like effects within the brain, acting in a nonsynaptic way (no synapses on astrocytes) on glial cells.

In the meantime, complementing these metabolic studies, I engaged with John Morrison on the immunohistochemical characterization of VIP-containing neurons in the cerebral cortex. John and I were sharing with four other post-docs a room on the top floor on the ocean side of the south wing of the Salk Institute. The view was simply magnificent: the canyon sloping down to the cliffs and then the Pacific Ocean. During the months of January and February, we would see pods of whales swimming south toward Baja California. Once they had reached the tip of Baja, they eventually would move north in the Sea of Cortex to give birth to their calves. The other post-docs did not use this room much, which was actually quite far from the lab, located in the basement on the east side. There was a feeling of quietness up there, which, along with the inspiring view, was conducive to the reflections that John and I liked (and still like 40 years on) to share about brain function. A long-lasting friendship started in that office. John, his wife Abbie, and his children Alex and Kelsey have become close friends with Christine, and our children. We still meet regularly and enjoy lively conversations sparked by great wines and food.

John (Figure 2) had joined Floyd's lab in the summer of 1980 from the lab of Mark Molliver at Johns Hopkins. His doctoral thesis was about the immunohistochemical characterization of the noradrenergic innervation of the cortex (Morrison et al., 1978). Using an excellent antibody against dopamine beta-hydroxylase developed by Reinhardt Grzanna and Joe Coyle (Grzanna et al., 1978), John had revealed that intracortical noradrenergic fibers are organized tangentially, spanning from the rostral to the occipital poles with a trajectory parallel to the pial surface (Morrison et al., 1981). This particular organization suggested that noradrenergic fibers would exert their actions globally, throughout the cortex

Fig. 2. John Morrison (center), Gary Aston-Jones (left), and me. The Salk Institute, 1981. *Photo credit*: Jamie Simon

(Morrison et al., 1979). I remember John telling me that before immunohistochemistry, the cerebral cortex was taken as a negative control for the presence of NA, since the classical Falck-Hillarp histochemical technique could not reveal a signal for the presence of monoamine fibers (Falck et al., 1962). Because NA and VIP shared the same metabolic effect, we decided to characterize the morphology and distribution of VIP-containing neurons in the cerebral cortex. Using a selective antibody raised against porcine VIP, we showed that VIP neurons represent a homogeneous population of radially oriented intracortical bipolar cells spanning across the cortical thickness with a maximal dendritic span of 100 um (Morrison, et al., 1984; Magistretti and Morrison, 1985). This morphology indicated that VIP neurons were defining what one could consider cortical columns (Magistretti and Morrison, 1988). Following the advice of Floyd, we also performed a quantitative analysis of the density and distribution of these neurons. We used a rather rudimentary approach that involved identifying on transparent sheets the localization of the cell bodies of VIP neurons visible on horizontal sections and then piling up these sheets to perform a nearest-neighbor analysis (Morrison et al., 1984). This type of analysis, which took several weeks to accomplish at that time, can now be performed in minutes with similar results using quantitative neuromorphology software. Francis Crick became quite interested in this quantitative approach. John and I had the privilege of having several discussions with him, sometimes in the lab, looking at slides on a fluorescence microscope. We were of course thrilled by this unique opportunity and thanked him in the acknowledgment section of our article, which he had read and commented before submission (Morrison et al., 1984).

The combination of our neurochemical and morphological work was synthesized in a theoretical formulation whereby the VIP and NA neuronal systems in the neocortex were regulators of energy metabolism. VIP neurons within radially oriented cortical domains, or columns, translating incoming modality-specific inputs into a metabolic response, while the role of the NA system would be to prime metabolically a vast rostrocaudal expanse of neocortex across modality-specific regions (Figure 3) (Magistretti and Morrison, 1988). This proposal was consistent with work at the EM level by Alan Peters, which showed that VIP-containing neurons received direct thalamo-cortical inputs (Peters and Kimerer, 1981), and with the recently demonstrated role of the ceruleo-cortical system in non-noxious, attentional mechanisms described by Steve Foote and Gary Aston-Jones (Foote et al., 1983).

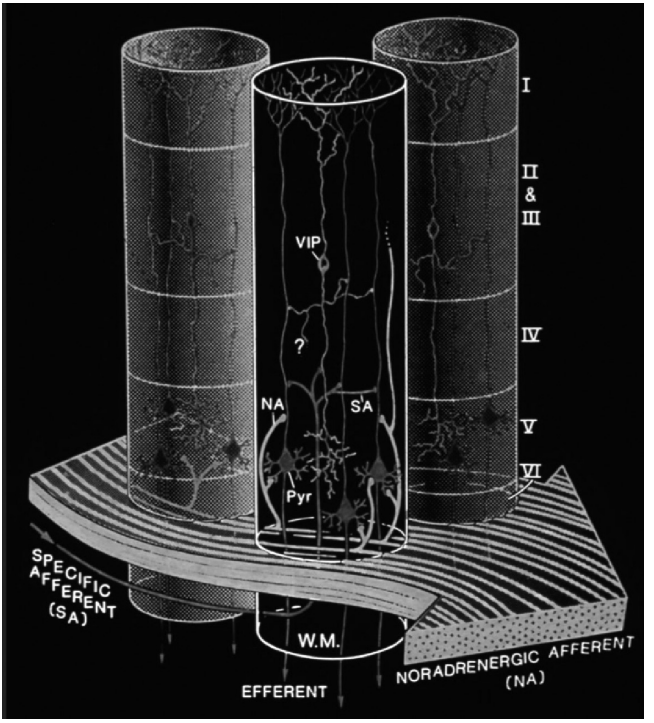

Fig. 3. Graphic representation of the interaction between VIP neurons and NA fibers in the neocortex (Magistretti and Morrison, 1988). Vasoactive intestinal peptide neurons promote glycogenolysis in astrocytes. Given the bipolar nature of the VIP neurons, this effect is restricted to cortical columns. VIP neurons are activated by corticocortical and thalamocortical specific afferents (SA). The noradrenergic afferent (NA) fibers span horizontally across cortical domains and hence can metabolically prime a vast expanse of neocortex by promoting glycogenolysis in astrocytes. I–VI refer to cortical layers. W.M., white matter. Original drawing by Jamie Simon.

In the spring 1982, as I was getting ready to wrap up my work for the thesis, Silvio Varon who was my co-advisor as a UCSD faculty, came up with a proposal for some additional experiments. I valued very much Silvio's insights: he had worked with Rita Levi-Montalcini at Washington University on pioneering studies of neurotrophic factors and recently had developed techniques for culturing neurons and astrocytes separately. He brought a complementary type of mentorship to that of Floyd. Still today, I realize how fortunate I have been to have had such remarkable advisors, yet with such different personalities. Silvio suggested that I study the glycogenolytic effect of VIP on the astrocyte cultures that had been recently established in his lab. Although this suggestion was logical and would complement my other studies, I was less than enthusiastic at this idea as I knew that it would postpone my thesis defense by several months. Nevertheless, I performed the experiments, which indeed demonstrated the glycogenolytic effect of VIP on astrocytes (Magistretti et al., 1983). I think that it was one of the very first demonstrations for the existence of neurotransmitter peptide receptors on glial cells. More important, it opened the way to further experiments I did throughout the next decades in my lab back in Switzerland.

In September 1982, I eventually defended my doctoral thesis at UCSD, entitled "Vasoactive Intestinal Polypeptide: A Regulator of Cellular Homeostasis in Cerebral Cortex" (Magistretti, 1982). On September 30, 1982, the day of my 30th birthday, I landed at Geneva airport, bringing back with me myriad memories that were going to shape my future. The years at Salk and UCSD determined my subsequent scientific journey. The Californian experience opened my mind to different lifestyles and values that would influence my personal life back in Switzerland.

In La Jolla, Christine and I lived in a one-bedroom flat close to the ocean on Windansea Beach. The years we spent in La Jolla are among the happiest ones in our life. We were experiencing a new cultural life, away from our social connections and family and the sometimes-overbearing environment in Switzerland, making new friends, and experiencing a great sense of novelty and freedom. We still jokingly ask to each other, "When are we going back to live in San Diego?"

Establishing a Lab in Geneva

I returned in the Department of Pharmacology of the Geneva Medical School, where I had studied and was first exposed to research. The department had moved, along with all preclinical departments, from the old medical school built at the end of the 19th century, into a brand new building close to the hospital. Despite the novelty, I felt a sense of *déjà vu*: I was sharing an office and a lab with Michel Schorderet, my medical thesis advisor. Granted, Michel was gracious and supporting, the space was modern and larger, and I had a position of maître-assistant (something between post-doc and

assistant professor), but I was asking myself, "Am I really moving forward?" I saw myself stuck in a system that would at best allow me to slowly climb the academic ladder and become a professor, if I was fortunate, 20 years down the road. And how about the science: would I be able to develop original research projects that would bring me closer to my initial goal to understand the mind? Fortunately, the personal side was looking bright, and within a year, some exciting experimental results reassured me.

Christine and I settled in a nice apartment close to the lab and married in March 1983. The proceedings of the wedding ceremony brought us radically back to our own cultural environment, after the west-coast life that we had become so fond of. The ceremony was officiated by the senior Calvinist pastor in the Geneva Cathedral in the Old Town. After almost a millennium as a Catholic church, in 1535, the cathedral had become a protestant religious site, established by Jean Calvin. In 1506, Christine's family, the Naville, had moved from the nearby Savoy Duchy to Geneva and her family was closely linked to the establishment of Calvinism in Geneva; hence, the certain formalism of our wedding ceremony. On July 20, 1984, our first child, Ambroise, was born. At the risk of appearing too sentimental, this day remains, along with those when our two other children, Bérénice and Henri were born, the nicest day of my life.

The first experiments I started in Geneva were to test whether an interaction existed between the VIP and NA neuronal systems in the cortex. Because NA was globally priming the cortex and the bipolar VIP neurons were activated by specific inputs, it was conceivable that they could interact within the cortical volumes where the two systems intersected. The readout for their potential interaction was cAMP formation. The results turned out to be positive, revealing a synergistic interaction between VIP and NA in forming cAMP; the pharmacological basis for this interaction was the potentiation by NA, acting at alpha1-adrenergic receptors, of the formation of cAMP induced by VIP (Magistretti and Schorderet, 1984, 1985). The signaling for this synergy was mediated by prostaglandins formed by activation by NA of alpha1-receptors (Schaad et al., 1987). These observations led me to propose that the two orthogonally oriented neuronal systems could generate cortical hot spots at their intersection when the ceruleo-cortical noradrenergic system and the radially oriented VIP neurons were simultaneously active, a behavioral modality achieved during an attention-associated specific sensory input (Magistretti, 1990). This project, which resulted in two *Nature* articles (Magistretti and Schorderet, 1984; Schaad et al., 1987), gave me a great boost for establishing my group and obtaining my first grant from the Swiss National Science Foundation, which I then received without interruption for the next 33 years.

From 1983 to 1988, I continued to further characterize the signaling mechanisms of VIP and the coupling between neuronal activity and energy metabolism in various central nervous system regions. With my

first graduate student, Jean-Luc Martin, we decided to study the molecular mechanisms for VIP release from the cortical bipolar neurons that contain it. Indeed, a striking feature of these neurons is their strong staining by immunohistochemistry that reveals a Golgi-like appearance and indicates the presence of VIP in dendrites (Morrison et al., 1984). We identified a particular voltage-sensitive calcium channel that was necessary to trigger release, as well as a key role of arachidonic acid metabolites in this process (Martin and Magistretti, 1989a, 1989b). With my other student, Patrick Hof, who had just completed his medical studies at the University of Geneva, we found that potassium, at concentrations that are reached in the extracellular space during physiological neuronal activation, promoted glycogenolysis, adding a new player to the activity-dependent neuron-glia metabolic coupling (Hof et al., 1988). Interestingly, two decades later the labs of Brian McVicar and Felipe Barros independently described the involvement in this process of a potassium-dependent sodium–bicarbonate exchanger activating adenylate cyclase (Ruminot et al., 2011; Choi et al., 2012). We eventually also showed that adenosine, which is similarly released by active neurons, is a glycogenolytic agent (Magistretti et al., 1986).

Thirty-five years on, I have continued to collaborate with Jean-Luc Martin. We currently are collaborating on the role of lactate, the metabolite formed by glycogenolysis in astrocytes, as an antidepressant agent, a recent result that I will discuss later (Carrard et al., 2016). As to Patrick Hof, after a couple of years in my lab, he joined John Morrison's group at Scripps Research Institute, where Floyd's lab had moved from Salk in 1985. Patrick has gone on to a brilliant career as a distinguished comparative neuroanatomist and is now vice chair of the Department of Neuroscience at Mount Sinai School of Medicine. He is also the editor-in chief of the respected *Journal of Comparative Neurology*. With Jean-Luc and Patrick, we also collaborated during those years with José Maria Palacios, Chema as he was dubbed, who had set up a kind of "factory" at Sandoz in Basel, to characterize by autoradiography the localization of a variety of neurotransmitter receptors. In his freezers, you could select sections of your preferred species and brain region. This collaboration led to several publications on the distribution of VIP receptors (Martin et al., 1987; Hof et al., 1991).

In 1986, Professor Ralph Straub, the chair of the Department of Pharmacology at Geneva Medical School, suggested that I apply for a new funding scheme of the Swiss National Science Foundation called START, an acronym for Swiss Talents for Academic Research and Teaching. It was essentially a career development award aimed at supporting young promising academics who potentially could apply for professorial positions in the years to come in any academic discipline. Ralph Straub was a short, discreet, and shy man who frequently brought to his office a big Dane, named Dasso. As you entered Straub's office, Dasso would move toward you with his big mouth open: needless to say, you would not do or request anything that

could upset him or his owner. Straub was a fine neurophysiologist trained in the British school of physiology of axonal conduction. He had worked with Richard Keynes and Murdoch Ritchie and had published a few articles in late 1950s and early 1960s with Paul Greengard on conduction and metabolism in the rabbit vagus nerve, a preparation that Straub continued to study until his death in 1988 (Greengard and Straub, 1959, 1962). Interestingly, these studies by Greengard and Straub were already focused on the metabolic cost of neuronal (axonal) activity. In January 1987, I was one of the first four awardees of the new START program and decided to take a sabbatical and return to Floyd's lab, now at the Scripps Research Institute, to learn some molecular biology, an approach that Floyd had just introduced in his lab.

As we landed in San Diego in October 1987, Christine and I felt like we were returning home, now with our small family including Ambroise and Bérénice, who was born a few months earlier. We rented a house in Del Mar Heights located in Lozana Road, a name that was prophetic of events to come shortly. All the dear friends that we had left a few years earlier were still there and incredibly welcoming: of course Floyd and his charming wife Jody, John and Abbie, Bob Siggins, and Tibor Safar. Tibor deserves a special mention. One could define him as a hippie 20 years after it was in fashion, but doing so would not do justice to the wonderful person that he is: a true hedonist living without compromises for quality, in particular, as far as food and wine are concerned, and friendship. He had received a doctorate in psychology from UCSD, but he worked in a specialty shop in Sorrento Valley that produced Plexiglas lab equipment. As of today nobody really knows where his house is and even if he has one. To my great delight, I joined again the reunions of what its members like to consider the most exclusive wine tasting club in the world: the LJB&T, the La Jolla Bragging and Tasting Club. It was founded in 1981 while we all were at Salk, by Floyd, John, Bob, Tibor, Cary Lay (who eventually became professor at University of Indiana), and Joe Rogers (who left in 1982, for a position at Boston University). We did blind tastings, each one of us bringing one or more bottles: most of the time we made fools of ourselves in trying to identify the wines. Since 1984, when the Society for Neuroscience meeting was held in New Orleans, we have held a reunion of the LJB&T in a good restaurant on the first evening of the meeting, and we taste many great bottles of wine. All of us are quite fond of this reunion.

In April 1988, while I was enjoying my found-again life in San Diego, Professor Straub called and said that I should apply for a full professorship at the Medical School in Lausanne. His argument was that, while the START program could support the awardees for up to nine years, they were requested to apply for any professorial position that opened up in a Swiss university in her or his field. Professor Michel Dolivo, a neurophysiologist and chair of the Institute of Physiology at the Medical School of Lausanne, was retiring in the fall of 1988 and the search for his replacement was on.

Straub mentioned that my chances to be appointed to this position were close to nil, given my far too young age, but he thought that it would be a good move to get my file known by some prominent Swiss academics who were part of the search committee. I flew back to Geneva for a week, and without much enthusiasm, I prepared the application. During the month of May, events accelerated. First, I received a phone call from Jean-Luc Martin telling me that Professor Straub had suddenly died of a heart attack and that I was expected to return to Geneva as soon as possible. Second, a few days later I received a notice from the search committee that I was short-listed for the position at the University of Lausanne, which provided yet another reason to cut short my stay in San Diego.

For the position in Lausanne, I gave two lectures, one aimed at students and one presenting my research and future plans, and I was interviewed by the search committee. Within a couple of weeks, I was informed that I was the first choice of the search committee, and in August, one month before my 36th birthday, I received the official appointment to the position of full professor (*professeur ordinaire*) at the Institute of Physiology of the University of Lausanne. Things had definitely accelerated, taking a completely unexpected turn. In the meantime, since the position of Professor Straub had become vacant, the University of Geneva Medical School had offered me an associate professor position, considering that I was too young for a full professorship. I faced a dilemma: I had just bought an apartment in Geneva, near the Medical School and my lab was running well. I would have to commute every day to Lausanne (an almost three-hour commute overall each day) if I accepted the position there. I sought advice from several people I trusted. I recall in particular a discussion with the chair of medicine in Geneva, Professor Alex Muller, who had a special aura in the Medical school and whose lectures in internal medicine had struck me for their clarity. He had no hesitation: the move to a new environment such as Lausanne, a very good university providing appreciable support, was much better than staying in a place where I had been since I was a medical student, in addition to the significant difference in professorial positions that I was being offered. In Muller's thinking, this was an opportunity not to be missed. He very graciously said that it would be Geneva's loss. I am still today very grateful to the University of Lausanne who entrusted me and provided a unique opportunity for a professional experience that, at least in Switzerland, occurs usually a decade later in one's scientific career.

The Astrocyte Neuron Lactate Shuttle

The Institute of Physiology in Lausanne was located in a 19th-century building, close to the hospital. Until the 1950s, the chairs of the Institute lived with their families on the top floor. The building underwent several

renovations over the years. My new lab was located in an annex built in the 1970s. I had to start everything from scratch: equip my lab, hire personnel, prepare my lectures and develop practical demonstrations for students, and participate in administrative tasks. The other three, more senior, full professors were very helpful. In particular Eric Jéquier, an internationally recognized expert in human energy metabolism and nutrition, who had been appointed chair, was very supportive: he made sure that I had enough time to develop my research and that I would not be "burned" by the task of combining it with heavy teaching and administrative loads. I am grateful to him for his benevolent support, which lasted until I took over the chairmanship when he retired 10 years later.

I decided to focus on what I considered my core biological question: what are the mechanisms that couple neuronal activity to local energy delivery? I had identified four neuronal signals that could mobilize energy from astrocytes by promoting glycogenolysis: VIP, NA, adenosine, and potassium (Magistretti et al., 1981; Magistretti et al., 1986; Magistretti and Morrison, 1988; Hof et al., 1987). I had a burning question that I wanted to tackle: how does glucose enter the brain parenchyma in register with neuronal activity, possibly to replenish the glycogen stores mobilized by activity (Swanson et al., 1992)? Lou Sokoloff had developed the elegant 2-deoxyglucose autoradiographic technique, which allowed for the determination of basal and activity-dependent glucose utilization in a variety of laboratory animals (Sokoloff et al., 1977). The technique recently had been extended to functional brain imaging in humans using ^{18}F-2DG positron emission tomography (PET) (Sokoloff, 1981). The technique was powerful and its application to human functional brain imaging represented a major breakthrough, yet it was not affording a cellular resolution. The dogma was that glucose would enter directly neurons from the circulation. Because of my interest in astrocytes and the fact that intraparenchymal brain capillaries are literally covered by particular astrocytic processes called endfeet, I wondered whether glucose would not transit through astrocytes before reaching neurons. An elegant experiment by Lou Sokoloff on the autoradiographic localization of 2DG following somatosensory stimulation had caught my attention: the label was localized in the synapse-rich dorsal horn rather than in the dorsal root ganglia, where the cell bodies of the sensory neurons are located (Kadekaro et al., 1985). This observation along with the fact that many synapses are surrounded, at least partially, by astrocytic lamellar processes, where receptors for neurotransmitters had been recently identified, suggested to me that astrocytes definitely could sense synaptic activity and couple it to the uptake of glucose entry into the brain parenchyma (for review, see Magistretti and Allaman, 2015). We therefore set up the 2DG technique in the lab to monitor potential neurotransmitter-evoked glucose uptake in cultured astrocytes. In particular, because VIP and NA promoted glycogenolysis, I wondered whether

they also could promote glucose uptake as a mechanism to replenish glycogen stores in astrocytes.

This study was implemented by a graduate student, Naichen Yu, whom I had met in China during a course sponsored by the World Health Organization, along with Nephi Stella, another student who had joined my lab as part of a co-tutelle thesis with Jacques Glowinski at the Collège de France in Paris. Naichen and Nephi showed that, indeed, NA-stimulated glucose uptake in astrocytes. The signaling mechanism did not involve cAMP, but rather activation of cyclo-oxygenase and arachidonic acid formation (Yu et al., 1993). Not surprisingly, VIP was without effect, as the observed effect was not cAMP dependent. Both Naichen and Nephi, completed their theses and went on as post-docs in San Diego: Naichen worked in Floyd's lab first and then as a staff scientist at Merck; Nephi started working on endocannabinoids in Daniele Piomelli's lab at the Neurosciences Institute in La Jolla, a research program that he has since developed successfully at the University of Washington in Seattle, where he has been for several years now as full professor in the Department of Pharmacology.

In 1991, a Canadian post-doc, Luc Pellerin, joined my lab after completing his doctoral thesis with Leon Wolfe at the Montreal Neurological Institute. With him, I extended the study of glucose uptake by astrocytes to other neurotransmitters and found some interesting results with glutamate. Indeed, glutamate not only stimulated glucose uptake but also promoted lactate production by astrocytes (Pellerin and Magistretti, 1994), a biochemical pathway known as aerobic glycolysis or the Warburg effect (Warburg, 1956). Furthermore, this effect of glutamate was mediated by its uptake through sodium-coupled transporters and not by receptors. This observation identified a second mechanism by which neuronal activity—in this case mediated by glutamate, which is released at 80% of the synapses in the cerebral cortex (Braitenberg and Schuz, 1998)— is coupled to energy delivery (Figure 4). Over the next few years, through the work of several students and post-docs, we described the key molecular steps that mediate this process for neuron-glia metabolic coupling. In brief, glutamate uptake by astrocyte-specific transporters, which is driven by the electrochemical gradient of sodium with a stoichiometry of one glutamate for three sodium ions, results in activation of the alpha2 subunit of Na/ATP-ase. Through this process, one ATP molecule is consumed to extrude three sodium ions (Pellerin and Magistretti, 1997). Glutamate taken up is converted partially to glutamine by glutamine synthase, also at the expense of one ATP molecule, and is transferred back to neurons to replenish the neurotransmitter pool of glutamate, through a mechanism known as the glutamate-glutamine cycle (Berl et al., 1968).

We then characterized the cell-specific distribution of key molecular operators of glutamate-stimulated aerobic glycolysis, including in the human brain. By this means, we demonstrated that lactate dehydrogenase 5,

the isoform of the enzyme that favors the conversion of pyruvate to lactate, is only present in astrocytes, whereas neurons express exclusively lactate dehydrogenase 1, which is also present in tissues like the heart that can use lactate as a substrate (Bittar et al., 1996; Laughton et al., 2000). We also showed a cell-specific distribution of monocarboxylate transporters (MCT), with MCT1 and MCT4 present in astrocytes and MCT2 present only in neurons (Bröer et al., 1997; Pellerin et al., 1998; Pierre et al., 2000). This set of observations led to the formulation of the Astrocyte Neuron Lactate Shuttle (ANLS) model (for review, see Pellerin and Magistretti, 2012; Magistretti and Allaman, 2015, 2018). As I coined these terms, I was reassured by the fact that lactate shuttles also had been recently described in muscle (Brooks, 1986, 2018).

As I presented the ANLS model at conferences (Figure 5), I experienced a strong resistance from classical neurochemists, sometimes in vehement terms. I still remember that one of the first times I did so, a senior neurochemist took the floor and said, "Pierre, what you just presented is a major conceptual step backwards." Two points in the ANLS model were difficult to swallow for experts who had studied brain energy metabolism for decades:

Fig. 4. My lab at the Institute of Physiology of the University of Lausanne Medical School. Pictured left to right are as follows: (Front row) Jean-Marie Petit, Béatrice Roth, Selma Abdelmoumene, Sabrina Zerarka, myself, Jean-Luc Martin, Isabelle Jammes, Igor Allaman. (Back row) Maria Kiraly, Jean-Marie Brunet, Mauricette Maillard (partly hidden), Hubert Fiumelli, Hugues Cadas, Pierre Marquet, Karine Pierre, Stavros Therianos, Jean-Yves Chatton, Ruth De Bernardi.

first, the main site for glucose uptake was in astrocytes, and second, the energy substrate that was delivered to neurons was lactate, which generally was considered a metabolic waste product produced by ischemia and anoxia, despite the fact that Henry McIlwain had shown in the 1950s that lactate in the presence of oxygen is a perfectly adequate energy substrate to sustain neuronal activity (McIlwain, 1953). Fortunately, I also found early support for the ANLS model, particularly so in functional brain imaging circles, which were certainly more open to novelty. This support included Lou Sokoloff, who replicated our original findings (Takahashi et al., 1995; Itoh et al., 2003). I had, and still have, very stimulating exchanges with Marc Raichle, one of the pioneers of *in vivo* brain metabolism studies. Marc published an observation that also generated some resistance: in PET studies, he described the occurrence of an uncoupling between glucose utilization and oxygen consumption during neuronal activation (Fox and Raichle, 1986; Fox et al., 1988). Biochemically, that meant that glucose taken up during neuronal activation was not fully oxidized, a conclusion consistent with the glutamate-evoked aerobic glycolysis and lactate production that we had described (Pellerin and Magistretti, 1994). The controversy about the ANLS model went on for several years, particularly in neurochemistry meetings and journals, mostly on theoretical grounds (Bak and Walls, 2018). Despite this resistance we, and others, were publishing experimental results in support of the model (e.g., see Cholet et al., 2001; Voutsinos-Porche et al., 2003; Bernardinelli et al., 2004; Magistretti and Chatton, 2005) (for review, see Magistretti and Allaman, 2018; Weber and Barros, 2015; Barros and Weber, 2018).

A major confirmation of the ANLS model came through a fruitful collaboration with Cristina Alberini, at Mount Sinai School of Medicine and now at NYU. We had gathered, through work in the lab in Lausanne, evidence that the expression of certain genes involved in the ANLS—in particular, in glycogen metabolism—were upregulated in the hippocampus following spatial learning and fear conditioning (Cardinaux and Magistretti, 1996; Allaman et al., 2000; Tadi et al., 2015). This observation pointed at glycogen and lactate, the main metabolite formed by astrocytes. With Cristina and her colleagues, we showed that pharmacological blockade of glycogenolysis in the hippocampus prevented long-term potentiation and memory consolidation in a manner that was rescued by intrahippocampal lactate delivery (Suzuki et al., 2011). This result, along with several others, led us to conclude that the transfer of lactate from astrocytes to neurons is necessary for memory consolidation (Suzuki et al., 2011; Gao et al., 2016). These findings, which were published in *Cell*, were quite antidogmatic as they showed that a molecule considered to be a metabolic end-product and a cell type considered to be some sort of "brain glue" were necessary for memory. Recently we extended these data through an electron microscopy study in a novel object recognition paradigm and found that learning increases the

number and size of both dendritic spines and astrocytic glycogen granules in the hippocampus (Vezzoli et al., 2019). Blocking glycogenolysis during training inhibits the increase in the number of dendritic spines in a manner that is reversed by lactate (Vezzoli et al., 2019).

Work on the ANLS represented the main scientific focus of my lab at the Institute of Physiology at Lausanne Medical School until 2004 (Figure 5). That year, I was offered the directorship of the Douglas Research Institute in the Department of Psychiatry at McGill; the appointment came with the support of a senior Canada research chair. After 15 years in the Institute of Physiology and still in my early 50s, I felt ready for a new challenge. When I announced that I was going to leave Lausanne, the academic authorities moved fast. Within one week, I was appointed director of the Center for Psychiatric Neuroscience in the Department of Psychiatry, for which I had been a strong proponent within the Medical School. It was also agreed that I would have a joint appointment in the newly created Brain Mind Institute (BMI) at Ecole Polytechnique Fédérale de Lausanne (EPFL). My intention to move to Montreal was genuine, and Christine and I were very much looking forward to this cultural change. Ambroise had left Lausanne to study biochemistry at University College in London. Bérénice had been accepted to study economics at

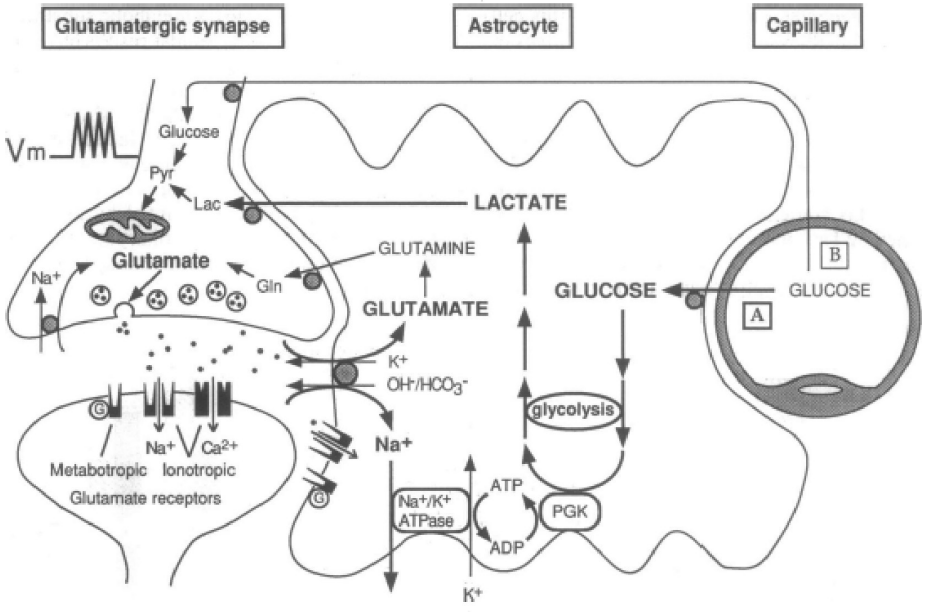

Fig. 5. Astrocyte-Neuron metabolic coupling. First graphic representation of the Astrocyte Neuron Lactate Shuttle (Pellerin and Magistretti, 1994).

McGill, and Henri, our third child born in 1990, had been accepted in a very good high school in Montreal. McGill had been forthcoming in ensuring that Christine would be able to continue the type of work that she was doing through the foundation that she had just started, developing programs to fight poverty and support the reproductive health of women in the slums of Mumbai. We had found a house in Montreal and arranged for the move. The offer from Lausanne caught me by surprise. It touched on two points that I was particularly sensitive to: being part of the launch of two new institutes. One of these centered on biological research in psychiatry, a topic that had been my main motivation to engage in neuroscience. The other was destined to become one of the premier institutes of neuroscience in Europe, given the ambition and resources that it had been allocated. It would be an understatement to say that the choice was difficult. Eventually, I decided to accept the offer by Lausanne. The appointment at the BMI at EPFL was rapidly implemented. In fact, shortly after joining the BMI, Patrick Aebischer, the president of EPFL and a neurobiologist himself, asked me to take over the directorship of the BMI from Henry Markram to allow Henry to focus on his pet Blue Brain Project, which was a truly original and pioneering modeling effort in neuroscience, jointly developed between IBM and EPFL. Eventually the Blue Brain Project morphed into the Human Brain Project, one of the flagship projects of the European Community. Within a few months, without having planned it, I found myself working in two new neuroscience institutes.

In the course of the experiments we did with Cristina Alberini, we reported that, unlike lactate, glucose could not efficiently replace the blockade of glycogenolysis to rescue memory consolidation (Suzuki et al., 2011). This observation led us to think that energy deficit was not the cause of amnesia. After a long search, through work led by Igor Allaman, one of the pillars of my lab over the past 20 years, we found that lactate, and not glucose or pyruvate, induces the expression of genes involved in neuronal plasticity through the potentiation of N-methyl-d-aspartic acid (NMDA) receptor signaling (Yang et al., 2014). These observations indicated that lactate is not only an energy substrate but also a signaling molecule. A recent review expands on the notion that lactate in the brain should no longer be considered a metabolic waste product but is actually a signaling molecule (Magistretti and Allaman, 2018). Current experiments in the lab are actively exploring the molecular mechanisms of this action of lactate on NMDA receptors. Changes in the redox state of neurons evoked by lactate seem to play a critical role.

In fact, having identified the role of lactate produced by astrocytes has opened a Pandora's box. Thus, we and others have shown that lactate is involved in other behavioral paradigms related to neuronal plasticity, such as addiction (Boury-Jamot et al., 2015) and the sleep-wake cycle

(Petit et al., 2013; Petit and Magistretti, 2015). Lactate exerts neuroprotective effects (Berthet et al., 2009; Allaman et al., 2010; Morrison et al., 2012; Berthet et al., 2012; Bouzat et al., 2014; Carteron et al., 2018) via mechanisms that have been at least partially identified (Bliss et al., 2004; Bélanger et al., 2011a, 2011b; Jourdain et al., 2016, 2018; Margineanu et al., 2018; Tauffenberger et al., 2019) With my long-time collaborator Jean-Luc Martin, we recently have shown antidepressant effects of lactate in three animal models of depression (Carrard et al., 2016). Somehow I have the impression that we are witnessing a rehabilitation of lactate in the brain (Magistretti and Allaman, 2018) in a manner analogous to what occurred for glutamate in the late 1970s. Indeed, when I entered neuroscience, there were doubts as to whether glutamate, a metabolic intermediate of energy metabolism, actually could act as a signaling molecule in the nervous system. Today, nobody would question that glutamate is the main neurotransmitter in the brain, released at the majority of synapses (Braitenberg and Shuz, 1998). The story for lactate may well unfold in a similar way, in this case pointing at a role for lactate as a glia-derived signaling molecule.

Service Engagement and Outreach

As mentioned earlier, during the 1990s, I was able to focus almost exclusively on my research, thanks to the ideal conditions that I was offered at the University of Lausanne and to the shield from excessive teaching and administration that the chair of physiology, Eric Jéquier, generously provided to me. By the end of the decade, however, I had become increasingly involved in a variety of engagements at the medical school and in learned societies. I guess that this is inevitable as a career matures; the process was certainly enhanced by my reluctance to say "no" when approached about committing some time to the community. Among the positions that I accepted, I recall very fondly my presidency (2002 to 2004) of the Federation of European Neuroscience Societies (FENS). FENS was born from the ashes of ENA, the European Neuroscience Association, which by the end of the 1990s had lost, for a variety of reasons, its ability to represent the burgeoning neuroscience community that was developing in Europe. A group of presidents of national neuroscience societies (I represented Switzerland as the first president of the newly established Swiss neuroscience society) met in 1997 and drafted the vision for a new umbrella society for European neuroscience. The winning concept was the establishment of a biennial forum, which over the years has become a vibrant and scientifically outstanding international neuroscience gathering. My presidency was responsible for the fourth forum, which took place in Lisbon. The chances of success of this fourth forum were uncertain, because of the still-fragile nature of FENS, which was in its infancy, and because of the limited membership of the local neuroscience society. The Iberian solidarity worked very well, however, as flocks of Spanish

neuroscientists were in attendance along with an excellent participation from across Europe, particularly from young neuroscientists, a feature that continues to characterize the FENS forums.

In the spring of 2008, Torsten Wiesel and Carlos Belmonte contacted me to ask if I was interested in the position of secretary general of the International Brain Research Organization (IBRO). I didn't know much about this organization, except that like ENA at the end of the 1990s, it had become dormant, but it recently had been reenergized by Torsten and Carlos. Carlos explained to me how the contribution of IBRO to international neuroscience was vital, through the promotion of education, training, and research not only in economically well-developed parts of the world, but also, and more important, in less favored countries. I vividly remember when I received the call: I was in the small apartment where I was living with Christine in the Marais neighborhood of Paris, preparing my lectures for the Collège de France, where I had been appointed to the 2007–2008 international chair. The Collège provides a very special academic environment: it was founded by King François I in 1530 and its professors mainly teach to a public audience the original research that they are conducting. The intellectual heroes of my adolescent years, Roland Barthes, Claude Lévi-Strauss, and Michel Foucault occupied permanent chairs. I felt privileged to have been selected for one of the annual chairs. When I received the call from Carlos, my mind was somehow floating in the ethereal atmosphere of the Collège and I had a hard time fully appreciating what kind of time commitment accepting the position of IBRO Secretary General would entail. Of course, I could not refuse a proposal coming from two neuroscientists I greatly admired. Later, I actually became president of IBRO (2014–2019). It has been an enriching experience during which I have seen how an organization like IBRO can literally change the life of so many young neuroscientists worldwide, by providing them with opportunities for education that in many cases lead to amazing professional success. This came as a lesson and incentive to relentlessly mobilize all efforts to nurture talent worldwide.

Over the past 20 years, I also have been committed to neuroscience outreach. I think that as scientists, it is our duty to reach out to the public and explain the nature of our research. In these efforts I have been associated with the Dana Alliance for Brain Initiatives, in particular its European Dana Alliance for the Brain (EDAB). The Dana Alliance was founded by David Mahoney, a visionary businessman who captured the need for neuroscience outreach. The Dana Alliance has established the now extremely popular yearly "Brain Awareness Week" occurring worldwide every second week of March.

Recent Years

As I was approaching my 60th birthday I began to seriously worry about what would happen when I would reach 65, the mandatory age for

retirement in Switzerland. I was certainly not ready to bring my research projects to a halt. I started looking in obvious places, such as the United States or Singapore. An unexpected opportunity entered in my reflections: Stefan Catsicas, a former vice-president of EPFL, and a dear friend from the time of Floyd's lab at Scripps and later in Lausanne, had been appointed provost at a brand new university in Saudi Arabia: King Abdullah University of Science and Technology (KAUST). He proposed that I helped him as dean, to establish a division of biology and environmental sciences there. I visited the campus in the winter of 2011 and was stunned by the place, like everyone who visits KAUST for the first time. This coed and graduate-only university was established in 2009 on the shores of the Red Sea; it has considerable resources, the main one being the quality of the faculty that it has recruited. In the spirit of its founder, the late King Abdullah, KAUST was to reproduce the House of Wisdom in Baghdad at the turn of the first millennium, where the best scholars, independent of nationality and religion, would gather to advance knowledge. Though very new, KAUST has achieved considerable progress, ranking as the number one university in the world over the past four years in terms of citations per faculty.

Thanks to KAUST, I have been able to continue developing research projects there, in fact even expanding them in collaboration with EPFL. This new work is in areas that I was initially not considering, such as for example modeling and digital reconstruction of neuron-glia interactions, as KAUST provides an amazingly strong environment in computational sciences (Cali et al., 2016, 2019; Coggan et al., 2018, 2019). Corrado Cali and Hubert Fiumelli have been instrumental in setting up the lab at KAUST. Corrado recently was appointed assistant professor at the University of Torino in Italy. Hubert had been a graduate student in my lab in the 1990s. He spent six years with Mu-ming Poo at Berkeley, before returning to Lausanne to work with Jean-Luc Martin at the Center for Psychiatric Neuroscience (CNP). With some hesitation, Hubert took on the challenge to set up a lab with me at KAUST, but he is now enjoying life on the shores of the Red Sea. I continue research projects in Lausanne with Jean-Luc Martin at the CNP, of which I was the founding director from 2004 to 2012.

Establishing the CNP had been the inspiration for an initiative that I began in 2010. The Swiss National Science Foundation launches, usually every three to four years, very competitive calls for applications for National Centers for Competence in Research (NCCRs). The main goal of the NCCRs is the promotion of scientific excellence in areas of major strategic importance for the future of Swiss research, economy, and society. In 2010, we were awarded the NCCR SYNAPSY, one of the eight NCCRs awarded out of 60 applications, with the goal to establish a strong collaboration between basic neuroscientists and psychiatrists through well-integrated research projects based on clinical cohorts. The NCCR SYNAPSY aimed also to

introduce a neuroscience culture in the Department of Psychiatry with the target of training promising young clinicians and promoting the emergence of a new generation of psychiatrists strongly grounded in neuroscience. The NCCR SYNAPSY has been renewed for a total of three four-year phases. When I stepped down as director in 2016, the directorship was assumed by Alexandre Dayer, a talented psychiatrist and neuroscientist who embodies the spirit of the NCCR. It is rewarding to see that, now 10 years on, more than 10 early members of the NCCR SYNAPSY have been appointed to professorial positions in the Departments of Psychiatry of the Universities of Geneva and Lausanne. A NCCR SYNAPSY member, Pierre Marquet, has been awarded a senior Canada research chair in the Department of Psychiatry at Laval University in Quebec. All of these individuals developed a dual career as clinician scientists who were practicing psychiatry.

Pierre Marquet, a remarkable scholar and physician, had joined my lab just before my move to EPFL, as part of the MD-PhD program. He previously had graduated in physics from EPFL and had enrolled in medical studies in Lausanne, eventually completing a full training in clinical psychiatry. Leveraging his strong physics background, particularly in optics, we applied digital holographic microsocopy—an advanced imaging technology that Pierre had developed with his master advisor at EPFL, Christian Depeursinge—to biological questions. This interferometric technique allows the visualization of ionic fluxes and cellular dynamics noninvasively and without any dye (Jourdain et al., 2011; Marquet et al., 2013). This experience showed me the incredible gains that can be achieved by establishing a biology lab in a technology school such as EPFL.

Coda

I am fascinated by what I would call, for lack of better words, the tricks that life plays on you. In my teens, I was interested in understanding the mind and concluded that I should study the brain. As I finished medical school, psychiatry was my clinical interest, but I postponed it to try first to understand how the brain worked and engaged in graduate studies in neuroscience. Thirty or so years later, here I was, after a winding journey through brain metabolism, astrocytes and a variety of signaling molecules and energy substrates, a professor of psychiatry, steering together with competent colleagues a major research effort involving large cohorts of psychiatric patients and even exploring experimentally mechanisms of depression.

I feel as if there were a force, like a magnetic field for paramagnetic molecules, which orients your life, unbeknownst to you, toward a certain goal. Some call it God, others a metaphysical force, others randomness in a complex self-organizing system. The psychoanalytical theory has suggested the terms of drive and libido. Unfortunately, these terms have had, from the beginning of Freud's writings, a strong association with sexuality, but they

in fact encompass all aspects of life. Over the years, I have given considerable thought to the psychoanalytical theory. In fact, I underwent a personal psychoanalytic experience and eventually wrote two books and several articles with a colleague psychiatrist and psychoanalyst François Ansermet (he was not my analyst) (Ansermet and Magistretti, 2004, 2010; Tran The et al., 2018; Arminjon et al., 2010). François is the former chair of the Department of Psychiatry at the University of Geneva: he is the most open-minded psychoanalyst I know, a scholar, a great clinician, and above all a wonderful person. Expanding on my personal considerations about the psychoanalytical theory is beyond the scope of this essay; these were developed in the two books with Ansermet. However, I think that it is worth mentioning here the notion of *unconscious drive*, which is linked to what Freud defined as the pleasure principle. This unconscious drive can account for the sort of force that brings you to situations that come as a surprise. This notion is not far from the theory of decision-making elaborated by Antonio Damasio in his writings, notably "Descartes' error" (Damasio, 1994; Arminjon et al., 2011). Of interest is also the fact that John Maynard Keynes referred to the role of what he called "animal spirits," in decision-making processes in economics and finance (Keynes, 1936).

This past decade has been intense, with all the engagements that I have followed up to now, coexisting: research projects in Lausanne and KAUST; service and administration with IBRO and KAUST; translational activities with the NCCR; and a recent initiative, the creation of GliaPharm, a spin-off from my lab at EPFL co-founded with Sylvain Lengacher, a collaborator of mine since the mid1990s, Charles Finsterwald, who was trained by my first graduate student Jean-Luc Martin, and my son Ambroise. Not surprisingly, I can't help thinking that GliaPharm is somehow a reflection of my scientific and personal life.

My four-decade scientific journey started serendipitously (and with a certain degree of ignorance) with glycogen. This molecule brought my interest to glia and astrocytes, later allowing me to reveal the unexpected role of lactate in the brain, with its implications for plasticity, memory, and brain disorders (Finsterwald et al., 2015; Elsayed and Magistretti 2015). In hindsight, it may seem like a logically, quasi-planned sequence of events. But of course it is not: curiosity, chance, and the unexpected made this happen. Maybe the main lesson that I draw is this: keep an open mind and cherish the unexpected.

Selected Bibliography

Allaman I, Pellerin L and Magistretti PJ (2000) Protein targeting to glycogen (PTG) mRNA expression is stimulated by noradrenaline in mouse cortical astrocytes. *Glia* (4):382–91.

Allaman I, Gavillet M, Bélanger M, Laroche T, Viertl T, Lashuel HA and Magistretti PJ (2010) Amyloid beta-aggregates cause alterations of astrocytic metabolic phenotype: Impact on neuronal viability. *J Neurosci* 30(9):3326–38.

Ansermet F and Magistretti PJ (2004) *A chacun son cerveau: plasticité neuronale et inconscient.* Odile Jacob, Paris.

Ansermet F and Magistretti PJ (2010) *Les énigmes du plaisir.* Odile Jacob, Paris.

Arminjon M, Ansermet F and Magistretti PJ (2010) The homeostatic psyche: Freudian theory and somatic markers. *J Physiol Paris* 104(5):272–8.

Arminjon M, Ansermet F and Magistretti PJ (2011) Emergence of the cerebral self, from Theodor Meynert to Antonio Damasio. *Psychiatr Sci Hum Neurosci* 9:153–61.

Bak LK and Walls AB (2018) CrossTalk opposing view: lack of evidence supporting an astrocyte-to-neuron lactate shuttle coupling neuronal activity to glucose utilisation in the brain. *J Physiol* 596(3):351–53. doi: 10.1113/JP274945. [Epub 2018 Jan 2.]

Barros LF and Weber B (2018) CrossTalk proposal: an important astrocyte-to-neuron lactate shuttle couples neuronal activity to glucose utilisation in the brain. *J Physiol* 596(3):347–50.

Beaudet A and Descarries L (1978) The monoamine innervation of rat cerebral cortex: synaptic and nonsynaptic axon terminals. *Neuroscience* 3(10):851–60.

Bélanger M, Allaman I and Magistretti PJ (2011a) Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. *Cell Metab* 14(6):724–38.

Bélanger M, Yang J, Petit JM, Laroche T, Magistretti PJ* and Allaman I* (2011b) Role of the glyoxalase system in astrocyte-mediated neuroprotection. *J Neurosci* 31(50):18338–52.

Berl S, Nicklas WJ and Clarke DD (1968) Compartmentation of glutamic acid metabolism in brain slices. *J Neurochem* 15:131–40.

Bernardinelli Y, Magistretti PJ and Chatton JY (2004) Astrocytes generate Na+-mediated metabolic waves. *Proc Natl Acad Sci USA* 101(41):14937–42.

Berthet C, Lei H, Thevenet J, Gruetter R, Magistretti PJ and Hirt L (2009) Neuroprotective role of lactate after cerebral ischemia. *J Cereb Blood Flow Metab* (11):1780–9.

Berthet C, Castillo X, Magistretti PJ and Hirt L (2012) New evidence of neuroprotection by lactate after transient focal cerebral ischaemia: extended benefit after intracerebroventricular injection and efficacy of intravenous administration. *Cerebrovasc Dis* 34(5-6):329–35.

Bittar PG, Charnay Y, Pellerin L, Bouras C and Magistretti PJ (1996) Selective distribution of lactate dehydrogenase isoenzymes in neurons and astrocytes of the human brain. *J Cereb Blood Flow Metab* (6):1079–89.

Bliss TM, Ip M, Cheng E, Minami M, Pellerin L, Magistretti PJ and Sapolsky RM (2004) Dual-gene, dual-cell type therapy against an excitotoxic insult by bolstering neuroenergetics. *J Neurosci* 24(27):6202–8.

Bloom F, Segal D, Ling N and Guillemin R (1976) Endorphins: profound behavioral effects in rats suggest new etiological factors in mental illness. *Science* 194(4265):630–2.

*Co-last authors

Bloom FE (1977) Peptide transmitters: clues to the chemical cryptogram of interneuronal communication? *Biosystems* (4):179–83.

Bloom FE (2012) *The history of neuroscience in autobiography*, Volume 7. Edited by Larry R. Squire, 1–56, Oxford University Press.

Boury-Jamot B, Carrard A, Martin JL, Halfon O, Magistretti PJ* and Boutrel B* (2015) Disrupting astrocyte-neuron lactate transfer persistently reduces conditioned responses to cocaine. *Mol Psychiatry* doi: 10.1038/mp.2015.157. [Epub ahead of print.]

Bouzat P, Magistretti PJ and Oddo M (2014) Hypertonic lactate and the injured brain: facts and the potential for positive clinical implications. *Intensive Care Med* 40(6):920–1.

Braitenberg V and Schuz A (1998) *Cortex: statistics and geometry of neuronal connectivity.* Springer, Berlin.

Bröer S, Rahman B, Pellegri G, Pellerin L, Martin JL, Verleysdonk S, Hamprecht B and Magistretti PJ (1997) Comparison of lactate transport in astroglial cells and monocarboxylate transporter 1 (MCT1) expressing Xenopus laevis oocytes. *J Biol Chem* 272(48):30096–102.

Brooks GA (1986) Lactate production under fully aerobic conditions: the lactate shuttle during rest and exercise. *Fed Proc* 45(13): 2924–9.

Brooks GA (2018) The science and translation of lactate shuttle. *Theory Cell Metab* 27(4):757–85.

Bucher MB and Schorderet M (1975) Dopamine- and apomorphine-sensitive adenylate cyclase in homogenates of rabbit retina. *Naunyn Schmiedebergs Arch Pharmacol* 288(1):103–7.

Burt DR, Enna SJ, Creese I and Snyder SH (1975) Dopamine receptor binding in the corpus striatum of mammalian brain. *Proc Natl Acad Sci USA* 72(11):4655–9.

Calì C, Agus M, Kare K, Boges DJ, Lehväslaiho H, Hadwiger M and Magistretti PJ (2019) 3D cellular reconstruction of cortical glia and parenchymal morphometric analysis from Serial Block-Face Electron Microscopy of juvenile rat. *Prog Neurobiol* 183:101696. doi: 10.1016/j.pneurobio.2019.101696. [Epub 2019 Sep 21.]

Calì C, Baghabra J, Boges DJ, Holst GR, Kreshuk A, Hamprecht FA, Srinivasan M, Lehväslaiho H and Magistretti PJ (2016) Three-dimensional immersive virtual reality for studying cellular compartments in 3D models from EM preparations of neural tissues. *J Comp Neurol* 524(1):23–38.

Cardinaux JR and Magistretti PJ (1996) Vasoactive intestinal peptide, pituitary adenylate cyclase-activating peptide, and noradrenaline induce the transcription factors CCAAT/enhancer binding protein (C/EBP)-beta and C/EBP delta in mouse cortical astrocytes: involvement in cAMP-regulated glycogen metabolism. *J Neurosci* 16(3):919–29.

Carrard A, Elsayed M, Margineanu M, Boury-Jamot B, Fragnière L, Meylan EM, Petit JM, Fiumelli H, Magistretti PJ* and Martin JL* (2016) Peripheral administration of lactate produces antidepressant-like effects. *Mol Psychiatry* doi:10.1038/mp.2016.237.

Carteron L, Solari D, Patet C, Quintard H, Miroz JP, Bloch J, Daniel RT, Hirt L, Eckert P, Magistretti PJ and Oddo M (2018) Hypertonic lactate to improve

cerebral perfusion and glucose availability after acute brain injury. *Crit Care Med* doi: 10.1097/CCM.0000000000003274. [Epub ahead of print.]

Chavkin C, Bakhit C, Weber E and Bloom FE (1983) Relative contents and concomitant releases of prodynorphin/neoendorphin-derived peptides in rat hippocampus. *Proc Natl Acad Sci USA* 80(24):7669–73.

Cholet N, Pellerin L, Welker E, Lacombe P, Seylaz J, Magistretti PJ and Bonvento G (2001) Local injection of antisense oligonucleotides targeted to the glial glutamate transporter glast decreases the metabolic response to somatosensory activation. *J Cereb Blood Flow Metab* 21(4):404–12.

Choi HB, Gordon GR, Zhou N, Tai C, Rungta RL, Martinez J, Milner TA, Ryu JK, McLarnon JG, Tresguerres M, Levin LR, Buck J, MacVicar BA (2012) Metabolic communication between astrocytes and neurons via bicarbonate-responsive soluble adenylyl cyclase. *Neuron* 75(6):1094–104.

Clement-Cormier YC, Kebabian JW, Petzold GL and Greengard P (1974) Dopamine-sensitive adenylate cyclase in mammalian brain: a possible site of action of antipsychotic drugs. *Proc Natl Acad Sci USA* 71(4):1113–7.

Coggan JS, Calì C, Keller D, Agus M, Boges D, Abdellah M, Kare K, Lehväslaiho H, Eilemann S, Jolivet RB, Hadwiger M, Markram H, Schürmann F and Magistretti PJ (2018) A process for digitizing and simulating biologically realistic oligocellular networks demonstrated for the neuro-glio-vascular ensemble. *Front Neurosci* 12:664. doi: 10.3389/fnins.2018.00664. [eCollection 2018.]

Coggan JS, Keller D, Markram H, Schürmann F, Magistretti PJ (2020) Excitation states of metabolic networks predict dose-response fingerprinting and ligand pulse phase signalling. *J Theor Biol* 487:110123. doi: 10.1016/j.jtbi.2019.110123. [Epub 2019 Dec 19.]

D'Angour A (2013) Love's battlefield: rethinking Sappho fr 31. *In « Erôs in Ancient Greece »*

Ed Sanders, Chiara Thumiger, Christopher Carey, and Nick Lowe, Editors, Oxford Scholarship Online: May 2013 DOI: 10.1093/acprof:oso/9780199605507.001.0001

Djamgoz MB and Wagner HJ (1992) Localization and function of dopamine in the adult vertebrate retina. *Neurochem Int* 20(2):139–91.

Elsayed M and Magistretti PJ (2015) A new outlook on mental illnesses: glial involvement beyond the glue. *Front Cell Neurosci* 9:468.

Enna SJ, Bennett JP Jr, Bylund DB, Creese I, Burt DR, Charness ME, Yamamura HI, Simantov R and Snyder SH (1977) Neurotransmitter receptor binding: regional distribution in human brain. *J Neurochem* 28(1):233–6.

Falck B, Hillarp N-Å, Thieme G and Torp A (1962) Fluorescence of catecholamines and related compounds condensed with formaldehyde. *J Histochem Cytochem* 10(3):348–54.

Finsterwald C, Magistretti PJ and Lengacher S (2015) Astrocytes: new targets for the treatment of neurodegenerative diseases. *Curr Pharm Des* 21(25):3570–81.

Foote SL, Aston-Jones G and Bloom FE (1980) Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. *Proc Natl Acad Sci USA* 77(5):3033–7.

Foote SL, Bloom FE and Aston-Jones G (1983) Nucleus locus ceruleus: new evidence of anatomical and physiological specificity. *Physiol Rev* 63(3):844–914.

Fox PT and Raichle ME (1986) Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci USA* 83(4):1140–4.

Fox PT, Raichle ME, Mintun MA and Dence C (1988) Nonoxidative glucose consumption during focal physiologic neural activity. *Science* 241(4):462–4.

Gao V, Suzuki A, Magistretti PJ, Lengacher S, Pollonini G, Steinman MQ and Alberini CM (2016) Astrocyte β2-adrenergic receptors mediate hippocampal long-term memory consolidation. *Proc Natl Acad Sci USA* 113(30):8526–31. doi: 10.1073/pnas.1605063113.

Garau L, Govoni S, Stefanini E, Trabucchi M and Spano PF (Oct 1978) Dopamine receptors: pharmacological and anatomical evidences indicate that two distinct dopamine receptor populations are present in rat striatum. *Life Sci* 23(17–18):1745–50.

Giulietti I (2008) *Magistretti e Trefogli, medici chirurghi del '700 e '800, patrizi di Torricella-Taverne*. Storia Medica Ticinese, Taverne.

Greengard P and Straub RW (1959) Effect of frequency of electrical stimulation on the concentration of intermediary metabolites in mammalian non-myelinated fibres. *J Physiol* 148(2):353–61.

Greengard P and Straub RW (1962) Metabolic studies on the hyperpolarization following activity in mammalian non-myelinated nerve fibres. *J Physiol* 161:414–23.

Grzanna R, Molliver ME and Coyle JT (1978) Visualization of central noradrenergic neurons in thick sections by the unlabeled antibody method: a transmitter-specific Golgi image. *Proc Natl Acad Sci USA* 75(5):2502–6.

Hof PR, Pascale E and Magistretti PJ (1988) K+ at concentrations reached in the extracellular space during neuronal activity promotes a Ca++-dependent glycogenolysis. *J Neurosci* (6):1922–8.

Hof PR, Dietl MM, Charnay Y, Martin JL, Bouras C, Palacios JM and Magistretti PJ (1991) Vasoactive intestinal peptide binding sites and fibers in the brain of the pigeon Columba livia: an autoradiographic and immunohistochemical study. *J Comp Neurol* 305(3):393–411.

Hoffer BJ, Siggins GR and Bloom FE (1971) Studies on norepinephrine-containing afferents to Purkinje cells of rat cerebellum. II. Sensitivity of Purkinje cells to norepinephrine and related substances administered by microiontophoresis. *Brain Res* 25(3):523–34.

Hokfelt T, Elfvin LG, Elde R, Schultzberg M, Goldstein M and Luft, R (1977) Occurrence of somatostatin-like immunoreactivity in some peripheral sympathetic noradrenergic neurons. *Proc Natl Acad Sci USA* 74(8):3587–91.

Hökfelt, T (1991) Neuropeptides in perspective: the last ten years. *Neuron* 7(6):867–879.

Irace F and Pasca, V (1999) *Vico Magistretti: architetto e designer.* Electa, Milano.

Itoh Y, Esaki T, Shimoji, K, Cook M, Law MJ, Kaufman E and Sokoloff L (2003) Dichloroacetate effects on glucose and lactate oxidation by neurons and astroglia in vitro and on glucose utilization by brain in vivo. *Proc Natl Acad Sci USA* 100(8):4879–84.

Jourdain P, Pavillon N, Moratal C, Boss D, Rappaz B, Depeursinge C, Marquet P and Magistretti PJ (2011) determination of transmembrane water fluxes in neurons elicited by glutamate ionotropic receptors and by the cotransporters KCC2 and NKCC1: a digital holographic microscopy study. *J Neurosci* 31(33):11846–54.

Jourdain P, Allaman I, Rothenfusser K, Fiumelli H, Marquet P and Magistretti PJ (2016) L-Lactate protects neurons against excitotoxicity: implication of an ATP-mediated signaling cascade. *Sci Rep* 6:21250. doi: 10.1038/srep21250.

Jourdain P, Rothenfusser K, Ben-Adiba C, Allaman I, Marquet P, Magistretti PJ (2018) Dual action of L-Lactate on the activity of NR2B-containing NMDA receptors: from potentiation to neuroprotection. *Sci Rep* 8(1):13472.

Karnovsky M and Bolis L (1982) *Phagocytosis: past and future*. Academic Press, New York.

Kebabian JW, Petzold GL and Greengard P (1972) Dopamine-sensitive adenylate cyclase in caudate nucleus of rat brain, and its similarity to the "dopamine receptor." *Proc Natl Acad Sci USA* 69(8):2145–9.

Kadekaro M, Crane AM and Sokoloff L (1985) Differential effects of electrical stimulation of sciatic nerve on metabolic activity in spinal cord and dorsal root ganglion in the rat. *Proc Natl Acad Sci USA* 82(17):6010–13.

Kerr SE (1938) The carbohydrate metabolism of brain: VI isolation of glycogen. *J Biol Chem* 123:443–9.

Keynes JM (1936) *The general theory of employment, interest and money. Volume VII of collected writings*, 161–162. Macmillan, London.

Kilic K, Karatas H, Donmez-Demir B, Eren-Kocak E, Gursoy-Ozdemir Y, Can A, Petit JM, Magistretti PJ and Dalkara T (2017) inadequate brain glycogen or sleep increases spreading depression susceptibility. *Ann Neurol* doi: 10.1002/ana.25122. [Epub ahead of print.]

Laughton J, Charnay Y, Belloir L, Pellerin L, Magistretti PJ and Bouras C (2000) Differential mRNA distribution for lactate dehydrogenase LDH-1 and LDH-5 isoforms in the rat brain. *Neuroscience* 96(3):619–25.

Locatelli R (2012) *Homines loci torrexelle et tabernarum*. Patriciato e Comune di Torricella-Taverne.

McAfee DA, Schorderet M and Greengard P (1971) Adenosine 3′,5′-monophosphate in nervous tissue: increase associated with synaptic transmission. *Science* 171(3976):1156–8.

McIlwain H (1953) Substances which support respiration and metabolic response to electrical impulses in human cerebral tissues. *J Neurol Neurosurg Psych* 16(4):257–266.

Magistretti PJ (1990) VIP neurons in the cerebral cortex. *Trends Pharmacol Sci* 11(6):250–4.

Magistretti PJ and Schorderet M (1979) Dopamine receptors in bovine retina: characterization of 3H-spiroperidol binding and its use for screening dopamine receptor affinity of drugs. *Life Sci* 25(19):1675–86.

Magistretti PJ, Morrison JH, Shoemaker WJ, Sapin V and Bloom FE (1981) Vasoactive intestinal polypeptide induced glycogenolysis in mouse cortical slices: a possible regulatory mechanism for the local control of energy metabolism. *Proc Natl Acad Sci USA* 78(10):6535–9.

Magistretti PJ, Manthorpe M, Bloom FE and Varon S (1983) Functional receptors for vasoactive intestinal peptide in cultured astroglia from neonatal rat brain. *Regul Pept* (1):71–80.

Magistretti PJ and Schorderet M (1984) VIP and noradrenaline act synergistically to increase cyclic AMP in cerebral cortex. *Nature* 308(5956):280–2.

Magistretti PJ and Morrison JH (1985) VIP neurons in the neocortex. *Trends Neurosci* 8:7–8.

Magistretti PJ and Schorderet M (1985) Norepinephrine and histamine potentiate the increases in cyclic adenosine 3':5'-monophosphate elicited by vasoactive intestinal polypeptide in mouse cerebral cortical slices: mediation by alpha 1-adrenergic and H1-histaminergic receptors. *J Neurosci* (2):362–8.

Magistretti PJ, Hof P and Martin JL (1986) Adenosine stimulates glycogenolysis in mouse cerebral cortex: a possible coupling mechanism between neuronal activity and energy metabolism. *J Neurosci* (9):2558–62.

Magistretti PJ and Morrison JH (1988) Noradrenaline- and vasoactive intestinal peptide-containing neuronal systems in neocortex: functional convergence with contrasting morphology. *Neuroscience* (2):367–78.

Magistretti PJ and Chatton JY (2005) Relationship between L-glutamate-regulated intracellular (Na (+) dynamics and ATP hydrolysis in astrocytes. *J Neural Transm* 112(1):77–85.

Magistretti, PJ and Allaman I (2015) A cellular perspective on brain energy metabolism and functional imaging. *Neuron* 86(4):883–901.

Magistretti PJ and Allaman I (2018) Lactate in the brain: from metabolic end-product to signalling molecule. *Nat Rev Neurosci* 19(4):235–49. doi: 10.1038/nrn.2018.19.

Margineanu MB, Mahmood H, Fiumelli H and Magistretti PJ (2018) L-lactate regulates the expression of synaptic plasticity and neuroprotection genes in cortical neurons: a transcriptome analysis. *Front Mol Neurosci* 11:375. doi: 10.3389/fnmol.2018.00375. [eCollection 2018.]

Marquet P, Depeursinge C and Magistretti PJ (2013) Exploring neural cell dynamics with digital holographic microscopy. *Annu Rev Biomed Eng* 15:407–31.

Martin JL, Dietl MM, Hof PR, Palacios JM and Magistretti PJ (1987) Autoradiographic mapping of [mono (125I) iodo-Tyr10, MetO17]-vasoactive intestinal peptide binding sites in the rat brain. *Neuroscience* 23(2):539–65.

Martin JL and Magistretti PJ (1989 a) Pharmacological studies of voltage-sensitive Ca^{2+}-channels involved in the release of vasoactive intestinal peptide evoked by K+ in mouse cerebral cortical slices. *Neuroscience* 30(2): 423–31.

Martin JL and Magistretti PJ (1989 b) Release of vasoactive intestinal peptide in mouse cerebral cortex: Evidence for a role of arachidonic acid metabolites. *J Neurosci* (7):2536–42

Morrison JH, Grzanna R, Molliver ME and Coyle JT (1978) The distribution and orientation of noradrenergic fibers in neocortex of the rat: an immunofluorescence study. *J Comp Neurol* 181(1):17–39.

Morrison JH, Molliver ME and Grzanna R (1979) Noradrenergic innervation of cerebral cortex: widespread effects of local cortical lesions. *Science* 205(4403): 313–6.

Morrison JH, Molliver ME and Grzanna R and Coyle JT (1981) The intra-cortical trajectory of the coeruleo-cortical projection in the rat: a tangentially organized cortical afferent. *Neuroscience* 6(2):139–58.

Morrison JH, Benoit R, Magistretti PJ and Bloom FE (1983) Immunohistochemical distribution of pro-somatostatin-related peptides in cerebral cortex. *Brain Res* 262(2):344–51.

Morrison JH and Magistretti PJ (1983) Monoamines and peptides in cerebral cortex. *Trends Neurosci* 6:146–15.

Morrison JH, Magistretti PJ, Benoît R and Bloom FE (1984) The distribution and morphological characteristics of the intracortical VIP-positive cell: an immunohistochemical analysis. *Brain Res* 292(2):269–82.

Morrison BM, Lee Y, Li Y, Lengacher S, Farah MH, Liu Y, Tsingalia A, Jin L, Zhang PW, Griffin JW, Pellerin L, Magistretti PJ and Rothstein JD (2012) Oligodendroglia have a fundamental role in metabolic support of axons and contribute to neurodegeneration. *Nature* 487(7408):443–8.

Nelson SR, Schulz DW, Passonneau JV and Lowry OH (1968) Control of glycogen levels in brain. *J Neurochem* (11):1271–9.

Pasca V (1991) *Vico Magistretti: designer*. Thames & Hudson, London.

Pellerin L and Magistretti PJ (1994) Glutamate uptake into astrocytes stimulates aerobic glycolysis: A mechanism coupling neuronal activity to glucose utilization. *Proc Natl Acad Sci USA* 91(22):10625–9.

Pellerin L and Magistretti PJ (1997) Glutamate uptake stimulates Na+/K+-ATPase activity in astrocytes via activation of a distinct subunit highly sensitive to ouabain. *J Neurochem* 69(5):2132–7.

Pellerin L, Pellegri G, Martin JL and Magistretti PJ (1998) Expression of monocarboxylate transporter mRNAs in mouse brain: support for a distinct role of lactate as an energy substrate for the neonatal vs. adult brain. *Proc Natl Acad Sci USA* 95(7):3990–5.

Pellerin L and Magistretti PJ (2012) Sweet sixteen for ANLS. *J Cereb Blood Flow Metab* 32(7):1152–66.

Peters A and Kimerer LM (1981) Bipolar neurons in rat visual cortex: a combined Golgi-electron microscope study. *J Neurocytol* 10(6):921–46.

Petit JM, Gyger J, Burlet-Godinot S, Fiumelli H, Martin JL and Magistretti PJ (2013) Genes involved in the astrocyte-neuron lactate shuttle (ANLS) are specifically regulated in cortical astrocytes following sleep deprivation in mice. *Sleep* 36(10):1445–58.

Petit JM and Magistretti PJ (2015) Regulation of neuron-astrocyte metabolic coupling across the sleep-wake cycle. *Neuroscience* pii: S0306-4522(15)01090-8.

Phelps CH (1972) Barbiturate-induced glycogen accumulation in brain. An electron microscopic study. *Brain Res* 39(1):225–34.

Pierre K, Pellerin L, Debernardi R, Riederer BM and Magistretti PJ (2000) Cell-specific localization of monocarboxylate transporters, MCT1 and MCT2 in the adult mouse brain revealed by double immunohistochemical labeling and confocal microscopy. *Neuroscience* 100(3):617–27.

Pittman QJ and Siggins GR (1981) Somatostatin hyperpolarizes hippocampal pyramidal cells in vitro. *Brain Res* 221(2):402–8.

Pliteri S (2003) *Il pancreas esocrino*. Masson & Cie, Paris.

Pliteri S and Sironi, PG (2005) *Storia di un chirurgo clinico*. M&B Publishers, Milano.

Quach TT, Rose C and Schwartz JC (1978) [3H]Glycogen hydrolysis in brain slices: responses to neurotransmitters and modulation of noradrenaline receptors. *J Neurochem* (6):1335–41.

Quik M, Iversen LL and Bloom SR (1978) Effect of vasoactive intestinal peptide (VIP) and other peptides on cAMP accumulation in rat brain. *Biochem Pharmacol* 27(18):2209–13.

Rall TW and Sutherland EW (1958) Formation of a cyclic adenine ribonucleotide by tissue particles. *J Biol Chem* 232(2):1065–76.

Ruminot I, Gutierrez R, Pena-Munzenmayer, G., Anazco, C, Sotelo-Hitschfeld, T, Lerchundi, R, Niemeyer MI, Shull GE and Barros LF (2011) NBCe1 mediates the acute stimulation of astrocytic glycolysis by extracellular K+. *J Neurosci* 31(4):14264–71.

Schaad N, Schorderet M and Magistretti PJ (1987) Synergism between VIP and noradrenaline in increasing cAMP in the cerebral cortex: role of prostaglandins. *Nature* 328(6131):637–40.

Siggins GR, Oliver AP, Hoffer BJ and Bloom FE (1971) Cyclic adenosine monophosphate and norepinephrine: effects on transmembrane properties of cerebellar Purkinje cells. *Science* 171(3967):192–4.

Siggins GR, McGinty JF, Morrison JH, Pittman QJ, Zieglgänsberger W, Magistretti PJ and Gruol DL (1982) The role of neuropeptides in the hippocampal formation. *Adv Biochem Psychopharmacol* 33:413–22.

Siggins GR, Henriksen SJ, Chavkin C and Gruol D (1986) Opioid peptides and epileptogenesis in the limbic system: cellular mechanisms. *Adv Neurol* 44:501–12.

Sokoloff L, Reivich M, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD, Sakurada O and Shinohara M (1977) The [14C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *J Neurochem* 28(5):897–916.

Sokoloff L (1981) Localization of functional activity in the central nervous system by measurement of glucose utilization with radioactive deoxyglucose. *J Cereb Blood Flow Metab* 1(1):7–36.

Sotelo C and Palay SL (1968) The fine structure of the lateral vestibular nucleus in the rat: I. Neurons and neuroglial cells. *J Cell Biol* 36(1):151–79.

Sutherland EW and Robison GA (1966) The role of cyclic-3',5'-AMP in responses to catecholamines and other hormones. *Pharmacol Rev* 18(1):145–64.

Suzuki A, Stern SA, Bozdagi O, Huntley GW, Walker RH, Magistretti PJ and Alberini CM (2011) Astrocyte-neuron lactate transport is required for long-term memory formation. *Cell* 144(5):810–23.

Swanson RA, Morton MM, Sagar SM, Sharp FR (1992) Sensory stimulation induces local cerebral glycogenolysis: demonstration by autoradiography. *Neuroscience* 51:451–61.

Tadi M, Allaman I, Lengacher S, Grenningloh G and Magistretti PJ (2015) Learning-induced gene expression in the hippocampus reveals a role of neuron–astrocyte metabolic coupling in long term memory. *PLoS One* 10(10):e0141568.

Takahashi S, Driscoll BF, Law MJ and Sokoloff L (1995) Role of sodium and potassium ions in regulation of glucose metabolism in cultured astroglia. *Proc Natl Acad Sci USA* 92(10):4616–20.

Tauffenberger A, Fiumelli H, Almustafa S and Magistretti PJ (2019) Lactate and pyruvate promote oxidative stress resistance through hormetic ROS signaling. *Cell Death Dis* 10(9):653.

Tran The J, Magistretti P and Ansermet F (2018) The epistemological foundations of Freud's energetics model. *Front Psychol* 9:1861. doi: 10.3389/fpsyg.2018.01861. [eCollection 2018.]

Vezzoli E, Calì C, De Roo M, Ponzoni L, Sogne E, Gagnon N, Francolini M, Braida D, Sala M, Muller D, Falqui A and Magistretti PJ (2019) Ultrastructural evidence for a role of astrocytes and glycogen-derived lactate in learning-dependent synaptic stabilization. *Cereb Cortex* 6. pii: bhz226. doi: 10.1093/cercor/bhz226. [Epub ahead of print.]

Voutsinos-Porche B, Bonvento G, Tanaka K, Steiner P, Welker E, Chatton JA, Magistretti PJ and Pellerin L (2003) Glial glutamate transporters mediate a functional metabolic crosstalk between neurons and astrocytes in the mouse developing cortex. *Neuron* 37(2):275–86.

Warburg O (1956) On the origin of cancer cells. *Science* 123(3191):309–14.

Weber B and Barros LF (2015) The astrocyte: powerhouse and recycling center. *Cold Spring Harb Perspect Biol* 7(12):a020396.

Yang J, Ruchti E, Petit JM, Jourdain P, Grenningloh G, Allaman I and Magistretti PJ (2014) Lactate promotes plasticity gene expression by potentiating NMDA signaling in neurons. *Proc Natl Acad Sci USA* 111(33):12228–33.

Yu N, Martin JL, Stella N and Magistretti PJ (1993) Arachidonic acid stimulates glucose uptake in cerebral cortical astrocytes. *Proc Natl Acad Sci USA* 90(9):4042–6.