The History of Neuroscience in Autobiography
Volume 2

Edited by Larry R. Squire
Published by Society for Neuroscience
ISBN: 0-12-660302-2

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pp. 168–190

https://doi.org/10.1016/S1874-6055(99)80008-5

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Masao Ito discovered long-term depression in the cerebellum and carried out fundamental studies of the physiology and function of the cerebellum. In his later career, he became a highly visible scientific leader in Japan and an effective spokesperson for international cooperation in science.

The History of Neuroscience in Autobiography, Volume 2

Masao Ito

I am not sure if my personal history will be of interest to the reader, but since whenever I face a difficulty I think of what my predecessors would have done, I would like to write here about major events and related anecdotes in my life so far, in the hope that they may contain some useful information for succeeding generations of neuroscientists.

My Parents

I was born in 1928 in Nagoya, Japan. My father, Mutuo, was the proprietor of a small enterprise that produced soft drinks. He died in 1935. I remember little about him, but my mother, Chiyo, frequently commented that he was capable of fast mental arithmetic. When doing calculations, he moved the fingers of his right hand on his knee as if he were using a Japanese abacus. Because he left the enterprise to my mother, she was able to maintain a comfortable standard of living for her family, including her mother, her sister, my two sisters, and me. My mother was one of the early graduates of Nara Women's Higher Education School which, early in the 20th century, was one of only two colleges in Japan that were dedicated to training women to be qualified school teachers. Before marriage, she taught at the girls' middle school, which her uncle had founded in Nagoya. My relatives told me that she was a popular teacher. To me, she was a calm and modest lady with a hidden, high intellect.

Middle School and High School Days

In 1941, the year I entered middle school, the Pacific war began. It ended in 1945, the year I graduated from that school. Middle school students were mobilized to help construct a military airport, and my final year there was spent in labor service at a military arms factory. In February 1945, I entered the preparatory course of the military school, and until the end of August, I stayed in a camp which was first located near Tokyo and then moved to a mountainous area west of Tokyo. I have only a few pleasant memories from this wartime period, for example, a number of capable teachers in the middle school and the lessons and practice on car engines at the camp.

In October 1945, I entered the 8th High School, one of the eight prestigious high schools at that time. I was fortunate in that the 8th High school

had excellent teachers of mathematics, physics, chemistry, biology, English, and German, and that an emphasis on general culture had been a core of the high school traditions since prewar time. Along with many of my contemporaries, I am saddened that these traditions were lost when the entire Japanese school system was reformed shortly after the War.

One notable event from my high school days was that I spent 7 months in 1946 in a sanatorium near Nagoya recuperating from tuberculosis. At that time, the mortality rate for the disease was high and, in fact, during the rainy season in June, many patients died every day in the sanatorium. A young medical doctor who was a patient in the next room used to tell me how interesting medicine was to him, and how exciting his experiences at a university clinic were. His enthusiasm and stories opened my eyes to the existence of the immense fields of medical science. The director of the sanatorium, Rokuro Katsunuma, a tuberculosis expert with an enthusiastic mind for research, often tried to convince me that research is the only way to solve difficult medical problems, such as how to cure cancer and mental diseases. He also emphasized that any talented scientist can find his or her own comfortable niche somewhere in the vast fields of medical science. Thanks to the guidance I received from these people, I decided to study medicine.

University Days

In 1949 I entered the University of Tokyo Medical School. The initial months were full of new impressions, and I was particularly moved when I saw the brains of eminent politicians, scholars, and novelists kept in a storage room for anatomical reference material. However, I soon became bored with too many lectures that were purely descriptive in nature. I became nostalgic for physics, and audited a course in nuclear physics taught by San-īchiro Mizushima of the Faculty of Science. I did not formally register for this course, but no one minded that I attended the classes. Meanwhile, I found Shimane Sakamoto's physiology lectures on classic theories of membrane excitation and conduction very interesting. I then met a young physiologist, Masayasu Sato, and used to spend most of my time in his laboratory, just watching him experiment on single nerve fibers excised from toads using a Helmholtz pendulum for stimulation, and discussing saltatory conduction in myelinated nerve fibers, which was the most advanced theory before the epoch-making Hodgkin–Huxley theory was published in 1952. Baldwin's monograph on biochemistry also greatly affected me. I organized a series of seminars to read this book with a group of students and young researchers, including Masanori Otsuka, Seturo Ebashi, Masayasu Sato, and Sinji Ishikawa. Later, I had also a chance to engage in histological studies at the Brain Research Institute of the medical school. I was amazed by the numerous beautiful neurons I observed under a microscope, and enjoyed thinking about what these neurons do.

After graduating from medical school in 1953, I interned for 1 year at the Tokyo University Hospital where I completed rotations through a number of clinical sections. I was most interested in neurosurgery, psychiatry, and ophthalmology but, in the end, decided to pursue a career in physiology. During this internship, I had a chance to escape from the hospital from time to time to study in Takefusa Sakamoto's electroengineering laboratory in the Faculty of Engineering. Here I constructed direct current-coupled amplifiers and stabilized power supplies, which were frontier technology at that time; it was a good time which allowed me such an option at my own risk. In 1954, Masayasu Sato returned from University College London where he had been on a British Council Fellowship for 2 years, and was appointed as professor at Kumamoto University Medical School. I moved to Kumamoto to work as assistant professor in his new department.

Thesis Work in Kumamoto

Around 1950, Bernard Katz's discovery of quantal release of neurotransmitters and John Eccles' discovery of inhibitory synaptic transmission were two major breakthroughs which, together with the Hodgkin–Huxley theory, opened a new era of neurophysiology. The epoch-making new technology used for these discoveries was glass microelectrodes connected to electronic instruments. In Japan, Takuzo Otani and Yasuji Katsuki were pioneers who applied this technology to the study of toad spinal motoneurons and mammalian central auditory systems, respectively. For my work in Kumamoto, I chose toad dorsal root ganglion cells which, having only one axon and no dendrites and forming no synapses, provided a very simple model of nerve cells. After 1 year of struggle in a laboratory set up in a barracks with all hand-made electronic instruments, I made the first ever intracellular recording with a microelectrode from dorsal root ganglion cells, and studied the electrical properties of their membrane. I found a peculiar rectification of the membrane which, according to present knowledge, is apparently due to H currents.

When my first physiology paper on electrical properties of dorsal root ganglion cells was published in the *Japanese Journal of Physiology* (Ito, 1957), I received requests for reprints from abroad; it was a joy for me to find among these, letters from two great scholars. One was Harry Gundfest who recommended the term "transmembrane stimulation" as a replacement for direct stimulation of the membrane which I had used, and the other was from John Eccles, who invited me to join his laboratory. John Eccles' monographs *The Neurophysiological Basis of Mind* (1953) and *Physiology of Nerve Cells* (1957) were almost like bibles for young researchers, and I considered it a blessing to receive such an invitation from the author of these books.

After staying in Kumamoto for 3 years, I returned to Tokyo in 1957 and was employed as a lecturer at Nippon Dental College and, shortly after, as

assistant professor in the Second Department of Physiology, of the University of Tokyo, chaired by the late Isao Wakabayashi. While I continued to work on dorsal root ganglion cells, I planned a trip to Canberra. I had been married to my wife Midori since 1956, and in February 1959, we left Yokohama Harbor on a 3000-ton ship on which we traveled for 1 month to Hong Kong, Borneo, Cairns, Brisbane, and finally Sydney, from where we flew to Canberra.

Three Years in Canberra

Canberra was like paradise. We lived in a comfortably furnished flat four km from the John Curtin School of Medical Research of the Australian National University; it took no more than ten minutes to drive. John Eccles' department occupied the western half of the third floor of a long brick building. At one end of the corridor was a professor's study and laboratory. At the other end was a room for technicians and a storeroom. In between were small booths for individual researchers on one side of the corridor, while on the other side were three laboratories used by David Curtis, John Hubbard, and graduate students, respectively. The four laboratories were air-conditioned, and fully equipped with instruments designed by Jack Coombs. If any problem occurred, several technicians rushed to fix it. In the morning, technicians distributed anesthetized animals to each laboratory, and developed films that had been exposed the day before. Data were continuously collected in these four laboratories, and numerous papers were sent out for publication. At the John Curtin School library, current and past issues of almost all journals published at that time were available. These conditions are not extraordinary today, but it seems like a miracle to me that they existed forty years ago in a university department.

John Eccles' department attracted about seventy researchers from abroad. Its alumni association list includes the names of numerous eminent individuals presently considered leaders in the world of neuroscience. Among these, Per Andersen, Tatsunosuke Araki, Platon Kostyuk, Olov Oscarsson, Tomokazu Oshima, John Phillis, Tom Sears, Rod Westerman, and Bill Willis were my contemporaries. It seems to me to have been one of those rare occasions in which a single scholar attracts a large number of young talents who then became the leaders of the next generation.

During the first year of my stay I had a precious opportunity to work as part of a team with John Eccles and his daughter, Rose. We studied the ionic permeability of cat spinal motoneuron membranes by injecting two ion species in combination through double-barrelled microelectrodes, each barrel filled with a different solution. I learned the energetic and organized ways to conduct cat experiments. In addition, during the English-style tea time—often held at midnight during a break from an experiment—John Eccles often talked about his days in Oxford, and especially about Charles Sherrington. Apparently, John Eccles was taking Sherrington as his role

model. Eccles, born in 1903, used to ask how he could stop working when Sherrington had started to fully work only after the age of sixty.

During the second year of my stay, I continued ionic permeability studies using electrophoretic injection techniques (Araki et al., 1961; Ito et al., 1962). We tested 34 different anion species and found a sharp distinction between permeant and nonpermeant ions through inhibitory subsynaptic membranes, proof of the sieve-membrane hypothesis. During the third year, I recognized a peculiar multiple exponential behavior of motoneuron membrane for current steps, and devoted a considerable amount of time to analyzing it (Ito and Oshima, 1965). The 3 years passed quickly and fruitfully and, in 1962, I decided to return home. We took with us our two children who had been born in Canberra, and a great respect for John Eccles and his department. One year later, John Eccles was awarded the 1963 Nobel Prize for Medicine and Physiology.

Return to Tokyo

By the time I returned to the University of Tokyo, Koji Uchizono had succeeded to the chair of the Second Department of Physiology. I was appointed associate professor, and organized a research group with Nakaakira Tsukahara, Keisuke Toyama, Mituo Yoshida, and later also with Kunihiko Obata, Masanori Hongo, Yasuhiro Okada, Rikuo Ochi, and Masao Udo. Research funds were scarce, and we had to start by building a shielded room with wood and wire netting as well as building all our electronic instruments. Mr. Eichi Narishige made a cat frame, a micromanipulator, and a microelectrode puller for us according to blueprints given to me by John Eccles. We had no technicians working directly for us, and we took care of the animals and cleaned our laboratory ourselves. This situation, however, was not an obstacle, because we were all young and in high spirits.

Initially, I wished to continue my work on spinal motoneurons in order to solve one particular problem that was left unsolved in John Eccles' 1963 monograph, *The Physiology of Synapses.* It was clear that chloride ions contributed to the generation of inhibitory postsynaptic potentials (IPSPs); the belief at that time that potassium ions also contribute was based merely on the size of hydrated potassium ions being similar to that of hydrated chloride ions, and that permeation of potassium ions through a membrane was expected to generate a membrane hyperpolarization similar to IPSPs. I wanted to test the potassium contribution hypothesis, but to do this, it was necessary to deprive motoneurons of chloride ions. If IPSPs occurred in the absence of chloride ions, they must be generated, at least partly, I thought, by potassium ion flux. We perfused cat spinal cords *in vivo* with a chloride-free solution and exchanged the circulating blood with chloride-free artificial blood. We reduced the chloride content of the spinal cord by one-half, but this caused the heart to stop beating. After a number of un-

successful experiments, we gave up. We were ahead of our time in these experiments; today chloride deprivation can be achieved easily in *in vitro* experiments on brain slices, and it has been proven that IPSPs are caused solely by increases in chloride flux.

Inhibitory Action of Purkinje Cells

I had to choose the next theme for my group of researchers who were impatient. Recalling the impressive anatomy lectures in my medical student days by Teizo Ogawa on giant neurons in the nucleus of Deiters and the red nucleus, I took up the study of these two types of neurons in cat brain stems. We formed two teams, one on Deiters neurons and the other on red nucleus neurons, and used the single laboratory on alternate days. In the morning, the off-duty team would arrive and the other team, which had been working since the preceding morning, would have to stop even if they were in the middle of an experiment. It took some months before we successfully penetrated these neurons with glass microelectrodes in cat brain stem.

In November 1963, Yoshida and I made the surprising observation that large IPSPs were generated in a Deiters neuron upon stimulation of the cerebellum. The latency of the IPSPs was short enough to indicate that they were induced monosynaptically (Ito and Yoshida, 1966). We stimulated Purkinje cells both directly and indirectly via afferent pathways, and confirmed that IPSPs always accompanied Purkinje cell excitation (Ito et al., 1966). We also confirmed that the IPSPs were evoked only from the ipsilateral vermis from which Purkinje cells project to the nucleus of Deiters (Ito et al., 1968a). We made similar observations on neurons in cerebellar nuclei, which receive Purkinje cell projections from respective areas of the cerebellum (Ito et al., 1970). I was convinced that Purkinje cells establish direct inhibitory connections with Deiters neurons and that Purkinje cells are inhibitory in nature.

This discovery provoked objections. Because all previously identified inhibitory neurons were small Golgi type-II neurons with relatively short axons, such as Renshaw cells in the spinal cord and basket cells in the hippocampus, John Eccles was not immediately convinced by my proposal that large Purkinje cells with long axons are inhibitory neurons. In fact, stimulation of the cerebellum was known to produce dual effects on muscle tone—excitation under some conditions and inhibition under others. We actually detected excitatory responses in Deiters and cerebellar nuclear neurons after cerebellar stimulation, but we were able to explain these responses as being due to stimulation of cerebellar afferents which supply excitatory synapses through their collaterals to Deiters and cerebellar nuclear neurons (Ito et al., 1969), or to disinhibition, (i.e., removal of inhibitory influences of Purkinje cells via the inhibitory action of basket and stellate cells in the cerebellar cortex) (Ito et al., 1968b).

At that time, γ-aminobutyric acid (GABA) had been proposed to be an inhibitory neurotransmitter, but electrophoretic application of GABA to motoneurons had not induced IPSP-like membrane hyperpolarization. Our experiment on Deiters neurons (Obata et al., 1967) revealed that GABA induces membrane hyperpolarization, suggesting it is an inhibitory neurotransmitter of Purkinje cells. Later, GABA was found by neurochemical and immunohistochemical techniques to be richly contained in all Purkinje cells. This observation supports the hypothesis that Purkinje cells are exclusively inhibitory. A decade later, however, some Purkinje cells were found to contain a peptide-like motilin, which excites smooth muscle cells. A subsequent test, however, revealed that electrophoretically applied motilin inhibits the activity of Deiters neurons (Chan-Palay et al., 1982); the possibility that Purkinje cells containing the motilin-like peptide are excitatory was thereby excluded.

When I started to work on Deiters neurons in Tokyo, I was not aware that John Eccles had moved his focus to the cerebellum after I had left Canberra. He came to Tokyo in 1965, on the occasion of the 26th IUPS (International Union of Physiological Sciences) Congress, and we organized an IBRO (International Brain Research Organization)-sponsored symposium on the neuronal mechanism of the cerebellum. It was a fantastic meeting, attended by internationally renowned authorities on neuroscience such as Ragnar Granit, John Szentágothai, Robert Dow, Charles Phillips, Francis Schmitt, John Brookhart, Vernon Brooks, and a number of young researchers, including Kris Krnjevic, Per Andersen, Jan Jansen, and Rodolfo Llinás. Our studies in Tokyo were well received, and no one doubted that Purkinje cells are inhibitory.

Round-the-World Trip

The 1965 meeting on the cerebellum brought me two big rewards. One was that John Eccles asked me to write a monograph on the cerebellum with him and John Szentágothai, which was published by Springer Verlag in 1967 as *The Cerebellum as a Neuronal Machine.* The other reward was invitations to participate in three meetings in 1966: a 1-week workshop on the cerebellum held in January in a suburb of Boston as part of the Neuroscience Research Program (NRP), a second 4-week NRP workshop held that summer in Boulder, Colorado (both organized by Francis Schmitt), and the Nobel symposium on structure and function of inhibitory neuronal mechanisms organized by Curt von Euler, in Stockholm. To attend these meetings and visit many laboratories around the world, I left home for six months.

John Eccles brought to Boston a number of chapters which he had written for the monograph. As we discussed the structure of the book, I saw his inspiration emerge and grow. These discussions were some of the most vivid scenes in which I recall this fabulous hero of neuroscience, who passed away

in May 1997 at the age of 94. In 2 months while staying at the NRP center after the workshop, I wrote three chapters for my part of the monograph. I missed my laboratory, but it was a great joy to stay with three colleagues, Michael Arbib, Curt Bell, and Ray Kado. We chattered all day, discussing future perspectives of neuroscience. And, because I lived in the Vanderbilt dormitory of the Harvard Medical School—by courtesy of Stephen Kuffler—I also got a taste of American university life.

Network Models of the Cerebellum

By around 1965 our major understanding was that neurons in the brain are interconnected through excitatory and inhibitory synapses, forming intricate networks, as typically dissected in the cerebellum. However, when we tried to explain a brain function such as learning or motor control on the basis of the brain's neuronal network structures, we found it impossible to do so. At the symposium on information processing in the cerebellum held in 1967 at Salishan Lodge on the Oregon coast, mathematicians, computer scientists, and bioengineers were invited to look into every detail of the cerebellum in order to interpret its functional meaning. The meeting was exciting because of discussions on the wide range of topics unfamiliar to traditional neurophysiologists. I particularly enjoyed Don McKay's insightful analysis of the roles of inhibitory neurons in the brain. Even though the meeting ended without any tangible results, it symbolized the beginning of a new era of informational neuroscience. Indeed, David Marr's (1969) epochal theory of the cerebellum and J.S. Albus' (1971) simple perceptron model of the cerebellum were presented a short time later.

These are monumental issues in neuroscience. Neuronal network theories began with McCulloch and Pitt's (1943) model of the brain according to which neuronal networks are capable of logical calculus. I was amazed to see that inhibitory synapses were postulated in this model which was proposed a decade before John Eccles' discovery of IPSPs. Synaptic plasticity, which is an activity-dependent persistent change in synaptic transmission efficacy, was adopted in Hebb's (1949) cell assembly model as a counterpart of the learning and memory capabilities of the brain. Rosenblatt (1962) further demonstrated that his simple perceptron model, composed of three neuron layers, one of which incorporates synaptic plasticity, is capable of actual learning. Both Marr's (1969) and Albus' (1971) theories are based on the assumption that the cerebellar neuronal network is composed of excitatory and inhibitory synaptic connections, and contains another important element: synaptic plasticity. Albus (1971), in fact, adopted a close analogy to that of simple perceptron in his neuronal network theory of the cerebellum.

Hebb's (1949) cell assembly model assumes that coactivation of presynaptic and postsynaptic membranes leads to a persistent increase in the

efficacy of synaptic transmission. Each Purkinje cell receives two distinct excitatory inputs: one, arising from a number of parallel fibers, exerts a weak effect, while the other, arising from a single climbing fiber, exerts a strong effect by which the target Purkinje cell is invariably excited. Hence, coactivation of parallel fibers and climbing fibers leads to the Hebbian synapse situation. G.S. Brindley (1964) was the first to suggest that coactivation of parallel fibers and a climbing fiber induces a Hebbian type of strengthening of parallel fiber-to-Purkinje cell synapses, and this suggestion was incorporated into Marr's (1969) theory of the cerebellar cortex. However, Albus (1971) assumed for several reasons that such coactivation leads to sustained depression of parallel fiber-to-Purkinje cell transmission. These theories suggested that the elaborate cerebellar neuronal network acquires computational capability due to the synaptic plasticity of Purkinje cells. Different versions of the cerebellar neuronal networks capable of learning, proposed by Grossberg (1969), Gilbert (1974), and Fujita (1982), are also based on synaptic plasticity assumptions.

Around 1970, I anticipated that the postulated synaptic plasticity would be uncovered shortly, but unfortunately, experimental tests conducted in a number of laboratories failed to reveal such synaptic plasticity. While synaptic plasticity phenomena in the form of long-term potentiation and sensitization had been detected in the mammalian hippocampus and molluscan ganglia, respectively, in the early 1970s, the synaptic plasticity in the cerebellum assumption began to fall into disfavor. In spite of the beautiful theoretical prediction made around 1970, its verification had to wait a decade.

Vestibular Reflexes and Cerebellum

One of the important strategies which I learned in Canberra was to investigate microscopic neuronal events in spinal neurons in correlation with macroscopic phenomena at a reflex level. John Eccles' finding of spinal inhibitory neurons was guided by observations of the inhibitory interaction between afferent signals in inducing monosynaptic reflexes. In 1968, when we finished a series of experiments on Deiters neurons and Purkinje cells, I turned to examine vestibular reflexes with colleagues Tadashi Akaike, Victor Fanardjan, Jun Fukuda, Steve Highstein, Kyoji Maekawa, Hiroshi Nakajima, Tadao Ohno, Jerry Simpson, N. Sato, and T. Tsuchiya. We found that Purkinje cells in the flocculus, a hemispheric part of the so-called vestibulocerebellum receiving vestibular afferents, directly inhibit vestibular nuclear neurons from relaying the vestibulo-ocular reflex (VOR), whereas the vestibulospinal reflex (VSR) does not receive Purkinje cell inhibition from the vestibulocerebellum even though these two reflexes are mediated by three-neuron pathways of similar structure.

Student riots from 1968–1970 culminated in the closure of our laboratory for six months. During these days, I spent time reading many books,

including some on modern control theories. I noticed that the distinction between the VOR and VSR in their relationship with the vestibulocerebellum corresponds to their difference as control systems. Whereas the VSR is a classic feedback control system in which any change in the output (i.e., head position and movement) should be reflected in vestibular inputs, the VOR is a feedforward system, the output of which (i.e., eye position and movement) does not influence vestibular input.

It is a logical conclusion that the VOR requires the flocculus as a device which replaces the feedback loop and so secures its precision. I formulated this idea when I was invited to the symposium on the role of the vestibular organs in space exploration, held in Pensacola, Florida, in 1968. I elaborated on it further for the Fulton Society meeting in New York in 1969, but because I was hospitalized for abdominal pain, I was unable to attend the meeting. The proceedings of the meeting, in which my article was included, were published in an issue of the *International Journal of Neurology* (Ito, 1970). This article presents my initial idea about the control system structure of the cerebellum, and I regretted that it appeared in a journal almost unnoticed by colleagues in my field. However, I was told very recently by one of the participants at the New York meeting that my article was circulated among the cerebellum experts who attended. In the article, I predicted the presence of a teaching line in which the flocculus is informed of adequate performance of ocular movements. Kyoji Maekawa and Jerry Simpson (1973) subsequently found that retinal signals are, indeed, conveyed to the flocculus via climbing fibers. Thus, I completed the neuronal diagram including the VOR arc, flocculus, and retina on which I based my flocculus hypothesis of VOR control, according to which the flow of vestibular signals through the flocculus as a sidepath to the VOR arc is modified by retinal error signals conveyed by climbing fibers, so that the VOR dynamics undergo continuous adaptive correction toward minimization of retinal errors (Ito, 1974). This error-driven adaptive mechanism should enable the VOR to maintain precision even in the absence of feedback.

Flocculus Hypothesis of VOR Control

In 1970, I was promoted to chair the First Department of Physiology after Kojiro Matsuda. My major concern at that time was how to test the flocculus hypothesis. I presented the flocculus hypothesis at the 1971 IUPS Congress in Munich and G. Melvill-Jones described his amazing observation on human subjects that the VOR was extensively modified during vision reversal induced by Dove prism goggles (Gonshor and Melvill-Jones, 1974). It seemed obvious to me that this VOR modification was due to the adaptive mechanism of the flocculus that I was proposing. At that meeting I met Dr. David Robinson, who subsequently experimented on cats and demonstrated that lesions of the flocculus abolish the prism adaptation of the VOR (Robinson, 1976).

Through the 1970s, with colleagues Cesira Batini, Michel Dufossé, Brunello Ghelarducci, Pawel Jastreboff, Ray Kado, Yasushi Miyashita, Naoko Nisimaru, Igor Orlov, Takashi Shiida, Ichiro Shimoyama, Nobuya Yagi, Miyuki Yamamoto, and later also Carey Balaban, Soichi Nagao, Katuei Shibuki, Akira Ueki, and Eiji Watanabe, we constructed detailed neuronal circuit diagrams for VOR control, paying special attention to the microzonal structure of the flocculus; using Amanomori's method of combined rotations of a turntable for vestibular stimulation and a screen for optokinetic stimulation, we examined VOR adaptation in rabbits and monkeys. In-phase rotations of the turntable and the screen gradually inhibit the VOR, whereas out-of-phase rotations gradually enhance the VOR. After a long period of struggles against many obstacles (see Ito, 1992), it turned out that lesions of the flocculus abolish these VOR adaptations, and that Purkinje cells in the flocculus undergo changes in their responsiveness to head rotation in parallel with the VOR adaptation.

The data we collected are consistent with the flocculus hypothesis (summarized in Ito, 1982, 1984), but the hypothesis has been challenged a number of times. The most serious challenge was the report that discharge patterns in monkey Purkinje cells were inconsistent with the flocculus hypothesis (Miles and Lisberger, 1981). However, this conflict can be explained by two points (Ito 1994). One is that the part of the monkey cerebellum traditionally defined as the flocculus covers not only the genuine flocculus but also the ventral paraflocculus in its connections with brain stem structures (Gerrits and Voogd, 1989). Purkinje cells taken selectively from the genuine flocculus of monkeys respond to vestibular and optokinetic signals in a manner consistent with the flocculus hypothesis (Nagao, 1992). The second point is that Miles and Lisberger (1981) measured vestibular signals of Purkinje cells during visual suppression of the VOR, assuming that eye-velocity signals, which normally contaminate vestibular signals, are simply nullified during the VOR. However, in suppression of the VOR, a smooth pursuit mechanism is likely to drive the eye movement to counteract the VOR and hence, during the visual suppression, flocculus Purkinje cells could receive extra signals generated by the smooth pursuit mechanism, which would obscure vestibular signals. It now seems to be generally accepted that the flocculus plays a key role in induction of VOR adaptation, but whether or not maintenance of the VOR adaptation also involves plasticity in vestibular nuclei remains an unanswered question (Raymond et al., 1996). Evidence for such plasticity in vestibular nuclei or cerebellar deep nuclei is meager, and confirmation is required.

Long-Term Depression

Because the flocculus hypothesis of VOR control is consistent with the synaptic plasticity assumption, I became firmly convinced of the presence of

the postulated synaptic plasticity in Purkinje cells. Observations of Purkinje cell responses during hand movement adaptation against a suddenly altered load were also consistent with Albus' assumption (Gilbert and Thach, 1977).

In 1979, we found that lesions of the inferior olive—the sole source of climbing fibers—rapidly depress the inhibitory action of Purkinje cells on Deiters neurons (Ito et al., 1979). This phenomenon apparently represents trophic interactions among neurons required for developing and maintaining their proper connections, and is not related to Marr's (1969) or Albus' (1971) synaptic plasticity assumption. When I visited David Hubel and Stephen Kuffler at Harvard medical school in October 1979, David Marr attended my seminar on the trophic type of plasticity. This was my first and last meeting with him, and his words that he had been looking forward to seeing me for 10 years were deeply engraved in my mind. He also mentioned that because he was invited to Japan to receive an award, he would visit me if his health allowed him. He never showed up in Japan, and I still regret that at the time of our meeting I had no data to support his admirable cerebellar theory.

Immediately after I returned from Boston, I decided to test directly the hypothesis of synaptic plasticity in Purkinje cells with Masaki Sakurai and Pavich Tongroach. In order to monitor the parallel fiber-to-Purkinje cell transmission, we examined the probability of occurrence of spike responses in Purkinje cells to parallel fiber inputs. For the first step, we stimulated a vestibular nerve to excite a mossy fiber-granule cell-parallel fiber pathway to the flocculus. In December 1979, we clearly observed that, after conjunctive stimulation of the vestibular nerve and climbing fibers at the inferior olive, the probability of Purkinje cell responses to the vestibular nerve stimulation was reduced for a time period of 1 hour. By exploring with microelectrodes in and out of the flocculus, we examined the possibility that the vestibular nerve signals are reduced in the course of conduction to flocculus Purkinje cells, and we concluded that long-term depression (LTD) occurs at the parallel fiber-to-Purkinje cell synapses (Ito et al., 1982). Using stimulation of parallel fibers on the surface of the cerebellum, we obtained further evidence of sustained depression of parallel fiber-to-Purkinje cell transmission (Ito and Kano, 1982; Ekerot and Kano, 1985). Sakurai, in 1987, reproduced the LTD in an intracellular recording from Purkinje cells in rat cerebellar slices *in vitro*.

Despite my confidence about our observation on LTD, my presentations were unpopular at all four of the meetings held in 1980: The Cerebellum—New Vistas at NIH, Brain Mechanisms of Perceptual Awareness and Purposeful Behavior in Pisa, the 28th IUPS Congress in Budapest, and Neural Communication and Control in Debrecen, the first one in May and the latter three in July. Many colleagues in the field seemed to be of the opinion that no such plasticity exists, or that if it does, it is potentiation and not

depression. Nevertheless, I was warmly encouraged by Ragnar Granit who, one day during the Pisa symposium, invited me to a restaurant together with G. Moruzzi and quoted Danton's famous words on audacity. After the Debrecen meeting, B. Juresz, as he told me later, wrote to David Marr, who was seriously ill in bed at that time, that the synaptic plasticity hypothesis had received experimental support.

What we found was LTD, as predicted by Albus (1971), and not potentiation as assumed by Brindley (1964) or Marr (1969), but I don't think that this detracts from Brindley's or Marr's theoretical formulation. Learning in the simple perceptron is based on a combination of two types of plasticity: potentiation occurs when a machine's answer is correct, and depression occurs when it is erroneous, but the simple perceptron still learns, though with a reduced efficacy, with only one type of synaptic plasticity which can be either potentiation or depression. Because it would be difficult to equip a real synapse with both types of plasticity, nature appears to have chosen depression for several practical reasons, as pointed out by Albus (1971), but not for a theoretically logical reason.

After these meetings, I suffered from gallstones and was hospitalized. My further distress was that our short report on LTD was turned down by *Nature,* apparently reflecting the skepticism about the synaptic plasticity assumption prevailing among cerebellar physiologists at that time. I was relieved when our full report was later accepted for publication in the *Journal of Physiology (London)* (Ito et al., 1982).

Cerebellar Corticonuclear Microcomplex

Since 1976, I had been invited by Raven Press to write a monograph on the cerebellum, but I hesitated to start writing because of the uncertainty about the synaptic plasticity. When I obtained the first evidence of LTD in 1979, I immediately began to write the monograph, which was published in 1984 as *The Cerebellum and Neural Control.* With all Saturdays and Sundays devoted to it, it took about 1 month to complete each chapter, and more than 3 years to complete the entire monograph. In December 1983, I proofread the final draft in a hotel in downtown New York in 3 days, during which I slept for a total of only 3 hours. The book appeared in 1984 with my own simple cover design of Purkinje cells, and was dedicated to my mother, who had died in January of 1984 at the age of 92.

What I attempted in this book was integration of the three lines of information available on the cerebellum at that time: morphological, physiological, and chemical data of cerebellar cells and their networks, leading to formation of neuronal network models; morphological and electrophysiological data of neuronal connections in and out of the cerebellum, leading to a conception of control system models of the cerebellum; and functional and behavioral data suggesting the functional roles of cerebellar activity.

The core concept proposed in the book is that the cerebellum consists of numerous functional units, called cerebellar corticonuclear microcomplexes (referred to below as microcomplexes). A microcomplex consists of four components: (1) a microzone of the cerebellar cortex as defined by the late Olov Oscarsson (1976), (2) a small group of neurons in vestibular or cerebellar nuclei receiving Purkinje cell inhibition from the microzone, (3) bundles of cerebellar afferent fibers arising from small groups of precerebellar structures and supplying excitatory synapses to the nuclear neurons and mossy fiber terminals to the microzone, and (4) a bundle of fibers originating from a small group of inferior olive neurons and supplying climbing fibers to the microzone and excitatory synapses to the nuclear neurons. While a mossy fiber input is converted to a nuclear output through a microcomplex, the input–output relationship is modifiable due to LTD induced in the microzone by error signals conveyed by the climbing fibers. A microcomplex is an adaptive unit of the cerebellum; like a computer chip, it is attached to a bodily control system, affording it with adaptiveness.

With a microcomplex attached, a reflex or a compound movement system, such as is used for locomotion and saccadic eye movements, would be converted from a classic control system to an adaptive one. In addition to the flocculus control of the VOR, eye-blink conditioning (cf. Thompson, 1987) may be considered to be a case of reflex adaptation. Adaptive adjustment of perturbed locomotion has been shown to be a function of the cerebellar vermis (Yanagihara and Kondo, 1996). For voluntary movements, however, a microcomplex appears to be used in a different way, that is, for forming a functional model of the motor plant including muscles, bones, and associated spinal cord mechanisms, as I proposed earlier (Ito, 1970). When command signals for a voluntary movement are sent from the cerebral motor cortex to the motor plant, the emerging movement effect would be fed back through sensory systems to the motor cortex; a voluntary movement would be performed based on the external feedback through sensory systems. If the motor cortex sends the same command signals to the cerebellar model, which projects back to the motor cortex through the cerebrocerebellar communication loop, the voluntary movement can be performed without use of the external feedback, by using the internal feedback through the cerebellum.

A microcomplex is expected to form a model by the following mechanism: suppose that a microcomplex is connected in parallel to an original system to be modeled. While both the microcomplex and the original system are fed by common input signals, any difference between their output is fed back to the microcomplex as error signals through climbing fibers. While this is repeated, the dynamics of the microcomplex will become equivalent to that of the original system. The model formation is a consequence of the adaptive mechanism, and nature seems to have found this new use of the cerebellum when the cerebral cortex emerged during evolution.

Unified Theory of Cerebellar Control

Since 1984 there have been two lines of development in our knowledge of the roles and mechanisms of the cerebellum. Kawato et al. (1987) described a model of voluntary cerebellar control, in which a microcomplex is placed parallel to the cerebral motor cortex. The motor cortex acts as a feedback controller, while the microcomplex serves as a feedforward controller, and both receive the same instruction signals and act to control a common motor plant. This parallel combination of a feedback and a feedforward system constitutes a so-called 2 degrees of freedom control mechanism. If the microcomplex, as a feedforward controller, acquires through learning dynamics equal to the reciprocal of the arm's dynamics (i.e., an inverse dynamics), the trajectory represented by instruction signals fed to the microcomplex will be converted to the actual arm trajectory with fidelity. Kawato et al. (1987) demonstrated that a robot equipped with a 2 degrees of freedom control mechanism acquires a skillful arm movement after practice in a humanlike manner. Further, Shidara et al. (1995) found that Purkinje cell discharge in the ventral paraflocculus during eye movements represents an inverse dynamics of eyeballs.

The control system model proposed in 1970 matches the anatomically demonstrated cerebrocerebellar loop through the motor cortex and the intermediate part of the cerebellum, and explains how practice enables us to perform voluntary movements without feedback: for example, hitting a golf ball with your eyes closed. The Kawato et al. (1987) inverse dynamics model matches the parallel connections between the cerebral association cortex and the cerebellar hemisphere, and explains how practice enables us to perform voluntary movements without conscious attention. Currently, I think that these two control system models represent two different modes of learning in voluntary movements: one eliminates the need for external feedback and the other eliminates the need for conscious efforts to conduct movements. The former would involve the intermediate part of the cerebellum associated with the interpositus nucleus, and the latter, the cerebellar hemisphere associated with the dentate nucleus.

Another remarkable development concerning involvement of the cerebellum in mental activity was proposed by Leiner et al. (1986) based on the idea that the evolution of the human cerebellum parallels the enlargement of the cerebral association cortex. I turned to this problem when I was elected to serve as dean of the Faculty of Medicine of the University of Tokyo and so was completely deprived of opportunities to engage in laboratory work during the 2 years from 1986 to 1988. I paid attention to the close similarity between movement and thought from the viewpoint of their control mechanisms. To move, we operate parts of our body such as arms and legs, and to think, we manipulate ideas, concepts, and images encoded in our brain, presumably in the temporal-parietal association cortex. The tar-

gets of control are entirely different in these two types of control activity, but the mechanisms of control could be equivalent for them. I presented this view at the Principles of Design and Operation of the Brain symposium held in 1988 in the Pontifical Academy at the Vatican (Ito, 1990).

From a functional point of view, the brain evolved in five steps, with the cerebellum involved in all five: The brain stem and spinal cord developed three categories of function: reflexes, compound movements, and innate behaviors, the latter including food intake, drinking, and mating. Involvement of the cerebellum in reflexes and compound movement is now established, but cerebellar involvement in innate behavior is much less evident and needs further investigation; nevertheless, it is suggested by the existence of neural connections between the hypothalamus and the cerebellum. The fourth function of the brain is the sensorimotor cortical function, found in lower mammals. The above-mentioned control system models of voluntary movements should apply to this fourth brain function. The fifth brain function—thought—emerges from the association cortex as typically developed in primates, including humans. The inverse-dynamics control system model would apply to it. In this way, one could explain the diverse roles of the cerebellum systematically at all five of the hierarchical levels of brain function on the common ground of the microcomplex concept.

When my university career ended in March 1989, I gave my last physiology lecture to medical students and colleagues at the University of Tokyo. I explained how a normal person can touch the nose with his or her index finger accurately even with eyes closed, whereas cerebellar patients fail to perform this finger-to-nose test. This movement is apparently performed by using a model of the motor plant for fingers in the cerebellum, and cerebellar patients, lacking the model, are unable to touch the nose accurately unless the finger movement is controlled visually. At the end of my talk, I referred to the saying that while an unwise person only tries to adapt to his or her environment, a wise person thinks about how to change his or her environment. The cerebellum is an adaptive organ which may seem like an unwise person, but it enables the cerebrum to display its creativity. We must be aware of the important roles which the cerebellum plays behind the scenes. This is the answer to my long-standing question of what the cerebellum really does.

I presented this unified theory of cerebellar control in the first Ragnar Granit Lecture in Neuroscience in Stockholm in April 1991, but it was a most regrettable event that Ragnar Granit had passed away just a week before my lecture. I also had chances to present my theory in the symposium on Brain Mechanisms of Perception and Memory, held in Toyama, Japan, in 1991 (Ito, 1993a), and a Charcot lecture to neurologists in Paris, in June 1992 (Ito, 1993b). I wrote an article for a special issue of *Trends in Neuroscience* devoted to the debate on mental functions of the cerebellum, together with Robert Dow (Ito, 1993c), and was given a Robert Dow

Award in Neuroscience in August 1993 directly from this great authority of cerebellar pathology. Since those days, supportive evidence for the involvement of the cerebellum in thought has accumulated in brain imaging experiments, as recently compiled in a monograph edited by J.D. Schmahmann (1997).

Signal Transduction in LTD

In my last lecture at the University of Tokyo, I had little to say about signal transduction processes underlying LTD, except that Ca^{2+} entry into a Purkinje cell caused by climbing fiber signals is required for induction of LTD, and that LTD is basically due to sustained reduction of glutamate sensitivity of Purkinje cells. Based on the little information available in the literature, I speculated that cyclic guanosine 5'-monophosphate (GMP) plays a role in induction of LTD (Ito, 1989). In April 1989, I moved to the Institute of Physical and Chemical Research which was founded in 1917 and is commonly known by its nickname, Riken (based on its name in Japanese). My task was to establish a new neuroscience group in the frontier research program, which was launched in 1987 at Riken to cover emerging new research fields such as biotechnology, nanotechnology, glycobiology, and neuroscience. In the neuroscience group, I set up a laboratory to investigate cellular and molecular processes underlying LTD with a number of colleagues including, initially, Katsuei Shibuki, Daisuke Okada, Laddawan Karachot, Ray Kado, Tetuso Yamamori, Kazutosi Nakazawa, and Ayako Ajima, and later Nick Hartell, Mariko Miyata, Dai Yanagihara, Hiroshi Kojima, Hirokazu Hirai, and researchers in other frontier research program laboratories.

Since around 1990, LTD and related phenomena had been taken up in the laboratories of Francis Crepel, David Linden, Arthur Konnerth, Tomoo Hirano, Susumu Tonegawa, Roger Tsien, and others, and studies of LTD had become a popular theme in neuroscience. During the past 10 years, we collected data suggesting the roles of nitric oxide, cyclic GMP, protein kinases C and G, metabotropic glutamate receptors, protein phosphatases, corticotropin-releasing hormone, and immediate early genes in LTD induction. At the final step of the complex signal transduction processes involving these receptors and messengers, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors mediating parallel fiber-to-Purkinje cell synaptic transmission are likely to be phosphorylated, and my particular interest has been in visualizing those synapses undergoing LTD by using antibodies raised against phosphorylated AMPA receptors (Nakazawa et al., 1995). These new lines of knowledge provide new means to either facilitate or block LTD and to visualize its occurrence, which will be useful in identifying roles of LTD in cerebellar functions.

Question for the Future

In the fall of 1996, I was invited to deliver a Warner-Lambert lecture at the annual meeting of the Society for Neuroscience held in Washington, DC. After describing the development in cerebellar studies during the past 3 to 4 decades, I proceeded to speculate about future directions for neuroscience. It is evident that neuroscience has come of age and that, in the coming century, it will develop fully. Explosive expansion of our knowledge at cellular and molecular levels will eventually enable us to find ways to prevent or cure brain aging and neurological and psychiatric diseases. However, the path that will lead us toward an understanding of the brain mechanisms underlying our mind and behavior is still unclear. Around 1970, I anticipated two lines of development that might follow the great strides made in cerebellar studies. One is our understanding of the mechanisms and roles of synaptic plasticity in cerebellar networks, which, even though much slower than I expected, has advanced much during the past 3 decades. The other is the proliferation of network and system models, which could be applied to other parts of the brain such as the basal ganglia, hippocampus, thalamus, hypothalamus, and the cerebral cortex. Even though marked progress has been made by the discovery of multilayered perceptrons, so-called neurocomputers, these advances have not yet met my expectations. Some information about the brain essential for such modeling seems to be still missing. What we need to find in the brain in order to proceed beyond the framework of neuroscience so far set by cerebellar studies, is the profound question now before us.

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