The History of Neuroscience in Autobiography
Volume 6

Edited by Larry R. Squire
Published by Society for Neuroscience
ISBN: 0-12-538010-1

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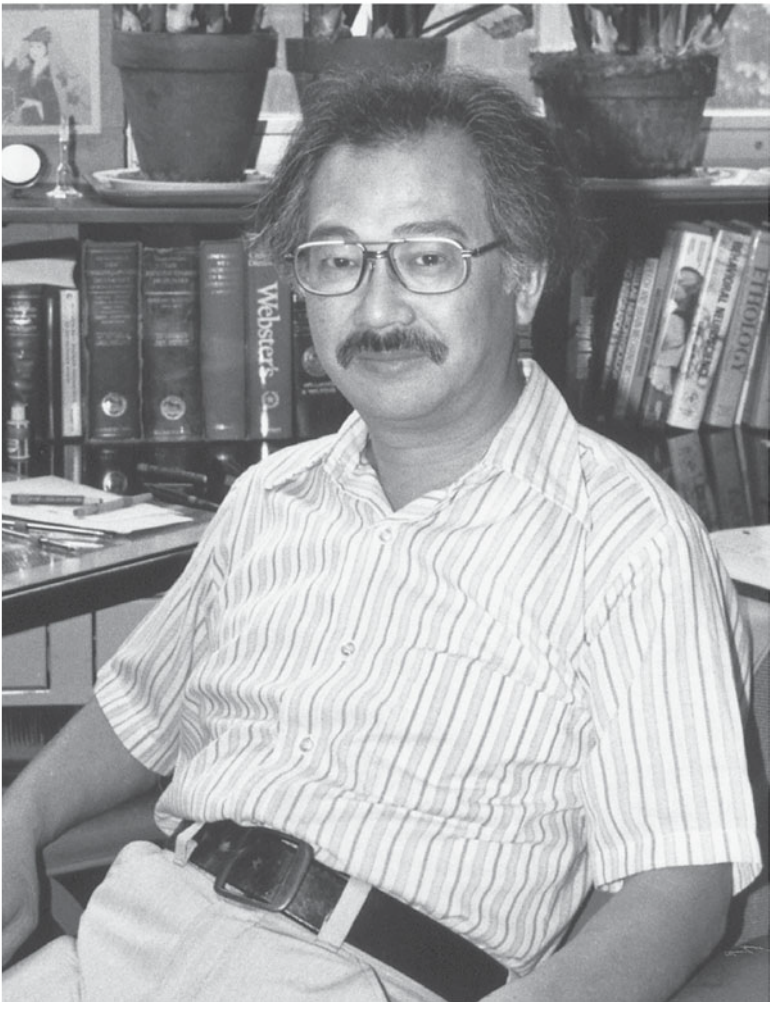
pp. 480–513

https://doi.org/10.1093/acprof:oso/9780195380101.003.0013


Webster's

Nobuo Suga

Born:

Kobe City, Hyogo Prefecture, Japan
December 17, 1933

Education:

Tokyo Metropolitan University, B.S. (1958)
Tokyo Metropolitan University, Ph.D. (1963)

Appointments:

Tokyo Medical and Dental University (1958)
Harvard University (1963)
University of California, Los Angeles (1965)
University of California, San Diego (1966)
Washington University (1969)

Honors and Awards (Selected):

American Academy of Arts and Sciences (1992)
National Academy of Sciences (1998)
Academy of Sciences in St. Louis, MO (2003)
Ralph W. Gerard Prize, The Society for Neuroscience (2004)

Nobuo Suga and his collaborators explored the neural mechanisms for parallel and hierarchical processing of biosonar information and the cortical maps representing different types of biosonar information. They also explored the role of the corticofugal (descending) auditory system in the improvement and adjustment of auditory signal processing and the neural circuit for plastic changes in the central auditory system elicited by auditory fear conditioning.

Nobuo Suga

Parents and Childhood

My father, Setsuzo Suga (1885–1966), and my mother, Sueno (Miyamoto) Suga (1897–1994), were born and grew up in northern Kyushu, the place of our ancestral home. My parents had four children: one daughter and three sons. Their daughter died at age 2 before I was born. I was the middle child of the three brothers. Just before I was born, my father's friend told my father, "If your next child is a boy, his name should be Nobuo, because this name with three kanjis (morphograms) is the best combination with Suga."

My father opened a printing house in Kobe City. I didn't know the reason why my father chose the printing business. Was it a good business for a new epoch after the long-lasting feudal period? I had heard from my mother that he was from a Samurai family in northern Kyushu. So, I wonder how he could have generated the money to purchase all the machines for his printing house. What I remember is that three men and one woman worked in the printing house and that one of the men occasionally brought me small crabs because he knew I liked animals. Two large printing machines on the first floor of the printing house made a sound "Gara gara ga-chan, Gara gara ga-chan." A large cutter used for cutting a pile of large sheets of paper was also on the first floor. Several racks of movable type were on the second floor.

Once, when my father sharply turned his car loaded with sheets of paper at the corner of a street, the big pile of paper shifted toward one side of the car and the car flipped over. His left upper arm was injured. In his daily life, however, he had no problem with his injury at all, but he could not use a rifle. This turned out to be lucky for him and his family because he was able to escape the draft of the Japanese Imperial Army. However, his luck ended on March 17, 1945, when U.S. bombers (B29s) dropped incendiary bombs to burn down Kobe City. Approximately 9,000 people were burned to death by this overnight bombing. My father lost everything, except fortunately his family members were spared. From early 1944 to August 1945, all schoolchildren were evacuated from the cities. So, I was living in a temple halfway up a mountain along with my classmates and a teacher. There, autumn was beautiful. Rice fields below us were like golden carpets. The winter was cold with a lot of snow, so we could enjoy sledding. During the night of March 17, 1945, our teacher told us "Kobe City is under attack by U.S. bombers, and the city is burning." We all stood on the open verandah of the temple, exposed to the cold air. A long stretch of sky far beyond the black mountains in front of us was reddish. Five days after the bombing, my parents came to

the temple to pick me up. We moved by train from Kobe City to northern Kyushu. On the train, my mother told me how close they came to being burned to death. They, along with neighbors, had escaped under an elevated railroad. However, soon houses on both sides of the railroad started burning, but those on the harbor side had burned down earlier, giving them time to escape from the flames to the harbor just before they were suffocated and burned.

When I was growing up in Kobe, my father frequently took me to the fields and mountains near Kobe to collect beetles, grasshoppers, cicadas, and so on. Because of these experiences in Kobe, my childhood was enjoyable, filled with fishing and catching insects. In late July 1945 when I was in a tree catching a large stag beetle, I fell out of the tree, landing on a dead tree branch that tore a large opening in the skin of my right armpit. While going to the doctor's office with my father, a U.S. fighter plane suddenly approached us. We heard a loud noise and saw splashes in the creek right alongside us on the road. We quickly hid under some nearby bushes. This brief moment was my last experience of the war.

The war ended on August 15, 1945. In Kyushu, my father purchased land and a farmhouse that had been partially damaged by a bomb. He became a farmer. My parents worked especially hard. However, they were not successful at all as farmers because they had no experience doing this type of work. By the time I graduated from middle school, my father's savings were depleted. Financial rescue came from my mother's younger brother who was successful in Tokyo. Heeding his suggestion and with his monetary support, I temporarily went to a nearby high school, and my father prepared to move our family from Kyushu to Tokyo. In Tokyo, I worked at a watch shop during the daytime, repairing and selling clocks, and went to high school and then to college at night.

High School

I liked biology and selected biology for extracurricular club activities. The club had just one microscope. After studying various sections of plants, there was nothing for the biology club members (only five to six people) to do, so we started going to the mountains whenever we had money and could take off work on Sundays. We mostly took a late-night train after our last class on Saturday and returned to Tokyo on a late-night train on Sunday. I remember very little from this period of my life, except the time spent in the mountains.

College

In Tokyo, there were several universities that had a night school. The professors and curriculum of these night schools were different from those of the regular schools, and the diploma stated that graduation was from the

night school. However, Tokyo Metropolitan University was unique. The same professors taught day and night classes, and there was only one type of diploma. I took only night classes so it took 5 years instead of the usual 4 years for me to graduate. Without hesitation, I majored in biology. My parents did not say anything to me about it, but my relatives expressed their surprise because a biology major was least likely to earn money. I was first interested in genetics and joined the Chromosome Society and then the Genetics Society. I changed my mind, however, when I enrolled in an experimental embryology class taught by Professor Katsuma Dan. It was so fascinating that I decided to perform an experiment for a graduation thesis in experimental embryology instead of in genetics. Professor Dan gave me a project: "Change in the Toughness of the Chorion of Fish Eggs." I studied the change in toughness of the chorion from just after fertilization through hatching. By the end of January 1958, I had written my thesis in Japanese. Professor Dan said, "This thesis is good enough to publish in English." My thesis in English was apparently not good at all. So, Professor Dan eventually wrote it for me for publication (Suga, 1963).

The Bridge to Auditory Neurophysiology

I occasionally walked to Toritsu Daigaku railway station to ride the train to Shibuya station and to take another train on another line together with Professor Dan after my last class at night. It was perhaps late December 1957. While we were waiting for the train at Shibuya station, he asked me, "What is your plan after graduation?" (In Japan, a graduation ceremony is always in late March.) I replied, "I want to be a biologist and be involved in research." Then, he said, "Well, our society has changed after the war. Like you, who has no money but wants to be a biologist." (In 2006, I attended a biology class reunion in Tokyo and learned that Professor Dan had said the same thing to one of my classmates who also took all her classes at night and later became a professor at a university in Tokyo.) The train came in and Professor Dan got off at the second station, Harajuku. I rode further to Mejiro station and thought to myself, "Well, he is right. The emperor and his princes are involved in biology research." It was not an option for me to go to graduate school because there was no graduate school at night. It was also not an option for me to work for a company just for money. I wanted to have a full-time job involved in research.

In January 1958, Professor Dan asked me to come to his office. He said, "You may be good in neurophysiology. Professor Yasuji Katsuki at Tokyo Medical and Dental University is one of my friends. He is a prominent auditory physiologist and has money to hire you. What do you think?" I knew neither neurophysiology nor auditory physiology. Professor Dan said, "Why don't you try neurophysiology? If you do not like it, you may come back to me, and I will think of another job for you." I replied, "I will try it. I'll do my best."

That is the standard response in this situation. Professor Dan looked for one of his business cards in his desk drawers. He found only a well-worn card on which something was written. He cleaned it with an eraser and wrote "Professor Yasuji Katsuki. I introduce Mr. Nobuo Suga. Please kindly meet him." And then he handed it to me, saying, "Please take this to Tokyo Medical and Dental University to see Professor Katsuki next Monday morning at 9 o'clock."

That Monday, I went to Ochanomizu railway station. Tokyo Medical and Dental University was just across the bridge, Hijiribashi. I still remember; it was a cold, but pure, bright and beautiful morning when I crossed that bridge. I now know, it was the bridge for me to become an auditory neurophysiologist.

Professor Katsuki, who was wearing a white lab coat, was a warm, soft-spoken person. His office was divided by a black curtain, with his desk on the window side and electrical instruments in two relay racks on the door side. He only asked me a few questions and showed me his lab. He then asked me to meet "his" Assistant Professor Susumu Hagiwara (who later became a professor at the University of California), who also asked me a few questions. That was all. Professor Katsuki said, "Please work here, starting on April the first." I got the job! There are no April Fool's jokes in Japan.

Five Years in Katsuki's Laboratory

In general, each department of a medical school consists of a full professor, an assistant professor, two assistants (who have a M.D. or M.D./Ph.D.), and a laboratory technician or laboratory assistant. A senior assistant can be a lecturer. I just had a bachelor's degree in biology and knew nothing of neurophysiology, so I was first hired as a laboratory assistant. I then became an assistant in The Anatomy Department when there was an open position, although I had performed all my research in the Physiology Department. The research on hearing was so interesting to me that I put all my time and energy into it, from 8:30 AM to ~ 11:00 PM. Professor Katsuki started to treat me as one of his collaborators by the midsummer of 1958, in spite of the fact that I was still busy learning auditory physiology through a review article written by Galambos (1954) and through my ongoing research on the cat's auditory system in Katsuki's laboratory. Professor Katsuki then gave me the research topic "The Neurophysiology of Hearing in Insects" for my Ph.D. dissertation. I immediately went to a department store on Ginza Street in Tokyo and purchased long-horned grasshoppers, "kirigirisu," *Gampsocleis buergeri* (Tettigoniidae), and started to work on this species on Tuesdays, Thursdays, and Saturdays. On Mondays, Wednesdays, and Fridays, I worked on cats or monkeys with Professor Katsuki and Dr. Takeshi Watanabe or Kei-ichi Murata. A short paper by Katsuki and me on hearing in 12 species of insects was published in late 1958. It was my first published paper. When the

reprints came in, I felt great satisfaction reading it on a late-night train to my home, although I found terrible misprints in Table 1 of the paper.

The research on insects (Suga and Katsuki, 1961), as well as on cats (Katsuki et al., 1959) and monkeys (Katsuki et al., 1960, 1962), went very well. Professor Katsuki briefly mentioned that the neurophysiology of vision might be an interesting topic for my future research, so I worked on the descending visual system of the kirigirisu in the summer of 1961 (Suga and Katsuki, 1962). However, the main focus of my research was on hearing in insects. There were periods of time during which I went to Katsuki's home almost every Sunday afternoon to write papers. He used to wake up early in the morning, so I often found him asleep in the late afternoon in front of me when I was having a difficult time with my writing. I tried to wake him up by making noise, but it did not work. This signaled the end of the day's activity. He and his wife often asked me to stay for dinner with them. After dinner, he used to make cocktails by referring to a booklet of recipes. He would pour half a cocktail into my glass and the other half into his. He used to make a few different cocktails during the course of the evening, so I felt very good on the train home. One particular evening, Professor Katsuki could not decide which cocktail to make next and handed the booklet to me to choose the next drink. I did not know anything about cocktails, so I pointed out "grasshopper" and said, "It might be interesting to try this." He then looked at the booklet. A moment later, he said, "I am one bottle short to make this." He suggested I choose something else, or else he would make the cocktail, saying, "This is a grasshopper, although one leg is missing."

Professor Katsuki was a very sincere person. He did not tell jokes, or perhaps he did, but the jokes were not funny. By contrast, Dr. Hagiwara (Hagi-san) frequently joked or told stories in a very interesting way. We all ate lunch together. Professor Katsuki did not talk much, but Hagi-san talked frequently, evoking constant laughter. In late 1965, when my wife (Hiroko) and I stayed at Hagi-san's house in La Jolla, California, for 3 days, he said, "The San Diego Zoo is wonderful. There are more than 100 giant tortoises from the Galapagos Islands." So, the next morning, Hiroko and I went to the zoo. There was a much smaller number of tortoises than expected. So, we counted them. Later, at dinner, I mentioned to Hagi-san that there were only 31 giant tortoises. Hagi-san declared, "I amplify a story, but never lie." Likewise, the job of a neurophysiologist, which I first learned in Katsuki's laboratory, was to amplify small signals.

Professor Katsuki had a research grant from the National Institutes of Health (NIH) of the United States to develop a dip-prism microscope. Hagi-san and Mr. Toshio Nakatsubo (Olympus Optical Co., Tokyo) were his coworkers for this project. The potential for the application of this microscope for neurophysiological research was not promising. Hagi-san gradually disassociated himself from this project, and I gradually became involved with it. In response to a suggestion from the NIH, Professor Katsuki decided to demonstrate the microscope at the NIH in Bethesda, Maryland, and at

the Congress of the International Union of Physiological Sciences held in Leiden, Holland. In the summer of 1962, we made a trip around the world. My schedule differed from Professor and Mrs. Katsuki's. I joined them in Bethesda, New York, Boston, and Leiden. For me, it was an eye-opening first trip abroad, visiting the United States, England, Holland, Germany, Switzerland, and Italy. Unlike when I travel now, I met almost no Japanese people during my trip. The dip-prism microscope was not at all successful, but I was rewarded by the trip itself.

I spent 5 wonderful years in Katsuki's laboratory, which was in its golden period at that time. I learned a great deal from Professor Katsuki, and I am proud to have written so many papers that were coauthored by Professor Katsuki. As I have previously stated, I had an opportunity to work on the hearing of several species of animals, including the cat and monkey as well as insects. Therefore, I still feel as though I can work on any animal, from a large macaque to a small cricket, if necessary, easily recognizing the merit of comparative auditory physiology. For me, the research on invertebrates and lower vertebrates is just as interesting and important as that on higher vertebrates such as primates because they all share the basic principles and mechanisms for hearing. Because my impression is that the speed of progress in neurophysiology is inversely related to the size of a species studied, I prefer to work on smaller animals rather than the larger ones.

In Katsuki's lab, I was involved in research which might be historically interesting to describe here: (1) binaural neuron, (2) two-tone suppression, (3) cochleotopic (tonotopic) map in the primary auditory cortex, and (4) sharpening of frequency tuning by lateral inhibition.

Binaural Neuron, T-Large Fiber

Long-horned grasshoppers have the tympanic organ (ear) at the proximal end of the tibia. Many sensory (primary auditory) neurons attach to the tympanic membrane through the attachment cells. They send their axons (tympanic nerve fibers) to the first thoracic ganglion and excite second-order auditory neurons. One of the second-order neurons has a large-diameter axon. We named it the "T-large fiber" because it is excited by the tympanic nerve fibers. This large fiber in the central nerve cord sends auditory signals to the brain and the third thoracic ganglion from the first thoracic ganglion in the same discharge pattern.

The T-large fiber is excited by stimulation of the ipsilateral tympanic organ but is inhibited by stimulation of the contralateral tympanic organ. Because of this binaural interaction, the response of the T-large fiber to a sound is very directional. When a singing kirigirisu was placed 1 to 2 meters away from one side of a kirigirisu from which the action potentials of the T-large fibers on both sides were simultaneously recorded, the T-large fiber on one side showed action potentials well synchronized with individual stridulatory sounds of the song, whereas the T-large fiber on the other side

did not (Suga and Katsuki 1961). Later, Solomon D. Erulukar, who wrote a review article on sound localization, told me that such a binaural neuron as the T-large fiber had not been previously found in any other animal, and that our finding fit into van Bergeijik's model for sound localization in mammals. It was interesting to know that a certain neural mechanism is shared by insects and higher vertebrates.

Two-Tone Suppression

Inhibitory responses of auditory neurons to tone bursts were first found in the cochlear nucleus of a cat by Galambos and Davis (1944). In a noctuid moth, I found inhibition that was different from that described by them. In the tympanic organ of the noctuid moth, there are only two sensory neurons attached to the tympanic membrane through the attachment cells. There are no efferent nerve fibers to the organ. These two sensory neurons are tuned to an identical frequency but one was 20 to 30 decibels more sensitive than the other. The low threshold sensory neuron adapted much more slowly than the high threshold neuron. When a short tone burst was delivered during a long tone burst, the response of the low threshold neuron to the long tone was immediately stopped (inhibited) during the period of the overlap, although this short tone burst alone excited the neuron. This inhibition, which is now called "two-tone suppression," was hardly explained at the time (Suga, 1961). Professor Katsuki then suggested examining whether the auditory nerve fibers of a monkey showed the same inhibition.

Because the frequency tuning of cats' peripheral auditory neurons was much sharper than that of the basilar membrane studied by Békésy, sharpening of the neural frequency tuning by lateral inhibition was suspected by the early 1960s. In 1962–1963, inhibition of background discharges and/or two-tone suppression of primary auditory neurons were reported in monkeys (Katsuki et al., 1962; Nomoto et al., 1964), cats (Rupert et al., 1963) and bullfrogs (Frishkopf and Goldstein, 1963). Nomoto et al. (1964) called two-tone suppression "peripheral inhibition," whereas Rupert et al. (1963) called it "direct or immediate inhibition." Two-tone suppression was further studied by Sachs and Kiang (1968) who called it "two-tone inhibition." The cochlear microphonic response showed two-tone suppression (Pfeiffer and Molnar, 1970) that was caused by cochlear nonlinearities (Pfeiffer, 1970). Two-tone inhibition is apparently not due to synaptic inhibition. Therefore, it has been called two-tone suppression.

The Cochleotopic (Tonotopic) Map or Representation in the Primary Auditory Cortex

When I learned of the cochleotopic map in the auditory cortices of anesthetized cats (Woolsey and Walzl, 1942) and dogs (Tunturi, 1944, 1960), I thought

that the functional organization of the auditory cortex was fascinating. These studies were based on evoked potentials recorded from the auditory cortex. When I was in Katsuki's lab, recording action potentials of single cortical auditory neurons of a cat with a glass micropipette electrode with a tip diameter of <0.3 μm was so difficult that only one frequency-tuning curve was measured on the average per each one-day experiment. This was presumably also the case in auditory physiology laboratories other than Katsuki's lab. Therefore, single-neuron data for the cochleotopic map was accumulated with many cats and the locations of the studied neurons were superimposed referring to the anterior or posterior ectosylvian sulcus. It was then noticed that neurons with best (characteristic) frequencies quite different from each other were located at a given small area of the auditory cortex. Therefore, single-neuron data obtained in Katsuki's lab and in a few other laboratories cast doubt on the presence of the strict cochleotopic map in the auditory cortex. Evans et al. (1965) recorded 105 cortical auditory neurons in unanesthetized cats and concluded that the distribution of best frequencies did not support the presence of the cochleotopic map in the auditory cortex. I understood that this conclusion was well accepted by most auditory physiologists. However, my single-neuron study on the auditory cortex of the little brown bat, *Myotis lucifugus*, showed the cochleotopic map (Suga 1965b). Therefore, I suspected that the auditory cortex of the bat might be different from that of the cat. Ten years later, the story of the cochleotopic map of the cat changed. That is, Merzenich et al. (1975) recorded single neurons or clusters of neurons from the auditory cortex of the anesthetized cat with glass-coated platinum-iridium electrodes and reestablished the presence of the cochleotopic map in the cat's auditory cortex.

Sharpening of Frequency Tuning by Lateral Inhibition

The processing of constant frequency (CF) or quasi-CF sounds is directly related to a problem of whether the central auditory system has a mechanism for the sharpening of frequency tuning of neurons, because frequency-tuning curves of peripheral neurons are very wide at high sound pressure levels. Katsuki et al. (1958, 1959) measured the frequency-tuning curves of single neurons at different levels of the ascending auditory system of the cat and found that the central auditory system of the cat has a neural mechanism for the sharpening of frequency tuning: the higher the level up to the medial geniculate body, the sharper the frequency tuning. Professor Katsuki believed that sharpening is accomplished by lateral inhibition. This was his major contribution to auditory neurophysiology at that time.

However, auditory physiologists had started to believe that there was no sign of neural sharpening and no sign of lateral inhibition in the central auditory system of the cat. This was based on findings made between the mid 1960s and early 1970s. (1) Frequency-tuning curves of cochlear nerve

fibers tuned to frequencies higher that 3 kilohertz are very sharp without lateral inhibition (Kiang et al., 1965). (2) Frequency-tuning curves of neurons in the medial geniculate body are broader than those of peripheral neurons and show no sign of sharpening (Aitkin and Webster, 1972), and (3) Frequency-tuning curves of central auditory neurons are mostly similar to or broader than those of cochlear nerve fibers (an experience shared by most cat physiologists who worked on auditory nuclei). Later, this consensus was strengthened by Calford et al. (1983) who wrote: "No difference in sharpness of tuning was found between samples of units from nuclei in the lemniscal auditory pathway, although units from the anterior auditory field showed broader tuning than those in the lemniscal pathway" (p. 395). Professor Katsuki apparently was disappointed with this consensus against his findings and asked my opinion about it on a few occasions when I was a postdoctoral research associate in the United States.

Through my own research in 1964 and thereafter, it was clear to me that the frequency tuning of single neurons is sharpened by inhibition in the central auditory system of the little brown bat and the mustached bat. Unlike quasi-triangular tuning curves of peripheral neurons, pencil-shaped or spindle-shaped tuning curves have been found in the central auditory systems of many different species of animals over the last 40 years. Inhibitory tuning curves are commonly associated with a very sharp excitatory tuning curve. The best frequency (BF) for an inhibitory tuning curve is slightly lower or higher than the BF for an excitatory tuning curve. An application of a γ-aminobutyric acid (GABA-A) receptor antagonist to thalamic (Suga et al., 1997) or midbrain (Yang et al., 1992) auditory neurons eliminates the inhibitory tuning curves and broadens the excitatory tuning curves. It has been well demonstrated that the sharpening of frequency tuning curves is accomplished by lateral inhibition in a cascaded manner. I reached the conclusion that the contradiction on the sharpening of neural frequency tuning curves originated from differences in defining the sharpness of frequency-tuning curves of neurons (Suga 1995).

The sharpness of a tuning curve has been expressed by a Q-n dB value, which is the BF divided by a bandwidth at n dB above the minimum threshold (n dB width). If a tuning curve is exactly triangular in shape, its sharpness can be appropriately expressed by a single value, for example, a Q-10 dB value. If it is not, a Q-10 dB value related only to the tip portion of a tuning curve is simply inadequate to describe the overall sharpness of the tuning curve. Frequency-tuning curves of peripheral neurons commonly show a deflection point at about 40 dB above the minimum threshold where the slopes of the passive and active filters join (Evans, 1972). Therefore, Q-20 dB and Q-50 dB values may be used to determine whether the passive and/or active portions of a tuning curve are sharpened by inhibition in the central auditory system.

The choice of parameters characterizing tuning curves should be contingent on the problem being discussed. To discuss sharpening, a change in the

skirt portion of a tuning curve (e.g., Q-50 dB) should be mainly considered, not the tip portion, because the tip portion is sharp at the periphery. On the other hand, to discuss broadening, the tip portion of a tuning curve (e.g., Q-20 dB) should be mainly considered, not the skirt portion, because the skirt portion is broad at the periphery (Suga and Tsuzuki, 1985). For me, it is quite appropriate to conclude that the cat's central auditory system has a mechanism for the sharpening of frequency tuning, and that this mechanism drastically sharpens the skirt of a tuning curve.

Different from tuning curves at the periphery, the tuning curves of certain central auditory neurons have a narrow width even at high stimulus levels. Such a tuning curve is called a "level tolerant" sharp frequency-tuning curve (Suga and Manabe, 1982). In the central auditory system, neurons with different response properties are clustered in different locations. Level-tolerant frequency tuning is common or concentrated in a particular region or regions along the cochleotopic axis (Casseday and Covey, 1992; Condon et al., 1994; Ehret and Moffat, 1985; Suga and Manabe, 1982; Suga and Tsuzuki, 1985) or along iso-BF lines (Schreiner and Mendelson, 1990; Schreiner and Sutter, 1992). The central auditory system also has a mechanism for the broadening of frequency tuning. Broadly tuned neurons are clustered separately from sharply tuned neurons. Therefore, the presence of broadly frequency-tuned neurons in the central auditory system cannot be used as evidence against the presence of sharply tuned neurons such as level-tolerant neurons.

Postdoctoral Research in the United States

In the summer of 1960, Professor V. B. Wigglesworth (an insect physiologist at the University of Cambridge in England) visited Katsuki's laboratory. I demonstrated to him the responses of the binaural neurons (T-large fibers) of kirigirisu. He apparently liked the demonstration because just before he left the laboratory he invited me to work in his laboratory after finishing my Ph.D. dissertation. However, he had no setup for auditory neurophysiology as well as no salary for me. So, I started to prepare for an English test and an application for a British scholarship to get travel and living expenses to work in England.

At that time, Dr. Takeshi Watanabe (one of Professor Katsuki's students) was at the Massachusetts Institute of Technology in Cambridge, Massachusetts, as a postdoctoral research associate. In 1961, he visited Professor Donald R. Griffin at the Biology Department of Harvard University. In Griffin's lab, Alan D. Grinnell, a graduate student (presently a professor at UCLA), was finishing his Ph.D. dissertation on the neurophysiology of audition in bats and was planning to go to Bernard Katz's lab at the University of London. So, Professor Griffin asked Watanabe whether Professor Katsuki knew of any young neurophysiologist who might want to come to his laboratory to work on the bat's auditory system. My name was

mentioned. Shortly afterwards, I received an invitation letter from Professor Griffin through Professor Katsuki. He apparently had a research grant to support me as well as the setup for auditory neurophysiology. Professor Katsuki suggested that I go to Griffin's lab after finishing our presentation of the dip-prism microscope at the Congress of the International Union of Physiological Sciences held in Leiden, Holland, in the summer of 1962, and after receiving my Ph.D. I earned my Ph.D. in March 1963 by presenting my thesis "Neurophysiology of Hearing in Insects" and by giving a public lecture at Tokyo Metropolitan University. On April 1, 1963, I began working in Griffin's lab as a postdoctoral research fellow. This was the beginning of my research on the bat's auditory system. I first repeated Grinnell's excellent pioneering work to become familiar with the auditory system of the little brown bat and then took advantage of a frequency modulated (FM) sound generator that was built by Dr. Jerry J. G. McCue in the MIT Lincoln laboratory. I found that the inferior colliculus consists of many different types of neurons in terms of excitatory and inhibitory frequency-tuning curves and responses to tone bursts, FM sounds, and noise bursts (Suga, 1969). Among them, FM-specialized neurons are particularly interesting, because they have no excitatory area, but instead an inhibitory area, and respond to a FM sound that sweeps across the inhibitory area. This "paradoxical" response is explained by a disinhibition or summation model. Many FM-specialized neurons respond to downward-sweeping FM sounds, but not to upward-sweeping ones, and some respond to upward-sweeping FM sounds, but not to downward-sweeping ones, while some respond to downward- and upward-sweeping FM sounds (Suga 1965a, 1965b). My research with the little brown bat went well. Professor Griffin promoted me to a lecturer in my 2nd year.

I had a wonderful time in Griffin's lab. Hiroko Kurihara Suga (my wife, a middle-school teacher) came to Cambridge in the summer of 1963 to join me. Particularly vivid in my memory are the bat hunting trips I took to Cape Cod and Vermont with Hiroko and Ms. Judy H. Friend. In late 1964, Professor Griffin came back from the William Beebe Tropical Research Station in Trinidad, West Indies, and told me and his students that there were unknown animals producing ultrasonic sounds that could be detected only by a bat detector. I asked him to show me the waveform of the sounds on the cathode-ray oscilloscope (CRO) screen in addition to playing back the tape-recorded sounds. By watching the waveform, I mentioned, "Those sounds must be produced by long-horned grasshoppers." Then, Professor Griffin immediately said, "Why don't you go to Trinidad to catch the insects?" So, Hiroko and I went to Trinidad in late January 1965. In the front yard of the research station, there were many "ultrasonic" insects singing in the afternoon, but I could not see any of them on the first day. In the late afternoon of the second day, I finally saw a faint green slender long-horned grasshopper (~ 23 mm long) singing and reflecting sunlight at the tip of a drooping leaf of a

Queen of India tree. When I moved my bat detector closer to the insect, its stridulatory sound became very loud. I was so excited that I missed catching it! However, once I knew what the insect looked like, it was not difficult to find and catch it. Eventually, I found three species of "ultrasonic insects": *Phlugis* sp.1, *Phlugis* sp.2, and *Drepanoxiphus modestus*. Phlugises are daytime singers that produce stridulatory sounds that are 40 to 60 kilohertz noise bursts, whereas Drepanoxiphus is a night singer that produces sounds that are 22 to 24 kilohertz "pure tone" pulses. They were reported as mutes although they belonged to the long-horned grasshopper family. I caught several other long-horned grasshoppers, for example, *Conocephalus saltator*, which produces sounds that are 18 to 66 kilohertz noise bursts. I also studied their hearing and mechanism of sound production (Suga, 1966). We fully enjoyed the 2 months we spent in Trinidad, together with Roderick A. Suthers (presently a professor at Indiana University in Bloomington) who was working on the fish-catching bat, and Hubert Markl (presently retired from numerous highly prestigious posts in Germany) who was researching the leaf-cutting ant and other insects.

I spent two highly productive years in Griffin's lab, working on the little brown bat at Harvard Biology and on ultrasonic grasshoppers in Trinidad. I wanted to publish papers coauthored by Professor Griffin. However, he said, "Everyone knows that I don't do neurophysiology. I can't be a coauthor." So, all seven papers of mine did not bear his name. Because of this, I felt something was missing, but I thought that this was the U.S. way of publishing. Toward the end of the first year in Griffin's lab, Professor Theodore H. Bullock (Zoology Department, UCLA) visited Griffin's lab and offered me a job as a research scientist. So, in May 1965, Hiroko and I moved to UCLA and I began working in Bullock's lab.

In Bullock's lab, all postdoctoral research associates worked independently of each other, choosing their own research topics and species. Bullock's lab had no setup for auditory neurophysiology. Therefore, after my arrival at UCLA, I ordered instruments for auditory neurophysiology as well as a soundproof chamber. While I waited for the instruments to arrive, I studied electric fish because a few species of electric fishes were kept in Bullock's lab and were easily available for research. A departmental machinist, who was said to be very difficult to deal with, was somehow very cooperative with me and quickly made me a Lucite trough and mouthpieces for my experiments on the fish, according to my design. So, I was able to start my research on the electric fish within 1 month after my arrival at UCLA. This electric fish experiment lasted approximately 5 months (Suga, 1967). This was a relatively relaxed period in my life. Hiroko and I lived in West Los Angeles and often walked along the rows of tall palm trees on Santa Monica Beach, looking at the Pacific Ocean. My first child, Ibuki, was born in November 1965.

In late 1965, Professor Bullock moved to the medical school of the University of California, San Diego (UCSD). So, I moved to UCSD from UCLA

in early 1966 and restarted my work on bats at Scripps Institute of Oceanography, La Jolla, because the medical school at UCSD was under construction. Bat hunting trips around Lake Henshow with Hiroko and Ms. Grace G. Kennedy (the lab assistant) were quite enjoyable. Professor Bullock provided me with unique experiences through his research collaborating with Katsuki's group on hearing in porpoises in Japan and also through the research conducted on the research vessel, *Alpha Helix*, which traveled to the Amazon in Brazil. On *Alpha Helix*, I worked on hearing in mole crickets that flew on the ship at night or silky anteaters and sloths that were brought to the ship by natives.

In Katsuki's lab, I studied the responses of the T-large fiber of the long-horned grasshopper to the species-specific call and had an opportunity to see its sound spectrogram. Therefore, it was not totally new for me to see sound spectrograms. In 1966, however, *Visible Speech* written by Potter et al. (1966) and several papers on the perception of speech sounds in humans (e.g., Cooper et al., 1952; Liberman et al., 1956, 1959) opened my eyes, because no neurophysiology textbook had ever described the acoustic patterns (sound spectrograms) of human speech and animal sounds that are processed by the auditory system. (All recent neurophysiology textbooks still have this tradition.) I examined the sound spectrograms of calls produced by many species of animals and found that calls of higher vertebrates contain three types of information bearing elements (IBEs): constant frequency (CF) tones, frequency modulated (FM) sounds, and noise bursts (NB) which respectively are comparable to formants, transitions, and fills in human speech sounds. Therefore, I first studied how central auditory neurons selectively responded to each of the three types of IBEs and how inhibition was contributing to the creation of the selectivity. I found that inhibition created various types of neurons: asymmetrical neurons, CF-specialized neurons, FM-specialized neurons, NB-specialized neurons, and so on (Suga, 1968, 1969, 1973). I then studied how central auditory neurons responded to combinations of IBEs. The stimuli designed for this experiment were not related to the sounds behaviorally relevant to the bat, and the progress in the research was mediocre. I had to wait 10 years to have success in this line of research.

I was quite comfortable as a research scientist in Bullock's lab, but in early 1968, Professor Susuma Hagiwara (UCSD) suggested that I become an independent scientist. The University of Hawaii in Honolulu, Indiana University in Bloomington, and Washington University in St. Louis, Missouri, offered me an assistant professor's job. I was not in a hurry at all to accept a faculty position and didn't respond to any of these offers. Later, Washington University offered me an associate professor's job instead of an assistant professor's job. At Hagiwara's suggestion, I took the job as an associate professor in the Department of Biology at Washington University.

My First Year at Washington University in St. Louis

I moved to St. Louis on the 4th of January in 1969. Having my own laboratory was the start of an exciting and wonderful phase of my research career. The first year at Washington University, I was particularly busy with writing papers on my research performed in California, lecture notes, and a laboratory manual for teaching as well as a proposal to get a research grant from the National Science Foundation (NSF). I also performed research on the cat's auditory system in the Medical School at Washington University. My second child, Yuko, was born in May 1969. Hiroko and I were both very busy during this time. In retrospect, I wonder how I managed to do all these things at once.

My First Research Grant

I had no experience in writing a research proposal, and many young scientists had a difficult time in getting a research grant because of the Vietnam War (1959–1975). Regardless, I submitted my research proposal "Studies in Comparative Auditory Neurophysiology" to the NSF instead of the NIH, because my research on the bat's auditory system was not directly related to human health. At that time, almost all auditory neurophysiologists had been working on cats, and the atmosphere was such that if you were not working on cats, you were not considered an auditory neurophysiologist. So, it appeared to be a disadvantage to keep working on bats. I could work on either cats or monkeys because I worked on cats and monkeys in Japan. I knew that the squirrel monkey, *Saimiri sciureus*, is not large and emits many different types of calls. Therefore, I chose the squirrel monkey for my next research project. In my proposal, I wrote something like "I will complete my research on bats in two years and then will start to work on the squirrel monkey." My proposal was assigned to the program for Regulatory Biology. One day, Dr. David B. Tyler, the NSF Program Director, called me from Washington, D.C., and mentioned that he wanted to see me in my office during his visit to St. Louis. While visiting me, he told me that my proposal was for a project that would easily last 10 years or more. He suggested that I write a well-focused proposal for the next funding period and promised to fund my research project because of my high productivity and the many interesting research papers that I had written. That was a good ol' days. The NSF supported my research from 1969 to 1981. I had a 2-month summer salary from the NSF. I had heard that the NIH allowed scientists to get a 3-month summer salary. So, in 1980, I submitted my research proposal, "Neural Basis of Complex-Sound Processing," to the NIH as well as the NSF. My approved NIH research grant was larger than my approved NSF grant, so I chose the NIH grant. Since then, my research has been supported by the NIH.

Animals for Auditory Neurophysiology in My Lab

Because the auditory system has evolved for detecting and processing behaviorally relevant sounds (species-specific sounds and sounds produced by prey and predators), the selection of the species of an animal for auditory neurophysiology is an important issue. Orientation sounds (biosonar pulses or, simply, pulses) are indispensable sounds for survival of insectivorous bats and are extensively used everyday by bats. The acoustic parameters characterizing the pair of the pulse and its echo are known to bear different types of biosonar information. Therefore, a neural basis of complex-sound processing can be explored by researching how biosonar information is processed in the bat's auditory system. However, the biosonar pulses of the little brown bat are simple FM sounds and are not particularly suited for discovering the basic mechanisms or principles for the neural processing of complex sounds. I was aware of the advantages and disadvantages of working on bats. However, I decided to work on bats for awhile because they were much smaller than the squirrel monkey and could easily be handled by myself without anyone else's help.

In 1973, Dr. James A. Simmons, an assistant professor in the Department of Psychology at Washington University in St. Louis (presently a professor at Brown University), suggested that we work together on the Panamanian mustached bat, *Pteronotus parnellii rubiginosus*. That was the beginning of my research on the mustached bat. Jim was a brilliant person from whom I learned a great deal. Since 1970, the number of auditory neurophysiologists working on bats gradually increased. The mustached bat was recognized as an excellent species for auditory research, although its auditory system is specialized for echolocation. In the early 1980s, collecting Panamanian mustached bats became difficult. Dr. William E. O'Neill, one of my former postdoctoral research associates (presently a professor at the University of Rochester) helped me collect mustached bats in Jamaica, graciously sharing with me the caves where he also collected bats for his research. Because several groups of scientists had been collecting bats from the same caves annually since the early 1980s, by the mid-1990s the bat colonies had become small, and the bats were hard to collect. In addition, getting an animal collection permit became more difficult. In the late 1990s, the collection of mustached bats in Jamaica became impossible. Professor Jeffrey J. Wenstrup (at Northeastern Ohio University College of Medicine) kindly helped me with the importing of Trinidadian mustached bats.

To work on bats from foreign countries, we have to spend extra time and effort on animal collection, exportation and importation permits, interacting with local village people, shipping the bats by air freight, clearing them through customs at the airport, and hand-feeding the bats until they start to eat by themselves from a dish. In the long run, ideally the bats should be bred in the animal facility of the research university. The mustached bat is arguably one of the best species for auditory research. However, collecting

them became a problem. So, I decided to work on the big brown bat, *Eptesicus fuscus*, (a common species in Missouri and Illinois) and the Mongolian gerbil, *Meriones unguiculatus*, in addition to the mustached bat. The comparative studies of different species of mammals turned out to be very interesting and important for the understanding of the neural specialization of the auditory system.

Setting up the Suga Lab (Transitional Period)

I had to wait approximately 10 months to set up my laboratory. Professor Russell Pfeiffer (Dept. of Electrical Engineering) offered me his auditory physiology setup to use that was designed for cats and located on the Medical School campus across Forest Park. I chose a topic familiar to me for our joint project with the cat: properties of two-tone suppression. One of Pfeiffer's postdoctoral fellows, Randolph Martin Arthur (presently a professor at Washington University in St. Louis) joined this project and became its driving force (Arthur et al., 1971). When the minimum essential instruments to deliver single-tone bursts and record action potentials arrived at my lab and a soundproof chamber was installed, I wanted to start my research on bats, although our cat project was not completed. I didn't know a place where I could collect bats in Missouri. At the end of one of my lectures at our medical school, Professor Louis S. D'Agrosa of St. Louis University Medical School introduced himself to me, saying that he had been working on the microcirculation of the bat's wing. Soon after, we started collecting little brown bats in Missouri caves together.

In the first experiment in my lab, I found that some collicular neurons showed a constant response latency regardless of the stimulus intensities and rise times. To very weak tone bursts or tone bursts with slowly rising amplitudes, these constant latency neurons did not shift their response latencies at all. They were suited for coding echo delays (Suga, 1971).

My first postdoctoral research associate was Peter Schlegel, who was followed by Tateo Shimozawa. Together, we performed enjoyable experiments. We found that in five different species of bats, vocalization of species-specific biosonar pulses were elicited by electrical stimulation of the central gray matter or reticular formation of the midbrain (Suga et al., 1973), and that the auditory neural response evoked by a self-vocalized sound was attenuated by ~25 dB in the midbrain by the efferent copy from the vocalization system (Suga and Schlegel, 1972; Suga and Shimozawa, 1974). Phillip H. S. Jen was my first graduate student. He stayed with me as a postdoctoral research associate for one year after graduation. To extend the findings of the neural attenuation of vocal self-stimulation, we worked on the muscular attenuation of vocal self-stimulation. We found that the middle ear muscles contracted synchronously with sound emission and attenuated vocal self-stimulation by 15 ~ 30 dB: the lower the frequency of the emitted sound, the larger the attenuation. We also found that the tetanus fusion frequency of the

stapedius muscle was as high as 320/s (Suga and Jen, 1975). We were quite satisfied with these experiments that we performed on the little brown bat.

Research on the Mustached Bat

The biosonar pulse of the little brown bat and the big brown bat is FM. It sweeps downward about one octave within a range between 100 and 15 kilohertz. The properties of FM pulses vary depending on echolocation situations. In target-directed flight, the FM pulse becomes lower in frequency, shorter in duration, and higher in emission rate. Echoes that elicit behavioral responses of the bat usually do not overlap with the emitted pulse. On the other hand, the biosonar pulse of the mustached bat always consists of a long CF component followed by a short FM component. Because each biosonar pulse contains four harmonics (H_{1-4}), there are eight major components (CF_{1-4}, FM_{1-4}). The second harmonic (H_2) is always predominant, with CF_2 at ~ 61 kilohertz and FM_2 sweeping from 61 kilohertz to ~49 kilohertz. The CF_2 frequency slightly differs among individual mustached bats and is sexually dimorphic: the males' CF_2 is ~ 1.04 kilohertz lower than the females' on the average. In target-directed flight, the CF–FM pulse becomes shorter in duration and higher in emission rate, but its spectrum changes little. Echoes that elicit behavioral responses in the mustached bat usually overlap with the emitted pulse, so that biosonar information is extracted from a complex sound potentially containing up to 16 components. The long CF and short FM sounds are most suited for bearing velocity and distance information, respectively. Specifically, the difference in frequency between the CF components in the emitted pulse and its echo (Doppler shift) carries information about the relative velocity of a target, whereas the time delay of the echo from the emitted pulse carries information about target distance. Therefore, the auditory system of the mustached bat is particularly suited for exploration of the neural mechanisms for processing complex sounds by combination-sensitive neurons. I considered that the CF and FM components were comparable to the formants and transitions in human speech sounds and that the neural mechanisms found in the mustached bat would significantly contribute to understanding the basic neural mechanisms for processing the formants, transitions, and combinations of these (Suga, 1972). However, as expected, this view has not necessarily been well accepted because some think that the auditory system of the bat specialized for echolocation is very different from that of nonecholocating mammals, although the bat uses a variety of communication calls as do nonhuman primates (Kanwal et al., 1994).

Auditory Periphery

I began the research on the mustached bat in my lab, first with Simmons and then Jen. Later, many postdoctoral research associates came to my lab

from Japan. The cochlea of the mustached bat is extremely sharply tuned to the frequency of ~61 kilohertz. So, we first studied the auditory periphery (Suga and Jen, 1977). I was quite satisfied with the data on the auditory periphery of the mustached bat, which showed the dramatic specialization for analyzing the CF_2 of the species-specific biosonar pulse. Professor Gerhart Neuweiler (Goethe University of Frankfurt, Germany) invited me to work on the horseshoe bat, *Rhinolophus ferrumequinum*, the so-called 83-kilohertz CF-FM bat in the Old World. I first considered not going to Germany because the experiments in my lab had been going very well. However, I changed my mind because Jen could continue our experiments on the mustached bat without me and because I thought it would be interesting to work on the CF–FM bat in the Old World in comparison to the mustached bat that is the 61-kilohertz CF–FM bat in the New World. The 5 months in Frankfurt were successful (Suga et al., 1976). The data obtained from the auditory peripheries of the mustached, horseshoe, and little brown bats are the best demonstration of the specialization that the sharpness of the frequency tuning of peripheral neurons varies according to the amplitude spectrum of behaviorally important species-specific sounds (Suga and Jen, 1977).

Auditory Cortex

My experimental philosophy was first to find cortical auditory neurons that were quite different from peripheral ones in their response properties and then explore how the differences were created by neural interaction in the central auditory system, using the top-down approach. Because the auditory periphery was successfully studied, I began working on the auditory cortex with Jen. We first examined the columnar organization in terms of the BF and then the cochleotopic (tonotopic) map in the auditory cortex. That is, we first performed the most basic study. The cochleotopic map of the auditory cortex of the mustached bat was unique, because the frequency of CF_2 at ~61 kilohertz was overrepresented and the iso-BF contour lines were concentric (Suga and Jen, 1976). Such a cochleotopic map had not been found in any other animal at that time. This large area representing CF_2 was apparently related to the processing of Doppler shifted (DS) CF signals. So, we named it the DSCF processing area.

Amplitopic Representation

Different from other cortical auditory areas, the DSCF area represents identical frequencies at ~61 kilohertz with a larger number of neurons. So, an obvious question was what was different among neurons tuned to identical frequencies. I particularly remember the summer months of 1976 when I did not have a research associate because an expected research associate was not able to come to my lab in time. So, I alone continued the acute cortical mapping

experiments, working from morning until midnight, because it was essential to have the data, as much as possible, from one auditory cortex within one day. Hiroko came to the lab in the evening with our two children, bringing dinner, so that we all could eat and spend time together. This 3-month summer research produced very interesting data: (1) each DSCF neuron was tuned to a specific combination of frequency and amplitude of a sound, (2) each cortical column represented a specific combination of frequency and amplitude, and (3) the DSCF area had the frequency-versus-amplitude coordinates (Suga, 1977; Suga and Manabe, 1982). This was the first neurophysiological map beyond the cochleotopic map. We also found that the DSCF area consisted of two subdivisions in terms of the distribution of two types of binaural neurons (Manabe et al., 1978), and one type of binaural neuron was callosally connected, but the other type was not (Liu and Suga, 1997). Knudsen and Konishi (1978) found the auditory space map in the midbrain of the barn owl. So, the auditory physiology of noncat species became very interesting. The number of auditory physiologists working on noncat species gradually increased, and they became a nonminority in the field of auditory physiology.

Combination-Sensitive Neurons

Toshiki Manabe and I further studied the frequency and amplitude tuning of DSCF neurons and started to examine other cortical areas that were interesting enough for further exploration. The area dorsoanterior to the DSCF area showed very poor responses to single tone bursts, so we initially did not pay attention to this area. However, we occasionally found combination-sensitive neurons in this area. A "combination-sensitive" neuron means that the response of the neuron to a combination of two or more sounds is larger than the algebraic sum of the responses to the individual sounds combined. At that time, Mudry et al. (1977) found a combination-sensitive area in the frog's auditory thalamus, and Feng et al. (1978) found combination-sensitive neurons tuned to echo delays in the midbrain of the big brown bat. One year after Manabe's arrival, William E. O'Neill and then Kazuro Kujirai came to my lab as postdoctoral research associates. We found many types of combination-sensitive neurons. Among these, CF/CF neurons tuned to Doppler shifts for processing velocity information and FM–FM neurons tuned to echo delays for processing target ranges were easily recorded. These two types of neurons are separately clustered at the dorsoanterior areas of the auditory cortex and form the velocity (Suga et al., 1983) or distance (Suga and O'Neill, 1979) axis or map, respectively. We published a dozen papers on combination-sensitive neurons. Among them, the longest original article was 53 pages long and became one of my favorite papers (Suga et al., 1983). Thereafter, several postdoctoral research associates came to my lab: Kohichi Tsuzuki, Junsei Horikawa, Dan Margoliash, Masashi Kawasaki, Robert F. Burkard,

Hideo Edamatsu, Doug Fitzpatrick, Hayato Misawa, and Atsushi Tanahashi. They particularly contributed to extending our research on combination-sensitive neurons in the auditory cortex. The number of combination-sensitive areas in the auditory cortex increased (Suga, 1990). Two graduate students, John F. Olsen (Olsen and Suga, 1991) and John A. Butman, worked on combination-sensitive neurons in the auditory thalamus and significantly contributed to furthering our understanding of the processing of complex sounds. It became clear that different types of auditory information are processed in a parallel and hierarchical way in the central auditory system.

In addition to combination-sensitive neurons, non-combination-sensitive neurons in the auditory cortex and the inferior colliculus of the mustached bat were studied by several of my collaborators: Isao Saitoh, Taku Hattori, Atsushi Asanuma, and so on. Among their works, I particularly remember these two findings—that the inferior colliculus has the frequency-versus-latency coordinates (Hattori and Suga, 1997) and that long latencies (delay lines) of collicular neurons are created by inhibition (Saitoh and Suga, 1995).

All the research on combination-sensitive neurons and the functional map of the auditory cortex were obtained through neurophysiological studies performed delivering a synthesized biosonar pulse and echo in a soundproof room. Therefore, we had to demonstrate that combination-sensitive neurons responded to echoes when the bat emitted biosonar pulses. Kawasaki and Margoliash placed the mustached bat outside of our 2nd-floor lab window facing a large parking lot. When the bat emitted biosonar pulses, they delivered synthesized echoes to the bat that were variously delayed from the vocalized biosonar pulses and proved that "delay-tuned" FM–FM neurons studied with the synthesized biosonar pulse and echo were indeed tuned to the pair consisting of the vocalized biosonar pulse and the synthesized echo, as predicted (Kawasaki et al., 1988).

Assistant Professor Stephen J. Gaioni (Dept. of Psychology) and I had a research grant from the Air Force Office of Scientific Research to study echolocation behavior in relation to the cortical auditory map. That is, I had extra money and an open position for an extra postdoctoral research associate. Hiroshi Riquimaroux, who had a Ph.D. in psychology applied for this position. So, Gaioni and Riquimaroux conditioned the mustached bat for either fine frequency or time interval discriminations and then inactivated either the cortical DSCF area which systematically represents the frequency of sound with very sharply frequency-tuned DSCF neurons or the cortical FM–FM area which systematically represents a time interval (i.e., echo delay) between two sounds with FM–FM combination-sensitive neurons. As expected, inactivation of the DSCF area disrupted the frequency but not the delay discriminations, whereas inactivation of the FM–FM area disrupted the delay but not the frequency discriminations (Riquimaroux et al., 1991).

Through this experiment, we learned (1) acoustic stimuli for behavioral experiments should be designed according to behaviorally relevant sounds, (2) inactivation experiments of each cortical auditory area to examine its auditory function should be designed in relation to its functional organization electrophysiologically explored, and (3) the auditory cortex which is cochleotopically (tonotopically) organized plays a role in fine frequency discrimination, not in course frequency discrimination.

By 1993, the response properties of cortical auditory neurons and the neurophysiological map of the auditory cortex of the mustached bat had been extensively studied with acoustic stimuli designed on species-specific biosonar pulses and their echoes. Although further important data were still coming out at the time, I thought that it was time to study how species-specific communication sounds are processed in the auditory cortex that is highly specialized for processing biosonar information. Are there cortical areas specialized for processing communication sounds? Are the areas specialized for processing biosonar information also involved in processing communication sounds? When Jagmet S. Kanwal, Sumiko Matsumura, and Kevin K. Ohlemiller joined my lab, it was indeed the time to study the responses of cortical auditory neurons and the cortical map in terms of the processing of species-specific communication sounds. As the first step, the communication sounds of the adult mustached bat were classified. We were surprised with the complexity of the communication sounds: there were at least 33 discrete types of syllables that could be further classified as 19 single syllables, 14 composites and three subsyllables (Kanwal et al., 1994). Acoustic stimuli were synthesized by utilizing these communication sounds (Ohlemiller et al., 1994) and used for neurophysiological studies, as suggested by Suga (1992). It then became clear that cortical neurons specialized for processing biosonar information are also involved in processing communication sounds that have acoustic properties similar to, but not the same as, those of biosonar pulses, and that neurons change their tuning according to a difference in the amplitude spectrum between the biosonar pulses and communication sounds (Ohlemiller et al., 1996).

When the project on the processing of communication sounds was progressing, I considered that the corticofugal (descending) auditory system had not been appropriately studied and that we could perform innovative research on it. So, we started to study the function of the corticofugal auditory system. Thus, my lab had three projects going at that time: #1: further studies on the cortical representation of biosonar information conducted by Heibin Teng; #2: cortical processing of communication sounds conducted by Kanwal and others; and #3: corticofugal modulation of collicular neurons conducted by Jun Yan and others. The research project on the cortical processing of communication sounds was taken on by Kanwal for his research as an assistant professor at Georgetown University. I compared projects #2 and #3 and decided to stop project #2 in my lab and concentrate on project

#3 because project #2 had been in my mind for many years and was not fresh for me, whereas I was strongly motivated to perform innovating research on the function of the corticofugal system.

Functions of the Corticofugal Auditory System

It had been considered that auditory signal processing is performed through divergent and convergent projections of neurons in the ascending auditory system (Covey and Casseday, 1999; Suga, 1990), although the auditory cortex sends out descending nerve fibers much more than the thalamocortical ascending nerve fibers. The corticofugal auditory system forms multiple feedback loops, so the exploration of its function is quite challenging. By the middle of the 1990s, progress in the neurophysiology of the corticofugal system was very limited and neurophysiological data of corticofugal effects on thalamic and midbrain auditory neurons had been controversial: (1) only or predominantly inhibitory, (2) only or predominantly excitatory, or (3) equally excitatory or inhibitory. These data, regardless of the excitatory or inhibitory effect, indicate that one of the corticofugal functions can be nonspecific gain control. However, I strongly felt that the corticofugal system should have much more elegant functions than simple gain control because there is a much larger number of corticofugal fibers than thalamocortical fibers.

I had noticed a significant problem in all the neurophysiological research on the corticofugal system, that is, cortical activation by electric stimulation and cortical inactivation by a drug or cooling were too widely spread to explore corticofugal function, even in the experiments that performed so-called focal activation or inactivation. To study the function of the corticofugal system, I considered (1) the tuning of stimulated cortical and recorded subcortical neurons should be first measured because the cortical and subcortical neurons both are tuned to particular values of acoustic parameters, (2) electric stimulation or a drug application for activation or inactivation should be highly focal except for the initial phase of corticofugal research, and (3) corticofugal effects on subcortical neurons should be evaluated with regard to the relationship in tuning between the stimulated or inactivated cortical neurons and the recorded subcortical neurons. Therefore, our research performed since 1995 has been designed on this philosophy.

The rapid progress in our research on the function of the corticofugal system depended on excellent collaborators of mine. Jun Yan (Yan and Suga, 1996), Yungfeng Zhang (Zhang et al., 1997), and Wei Yan (Yan and Suga, 1998) made several important discoveries in the initial phase of this project. Then, Syed A. Chowdhury, Xiaofeng Ma, Masashi Sakai, Zhongju Xiao, Yongkui Zhang, and Jie Tang extended the research on this project. We first found that repetitive stimulation of the auditory cortex with 0.2 ms, 100 nA electric pulses evoked changes in the response properties of subcortical

auditory neurons. Then, we found that the stimulation also evoked changes in the response properties of cortical auditory neurons (Suga et al., 2000, 2002) and even changes in the cochlear hair cells when the rate of the stimulation was high (Xiao and Suga, 2002a), and that all the subcortical changes originate from the cortical changes as reviewed by Suga and Ma (2003). The most basic findings of ours are described below.

Focal electric stimulation of cortical auditory neurons facilitates the response and sharpens the tuning of cortical and subcortical auditory neurons whose tuning matches that of the stimulated cortical neurons, whereas it slightly suppresses the response and shifts the tuning of cortical and subcortical neurons whose tuning does not match the stimulated cortical ones. We named this corticofugal function "egocentric selection," which is the improvement of cortical and subcortical auditory signal processing and the adjustment of a neural representation (representational map) of an acoustic parameter in the cortex and subcortical auditory nuclei. In other words, egocentric selection occurring in the subcortical nuclei improves and adjusts the cortical input for signal processing and representation in the cortex (Suga et al., 2000, 2002). Focal inactivation of cortical auditory neurons shifts the tuning of subcortical neurons in the opposite direction to the shift evoked by the focal electric stimulation. However, nonfocal or uniform inactivation of cortical auditory neurons, including cortical neurons matched and unmatched to recorded subcortical neurons, reduces the auditory responses of the subcortical neurons but does not shift their tuning (Yan and Suga, 1999; Zhang and Suga, 1997).

There are two types of tuning shifts of the subcortical neurons: shifts toward and away from the tuning of the stimulated cortical neurons, which are, respectively, named "centripetal" and "centrifugal" shifts. The centripetal and centrifugal shifts of the tuning of subcortical neurons, respectively, result in the expanded and compressed reorganizations of the subcortical auditory map. An antagonist of GABA-A receptors applied to the auditory cortex changes the compressed reorganization into the expanded reorganization. Strong inhibition relative to excitation in the auditory cortex apparently evokes the compressed reorganization. The expanded reorganization has been found in the auditory system as well as in the visual and somatosensory systems of several species of mammals, whereas the compressed reorganization has thus far been found in the subsystems of the auditory system of the mustached bat which are highly specialized for processing certain types of biosonar information. Our results, however, indicate that the mustached bat and nonbat species basically share identical corticofugal neural mechanisms, and that the specialization in the mustached bat is partly created by strengthening inhibition in the auditory cortex (Xiao and Suga, 2002b).

Electric stimulation of the nervous system to explore the function of its particular portion is an old technique, but it is still a valuable technique. For example, focal electric stimulation of the inferior colliculus evokes the

BF shifts of the collicular neurons surrounding the stimulated collicular neurons, just like those elicited by cortical electric stimulation. Inactivation of the auditory cortex blocks the development of these BF shifts (Zhang and Suga 2005). Electric stimulation of the ventral division of the medial geniculate body of the house mouse evokes the collicular BF shift, and this collicular BF shift is blocked by inactivation of the auditory cortex (Wu and Yan, 2007). Therefore, it becomes clear in the big brown bat and house mouse that the plastic changes in the auditory cortex elicited by focal electric stimulation of the subcortical auditory nuclei are transmitted back to the subcortical auditory nuclei.

Corticofugal Feedback and Tone-Specific Plasticity Elicited by Auditory Fear Conditioning

Because the effects of the cortical electric stimulation lasted up to 3.5 hours, I thought that corticofugal modulation was involved in plastic changes in the central auditory system caused by learning. So, we started doing research to explore the relationship between plastic changes evoked by the corticofugal system and auditory fear conditioning, although no one speculated that corticofugal feedback would be involved in the plasticity elicited by auditory fear conditioning. In our first experiment (Gao and Suga, 1998), we immediately noticed that the neural circuit model proposed by Weinberger (1998) to explain the cortical tone-specific changes elicited by the conditioning was most likely incorrect or incomplete. Enquan Gao (Gao and Suga, 1998, 2000), Weiqing Ji (Ji et al., 2001, 2005; Ji and Suga, 2003) and Xiaofeng Ma (Ma and Suga, 2001, 2003) established that corticofugal feedback and the somatosensory cortex, which were neglected by the Weinberger model, play an important role in plastic changes in the central auditory system evoked by the conditioning. Gao and Suga (1998) proposed the neural circuit for the tone-specific changes, represented by BF shifts elicited by auditory fear conditioning. The Gao-Suga model, elaborated upon by Suga and his collaborators (2000), states that small or subthreshold short-term cortical and collicular BF shifts specific to a conditioning tonal stimulus (CS) are evoked by the neural circuit within the auditory cortex and corticofugal feedback loops activated by the CS alone, and that this cortical BF shift is augmented and changed into the long-term BF shift by acetylcholine released into the auditory cortex from the cholinergic basal forebrain. In this model, the cholinergic basal forebrain is activated by the auditory and somatosensory cortices via the association cortex and the amygdala where the CS is associated with an unconditioned leg-stimulus (US). In addition, CS–US association may also occur in the association cortex. The collicular BF shift is increased by the augmented cortical BF shift through corticofugal feedback and contributes to the development of the large long-term cortical BF shift (Suga and Ma, 2003). This model is fundamentally different from the Weinberger

model (1998). The Gao-Suga model proposes that the small short-lasting cortical BF shift is evoked by the neural net intrinsic to the central auditory system without CS–US association, whereas the Weinberger model proposes that it is evoked by the multisensory thalamic nuclei, only after CS–US association occurs in these nuclei.

Retirement

I retired from "teaching" at the age of 70½ years (June 2004). However, I have three soundproof chambers with many instruments, rooms for my research associates, and a room for my lab technician, in addition to my office. So, my research situation hasn't changed at all. The only change due to my retirement is that I have no teaching duties. What a wonderful situation I am in! I am fortunate to have three research associates and three ongoing projects to explore further: (1) the neural circuit for tone-specific plasticity elicited by fear conditioning and nonspecific plasticity elicited by pseudoconditioning, (2) interaction between different auditory cortical areas, and (3) plasticity of the lemniscal and nonlemniscal auditory systems.

What Is Interesting in the Neurophysiology of the Central Auditory System

In physiology and neurophysiology textbooks, the number of pages devoted to vision has dramatically increased relative to that of hearing over the last 40 ~ 50 years. Professor Vernon B. Mountcastle edited *Medical Physiology* (C.D. Mosby Co., 1968), and he himself wrote Chapter 65 "Central Neural Mechanisms in Hearing" for this book. He once told me, "Nothing is interesting in the neurophysiology of hearing." In the early 1980s, when we had published several papers on combination-sensitive neurons, nonauditory physiologists on different occasions said to me, "It is hard to teach auditory neurophysiology. What are interesting topics in the central auditory system to teach to students?" At that time, I had been teaching an undergraduate course, "Sensory Physiology," and had felt the same way. In book chapters on hearing, the story about cochlear anatomy and physiology had been well written and was interesting enough to excite readers, whereas the story about the central auditory system had been much less interesting, although the tonotopic representation in the auditory system and the neural basis of sound localization had been described.

This is still true, even in recent neuroscience textbooks. They contain an interesting chapter on cochlear anatomy and physiology and, at most, a mediocre chapter on the central auditory system. For hearing, the responses of central auditory neurons to tone bursts have been well studied by changing the values in the frequency, amplitude or time domain, or by changing the values of binaural cues. However, it has apparently been questionable

what topics are really interesting, except for the processing of binaural cues. A few hundred papers on hearing have been published every year, and the authors of these papers, including me, have thought that their papers are interesting and important to further the understanding of auditory mechanisms. However, these papers are apparently not particularly interesting to nonauditory neurophysiologists. This may be the reason why textbook chapters on the central auditory system have been mediocre.

The most fundamental neural mechanism for processing sound is creating neural tuning in the frequency, amplitude, time, and spatial domains and sharpening it by inhibition. Sound is the changes in atmospheric pressure in time, so the story of the fundamental neural mechanism should include the processing of sound in the frequency-time and amplitude-time domains. A book chapter on the central auditory system must describe these basic stories and then must introduce the story of the processing of behaviorally relevant sounds after describing the acoustic properties of these behaviorally relevant sounds.

Epilogue

I began my career in auditory neurophysiology according to Professor Dan's suggestion and learned under Professor Katsuki's guidance. I think that I entered a field that was just right for me. Since 1970, I have had many postdoctoral research associates. All of them, except four, came to my lab without any experience in working on the central auditory system. These research associates learned how to perform auditory neurophysiology within 3 ~ 4 months in my lab and then performed excellent goal-oriented research for 1 to 3 years. The progress of my (our) research has depended on their talent and devotion to the research. My wife, Hiroko Suga, has been a consistent source of support to me since 1963, without which my activity in research might not have been so smooth and enjoyable. I sincerely acknowledge the contributions of all these individuals.

I like mountains, climbing up beyond the timberline to see a vast open space. When I went to The Nature Place in Colorado Springs, I found a small, inspirational plaque in the computer-telephone room that said, "History is not closed. The future remains open and depends on our imagination and bold initiatives."

(My photograph used for this autobiography was taken sometime in the early 1980s when I was most actively engaged in research.)

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