Curr Neurobiol 2018; 9(3): 101-105 *ISSN 0975-9042*

Sir Bernard Katz (1911-2003): An Icon of Neurophysiology

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Abstract

This article highlights the life and career of Sir Bernard Katz, a member of a generation of eminent physiologists who was a refugee from the Third Reich. Despite setbacks incurred by anti-Semitism early in life, Katz had the tenacity to achieve fulfillment in his extraordinary career. With the support of the eminent A.V. Hill, who had a pivotal influence on his life and career, Katz conducted research at University College London mainly in the 1950's and 60's. His work included the study of miniature end-plate potentials, quantal secretion of neurotransmitters, the role of calcium in transmitter release, and the postsynaptic action of acetylcholine. In addition, his department was a center for pre- and postdoctoral students from all over the world and his influence on the training of a large number of the world's most prominent neurophysiologist was monumental. Because Bernard Katz's work remains the basis of our understanding of the release and actions of neurotransmitters, he was awarded the Nobel Prize in 1970.

Keywords: Bernard Katz, Neuromuscular Junction, Quantal release, End-Plate potential.

Early Years

Sir Bernard Katz was one of the generation of distinguished physiologists who was a refugee from the third Reich and who contributed immeasurably to the scientific reputation of his adopted country. Katz was born in Leipzig Germany the only son of a Russian-Jewish fur trader. Because Katz's father considered it an unnecessary procedure, he never bothered to apply for naturalization. Thus, being of Russian heritage, the Katz family was considered enemy aliens during World War I [1] **(Figure 1)**.

Figure 1. *Sir Bernard Katz (taken from Sir Bernard Katz – Biographical. Nobel Lectures, Physiology or Medicine 1963-1970. Elsevier Publishing Company, Amsterdam, 1972.*

After the Russian revolution of 1917, the members of the Katz family- along with other Russian expatriates- lost their nationality and became stateless. Katz began to resent the fact that he was growing up as an alien and not as a German citizen. In addition, he began to consider a possible departure from Germany because of the episodes of ant-Semitism that he encountered even at an early age. At the age of nine, he was denied entrance by the headmaster of a fashionable secondary school because he was considered a foreigner. However, it was the dismissal from office of the prime minister Heinrich Bruning in 1932 that prompted Katz to make the final decision to eventually leave Germany after completing his medical education.

Katz continued his studies at the University of Leipzig where he received his medical degree in 1934. Doing part-time research at Leipzig under Martin Gildermeister, Katz was able to publish several papers in *Pfluger's Archiv* and used these papers to publish his thesis in late 1934. Katz was awarded the Siegfried Garten prize for this work; but because the award could not be given to a non-Aryan student, Katz received the prize money in secret [2].

After receiving his degree in Medicine, Katz worked for a few months as an unpaid intern in a hospital in Leipzig. From about 1930, Katz was attracted to neurophysiology and was fascinated by the fact that one was now able to make accurate measurements of electrical excitability and express them by simple mathematical equations. This experience laid the foundation for the Katz's future area of research.

Prelude to Emigration

Bernard Katz was reared in a Jewish household which was unorthodox and liberal. However, because of his anti-

Semitic experiences and observing that non-Aryans were being subjected to arbitrary dismissals from their positions, he began to perceive a world where people were excluded without cause, and violence and threats replaced rational discourse.

Although as a teenager Katz had become an active Zionist and considered emigrating to Palestine, in 1934 he read an article authored by the renowned British physiologist Archibald Vivian Hill in the prestigious publication *Nature* [3]. At the time, it was still possible to obtain this publication in the university library. In this article, Hill corresponded with the Nazi scientific czar Johannes Stark, a physicist who had become a strong supporter of the Nazi party. Taking issue with the new policy of excluding non-Aryans from positions in Germany, Hill condemned the treatment of his German colleagues. Katz was impressed with Hill's stance and made the decision to continue his development as a scientist in Hill's laboratory [4].

During the early 1930's, the scientists who emigrated still had a fair chance to find safe haven and continue their careers, particularly in Great Britain and the United States. However, Katz's alien status made it more difficult to obtain visa requirements for travel. However, with his degree in hand, Katz departed for England in 1935 with a letter from his research mentor and four pounds in his pocket. At the time, strict visa requirements made foreign travel very difficult and Katz lacked a true passport. But armed with an identification certificate that was issued to stateless persons by the League of Nations, Katz left his homeland with the anticipation of a new life in Great Britain. Katz looked to relatives living in England to aid him in obtaining his British visa and support him upon his arrival.

Years later, Katz reflected upon how much he owed his father for his decision not to seek German citizenship, which proved most valuable to him after the outbreak of World War II in 1939. Being a stateless individual of Russian descent, Katz was not considered an enemy alien by the United Kingdom and was able to become both an Australian citizen and a British subject [5].

Training at University College

Recognized as an extraordinary figure in Neurophysiology/ Pharmacology, Bernard Katz was arguably the most celebrated case of Hill's commitment to helping German colleagues who were being persecuted by the Nazi government during the 1930's. Hill had shared the Nobel Prize with the German chemist Otto Meyerhof in 1922 for discoveries related to the mechanical and biochemical events during muscle contraction. He was also considered a pioneer in the field of exercise physiology [6].

Hill also performed the role of a statesman by aiding the exodus of refugees from Germany during the 1930's. After serving as a representative to the British Parliament for Cambridge University during World War II, he also became a wartime cabinet scientific advisor for Winston Churchill, and remained an informal advisor of the government for many years thereafter.

Hill first met Katz when he was 24 and despite the fact that their first meeting was bilingual, Hill agreed to take him on "as an experiment" [7]. As a member of Hill's biophysics unit (1935-1939), Katz would return the favor by experimentally testing the predictions of Hill's theory of membrane excitation. The theory was based upon fundamental assumptions that an electric current produces excitation if it displaces the membrane potential (in the depolarizing direction) by a critical amount (threshold). These experiments proved of immense value to Katz for his future work since it acquainted him with techniques capable of making reproducible and accurate measurements by simple experiments. In addition, discrepancies in experimental values from theoretical predictions of simple excitation theory provided a clue for Katz in his future work on the mechanisms involved in the generation of an impulse.

Katz cultivated a long-term relationship with A.V. Hill, who was later to become his friend and mentor. Hill's laboratory became his home and Katz considered the time spent in the Hill laboratory as "the most inspiring period of my life" [8]. During the first years of his time at University College, Katz found himself in the company of a number of other eminent physiologists, including Lord Adrian, Joseph Barcroft, and a young Alan Hodgkin, who exposed Katz to a new world of ideas and debate. Katz also spent time at the Marine Biological Laboratory at Plymouth where he investigated the crustacean nerve-muscle preparation [9].

Time in Australia (1939-1945)

In 1939, Katz won a Carnegie Fellowship to work in Sydney Australia with John Carew Eccles. But before he left England with great regret, Katz completed his PhD degree at University College in 1938, and in 1941 he became a naturalized British citizen [10]. Katz's time in Australia was partly spent carrying out neurophysiological studies on the sartorius muscle of the frogs. There, he was greatly helped by a young Stephen Kuffler, who had arrived a year before. Kuffler had begun a study of single cell muscle fiber preparations, which revealed his great talents as an experimenter **(Figure 2).**

Katz published several papers with Eccles and Kuffler, including the nature of the end-plate potential in curarized muscle and the effect of the cholinesterase inhibitor eserine on neuromuscular transmission [11]. In addition, he joined the Royal Australian Air Force (RAF) and served as a Radar Officer until the end of the second world war. His four years with the RAF taught him a great deal about electronics and constructing electronic apparatus. Katz's commitment to his new life was solidified first by his marriage to a non-Jewish woman from New South Wales, and then by an invitation to return to England.

Return to London and Beyond

After the war, Katz received a telegram from Hill inviting him to return to England in 1946 to become Assistant Director of Biophysics Research. In 1950, he was appointed Reader in Physiology and in 1952 he became Head of the Department and

Figure 2. *Stephen Kuffler, Sir John Eccles and Sir Bernard Katz (left-right) in Sydney Australia. (Taken from: In Memory of Sir Henry Dale (Sir Paul Girolami, Lady Helena Taborikova and Giuseppe Nistico, Editors. Academia Romana di Scienze Mediche e Biologiche; Via IV. Novembre 152-00187 Roma.*

Professor of Biophysics [12]. Until his retirement in 1978, Katz headed a department of distinction, which became a center for fellows and postdoctoral students from all over the world.

Shortly before returning to Hill's laboratory, Katz spent time at the Marine Laboratory in Plymouth with Sir Alan Hodgkin and Sir Andrew Huxley, who were then engaged in research that described the electro-chemical signals in squid nerve fibers. During this early period of his return to England, Katz presented the first description of inward rectification and demonstrated with Alan Hodgkin that the overshoot of an action potential was a consequence of an influx of Na^+ [13]. This finding was the initial indication that during the conduction of an electrical impulse along a nerve, permeability to Na^+ and K^+ increases transiently and that the increase in Na^+ permeability causes membrane depolarization.

But Katz never wavered in his allegiance to A.V. Hill. Although Hill's research eventually went in another direction when he became interested in energy exchange and heat production in muscle, Katz showed his deep respect for his mentor by describing him as a "person from whom I have learned more than from anybody else about science and human conduct [14]." Clearly, the time spent with Hill was a transformative experience for Katz.

Chemical Nature of Synaptic Transmission

In England, Katz was now permanently settled in an environment that did not allow scientific progress to be stifled by dogma, intolerance, or politics. The mid 1940's was marked by enhanced interest in the mechanisms regulating the nerve impulses that control brain and peripheral nerve function. Katz, who was destined to unravel these events, was influenced by the single axon approach which he learned from Alan Hodgkin, and the discovery by Dale and his colleagues of chemical neurotransmission at the neuromuscular junction [15].

Katz and his co-workers employed the frog neuromuscular junction which had a peripheral synapse that was readily accessible. This method measured resting and action potentials in whole muscles without the need for microdissection and or removing the muscle from the bath [16]. In addition, by utilizing then novel electrophysiological techniques that included intracellular recording and micro-iontophoresis on single cells, they were able to record postsynaptic events.

Katz, working with Ricardo Miledi, employed the micro-pipette, to establish that acetylcholine is released in quanta, each of which produces a small signal at the muscle fiber. When Katz began to measure the end plate potential, the minute voltage generated at the synapse registered a random reading of approximately half a millivolt in the absence of any nerve stimulation [17]. Initially, Katz thought he was observing only random interference from the apparatus, but when curare (muscle poison) was found to terminate the voltage readings, Katz realized that they must represent true activity at the nerve ending. He then found that the size of the voltage potential was always a multiple of this minimum value when the nerves were not firing; they were called mini-end plate potentials (MEPPs) [18]. A rise in the frequency of electrical impulses was mirrored by a step-wise rise in the release of acetylcholine packets. This work provided the first perception of neural function at the molecular level.

The concept elaborated by Katz was based upon the fact that the resting signal between nerve and muscle did not depend upon individual molecules of acetylcholine but rather on the random release of small packets or *quanta* of the neurochemical transmitter, with each packet composed of several thousand molecules of acetylcholine [19]. When the stimulating impulse arrived at the nerve ending, the rate of quanta released greatly increased. Katz's discovery of the "quantum" character of nerve function and synaptic transmission would transform perception of the nature of the signaling process across synapses. This theory was corroborated by electron microscopic analysis, revealing the presence of packets of granules at nerve endings thought to contain acetylcholine.

Together with Paul Fatt, Katz also found that the post synaptic receptors, when stimulated by acetylcholine, open pores in the muscle end plate which caused the muscle to depolarize and contract. However, the change in the membrane potential alone was not sufficient to enhance the quantum event, but the presence of calcium in the external medium was also required to make the depolarization effective. The receptor proteins, which were to be called "ion channels", formed the basis of nerve activity at the neuromuscular junction.

Then using the end plate potential (EPP) to monitor acetylcholine release from the motor nerve endings, Juan del Castilllo and Katz concluded that the EPP consisted of multiple quanta of acetylcholine and that calcium regulated the probability of a given quantum being released [20].

The work of Bernard Katz and his associates was far-reaching. Their studies became a hallmark for future investigations on synaptic mechanisms and were widely referenced in textbooks of neurophysiology. Their studies not only described the steps involved in acetylcholine-induced transmission at the neuromuscular junction, but they contributed in a major way to our understanding of drug-receptor interactions at other non-excitable membranes.

The mechanisms underlying transmission of a signal from nerve to muscle produced by acetylcholine-induced depolarizations of the end plate were also found to be fundamentally different from impulse transmission in nerve, which was chronicled in a series of papers published by Hodgkin and Huxley [21]. In addition, many of the basic features of synaptic transmission which Katz and his associates elucidated at the neuromuscular junction were subsequently found to exist at many other peripheral synapses, as well as in the brain. Their findings also serve as a basis of our understanding of mechanisms involved in neurotransmitter release at other synaptic sites.

In discussing the possible role of calcium in neurotransmitter release in a paper published in 1970, Katz and Miledi [22] note that "the exact place of calcium action in the process of transmitter release remains unknown" but…. "may be due to a residual change in the ionized calcium concentration at some important site of the membrane." The ubiquitous role of calcium on secretory mechanisms through its effects on exocytosis has remained a controversial question for future experimentalists.

Katz's final major achievement published in the 1970's, provided insight into the behavior of a single ion channel. Together with Ricardo Miledi, he measured macroscopic conductance fluctuations after the addition of acetylcholine, which provided estimates for single channel conductance and channel open times [23]. Bert Sakmann and Erwin Neher followed up this study by recording from one single channel, and described changes in conductance when single channels are open or closed. For this work, Sakmann and Neher were subsequently awarded the Nobel Prize [24].

Personal Qualities and Accomplishments

Although an intense and private individual, and possessing a serious nature, Katz was nevertheless endowed with enormous enthusiasm and always willing to offer advice. Katz spoke little English when he arrived in the Great Britain. However, he quickly learned the language, became able to correct the style of many native speakers of English, and communicate with astonishing clarity. Although the seriousness and determination he employed in his work would make him appear at times withdrawn, Katz remained a colleague with enormous enthusiasm, always willing to discuss with even students or junior faculty the details of their work and offer advice.

In recognition of his prodigious accomplishments, Sir Bernard Katz became a Nobelist in 1970 along with Julius Axelrod and Ulf_von Euler, who investigated the role and storage of noradrenaline as a neurotransmitter at adrenergic nerve endings [25]. Together, their collective work established the ultimate acceptance without equivocation of the concept of neurochemical neurotransmitter release and completely abrogated the concept of electrical transmission. In addition, establishing acetylcholine and norepinephrine as neurotransmitters greatly enriched our understanding of neurochemical processes and provided insights into the causes and treatments of such diseases as Parkinsonism, depression, anxiety, hypertension, and Alzheimer's Disease. Katz's discoveries also had a significant effect on the study of organophosphates and organochlorines, which formed the basis for post-war studies on nerve gases and pesticides.

Bernard Katz was honored with a plethora of other awards [26]. He was elected a Fellow of the Royal Society in 1952, served as Vice-President of the Society twice, and was knighted in 1969. He was also elected to the Royal College of Physicians in 1968. He was also a Foreign Member of the American Academy of Sciences, Fellow of University College, London (1961), and recipient of the Feldberg Foundation award, and the Ralph Gerard Prize from the Society of Neuroscience. He also received the coveted Copley Medal in 1967. After his retirement in 1978 at the age of 67, he remained active in the Research Council. He was also the author of the monographs: *Electric Excitation of Nerve (1939) and Nerve Muscle and Synapse (1969), w*hich contain details of his research [27].

Katz trained five PhD students, Paul Fatt, Donald Jenkinson, Liam Burke, John Nichols and Robert Martin, all of whom had successful careers, and his department became a center for postdoctoral fellows [28]. Bert Sackmann, a future Nobelist, worked in Katz's laboratory for three years, where he determined the conductance and gating properties of nerves by recording from single ion channels.

Despite experiences with anti-Semitism in his youth, after World War II, Katz visited Germany on a regular basis, where he did much to inspire young researchers. The gracious and forgiving attitude that he expressed for his native country who once rejected him, was rewarded by an honorary medical degree from the faculty at the University of Leipzig and a street in Leipzig being named after him. In his memory, a bronze plate was placed in the garden of the University Hospital [29].

Bernard Katz was an extraordinary figure in neurophysiology/pharmacology. Most significantly, he had the uncanny ability to identify the most significant aspect of a problem and leave it to his colleagues to ponder its peripheral aspects. This unique trait enabled Katz to bring into focus for future experimentalists the basic nature of signal processing in the nervous system. There is no doubt that the paradigmatic experiments of Bernard Katz earned him a place in the pantheon of scientific luminaries for his monumental contributions to biomedical science.

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