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NOBEL PRIZE WINNERS ARVID CARLSSON, PAUL GREENGARD AND ERIC KANDEL: THE RESEARCH OF SIGNAL TRANSDUCTION IN THE NERVOUS SYSTEM

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For many decades, scientists have tried to unravel the mysteries of the nervous system – the complex phenomenon that receives messages, processes information, and sends signals to different organs. The most important scientific discoveries of the 19th and the 20th centuries paved the way for the 2000 Nobel Prize in Physiology or Medicine awarded to Arvid Carlsson, Paul Greengard and Eric Kandel " for their discoveries concerning signal transduction in the nervous system". So, the beginning of the new millennium was "marked" by pioneering research into the chemical transmission of signals in the central nervous system, which created the foundation for a deeper understanding of the mediatory role of dopamine, the processes of slow synaptic transmission, short-term and long-term memory, and the mechanisms of action of antipsychotic and antidepressant drugs. The paper aims to outline the main stages of scientific activities of a Swedish neuropharmacologist Per Arvid Emil Carlsson and the American neurobiologists Paul Greengard and Eric Richard Kandel.

K e y w o r d s: Arvid Carlsson, Paul Greengard, Eric Kandel, nervous system, brain, dopamine, slow synaptic transmission, learning, memory, the 2000 Nobel Prize in Physiology or Medicine.

"He who owns the information, owns the world" is the legendary saying ascribed to an English-German businessman and banker Nathan Mayer Rothschild. And this is true, since information has always played an extremely important role in human life and human society [1]. Since ancient times, information about the world has helped human beings to survive, to develop themselves and their living conditions, and to move on to the next more elaborated, more complex stage. Information has become one of the most important strategic resources, because it provides the basis for the effective functioning and development of various spheres of life.

The information component permeates the entire universe accessible to us (Macrocosm, according to the ancient Greek philosophers). The human body, as a Microcosm, also has a system responsible for processing and exchanging information in it. We are talking about the nervous system that receives messages, processes information, and sends signals to the rest of the body telling them what to do. For many decades, scientists have tried to unravel the mysteries of this complex phenomenon. Arvid Carlsson, Paul Greengard, and Eric Kandel were among them. For "their discoveries concerning signal transduction in the nervous system" [2], they were awarded the 2000 Nobel Prize in Physiology or Medicine.

The study of synaptic connections started long before this award was received. In the 19th century,

an Italian biologist and pathologist C. Golgi [3], the inventor of a staining technique called black reaction (Golgi's method) supported the idea that the nerve cells are interconnected by reticular or protoplasmic connections into a single network. Around the same time, his scientific opponent S. Ramón y Cajal [4], a Spanish neuroscientist, pathologist, and histologist, who is called a pioneer of modern neuroscience, used the Golgi's method to demonstrate the discreteness of neurons that interacted with each other through specialized contacts. Ironically, they became the co-recipients of the 1906 Nobel Prize in Physiology or Medicine awarded "in recognition of their work on the structure of the nervous system" [5].

Twenty-six years after C. Golgi and S. Ramón y Cajal had laid the foundation for the modern conception of the structure of the nervous system, the Nobel Prize in Physiology or Medicine was awarded to the English researchers, a neurophysiologist C. S. Sherrington [6] and an electrophysiologist E. D. Adrian [7] "for their discoveries regarding the functions of neurons" [8]. It was C. S. Sherrington who coined the notion "synapse" to define the connection between two neurons.

At the end of the 19th – beginning of the 20th century, there was a lot of controversy regarding synaptic transmission: whether it was electric or chemical. In 1914, an English pharmacologist and physiologist H. H. Dale [9] and his colleagues first identified acetylcholine as a possible neurotransmitter. A German-American pharmacologist and psychobiologist O. Loewi [10] discovered the role of acetylcholine [11] as an endogenous neurotransmitter.

By the middle of the 1930s, the chemical transmission of nerve impulses had already got so many confirmations that O. Loewi jointly with an English pharmacologist and physiologist H. H. Dale [9] received the 1936 Nobel Prize in Physiology or Medicine "for their discoveries relating to chemical transmission of nerve impulses" [12].

One more great hero of neuroscience was an Australian neurophysiologist and philosopher J. C. Eccles [13]. For a long time, he believed that synaptic transmission was primarily electrical rather than chemical. However, after performing series of experiments, he changed his mind. Together with B. Katz, he worked on the experiments which elucidated the role of acetylcholine as a transmitter in the brain. As a philosopher, he was deeply interested in the enigma of brain-mind interaction. In 1963, the Nobel Prize in Physiology or Medicine was awarded jointly to J. C. Eccles and the English physiologists and biophysicists A. L. Hodgkin and A. F. Huxley for "their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane" [14]. All these scientific discoveries paved the way for the 2000 Nobel Prize in Physiology or Medicine awarded to A. Carlsson, P. Greengard, and E. Kandel.

Arvid Carlsson [15]

A prominent Swedish neuropharmacologist **Per Arvid Emil Carlsson**, who is best known for his research on dopamine and its effects in Parkinson's disease, was born on January 25, 1923, in Uppsala, Sweden, in academic, middle-class family. Both his parents prioritized the humanitarian sphere: his father was a historian and his mother, passing the Master of Arts examination, devoted herself to her four children – three sons and a daughter. When Arvid was three years old, his family moved to Lund where his father became a Professor of History at the University of Lund.

Arvid's young years were happy. He wrote: "*I grew up in a stable environment with loving and supportive parents*" [16]. Unlike his elder sister and brother who chose a scope of humanities, young Arvid decided to choose a medical path and began his education in Lund in 1941.

World War II left a mark on Carlsson's life: one of the saddest contacts occurred in 1944 during his first year of clinical trial. Arvid had a task of examining the prisoners escaped from the German concentration camps. As he put it: "*Many were children who suffered from malnutrition. Tuberculosis was not uncommon. However, most shocking was their mental status. They behaved like wild animals, obvi-*

ously suffering from severe anguish and suspicion and they trusted nobody" [16]. This year, Arvid decided to become a researcher and started working on pentylenetetrazol and nikethamide, eventually shifting to the area of calcium metabolism. This work resulted in M.D. thesis.

In 1951, Arvid Carlsson received a medical degree from the University of Lund. He had held teaching positions there until 1959, when he became a professor of pharmacology at the University of Göteborg [17].

In 1955, Carlsson was invited to work at the Laboratory of Chemical Pharmacology headed by Bernard Brodie at the National Heart Institute, USA. There, he was focused on the action of reserpine on the storage of serotonin in blood platelets in vitro. As Carlsson mentioned, Brodie played the most important role in his scientific carrier [16], though their scientific paths and views diverged later.

After returning to Sweden, Arvid Carlsson and his colleagues made a discovery that reserpine caused a depletion of the adrenal medullary hormones and similar depletion took place in other tissues including brain [18]. Further research showed that the behavioral action of L-3,4-dihydroxyphenylalanine (dopa) "was closely correlated to the accumulation of dopamine in the brain and that dopamine is a normal brain constituent and is released by reserpine, as are noradrenaline and serotonin" [16]. Unfortunately, these ideas were met with resistance during 1960 Ciba Symposium on adrenergic mechanisms, held in London, because brain research was dominated by electrophysiology at that time. However, during 1965 International Symposium in Stockholm it became clear that the situation had changed dramatically: there was no doubt on the role of biogenic amines as neurotransmitters. This paradigm shift gave space to the investigation of the fundamental role of dopamine in the reward system that had significant medical implications. Arvid Carlsson and colleagues started working on the concept of dopaminergic autoreceptors (the notion coined by Carlsson) and their role as targets for drugs, which led to the new horizons of research in psychopharmacology.

Arvid Carlsson elaborated a method for measuring the amount of dopamine in brain tissues. His laboratory showed that the distribution of dopamine in animal brain was the highest in the striatum, which led to the idea that dopamine was important for motor function. Carlsson's experiments demonstrated that L-dopa (the precursor of dopamine) could alleviate the immobility induced by reserpine in animals [19].

His significant findings gave impetus to the idea of using L-dopa, which the body converted to dopamine, as a treatment for Parkinson's disease [20], and it eventually became the single most important medication for the disease [17].

Arvid Carlsson suggested that dopaminergic hyperfunction caused by amphetamines or dopa, might lead to a dysfunction mimicking paranoid schizophrenia. This idea supported the role of dopamine in mental function. However, he noted that "*while a primary disturbance in dopamine function in schizophrenia cannot be ruled out, the intimate relationship between dopaminergic and other neuronal systems must be emphasized. The possible involvement of other amine, aminoacid or peptide transmitters in schizophrenia cannot be disregarded*" [21].

In 1959, Arvid Carlsson moved to Göteburg, where he was an appointed Professor at Sahlgrenska Academy. There, he continued to conduct research until his death [22]. From 1960, Carlsson had been engaged in many projects jointly with different drug companies that had a significant impact on his research including more financial resources. In collaboration with his colleagues from Astra group, he developed zimelidine – the first selective 5-HT uptake inhibitor [16]. Zimelidine turned out to be an active antidepressant agent, though with quite rare, but serious side effects [23]. Therefore, it was withdrawn from the market. However, it stated the development of the several other selective serotonin reuptake inhibitors (SSRIs), among which Prozac is especially well-known as an effective medical treatment for depression and anxiety disorders [24].

Arvid Carlsson's pioneering research culminated in many awards, including the 2000 Nobel Prize in Physiology or Medicine (jointly with Paul Greengard and Eric Kandel). In his Nobel Lecture, he stressed: "*it might be recognized that the brain is not a chemical factory but an extremely complicated survival machine. In order to bring all the forthcoming biochemical observations into a meaningful framework it will prove necessary to emphasize more strongly aspects of neurocircuits and connectivity and to do so both at the microscopic and macroscopic level*" [23].

Arvid Carlsson acknowledged that he credited his wife Ulla-Lisa for his successful career. They

married in 1945 and had five children, twelve grandchildren and seven great grandchildren. Arvid Carlsson died on June 29, 2018, at the age of 95.

In addition to the Nobel Prize, Arvid Carlsson won many other awards including the Wolf Prize in Medicine, which is awarded annually by the Wolf Foundation in Israel (1979) [25]; the Japan Prize awarded to people from all parts of the world whose "original and outstanding achievements in science and technology are recognized as having advanced the frontiers of knowledge and served the cause of peace and prosperity for mankind" (1994) [26]; Antonio Feltrinelli International Award (1999) [27]. In 1975, Arvid Carlsson was elected as a member of the Royal Swedish Academy of Sciences.

Since 2017, Sahlgrenska Science Park awards the Arvid Carlsson Award: "The aim is to pay tribute to innovation, knowledge and competence in conjunction with good entrepreneurship through an award in Nobel Prize winner Arvid Carlsson's name" [28].

Paul Greengard [29]

A famous American neuroscientist **Paul Greengard**, best known for his work on the molecular and cellular functions of neurons, was born on December 11, 1925, in New York City in the family of Benjamin Greengard and his wife Pearl (née Meister). His ancestors, German Jews, emigrated from Königsberg to the Mid-Western United States. Paul's father had had success in vaudeville, later he became a businessman. Paul's mother died giving birth to him. When he was 13 months old, his father married again to a woman who was Episcopalian. Thereby, despite his Jewish roots, Paul was brought up in Christian tradition [29].

Paul attended public schools in Brooklyn and Queens. During World War II, he spent three years in the Navy as an electronics technician developing an early-warning system to intercept Japanese Kamikaze planes. In 1948, he graduated from Hamilton College, New York, with Major in Mathematics and Physics. Though Paul needed the financial assistance to continue his education, he turned down a graduate school scholarship funded by the Atomic Energy Administration, because "*this was only three years after dropping the atomic bombs on Japan, and I didn't want to contribute to research the fruits of which might contribute to creating more powerful weapons of mass destruction*" [29].

Unwilling to be involved in weapons-based research, Paul chose the emerging field of medical physics [30]. Settled on biophysics at The John Hopkins University, he did his first laboratory research under the supervision of H.K. Hartline, a co-recipient of the 1967 Nobel Prize in Physiology or Medicine. The lecture of the other Nobel Prize winner A.L. Hodgkin inspired Paul to consider combining biophysical and biochemical techniques to reveal the molecular and cellular basis of nerve cells' function.

In 1953, Paul received his Ph.D. in Biophysics from The John Hopkins University [31] and went to Europe for postdoctoral studies. He spent several years in the United Kingdom and the Netherlands. Paul seriously considered staying in England, but the low level of financial support for the scientists, bewildering choice of schools for his sons, and the lack of central heating forced him to return to the United States in 1959 [32]. In the United States, Paul became a Director of the Department of Biochemistry at the Geigy Research Laboratories. His initial idea was to apply scientific principles to the development of new drugs for the treatment of neurological and psychiatric disorders. However, his dreams were not meant to come true: "*at that time, Geigy, like most, if not all, other pharmaceutical companies, was very conservative with regard to the nature of the research programs which they found acceptable. It was extremely difficult to obtain authorization to embark on innovative research approaches*" [29]. And he left the Geigy Research Laboratories in 1967.

After working at the Albert Einstein College of Medicine and the Vanderbilt University School of Medicine for a very short time, he took a position as a Professor at the Department of Pharmacology at Yale University, where he started his work on signal transduction in the nervous system. Greengard emphasized that the work which formed the founda-

tion for the Nobel Prize was all carried out at Yale [33]. In 1983, Paul Greengard joined The Rockefeller University faculty and was Vincent Astor Professor and Director of the Fisher Center for Alzheimer's Disease Research [34].

In the 1950s, when Greengard started his career, the prevailing opinion was that nerve transmission was purely electrical and nerve cells communicated through transmitters that triggered electrical impulses in their neighbors. As opposed to the mainstream paradigm, Greengard decided to go deeper into biochemistry underlying neuronal communication. His work revealed the alternative signaling method known as slow synaptic transmission. For a long time, his work was ignored. He noted that coming into conflict with the dominant paradigm, he thought that the results of his experiments would not be accepted in his lifetime [35]. However, eventually his hypothesis proved correct, "he showed that phosphorylation cascades triggered by second messengers play a fundamental role in mediating effects of neurotransmitters and neuronal activity on neuronal function. He then identified brain proteins whose phosphorylation was controlled by these second messengers and characterized their function. Not surprisingly, some of these proteins turned out to act as central nodes in neuronal physiology, and their study advanced not only neuroscience but also cell biology and medicine… Electrical mechanisms of fast signal propagation in the brain and slower biochemical mechanisms function together and synergistically. Biochemical machinery mediates learning and helps encode memories" [36]. Paul Greengard was a pioneer in the field called signal transduction. In 2000 for his discoveries within this field, he was awarded the Nobel Prize in Physiology or Medicine (jointly with Arvid Carlsson and Eric Kandel).

Trying to understand how aberrations in specific pathways might lead to brain disorders, Paul Greengard investigated the molecular basis of the drugs aimed at those conditions. Being the Head of the Fisher Center for Alzheimer's Disease Research, he and his group worked on drug targets for degenerative brain diseases, schizophrenia, and depression [32, 34]. Paul Greengard was the founder of Intra-Cellular Therapies – a biopharmaceutical company whose mission is "to deliver innovative treatments to improve the lives of individuals with neuropsychiatric, neurologic, and other disorders to reduce the burden on patients and their caregivers" [37].

Being an active scientist up until the end, Paul Greengard into his 10th decade worked on research that could lay foundation for a new class of antidepressants [38]. Getting great joy out of his work, Paul Greengard was always surrounded by brilliant young colleagues whom he supported: "He had a unique ability to connect to people, and he was genuinely interested in knowing them" [34].

Being an advocate of gender equality and thinking that women are underrepresented and underrewarded in science, Paul Greengard and his wife, a distinguished sculptor Ursula von Rydingsvard, established The Pearl Meister Greengard Prize – an award for outstanding women-scientists given annually by the Rockefeller University [39]. Paul Greengard named the award after his mother, Pearl Meister Greengard, who died giving birth to him, and donated the full share of his 2000 Nobel Prize to the fund. "*I don't have a single photograph of my mother*", Paul said, "*since there's not a shred of physical evidence that my mother ever existed, I wanted to do something to make her less abstract*" [40].

Paul Greengard who dedicated his whole life to science died on April 13, 2019. He was married three times and divorced twice. He had three children and six grandchildren.

Paul Greengard's activities have been marked by a number of awards and recognitions, including NAS Award in the Neurosciences from the National Academy of Sciences (1991); Karl Spenser Lashley Award (1993); Golden Plate Award of the American Academy of Achievement (2002); Honoris Causa Degree in Medicine of University of Brescia (2007). He was an Elected member of the National Academy of Sciences (1978), the American Academy of Arts and Sciences (1978), the American Philosophical Society (1994).

They say that people who do what they love are happy people. Through this lens, Paul Greengard was a happy person. He stated, "*It's much more fun understanding the brain than doing a crossword puzzle. It's the same kind of cognitive challenge, but it's much more fun and you feel you're doing something worthwhile*" [41].

A prominent American neurobiologist **Eric Richard Kandel** was born on November 7, 1929, in Vienna, Austria, in the family of Hermann Kandel and Charlotte Zimels, who moved to Vienna from Olesko, Galicia, and Kolomyya, Pokuttya (then parts of Austria-Hungary, now modern Ukraine). Eric's fa-

Eric Kandel [42]

ther established a toy store where he worked with his wife. Eric and his elder brother Lewis attended the elementary school not far from their house. Despite admiring Vienna as one of the great cultural centers, Eric, who was brought up in a Jewish family, felt the tension that prevailed in society: "*anti-Semitism was a chronic feature of Viennese life. Jews, who made up nearly 20% of the city's population, were discriminated against in the Civil Service and in many aspects of social life. Nonetheless, they were fascinated by the city in which they had lived for over a thousand years. My parents genuinely loved Vienna, and in later years I learned from them why the city exerted a powerful hold on them and other Jews*" [43]. As he realized later, the oppressive conditions in Vienna affected his early youth [43]. Kristallnacht and its consequences were etched on his memory forever. Most likely, this painful experience to some extent determined Eric' interest in mind, memory, motivation, and behavior.

In 1939, after the Anschluß Österreichs, Eric's family left Austria and emigrated to New York, the United States, where Eric's uncle Berman Zimels established himself as an accountant. Settling in Brooklyn, Eric Kandel was tutored by his grandfather Hersch Zimels in Hebrew, so young boy was accepted at the Yeshiva of Flatbush – a Hebrew school that combined Judaic studies and the liberal arts. Eric graduated from the yeshiva in 1944 and attended Erasmus Hall High School – a local public school in Brooklyn. Later Kandel wrote he had felt sheer joy at the school where he became interested in history, writing, and girls [43]. After applying to Harvard College, he was admitted and got a scholarship.

Eric Kandel's Major was History and Literature. In his dissertation "The Attitude Toward National Socialism of Three German Writers: Carl Zuckmayer, Hans Carossa, and Ernst Junger", Eric explored the different positions on the political spectrum of fascism – the topic related to his existential experience.

A friendship with Anna Kris, a daughter of psychoanalysts Ernst and Marianne Kris, who also emigrated from Vienna, changed the scope of Eric's interests – his attention turned to memory and learning. Influenced by Anna's parents, Eric "*was converted to their view that psychoanalysis offered a fascinating new approach, perhaps the only approach, to understanding the mind, including the irrational nature of motivation and unconscious and conscious memory. With time this began to seem much more exciting and interesting to me than European literature and intellectual history*" [43]. And to become a practical psychoanalyst, Eric decided to go to a medical school.

In 1952, Eric Kandel entered the New York University Medical School. Here he became interested in the biological basis of medical practice and started learning the biology of mind. Therefore, he took an elective period at Columbia University joining H. Grundfest's laboratory. During this time, he met his future wife Denise Bystryn, a Jewish young woman whose family emigrated to the United States after World War II [44]. Denise was a graduate student at Columbia University and later she became a Professor of Sociomedical Sciences and Psychiatry at Columbia University and a Head of the Department of Epidemiology of Substance Abuse at the New York State Psychiatric Institute [45]. They married in 1956.

Eric Kandel started his work on the electrophysiology of the cerebral cortex and very soon he was impressed by a Viennese trained physician turned physiologist S. Kuffler who became one of Kandel's "neurobiological heroes" [43]. S. Kuffler used a much more experimentally accessible system: neurons isolated from marine invertebrates.

In 1956, Eric Kandel graduated from the Medical School and started an internship at Montefiore Hospital. In 1957, he joined the Laboratory of Neurophysiology at the US National Institutes of Health. Here Kandel began his "triumphal procession" within the field of the biology of memory gradually reappraising his scientific strategy. In 1960, Eric Kandel started his psychiatric residency at the Massachusetts Mental Health Center of the Harvard Medical School. During his residency, Eric Kandel decided to select a simple animal model that would

facilitate electrophysiological analysis of the synaptic changes involved in learning and memory storage and then to apply these results to humans, he "*began to think about simple forms of learning in preparation for work on Aplysia*" [43].

Based on this idea, Kandel applied for an NINCDS postdoctoral fellowship; he and his wife and son Paul who was born a year before left for Paris, France, in 1962. He worked in the Laboratoire de Neurobiologie Cellulaire et Moléculaire of the French National Center for Scientific Research. A French neuroscientist L. Tauc, the founder and director of the laboratory, became Kandel's teacher. Kandel started to investigate the gill-withdrawal reflex and postsynaptic potentials in identified neurons in the abdominal ganglion of Aplysia [46].

Eric Kandel returned to Harvard in 1963. Soon he accepted an invitation to start a neurophysiology group focused on the neurobiology of behavior in the Department of Physiology and Psychiatry at the New York University Medical School. He arrived there in 1965. This year was significant for him in another way too – his daughter Minouche was born.

Together with I. Kupfermann and H. Pinsker, Kandel developed protocols for demonstrating simple forms of learning by intact Aplysia. The researchers found that the gill-withdrawal reflex could be modified by two forms of learning: habituation and sensitization. In 1971 in collaboration with T. Carew, they shifted from studies of restrained to unrestrained animals that led to the study of long-term memory. Later, researchers extended the Aplysia system into the study of classical conditioning. This finding helped to bridge the gap between the simple and more complex forms of learning. The study of the neuronal circuits of sensory neurons, interneurons and motor neurons contributed to analysis of the specific synaptic connections modified by learning in the intact animals.

In 1974, Eric Kandel moved from New York University to the Columbia University College of Physicians and Surgeons. He became a Founding Director of the Center for Neurobiology and Behavior. Using a quantal analysis, Kandel and his colleagues found that the synaptic facilitation characteristic of sensitization was presynaptic and that inhibitors of serotonin blocked this presynaptic facilitation. In collaboration with P. Greengard, it was demonstrated that cAMP-dependent protein kinase acted in this biochemical pathway in response to elevate levels of cAMP. In collaboration with S. Siegelbaum, they defined some of the targets of PKA and focused on a novel K^+ channel. S. Siegelbaum identified the channel that could be regulated by PKA. In 1984, Eric Kandel became an investigator at the Howard Hughes Medical Institute.

The laboratory headed by Eric Kandel experimented with transgenic mice to investigate the molecular basis of memory storage in the vertebrate hippocampus [47-49]. Kandel's idea that learning mechanisms would be conserved between all animals has been confirmed.

As Eric Kandel put it, milestones of his science path are "*from psychoanalysis to Aplysia to the role of attention in the cognitive representation of extrapersonal space*" [43]. Summarizing his work, he said: "*We combine behavioral, cellular, and molecular biological approaches to delineate the changes that underlie simple forms of learning and memory in invertebrates and vertebrates. In invertebrates the focus of our research is on the gill-withdrawal reflex of Aplysia. We study three elementary forms of learning: habituation, sensitization, and classical conditioning. Recently we have reconstituted critical components of this learning in dissociated cell culture, and we now use the reconstituted system to examine the molecular mechanisms which contribute to short- and long-term memory. In vertebrates we use genetically modified mice to examine the mechanisms of long-term potentiation in the mammalian hippocampus and its relation to spacial memory and maintenance*" [50].

Eric Kandel's breakthrough research in neuroscience earned him the Nobel Prize in Physiology or Medicine in 2000 (jointly with Arvid Carlsson and Paul Greengard).

In his Nobel Lecture, Eric Kandel stated: "*For the biology of the mind has now captured the imagination of the scientific community of the 21st century, much as the biology of the gene fascinated the scientific community of the 20th century. As the biological study of the mind comes to assume the central position within biology and medicine that it deserves, we have every reason to expect that a succession of brain scientists will be called to Stockholm and honored for their own leaps of faith*" [51].

Eric Kandel emphasizes the predominant role of biology and neurology in mental health and human behavior. He argues that it is biology and neurology that should be the basis of psychiatry. Kandel's approach to psychiatry is derived from the modern biological views on the "brain – con-

sciousness" relationship. Kandel highlights that "the biological framework… is not only important conceptually; it is also important practically" [52]. He stresses that future psychiatrists need a much deeper understanding of the structure and functioning of the brain, as well as of the biological components of behavior.

The prominent scientist was honored with a number of awards: Fellow of the American Academy of Arts and Sciences (1976); Karl Spencer Lashley Award (1981); Albert Lasker Award for Basic Medical Research (1983); Member of the American Philosophical Society (1984); Gairdner Foundation International Award (1987); NAS Award for Scientific Reviewing of the National Academy of Sciences (1988); National Medal of Science (1988); Pasarow Award (1988); Harvey Prize (1993); Ralph W. Gerard Prize in Neuroscience (1997); Charles A Dana Award for Pioneering Achievement in Health (1997); Wolf Prize in Medicine (1999); Benjamin Franklin Medal for Distinguished Achievement in the Sciences of the American Philosophical Society (2006); Viktor Frankl Award of the City of Vienna (2008); Honorary citizen of the City of Vienna (2009); Honorary Doctor at the Norwegian University of Science and Technology (2011); Foreign Member of the Royal Society (2013); Elected Honorary Fellow of the Royal Society of Edinburgh (2018) [53-58].

Eric Kandel was always ready to face new scientific challenges. He retired in 2022 at the age of 92 [59]. His wife Denise Kandel has also been retired since 2022. Now they have enough time to spend it together and enjoy the beauty of the world.

Describing Denise as his partner, best friend and most honest critic, Eric Kandel said: "*Being married to her has been the greatest privilege of my life*" [45].

Eric Kandel is the author of many books including "In Search of Memory: The Emergence of a New Science of Mind" [60]; "The Age of Insight: The Quest to Understand the Unconscious in Art, Mind, and Brain, from Vienna 1900 to the Present" [61], "The Disordered Mind: What Unusual Brains Tell Us About Ourselves" [62].

So, the beginning of the new millennium was "marked" by pioneering research into the chemical transmission of signals in the central nervous system, which created the foundation for a deeper understanding of the mediatory role of dopamine, the processes of slow synaptic transmission, short-term and long-term memory, and the mechanisms of action of antipsychotic and antidepressant drugs.

The great discoveries made by Arvid Carlsson, Paul Greengard, and Eric Kandel paved the way for the deeper and more comprehensive study of a human being, which is especially important in the times of changes, uncertainty and contradictions [63, 64]. Hopefully in the future, scientists will finally be able to solve the "body – mind" problem and interpret a person as an integral holistic phenomenon [65].

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ЛАУРЕАТИ НОБЕЛІВСЬКОЇ ПРЕМІЇ АРВІД КАРЛССОН, ПОЛ ГРІНГАРД І ЕРІК КЕНДЕЛ: ДОСЛІДЖЕННЯ ПЕРЕДАЧІ СИГНАЛІВ У НЕРВОВІЙ СИСТЕМІ

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Багато десятиліть вчені намагаються розгадати таємниці складного феномену нервової системи, яка отримує повідомлення, обробляє інформацію та надсилає сигнали до різних органів. Найважливіші наукові відкриття 19-го та 20-го століть проклали шлях до Нобелівської премії з фізіології або медицини 2000 року, присудженої Арвіду Карлссону, Полу Грінгарду та Еріку Кенделу «за відкриття щодо передачі сигналів у нервовій системі». Отже, початок нового тисячоліття був "ознаменований" піонерськими дослідженнями хімічної передачі сигналів у центральній нервовій системі, що створили фундамент для глибшого розуміння медіаторної ролі дофаміну, процесів повільної синаптичної передачі, короткочасної та тривалої пам'яті, механізмів дії антипсихотичних та антидепресантних лікарських засобів. У статті представлено короткий огляд основних етапів

наукової діяльності шведського нейрофармаколога Пера Арвіда Еміля Карлссона та американських нейробіологів Пола Грінгарда та Еріка Річарда Кендела.

Ключові слова: Арвід Карлссон, Пол Грінгард, Ерік Кендел, нервова система, мозок, дофамін, повільна синаптична передача, навчання, пам'ять, Нобелівська премія 2000 року з фізіології або медицини.

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