What do neurologists owe to the Nobel laureates?

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ABSTRACT

Introduction. This study aims to establish what aspects of neurologists' daily practice have changed due to discoveries made by winners of the Nobel Prize in Physiology or Medicine.

Methods. A review was conducted of the Nobel laureates who made discoveries regarding the central and peripheral nervous systems, from the creation of the Prize to today. For each decade, the discovery of greatest importance to neuroscience was selected.

Results. The review identified 17 Nobel Prizes for discoveries with a great impact on neuroscience, with the Prize nearly always being awarded to more than one scientist. For each Prize, the discovery and its clinical impact are briefly described.

Conclusions. Most of the discoveries are related to the transmission of information in the nervous system, build upon on the discoveries of previous Nobel laureates, and have changed the daily practice of clinical neurologists today.

KEYWORDS

History of neurology, history of neuroscience, neuroscience, Nobel Prize, synaptic transmission

Introduction

Alfred Nobel created awards in five disciplines, which are awarded annually for the discoveries that "have conferred the greatest benefit to Mankind"[1]; over the 120-year history of the Prizes, they have been awarded 609 times to 975 individuals and organisations. Within the discipline "physiology or medicine," a significant number of Prizes have been awarded for advances in neuroscience. In addition to his altruism, Alfred Nobel had sufficient health problems to believe in the need for medicine to progress. Among other neurological conditions, he suffered with headache and depressive episodes, and a stroke that left him with motor sequelae.

Methods

A review was conducted of all Nobel Prizes in Physiology or Medicine, and those with the greatest impact on clinical neurology were selected. Information was gathered from public resources published by the Nobel Foundation,[2] review articles on Nobel Prizes in neurosciences,[3-5] and a search of the PubMed and Google Scholar databases, using the names of the winners and the prize for each year. Only one Prize was selected per decade, except when two discoveries were deemed so important that both had to be mentioned. For each Nobel laureate, the references section includes several key texts on the discovery for which they were awarded the Prize.

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Table 1. Year, researchers, and neuroscientific discoveries awarded the Nobel Prize.

Year	Prize winners	Discovery
1906	C. Golgi, S. Ramón y Cajal	Microstructure of the nervous system
1914	R. Bárány	Vestibular apparatus
1929	C. Eijkman, F.G. Hopkins	Antineuritic vitamins
1932	C.S. Sherrington, E.D. Adrian	Functions of neurons
1936	H.H. Dale, O. Loewi	Transmission of nerve impulses
1944	J. Erlanger, H.S. Gasser	Functions of different nerve fibres
1949	W.R. Hess, E. Moniz	Functional organisation of the midbrain, frontal leucotomy
1954	J.F. Enders, T.H. Weller, F.C. Robbins	Culture growth of poliomyelitis virus
1963	J.C. Eccles, A.L. Hodgkin, A.F. Huxley	Ionic mechanisms in the neuronal membrane
1970	B. Katz, U. von Euler, J. Axelrod	Transmitters in nerve terminals
1979	A.M. Cormack, G.N. Hounsfield	Computed tomography
1981	R.W. Sperry, D.H. Hubel, T.N. Wiesel	Specialisation of the brain hemispheres
1991	E. Neher, B. Sakmann	Cell ion channels
1997	S.B. Prusiner	Prions
2000	A. Carlsson, P. Greengard, E.R. Kandel	Signal transduction in the central nervous system
2003	P.C. Lauterbur, P. Mansfield	Magnetic resonance imaging
2004	L.B. Buck, R. Axel	Odorant receptors and the organisation of the olfactory system
2014	J. O'Keefe, M.B. Moser, E.I. Moser	Brain positioning system
2017	J.C. Hall, M. Rosbash, M.W. Young	Molecular control of the circadian rhythm
2021	D. Julius, A. Patapoutian	Temperature and pressure receptors

Results

The following Nobel laureates have contributed essential discoveries to neuroscience (Table 1):

1906 – Camillo Golgi, Santiago Ramón y Cajal: structure of the nervous system

Golgi lived and worked for his entire life in Pavia (Italy), where he converted the kitchen at the Hospital for the Chronically Sick in Abbiategrasso into a laboratory. He was the first person to observe individual neurons; they had previously been indistinguishable as the entire brain tissue was stained at once. He discovered a *reazione nera* that stained neurons black; the technique involved hardening the nervous tissue with potassium dichromate and subsequently impregnating it with silver salts.[6] His name was given to the Golgi apparatus (an intracellular organelle that was considered an artefact until it was rediscovered 50 years later with electron microscopy),[7] the Golgi tendon organ, which senses changes in muscle tension,[8] and the type I (projection neurons with long axons) and type II Golgi neurons (local interneurons whose axons do not project beyond the grey matter) in the granular layer of the cerebellum. Even in his Nobel Prize acceptance speech, Golgi continued to argue that what he had observed was a network. Other authors, particularly Santiago Ramón y Cajal (Figure 1), correctly interpreted those images, which in fact showed individual cells, giving rise to the neuron doctrine, which formed the basis of discoveries in subsequent decades.

Cajal had accompanied his father, a physician, to anatomical dissection sessions; after completing his medical studies, he was deployed to serve as an army doctor in the Cuban War of Independence, where he contracted malaria. Upon his return to Valencia, he started work as a lecturer in anatomy and was taught by the neurologist Luis Simarro to prepare samples for microscopy study of neurons stained with the Golgi

Figure 1. Santiago Ramón y Cajal (CC BY-SA 2.0).

technique, which Cajal improved and used intensively.[9] He drew thousands of sheets on the structure of the nervous system, particularly in animal embryos, in which he was better able to study individual neurons due to their reduced number and lack of myelination.[10] Cajal described the axonal growth cone and dendritic spines (which he believed to be artefacts). As well as his interest in the structure of neurons, Cajal also proposed the direction in which impulses travelled:

> The soma and the dendrites possess axipetal conduction, that is to say they transmit nervous waves to the axon. Inversely, the axon or axis cylinder presents somatofugal or dendrifugal conduction, propagating the impulses received by the soma or the dendrites towards the arborisations of nerve terminals.[11(p.198-199)]

His name is used to refer to the interstitial nucleus of the midbrain, near the longitudinal fasciculus, and to Cajal bodies, observed in neurons and cells presenting active metabolism. Despite not sharing the same interpretation of what they saw under their microscopes, Golgi and Cajal were the first Nobel laureates to share the Prize in Physiology or Medicine, awarded in a tense ceremony.

1914 – Robert Bárány: vestibular apparatus

This Austrian physician, who worked at the General Hospital of Vienna, dedicated nearly all his research to the inner ear, and more specifically to the vestibular apparatus, giving a detailed description of the effect of caloric irrigation.[12,13] When he used cold water, the endolymph of the semicircular duct became more dense and fell, causing vertigo and fast-phase nystagmus toward the contralateral ear; the opposite occurred when warm water was used. When he was awarded the Nobel Prize, he was a prisoner of the Russian army, as he had enlisted in the Austrian army as a surgeon during the First World War. Bárány discovered benign paroxysmal positional vertigo, which he attributed to

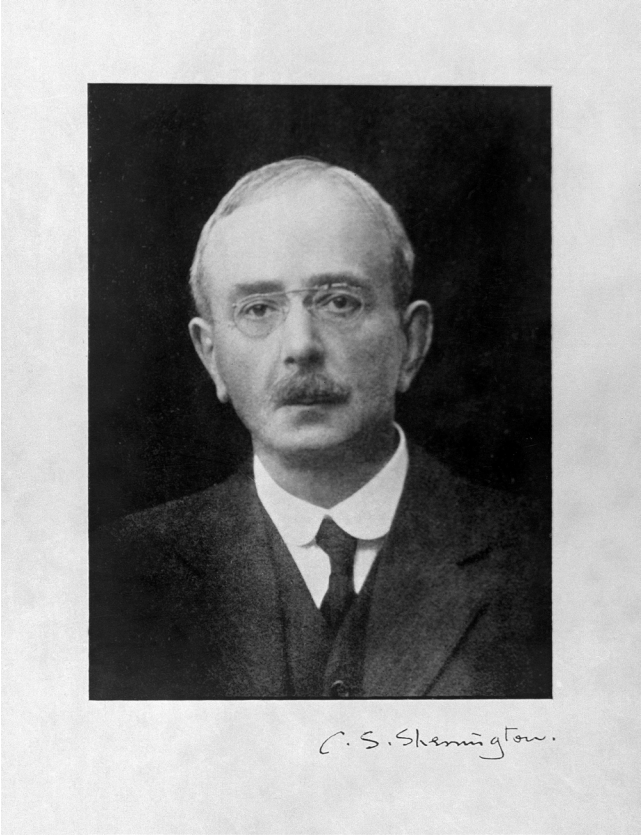

Figure 2. Charles S. Sherrington (© Wellcome Collection Gallery. CC BY-4.0).

the detachment of otoliths[14]; his name was given to a pointing test in which the finger deviates towards the hypoactive vestibule. Another eponym is the Nylen-Bárány (or Dix-Hallpike) manoeuvre, used in clinical practice to provoke positional vertigo in order to observe nystagmus, which can determine whether the cause of vertigo is central or peripheral.

1929 – Christiaan Eijkman, Frederick G. Hopkins: antineuritic vitamins

Dry beriberi is a neuropathy caused by thiamine (vitamin B_1) deficiency. Symptoms were recognised as early as 1300 BCE, in China; as it appeared in waves, it was thought to be of infectious aetiology. The Dutch military physician Eijkmann discovered in Java that hens fed exclusively with polished rice presented paralysis resembling beriberi in humans; symptoms reverted when the animals were fed unpolished whole-grain rice.[15] Subsequent studies in his laboratory isolated thiamine in whole-grain rice.[16]

Hopkins, an English researcher at Cambridge, discovered that when mice were fed only with purified protein, fat, and carbohydrates from milk, their growth stopped, subsequently resuming when very small amounts of whole milk were added. These substances, needed in very small quantities, were called vitamins. Hopkins also discovered tryptophan, an essential amino acid that must be obtained from food, as it is not synthesised by the body,[17] as well as the glutathione oxidation-reduction reaction.[18] Over the following years, other vitamin deficiencies were found to cause such diseases as rickets (vitamin D deficiency) and pellagra (niacin deficiency).

1932 – Charles S. Sherrington, Edgar D. Adrian: functions of neurons

The spinal reflex arc that neurologists explore through percussion of the patellar and other tendons was studied in thousands of cats by the English scientist Sherrington (Fig. 2), who was a member of the Cambridge rowing team as a student but subsequently lectured at Oxford. These experiments showed that stretch reflexes are the result of simultaneous activation of the agonist muscle responsible for the movement and inhibition of the antagonist.[19] He coined the terms synapse and proprioception[20,21] when he discovered that the spinal reflex arc involved sensory nerves from the muscles. It is also thanks to Sherrington's work that we know about dermatomes, that the pyramidal tract constitutes the motor connection between the brain and spinal cord, and about decerebrate rigidity, which can be induced in cats by separating the brain from the spinal cord, in order to study spinal reflexes without cerebral influence.

At his laboratory in Cambridge, Adrian confirmed the existence of the proprioception described by Sherrington, identifying nervous discharges in frogs when their feet were moved.[22] He also isolated a single axon innervating the diaphragm in frogs and, by stimulating it at different intensities, discovered that potentials always presented the same voltage and conduction velocity. He deduced that nerve fibres must have an "all or nothing" response and that the nerve fibre would only transmit an impulse if the electric signal reached a certain threshold.[23] He proposed that neurons encode sensations as a frequency of nervous discharge; thus, when we perceive a sensation to be more intense, it is because sensory neurons are

discharging not with greater intensity, but rather at higher frequencies.[24]

1936 – Henry H. Dale, Otto Loewi: transmission of nervous impulses

In the first decades of the 20th century, the scientific community was divided into those who, like Eccles (who later won a Nobel Prize for other discoveries), believed that the transmission of impulses between neurons, or from neurons to muscle, was purely electrical; and those who, like the English researcher Dale, believed that a chemical process was also involved. Dale defended this theory because he had discovered through his work at the Wellcome Institute in London that muscarine and nicotine had the same effect as stimulating nerves of the parasympathetic nervous system,[25,26] and that the effect of muscarine was blocked by atropine.

However, the definitive experiment was conducted by the German Otto Loewi, who was working at New York University after fleeing Nazi Germany. Stimulation of vagus nerve fibres connected to an isolated frog heart was known to reduce the strength and frequency of heartbeats. Loewi discovered that a fluid was released in this experiment that, when applied to a second, denervated, frog heart, also slowed the heartbeat in the same way as was observed with stimulation of the vagus nerve.[27] This demonstrated that neurons communicated not by electrical signals but with chemical substances. The substance discovered in the experiment was acetylcholine. Dale continued this research in other tissues, finding that the substance was released by nerve terminals[28] and confirming its function and the fact that it is destroyed by another chemical substance (acetylcholinesterase) after release into the synapse. These findings enabled D. Bovet to synthesise antagonists of acetylcholine (eg, curarising agents, used in anaesthesia) or of receptors of the sympathetic nervous system (eg, certain antihypertensive drugs). Bovet received the Nobel Prize for this work in 1957.

1944 – Joseph Erlanger, Henry S. Gasser: functions of different nerve fibres

The American scientist Erlanger initially studied the neurophysiology of the heart,[29] but he and his student Gasser (not to be confused with the Austrian anatomist who discovered the trigeminal ganglion in the 18th century) later focused their research on the nervous system. Working at the University of Wisconsin, they modified the oscilloscope invented by K.F. Braun (winner of the 1909 Nobel Prize in Physics) and recorded electrical current in different axons of the peripheral nervous system after electrical stimulation,[30] in a similar procedure to that used today in clinical electroneurography studies. This led to the discovery of the large myelinated nerve fibres of motor neurons and neurons associated with tactile and proprioceptive sensitivity; the small, non-myelinated fibres that transmit pain and temperature; and the fibres of the autonomous nervous system.[31,32]

1949 – Walter R. Hess, António C.A.F. Egas Moniz: organisation of the midbrain and frontal leucotomy

The Swiss author Hess cut short his career in ophthalmology and transferred to the physiology department at the University of Zurich, where he became interested in the control of certain functions of the body by the central nervous system. By placing electrodes in various points in the diencephalon, midbrain, and medulla oblongata of a cat, he was able to make the animal fall asleep, become aggressive, or urinate, and to change its arterial blood pressure or respiratory frequency.[33,34]

Egas Moniz demonstrated that bilateral frontal leucotomy reduced disruptive manifestations of emotion in patients with schizophrenia, depression, or obsessive disorders[35] and that patients ceased to be bothered by chronic pain, despite its persistence. This Prize was controversial, as leucotomy was commonly used in psychiatric patients in the 1930s and 1940s, when few treatment options were available, and the neuropsychological sequelae were only discovered later. In the 1950s, the discovery of chlorpromazine and other effective psychoactive drugs meant that the technique fell into disuse. Moniz was also the first person to perform a cerebral angiography.[36]

1954 – John F. Enders, Thomas H. Weller, Frederick C. Robbins: growth of poliomyelitis virus culture

In 1954, the public were surprised that the Nobel Prize related to poliomyelitis should not have been awarded for the development of vaccines (J. Salk and A. Sabin) rather than for the growth of the virus in cultures of different cells.[37] This work first required the authors to discover how to cultivate the cells in which the poliomyelitis virus and other viruses would reproduce, as had previously

been achieved with bacteria. This discovery led to the development of vaccines for poliomyelitis and other diseases, and it became easier to diagnose viral infections.

1963 – John C. Eccles, Alan L. Hodgkin, Andrew F. Huxley: ionic mechanisms in the membrane of neurons

A.L. Hodgkin and his student A.F. Huxley measured axonal depolarisation and repolarisation in the squid giant axon, which is a thousand times thicker than human axons.[38] The authors proposed that depolarisation is explained by sodium entering the cell and repolarisation by potassium exiting the cell across its membrane.[39,40]

As mentioned above, Eccles initially believed that signal transmission between neurons was purely electrical. Later, he met the philosopher Karl Popper, who proposed that a scientific hypothesis must be able to withstand attempts at falsification: finding a single black swan is sufficient to disprove the hypothesis that all swans are white, even if millions of white swans are found. When Eccles placed electrodes at the synapse and recorded postsynaptic potentials, which were sometimes excitatory and sometimes inhibitory,[41] he recognised that he had found a black swan, falsifying the theory of electric transmission. He also explained how, via the synapse, a neuron can either excite or inhibit a postsynaptic neuron, depending on the balance of excitatory or inhibitory synapses reaching the latter.[42] After accepting his error, he won the Nobel Prize. Later, he contributed a detailed description of the functional organisation of the cerebellum.[43]

1970 – Bernard Katz, Ulf von Euler, Julius Axelrod: transmitters in nerve terminals

These authors received the Nobel Prize for their work on the storage, release, and inactivation of neurotransmitters.

Katz worked with acetylcholine,[44] and discovered that it is released both in synaptic terminals between neurons and in the neuromuscular junction, where its release in "quanta" from the emptying of vesicles causes miniature end-plate potentials.[45]

Von Euler, son of the winner of the 1929 Nobel Prize in Chemistry and a former student of Eccles', discovered that the sympathetic nervous system uses norepinephrine as a neurotransmitter,[46,47] and observed low levels of the substance in patients with postural hypotension and increased levels in controls who moved from a decubitus to a supine position. He also discovered substance P while working at Dale's laboratory,[48] as well as prostaglandins, which he named after finding them in the seminal fluid and which were the motivation for the 1982 Nobel Prize.

Axelrod's beginnings could not have been more different from those of the aristocrat von Euler: his father was a basket weaver, he received scholarships, and, as he was not admitted to any medical school, he began working as a laboratory technician. At the National Institutes of Health, in Bethesda, he discovered catechol-O-methyltransferase (COMT) enzymes,[49] whose inhibition would later be used in the treatment of Parkinson's disease. While some norepinephrine is degraded by COMT in the synaptic cleft, injection of radioactive norepinephrine demonstrated that the majority is recaptured by the presynaptic terminals, and that cocaine and amphetamines inhibited this reuptake.[50] These findings have contributed to our knowledge of the functioning of the autonomous nervous system, the neuromuscular junction, such drugs as cocaine and amphetamines, and antidepressants with different action mechanisms (monoamine oxidase inhibitors and serotonin reuptake inhibitors).[51] Axelrod also worked with paracetamol and melatonin.

1979 – Allan M. Cormack, Godfrey N. Hounsfield: computed tomography

While W.C. Röntgen had received the first Nobel Prize in Physics for the discovery of X-rays, leading to the development of simple radiography, it would be 60 years before another great advance in radiology was made. Cormack made the mathematical calculations by which two perpendicular series of parallel X-rays passing through an organ can be used to determine the amount of radiation absorbed by the tissue at each point of intersection,[52] which could subsequently be displayed in grey-scale images.

Several years later, unaware of Cormack's article, Hounsfield made the same calculations and created the first computed tomography scanner[53]; it is for this reason that the grey scale used in these studies is expressed in Hounsfield units. The first application of the new technique was in the diagnosis of neurological diseases; this inaugurated a new era, spelling the end of pneumoencehalography and echoencephalography.

1981 – Roger W. Sperry, David H. Hubel, Torsten N. Wiesel: specialisation and connections of the hemispheres of the brain

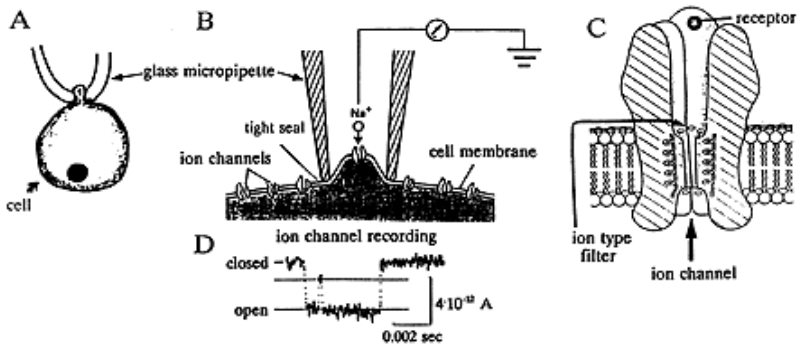

Figure 3. The flow of ions through individual channels, recorded using Neher and Sakmann's patch clamp technique. A) The glass micropipette is placed in contact with the cell. B) This image, at greater magnification, shows the ion channels and the tip of the pipette, whose interior is connected to a voltage amplifier. C) A detailed view of the ion channel, showing the receptor on the outer surface of the cell and the ion filter. D) The change in current detected by the amplifier when the channel opens and an ion passes through it (Copyright: The Nobel Committee for Physiology or Medicine. Illustrator: Annika Röhl).

At the California Institute of Technology, the American researcher Sperry studied patients who had undergone callosotomy to treat refractory epilepsy,[54] finding different functions in the left (abstract thought, symbolic relationships and logical analysis, temporal relationships, calculation) and right hemispheres of the brain (concrete thought, spatial relationships and comprehension of complex relationships, interpretation of music, intonation of voice and non-verbal sounds). However, Sperry also conducted experiments in which he severed the optic nerve in fish and amphibians, demonstrating that, when they regenerated in the absence of light, they made the same tectal connections that they had previously possessed.[55] Thus, he disproved the prevalent notion at the time that during their development, neurons only established connections as a function of their activity and the organism's experiences and learning. He also confirmed Santiago Ramón y Cajal's prediction that the connections between neurons are largely determined by genetics, and follow chemical signals by which one neuron recognises another with which it will form a synapse. However, experience was also essential to the proper development of these connections: newborn cats and chimpanzees raised in darkness and exposed late to light presented permanent visual defects.

Experiments by Hubel and Wiesel showed both genes and experience to be determinants: although visual synaptic connections follow very specific patterns in the immature nervous system,[56] stimulation during these periods can modify some connections. They also demonstrated that upon reaching the occipital cortex, the image transmitted by the retina makes successive synapses with neurons distributed in columns,[57] with each neuron finally incorporating into the perceived image a specific element that is always the same (contrast, movement, etc). Sperry had also proposed this preferentially column-based distribution of connections in motor areas, when he observed that vertical cuts made to the cortex, respecting the columns, did not affect its function.

1991 – Erwin Neher, Bert Sakmann: cellular ion channels

Since the work by Hodgkin and Huxley with the squid giant axon, depolarisation was known to be associated with the entry of sodium and exit of potassium. However, the German scientists Neher and Sakmann, of the Max Planck Institute, were the first to demonstrate the existence of specific channels for each ion. They did this using the patch clamp technique[58]: a single ion channel was isolated in the lumen of a glass micropipette of one-thousandth of a millimetre in diameter that was placed in contact with the cell and acting as an electrode, was able to register the change in potential corresponding to the entry of a single ion into the cell (Figure 3).[59] Ion channels are also the basis for the transmission of neuronal action potentials, and their characterisation has enabled the development of drugs to treat dysfunction of each type of channel (eg, sodium channels in epilepsy, calcium

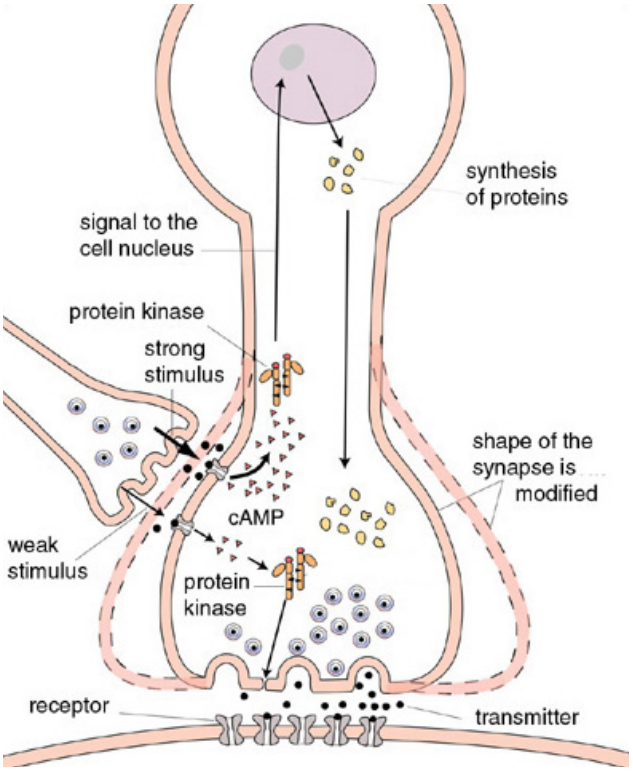

Figure 4. Molecular changes in the synapse of the sea slug *Aplysia*. Gentle stimulation (thin arrow in the lower left) generates "short-term memory" via phosphorylation of ion channel proteins, leading to greater release of the neurotransmitter. "Long-term memory" results from a more intense aversive stimulus (thick arrow) that, by increasing levels of the second messenger (cAMP), activates kinase proteins that phosphorylate other proteins, which enter the nucleus and trigger the production of new proteins. As a result, the shape of the synapse may change, and changes in the release of neurotransmitters are maintained (Copyright: The Nobel Committee for Physiology or Medicine. Illustrator: Annika Röhl).

channels in Lambert-Eaton syndrome, and potassium channels in episodic ataxia type 1, among many other neurological and systemic diseases). They were also able to register the fusion of individual vesicles (transporting neurotransmitters, for example) with the membrane for emptying into the extracellular space.[60] These studies were complemented by others by R. MacKinnon and P. Agre, who received the 2003 Nobel Prize in Chemistry for their work on the structure and function of ion channels and water channels, respectively.

1997 – Stanley B. Prusiner: prions

Since the 1976 Nobel Prize,[61] kuru was known to be transmitted by extracts from the brain; the same was also known of Creutzfeldt-Jakob disease and scrapie (spongiform encephalopathy in sheep). However, the causal agent had not been identified. When the American researcher Prusiner, of the University of San Francisco, discovered that the cause was a protein, he was not believed; many more doubts surfaced when the gene encoding the protein was also found to exist in healthy individuals.[62] These contradictions were resolved when it was discovered that, while we all have the normal prion protein (PrP^{C}), it is only when it folds in a way that renders it insoluble (PrP^{Sc}) that it accumulates to form harmful particles. These are contagious as they induce the misfolding of normal prion proteins.[63] PrP knockout mice could not be infected with the disease. Since this discovery was made, neurologists routinely diagnose several prion diseases, and specific disinfection measures have been developed that differ from those used for conventional infectious agents.

2000 – Arvid Carlsson, Paul Greengard, Eric R. Kandel: signal transduction in the nervous system

While the action of acetylcholine and norepinephrine was already known, the action of dopamine was not understood until the Swedish researcher Carlsson, working at the University of Gothenburg, observed that the neurotransmitter is abundant in the basal ganglia and participates in controlling movement.[64] It was soon discovered that dopamine production is reduced in Parkinson's disease as a result of lesions to the nigrostriatal pathway.[65] This discovery led to the synthesis of levodopa for the treatment of Parkinson's disease. Carlsson also demonstrated that antipsychotic drugs work by blocking dopamine receptors.[66]

The American scientist Greengard, at Yale University, discovered that the dopamine receptor increased intracellular cAMP, causing phosphorylation of proteins that opened ion channels in the postsynaptic membrane and induced the transmission of neuronal impulses.[67] This clarified the action mechanism of some drugs on neurons.[68]

Another American researcher, Kandel of Columbia University, studied the gill and siphon withdrawal reflex and recall in the sea slug *Aplysia*. He discovered the synaptic changes underlying the short-term memory of

gentle stimulation (synaptic phosphorylation) and long-term memory of intense stimulation (protein synthesis) (Figure 4).[69] This research revealed that memory is based on changes in synaptic function.[70] Kandel's book on the physiology of the nervous system is an essential reference in neurology training.[71]

2003 – Paul C. Lauterbur, Peter Mansfield: magnetic resonance imaging

It had been known since the 1952 Nobel Prize in Physics that atomic nuclei in a strong magnetic field spin at a frequency determined by the strength of the field, and that their energy is increased if they absorb radio waves at the same frequency (resonance). When nuclei return to their previous level of energy, radio waves are emitted. The American researcher Lauterbur, of Stony Brook University, discovered that applying gradients in the magnetic field made it possible to analyse the characteristics of the radio waves emitted and to determine their source.[72] This enables the creation of a two-dimensional image providing information on deep structures, resulting in much more precise anatomical diagnosis in neurology.

The English scientist Peter Mansfield of the University of Nottingham conducted mathematical analyses of the signals, generating an image that could be used in diagnosis.[73]

2004 – Linda B. Buck, Richard Axel: olfactory receptors and the organisation of the olfactory system

These two American Nobel laureates worked at Columbia University. They discovered that each cell of the olfactory epithelium presents a single olfactory receptor, which is activated at different intensities for different smells, encoded by one gene (this gene family has a thousand members, and accounts for 3% of the human genome),[74,75] and that cells project axons to the same type of glomerulus in the olfactory bulb, which makes contact with a specific type of mitral cell, maintaining the specificity of the receptor. The mitral cell sends projections to various regions of the olfactory cortex,[76] where they are combined in different patterns corresponding to the 10 000 smells we are able to identify. These researchers also discovered pheromone receptors[77] and the functioning of taste buds. These three types of receptors are coupled to an intracellular G protein.

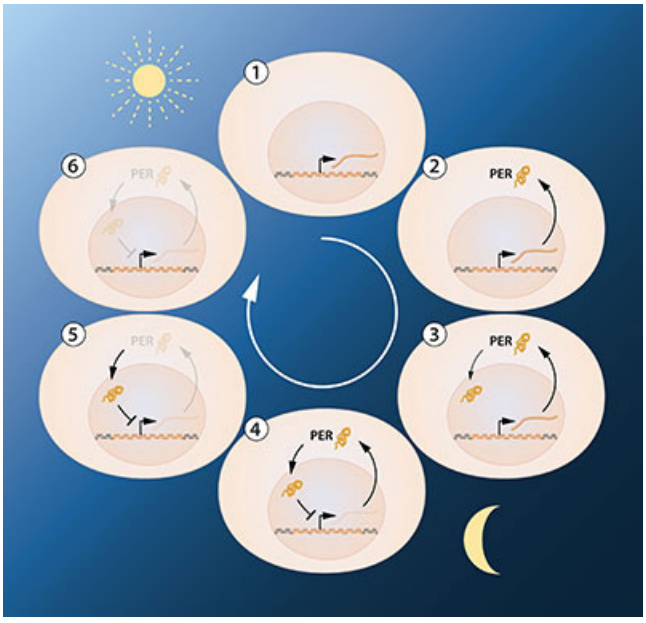

Figure 5. Feedback regulation of the period gene (*PER*), which oscillates over 24 hours. When the gene is activated, its mRNA is synthesised, and passes to the cytoplasm to synthesis the PER protein (drawings 1 and 2). The PER protein accumulates in the nucleus, repressing the period gene, and consequently production of the protein (drawing 3-6), in an inhibitory feedback mechanism that constitutes the basis of the circadian rhythm (Copyright: The Nobel Committee for Physiology or Medicine. Illustrator: Mattias Karlén).

2014 – John O'Keefe, May-Britt Moser, Edvard I. Moser: brain positioning system

O'Keefe is an American psychologist who has always worked at University College London, where he discovered that the hippocampus contains "place" cells that are activated when we are in a specific place.[78,79] The Mosers worked at his laboratory and, after returning to their native Norway, discovered a related type of cell in a structure near the hippocampus, the entorhinal cortex. These so-called "grid cells"[80-82] act as coordinates and, combined with place cells, work as a GPS to locate one place with respect to others, enabling us to orient ourselves and to memorise journeys. These cells also exist in humans, and partially explain problems with orientation and spatial memory when the hippocampus is damaged, for example in Alzheimer disease.

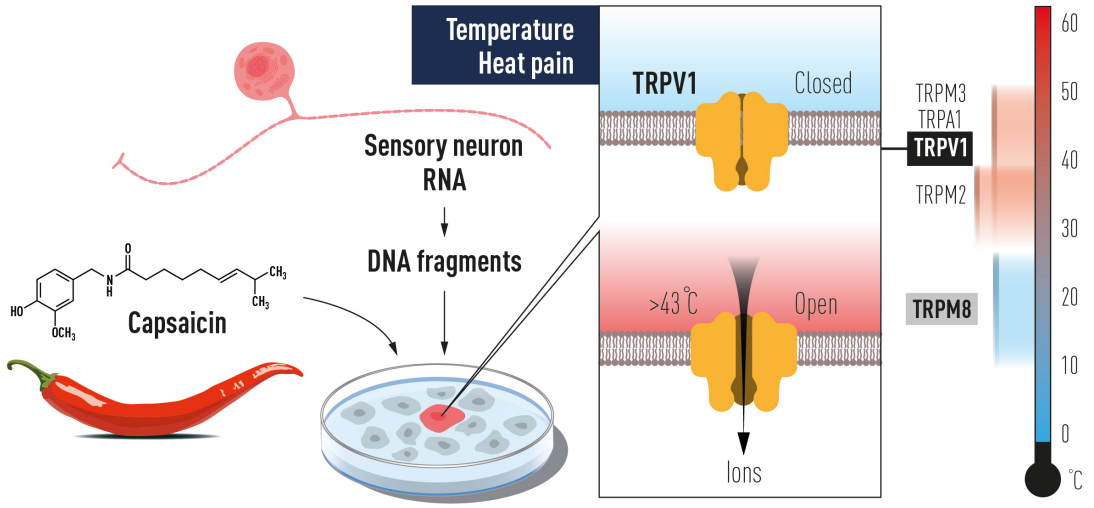

Figure 6. David Julius used capsaicin to identify TRPV1, a heat-sensitive ion channel that causes pain, and TRPM8, which detects cold (Copyright: The Nobel Committee for Physiology or Medicine. Illustrator: Mattias Karlén).

2017 – Jeffrey C. Hall, Michael Rosbash, Michael W. Young: molecular control of circadian rhythm

These American researchers (Hall works at the University of Maine, Rosbach at Brandeis University, and Young at Rockefeller University) explained how the biological clock of plants and animals is adjusted to the 24-hour rotation of the Earth. This rhythm is achieved through the gene encoding the PER protein, which accumulates at night and is degraded during the day; these oscillations constitute the basis of the circadian rhythm of all cells in the body (Figure 5), not only in the nervous system.[83-85] These authors added to the existing knowledge of the regulation of circadian rhythm by the suprachiasmatic nucleus (which controls the secretion of melatonin by the pineal gland) with exposure to light, which is used to treat advanced or delayed phase sleep disorders.

2021 – David Julius, Ardem Patapoutian: temperature and pressure receptors

How are temperature and mechanical stimuli converted into electrical impulses in the nervous system? This question was answered by Julius, an American researcher at the University of California, when he discovered heat- and cold-sensitive receptors (TRPV1 and TRPM8, respectively[86,87]), and by Patapoutian, an American researcher of Lebanese origin who, working at the Howard Hughes Medical Institute in California, discovered pressure receptors (Piezo1 and Piezo2).[88] In addition to the ability to sense the temperature of the skin, heat- and cold-sensitive receptors also regulate body temperature and mediate neuropathic and visceral pain. The temperature receptor is inhibited by capsaicin (Figure 6), an irritant extract of chilli peppers that is used in clinical practice to treat peripheral neuropathic pain, such as postherpetic neuralgia. In addition to tactile sensitivity (they are found in Merkel cells[89]), pressure receptors also detect when the bladder is full; receptors in the vagus nerve enable the maintenance of arterial blood pressure through the baroreceptor reflex described by the Belgian researcher C. Heymans, winner of the 1938 Nobel Prize in Physiology or Medicine.[90]

Discussion

Of the 112 Nobel Prizes in Physiology or Medicine (awarded to 224 individuals), 35 (31.2%) can be considered to have been awarded for discoveries in the area of neurosciences or to have had a direct impact on

neurological practice. I have not included Prizes awarded for discoveries related to the senses of sight or hearing or the 1927 Nobel Prize awarded for research on the inoculation of malaria to treat syphilitic dementia, which is somewhat erroneous in the light of current knowledge. Most of these neuroscientific discoveries contributed new details on the transmission of information in the nervous system, and there is a common thread between them that has enabled more recent researchers to base their work on discoveries made by their predecessors, advancing our knowledge. At a time when scientific publications were less accessible than today, many Nobel laureates were in contact with one another and "passed the baton" of their knowledge, which others expanded on: Sherrington met Cajal on a trip to Spain, Eccles was a favourite student of Sherrington's, Katz and von Euler were students of Dale, and Sakmann worked under Katz. The autodidacts Golgi and Cajal were the first to forge this path, showing the microstructure of the nervous system with the axonal arborisations that transmit information. Their work was continued by Sherrington and Adrian, who showed that neurons can have either inhibitory or excitatory function, and Erlanger and Gasser discovered the existence of different types of nerve fibres, depending on the motor, sensory, or autonomic function of the cell. In 1963, Hodgkin and Huxley received the Prize for explaining neuron action potentials as the result of the passage of ions across the cell membrane, and Neher and Sakmann won in 1991 for detailing how ions cross the membrane, isolating a single ion channel. Von Euler's discovery of prostaglandins led to further research that received the Prize in 1982. Prusiner was the 2006 winner for his discovery of prions, after Gajdusek had won the 1976 Prize for describing the transmission of kuru. Synaptic transmission of information between neurons was the motivation for several Nobel Prizes: Dale and Loewi ascertained that it was a chemical process; Eccles studied the properties of synapses; Katz, von Euler, and Axelrod showed that vesicles release "quanta" of neurotransmitters into the synapse that are subsequently recaptured; Neher recorded the fusion of individual vesicles with the cell membrane; and Carlsson, Greengard, and Kandel explained the transduction of neuronal signals. In his *Discourse on the method*, Descartes advises that we study individual elements in order to understand complex processes; following this approach, the Nobel laureates have sought to measure isolated elements of the nervous system. Cajal was able to visualise them by selectively staining a small number of neurons; isolated axons were recorded in the peripheral nervous system by Erlanger and Gasser, in the vagus nerve by Adrian, and in the spinal cord by Eccles; Hodgkin and Huxley isolated axons in squid; and Neher and Sakmann isolated a single ion channel. These discoveries were frequently facilitated by a novel technique (whether a technology or an experimental model), often developed by another Nobel laureate. Cajal would not have made his discoveries if Golgi had not previously discovered silver staining. Sherrington's discoveries on the reflex arc were made possible by the isolated cat spinal cord model. Adrian discovered the "all or nothing" axonal transmission thanks to the ability to isolate a single axon. Erlanger and Gasser measured axonal conduction by modifying the oscilloscope developed by the winner of the 1909 Nobel Prize in Physics, Ferdinand Braun. Hodgkin and Huxley made their discoveries in the squid giant axon, and Kandel used the sea slug *Aplysia*. Neher and Sakmann identified specific ion channels thanks to the use of micropipettes.

Conclusions

Many of the neuroscientific works awarded Nobel Prizes report the mechanisms of information transfer between neurons, the main function of the nervous system. Most built upon the research of previous Nobel laureates. These discoveries have had an impact on the everyday practice of clinical neurologists, with changes in history-taking, examination, and complementary tests.

Conflicts of interest

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