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Chapter

Introductory Chapter: The Neurotransmitter Acetylcholine – A Young Centenarian

Thomas Heinbockel

1. Introduction

If you are fortunate enough to grow in age and turn 100 years old, you are a centenarian. That is the term used for those human folks who are 100 years or older. The term is not typically applied to neurotransmitters. However, the neurotransmitter acetylcholine was discovered a little more than one hundred years ago, in 1921, by German-born scientist Otto Loewi. While human folks might face their final farewell at this age, current research on acetylcholine is testament to its young age, making it a young centenarian. As a PhD student in the Neuroscience program at the University of Arizona [https://neuroscience.arizona.edu/], my fellow students and I learned about acetylcholine as one of the major neurotransmitters in the nervous system, its synthesis, breakdown, and recycling [1, 2]. The fascinating story of acetylcholine's discovery and its functional importance for brain signaling upheld my continuous interest in this neurotransmitter.

2. Otto Loewi and his famous experiments

At the beginning of the 20th century, Loewi had worked on cardiac physiology for several years and published a continuous stream of papers in Pflügers Archiv (Pflüger's Archiv für die gesamte Physiologie des Menschen und der Tiere; today: Pflügers Archiv: European Journal of Physiology), the oldest physiological journal [3, 4]. The question that concerned scientists at the time was the mechanism that changed the beating frequency of the heart. Two alternatives presented themselves. In one of them, the heart itself released a substance that changed its beating frequency, whereas the other one postulated that some substance was released by nerve fibers, i.e., a form of chemical transmission existed [5]. In 1921, Loewi published a short paper [6] in this regard that described the key experiment carried out by him. It was a series of fortunate circumstances that led to his discovery of chemical transmission with acetylcholine as the messenger [7].

Loewi has recounted the nights before the critical experiment as he dreamt about it in his sleep [5]. The experiment used one frog heart where the vagus nerve was stimulated with electrical impulses. Electrical stimulation of the vagus nerve slowed

down the heartbeat. The liquid from that heart (saline solution, i.e., Ringer's solution) was collected and applied to a second heart. The application resulted in a reduction in the beating frequency of the second heart. Loewi interpreted the slowing down of the second heart to mean that the vagus nerve had released a substance, the 'Vagusstoff' or vagus substance (acetylcholine) and proved that a soluble chemical released by the vagus nerve was controlling the heart rate. The chemical substance affected the heart rate through a process of chemical transmission [8]. The solution from the first heart slowed the second heart, and its beats diminished exactly as if its vagus nerve had been stimulated. In an additional experiment, Loewi stimulated the accelerator nerve of the first heart. When the nerve was stimulated and the Ringer solution from this heart was transferred, the second heart accelerated, and its beats increased [9]. Through these experiments, Loewi had solved the problem of determining whether any substance originated in the heart muscle to inhibit or activate it or whether the substance originated from the innervating nerve. In 1922, Loewi published a companion paper in which he ruled out the possibility that the chemical substances came from the heart [10]. In these experiments, he used high doses of nicotine which paralyzed the donor heart. Nevertheless, it was still possible to collect and transfer the Vagusstoff or the Acceleransstoff (adrenaline or epinephrine) from the paralyzed heart after stimulating the nerve. The idea for the initial experiment came to Loewi in a dream which prompted him to immediately go the lab after he woke up and carry out the experiment at 3 am in the morning [5, 11, 12]. His hypothesis of chemical transmission that he had postulated years earlier was proved by 5 am in the morning [11]. Loewi was lucky to carry out the experiment in a specific frog species at the time of day (diurnal cycle of the frog) and year that he did. The enzyme acetylcholinesterase rapidly metabolizes acetylcholine and could have prevented its effect on the heart. It was no surprise that chemical transmission was discovered in the peripheral nervous system as it affected visceral organs and skeletal muscles [5]. The experimental preparations were more accessible, and it was feasible to study drug effects. Moreover, chemical transmission was realized because certain drugs mimicked the stimulation of the autonomic nervous system that innervated visceral organs.

3. Henry Hallett Dale: friend and colleague

The other key player in the discovery of acetylcholine is Henry Hallett Dale who described acetylcholine as a neurochemical in 1914 [13]. In 1902 and subsequent years, Loewi visited the lab of Ernest Starling in London, England [12]. During those visits, he met Dale who, just like Loewi, was focused on biomedical bench work instead of clinical practice. Both became colleagues and lifelong friends. Dale's work included the isolation and identification of neurochemicals such as histamine and acetylcholine. He distinguished muscarinic and nicotinic acetylcholine activity which was instrumental for the later discovery of acetylcholine receptor classes and subtypes. Furthermore, based on the relatively transient effect of acetylcholine, Dale proposed the existence of an esterase that rapidly metabolized acetylcholine. Dale's findings laid the groundwork for Loewi's innovative discoveries. As a result of their cutting-edge and transformative research, 'the Nobel Prize in Physiology or Medicine 1936 was awarded jointly to Sir Henry Hallett Dale and Otto Loewi for their discoveries relating to chemical transmission of nerve impulses' [14]. Their work and discoveries were not without opposition in the field [15]. The famous neurophysiologist John Eccles believed that transmission at synapses was too fast to be carried out with

chemicals. He thought that synaptic excitation had to be an electric process instead of a chemical one. The debate went on for several years in the middle of the 20th century. While Eccles initial idea was shown to be incorrect, he inadvertently helped Dale and others in the field to accomplish key experiments which proved chemical synaptic transmission in the peripheral and central nervous system. Eccles changed his opinion in the early 1950's after carrying out microelectrode experiments in his own lab. From then on, he was convinced of the existence of chemical synaptic transmission which he shared in a letter with Dale [5].

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Conflict of interest

The author declares that there is no conflict of interests regarding the publication of this chapter.

Author details

Thomas Heinbockel
Department of Anatomy, Howard University College of Medicine, Washington, DC, USA

*Address all correspondence to: theinbockel@howard.edu

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