The First Hormone: Adrenaline

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Abstract

It is not often that three mistakes are associated with one molecule for more than a century. This is the case with adrenaline. The record is set here that adrenaline is the first hormone with the discovery of its activity and chemical purification prior to secretin. Adrenaline is the correct name given by Jōkichi Takamine, epinephrine being its inactive benzoyl derivative.

While adrenaline is a well-known molecule, there have long been three misconceptions. Adrenaline has not been recognized as the first hormone, its discover remains obscure, and it has two names. This article sets the history straight and clarifies

these confusions.

Secretin vs Adrenaline

Most textbooks state that secretin is the first hormone, discovered in 1902 by the British cousins William Bayliss (1860-1924) and Ernest Starling (1866-1927), at the University College London (UCL).

In 1899, Bayliss and Starling followed up on one of Ivan Pavlov's observations published in 1898 that different kinds of substances in the food, after digestion into chyme and movement into the duodenum, induced the pancreatic to secrete different kinds of juices. Pavlov and others have performed experiments and concluded that the effects of chyme on pancreatic secretion were due to nerves (either the vagus, splanchnic or local). Bayliss and Starling made the novel discovery that this resulted from the chemical substance they called secretin, which was made by the mucous membrane of the upper parts of the small intestine, carried by the blood to the pancreatic gland cells. "The crucial experiment" was performed on January 16th, 1902, with all experiments finished by March, 1902, published in a preliminary form as Bayliss and Starling (1902a) and in

the full form as Bayliss and Starling (1902b). Starling coined the term hormone in 1905 (Starling, 1905a), and acknowledged (Starling, 1905b) that the first hormonal activity was the increase of blood pressure by the injection of supra-renal extracts observed by Oliver and Schäfer (Oliver and Schäfer, 1895).

The adrenal gland (or supra-renal capsule) is a small gland above the kidney. In 1855, Dr. Thomas Addison (1793-1860) of Guy's Hospital in London discovered what was later called Addison's disease, caused by damages to the adrenal glands. Soon researchers were interested in finding substances in the glands. Removal of adrenal capsules from animals often resulted in death (Schäfer, 1908).

George Oliver (1841-1915) was an English doctor with a home laboratory who might have experimented with his son, feeding adrenal extracts to his son (Barcroft and Talbot, 1968). Edward Albert Schäfer (1850-1935) was then a professor of physiology at UCL, whose contributions included the proposal of the term "endocrine" for ductless glands. In 1893, Oliver went to Schäfer, suggesting a collaboration on the physiological effects of adrenal extracts (Davenport, 1991). Oliver and Schäfer published two abstracts in 1894

and a full paper in 1895, showing the effects of adrenal extracts, including those of increasing the blood pressure and increasing the heart beat (Oliver and Schäfer, 1895). They determined that the active principle was from the medulla, not the cortex of the adrenal glands.

Secretin was not purified until almost six decades later (Jorpes and Mutt, 1961) and determination of its primary structure would take another decade (Mutt, Jorpes and Magnusson, 1970).

Thus, the first hormone was clearly adrenaline, because both the discovery of its activity in 1895 and its chemical purification in 1901 predated those of secretin in 1902 and 1961.

Purification of the Active Principle from the Adrenal Gland

In 1895, Schäfer asked two of his colleagues at UCL to study adrenal extracts chemically (Moore, 1895; Nabarro, 1895). In 1897, Sigmund Fränkel (1868-1939) of Germany extracted from the adrenal capsules what he called spygmogenin (Fränkel, 1897). From 1897 to 1901, John Abel of Johns Hopkins University published a series of

papers on what he called epinephrin from 1898 onwards (Abel and Crawford, 1897; Abel 1898, 1899, 1901). The molecular formula of epinephrine was $C_{17}H_{15}NO_4$ (Abel, 1898). In 1900, the Austrian scientist Otto von Fürth (1867-1938), then working at Strasbourg University, after pointing out that epinephrine was inactive, purified what he called suprarenin, with the molecular formula of $C_5H_9NO_2$ (von Fürth, 1900). In 1901, Abel offered a rebuttal to Fürth, claiming that his principle was active, although it was not the native principle, but might contain an extra benzoyl (Abel, 1901).

The pharmaceutical company Parke-Davis in Detroit, Michigan asked Takamine to purify the active principle from the adrenal gland. In 1900, Takamine and his assistant Keizo Uenaka (1876-1960) succeeded in purifying the highly active principle, with the molecular formula of $C_{10}H_{15}NO_3$. In January 1901, Takamine reported his findings to the Society of Chemical Engineering in New York and published in the *American Journal of Pharmacy* (Takamine, 1901). In December 1901, Takamine reported adrenaline to the British Physiological Society and published the *Journal of Physiology* in 1902 (Takamine, 1902).

By the summer of 1900, Thomas Aldrich of the Department of Biology of the Scientific Laboratory of Parke-Davis had also purified adrenaline, which he published in 1901. He recognized the priority of Takamine's report to the Society of Chemical Engineering. He compared the physical and chemical properties and concluded that he and Takamine had isolated the same molecule, with the same molecular formula: $C_9H_{13}NO_3$ (Aldrich, 1901). The correct formula was closer to that deduced by Takamine than those by Abel and Fürth.

Adrenaline vs Epinephrine

Adrenalin was the name in the patent of Takamine and Parke-Davis. After a lawsuit filed by Abel, Takamine won (Yamashima, 2003). Both the British and the European Pharmacopoeia used adrenaline but the US Pharmacopoeia used epinephrine.

Five years after Takamine died (and 25 years after losing the patent fight), Abel claimed that Takamine visited him and modified his method to purify adrenaline (Abel, 1927). A research note by Uenaka, was later found and its mixed Japanese and English text showed that Takamine and Uenaka had purified adrenaline before the date of

Takamine's presumable visit claimed by Abel (Yamashima, 2002).

Abel was the first chairman of the first department of pharmacology in the US, one of the two co-founders of the *Journal of Biological Chemistry* in 1905, and the founder of the *American Journal of Pharmacology and Experimental Therapeutics* in 1908. His influence was far greater than that of Takamine.

Thus, even though historians had argued for Takamine (Bett, 1953; Tansey, 1995; Aronson, 2000), it remains for a long time that American scientists believe more in Abel than in Takamine. For example, the American physiologist Horace Davenport in 1982 believed that Abel discovered the principle, although he changed his mind by 1991 to recognize the discovery of Takamine (Davenport, 1982, 1991). Even though there have been repeated arguments for the usage of adrenaline (e.g., Aronson, 2000), epinephrine is still used in American textbooks and by American scientists. Most assume that there had been priority disputes between American and European scientists, whereas the truth was that both names were proposed by scientists working in the US, though one of Japanese origin and the other of European origin.

Experts' Agreement: Adrenaline

In 1903, Hermann Pauly (1870-1950), then at the University of Bonn, determined the structure of adrenaline. He also believed the principle purified by Takamine to be active, whereas that by Abel inactive (Pauly, 1903, 1904). In 1904, the German chemist Friedrich Stolz (1860-1936) became the first scientist to synthesize what he also called adrenalin (Stolz, 1904). The British chemist Henry Dakin (1880-1952) also credited Takamine and Aldrich for discovering adrenaline (Dakin, 1905). In 1906, Henry Dale, the British pharmacologist who would win a Nobel prize in 1936, insisted that adrenaline was the correct name, with epinephrine as the name of the inactive principle (Tansey, 1995; Aronson, 2000). In 1908, Schäfer suggested the name of adrenin (Schäfer, 1908), though it was never used by him or others later.

Because Takamine and Parke-Davis patented Adrenalin, Henry Wellcome (1853-1936), the American founder of the British pharmaceutical company Burroughs-Wellcome was reluctant to use the name, even trying to block Dale who was working in the research laboratories of Wellcome from using adrenaline. Dale pointed

out that British scientists believed that adrenaline was the active principle while epinephrine of Abel was inactive, insisting the usage of adrenaline in his papers (Tansey, 1995). Because Parke-Davis patented Adrenalin, scientists use adrenaline. After Abel passed away, Dale wrote an obituary for Abel, still politely noting that Abel's epinephrine was "a monobenzoyl-derivative of the active principle" (Dale, 1939).

Credit Long Overdue

Adrenaline is important for both basic research and medical applications. In basic research, it is not only the first hormone, it also helped the discovery of the neurotransmitter noradrenaline which is the precursor in the biological synthesis of adrenaline. In medicine, adrenaline was used almost immediately and is still in use today, a record not matched by many molecules. One wonders whether racial and other biases resulted in the award of the first Nobel prize to a Japanese biologist in 2012 rather than a hundred years earlier.

Takamine has won respects and awards from Japan, including the gift of cherry trees by the Japanese emperor, but is not well recognized by the rest of the world. Using the

term adrenaline, instead of epinephrine, is a right step forward for credit long overdue.

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