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savchuk.tetiana@bsmu.edu.ua,**HISTORY OF ADRENAL DISCOVERY****Tetiana SAVCHUK, Alona KOVPAK**

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Савчук Тетяна, Ковпак Алена, Семененко Наталія. История открытия адреналина. Цель статьи.

Адреналин стал символом чего-то рискованного и по-своему привлекательного, но такое адреналин с точки зрения нейрофизиолога – цель предлагаемой статьи. Мы поставили также своей целью изучить исторические этапы, предшествовавшие открытию гормонов надпочечников, применяя сравнительный и исторический методы. **Актуальность исследования.** Важную роль в исследовании свойств адреналина сыграло предсказание хирурга из Лейпцига Генриха Брауна о возможности применения адреналина при местной анестезии. Так адреналин получил широкое применение в анестезиологии, что остается актуальным до сегодняшнего дня. **Выводы.** Исследование исторических сведений об открытии гормонов сформировывает целостное представление и расширяет знания в области физиологии и патофизиологии эндокринной системы.

Ключевые слова: адреналин, история нейрофизиологии, открытие нейромедиаторов.

Introduction. Since the discovery of the adrenal glands, no one knew their functions in the body. However, experiments have shown that they are critical to life, since their removal leads to the death of laboratory animals.

In the second half of the 19th century, extracts of the adrenal glands were studied by the Englishmen George Oliver and Edward Sharpey-Schafer, as well as the Pole Napoleon Cybulsky. They found that the administration of the extract greatly increased blood pressure in the test animals. The discovery led to a real race to find the substance responsible.

So, in 1898, John Jacob Abel obtained a crystalline substance that increases blood pressure from an extract of the adrenal glands. He named it epinephrine. At the same time, the German von Fruth independently isolated a similar substance and named it suprarenin. Both of these substances had the property of increasing blood pressure, however, their effects differed from the extract.

Two years later, the Japanese chemist Yokichi Takamine improved Abel's purification technology and patented the resulting substance, giving it the name adrenaline.

Adrenaline was first artificially synthesized in 1904 by Friedrich Stolz.

Historiography of the question. Foreign scientists W. Sneader studied the history of the discovery in The discovery and synthesis of epinephrine gives a complete description of the historical moments of the discovery¹. Aronson, J.K. in the work

Where name and image meet: The argument for adrenaline studied the history of the adrenal glands². Jeffrey Aronson is a clinical pharmacologist studying the main effects of adrenaline and the discovery of this amazing hormone.

The aim of our study was to analyze the historical stages of the discovery of adrenal hormones, namely adrenaline.

Main part. In 1894, George Oliver and Edward Shafer demonstrated the vasoconstrictor (vasoconstrictor) and pressor effects of adrenal extract. George Oliver, a doctor from Harrogate, used all his free time to conduct experiments, he developed the equipment himself, which he then used for research. Oliver used a device he had designed to measure the thickness of the radial artery.

The adrenal glands of slaughtered cattle served as the material for obtaining the extract of the adrenal medulla, and the object of the study and the first tester was his little son.

During the experiments, Oliver discovered a narrowing of the radial artery after an injection of an extract of the adrenal glands of sheep, which he reported to the London professor Schafer. He was initially skeptical of Oliver's results.

The doctor insisted on demonstrating the experiment and continued to convince the professor of the truth of his conclusions. In the end, Schafer allowed the substance brought by Oliver to be injected into the dog's vein, and, to his surprise, immediately after the injection of the extract into the animal, the level of mercury on the manometer began to rise - the drug worked³.

¹ Sneader W. "The discovery and synthesis of epinephrine", *Drug News Perspect*, 2001, Oct, N 14(8), P. 491–494 [in English].

² Cameron R. B., Beeson C. C., Schnellmann R. G. "Development of Therapeutics That Induce Mitochondrial Biogenesis for the Treatment of Acute and Chronic Degenerative Diseases", *J Med Chem*, 2016, Dec 8, N 59 (23), P. 1134–1138. [in English].

³ Faria J. C. P., Victorino C. A., Sato M. A. "Epinephrine in pediatric cardiorespiratory arrest: when and how much?", *Einstein (Sao Paulo)*, 2020, Jan, N 18 [in English]; Grevsen J. V., Kirkegaard H., Kruse E., Kruse P. R. "Early achievements of the Danish pharmaceutical industry", *Theriaca*, 2016, N 43, P. 9–61 [in English].

They conducted further research together, and by 1895 Oliver and Schaefer already had at their disposal aqueous, alcoholic and glycerin solutions of the adrenal gland extract, which had vasoconstrictor and pressor effects. In the same year, researchers for the first time prepared extracts of the adrenal glands of patients with Addison's (bronze) disease. It was found that these extracts do not contain the pressor substance previously found in normal glands.

In 1897 John Abel isolated pure adrenaline from the adrenal glands of sheep and reported on obtaining an active substance that can quickly increase blood pressure and heart rate, and improve airway patency. Abel published the results of his experiments and named the resulting substance "epinephrine".

Abel did not file a patent application for the discovery and use of the drug, which later served as a pretext for disputes about the discoverer of adrenaline. Following Abel in 1900, the technology for obtaining the active substance of the adrenal medulla was developed by Jokichi Takamine, who described the chemical formula of the substance and gave it the name "adrenaline". It was he who received the US patent for the manufacture of the drug. However, Abel did not try to defend his rights in court, only in articles in scientific journals he expressed his indignation. Although he acknowledged that Taccamine isolated the crystalline form of the substance, he believed that this substance was not pure and the chemical formula was not correct⁴.

His assumptions were confirmed - the formula obtained by Takamine was not entirely correct, and the first commercial drug of one of the US pharmaceutical companies was a mixture of adrenaline and norepinephrine. But Abel himself did not single out the hormone in its pure form, but rather its benzene derivative. In 1900, the German scientist Otto von Furth published a report on his drug, isolated from an extract of the adrenal glands, suprarenin.

Using von Furth's methods, it was possible to obtain a substance that was sufficiently stable and had strong physiological effects. Abel, after the discovery of suprarenin, began to study the differences between it, adrenaline and epinephrine. The next researcher - Thomas Aldrich - in 1902 determined a more correct formula for adrenaline and gave a detailed description of the structure of adrenaline and norepinephrine. While scientists were engaged in elucidating the effects of the substances obtained, the drug was produced and sold under various names.

Doctors were not inferior to pharmacists - they tried to treat almost any disease with a new drug. NP Trinkler, for example, made a report on the treatment of cancerous tumors by subcutaneous injections of adrenaline; and this is not the only example.

As a result, epinephrine preparations under various trade names entered the pharmaceutical market in huge quantities.

These drugs often did not pass clinical trials and differed significantly in their effect on the body. Of course, it was not without sad consequences, since adrenaline has a lot of undesirable effects that have not yet been fully studied in the well-established production of the drug.

In addition, preparations produced by pharmaceutical companies often did not have the desired therapeutic effect, which was partly due to insufficiently careful manufacture, and partly to the poor quality of the dishes and solutions used when pouring the extract.

According to Schultz's study of samples of marketed adrenaline, which was produced by various companies, it turned out that of the 7 studied samples of epinephrine, only 3 had an activity equal to that of the standard. The activity of other drugs ranged from 3.75% to 71% of the required. Some solutions turned out to be unusable and even unsafe, others had an effect only immediately after opening from the package, and then quickly deteriorated.

Russian scientists also made a significant contribution to the discovery and study of adrenaline⁵.

Professor Cybulsky and his collaborator Simanovich began research on the function of the adrenal glands in 1891.: they made an aqueous extract from the adrenal medulla and began to study in detail its physiological effect on the blood circulation and respiration of animals.

Cybulsky tried to determine the chemical composition of the substance, but he failed, because after evaporating the extract, too small amounts of the pure product remained.

The real triumph of science was the artificial synthesis of adrenaline, carried out for the first time by Friedrich Stolz and, independently of him, by Kh. D. Dakin. Friedrich Stolz worked for the Holkest company. In 1904, the laboratory of the pharmaceutical company "Holkest" launched the industrial production of adrenaline by chemical synthesis, which began to be produced under the trade name "Suprarenin". The advantage of an artificial preparation was that, due to the constancy of its composition and purity, it can be dosed more accurately. In addition, it stored better and did not have many of the side effects of natural adrenaline preparations. The synthesis of adrenaline soon led to the establishment by Ernst Josef Friedmann in 1906 of its exact structural formula⁶.

Of great importance for the further spread of the medical use of adrenaline was the proposal of the Leipzig surgeon Heinrich Braun to use adrenaline for local anesthesia by adding it to a cocaine solution. In 1902, Brown introduced the method of adding adrenaline to cocaine solutions into clinical practice and showed that this agent endows anesthetic solutions with exceptionally valuable properties: it enhances the anesthetic effect of cocaine and increases the duration of pain relief. At the same time, the risk of general intoxication with cocaine is significantly reduced, since the slowdown in the absorption of the solution prevents excessive intake of cocaine into the blood.

In addition, the vasoconstrictive effect of adrenaline causes vasospasm and, consequently, anemia in the area of the surgical field, which reduces bleeding during surgery and improves the conditions for examining the surgical field.

All these properties proved to be extremely valuable, and to this day, an indispensable requirement for every new local anesthetic is the ability to combine it with adrenaline.

⁴Grevesen J. V., Kirkegaard H., Kruse E., Kruse P. R. "Early achievements of the Danish pharmaceutical industry", *Theriaca*, 2016, N (43), P. 9-61 [in English].

⁵Boyanova L. "Stress hormone epinephrine (adrenaline) and norepinephrine (noradrenaline) effects on the anaerobic bacteria", *Anaerobe*, 2017, Apr, N 44, P. 13-19 [in English].

⁶Sheikh A., Shehata Y. A., Brown S. G., Simons F. E. "Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock", *Cochrane Database Syst Rev*, 2008, Oct 8, 2008, N 4 [in English].

Adrenaline has also found wide application in other areas of medical practice: in surgery – to stop bleeding; in therapy – to stimulate alpha – and beta-adrenergic receptors in various diseases and for relief, for example, attacks of bronchial asthma; in endocrinology – with an overdose of insulin (with hypoglycemic coma); in ophthalmology – to lower intraocular pressure in glaucoma in the form of eye drops, in otorhinolaryngology – as vasoconstrictor drops for rhinitis and nosebleeds; in allergology – with laryngeal edema and with immediate allergic reactions caused by drugs, sera and other allergens; in anesthesiology and resuscitation – with allergic reactions during anesthesia, cardiac arrest, to eliminate atrioventricular blockade.

Conclusions. The study of historical information about the discovery of hormones forms a holistic view and expands knowledge in the field of physiology and pathophysiology of the endocrine system.

Савчук Тетяна, Ковпак Альона, Семененко Наталія. Історія відкриття адреналіну. Назви більшості нейромедіаторів мало відомі пересічному громадянину. Але згадка про адреналін відразу породжує цілу бурю асоціацій. У чийсь голові виникне профіль Джейсона Стетхема з однойменного фільму. **Мета статті.** Адреналін став символом чогось ризикованого та по-своєму привабливого, але що таке адреналін з погляду нейрофізіолога – мета пропонованої статті. У низці досліджень було показано, що у спортсменів під час тренувальних та змагальних навантажень посилюється активність симпат-адреналової та гіпоталамо-гіпофізарно-надниркової систем. У цьому випадку спостерігається активація фізичного навантаження механізмів загальної адаптації, що призводить до змін у гормональному спектрі, що забезпечує мобілізацію як енергетичного, так і пластичного резерву організму, а також його відновлення. Одна з груп стресових гормонів виробляється мозковим шаром надниркових залоз і називається катехоламінами. До цієї групи входять гормони адреналін та норадреналін. Обидва гормони синтезуються з амінокислоти тирозину під впливом нервових імпульсів. Головним гормоном цієї групи є адреналін. Ми поставили за мету вивчити історичні етапи, які передували відкриттю гормонів наднирників, застосовуючи порівняльний та історичний методи. **Актуальність дослідження.** У 1894 р. Джордж Олівер та Едвард Шефер продемонстрували

вазоконстрикторний (судинозвужувальний) та пресорний ефект витяжки з надниркових залоз. Важливу роль в дослідженні властивостей адреналіну відіграло передбачення хірурга з Лейпцига Генріха Брауна, про можливість застосування адреналіну при місцевій анестезії. Так адреналін, здобув широкого застосування в анестезіології, що залишається актуальним до сьогоднішнього дня. **Висновки.** Вивчення історичних відомостей про відкриття гормонів формує цілісне уявлення і розширяє знання в галузі фізіології і патофізіології ендокринної системи.

Ключові слова: адреналін, історія нейрофізіології, відкриття нейромедіаторів.

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