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The history of uncovering of enzymes inactivating catecholamines

HISTORICAL OUTLINE AND THE MOST IMPORTANT EVENTS CONCERNING THE DISCOVERY OF ENZYMES

Until the 19th century *vis vitalis* theory dominated among scientists. It said that natural compounds can be produced only by living organisms which have living power to do it (1). In 1897 Buchner accidentally discovered zymase by the experiment in which he showed that crashed yeast (without cells) caused fermentation. It was undeniable proof that chemical substance without any vital characteristics can be responsible for biochemical transformations. Buchner's experiment finally abolished *vis vitalis* theory (2). Great significance for development of biochemistry had the discovery and analysis of hormones and vitamins. Hormone research was initiated by Cybulski in 1897 by discovery of epinephrine (1).

One of the basic features of living organisms is performing of complex chemical reactions with high velocity at the room temperature. It is possible due to the presence of enzymes – protein catalysts. For a long time man unwittingly encountered enzyme activity for example: during beer or wine production, cheese making, food rotting. First experiments showing the presence of and explaining enzyme functions were conducted by Rene Reamur and Lazzaro Spallanzani. Reamur examined the dissolving process of meat wrapped in gauze which was placed in the stomach of a vulture (1). Spallanzani is known for numerous experiments in various scientific fields. He gained the greatest publicity by examination of stomach juice conducted in 1783. Stomach juice was retrieved from stomach due to a sponge tied up with thread. The sponge was swallowed and after some time it was pulled out from the stomach. He found that stomach juice dissolved meat but did not dissolve flour. Too low development level of chemistry of the time did not let better examine digestive juices and their role in living organisms. Theodor Schwann discovered pepsine in stomach juice and demonstrated its ability to split proteins. The 30s of the 19th century were a crucial breakthrough in enzymes research. In 1830 Edmont Dubrunfaut showed that malt extract changed sucrose into simpler sugar. Three years later Anselme Payen and Jean Persoz isolated the substance from malt extract which catalyzed the disintegration process of sucrose. This substance was called diastase. Only at the end of the 19th century scientists proved that the living organism owed specific abilities of synthesis and lysis to catalysts produced in specific cells (2). In 1836 Jöns Berzelius announced the classic theory of chemical catalysis and some time later Ludwig Pasteur and Wilhelm Kuhne started the research on enzymic catalysis (1). In 1897 W. Kuhne introduced the word enzyme. In 1897 Buchner brothers performed alcoholic fermentation *in vitro* using liquid extracted from yeast. In 1906 Arthur

Harden stated that enzymes co-operated with non-protein substances which he called coenzymes. In 1914 Kirchhoff carried out hydrolysis of sucrose using malt extract. In 1926 James Sumner obtained urease in crystalline state. In 1953 primary structure of ribonuclease was established.

THE HISTORY OF AMINE OXIDASE (MAO) DISCOVERY

Amine oxidase is one of the enzymes which catalysed transformations of neurotransmitters, amines supplied to organisms in diet and xenobiotics to inactivated compounds (3). The history of amine monoaminoxidase dates back to the 19th century. H. Blashko announces that amine oxidase was discovered by one of the creators of contemporary pharmacology Oswald Schmiedeberg in 1877. He stated experimentally that benzylamine was excreted in urine as hipuric acid (4), whereas T. Slotkin suggests that 26-year old doctoral student Mary Bernheim is the discoverer of MAO. Bernheim examined the liver of a rabbit and described the new mechanism of oxidation, different than known so far. She claimed that a principal role of tyramine oxidase was metabolizing potentially toxic amines originating from bacteria absorbed by the organism from intestines (5). The first name of hypothetic enzyme which deaminates the epinephrine, epinephrine oxidase, was introduced by H. Blaschko in 1937. A year later E. Zeller suggested the currently used name – monoaminoxidase (4). Blaschko's and Zeller's work indicated that substrates in this reaction are also catecholamines and histamine. Therefore they changed the name of enzyme for this currently functioning (6, 7). The discovery of MAO evoked huge interest in monoamines, particularly in the 50s of the 20th century when scientists observed psychotropic activity of antituberculotic drug – iproniaside which consisted in changes in mood (5). In the 50s and 60s of the 20th century the attempts of antidepressive properties of iproniaside and other inhibitors of MAO were performed. This drug turned out impossible to be used in medical practice regardless of toxic activity of iproniaside on liver and interactions with other drugs and some foods rich in tyramine ("cheese reaction", "cheese effect"). Various kinds of cheese, alcoholic beverages, salami, sauerkraut stew, soya sauce contain huge amounts of tyramine. Tyramine and other amines present in food that act sympathicomimetically are metabolised in the presence of MAO to inactivated metabolites. Sympathicomimetic amines release norepinephrine from synaptic vesicles, which involves occurrence of dangerous hypertensive crises (8). M. Sandler and A. Davison first examined and described MAO in the human organism in 1956. Looking for the reason of occurring carcinoid syndrome in a hospitalized patient, caused the beginning of oxidase amine examination (9). J. Johnson advanced the hypothesis that MAO exists in a few forms. We can distinguish two forms of MAO in brain and majority of tissues on the basis of enzyme affinity to clorgiline (inhibitor) (10). MAO is the mitochondrial enzyme having two isoforms: A and B (11). This classification is the result of different chemical structure, different tissue localization, substrate preference and occurrence of the specific inhibitors. The role of isoenzymes has not been revealed completely yet, though it is known that they influence the regulation of circulation and proper using of biogenic amines (12, 13). MAO-A form catabolizes dopamine, serotonine and norepinephrine. It is irreversibly inhibited by clorgiline (10). MAO-B form is specific to dopamine, phenyltylamine and benzilamine. It is irreversibly inactivated by pargiline and dephrenyle (14). Both isoenzymes can be found in fibroblasts and brain tissue. The highest concentration of MAO-A is in the nucleus of *locus cinereus* (in dopaminergic and noradrenergic neurons), striatum and grey matter. MAO-B is located mostly in striatum and grey matter (mostly in serotonergic neurons). There is more MAO-B form than MAO-A in the brain (13, 15). MAO-A form is present in trophoblast and MAO-B is present in blood platelets and lymphocytes (16). MAO has various isoenzyme expression during human ontogenic development: MAO-A appears before MAO-B activity in brain tissue of foetus, but MAO-B activity is higher in adult brain tissue (17). Formerly it was claimed that low MAO activity is an important factor predisposed to schizophrenia development (18). Low level of MAO may be connected with different forms of behavioral disorders.

THE HISTORY OF O-METHYLOTRANSPHERASE CATECHOLAMINE (COMT) DISCOVERY

There is little data concerning the discovery of O-methylotranspherase catecholamine (COMT) in medical literature. It is known that COMT-cytosolic enzyme was discovered by Axelrod and Tomchick in 1958 (19). The first research of COMT was performed by analysis of epinephrine and norepinephrine metabolism in rabbit by Axelrod (20, 21). Then it was discovered that dopa (22, 23), dopamine (20), xanturic acid (24) and estradiol (25) are excreted in urine as O-methylated metabolites. These observations could indicate that COMT had critical significance in catecholamine metabolism. Axelrod suggested that COMT acted locally in these organs that contained norepinephrine and epinephrine which caused transformation of these hormones (19). COMT is found in many tissues and is responsible for inactivation of norepinephrine, epinephrine and dopamine. It catalyzes binding the methyl group to benzene ring of various catecholamines usually in the third position.

There are two forms of this enzyme coded by the same gene: soluble form (S-COMT) and connected to the membrane (MB-COMT) (26). MB-COMT form is most often present in brain tissue (27), and S-COMT form is present in the liver, blood and kidney (28). COMT activity is 20–30% lower for women than for men (29). The lower COMT activity is also found in erythrocytes of people who suffer from schizophrenia or schizophrenia-like psychoses (30). Together with MAO, COMT takes part in the pathogenesis of hypertension. Interest in COMT as a gene determining the appearance of mental disorders appeared together with discovery of velo-cardiac-facial syndrome (VCFS) (31). This syndrome is a congenital disorder that consists in microdeletion among the 22q11.2 chromosome and is characterized by physical anomalies and increased incidence of mental disorders particularly of schizophrenia, bipolar disorders and deficiencies of concentration (32).

THE HISTORY OF RENALASE DISCOVERY

Recently Jianchao Xu et al. (2003) described a renalase in order to identify novel proteins secreted by the kidney. It is a flavin adenine dinucleotide-dependent amine oxidase (33). The kidneys are the major source of circulating renalase, but renalase gene and protein expression are also detectable, at lower levels, in heart, skeletal muscle, and small intestine. The skeletal muscle expresses high renalase levels, which suggests that the enzyme may play an important role in regulating local and perhaps systemic catecholamine concentration (34). Renalase circulates in an inactive form – prorenalase. Prorenalase is rapidly (30–60 s) activated by increased plasma catecholamines and systolic blood pressure. Catecholamine administration promotes the secretion of preformed renalase within 5 min. Plasma renalase is markedly reduced in patients with chronic kidney disease and end-stage renal disease (35).

Renalase degrades catecholamines, regulates cardiac function and systemic blood pressure. Renalase specifically metabolizes cathecholamines, with dopamine being the preferred substrate, followed by epinephrine, and then norepinephrine. The plasma concentration of renalase is markedly reduced in patients with end-stage renal disease, as compared with healthy subjects (34). Abnormalities in the renalase pathway are evident in animal models of chronic kidney disease and hypertension (36). The renalase might be an important regulatory factor also in human (patho)physiology. Previous investigations were found catecholamines to be stable in human plasma, provided autoxidation is prevented by an antioxidant. The claim of catecholamine-metabolising activity of renalase is based on the generation of H_2O_2 during incubation of the enzyme with catecholamines. The rate of H_2O_2 generation is far too low to be ascribed to enzymatic conversion of catecholamines by renalase (37). Its discovery may provide novel insights into the mechanisms of blood pressure regulation and the pathogenesis of essential hypertension (38).

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SUMMARY

O-methylotranspherase catecholamine (COMT), amin oxydase (MAO) and renalase are the enzymes which catalyse chemical reactions of biogenic amines such as norepinephrine, epinephrine and dopamine. They play a crucial role in pathogenesis of mental disorders (schizophrenia, affective disorders, some forms of alcohol dependence, personality disorders), but also they can regulate cardiac function and systemic blood pressure. The history of amine monoaminoxidase dates back to the 19th century. M. Sandler and A. Davison first examined and described MAO in the human organism in 1956. J. Johnson advanced the hypothesis that MAO exists in a few forms: MAO-A and MAO-B. There is little data concerning the discovery of COMT in medical literature. It is known that this enzyme was discovered by Axelrod and Tomchick in 1958. There are two forms of this enzyme coded by the same gene: a soluble form (S-COMT) and the one connected to the membrane (MB-COMT). In 2003 renalase was described, in order to identify novel proteins secreted by the kidney. This enzyme circulates in an inactive form (prorenalase) and may play an important role in regulating catecholamine concentration.

Historia odkryć enzymów inaktywujących katecholaminy

O-metylotransferaza katecholowa (COMT), oksydaza aminowa (MAO) i renalaza są enzymami uczestniczącymi w metabolizmie katecholamin, takich jak noradrenalina, adrenalina i dopamina.

Enzymy te odgrywają ważną rolę w patogenezie zaburzeń psychicznych (schizofrenii, zaburzeń afektywnych, niektórych postaci uzależnienia od alkoholu, zaburzeń osobowości), ale także regulują pracę serca i ciśnienie krwi. Historia monoaminooksydazy sięga XIX wieku. M. Sandler i A. Davison jako pierwsi zbadali i opisali MAO u człowieka w roku 1956. J. Johnson wysunął hipotezę, że MAO istnieje w kilku formach: MAO-A i MAO-B. W literaturze przedmiotu badań można znaleźć niewiele danych dotyczących odkrycia COMT. Ten enzym został odkryty przez Axelroda i Tomchicka w roku 1958. Istnieją dwie formy enzymu kodowane przez ten sam gen: postać rozpuszczalna (S-COMT) i związana z błoną (MB-COMT). Renalaza została opisana w roku 2003 w związku z poznawaniem białek wydzielanych przez nerki. Enzym ten obecny jest w ustroju w nieaktywnej formie (prorenalazy) i może odgrywać ważną rolę w regulacji rozmieszczenia katecholamin.