

## The heart's own acetylcholine important in health and disease

Tissues and organs of our body are under the control of active chemical compounds. Hormones are released from endocrine glands and reach the targets with blood. Transmitters are released from the endings of nerve fibers. If the ending contacts other nerve cell (neuron) the released compound transmits excitatory or inhibitory signals between the cells. The endings may also contact non nerve cells like those of skeletal muscle or heart. The released compounds change the function of their targets.

The heart is innervated by two components of the autonomic nervous system: parasympathetic represented by the vagus nerves and sympathetic. The transmitter released from the endings of vagus nerves is acetylcholine, the ester of choline and acetyl-coenzyme A. Acetylcholine decreases the rate of heart beating and decreases the force of its contractions. The sympathetic nerves release noradrenaline, which exerts the action opposite to that of acetylcholine.

It has been generally believed that the only sites of synthesis and release of acetylcholine in the heart are the endings of vagus nerves. However, since the first half of the twentieth century experimental evidence was accumulating suggesting that acetylcholine is synthesized and released in the heart even when vagus nerves are not active, and that it is tightly connected with the heart beats. This evidence was largely neglected and forgotten since the present century when the modern methods enabled to prove that cells of the heart muscle (cardiomyocytes) are equipped with all chemical machinery necessary for synthesis of acetylcholine which is eventually released into the intercellular space. There acetylcholine bounds to its receptors on the outer surface of the cells membranes leading to the changes in cells functioning. It has been also proved that cardiomyocytes are the main source of acetylcholine in the heart and that small amount of acetylcholine released from the nerve endings stimulates synthesis and release of large amount of acetylcholine in the myocytes ( amplification system).

The non-neuronal acetylcholine affects several important functions and properties of cardiomyocytes:

It reduces the cardiomyocytes demand of oxygen rendering them more resistant to the reduced oxygen supply which may result from the obstruction of coronary arteries by atherosclerosis. The area of experimental infarction was reduced by ~50% in animals in which cardiomyocytes acetylcholine synthesis was largely increased by genetic manipulations.

It controls growth of cardiomyocytes. They increase their volume (hypertrophy) in animals in which acetylcholine synthesis has been eliminated. Cardiomyocytes are hypertrophied when the heart is mechanically overloaded for example in arterial hypertension.

Cardiomyocytes of animals devoid of acetylcholine synthesis are more susceptible to the

overload. Hypertrophy of cardiomyocytes may lead to the heart failure. So the non-neuronal acetylcholine contributes to prevention of heart failure.

It is necessary for the balance between parasympathetic and sympathetic heart innervation. In the heart failure parasympathetic tone is decreased, and sympathetic increased.

This lead to the concept that patients suffering from the heart failure might benefit from restoring the proper parasympathetic/sympathetic balance. This was accomplished first in experimental animals and eventually in patients by chronic stimulation of vagus nerves with the electrodes connected to miniature implantable stimulators. Results obtained in relatively small groups of patients are mildly optimistic as the heart function and the life comfort improved in majority of them. The clinical observations are continued.

The story of non-neuronal heart's acetylcholine illustrates how the seemingly theoretical investigations lead to the practical solutions. Moreover, it contributes to the growing evidence that active compounds when discovered seem to have very precise and unique site of synthesis and function but with time it appears that they have multidirectional activities (pleiotropism).

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