

HEART AS AN ENDOCRINE ORGAN

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Keywords: Natriuretic peptide, heart failure, blood pressure.

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Summary

The heart produces two major hormones, A- and B-type natriuretic peptides (ANP and BNP), which are synthesized and secreted in response to increased workload of the heart. Their main function is to alleviate cardiac load by decreasing the amount of extracellular fluid and lowering the blood pressure. They also limit the development of cardiac hypertrophy and fibrosis, severe consequences of prolonged overloading of the heart. ANP and especially BNP can be used as drugs in the treatment of acute heart failure. Finally, increased circulating levels of ANP and BNP or their propeptides can be used as sensitive markers of impaired cardiac function.

1. Introduction

The heart is a muscular pump which circulates blood to facilitate oxygen and nutrient supply to the tissues and the disposal of waste. Heart function is essential for life; even a short cardiac arrest results in the loss of consciousness, and death usually ensues within minutes.

The vertebrate heart consists of four chambers, the relatively thin-walled right and left atria and the robust right and left ventricles. The arrangement is, however, not invariable: in the fish heart, for example, there is only one atrium and one ventricle. The atria are primer pumps which help the ventricle to fill. The right atrium receives "used" deoxygenated blood from the veins and pumps it to the right ventricle which in turn generates the force required to circulate blood through the lungs. The amount of filling of the ventricle (or the atrial pressure) is called the preload. While passing the lungs the blood is rejuvenated with oxygen and purified from the carbon dioxide produced by

tissue metabolism. The well-oxygenated blood enters the left atrium which pumps it further to the left ventricle. Finally, the left ventricle has to work hard to be able to pump blood to the peripheral tissues against the high pressure of the aorta. This arterial resistance is called the afterload of the ventricle.

The heart receives both sympathetic and parasympathetic fibers of the autonomous nervous system. Sympathetic stimulation increase and parasympathetic stimulation decrease the heart rate and the force of contraction. Hormonal signals from elsewhere in the body can regulate heart function, too. For example, hormones of the adrenal medulla stimulate heart electrical activity and contractions. Endothelin, a hormonal substance produced by the endothelium, the inner cellular lining of the cardiovascular system, is an inducer of growth and function of vascular smooth muscle and cardiac muscle. On the other hand, the heart itself appears to produce and secrete hormones which regulate cardiac function, blood pressure and fluid balance. Thus, both the blood vessels and heart are capable of regulating the cardiovascular system by means of hormonal signals. This review will concentrate on the role of the heart as a source of hormones, rather than as a target of them.

2. Adaptation of the Heart to Increased Load

The heart appears to be a self-regulated pump—pumping into the arteries increases in proportion to the filling of the heart from the venous side. This has its costs and limits. The oxygen consumption of the heart is directly related to the amount of blood it pumps, and also to the pressure against which the ventricles (especially the left) have to work. Heart failure is a condition in which the heart cannot pump all the blood it receives without increasing the filling pressure. This is a serious consequence of many cardiovascular diseases, such as hypertension and valvular defects, but it can also occur in otherwise healthy people. In fact, during maximal exercise tests, transient "heart failure" usually marks the limit of performance of a healthy person.

Fortunately, the heart is not helpless in the face of increased demand for pumping blood. In the short term the stroke volume and heart rate can increase greatly, raising the cardiac output up to seven times higher compared with the basal resting level. Prolonged elevated load increases the muscle mass of the heart, i.e. it causes cardiac hypertrophy. Because mature cardiac muscle cells cannot divide, hypertrophy results from increased muscle cell size rather than cell number.

Initially this is a beneficial adaptive change which increases the pumping capacity of the heart. Eventually, however, it leads to reduced cardiac function and dire consequences, especially if the supply of oxygen or nutrients to the cardiac muscle cells is compromised. Increased muscle cell mass raises the oxygen consumption and therefore predisposes the hypertrophic heart to ischemia, lack of oxygen. It also makes the heart more susceptible to arrhythmias. Moreover, the amount of cardiac connective tissue increases hand in hand with increased muscle cell mass causing cardiac fibrosis. This makes the heart stiffer and therefore more difficult to fill, a condition known as diastolic heart failure. In the long run a perhaps more constructive response of the heart to increased load is to send hormonal signals which cause physiological reactions that reduce cardiac load.

3. Discovery of Cardiac Hormones

In addition to being a pump the heart has also been found to have an endocrine function, i.e. it sends hormonal signals which cause changes in the function of other organs and cells of the body. While many hormones which are also produced elsewhere in the body can be found in the heart, natriuretic peptides appear to be the only ones that are characteristically cardiac hormones.

In retrospect it can be seen that electron microscopical studies had hinted for a secretory, perhaps endocrine, role for the heart as early as the 1950s and 1960s. The Canadian scientist Adolfo de Bold, however, is the real discoverer of the endocrine heart. He found in the early 1980s that injection into rats of acid extracts of cardiac atria caused briskly increased output of water and sodium to the urine, i.e. diuresis and natriuresis, and lowered the blood pressure. He and his compatriot Geoff Flynn rapidly isolated and characterized the novel 28-amino acid peptide hormone responsible for the activity. They initially named it cardionatrin, but nowadays it is called atrial natriuretic peptide or A-type natriuretic peptide (ANP). A few years later, two related peptides, B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) were isolated. BNP is a 32-amino acid peptide in humans, and it is mainly produced by the heart ventricles. The 22-amino acid CNP is not, however, a cardiac hormone in mammals. Rather, it is distributed in low concentrations in many tissues. Similar peptide hormones can be found in all vertebrates, and functional studies have shown that they serve important well-conserved regulatory functions. The structures of the genes encoding the natriuretic peptides are known. On the basis of the structures it seems clear that they belong to the same peptide family which has risen by repeated gene duplications. Of the mammalian hormones, CNP is structurally the most conserved and appears to be the most ancient, perhaps representing the parent peptide. ANP is also highly conserved in different species, whereas the structure of BNP varies to a surprising degree. The structure of BNP, for example, sometimes bears more resemblance to ANP of the same species than to BNPs of other species (see Figure 1).

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Biographical Sketch

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