Biochemical assessment of Certain adipokines in SVT Cardiac Arrhythmia cases

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Abstract
Cardiac arrhythmias can be serious, life threatening, and can impose a significant burden on healthcare systems. The supraventricular tachycardia (SVT) is a term used to refer to a category of arrhythmias that involve or are located above the atrioventricular node. there is growing evidence that localized fat accumulation, its function, and its endocrine consequences are more significant when assessing the risk of the development of a wide range of a heart disease.In this review, the key adipokines' roles in the such cases will summarize.

Introduction

Cardiac Arrhythmia, Basic Mechanisms:

Arrhythmia is a heart rhythm disorder in which the heartbeat is irregular, too slow, or too fast. In general, arrhythmias result from abnormalities in impulse initiation, impulse conduction, or a combination of both (1). Abnormal impulse initiation can be caused by either automaticity or triggered activity in the heart, while abnormal impulse conduction could lead to reentry. Cardiac arrhythmias are alterations of the normal cardiac rhythm, and the sequence of activation. During an arrhythmia episode, the heart rate can increase (tachycardia, above 100 beats/min), decrease (bradycardia, below 60 beats/min) or became irregular. Of particular interest for this review is an idiopathic ventricular tachycardias (VTs) which are tachycardias originated in ventricles with the absence of any significant structural disease. The most common way to diagnose an arrhythmia is by evaluating the patients ECG (2)

Supraventricular tachycardia (SVT):

It is a heterogeneous group of arrhythmias used to describe tachycardias that involve cardiac tissue at the level of the bundle of His or above. The prevalence of SVT is 2.25/1000 persons with a female predominance of 2:1 across all age groups (3). SVT increases patient morbidity, particularly when symptoms are frequent or incessant. It is a common cause of hospital admissions and can cause significant patient discomfort and distress. The most common SVTs include atrioventricular nodal re-entrant tachycardia, atrioventricular re-entrant tachycardia and atrial tachycardia. In many cases, the underlying mechanism can be deduced from electrocardiography during tachycardia, comparing it with sinus rhythm, and assessing the onset and offset of tachycardia. supraventricular arrhythmias have a narrow QRS complex because there's a rapid excitation of the ventricles, which means the arrhythmia is originating above or within the bundle of His. (4)

Early life factors may be involved in the pathogenesis of arrhythmia (5) Obesity was associated with an increased arrhythmia risk in community- and population-based cohort studies, and in cardiothoracic surgery cohorts, independent of type of cardiac surgery (6).

Adipose tissue itself may be directly involved in the pathogenesis of cardic disease, considering that obesity has been associated with generalized enlargement of fat depots, involved in the production of pro-inflammatory cytokines and reactive oxygen species and uncontrolled release of fatty acids (7). Cardiac adiposity is characterized by an increase in intramyocardial triglyceride content and an enlargement of the fat tissue surrounding the heart and vessels, which can lead to myocardial damage. Fatty acid infiltration and overload promotes fatty acid oxidation, accumulation of triglycerides and metabolites which can impair calcium signaling, beta-oxydation and glucose utilization, damage mitochondrial function with increased production of reactive species, proapoptotic and inflammatory molecules (8) . Fatty infiltration or "fatty metamorphosis" can induce abnormal automaticity from degenerated myocardial cells (9).

Epicardial fat tissue modulates atrial electrophysiological and contractive properties, through inflammatory cytokines, adipocytokines and adipocyte-cardiomyocyte interactions, and heart failure epicardial fat has a greater arrhythmogenic effect on the left atrium, prolonging action potential duration (10). Epicardial adipose tissue was also suggested to be involved in the maintenance of atrial fibrillation (11). The right atrium is more resistant to hypoxia/ reoxygenation than the left atrium, due to higher heat shock proteins (12). Several experiments showed that epicardial adipocytes modulate atrial cardiac ionic currents with decrease of delayed rectifier inward and outward currents and increase of late sodium currents and L-type calcium currents (13).

Increased intracellular lipid content can impair repolarization due to a decrease in potassium channel protein levels, causing ventricular

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tachycardia and sudden cardiac death (14). Adipocytokines from epicardial fat significantly decrease delayed rectifier outward currents in cardiomyocytes, prolonging action potential duration and facilitating triggered activity with early after depolarizations (15).

Arrhythmia detection Tools, New Proposed biochemical markers (Adipokines)

Adipose tissue is a highly active organ that is now recognized to be an active participant in energy homoeostasis and physiological functions such as immunity and inflammation. Adipose tissue is known to express and secrete a variety of products known as "adipokines", including leptin, adiponectin, resistin and visfatin. The release of adipokines by either adipocytes or adipose tissue-infiltrated macrophages leads to a chronic sub-inflammatory state that could play a central role in the development of many associated cardiovascular disease (16)

Moreover, it expresses a wide range of receptors, which causes it to respond to numerous metabolic and endocrine stimuli involved in modulating blood pressure, glucose metabolism, inflammation and atherosclerosis (17).

1.4 Chemerin

Chemerin, a chemokine highly expressed in liver and white adipose tissue, was initially described as a protein with a complex immune system function. Parallel lines of investigation also support the notion that chemerin as a novel adipokine regulates adipocyte development and metabolic function as well as glucose metabolism in liver and skeletal muscle tissues. A growing body of human experimental data indicates that serum chemerin levels are elevated in patients with obesity and that they exhibit a positive correlation with various aspects of the metabolic syndrome. Thus, the role of chemerin in inflammation and metabolism might provide a link between chronic inflammation and obesity, as well as obesity-related disorders such as type 2 diabetes and cardic disease (18) (19).

Chemerin in cardiovascular disease

Chemerin performs various functions as a growth factor, chemokine and as an adipokine in vascular disease complications. Ferland and Watts proposed that Chemerin may be considered a growth factor in addition to its previously known chemo- and adipokine-like functions (20).

As a growth factor, Chemerin induces Matrix Metalloproteinase (MMP)-2 and -9 activities causing growth and remodelling of blood vessels, including EC proliferation, migration, and angiogenesis. Angiogenesis is another well-known and essential process in EC biology which is tightly regulated in fetal vasculogenesis and EC formation. A research group reported for the first time that Chemerin increased angiogenesis in microvascular ECs in a time, further implicating its role in human vasculature. Acting via MMP2 and -9 proteinases, Chemerin further plays an important role in vascular remodelling and regeneration (21). CMKLR1 is selectively present on the cells of the immune system and Chemerin-CMKLR1 binding stimulates the receptor and promotes chemotaxis of all leukocyte cell populations expressing CMKLR1 receptor (22).

Additionally, other reported that Chemerin promotes macrophage adhesion to extracellular matrix protein fibronectin and Vascular Cell Adhesion Molecule (VCAM)-1. It also encourages the clustering of Very Late Antigen (VLA)- 4 and -5 integrins (23) . Chemerin stimulates an increase in intracellular Ca2+ concentrations, activates Nuclear Factor-kappa (κ) B and Matrix- activated Protein Kinases (MAPK) pathways in monocytes, macrophages (24).

To date, it remains inconclusive if Chemerin is a pro- , inflammatory, and/ or an anti-inflammatory molecule as literature appear to show that it depends upon the 'type and number of enzymes involved in Chemerin cleavages , Chemerin peptides binding to one or more receptors (25).

Circulating Chemerin levels positively correlate with various factors of MetS such as high circulating glucose levels, triglycerides, high blood pressure and low levels of High-density Lipoprotein (HDL), and high Low-density Lipoprotein (LDL) levels (26).

Additionally, furthers reported that Chemerin, similar to traditional markers of arterial stiffness and carotid intima-media thickness (CIMT) including non-HDL-cholesterol and Triglyceride/HDL ratio was associated with these risk factors (27).

Increased serum Chemerin levels are reported to be positively correlated with presence of atrial fibrillation, with patients diagnosed a permanent atrial fibrillation having highest serum Chemerin concentrations compared to patients with persistent and paroxysmal atrial fibrillation (28).

Nesfatin-1

Nesfatin-1 is an 82-amino acid peptide highly expressed in several regions of the hypothalamus and later in peripheral tissues. It is derived from the protein nucleobindin-2 (NUCB2) (29). It exerts a large array of behavioral effects and acts as an integral regulator of energy balance, circadian feeding rhythm, and related endocrine functions (30). In the cardiovascular system, central Nesfatin-1 activates the nervous circuits that are responsible for hypertension (31). Endogenously expressed Nesfatin-1 was recently identified in the heart of mammals (32), suggesting that Nesfatin-1 may be an endogenous modulator of cardiac performance (33). However, the mechanisms underlying these effects of Nesfatin-1 in cardiomyocytes remain unknown.

It is a newly discovered as a adipokine, inhibits inflammatory response which is involved in the

mechanism of atrial fibrillation (AF). Inflammation is closely correlated with AF development. AF prevalence was significantly higher in individuals with inflammatory conditions (34) .

Nesfatin-1 was originally identified as a neuropeptide of the hypothalamus, which is a key integration area of the brain, where numerous neuropeptides and transmitters are released to participate in the control of essential body functions (35). Nesfatin-1 signaling in the brain has also been involved in the modulation of cardic responses potentially involved in stress adaptation, such as causing an increase in mean arterial pressure in rats (36).

Electrophysiological analyses demonstrated that nesfatin-1 hyperpolarizes the neuropeptide-Y (NPY) neurons in the arcuate nucleus (37), suggesting that the anorexigenic action of the peptide was due to an inhibition of the activity of the neurons producing the orexigen, NPY. Nesfatin-1 directly affects the membrane potential of the paraventricular neurons. It has been shown recently that nesfatin-1 immunoreactivity can be detected throughout the hypothalamus in neurons that produce vasopressin, oxytocin, melanin-concentrating hormone, and somatostatin (38).

Neuropeptide-Y is released at the sympathetic nerve terminals of the heart and inhibits vagal stimulation. It was shown that nesfatin-1 inhibits the NPY neurons in the arcuate nucleus (39).

The nesfatin-1 is involved in several inherited diseases collectively known as cardiac channelopathies. These cardiacdisorders manifest with different electrocardiographic patterns and sometimes with different clinical features, although they are often characterized by similar arrhythmic events. L-type voltage-gated Ca2+ channels (VGCC) are voltage-dependent channels that open in response to membrane depolarization, permitting entry of Ca2+ into the cell (40).

The depolarizing current through L-type VGCC contributes to the plateau phase of the cardiac action potential as well as to pacemaker activity in nodal cells (41). The influx of Ca2+ subsequently triggers the release of intracellular Ca2+ stores from the sarcoplasmic reticulum, and the ensuing intracellular Ca2+ transient results in the activation of the myofilaments, allowing cell contraction (42).

Additionally, L-type VGCC can affect other cellular processes modulated by intracellular Ca2+, including gene expression and excitation-secretion coupling (43). Therefore, alterations in density or function of L-type VGCC have been implicated in a variety of cardiovascular diseases, including atrial fibrillation, heart failure, and ischemic heart disease (44).

Altering the properties of the VGCC could have detrimental effects on cardiac electrical and contractile functions (45). Importantly, these channels are modulated by a variety of hormones, neurotransmitters, and cytokines, operating via G-protein coupled receptors and second messengers, and thereby profoundly affecting the functions of target tissue (46).

Implications and contribution to knowledge

It has been reported that Certain adipokines are strongly involved in the heart contraction. Serum nesfatin-1 & chemerin are a novel prognostic indicator of major adverse cardiac events. Circulating chemerin can improve early risk stratification for Arrhythmia patients. This study might be highlighted the relevance of these adipokines within cellular environment and link with cardiac channelopathies disease. (47)

increasing literary evidence suggests that Chemerin is strongly associated with markers of inflammation. To date, the ambiguous role of Chemerin in inducing 'inflammation' is still debatable with divided opinions.

In addition, along with studying additional Chemerin levels in human health and disease, more research is required to understanding their role. No previous study was linked nesfatin-1 & chemerin with SVT arrhythmias.

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