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Orphan Drugs 2020: Overlap of metabolic and endocrine dysregulation during orphan disease-special focus on cardiovascular disease - Prasanth Puthanveetil - Roosevelt University College of Pharmacy.

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Abstract:

Statement of the Problem: The prediction of rare diseases has always been a limiting factor related to these complications. By the time the presence of disease is confirmed the onset of disease must is prominent resulting in devastating and uncontrollable aftermaths. Understanding the complexity of events occurring during these disease conditions would offer us with a far better insight not only to treat these diseases but also to stop the debilitating effects within the respective tissues and save the organ systems or prolong or hinder the damage. This study demands the necessity for understanding the metabolic and endocrine dysfunctions during a rare disease intimately and thus not only opens up a replacement path for the scientists to explore the pathophysiological molecular mechanisms intimately but specifically help the clinicians/physicians to know therapeutic strategies.

We have focused on the micro- and macro-environments that the guts use to supply fatty acids to the cardiomyocyte. Specifically, we will discuss the cross talk between endothelial cells, smooth muscles and cardiomyocytes, and their respective secretory products that allows for this shift in metabolism. These changes will then be linked to alterations in the cardiovascular system and the augmented heart disease. The heart acts an endocrine organ has also been suggested. Secreted products from the cardiomyocytes include the natriuretic peptides atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). Both have been shown to have vasodilatory, diuretic and antihypertensive effects. These peptides have been extensively studied and their deficiency is considered to be a major cause for the initiation of cardiovascular and cardiometabolic disorders. Another secretory enzyme, lipoprotein lipase (LPL), has been implicated in diabetic heart condition. LPL is synthesized within the cardiomyocyte and secreted towards the lumen under various conditions. For example, moderate or short-term hyperglycemia stimulates the release of LPL from the cardiomyocytes towards the endothelial cells. This process allows LPL to contact lipoprotein triglycerides, initiating their break down, with the product of lipolysis translocating towards the cardiomyocytes for energy consumption. This mechanism compensates for the shortage of glucose availability following diabetes. Under prolonged, chronic conditions of hyperglycemia, there's a requirement to inhibit this mechanism to avoid the surplus delivery of FA to the cardiomyocytes, an impact that's known to induce cardiac cell death. Thus, LPL inhibition is formed possible by a FA-induced activation of PPAR β/δ, which augments angiopoietin-like 4 (Angptl4), an inhibitor of LPL activity.

Glucocorticoids include steroid hormones released from the cortex or synthetic analogues developed for various inflammatory and immune disorders. GCs are known to play an important role in maintaining the body's metabolic balance, but their irregular activity is associated with complications like Cushing's syndrome, insulin resistance, and heart disease. Conventional glucocorticoids action is from their nuclear receptor activation, but specific and non-specific membrane bound receptor mediated non-genomic actions has been reported. GCs increase AMPK phosphorylation at Thr172, in addition to augmenting AMPK protein and gene expressions. AMPK is insulin mimetic in many of its actions like glucose uptake and inhibition of lipolysis, and these properties of AMPK is made use of in conditions like insulin resistance and diabetes. Nevertheless, if AMPK is activated by glucocorticoids within the decreased insulin rate, absence of diabetes, accumulation of substrates within the type of glycogen and triglycerides could precipitate cardiac abnormalities. Glycogen storage can cause many disorders like hypertrophy, conduction system disease and Wolff Parkinson White syndrome. TG accumulation is related to generation of free radicals, ceramide formation, mitochondrial dysfunction and cardiac necrobiosis . In this review, we outline the cardiometabolic changes associated with GC, and link these changes to cardiac dysfunction.

Hypothesis and Methodology:

Wolff Parkinson White Syndrome is one among rare disease connected to the circulatory system. Multiple factors have been shown to play an important role in the etiology of this disease. A major share goes to PRKAG2 point mutation resulting in glycogen accumulation within the cardiac tissue and resulted in fibrillation in patients. Studies from preclinical data suggest that over activation of AMPK protein, the main energy sensor or metabolic switch might be playing a crucial metabolic role in bringing about this complication. Some of my previous studies using glucocorticoid excess revealed that they were able to increase AMPK. Thus using in vitro and in vivo model systems, I was able to see an increase in cardiac AMPK and glycogen accumulation. This raises the priority that the pathogenesis of Wolff Parkinson White Syndrome may result from the other route instead of just PRKAG2 conclusion.

Conclusion & Significance:

If the rate of Glucocorticoids is excess in heart, it results in uncontrollable AMPK activation with resulting glycogen accumulation in cardiac tissue. Physiological situations like fasting and stress and pathological conditions like Cushing's syndrome could result a rise in glucocorticoid excess release into the circulation. Now whether these metabolic changes related to endocrine abnormalities could end in Wolff Parkinson White like syndrome or no isn't fully studied and is one among the world I would like to shed more light upon and tried to minimize the detrimental effects.

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