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Review

The role of natriuretic peptides in diabetes and its complications

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ABSTRACT

This review aimed to summarize recent findings on the role of natriuretic peptides (NPs) in diabetes and its important complications. Although the treatment of diabetes mellitus has benefited from recent advances, aggressive glycemic control can increase the risk of hypoglycemia and weight gain. Therefore, innovative therapies are required to address this issue. Natriuretic peptides (NPs) may have such novel therapeutic potential. NPs comprise a family of structurally related peptides, including atrial, brain, C-type, and dendroaspis. Each of these NPs has a wide range of specific functions to regulate and maintain cardiovascular, renal, and endocrine homeostasis. NPs exert their effects by interacting with three receptor subtypes including NPR-A, NPR-B, and NPR-C. The coronary NP system has been suggested to be involved in regulating water and salt balance, as well as vascular remodeling. In this review, we provide evidence that NPs play an important role in diabetes mellitus and its related complications including macrovascular and microvascular disorders. NPs hold promise as markers for early diagnosis, risk assessment, and intervention guidance in diabetes and its complications and may thus improve diabetes care.

Contents

1. Natriuretic peptides and receptors

Natriuretic peptides (NPs) are a family of peptides that have similar sequences and conformations and include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP) and dendroaspis natriuretic peptide (DNP). NPs are genetically distinct and play a significant role in the maintenance of circulation, renal function and endocrine status [1–3]. ANP is produced by the heart, whereas pro-ANP is a peptide with 126 amino acids that is stored in atrial myocytes. Pro-ANP plays an important role in protecting cardiovascular and renal function by reducing blood pressure and cell fibrosis in response to cardiac overload [4]. BNP is mainly produced in the ventricle [6] but was first identified in the porcine brain [5]. Previous studies showed that BNP is more efficient than the other peptides in predicting cardiac dysfunction in patients with suspected cardiac disease [7],

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and the stress on the ventricular wall secondary to cardiac overload is also an inducer of BNP transcription [8,10]. ProBNP is cleaved to yield mature functional BNP and N-terminal fragments of proBNP, both of which may serve as markers of cardiovascular health [8,10]. CNP is primarily derived from endothelial cells, the central nervous system and the reproductive system [9,11]. CNP is known to have an important role in endochondral bone development [12]. DNP was originally isolated from the venom of the green mamba snake (*Dendroaspis augustriceps*) [13] and has more recently been identified in human serum; however, its exact localization remains unclear [14]. Previous evidence demonstrated its potential in natriuresis [15] and the relaxation of smooth muscle cells [16].

Natriuretic peptides play an important role in the maintenance of salt and water homeostasis and the regulation of vascular tone. Under certain pathological conditions, such as heart failure and acute ischemic stroke, NP levels are significantly higher [17,18]. NPs exert effects by interacting with three receptor subtypes, including the NP receptors (NPR)-A, NPR-B, and NPR-C. NPR-A and NPR-B convert guanosine triphosphate into cyclic guanosine monophosphate. NPR-A binds ANP, BNP, and DNP, whereas NPR-B activation modulates CNP. ANP is known to be more active than BNP, especially in the stimulation of lipolysis [19]. Some studies revealed that the affinity of NPR-A binding to ANP is ten-fold more than its binding to BNP [20]. However, other evidence suggested that NP receptors prefer BNP over ANP [21]. This controversy warrants evaluation in future studies. NPR-C binds ANP, BNP, CNP and DNP with similar affinity but lacks kinase and guanylyl cyclase activities. NPC-C not only plays a role in NP clearance but also mediates NP actions in cardiovascular diseases (see Fig. 1). Further studies are needed to elucidate the exact roles of NPR-C in various pathophysiological states.

2. Natriuretic peptides in diabetes and diabetes-related complications

The global burden of diabetes is projected to increase over the next few decades. Type 2 diabetes is projected to occur at a substantially earlier age compared to the present age of onset. The pathogenesis of diabetes is not clear. However, it is acknowledged to be related to insulin resistance, chronic low-grade inflammation, hereditary factors, as well as an unhealthy lifestyle. Diabetes-related complications could lead to increased morbidity, mortality, and enormous health expenditure. Therefore, an enhanced understanding of the pathophysiological progression of diabetes and its complications is critical to prevent its morbidity and mortality. Magnusson M suggested that there may be an association between serum NP levels and the risk of developing diabetes [22]. In this review, we explored the current status for the role of NPs in diabetes and its complications.

2.1. Natriuretic peptides and insulin resistance

Insulin resistance is common in patients with type 2 diabetes [23]. Many studies showed a close association between insulin resistance and NPs, especially in hypertensive elderly patients. Low NP levels have been demonstrated to contribute to an increased risk of hypertension and its sequelae in African–Americans in an Atherosclerosis Risk in Communities Study [24]. Previous data supports the hypothesis that low ANP levels increase the risk of developing insulin resistance, likely through the activation of the renin–angiotensin system [25–30]. However, chronic heart failure or hypertension leads to an increase in serum insulin, demonstrating that ANP does not interfere with insulin secretion but exclusively inhibits insulin degradation in the liver and/or kidney and other organs [31]. A clinical trial found that a higher serum NT-proBNP level is associated with higher insulin sensitivity both at baseline and during the Diabetes Prevention Program (DPP) for type 2 diabetes; this was independent of waist circumference, body mass index, and treatment. Hence, NT-proBNP may be a robust indicator of insulin sensitivity [32]. A number of epidemiological studies have demonstrated that insulin-resistant individuals who later developed type 2 diabetes tend to have lower concentrations of ANP and BNP [33–35]. The widely acknowledged role of natriuretic peptides to promote natriuresis, diuresis and vasodilation may further support their role in the development of diabetes. In patients with hypertension, insulin resistance plays a potential role in the occurrence of diminished nocturnal blood pressure fall, left ventricular hypertrophy, and increased processing of plasma ANP and BNP [36]. Moreover, hyperinsulinemia and insulin resistance have been implicated in the etiology of hypertension. The underlying mechanism could be that ANP significantly increases urinary sodium excretion but that insulin

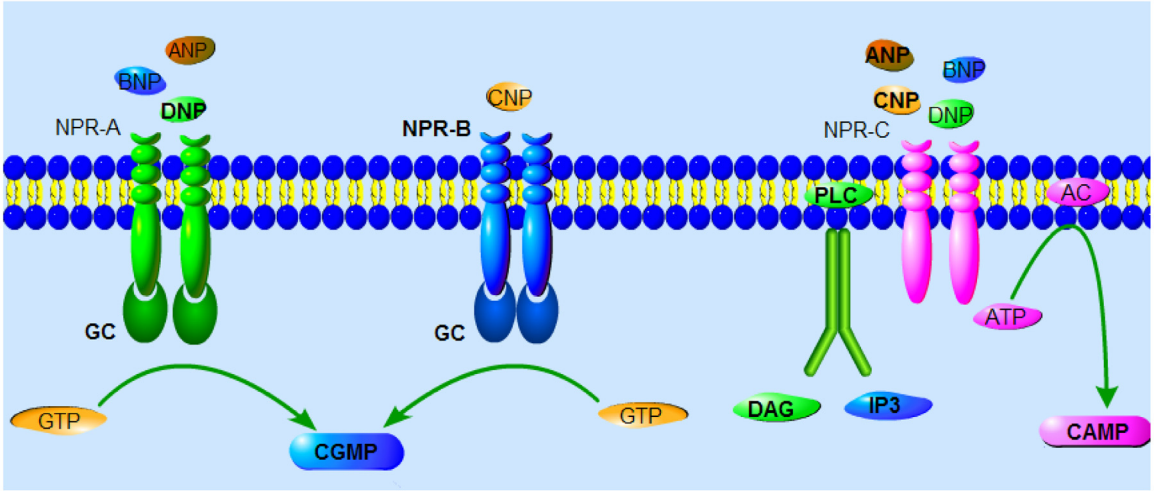

Fig. 1. The family of NPs includes ANP, BNP, CNP, and DNP. They have three receptors. NPR-A binds ANP, BNP, and DNP. NPR-B activation mediates CNP effects through guanylyl cyclase (GC). NPR-C, coupled with AC activity, produces cAMP or activates PLC to generate DAG and IP3. NPs: natriuretic peptides; ANP: atrial natriuretic peptide; BNP: brain natriuretic peptide; CNP: C-type natriuretic peptide; DNP: dendroaspis natriuretic peptide; NPR: natriuretic peptide receptor; AC: adenylate cyclase; GC: guanylyl cyclase; cAMP: cyclic adenosine monophosphate; PLC: phospholipase C; DAG: generate diacylglycerol; IP3: inositol trisphosphate; GTP: guanosine triphosphate.