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SMALL INTERFERING RNA AGAINST NATRIURETIC PEPTIDES AS ADJUVANT FOR TREATING NEPHROPATHY

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ABSTRACT

The presence of renal dysfunction in patients with diabetes mellitus affects the plasma levels of atrial natriuretic peptide (ANP). In the present study, the influence of natriuretic peptide on the plasma levels of BNP and ANP and their relationship in normotensive diabetic patients with normo-albuminuria and microalbuminuria is evaluated. Down-regulation of A-type guanylate cyclase-coupled receptor of renal tubules may explain the increased plasma levels of both BNP and ANP in normotensive diabetic patients with microalbuminuria. A novel approach to treat this serious disorder by using siRNA is envisaged.

Key Words: ANP, BNP, Nephropathy, SiRNA, Kidney, Heart Failure

INTRODUCTION

Atrial natriuretic peptide (ANP) and B-type NP (BNP) are endogenous hormones that are essential for cardiovascular homeostasis (Kuhn, 2003 and Garbers *et al.*, 2006). In response to cardiomyocyte stretch, ANP and BNP are released into the circulation from the heart, where they bind to their receptors in target tissues like the heart, kidneys adrenal gland, endothelium, and vasculature. NP receptor-A (NPR-A), or guanylyl cyclase-A, is the primary signaling receptor for ANP and BNP. It is a transmembrane receptor guanylyl cyclase with intracellular regulatory, dimerization, and catalytic domains (Potter and Hunter, 2001 and Tyagi and Naik, 2012). Activation of NPR-A leads to the synthesis of the intracellular second messenger cyclic cGMP, which mediates the vast majority of NP effects (Nussenzveig, Lewicki, Maack, 1990). ANP and BNP also bind the NP clearance receptor (NPR-C), which mediates intracellular NP degradation and may reduce cellular cAMP concentrations (Anand-Srivastava, 1992 and Nakao *et al.*, 1992).

The plasma levels of the atrial natriuretic peptide (ANP) were previously shown to increase in normotensive diabetic patients with microalbuminuria (Ferri *et al.*, 1994; Zietse *et al.*, 1997 and Bell *et al.*, 1989). The secretion of ANP is stimulated by increased atrial pressure associated with volume or pressure overload. However, the elevation in the plasma level of ANP in diabetic patients cannot be completely explained by increased plasma volume or elevation of the right atrial pressure (Dussaule *et al.*, 1988 and Benigni *et al.*, 1990). Natriuretic peptides like the BNP have been found to be useful in patients with contrast induced nephropathy. BNP may lower the incidence of contrast induced nephropathy by indirect mechanisms. First, early administration of BNP can protect ischemic myocardium and limit infarct size via K ATP channel opening (Zhang *et al.*, 2010), as well as increase in coronary artery diameter and decrease of myocardial oxygen uptake (Michaels, 2003).

The natriuretic response to volume expansion during saline infusion or water immersion is attenuated in diabetic patients (Trevisan *et al.*, 1990). It was previously shown that elevation of ANP is caused by down-regulation of NPR-A in target tissues, such as renal tubules (Hebden *et al.*, 1989). This study highlights the importance of using siRNA against ANP gene in refractory cases of diabetes nephropathy.

NATRIURETIC PEPTIDES AND HYPERGLYCAEMIC NEPHROPATHY

The biological effect of BNP is mediated by NPR-A in vascular tissue and renal tubular cells. BNP regulates the fluid volume and blood pressure in the systemic circulation by suppressing the reabsorption of sodium in renal tubules (Feldt-Rasmussen *et al.*, 1987). Elevation of plasma BNP levels has been

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previously described in patients with congestive heart failure, essential hypertension, or myocardial infarction. The mechanism by which the plasma levels of BNP increase in diabetic patients with nephropathy is not clearly understood. It was previously reported that vascular volume expansion is not significantly different between diabetic patients with normo-albuminuria and micro-albuminuria (Yoshimoto *et al.*, 1996) and that impairment of ANP response to volume expansion occurs in normotensive diabetic patients. These results may be explained by down-regulation of NPR-A in renal tubules. In this connection, elevation in the plasma levels of ANP was found associated with decreased mRNA levels in the kidneys of rats with hyperglycemia. Moreover, low renal response to exogenous ANP was observed in streptozotocin-induced diabetic rats with a decreased number of biological active NPR-A. In this study, the plasma levels of BNP were found to be significantly correlated with the plasma levels of ANP. Because the biological activity of BNP is also mediated by NPR-A, it is conceivable that the elevation in the plasma levels of BNP also occurs because of down-regulation of renal NPR-A in diabetic patients with nephropathy.

STRUCTURAL DEFECTS ATTRIBUTED TO INCREASED LEVELS OF NATRIURETIC PEPTIDES IN NEPHROPATHY

Diabetic nephropathy-associated structural abnormalities of glomeruli alter the charge and size selectivity in the glomerular protein filtration. Elevation of urinary albumin excretion is induced by ANP infusion in diabetic patients, probably because of the occurrence of both structural and pressure abnormalities. Because both BNP and ANP bind to the same receptor and have the same biological activity, it is conceivable that abnormally elevated levels of BNP also cause increased glomerular hydraulic pressure and thus induce increased albumin excretion in diabetic patients. However, it is postulated that the primary cause of the increased circulating levels of BNP and ANP is probably the decrease in the number of its receptors in renal tissue of patients with diabetic nephropathy.

siRNA FOR TREATING DIABETIC NEPHROPATHY

Despite a significant breakthrough in studying the pathogenesis of peripheral diabetic neuropathy and identification of multiple mechanisms contributing to this complication, there is still no pathogenetic treatment for this condition (Zhang *et al.*, 2006 and Kiemer *et al.*, 2003). siRNAs have become a powerful tool for gene silencing and have the potential to become the preferred form of treatment for cancer and infectious disease (Figure 1). Phase I results of the first two therapeutic RNAi trials (indicated for age-related macular degeneration, aka AMD) reported at the end of 2005 that siRNAs are well tolerated and have suitable pharmacokinetic properties. Proof of concept trials have indicated that Ebola-targeted siRNAs may be effective as post-exposure prophylaxis in humans, with 100% of non-human primates surviving a lethal dose of Zaire Ebolavirus, the most lethal strain (Boulton *et al.*, 2005). The combination of gene-silencing through siRNA with the greatly enhanced delivery offered by nanoparticles provides a therapeutic system with a high degree of flexibility, specificity and safety. Previously, cationic lipids were reported to successfully deliver siRNA across mucosal surfaces. siRNA can be targeted against the natriuretic peptide gene by liposomal delivery system into the blood cells like the monocytes and macrophages. There is also speculation that increased ANP level may cause increase in heat shock protein 32 (Veves *et al.*, 2008). Evidence of the importance of nitrosative stress in diabetic complications including diabetic neuropathy is emerging (Frustaci *et al.*, 2000 and Thuraisingham *et al.*, 2007) and nitrotyrosine accumulation has been identified in numerous tissue-sites for chronic complications in diabetic animal models, as well as circulation, microvasculature, myocardium, and renal proximal tubules and the loop of Henle of human subjects with diabetes mellitus (Thomas *et al.*, No year). It is quite likely that inhibition of natriuretic peptide levels by siRNA may be a useful method and adjuvant therapy for treating diabetic nephropathy in refractory conditions as nitrotyrosine a marker of peroxynitrate may

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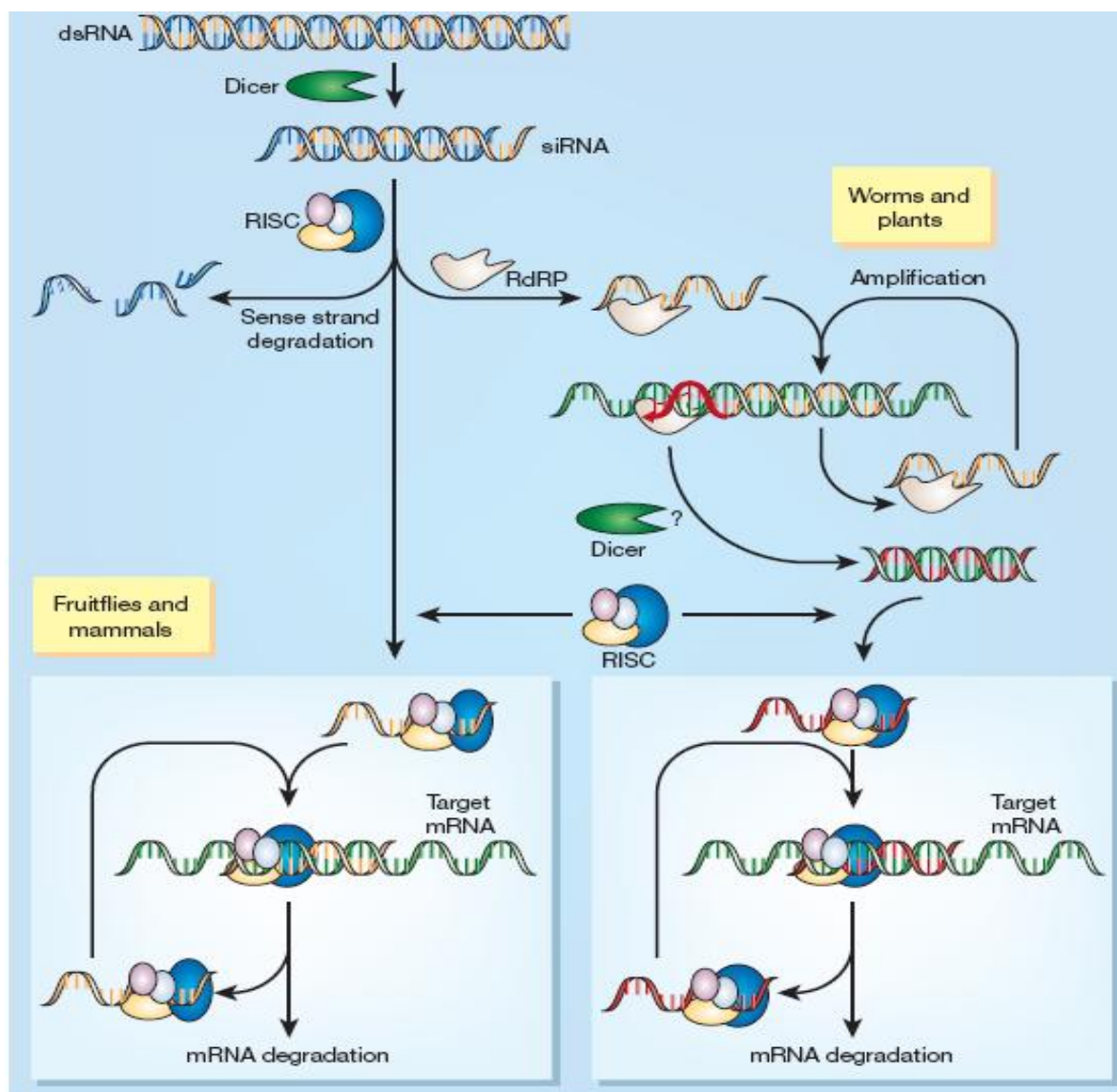


Figure 1: Mechanism of action of small interfering RNAs

be attenuated after reduction in levels of natriuretic peptides like BNP and ANP (Zhang *et al.*, 2007). More research work is required to clearly elucidate the clinical aspects of this usage.

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