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Mini-Review

Molecular Biological Researches in Sleep Apnea Syndrome (SAS) Intermittent Hypoxia

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ABSTRACT

Sleep Apnea Syndrome (SAS) exposes cells throughout the body to Intermittent Hypoxia (IH). IH resulted from SAS is a main risk factor not only for hypertension, cardiac disorders, decreased insulin secretion, and insulin resistance but also for vascular dysfunction. We have reported correlations between IH and decreased glucose-induced insulin secretion from pancreatic β-cells, insulin resistance in skeletal muscle cells and adipocytes, hypertension *via* upregulation of renin, dopamine β-hydroxylase, and phenylethanolamine N-methyltransferase, and cardiac disorders. In this mini-review, I would like to discuss the problems of IH research in SAS using most recent vascular endothelial cell dysfunction as an example.

Keywords: Sleep apnea syndrome; Intermittent hypoxia; Vascular dysfunction; MicroRNA

INTRODUCTION

Although Sleep Apnea Syndrome (SAS) affects over 1 billion people worldwide, it is a disease that is poorly researched. In medical research, there are broadly three types of research approaches:

1. Research using patients as research subjects
2. Research using disease model animals as controls
3. Research targeting cells in culture.

An easy-to-understand example of (1) is research using surgically removed organs and cells. In cancer research, removing cancerous tissues and cells is considered as “effective and/or curative treatment”, so this approach is easily accepted as appropriate. On the other hand, for diseases that do not directly lead to death (e.g., SAS), this method is extremely difficult. (2) In the case of disease models, there are animals that are genetically prone to the disease, or such animal models are created through breeding and selection. Examples include type 1 diabetes model of Non-Obese Diabetic (NOD) mice and type 2 diabetic model of Goto-Kakizaki rats [1,2]. Another example is a diabetic model using streptozotocin (2-deoxy-2-({[methyl(nitroso)amino]carbonyl}amino)-β-D-glucopyranose) or alloxan (1,3-diazinane-2,4,5,6-tetrone) administration in rats or mice [3-5]. In the case of SAS, there are no experimental animal model other than bulldogs that naturally develop this disease for anatomical reasons [6], so a method that forcibly brings the oxygen concentration in the inhaled air close to the blood oxygen concentration of SAS patients has been adopted to the extent that the animal does not die. However, the experimental animals that can be used are limited to small animals such as rats and mice due to the need to efficiently change the breeding space and the gas concentration in the inhaled air. Also, in both cases (1) and (2), it is clear that "X became Y due to SAS", but is this the effect of IH due to SAS? Or is it the effects of insomnia caused by SAS? Since we do not know the mechanism, there is a disconnect between researchers and medical practitioners who wish to clarify the mechanism. (3) Is a study in which cells are exposed to IH, the main component of SAS, and this method is necessary to elucidate the molecular mechanisms of why/how SAS causes various pathological conditions? It is possible to ensure a sufficient number of experiments and sufficient amounts of cells.

Considering these disease characteristics and the above research characteristics, we have used an experimental system in which cells are exposed to IH to elucidate the mechanisms by which SAS causes or worsens diabetes, hypertension, and

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cardiovascular disease. A typical example of vascular endothelial cell dysfunction is shown below.

INTERMITTENT HYPOXIA IN SAS

Vascular endothelial cells (human HUEhT-1 and mouse UV2 cells) were exposed to normoxia and IH. The IH conditions were the same as in previous experiments (70 cycles of 5 min hypoxia [1% O_2, 5% CO_2, and balanced N_2] and 10 min normoxia) using insulin producing pancreatic β cells, hepatocytes, neuronal cells, vascular smooth muscle cells, adipocytes, skeletal muscle cells, intestinal endocrine cells, cardiomyocytes, juxtaglomerular cells, etc. [7-16].

INCREASED EXPRESSION OF ICAM-1 AND ESM1 BY IH IN VASCULAR ENDOTHELIAL CELLS

IH exposure increased the mRNA expression of intercellular adhesion molecule-1 (Icam-1; CD54), a cell surface glycoprotein known as an adhesion receptor that directs leukocytes from circulation to sites of inflammation, and endothelial cell specific molecule-1 (Esm1; endocan), an endothelial cell-associated proteoglycan and is upregulated by proangiogenic molecules and pro-inflammatory cytokine stimulation, in vascular endothelial cells. Increased expression of Icam-1 and Esm1 by IH was also confirmed at the protein level in the culture medium [17].

INCREASED ESM1 CAUSED ICAM-1 INCREASE

In order to understand the correlation between the increased expression of Icam-1 and Esm1, we performed a knockdown experiment using small interfering RNA (siRNA) introduction for Icam-1 and Esm1, and the experiments became clear that Icam-1 expression increased when Esm1 expression increased due to IH [17].

IH CAUSED DOWNREGULATION OF MIR-181A1, RESULTING IN INCREASED ESM1 AND ICAM-1 IN VASCULAR ENDOTHELIAL CELLS

Since we found that the increased expression of mRNAs for Esm1 and Icam-1 is due to post-transcriptional regulation, we searched for microRNA (miR)s that are complementary to human and mouse Esm1 mRNAs and found that the *miR181* family (*miR-181a1*, *miR-181a2*, *miR-181b1b1*, *miR-181b2*, *miR-181c*, and *miR-181d*) were complementary to Esm1 mRNA. When we examined the expression of all the miR-181 family (*miR-181a1*, *miR-181a2*, *miR-181b1b1*, *miR-181b2*, *miR-181c*, and *miR-181d*) after IH stimulation, only *miR-181a1* was significantly decreased by IH. Therefore, when *miR-181a1* mimic was synthesized and introduced into mouse UV2 cells, the IH-induced increases in Esm1 and Icam-1 were canceled [17].

CONCLUSION

As described above, using vascular endothelial cells, we were able to clarify the IH-induced changes in Esm1 and Icam-1 gene expression and the mechanism mediated by *miR-181a1*. In the future, based on the cell-by-cell gene expression changes and their mechanisms that have been revealed in this way. We hope that by accumulating research using animal models, we will be able to advance our understanding of the entire molecular mechanism of SAS.

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