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Short Communication

Short Note on Orally Administered of Drugs into the Lymphatics Vessels

Pragya Srivastava*

Department of Cardiology, University of Medical Center, Maastricht, Netherlands

INTRODUCTION

Dietary lipids, highly lipophilic drugs, antigens, and immune cells are transported from the intestine to the Mesenteric Lymph Nodes (MLNs) *via* mesenteric lymphatics. Recently, our laboratory has shown that mesenteric lymphatic vessels are extensively branched and lymph leaks into the surrounding Mesenteric Adipose Tissue (MAT) in obese mice and humans, promoting insulin resistance. The aim of this study is to investigate the effects of obesity related mesenteric lymphatic leakage on the transport of dietary lipids (oleic acid), lipophilic drugs (cyclosporine A), and antigens (ovalbumin) from the intestine to the MLN. C57BL/6J mice were fed a Control Fat Diet (CFD) or a High Fat Diet (HFD) for up to 35 weeks, resulting in obesity and impaired glucose tolerance. 14C oleic acid, 3H-cyclosporine, or Cy5.5-ovalbumin were orally administered and plasma and tissues were collected to measure radioactivity or fluorescence levels [1].

DESCRIPTION

Accumulation of 14 C oleic acid, 3H-cyclosporine, and Cy5.5-ovalbumin in MAT was significantly increased in HFD compared to CFD-fed mice, whereas MLNs (3H-cyclosporine and Cy5. 5-ovalbumin) accumulated less or not at all. Therefore, the mass ratio of these molecules within the HE MLN compared to the MAT was significantly reduced. Obesity associated mesenteric lymphatic leakage appears to divert dietary lipids, lipophilic drugs, and antigens from the normal lymphatic transport pathway from the gut to the MLN, resulting in leakage to the MAT instead. This may contribute to known deleterious alterations in lipid metabolism, immunotherapy, and mucosal immunity in obesity [2].

Obesity has reached epidemic proportions worldwide due to sedentary lifestyles and overeating. Obesity affects virtually every organ system and increases the risk of many diseases, especially heart and metabolic diseases. A network of tissues with three main functions: Maintaining fluid balance, facilitating the absorption of dietary lipids, and regulating the immune response. In the small intestine, entry into the lymph through the first lymphatic vessels called ducts, which take up fluids, antigens, immune cells, and lipids (in the form of lipoproteins) from the lamina propria [3]. From there, the lymph is collected after pre collecting mesenteric lymph vessels that pass through the Mesenteric Adipose Tissue (MAT) and enter the Mesenteric Lymph Nodes (MLN). The lymph then flows into the mesentery and then into the thoracic lymphatic, which finally drain the lymph into the systemic circulation in the subclavian vein.

Mesenteric lymphatics are important sites for immune cell trafficking, antigen presentation, and immune cell activation. Lymphatic vessels from various regions of the intestine drain to specific lymph nodes within the MLN chain. The MLN is a highly organized structure consisting primarily of the cortex, where B cells reside, the para cortex, where T cells reside, and the medulla, where lymphoid tissue resides. Gut derived antigens or MATs derived from food, commensal microbes, or infectious agents enter the MLN either in free form or after being taken up by tissue resident APCs *via* the mesenteric lymphatics. Within the MLN, antigen presentation by APCs to resident lymphocytes regulates immune responses and tolerance induction [4].

Mesenteric lymphatics also play an important role in lipid metabolism. Dietary lipids are packaged into lipoproteins (chylomicrons) within enterocytes and transported out of the small intestine via the mesenteric lymphatics [5]. The mesenteric lymphatics and MLN are also completely surrounded and embedded in the MAT, so they interact. In addition to their physiological role, lymphatics are now involved in the pathology of many diseases, including immune and inflammatory diseases, cancer growth and metastasis, viral replication, and cardio metabolic diseases, and are active and plastic known to be involved tissue specifically [6].

CONCLUSION

Therefore, delivery of therapeutics and vaccines to lymphatic vessels and lymph nodes is gaining increasing attention as a strategy to facilitate disease management. For example, immune cells within lymph nodes are important targets, and studies have shown that lymphatic delivery can improve the efficacy of vaccines and immunotherapies. However, since mesenteric lymphatic blood flow is approximately 100 times-500 times

Correspondence to: Pragya Srivastava, Department of Cardiology, University of Medical Center, Maastricht, Netherlands; E-mail: pragyasristava@gmail.nl

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greater than lymphatic fluid, most small drug molecules are minimally absorbed into lymphatic fluid after oral administration, instead flowing through mesenteric capillaries and portal veins. Discharged through exceptions are small pro/drug molecules that are highly lipophilic (typically log P>5 and long chain triglyceride solubility >50 mg/g), which after oral administration are associated with the intestinal lipoprotein transport pathway, are associated with lymphatic transported in tubes. Furthermore, in the gastrointestinal tract, stable macromolecular structures such as antigens, proteins, and nanoparticles are transported through the lymphatics after passing through the gastrointestinal epithelium. In laboratory recently reported that both mice on a High Fat Diet (HFD) and obese humans develop highly branched and improperly structured mesenteric lymphatics.

In HFD-fed mice, this was associated with extensive leakage of lymph from branching lymphatics into the surrounding his MAT from his HFD feeding for 15 weeks. Lymphatic extravasation into the surrounding MAT has been found to promote MAT expansion and insulin resistance, demonstrating a direct link between mesenteric lymphatic dysfunction and metabolic disease. Other studies have reported alterations in lymphatic structure and/or function in obesity and other inflammatory diseases. The rats with high fructose diet induced metabolic syndrome exhibited mesenteric collecting lymphatic remodeling, including reduced lymphatic diameter and impaired pumping capacity. Similarly, collecting mesenteric lymphatics in diabetic mice has been described to be hyper permeable due to changes in nitric oxide production. In TNFΔARE mice, a model of ileitis, we found that tertiary lymphoid organs formed around the collecting mesenteric lymphatics, causing lymphatic leakage into the surrounding MAT. Furthermore, it was presented that the intrinsic permeability of intestinal collecting lymphatics facilitates the distribution of antigen and antigen bearing dendritic cells to the surrounding mat. Importantly, lymphatic leakage from the mesenteric lymphatics after acute intestinal infection results in antigen deflection and translocation of antigen loaded dendritic cells from the mesenteric lymphatics to the surrounding MATs, leading to migration to the MLN. It interfered with antigen entry and resulted in impaired immune response.

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