The Role of the Autonomic Nervous System in Atherosclerosis
Targeting the Cholinergic Anti-inflammatory Pathway in Humans and Mice

Akademisk avhandling

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av

Marcus Ulleryd

Fakultetsopponent:
Jacob Fog Bentzon, MD, PhD
Aarhus University, Dept. of Clinical Medicine, Denmark
Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain

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Marcus Ulleryd

Department of Physiology
Institute of Neuroscience and Physiology
Sahlgrenska Academy at University of Gothenburg

Abstract

The autonomic nervous system (ANS) has been implicated in numerous atherosclerosis-induced cardiovascular disease, such as myocardial infarction and stroke. Although evidence suggests a relationship between autonomic dysfunction and atherosclerotic disease, the mediating mechanisms are still elusive. Considering the inflammatory pathophysiology of atherogenesis, we have investigated the role of nerve-driven immunity in this relationship, with focus on the α7 nicotinic acetylcholine receptor (α7nAChR).

The link between ANS dysfunction, inflammation and prevalent disease was assessed in male subjects. The athero-protective effects of sympathetic inhibition and α7nAChR-signaling were investigated in atherosclerosis-prone mice, by β1-blocker treatment with metoprolol, α7nAChR-stimulation with AZ6983, or by hematopoietic ablation of α7nAChR.

Our original contribution to knowledge includes data showing that inflammation could be a mediator in the association between dysfunction in the ANS and carotid atherosclerosis in humans, and that the athero-protective effects of metoprolol may include suppression of atherogenic cytokines. Further, for the first time, we show that α7nAChR-deficiency was associated with increased atherosclerosis, whereas α7nAChR-stimulation with AZ6983 reduced atherosclerosis and modulated both innate and adaptive immune responses. The α7nAChR was identified on immune cells in human carotid plaques, and stimulation by AZ6983 inhibited cytokine production in human blood, suggesting athero-protective effects of AZ6983 also in humans.

Taken together, our findings suggest that the balance between the sympathetic and parasympathetic branch of the ANS have an impact on atherosclerosis, and that inflammation is a mediator. We propose that the α7nAChR is an interesting pharmacological target in this pathway.

Keywords: atherosclerosis, inflammation, autonomic dysfunction, ANS, alpha 7 nicotinic acetylcholine receptor, cytokines