

# The Role of the Autonomic Nervous System in Atherosclerosis

## *Targeting the Cholinergic Anti-inflammatory Pathway in Humans and Mice*

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras i Arvid Carlsson, Medicinaregatan 3, Göteborg, fredagen den 17 februari 2017, klockan 09:00

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Avhandlingen baseras på följande delarbeten

- I. Ulleryd MA, Prah U, Börsbo J, Schmidt C, Nilsson S, Bergström GML, Johansson ME. The association between autonomic dysfunction, inflammation and atherosclerosis in men under investigation for carotid plaques. *Manuscript under review*.
- II. Ulleryd MA, Bernberg E, Yang LJ, Bergström GML, Johansson ME. Metoprolol reduces proinflammatory cytokines and atherosclerosis in ApoE<sup>-/-</sup> mice. *BioMed Research International*. 2014; 548783
- III. Johansson ME, Ulleryd MA, Bernardi A, Lundberg AM, Andersson A, Folkersen L, Fogelstrand L, Islander U, Yan ZQ, Hansson GK. alpha7 Nicotinic acetylcholine receptor is expressed in human atherosclerosis and inhibits disease in mice. *Arteriosclerosis, thrombosis, and vascular biology*. 2014; 34: 2632-2636
- IV. Ulleryd MA, Panagaki D, Yang LJ, Michaëlsson E, Nilsson H, Johansson ME. The alpha nicotinic acetylcholine receptor ( $\alpha 7nAChR$ ) agonist AZ6983 reduces atherosclerosis in ApoE<sup>-/-</sup> mice and reduces inflammatory cytokines in human blood. *Manuscript in preparation*.

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# The Role of the Autonomic Nervous System in Atherosclerosis

## *Targeting the Cholinergic Anti-inflammatory Pathway in Humans and Mice*

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### 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 alpha 7 nicotinic acetylcholine receptor ( $\alpha 7nAChR$ ).

The link between ANS dysfunction, inflammation and prevalent disease was assessed in male subjects. The athero-protective effects of sympathetic inhibition and  $\alpha 7nAChR$ -signaling were investigated in atherosclerosis-prone mice, by  $\beta_1$ -blocker treatment with metoprolol,  $\alpha 7nAChR$ -stimulation with AZ6983, or by hematopoietic ablation of  $\alpha 7nAChR$ .

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  $\alpha 7nAChR$ -deficiency was associated with increased atherosclerosis, whereas  $\alpha 7nAChR$ -stimulation with AZ6983 reduced atherosclerosis and modulated both innate and adaptive immune responses. The  $\alpha 7nAChR$  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  $\alpha 7nAChR$  is an interesting pharmacological target in this pathway.

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