ROLE OF ABC-PROTEINS IN PURINE-MEDIATED PRODUCTION OF FACTORS INVOLVED IN THE PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

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Epidemiological and clinical studies suggest that several neurodegenerative diseases have also a significant vascular component. A growing body of evidence indicate a link between atherosclerotic markers and dementia including Alzheimer's disease (AD) where neuropathological studies carried out on autoptic tissues have showed cerebral arteriosclerotic changes. Increased cholesterol levels have been shown to increase the accumulation of amyloid beta (Abeta) peptides, leading to an increased formation of extracellular amyloid plaques. More recently it has been shown that Abeta and/or Abeta like peptides are also present in human atherosclerotic plaques, mainly in activated macrophages. ATP-binding cassette (ABC) transporters represent a family of membrane proteins involved in the cellular efflux of both xenobiotics and endogenous substrates including cholesterol, Apolipoprotein E (ApoE) and agents involved in inflammatory processes. Moreover, some members of this family, namely ABCA1 and ABCG1, have been recently reported to suppress amyloid precursor protein processing linked to generation of Abeta peptides and to modulate the production of ApoE. A role for P2 purinergic receptors in atherosclerosis has been pointed out given their capability of modulating the activity of leukocytes, endothelial cells and, above all, platelets. We evaluated whether P2Y1 and P2X7 activation were able to modulate the release of cholesterol (Ch) and of cysteinyl-leukotrienes (CysLTs), proinflammatory agents reported to play a role in both atherosclerosis and neurodegenerative disorders in glial cells and macrophages. Their effects on the expression of the ABC transporters involved in the efflux of these substances was also assayed. Based on our previous results on the neuroprotective effects of non-adenine based purines we then focused our attention on the possible role exerted by guanosine in the above mentioned mechanisms. Our results showed that guanosine was able to increase the efflux of cholesterol and the expression of some ABC proteins. Another important factor involved in the pathophysiology of atherosclerosis is represented by Apolipoprotein E (ApoE), indeed ApoE deficient mice have high levels of plasma cholesterol. Moreover the administration of ApoE-mimetic peptides reduces microglial activation and early inflammatory events in an animal model of AD thus suggesting its protective role also in neurological diseases. Guanosine increased the production of ApoE in both glial cells and macrophages. Thus it is possible to hypothesize that this nucleoside could provide protection against the progression of both atherosclerosis and neurodegeneration.