ABSTRACT

A2A adenosine receptor over-expression correlates with motor symptoms in Parkinson’s disease

Adenosine receptors (ARs) are seven trans-membrane domain G-protein coupled receptors named A1, A2A, A2B and A3. Adenosine, the main agonist, acting on these receptors exerts a broad spectrum of physiological and pathological functions. Adenosine production increases dramatically when there is a discrepancy between the rates of ATP synthesis and ATP utilization, for example when work load is markedly enhances or when the supply of oxygen and glucose is limiting as in ischemia. Adenosine receptors are expressed in all body tissues with different concentrations and functions. One of the most important role is explain in the regulation of inflammatory function, a field where A2AAR is an important player.

Parkinson’s disease (PD) is a pathology with a complex etiology, involving both genetic and environmental factors. The cardinal signs of PD relate to motor dysfunction, psychiatric and dysautonomic symptoms. PD is characterized by prominent loss of dopaminergic neurons in the substantia nigra pars compacta in relatively early stages of the disease, depletion of striatal dopamine, and the presence of intraneuronal inclusions called Lewy bodies. Current knowledge highlight the important role of inflammation in Parkinson’s disease. The central nervous system was supposed to be an immune privileged site, in which immune cells of the periphery could not enter or rarely entered. Today we know that peripheral immune responses can trigger inflammation and exacerbation of central nervous system degeneration in several neurodegenerative diseases. When cytokines, such as tumor necrosis factor (TNF)-α, are secreted by activated glia in the brain or are present in circulating blood, permeability of the blood brain barrier is increased.

The primary aim of this study was to investigate the expression, affinity and density of adenosine receptors in lymphocytes and neutrophils of PD patients compared to healthy subjects. This study revealed a specific A2AAR alteration correlating with disease severity: patients with higher A2AAR density and lower affinity were more likely to exhibit motor complications. An increase in A2AAR density in putamen patients was found, an alteration that mirrors a similar up-regulation in human peripheral blood cells. Moreover, how expected, we measured high levels of adenosine and TNF-α in plasma of PD patients. Interesting we found out a statistically significant linear correlation among the A2AAR density and TNF-α levels. Elevated levels of TNF-α in PD brains amplify and sustain the neuroinflammation leading to dopaminergic neurons destruction. Moreover, several studies highlight a close relation between TNF-α release and A2AAR. To shed some light on the functional adenosine-dopamine interaction, we examined the effects of well-known A2AAR agonists and antagonists on dopamine uptake in the rat adrenal pheochromocytoma cell line after differentiation into a neuronal phenotype by nerve growth factor. Our results show that A2AAR antagonists decreased dopamine uptake, and an opposite effect was mediated by A2AAR agonists.

In conclusion our data prove the double importance of A2AAR in Parkinson’s disease: a biomarker useful for diagnose and a potential therapeutic target for PD.