MARAVIROC, A CHEMOKINE CCR5-RECEPTOR ANTAGONIST, INHIBITS THE E-NTPDASE ACTIVITY IN HUMAN LYMPHOCYTES IN VITRO


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Introduction: Human immunodeficiency virus (HIV) infection has been reported to increase the activity and expression of human lymphocytes nucleoside triphosphate diphosphohydrolases (NTPDases; CD39), a physiologically important class of membrane-bound ecto-nucleotidases responsible for the regulation of extracellular nucleotides levels. Nevertheless, few studies have investigated the influence of anti-HIV agents on purinergic system, particularly on ecto-nucleotidases activity. Objectives: Considering the potential relevance of nucleotidases in coordinating the inflammation processes, we evaluated the influence of some antiretroviral drugs on NTPDase activity in healthy human lymphocytes in vitro. Material and Methods: Based on pharmacokinetic information, therapeutic plasma concentrations of 5 anti-HIV drug classes were tested, named: Nucleoside analog reverse-transcriptase inhibitors Zidovudine (8.5µM), Lamivudine (8.8µM) and Didanosine (6.0µM); Nucleotide analog reverse-transcriptase inhibitor Tenofovir (5.0µM); Protease inhibitor Atazanavir (7.6µM); Integrase inhibitor Raltegravir (3.6µM); Fusion inhibitor Enfuvirtide (1.0µM) and Entry inhibitor Maraviroc (1.7µM). The drugs (two concentrations above and one below the therapeutic dose) were incubated with human peripheral blood lymphocytes (0.1-0.2µg/µL) and exogenous ATP/ADP substrates. NTPDase activity was determined using the colorimetric malachite green phosphate assay. Results: Our findings revealed that the exposure to higher concentration of Maraviroc (170 µM) provoked a significantly decrease in the ATP hydrolysis (28%) of lymphocytes when compared to the control. A decrease was also observed in the ADP hydrolysis (15%). However, this effect was not statistically different from control (p>0.05). The inhibition induced by sodium azide (positive control) in the ATP and ADP hydrolysis was 35% and 34%, respectively. The other anti-HIV drug classes did not modify the activity of NTPDase. Conclusion: Here we show, for the first time, that only the supratherapeutic dose of CCR5 receptor antagonist Maraviroc may induce changes in NTPDase activity from lymphocytes. Thus, we believe that this enzymatic system is not significantly affected in HIV-infected subjects under treatment. However, studies evaluating the NTPDase activity in lymphocytes from HIV-infected subjects are needed.

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Key Words: Anti-HIV drugs, NTPDase, Lymphocytes