EVALUATION OF ANTIPROLIFERATIVE ACTIVITY OF CHOLESTERYL BUTYRATE SOLID LIPID NANOSPHERES ON LEUKEMIC CELL LINES

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Butyric acid, a short-chain fatty acid naturally present in the human colon, is able to modulate several cellular processes and to induce cell cycle arrest, differentiation and apoptosis in transformed cells. Parenteral administration of butyrate is problematic due to its short plasma half-life, which necessitates continuos i.v. infusion dosing, and potential complications associated with the sodium or arginine cations present in the available salt forms of butyric acid. Cholesteryl-butyrate (chol-but) used as lipid matrix of nanoparticles (SLN) could be a suitable formulation to deliver butyric acid.
We compare the antiproliferative effect of chol-but SLN and sodium butyrate (0.1, 0.25, 0.5 and 1 mM) on three leukemic cell lines (Jurkat, HL-60 and U-937) for 24, 48, 72 and 96 hours. Growth rate and cell viability were monitored by trypan blue exclusion test, distribution in the cell cycle and apoptosis were measured by flow cytometric analysis of DNA content. Sodium butyrate (Na-but) 0.1 mM was uneffective on cell growth for all the cell lines tested. A slight, but not significant, reduction in growth rate was observed with 0.25 and 0.5 mM Na-but in Jurkat and U-937 cell lines. With the highest concentration tested of Na-but (1 mM), in all the three cell lines we observed a significant reduction in growth rate. The trypan blue dye exclusion test demonstrated that no necrosis occurred at any time, even in cells treated with the highest concentration (1 mM) of Na-but.
In all the three cell lines, a dose-dependent reduction in growth rate was observed after chol-but SLN treatments at concentration significantly lower than Na-but. The two highest concentrations tested (0.5 and 1 mM chol-but SLN) provoked a complete block of cell growth in all the cell lines tested.
The trypan blue dye exclusion test demonstrated that necrosis occurred after 0.5 and 1 mM chol-but SLN. Cell cycle analysis revealed little or any effect after Na-but exposure in the three cell lines. In the Jurkat cells chol-but SLN 0.25 mM determined a marked accumulation of cells in G_2/M phase, and a decrease in G_0/G_1 phase at 48h, and 0.5 mM induced a significant sub-G_0/G_1 apoptotic peak. In the U-937 cells exposure to 0.25 mM chol-but SLN led to a progressive increase of G_0/G_1 cells, with a decrease of G_2/M cells, and this phenomenon became more pronounced increasing chol-but SLN concentration. In the HL-60 cells chol-but SLN 0.25 mM increase the percentage of cells in the G_0/G_1 phase associated with a decrease of cells in G_2/M phase and an increase in the percentage of apoptotic cells at 48h. In conclusion in these cells, chol-but SLN determine alterations of cell cycle distribution more pronounced compared to the same concentrations of Na-but and a marked inhibition of proliferation, with significant level of apoptosis at the highest concentrations in the Jurkat and HL-60 cell lines.
These preliminary findings suggest that chol-but SLN may have important implications in view of the possible clinical applications as an interesting alternative approach for butyric acid delivery. Further in vivo studies are necessary to verify the ability of SLN to release butyric acid over a prolonged period of time.