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EFFECT OF METHYLXANTHINES DERIVED FROM PENTOXIFYLLINE ON P-GLYCOPROTEIN MEDIATED MULTIDRUG RESISTANCE

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Multidrug resistance (MDR) is a phenomenon when cells become resistant to a wide spread of drugs with a different chemical structure and a distinct mechanism of action. To understand the molecular mechanism of MDR, *in vitro* study with lines of neoplastic cells are often used. One of the proteins altered during in vitro development of resistance to antitumor agents is P-glycoprotein (PGP). It is plasma membrane glycoprotein extruding drugs out from cells. This process is ATP and Mg^{2+} dependent. Some of the drugs (especially those that influence the calcium homeostasis: calcium channel blockers, calmodulin inhibitors, etc.), called chemosensitizers, are able to depress the transport activity of PGP. The ability of pentoxifylline (PTX) to depress resistance mediated by overexpression of PGP in mouse leucemic cell line L1210/VCR resistant to vincristine (VCR) was described earlier. PTX depressed the resistance of these cells in a dose and time dependent manner. This effect was accompanied by increased level of [^{3}H]-vincristine accumulation by these cells. The presence of PTX (100 mg/l) in a cultivation medium caused two-fold decrease of *mdr1* mRNA level (with the maximum reached within 48 hours in comparison to control cells). Other methylxanthines like caffeine and teophylline were not able to depress MDR in L1210/VCR cells. PTX, in contrast to both above methylxanthines, contains the electrophilic carbonyl group on the aliphatic side chain that can interact with nucleophilic groups of aminoacid residues like $-NH_2$, -OH or -SH in biomacromolecules. The methylxanthines with different length of this aliphatic side chain were synthesized and their capability to depress MDR was tested. The results indicated that the position of carbonyl group plays a crucial role for the ability of the derivative to depress MDR of L1210/VCR cells.