ABSTRACT

PMEG [9-(2-phosphonomethoxyethyl)guanine] and PMEDAP [9-phosphonomethoxy-ethyl)-2,6-diaminopurine] are acyclic nucleoside phosphonates possessing cytotoxic properties. Antiproliferative effect of PMEG was demonstrated in various tumor cell lines *in vitro*. PMEG also represents an active component of some experimental prodrugs with enhanced selectivity and efficacy (such as GS-9219). PMEDAP seems to have weaker effect *in vitro* compared to PMEG, however it exhibited pronounced antitumor effect in SD-rats with spontaneous lymphoma. Therefore it was included in the present study as well. The aim of this study was to describe the interactions of PMEG and PMEDAP with p38 MAP kinase signaling and its relationship to the apoptosis. We investigated the influence of these compounds on the expression of four genes encoding p38 MAPK isoforms and whether this change is translated into the protein. It was found that PMEG up-regulates p38β and γ mRNA in CCRF-CEM cells and p38 β and δ in HL-60 cells. The effect of PMEDAP was less pronounced than that of PMEG. However, total p38 protein level remained unaffected by PMEG and PMEDAP. Activation of p38 MAPK cascade was also measured in the cells exposed to these agents using phospho-specific antibodies. We found that neither PMEG nor PMEDAP activated p38 kinase signaling pathway and the effect was independent of the cell line used. Next we evaluated apoptotic effects of PMEG a PMEDAP by monitoring PARP a caspase 3 cleavage. Apoptosis induction by the compounds was found to be concentration-dependent. The apoptotic effect was stronger in the case of PMEG, which is consistent with its higher antiproliferative potency. Finally, cells were pretreated with specific inhibitor of p38 MAPK SB203580 prior to PMEG or PMEDAP treatments and the effect of the inhibitor on apoptosis was followed. It turned out that inhibition of p38 MAPK pathway cannot completely reverse PMEG/PMEDAP-induced apoptosis but it is able to reduce its extent. These findings suggest that p38 kinase might play a role in the apoptotic effects of PMEG and PMEDAP. (In Czech)

Keywords: acyclic nucleoside phosphonates, MAP kinases, p38 kinase, apoptosis, anticancer therapy