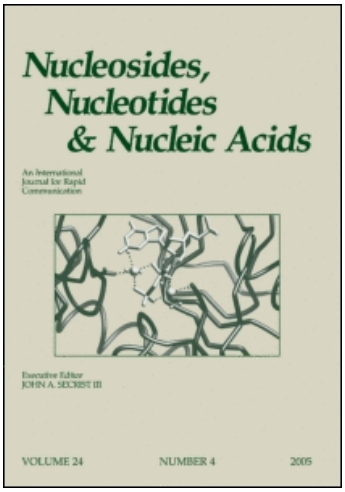

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Stimulation of Cytokine and Nitric Oxide Production by Acyclic Nucleoside Phosphonates

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STIMULATION OF CYTOKINE AND NITRIC OXIDE PRODUCTION BY ACYCLIC NUCLEOSIDE PHOSPHONATES

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ABSTRACT: Several antiviral acyclic nucleotide analogues activate expression of genes for cytokines, such as TNF-α, IL-10 in macrophages and IFN-γ in splenocytes. This is an underlying mechanism for substantially enhanced production of nitric oxide generated by IFN-γ. More lipophilic prodrugs, bis-POM-PMEA and bis-POC-PMPA, are cytocidal for macrophages and thus inhibit nitric oxide formation.

Acyclic nucleotide analogues possess prominent antiviral activitiy[1]. One of the prototype compounds, PMPA, has been shown to prevent the development of AIDS in a simian model of the disease[2]. We have investigated whether these drugs are endowed with immunomodulatory properties that play an important role in nonspecific defence. Included in the study were: 9-(2-phosphonomethoxyethyl)adenine [PMEA], 9-(2-phosphonomethoxyethyl)-2,6-diaminopurine [PMEDAP], (*R*)- and (*S*)-enantiomers of 9-(2-phosphonomethoxypropyl)adenine [(*R*)-, (*S*)-PMPA], (*R*)- and (*S*)-enantiomers of 9-(2-phosphonomethoxypropyl)-2,6-diaminopurine [(*R*)-, (*S*)-PMPDAP], 9-(2-phosphonomethoxyethyl)guanine [PMEG], and 1-(3-hydroxy-2-phosphonomethoxypropyl)cytosine [(*S*)-HPMPC]. Besides, effects of more bioavailable prodrugs, bis-POM-PMEA and bis-POC-PMPA, were studied. The effects on secretion of cytokines, such as IFN-γ, TNF-α, IL-2, and IL-10 were investigated in cultures of murine macrophages and lymphocytes (determined by ELISA). Also, interference of the compounds with production of nitric oxide (NO) by rat or mouse macrophages cultured in the absence or presence of lipopolysacharide (LPS) or IFN-γ, was analysed (determined by using a Griess reagent).

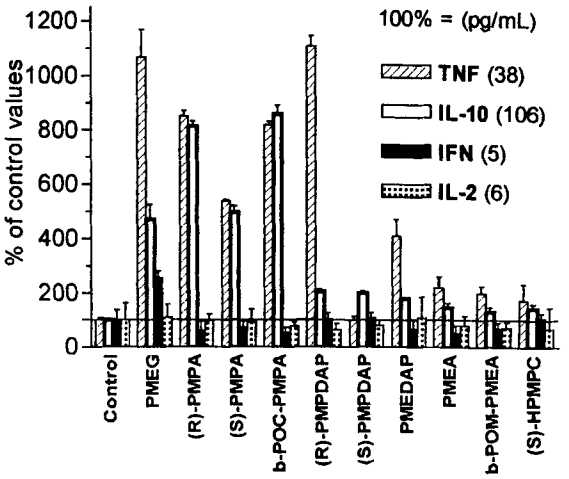

FIG. 1. Effects of analogues (200 μM) on *in vitro* secretion of cytokines by murine macrophages (assay: 6 h).

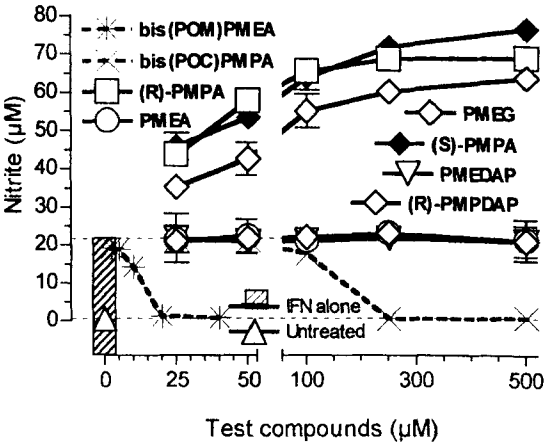

FIG. 2. Effects of analogues on *in vitro* production of nitric oxide generated in murine macrophages by IFN-γ (25 U/mL) (assay: 24 h).

All compounds stimulate secretion of TNF-α by murine splenocytes; some of them also enhance TNF-α and IL-10 secretion by macrophages (FIG. 1). Except HPMPC, the test compounds augment synthesis of INF-γ by splenocytes, PMEG being effective in macrophages, too. Analogues that stimulate both TNF-α and IL-10 secretion substantially enhance NO production by resident IFN-γ-primed murine macrophages (FIG. 2) and by unprimed rat macrophages. In contrast, the LPS-induced production of NO was not augmented. Due to their cytocidal effects, the two more bioavailable prodrugs, bis-POM-PMEA and bis-POC-PMPA, dose-dependently inhibit biosynthesis of NO (FIG. 2).

In sum, acyclic nucleotide analogues possess immunomodulatory potential. They are potent activators of cytokine gene expression and modulators of nitric oxide production.

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