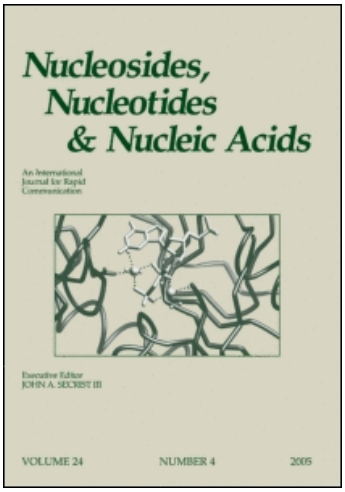

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Anti-inflammatory Effects of Phosphonomethoxyethyl Analogues of Adenine in a Model of Adjuvant Arthritis

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ANTIINFLAMMATORY EFFECTS OF PHOSPHONOMETHOXYETHYL ANALOGUES OF ADENINE IN A MODEL OF ADJUVANT ARTHRITIS

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ABSTRACT: The 9-(2-phosphonomethoxyethyl)adenine (PMEA) and its more bioavailable bis(pivaloyloxymethyl) ester, (bis-POM-PMEA), applied s.c. at doses of 5-50 mg/kg, profoundly suppress symptoms of rat adjuvant arthritis, such as paw swelling, sple-nomegaly, fibroadhesive perisplenitis and systemic NO levels. The 9-(2-phosphono-methoxypropyl)adenine, PMPA and bis-POC-PMPA are ineffective. The antiarthritic effect does not depend on the influence of the drugs on macrophage NO production.

We have studied effects of selected acyclic nucleotide analogues on development adjuvant-induced arthritis (AA), and experimental allergic encephalomyelitis (EAE) in rats, models of human rheumatoid arthritis, and multiple sclerosis, respectively. Included in the study were: 9-(2-phosphonomethoxyethyl)adenine (PMEA), 9-(2-phosphonoeth-oxypropyl)adenine (PMPA), and their more bioavailable prodrugs, bis(pivaloyloxymethyl) ester of PMEA (bis-POM-PMEA) and bis(isopropyloxycarbonyloxymethyl) ester of PMPA (bis-POC-PMPA). The drugs (5-50 mg/kg) were injected subcutaneously during the inductive phases of diseases.

Both PMEA and bis-POM-PMEA reduced swelling of paws (FIG. 1), splenomegaly (FIG. 2) and fibroadhesive perisplenitis. PMPA and bis-POC-PMPA were ineffective. Favorable therapeutic influence was associated with substantially suppressed serum (FIG. 3) and urine nitrite + nitrate levels. The effect has not been correlated with ability of the drugs to influence production of nitric oxide (NO) by macrophages (FIG. 4): PMPA stimulated, bis-POC-PMPA and bis-POM-PMEA inhibited, and PMEA did not affect NO formation. In contrast to AA, severity of EAE remained uninfluenced by the compounds.

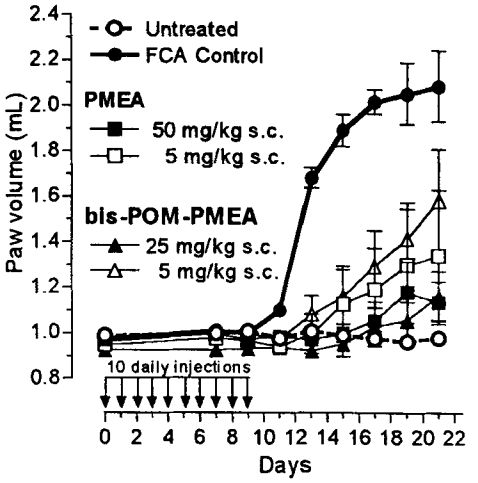

FIG. 1. Inhibition of rat arthritic paw swelling by PMEA and bis-POM-PMEA.

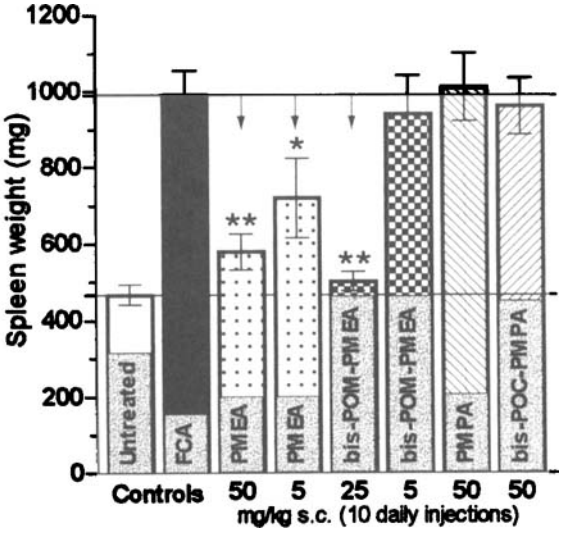

FIG. 2. Effests of compounds on adjuvant-induced splenomegaly in rats.

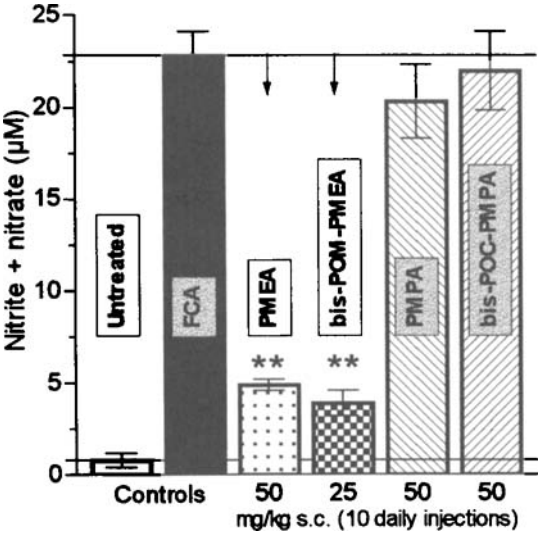

FIG. 3. Serum levels of NO_x^- in controls and drug/adjuvant-treated rats.

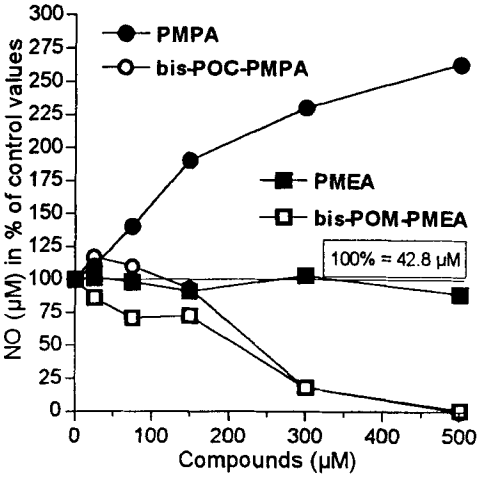

FIG. 4. *In vitro* effects of compounds on NO produced by macrophages from adjuvant-treated rats.

In conclusion, the present findings warrant further studies that would substantiate novel therapeutic applications of PMEA and/or other acyclic nucleotide analogues.

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