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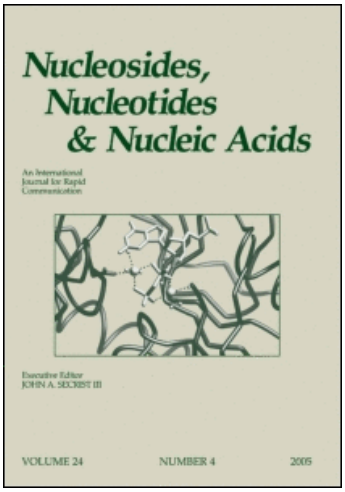

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Oligonucleotide Derivatives in Organism: Distribution Among Organs, Rates of Release and Degradation

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OLIGONUCLEOTIDE DERIVATIVES IN ORGANISM: DISTRIBUTION AMONG ORGANS, RATES OF RELEASE AND DEGRADATION

O.M.Bazanova, V.V.Vlassov, V.F.Zarytova, E.M.Ivanova, E.A.Kuligina L.A.Yakubov*, M.N.Abdukayumov†, V.N.Karamyshev†, G.Zon‡

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ABSTRACT oligonucleotide derivatives were observed partially degraded in all tissues of mice 30 min post-injection. Concentration in liver and kidney was 100-fold larger than in brain. Phosphorothioate oligos were more resistant than phosphodiesters.

We have studied the behaviour of deoxyribooligonucleotides and their phosphorothioate analogs bearing benzylphosphoramide groups at the 5'-end, in mice.

The labeled derivatives were prepared as described.[1-3] The injections were i.v., i.p. and s/c in 200 µl water. The mice were killed by decapitation and tissue samples were tested for ^{32}P-radioactivity. Fig.1 shows kinetics of accumulation and release of the labeled oligonucleotide derivatives in mice organism. In a few minutes they were likely to arrive to all organs and tissues with bloodstream. In 30 min the label concentrated in organs of excretion and reticuloendothelial system: kidney, liver and spleen. The concentration of the label in most tissues exceeded or equaled that in blood, thus indicating that the label did belong in tissues although the latters were not perfused. Distribution of the label after i.v. or i.p. injection differ only in the first few minutes. Also we have studied the labeled material in tissues. Tissue samples were phenol extracted in Tris-EDTA buffer, water phases were electrophoresed in 20% PAAG with urea and radioautographed (Fig.2). In an experiment with alkaline phosphatase treatment we have proved that all

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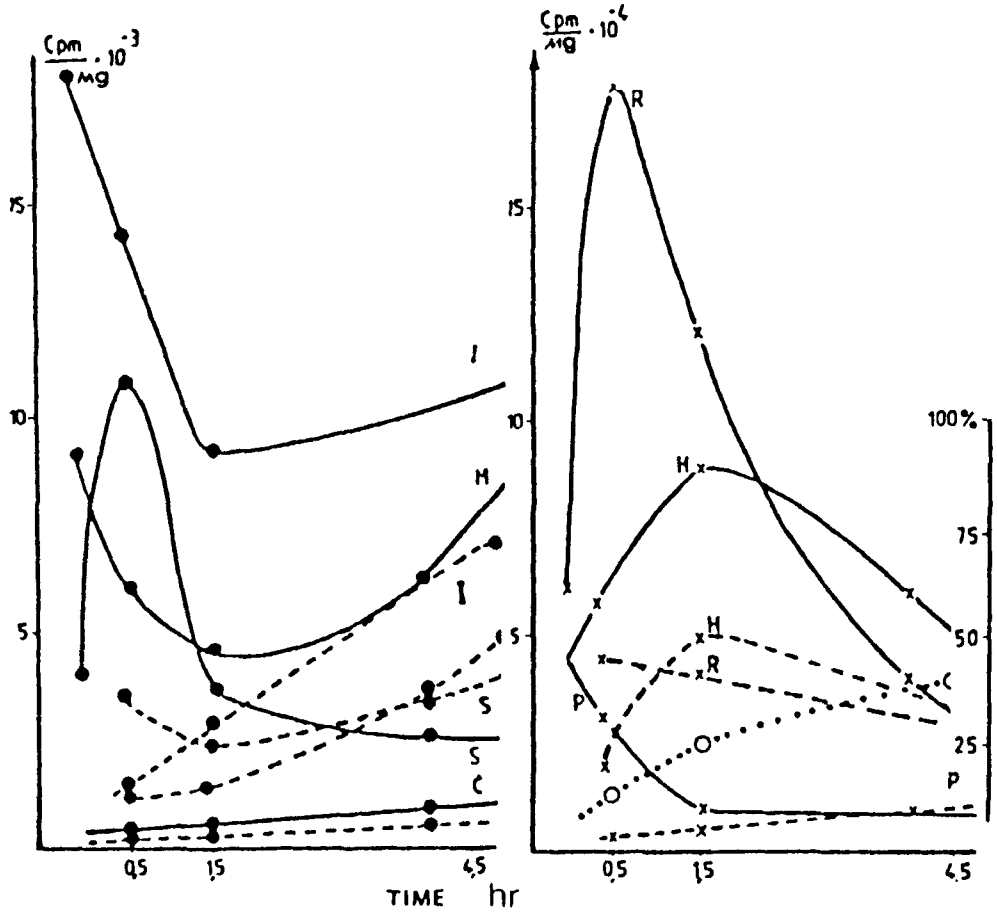

FIG.1 Accumulation and release of ^{32}P-oligonucleotide derivatives in mice. —, i.p.; --, s/c injection; , label excretion with urea (per cents to the right): R, kidney; H, liver; P, pancreas; I, spleen; M, muscle; S, blood; C, brain.

FIG.2 Oligonucleotide derivatives in mice tissues 30 min after injection of 5 nmol of benzyl-5'-^{32}P-phosphoramide oligonucleotide, $BzpE_{16}$, and the thioanalogs, $BzpSE_{16}$. L, liver; K, kidney; B, blood; P, pancreas; S, spleen; pE_{16}, pTGACCCTCTTCCCATT.

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radioactive bands correspond to the oligonucleotide derivatives with protected 5'-phosphates. The radioautographs were scanned and the content of derivatives with different extents of degradation was evaluated. 30 min post-injection the 11-16-mers represented 20-50% of radioactive material for different tissues. Phosphorothioate analogs are considerably more stable in animals than normal oligonucleotides. Degradation and distribution of oligonucleotides in mice do not depend on the dose (0.15-150 nmol per injection).

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