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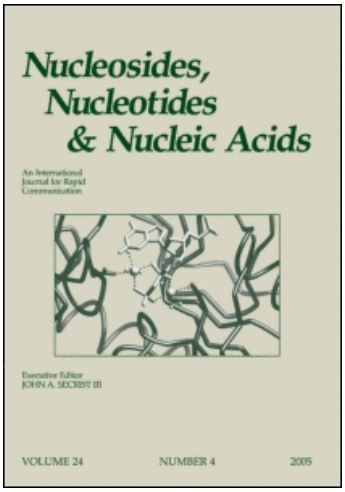

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MECHANISM OF ANTIVIRAL ACTIVITY OF 5-ETHYL-2'-DEOXYURIDINE

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Abstract. 5-Ethyl-2'-deoxyuridine (EDU) is phosphorylated to a much greater extent by herpes simplex virus (HSV)-infected Vero cells than by mock-infected cells. Within the infected cells, EDU is preferentially incorporated into viral DNA and more inhibitory to viral than cellular DNA synthesis.

Among the 5-substituted 2'-deoxyuridine analogues, EDU is one of those compounds that is presently being pursued for the chemotherapy, i.e. topical treatment, of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) infections[1,2]. To elucidate its mechanism of antiviral action, the phosphorylation pattern of [4-^{14}C]EDU* was examined in acid-soluble fractions of Vero cells which had either been mock-infected or infected with HSV-1 (strain KOS) or HSV-2 (strain G). The incorporation of [4-^{14}C]EDU into DNA of mock-infected and HSV-1-infected cells was determined by CsCl equili-

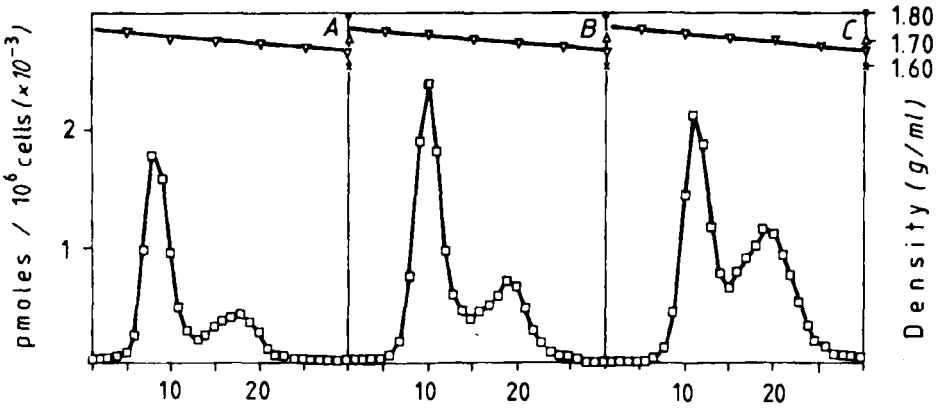

Fig. 1. CsCl gradient analysis of Vero cells, infected with HSV-1 (strain KOS) and incubated in the presence of [4-^{14}C]EDU at 0.5 μM (panel A), 1 μM (panel B) or 5 μM (panel C).

*Provided by Dr. D. Ilse (Ortho Pharmaceutical Ltd., Canada).

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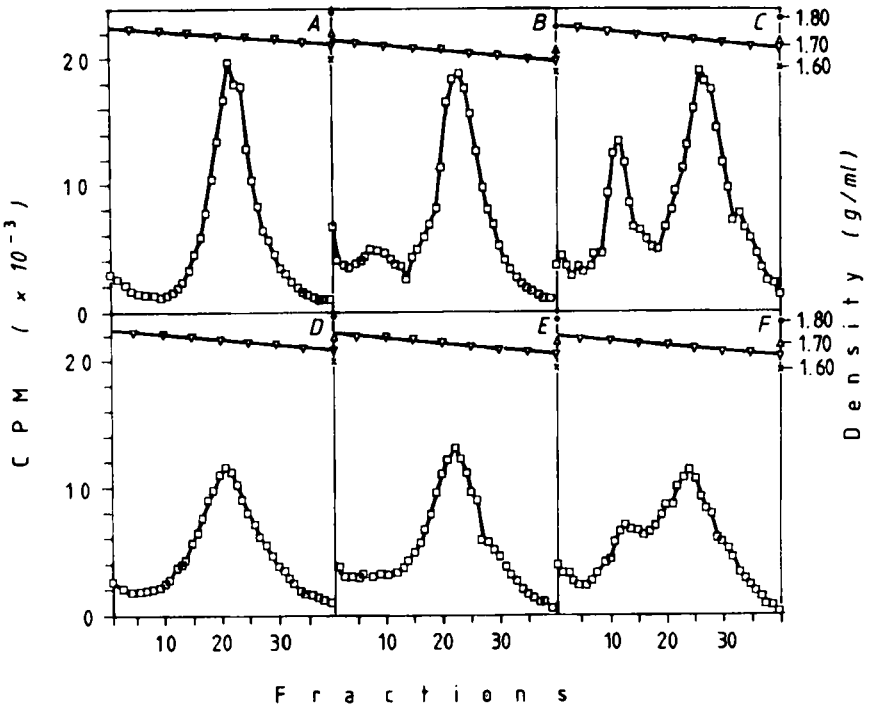

Fig. 2. CsCl gradient analysis of Vero cells which had either been mock-infected (panels A, D) or infected with HSV-2 (G) (panels B, E) or infected with HSV-1 (KOS) (panels C, F), and then incubated in the presence of [^{32}P]-orthophosphate, without (panels A, B, C) or with 1 μM EDU (panels D, E, F).

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brium gradient analysis. The effect of EDU on viral and cellular DNA synthesis in mock-infected and HSV-infected Vero cells was measured by [^{32}P]-orthophosphate incorporation.

Thin layer chromatography of acid-soluble fractions showed that [4-^{14}C]EDU is phosphorylated to a much greater extent in virus-infected than mock-infected cells (data not shown). Also, [4-^{14}C]EDU is incorporated to a much greater extent into viral DNA than cellular DNA (Fig. 1).
Within the HSV-1-infected cells, viral DNA synthesis, as monitored by [^{32}P]-orthophosphate incorporation, was inhibited to a much greater extent than cellular DNA synthesis (Fig. 2).

These findings indicate that EDU needs to be phosphorylated to exert its antiviral activity, that it is incorporated into viral DNA and, to a smaller extent, into cellular DNA, and that this incorporation is accompanied by an inhibition of viral DNA synthesis. Whether this inhibitory effect is due to substrate-inhibition (by EDU 5'-triphosphate) or to template-inhibition (by EDU-substituted DNA) remains to be clarified.

REFERENCES

(1) R.F. Schinazi, R.T. Scott, J. Peters, V. Rice, and A.J. Nahmias, Antimicrob. Agents Chemother. 28, 552 (1985).
(2) S.L. Spruance, D.J. Freeman, and N.V. Sheth, Antimicrob. Agents Chemother. 28, 103 (1985).