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Cell membranes, cell fusion and phospholipids: new targets and novel inhibitors of HIV-1. D. Kinchington[1], T. O'Connor[1], S. Galpin[1], B. Swords[2] and C. McGuigan[2].
1 Department of Virology, Medical College of St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK. 2 Department of Chemistry, University of Southampton, Highfield, Southampton, SO9 5NH, UK.

We herein report that novel synthetic phospholipid analogues have a selective anti-HIV activity. Compounds of the type RO P(O)(OH) $OCH_2CH_2NHCH_3$ inhibit HIV replication in the low μM range(1). Moreover clear structure-activity relationships emerge: lengthening of, and to a lesser extent, unsaturation within, the alkyl (RO) chain leads to an enhancement in activity. In separate experiments we noted that syncytium formation is associated with an increase in the cellular monounsaturated oleic acid(2); and it was proposed that the enzyme Δ-9-desaturase, is activated during HIV replication. This enzyme regulates the conversion of stearic acid (C18:O mp 69 C) to the monounsaturated, lower melting point oleic acid (C18:1 mp 13 C); biochemical events which lead to increased membrane fluidity and hence cell fusion. This concept was further strengthened by the finding that syncytium formation is enhanced by higher ambient temperatures (values at which normal metabolic activity is inhibited)(3). The mechanism of action of the phospholipid analogues remains unclear. A direct chaotrophic action within the cell membrane may be involved or it may be that phospholipid analogues moderate the cytopathic effect of HIV perhaps by inhibition of Δ-9-desaturase. This report will discuss the membrane effects of HIV and the possible modes of action of these phospholipids.

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1. Apostolov et al 1989. Febs Letters: 250, 241-244.
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Loss of synergy in AZT-resistant primary isolates of HIV. S.W. Cox, J.A. Albert, B. Wahren, Virology, SBL, Karolinska Institute, S 105 21, Stockholm, Sweden.

The use of combination chemotherapy holds promise for improved, less toxic therapy for AIDS, and possibly also for reducing the rate of development of resistance. Resistance to AZT has been shown to occur in HIV-infected persons after several months of treatment with AZT. Resistant isolates are usually sensitive to dideoxynucleoside analogues of a different type, such as dideoxyinosine (DDI) or fluorothymidine (FLT). AZT has been shown to synergistically inhibit HIV replication when combined with both DDI and FLT. As part of our ongoing studies on HIV resistance, we studied the synergism of AZT with DDI or FLT in paired sensitive and resistant isolates from patients treated with AZT. PBLs were infected with primary isolates of HIV in the presence of the drugs alone, and in combination according to the median effect method. Replication of HIV was measured after seven days by p24 ELISA of the supernatants. IC_{50}'s and drug interactions were calculated with a computer programme following the median effect method. The results showed that AZT was synergistic with both DDI and FLT in pre-treatment, AZT-sensitive isolates (CI = 0.4-0.6). However, in post-treatment, AZT-resistant isolates, these combinations showed only addition or sometimes antagonism (CI > or = 1). The combination of FLT and DDI, however, was also shown to be synergistic (CI = 0.3), and this synergism remained in the AZT-resistant isolates. The results suggest that the therapeutic advantage of synergistic combinations involving AZT is lost upon emergence of AZT resistance. However, synergism between drug combinations not involving AZT, and not showing cross-resistance, remains. Such combinations may be a better choice for treatment of AZT-resistant HIV.