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Hydrophobisation of virus-specific antibodies and antisense oligonucleotite promotes their antiviral actions

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The principle of artificial hydrophobisation was employed to enhance the delivery of antivirals to the viral intracellular targets. Two classes of molecules: (1) the monoclonal ab against internal influenza virus proteins, M1 and NP; (2) the oligo (TTG ACGAAATT),which is complementary to the loop-forming site of the PB2 virus segment, were tested. The Mabs were made hydrophobic with covalent-linked stearic residues and the oligo was combined with the undecyl residue added to the 5-terminal phosphate. The Mabs containing 1-3 residues of stearic acid per molecule were shown to retain their functional activity. Both modified drugs suppressed the Flu A/PR/8/34 virus replication and inhibited the synthesis of the virus polypeptides in MDCK cells. Similar results were obtained with Flu A/Aichi/68, and A/Chile/83 viruses. Under the same conditions, the non-modified Mabs and oligo did not affect the virus development.The effective antiviral concentrations of the hydrophobised Mabs and oligo in maintenance culture medium were 0.25 nM and 50 uM, respectively.These data show that artificial hydrophobisation of antivirals may be applied as a promoter of its antiviral targeting.

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PHARMACOKINETICS AND DISTRIBUTION TO THE BRAIN OF (R)-9-[4-HYDROXY-2-(HYDROXYMETHYL)BUTYL]GUANINE (H2G) AND PLASMA LEVELS OF H2G AFTER DOSING A H2G PRODRUG IN THE RAT

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Microdialysis was used to sample the extracellular fluid for unbound drug concentration in blood, muscle and brain of halothane anaesthetised male Sprague Dawley rats given H2G 25 mg/kg s.c. The drug was analysed by HPLC after UV detection. Plasma protein binding was determined by microdialysis in vitro. The free extracellular concentrations of H2G were equal in muscle and blood with C_{max} around 40 µM at 20 - 40 min after s.c. administration. Brain extracellular concentrations were lower than peripheral concentrations. In the brain C_{max} was 4.5 µM which was also attained at 20 - 40 min after injection. At this time point the difference in concentration between brain and blood was maximal. After 80 - 100 min the blood level was 7.2 µM and the level in brain 2.3 µM. The elimination half-life in blood was 28 min. Protein binding of H2G was negligible. After oral administration of a H2G prodrug (35 mg/kg) the concentration of H2G in plasma samples was measured after precipitation and centrifugation. The C_{max} of H2G in blood samples was 8.6 µM after 60 min. It is concluded that, in the rat, oral administration of the H2G prodrug results in relatively high plasma levels of H2G for at least 6 hours after administration of the prodrug and that H2G readily enters to the brain but not in as high concentration as in plasma. The results is encouraging for future studies in species more closely related to man.