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The nine carboxyterminal aminoacids of HSV ribonucleotide reductase fused to an heterologous protein are capable of binding the large subunit of the enzyme.

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The nine carboxyterminal aminoacids of herpes simplex virus ribonucleotide reductase small subunit are responsible for binding to the large subunit to form the dimeric active enzyme. Synthetic peptides corresponding to these aminoacids have been successfully used to inhibit the enzyme activity *in vitro*. Here we present the biochemical characterization of a chimaeric protein where these nine aminoacids have beeen genetically fused to the C-terminus of *E. coli* heat-labile enterotoxin B subunit (EtxB). The fusion protein (EtxB-RR2) is expressed in *E. coli* as a stable pentamer with five hybrid subunits reactive to specific monoclonals antibodies. EtxB-RR2 retains the ability to bind the natural gangliosidic receptor of the toxin (GM1) which is found on eukaryotic cell surfaces AND, at the same time, is able to bind the large subunit of HSV ribonucleotide reductase. The possibilty of exploiting the natural ability of the toxin to be internalized into eukaryotic cells for the delivery of a peptide active against a virally encoded enzyme is being investigated.

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Antiherpesvirus activity of BRL 44385 (9-(3-hydroxypropoxy)guanine) in animals.

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We have previously demonstrated that BRL 44385 (9-(3-hydroxypropoxy)guanine) is a highly selective antiherpesvirus agent in cell culture and is up to 10-fold more potent than acyclovir (ACV). We have now compared the efficacy of BRL 44385 and ACV in several animal models of herpes simplex virus infection. Initial studies in uninfected mice showed that the subcutaneous bioavailability of BRL 44385 and ACV was comparable, but that there was approximately a three-fold difference in oral bioavailability in favour of ACV. When administered via the drinking water, BRL 44385 was at least as active as ACV in the following murine models; a cutaneous HSV-1 infection of the ear pinna, an intraperitoneal HSV-1 infection, a genital HSV-2 infection and intranasal HSV-1 and HSV-2 infections. In mice infected intraperitoneally with HSV-1, a single 45mg/kg subcutaneous dose of BRL 44385 administered 24h after infection reduced virus replication within the peritoneal cavity more effectively than an equivalent dose of ACV ($P<0.05$). A study involving multiple dose schedules in this model demonstrated that BRL 44385 could be administered less frequently than ACV without loss of efficacy. In addition, BRL 44385 was significantly more active than ACV when applied topically (0.5% w/w) to guinea pigs with a cutaneous HSV-1 infection ($P<0.05$). There was evidence suggesting that BRL 44385 could be applied less frequently than ACV in this model without loss of efficacy. The data presented suggest that BRL 44385 has superior efficacy to ACV in animal models of herpesvirus infections. This is thought to reflect the rapid formation and stability of the triphosphate of BRL 44385 in herpesvirus-infected cells which has been previously reported (Brown *et al.*, 1992 Antiviral Res. 17 (Suppl. 1) Abstr. 97).