



THE OCULAR IMMUNOLOGY
AND UVEITIS FOUNDATION

Dedicated to Eye Disease Cure and Education

The Role of Cyclic Nucleotide Mediators in Latency and Reactivation of HSV-1 Infected Neuroblastoma Cells

C. Stephen Foster, MD

The mechanisms that control herpes simplex virus type 1 latency and reactivation are still poorly understood. We developed an *in vitro* murine neuroblastoma cell HSV-infected, acyclovir suppressed model to study the influence of different cyclic nucleotide mediators on the latency and reactivation of HSV-1. A positive cDNA *in situ* hybridisation of HSV genome was used to prove the establishment of a viral-host cell nuclear relationship. An ABC-immunoperoxidase reaction to cell surface HSV mature glycoproteins was also performed to determine the time of viral reactivation with formation of mature virions. Supernates of cultured cells were placed on Vero cells for confirmation of reactivation by classic cytopathic effect. Theophylline (50 ug/ml) and dibutyryl-cAMP (0.1, 0.5, 1 mg/ml) produced the most pronounced response, accelerating HSV reactivation time by 150%. Epinephrine (10, 20 ug/ml) had an intermediate effect on accelerating viral reactivation; and verapamil (20, 50 ug/ml), theophylline and epinephrine at lower doses had a small effect. Carbamylcholine (10 ug/ml) prolonged the time to viral reactivation by 100%, 36 hours compared to control time of 18 hours. Insulin (0.1, 0.5, 1 mg/ml) also prolonged HSV 'latency' by six hours. Exogenous dibutyryl-cGMP and carbamylcholine at lower concentrations did not have an effect on viral reactivation. These findings suggest that there is a relationship between changes of intracellular concentrations of cyclic nucleotides and HSV latency and reactivation.