MECHANISM OF HALOTHANE-INDUCED INHIBITION OF HERPES SIMPLEX VIRUS SYNTHESIS

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Introduction. The antiviral effects of halothane have been documented. Herpes simplex virus (HSV), like other viruses whose replication is sensitive to the action of halothane, is inhibited in a dose dependent and reversible manner. Work described here elucidates the mechanism by which this halothane-induced inhibition of HSV replication occurs.

Methods. HSV was propagated in Vero cells, a continuous primate line. Following inoculation, cultures were exposed to 95% air - 5% CO₂ with or without a concentration of 2.5% of halothane. Halothane concentrations were determined by gas chromatography; losses from the sealed bottles were less than 5% over a 36 hr period. Virus proteins were radio-labeled with [35S]-methionine and analyzed by polyacrylamide gel electrophoresis. HSV-specific nucleic acids were radio-labeled with [3H]-thymidine and analyzed by CsCl equilibrium centrifugation. Virus precursor elements (nucleocapsids) were radio-labeled with either or both of the above radiolabels, and analyzed by sucrose gradient rate zonal centrifugation.

Results. Both HSV total protein synthesis and total DNA synthesis are unaffected by halothane treatment. This was determined by examining the number of individual species of proteins synthesized, or the total level of virus DNA contained within the cells. However, when nucleocapsids (DNA-protein virus cores assembled from virus DNA and structural proteins) were examined, halothane-induced changes were observed. Two populations of nucleocapsids are normally synthesized by HSV, a heavier (sediments faster during centrifugation) group which contains DNA and a lighter group which does not contain any DNA. Figure 1 demonstrates that production of the DNA-containing heavier group is inhibited by halothane while the lighter nucleocapsids (the group of virus protein cores without DNA) continue to be synthesized. When halothane is removed, the DNA-containing particles again appear, however, their protein composition is altered following halothane removal. Two major proteins detected by polyacrylamide electrophoresis which only appear in non-DNA-containing nucleocapsids in the absence of halothane exposure are now found in the DNA-containing nucleocapsids. Thus it appears that HSV nucleocapsid assembly (and thereby the infectious virus) is effected by halothane.

Discussion. Viruses which are altered during the course of their replication will produce variants. Most of these variants are harmless but some may be undesirable. For example, a variant of measles virus causes a latent CNS disease of children, subacute sclerosing panencephalitis. Furthermore, following removal of halothane, measles virus-infected cells in cultures produce a preponderance of virus forms which are similar to those currently being implicated in chronic infections. Halothane effects the ability of measles virus to assemble properly as we report here for HSV. Since HSV is prone towards the establishment of chronic infections, anesthetized patients harboring acute HSV infections may be subjected to increased risks of chronic virus infections.

References.

HSV nucleocapsid proteins were labeled with [35S]-methionine (○) and DNA with [3H]-thymidine (○). Various forms were separated by rate zonal centrifugation as described in Methods.