Title: ROLE OF MEMBRANES IN HALOTHANE'S ANTIVIRAL EFFECT

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Introduction. Being obligate parasites, viruses are dependent upon their host cell(s) to provide many of the mechanical and structural elements necessary for replication. Many, but not all viruses, require a portion of the host cell membrane in the form of an outer envelope to complete the virus particle and facilitate subsequent infections. A number of viruses also induce a cell fusion step (syncytia formation) by insertion of virus-specific glycoproteins into the outer membrane during replication. The replication of measles virus, an enveloped syncytia-forming virus, is inhibited in the presence of clinical concentrations of halothane[1]. Examining a number of viruses we have found viral agents whose replication is insensitive, moderately sensitive, or highly sensitive to the presence of halothane. The extent of inhibition of virus replication in the presence of halothane correlates to the degree of involvement of the host cell outer membrane in virus replication.

Methods. All viruses were propagated and assayed in Vero cells, a continuous cell line derived from African green monkey kidney. Infected culture samples were treated with 95% air - 5% CO_2 with or without varying doses of halothane. Halothane concentrations were assessed by gas chromatography; losses from the sealed bottles not exceeding 5% over a 36 hr. period. Virus was harvested by sonic disruption of the cells at various times following inoculation. The cell extracts were then assayed for polio, herpes, vesicular stomatitis, Newcastle disease, or measles virus infectivity by determining the number of plaque-forming units (PFU) per ml of extract.

Results. Halothane did not inhibit polio virus replication at the concentrations tested. Replication of vesicular stomatitis virus and herpes (I) virus was moderately inhibited by halothane. At concentrations of 3.5% halothane, virus titers of these two viruses decreased by two to four orders of magnitude, but some infectious virus was always detectable. Newcastle disease virus and measles virus were highly sensitive to halothane. Total inhibition of these last two viruses occurred at 2.0% and 1.5% respectively. All of the viruses (except polio) were inhibited in a dose dependent manner by halothane (Figure 1).

Discussion. Polio virus, the only virus which is not enveloped by host cell outer membrane prior to release from the cell, is the only virus studied whose replication is insensitive to the presence of halothane. This virus does however, require host cell inner membranes for virus specific protein and RNA synthesis[2]. Vesicular stomatitis and herpes viruses, two viruses enveloped by host outer membrane, are moderately sensitive to halothane, whereas Newcastle disease virus and measles virus, two members of the paramyxovirus group, are extremely sensitive to halothane. These last two viruses not only require part of the host cell outer membrane for the production of infectious virus particles, but participation of this membrane in fusion to adjacent outer cellular membranes is an important step in the replication cycle. The insertion of virus specific proteins into the cell membrane and the interaction of these proteins with neighboring cells allows the paramyxovirus infection to proceed normally. Spatial alterations by halothane of the lipid matrix of the outer architecture of the cell membrane may result in the viral proteins not being properly embedded into the membrane resulting in loss of biological activity. Alternatively, rearrangement of intrinsic cell surface components may result in the membrane-bound, virus-specific glycoproteins losing biological activity or virus proteins on cells being "hidden". This report of the comparative effects of halothane on animal virus replication suggests that anesthetic-induced membrane alterations serve to control cellular function, thereby providing further insight into the mechanism of anesthetic action.

References.

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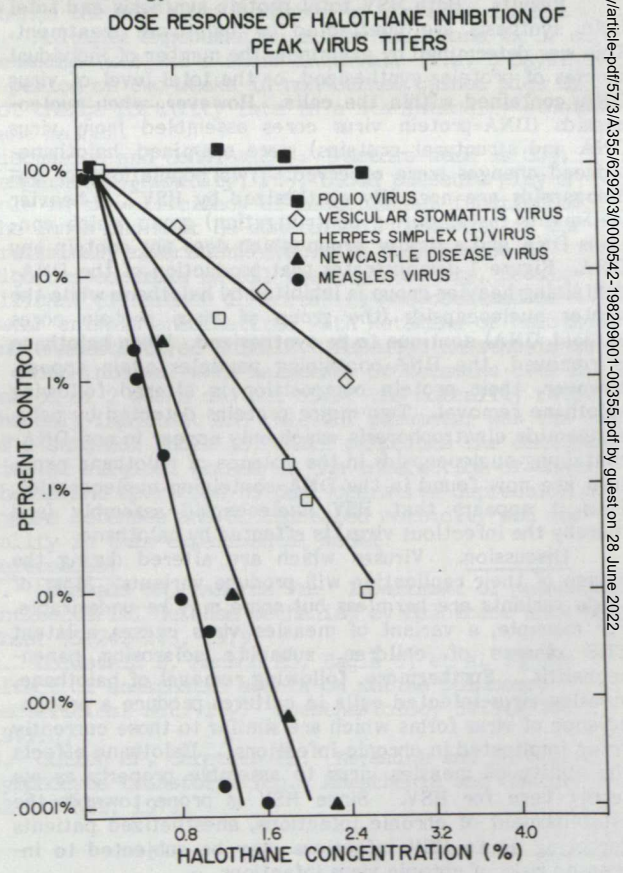
2. Caliguiri LA, Tamm I: Characterization of polio virus-specific structures associated with cytoplasmic membranes. Virology 42:112, 1970



Above is shown the survival of various viruses (as percentage of non-halothane treated controls) vs. halothane dosage.