Sodium and Potassium Transport in Herpes Simplex Virus-infected Cells

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SUMMARY

Sodium (Na⁺) and potassium (K⁺) flux in African green monkey kidney cells (Vero) was examined following infection by herpes simplex virus type 1 (HSV-1). A decline in the rate of K⁺ uptake at 5 h post-infection was shown using Sr⁺ as a K⁺ tracer. In contrast, host protein synthesis was inhibited by 3 h post-infection. The decrease in rate of K⁺ transport to levels 70 to 90% of that of mock-infected cells did not, however, reflect an inability of HSV-1-infected cells to maintain normal intracellular concentrations of Na⁺ and K⁺. At 7 h post-infection, intracellular Na⁺ and K⁺ concentrations were determined to be 26.6 ± 9.4 mM- and 33.3 ± 10.3 mM-Na⁺ and 130.1 ± 4.7 mM- and 137.1 ± 3.2 mM-K⁺ in mock-infected and HSV-1-infected cells respectively. Intracellular Na⁺ did not increase above control levels over at least a 9 h period following HSV-1 infection. The Michaelis constant (Km) of K⁺ transport in HSV-1-infected or mock-infected Vero cells at 6 h post-infection was determined to be the same with calculated values of 1.38 ± 0.51 mM and 1.79 ± 0.42 mM respectively. A virus-induced alteration of intracellular Na⁺ and K⁺ concentrations cannot, therefore, account for the HSV-1-induced inhibition of host protein synthesis at 3 h post-infection as has been suggested in other virus systems.

INTRODUCTION

Infection of cultured cells by herpes simplex virus type 1 (HSV-1) is known to result in modification of cytoplasmic membrane structure as evidenced by the appearance of virus-specific antigens (Norrild et al., 1978; Roane & Roizman, 1964) and insertion of virus-coded glycoproteins (Spear et al., 1970) early after infection. In addition, HSV-1 infection has been shown to induce altered cell-to-cell interactions (Keller et al., 1970) as well as increased binding of concanavalin A (Con A) (Tevethia et al., 1972). There is, however, little information concerning the effect of HSV-1 on functional aspects of the cytoplasmic membrane.

Infection by a number of viruses has been shown to result in an alteration of the permeability of cell membranes to ions. Farnham & Epstein (1963) demonstrated that a decrease in K⁺ uptake occurred in encephalomyocarditis ( EMC) virus-infected cells. Similarly, an alteration of the intracellular concentrations of Na⁺ and K⁺ has been found to be temporally associated with the Sindbis virus-induced inhibition of cellular protein synthesis (Garry et al., 1979). Interestingly, the messages specified by a number of DNA and RNA viruses including vaccinia (Oppermann & Koch, 1976), adenovirus type 5 (Cherney & Wilhelm, 1979), poliovirus (Saborio et al., 1974), Sindbis virus (Garry et al., 1979), vesicular

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stomatitis virus (VSV) and reovirus (Nuss et al., 1975) are efficiently translated under altered ion conditions which effectively block cellular protein synthesis.

The in vitro translation of EMC virus and adenovirus type 5 messages has been found to be stimulated by the addition of Na\(^+\), whereas cellular message, in general, was inhibited by the addition of Na\(^+\) to the translation mixture (Carrasco & Smith, 1976; Cherney & Wilhelm, 1979). The decrease in K\(^+\) uptake following infection with EMC virus and the translation of EMC message in the presence of Na\(^+\) added to concentrations inhibitory to translation of cellular message in cell-free translation systems led Carrasco & Smith (1976) to propose that a virus-induced influx of Na\(^+\) may be the mechanism by which picornaviruses selectively inhibit cellular protein synthesis. It was later suggested that influx of Na\(^+\) resulting from insertion of virus protein into the cytoplasmic membrane may represent a general mechanism for the shut off of cellular functions and the differential translation of virus message (Carrasco, 1977).

We report here the effect of herpesvirus infection on cytoplasmic membrane function as determined by the ability of HSV-1-infected cells to maintain normal intracellular Na\(^+\) and K\(^+\) concentrations via the membrane-bound Na\(^+\)/K\(^+\) ATPase. Results indicate a decrease in rate of K\(^+\) transport but suggest that changes in internal Na\(^+\) and K\(^+\) concentrations cannot account for the rapid inhibition of cellular protein synthesis following HSV-1 infection.

**METHODS**

**Cells and virus.** The African green monkey cells (Vero) used in this study were obtained from M. E. Frazier, Battelle Northwest Laboratories, Richland, Washington, U.S.A. Vero cells were routinely propagated in Eagle's minimal essential medium (MEM; Gibco) containing 8% (v/v) newborn calf serum (Gibco), 10 mM-HEPES buffer pH 7-4, and 50 \(\mu\)g/ml gentamicin sulphate. Normal and infected cells were maintained at 37°C in an atmosphere of 5% CO\(_2\) and 95% air. HSV-1, strain KOS, was provided by S. Kasuga, Eastern Washington University. The virus was plaque-purified and grown to high titre by low multiplicity passage. The virus used was plaque-purified and grown to high titre by low multiplicity passage. Results indicate a decrease in rate of K\(^+\) transport but suggest that changes in internal Na\(^+\) and K\(^+\) concentrations cannot account for the rapid inhibition of cellular protein synthesis following HSV-1 infection.

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**Uptake and incorporation of radiotracers.** Cells were seeded 24 h prior to use in six-well plastic tissue culture plates (Linbro) at a density of 6.2 \(\times\) \(10^4\) cells/cm\(^2\). For leucine incorporation, MEM-1 containing 0.01 \(\times\) the normal concentration of leucine was used with \(^3\)H\)leucine (20 to 50 Ci/mmol) added to give a final concentration of 1 \(\mu\)Ci/ml. Following incubation in the presence of label for the desired length of time at 37°C, the cells were processed on the plate by washing three times rapidly (within 15 s) with 3 ml ice-cold 0.14 M-NaCl, twice for 5 min each with 5 ml cold trichloroacetic acid (TCA), and once more with...
cold NaCl. The cells were solubilized in 0.1 M NaOH at 56 °C for 30 min, and this solution was neutralized by the addition of 1 M acetic acid. Aliquots were taken and incorporated radioactivity determined by liquid scintillation spectrometry using a toluene–Triton X-100 based scintillant. All results are reported as the average of duplicate assays at a minimum.

Uptake studies of $^{86}$Rb$^+$, an analogue of K$^+$ (Ledbetter & Lubin, 1977; Vaughn & Cook, 1972), were performed in MEM-1 lacking K$^+$ with $^{86}$RbCl (0.01 to 1.4 mCi/mmol) added to a concentration of 2 mM unless otherwise noted. In cases where a range of $^{86}$Rb concentrations was examined, the specific activity of the $^{86}$Rb was held constant. Following uptake for appropriate intervals, the cells were washed rapidly with four 3 ml vol. cold 0.14 M NaCl and lysed by the addition of glass-distilled water. Rubidium-86 content was determined either by scintillation counting using $^{32}$P settings or by measurement of Cerenkov radiation in a Beckman Biogamma II counting system. Potassium-free MEM-1 was supplemented with newborn calf serum which had been dialysed at 4 °C overnight against two changes of 0.14 M NaCl. The use of K$^+$-free medium with RbCl added to 2 mM for uptake studies appeared to have little adverse effect on cellular function as the cells retained a normal appearance and rates of leucine incorporation were equivalent to cells in MEM-1 (data not shown). Sodium uptake was assayed by incubation of cultures in MEM-1 containing 0.5 to 1.0 $\mu$Ci/ml $^{22}$NaCl (carrier-free) for the indicated times. Internal $^{22}$Na$^+$ concentrations were determined following washing and processing of the cultures as described for $^{86}$Rb$^+$.

Intracellular K$^+$ and Na$^+$ content. Intracellular K$^+$ concentrations were calculated from the radioactivity retained in cells equilibrated with 2 mM $^{86}$Rb$^+$ in K$^+$-free MEM-1. On the assumption that $^{86}$Rb$^+$ is equivalent to K$^+$ (Ledbetter & Lubin, 1977), the intracellular K$^+$ concentrations were determined from the measured specific activity of $^{86}$Rb$^+$. Calculations of internal K$^+$ were based on mean cell volumes of 2510 $\mu$m$^3$ for mock-infected cells and 3185 $\mu$m$^3$ for HSV-1-infected cells at 7 h post-infection. Cell volumes were determined on a Coulter model ZBI particle counter with attached Coulter Channelyzer using 20 $\mu$m diam. polystyrene beads for calibration. Intracellular Na$^+$ content was similarly calculated after equilibration of intracellular Na$^+$ with 1 $\mu$Ci/ml $^{22}$NaCl in MEM-1.

Polyacrylamide gel electrophoresis (PAGE) and fluorography. Virus-infected or mock-infected cells (1 x 10$^6$) in 25 cm$^2$ plastic tissue culture bottles (Corning) were labelled for 1 h with 2 ml MEM-1 containing 0.01 x the normal concentration of leucine plus 10 $\mu$Ci/ml [3H]leucine (20 to 50 Ci/mmol). Following 1 h labelling periods at 37 °C, the cells were washed three times with cold MEM lacking serum and scraped into 5 ml MEM. The cells were pelleted by centrifugation at 2500 rev/min for 10 min and solubilized by heating to 100 °C for 2 min in 62.5 mM-tris–HCl pH 6.7, 2.5% (w/v) SDS, 5% (w/v) 2-mercaptoethanol, 10% (v/v) glycerol. The samples were electrophoresed as described by Laemmli (1970) using a 7.5% acrylamide concentration in the slab gels and a 3% acrylamide concentration in the stacking gel. Labelled bands were detected by fluorography according to Bonner & Laskey (1974) using Kodak X-Omat R, X-ray film.

Protein determination. Protein was determined either by the method of Lowry et al. (1951) using bovine serum albumin as a standard or by the method of Bradford (1976) using Bio-Rad reagents and protein standard.

RESULTS

Analysis of protein synthesis in HSV-1-infected Vero cells

Analysis of the various classes of protein synthesized in HSV-1-infected cells was accomplished by pulse-labelling of infected cultures with [3H]leucine at various times post-infection followed by PAGE and detection of labelled polypeptides by fluorography.
Fig. 1. Fluorogram of polypeptides synthesized in HSV-1-infected Vero cells. Cells were infected at a multiplicity of infection of 30 to 50, labelled with [3H]leucine at hourly intervals and processed for SDS–PAGE and fluorography as described in Methods. Numbered intervals indicate the labelling period in h post-infection; M represents Vero cells pulse-labelled from 5 to 6 h following mock-infection. Each channel was loaded with 10⁴ ct/min.

Fig. 2. Effect of HSV-1 infection on rate of K⁺ transport by Vero cells. Cells were pulsed with 5 mM-86Rb in K⁺-free MEM for 20 min at each time point. Results were calculated on the basis of ct/min/mg protein and expressed as a percentage of uptake into mock-infected cells over the same interval. Each point represents the mean of three determinations. Uptake into mock-infected cells varied between 2.3 × 10⁴ and 5.2 × 10⁴ ct/min/mg protein. O, HSV-1 infected cells; ●, cycloheximide (50 μg/ml) added to mock-infected cells at the initiation of the experiment.

Fig. 3. Effect of HSV-1 infection on intracellular 22Na levels in Vero cells. Results are presented as ct/min/culture (2.10 × 10⁸ to 2.61 × 10⁸ cells/culture). ●, Mock-infected cells; □, HSV-1-infected cells; ○, mock-infected cells with 10⁻⁶ M-ouabain added at zero time.

(FIG. 1). In general, synthesis of host-specified proteins was rapidly (within 1 to 3 h following infection) inhibited. What appears to be early viral (α) proteins were detectable by 1 to 2 h post-infection, and other classes of virus polypeptides, presumably representing the β and γ...
classes of HSV-1 proteins (Hones & Roizman, 1975), were evident at later times following infection.

**Effect of HSV-1 on K⁺ transport by Vero cells**

Rubidium-86 has been shown to mimic K⁺ in both transport processes and stimulation of Na⁺/K⁺ ATPases, and mammalian cells do not appear to distinguish between the two (Ledbetter & Lubin, 1977; Vaughn & Cook, 1972). Uptake of ⁸⁶Rb by Vero cells was linear over a range of 0.1 to 20 mM for at least 30 min (data not shown). The ability of HSV-1-infected Vero cells to transport K⁺ was examined using ⁶⁶Rb⁺ as a K⁺ tracer in uptake studies. Potassium transport was typically depressed in HSV-1-infected cells by 5 h post-infection to levels of 70 to 90% of that present in mock-infected cells (Fig. 2). Rates of K⁺ transport remained depressed to these levels through at least 10 h post-infection. The onset of this effect is rapid and concurrent with the appearance of visible cytopathic effects (T. Hackstadt & L. P. Mallavia, unpublished observations). The observed depression of K⁺ transport does not appear to be due to lack of turnover of the membrane Na⁺/K⁺ ATPase resulting from virus inhibition of protein synthesis. When protein synthesis was blocked in Vero cells by cycloheximide, a decline in Rb⁺ uptake resulted. However, in contrast to HSV-1-infected cells, the decline in uptake rates resulting from cycloheximide treatment was gradual and did not, after 6 h of exposure, decrease Rb⁺ uptake to the extent that it was depressed in HSV-1-infected cells (Fig. 2). Thus, it appears that virus shut off of cellular protein synthesis does not account for the observed depression of K⁺ uptake.

**Effect of HSV-1 on Na⁺ transport by Vero cells**

To determine if there was an increase in intracellular Na⁺ concentration corresponding to the depression in K⁺ uptake following HSV-1 infection, sodium-22 was utilized in attempts to demonstrate increased levels of Na⁺ in the infected cells. Following a rapid equilibrium of ²²Na with internal Na⁺ pools, no further increase of Na⁺ content in either HSV-1-infected or mock-infected cells occurred over a 9 h period (Fig. 3). Inhibition of the Na⁺/K⁺ ATPase by 10⁻⁶ M-ouabain resulted in a rapid increase in intracellular Na⁺, thus indicating the adequacy of the system for demonstrating changes in the internal Na⁺ pools.

**Mechanism of HSV-1-induced depression of K⁺ transport**

Two mechanisms could, in theory, be responsible for the depression of K⁺ uptake occurring in HSV-1-infected cells. (i) Since the pulse time of 20 min used in these experiments was well within the linear portion of the uptake curve for cells in 5 mM-Rb⁺, it seemed likely that the decrease in K⁺ uptake represented only a decrease in the rate of K⁺ transport in infected cells. (ii) An increased rate of K⁺ efflux could result in an apparent decrease in the rate of K⁺ uptake. To rule out the latter possibility, rates of passive efflux of K⁺ from normal and infected cells were determined by preloading cells with ⁶⁶Rb and measuring retained radioactivity with time following removal of the labelling medium and resuspension in medium free of radiotracer. As shown in Fig. 4, efflux rates from mock-infected or HSV-1-infected cells were not significantly different. This result argues against the possibility of increased passive efflux being responsible for the observed depression in rates of K⁺ uptake. Careful examination of the rates of ⁶⁶Rb uptake into mock-infected and HSV-1-infected cells indeed demonstrated a decreased rate of transport in HSV-1-infected cells at 6 h post-infection. The results of a typical experiment are shown in Fig. 5.

The uptake of ⁶⁶Rb by HSV-1-infected or mock-infected Vero cells as a function of Rb concentration in the medium is depicted in Fig. 6. The curves are analysed as the sum of two components as has been described previously for analysis of alkali cation transport (Shaw, 1955; Vaughn & Cook, 1972). One component was saturable with an apparent Michaelis
Fig. 4. Rates of passive efflux of K⁺ from HSV-1-infected and mock-infected Vero cells. Cells were loaded with 20 mM 86Rb in K⁺-free MEM-1 between 5 and 6 h post-infection. The experiment was initiated by the removal of label and replacement with prewarmed K⁺-free MEM-1 containing 10⁻⁵ M ouabain; intracellular 86Rb was determined at the indicated intervals. O, Mock-infected cells; ●, HSV-1-infected cells.

Fig. 5. Rate of K⁺ transport in mock-infected and HSV-1-infected Vero cells at 6 h post-infection. Error bars indicate the range of triplicate determinations. ▲, HSV-1-infected cells; ○, mock-infected cells.

Fig. 6. Uptake of 86Rb into mock-infected and HSV-1-infected Vero cells as a function of Rb concentration in the medium. Insert illustrates an inverse plot of the data. The $K_m$ of K⁺ transport was calculated to be 1.79 ± 0.42 mM and 1.38 ± 0.51 mM for mock-infected and HSV-1-infected Vero cells respectively. O, Mock-infected cells; ●, HSV-1-infected cells.

constant ($K_m$) for transport of 1.38 ± 0.51 mM for HSV-1-infected and 1.79 ± 0.42 mM for mock-infected Vero cells at 6 h post-infection. These values are consistent with those determined for influx of Rb⁺ into other cultured cells (Vaughn & Cook, 1972). The second component of the uptake curve was a linear increase in rate of influx in proportion to
Na\(^+\)/K\(^+\) transport in HSV-1-infected cells

Table 1. Intracellular Na\(^+\) and K\(^+\) concentrations in mock-infected and HSV-1-infected Vero cells at 7 h post-infection*

<table>
<thead>
<tr>
<th>Concentration (mM) in</th>
<th>Mock-infected cells</th>
<th>HSV-1-infected cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>K(^+)</td>
<td>130.1 ± 4.7(^\dagger)</td>
<td>137.1 ± 3.2</td>
</tr>
<tr>
<td>Na(^+)</td>
<td>26.6 ± 9.4</td>
<td>33.3 ± 10.3</td>
</tr>
</tbody>
</table>

* Based on cell volumes of 2510 \(\mu m\(^3\)\) and 3185 \(\mu m\(^3\)\) for mock-infected and HSV-1-infected Vero cells respectively at 7 h post-infection.

\(^\dagger\) Mean ± standard error.

Intracellular concentrations of Na\(^+\) and K\(^+\) in mock-infected and HSV-1-infected cells were determined from the known specific activities of each following equilibration of radiotracer with the desired internal ion (Table 1). The internal K\(^+\) concentration calculated from \(^{86}\)Rb content was determined to be 130.1 ± 4.7 mM in mock-infected Vero cells and 137.1 ± 3.2 mM in Vero cells infected 7 h previously with HSV-1. Intracellular Na\(^+\) concentrations were calculated to be 26.6 ± 9.4 mM in mock-infected cells and 33.3 ± 10.3 mM in 7 h infected cells. Similar results were obtained when intracellular levels of Na\(^+\) and K\(^+\) were determined by atomic adsorption spectroscopy. These values are consistent with those reported for a number of cultured cells including human foreskin fibroblasts (Ledbetter & Lubin, 1977), mouse L-cells (QuisseU & Suttie, 1973), baby hamster kidney (BHK) (McDonald et al., 1972), 3T3 (Spaggiare et al., 1976; Tupper et al., 1977) and chick embryo fibroblasts (Garry et al., 1979).

**DISCUSSION**

A distinct depression in the rate of K\(^+\) uptake occurred at 5 h following infection of Vero cells by HSV-1 but was not of sufficient magnitude to result in the cells inability to maintain normal levels of intracellular Na\(^+\) and K\(^+\). Because the uptake of \(^{86}\)Rb was measured under conditions where uptake reflected the maximum velocity (\(V_{\text{max}}\)) of the Na\(^+\)/K\(^+\) ATPase and since rates of passive efflux are equivalent for HSV-1-infected and mock-infected cells, the depression of K\(^+\) uptake appears to reflect only a decrease in the rate of K\(^+\) transport.

The mechanism by which the activity of the Na\(^+\)/K\(^+\) ATPase is reduced is not clear. The direct interaction of a virus product with the Na\(^+\)/K\(^+\) ATPase to decrease activity of that enzyme is one possibility. An alternative consideration is that lower Na\(^+\)/K\(^+\) ATPase activity may be an indirect consequence of HSV-1 infection. There is considerable evidence indicating modification of cellular membrane structure following HSV-1 infection. The specific activity of the Na\(^+\)/K\(^+\) ATPase is dependent upon membrane fluidity as measured by lipid acyl chain order parameter (Sinensky et al., 1979). It is possible that the observed depression of active K\(^+\) uptake may represent a secondary effect of virus modification of the cytoplasmic membrane resulting in changes in membrane fluidity which in turn decrease the activity of the Na\(^+\)/K\(^+\) ATPase. A report that the cytoplasmic membrane may actually be stabilized during HSV-1 infection is of interest in this regard (Schlehofer et al., 1979).

The results presented here indicate that infection of cells with HSV-1 does not result in an alteration of the cells ability to maintain a concentration gradient of Na\(^+\) and K\(^+\) against the external environment. Despite a decrease in rate of K\(^+\) transport occurring at 5 h post-infection, intracellular K\(^+\) levels in HSV-1-infected cells at 7 h post-infection were increased concentrations of Rb\(^+\) in the medium. The slope of this component is equivalent to that observed for the influx of \(^{86}\)Rb into ouabain-treated Vero cells (data not shown).

Increased concentrations of Rb\(^+\) in the medium. The slope of this component is equivalent to that observed for the influx of \(^{86}\)Rb into ouabain-treated Vero cells (data not shown).
equivalent to those of mock-infected cells, and intracellular Na\(^+\) concentrations did not increase above control levels over a 9 h period following HSV-1 infection. Ledbetter & Lubin (1977) have shown that a 20 to 40\% reduction of the intracellular K\(^+\) concentration is required before cellular protein synthesis is inhibited. Therefore, the alteration of the internal Na\(^+\) and K\(^+\) concentrations cannot account for the inhibition of host protein synthesis which occurs by 2 to 3 h following infection by HSV-1.

Changes of internal Na\(^+\) and K\(^+\) concentrations have been shown to occur in cells infected with Sindbis virus (Garry et al., 1979), VSV (Francoeur & Stanners, 1978), EMC virus (Farnham & Epstein, 1963), and poliovirus type 2 (Nair et al., 1979). However, with the exception of Sindbis virus, inhibition of cellular protein synthesis was shown to occur before the alteration of Na\(^+\) and K\(^+\) levels. It seems then that this model does not describe a mechanism used by these viruses as a primary means of inhibiting cellular protein synthesis. It may be, however, that for these viruses increased intracellular Na\(^+\) represents a secondary means of inhibiting host cell synthesis to enhance the selective translation of virus message. The role of altered Na\(^+\)/K\(^+\) levels in the inhibition of host protein synthesis by other viruses remains to be determined. Despite the failure of HSV-1 to induce alteration of Na\(^+\) and K\(^+\) concentrations following infection, HSV-1-coded protein synthesis does appear to be significantly more resistant than host protein synthesis to inhibition by altered intracellular Na\(^+\) and K\(^+\) concentrations created by the addition of either ouabain or amphotericin B (T. Hackstadt & L. P. Mallavia, unpublished results).

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Na+/K+ transport in HSV-1-infected cells


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