Specific Increase in Pyrimidine Deoxynucleoside Transport at the Time of Deoxyribonucleic Acid Synthesis in 3T3 Mouse Cells*

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SUMMARY

Initiation of division of density-inhibited 3T3 mouse fibroblasts by fresh serum brought about increased uptake of thymidine and deoxycytidine which coincided closely in time with initiation of DNA synthesis. This increase was specific, for transport of deoxyadenosine, deoxyguanosine and orthophosphate did not change at the time of DNA synthesis. Although similar increases occurred for thymidine and deoxycytidine, kinetic studies indicated that they were taken up by different transport systems. The increased transport of thymidine represented an increase in net uptake, since uptake was stimulated more than efflux.

Increased thymidine uptake was not caused by increased rates of DNA synthesis, since inhibition of DNA synthesis did not prevent the transport increase. In addition, it did not require thymidine kinase, since 3T3 cells lacking this enzyme showed the transport increase. Kinetic studies revealed that the increase was accompanied by an increased \( V_{\text{max}} \) with no change in \( K_m \), indicating activation and/or increased amount of the same rather than a new transport system. Uptake of thymidine at both the basal and stimulated levels occurred by facilitated diffusion below about 5 \( \mu \text{M} \) and by passive diffusion above this concentration. Increased uptake of thymidine was prevented by cycloheximide and further increased by actinomycin D, suggesting that the increase required newly made protein(s) whose synthesis might be controlled at the post-transcriptional level.

Correlations between transport of specific nutrients and growth rates of animal cells in culture have strengthened suggestions that changes in membrane permeability might play an important role in controlling DNA synthesis and cell division (1-4). For example, when normal cells grow to confluency and form a density-inhibited monolayer, large decreases in transport occur for phosphate (5-7), uridine (6, 8), hexoses (9, 10) and thymidine (11, 12). These permeability changes appear to be specific, since growth to confluency is accompanied by decreased uptake of some but not all amino acids (13, 14). In addition, when density-inhibited cells are initiated to divide by adding fresh serum, there is a very rapid increase in transport of phosphate and uridine (6) and also glucose (9). This treatment results in no change of adenosine uptake (6) and rapid decreases in amino acid transport (15), demonstrating specific rather than generalized permeability changes.

Comparative studies of normal and malignant cells have further supported the idea that alterations in membrane permeability might affect growth rates. Transformation by tumor viruses leads to increased uptake of amino acids (13, 16), certain hexoses (10, 16-22), and thymidine (23). In addition, growth to confluency results in decreased uptake of phosphate and uridine by normal but not transformed 3T3 mouse cells (6).

The present studies on the relationship between deoxynucleoside transport and DNA synthesis were prompted by several observations relating pool sizes of DNA precursors to the onset of DNA synthesis. First, uptake of thymidine increases during G1 or at the time of DNA synthesis (24-28). In addition, synchronization of cells with high levels of thymidine which inhibit DNA synthesis can lead to shortening of the G1 period as measured by collection of cells at the G1/S boundary (29, 30). Finally, pool sizes of deoxynucleotides show considerable fluctuations which appear to correlate with the rate of DNA synthesis (7, 20).

Our experiments have shown that uptake of thymidine and deoxycytidine increases at the same time as DNA synthesis in confluent 3T3 cells initiated to divide by addition of fresh serum. In contrast, transport of deoxyadenosine, deoxyguanosine, and orthophosphate does not increase during the period of DNA synthesis. The increase in thymidine transport is prevented by inhibiting protein synthesis. It is not a consequence of increased rates of DNA synthesis, and it can take place in 3T3 cells lacking thymidine kinase (3T3TK- cells). The increase is accompanied by an increase in \( V_{\text{max}} \) with no change in \( K_m \). These results indicate that the increase in thymidine uptake results from increased synthesis of the same transport system or activation of it by a newly synthesized protein.

EXPERIMENTAL PROCEDURE

Materials—Plastic tissue culture flasks and dishes were purchased from Falcon Plastics. Calf serum, glutamine, antibiotics,
tion density of the 3T3 cells was about 3.5 to 4 X 10^4 cells per cm^2. The 3T3TK- cells grew to a final saturation density of always maintained at subconfluent densities. The final saturation density of the 3T3TK- cells, because measurements of thymidine transport should not be complicated by extensive metabolic alterations of intracellular thymidine. The extent to which intracellular thymidine was metabolized by 3T3TK- cells was examined by incubating nonconfluent and confluent cultures of these cells with [3H]thymidine for 10, 60, and 120 min, washing away extracellular [3H]thymidine, and determining the percentage of intracellular radioactivity in thymidine as described under "Experimental Procedure." These experiments demonstrated that over 90% of the intracellular radioactivity was located in thymidine, even after a 120-min incubation period. Similar experiments were carried out on 3T3 cells. As shown in Table I, approximately 10% of the intracellular radioactivity was located in thymidine in these cells regardless of the incubation time. The percentages of radioactivity in thymidine nucleotides are also shown in the

**RESULTS**

**Distribution of radioactivity in intracellular compounds following incubation with [3H]thymidine—Transport experiments were carried out on both 3T3 and 3T3TK- cells.** We employed the latter cells, because measurements of thymidine transport should not be complicated by extensive metabolic alterations of intracellular thymidine. The extent to which intracellular thymidine was metabolized by 3T3TK- cells was examined by incubating nonconfluent and confluent cultures of these cells with [3H]thymidine for 10, 60, and 120 min, washing away extracellular [3H]thymidine, and determining the percentage of intracellular radioactivity in thymidine as described under "Experimental Procedure." These experiments demonstrated that over 90% of the intracellular radioactivity was located in thymidine, even after a 120-min incubation period. Similar experiments were carried out on 3T3 cells. As shown in Table I, approximately 10% of the intracellular radioactivity was located in thymidine in these cells regardless of the incubation time. The percentages of radioactivity in thymidine nucleotides are also shown in the

**Distribution of radioactivity in intracellular compounds following incubation of 3T3 cells with [3H]thymidine**

Confluent cultures were prepared by plating 3T3 cells at a density of 1.5 X 10^6 cells per 35-mm dish and growing them to a final saturation density of 4 X 10^6 cells per cm^2 over a 5-day period. Nonconfluent cultures were prepared by plating 3T3 cells at a density of 2 X 10^6 cells per 35-mm dish. They were used 3 days later when their density was 1.8 X 10^6 cells per cm^2. Cultures were then incubated with [3H]thymidine (10 &mu Ci per ml, 1.0 Ci per mmole) for the period of time indicated in the table. The distribution of radioactivity in intracellular thymidine-containing compounds was measured as described under "Experimental Procedure."
These values varied only slightly with growth rate and labeling time. About 2 to 5% of the total intracellular radioactivity was located in other unidentified compounds.

Specific Increase in Pyrimidine Deoxynucleoside Uptake at Time of DNA Synthesis—Previous studies which demonstrated an increase in thymidine transport during the G1 and S periods of the cell cycle (24-28) prompted us to measure transport of DNA precursors during these periods and to compare the timing of increased rates with the initiation of DNA synthesis. These studies were conducted on confluent 3T3 cells initiated to divide by adding fresh serum. As shown in Fig. 1, this treatment brought about a synchronous wave of DNA synthesis which peaked at about 22 hours (36).

Transport of DNA precursors during G1 and S is also shown in Fig. 1. As can be seen, uptake of thymidine and deoxycytidine into the acid-soluble fraction of the cells increased about 4-fold during S. This increase appeared to coincide closely with the initiation of DNA synthesis. In contrast, transport of deoxyadenosine, deoxyguanosine, and orthophosphate did not increase at the time of DNA synthesis. Increased transport of thymidine and deoxycytidine was therefore specific and not a result of generalized permeability changes.

![Graphs showing uptake rates of various nucleosides and phosphates](image-url)

**Fig. 1.** Deoxynucleoside and phosphate uptake and DNA synthesis by confluent 3T3 cells after addition of fresh serum. Cells were plated at a density of $1.5 \times 10^4$ cells per 35-mm dish and grown to confluency over a 3-day period. Fresh calf serum was then added to a final concentration of 20%. Substrate uptake into the acid-soluble and acid-insoluble cell fractions was measured in parallel cultures as described under "Experimental Procedure" using a 10-min incubation period. ○, rate of DNA synthesis; ●, substrate uptake.
Kinetic experiments indicated that thymidine and deoxyctydine were taken up by different transport systems. Although deoxyctydine competitively inhibited thymidine uptake, the $K_i$ was much higher ($0.4 \times 10^{-4}$ M) than the $K_m$ for both deoxyctydine ($1.1 \times 10^{-4}$ M) and thymidine ($0.5 \times 10^{-4}$ M) uptake.

Effect of Inhibitors of DNA Synthesis on Increased Thymidine Uptake—The increase in thymidine transport during S might be a consequence of increased rates of DNA synthesis which could deplete pools of thymidine or thymidine deoxynucleotides and trigger increased transport. This possibility was assessed by inhibiting DNA synthesis during S and measuring transport of thymidine. Hydroxyurea, cytosine-β-D-arabinofuranoside, or mitomycin C was added to confluent 3T3 cells 18 hours after initiation with fresh serum. DNA synthesis and thymidine uptake were measured at 20 hours. As shown in Table II, each of these inhibitors markedly reduced the rate of DNA synthesis. In contrast, they had much less effect on thymidine transport. Hydroxyurea and cytosine-β-D-arabinofuranoside did not significantly lower thymidine uptake, while mitomycin C reduced it only about 30%. These results demonstrate that the increase in thymidine transport during S was not caused by increased rates of DNA synthesis.

Transport Increase in 3T3TK- Cells—The increase in thymidine transport might be caused by an increase in thymidine kinase. Levels of this enzyme increase during S (37), and it has been suggested that it plays a role in thymidine transport (38). Accordingly, we determined whether the increase in thymidine transport observed in 3T3TK- cells was due to increased thymidine kinase activity. We also employed 3T3TK- cells to determine whether the increase in thymidine transport resulted in a net uptake of thymidine. Efflux of thymidine was measured by equilibrating these cells for 2 hours with [3H]thymidine (2 μM), and then determining the rate of release of radioactivity at 37°C into nonlabeled medium by washed cells. These measurements were conducted on confluent 3T3TK- cells 6 and 22 hours after the addition of fresh serum. As shown in Table III, uptake of thymidine was increased over 2-fold 22 hours after adding fresh serum. Efflux was stimulated less than 2-fold. Stimulation by serum resulted in a 3-fold increase in net uptake of thymidine (Table III).

Effect of Inhibitors of Protein and RNA Synthesis on Increase in Thymidine Transport—To probe further the nature of the transport increase, we examined the requirements for protein and RNA synthesis in thymidine transport.

![Figure 2. Thymidine uptake and DNA synthesis by confluent 3T3TK- cells after addition of fresh serum.](http://www.jbc.org/)

**Table II**

| Inhibitor concentration | Incorporation into DNA | Uptake |
|-------------------------|------------------------|--------|
|                         | cpm/mg protein X 10^3 | μmoles/mg protein/10 min |
| 0                       | 30                     | 101    |
| 1 X 10^-4 M hydroxyurea | 6.1                    | 112    |
| 1 X 10^-3 M hydroxyurea | 1.6                    | 99     |
| 1 X 10^-4 M cytosine-β-D-arabinofuranoside | 6.9 | 103 |
| 1 X 10^-3 M cytosine-β-D-arabinofuranoside | 1.9 | 96  |
| 1 X 10^-4 M cytosine-β-D-arabinofuranoside | 1.3 | 91  |
| 25 μg per ml of mitomycin C | 4.0 | 81   |
| 50 μg per ml of mitomycin C | 2.1 | 66   |
| 70 μg per ml of mitomycin C | 1.9 | 73   |

**Table III**

| Time after serum addition | Uptake | Efflux | Net uptake |
|---------------------------|--------|--------|------------|
| 6 hr                      |        | 10 ± 2 | 14         |
| 22 hr                     | 57 ± 6 | 18 ± 3 | 39         |

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Fig. 3 (left). Effect of cycloheximide on serum-initiated increase in thymidine transport by confluent 3T3 cells. Cells were plated at a density of 1.5 \times 10^4 cells per 35-mm dish and grown to confluency over a 3-day period. Fresh calf serum was then added to a final concentration of 20%. At times indicated by the arrows, cycloheximide was added to a final concentration of 80 \mu M. Thymidine uptake into the acid-soluble fraction was measured as described under “Experimental Procedure.” ■, control cultures; ○, cycloheximide-treated cultures.

Fig. 4 (right). Effect of actinomycin D on serum-initiated increase in thymidine transport by confluent 3T3 cells. Cells were plated at a density of 1.5 \times 10^4 cells per 35-mm dish and grown to confluency over a 3-day period. Fresh calf serum was then added to a final concentration of 20%. At times indicated by the arrows, actinomycin D was added to a final concentration of 6.0 \mu g per ml. Thymidine uptake into the acid-soluble fraction was measured as described under “Experimental Procedure.” ■, control cultures; ○, actinomycin D-treated cultures.

and RNA synthesis. These experiments were carried out on confluent 3T3 cells initiated to divide by adding fresh serum. Preliminary experiments showed that addition of cycloheximide to a final concentration of 80 \mu M inhibited incorporation of [14C]leucine into an acid-insoluble product over 90% within 1 hour. The effect of this concentration of cycloheximide on the serum-initiated increase in thymidine transport is shown in Fig. 3. As can be seen, cycloheximide inhibited thymidine uptake as well as the transport increase brought about by fresh serum. Cycloheximide (80 \mu M) inhibited thymidine uptake about 25% 1 hour after its addition to nonconfluent 3T3 cells.

Analogous experiments were carried out using actinomycin D to inhibit RNA synthesis. This inhibitor was added to a final concentration of 6.0 \mu g per ml, a level which inhibited incorporation of [3H]uridine into an acid-insoluble product over 90% within 1 hour. As shown in Fig. 4, this treatment resulted in a stimulation of thymidine uptake. Treatment of mammalian cells with actinomycin D brings about increased activity of a number of enzymes, presumably by modifying translational controls of enzyme synthesis (39). The requirement for protein synthesis during the serum-initiated increase in thymidine transport, and the stimulation of transport by actinomycin D suggest that the synthesis of protein(s) required for the transport increase might be controlled at the level of translation.

Kinetic Studies on Thymidine Uptake by 3T3 and 3T3TK-Cells—The requirement for protein synthesis during the serum-initiated increase in thymidine transport, and the stimulation of transport by actinomycin D suggest that the synthesis of protein(s) required for the transport increase might be controlled at the level of translation.

Fig. 5. Inset, effect of thymidine concentration on thymidine uptake by confluent 3T3 cells 2 and 22 hours after addition of fresh serum. Cells were plated at a density of 1.5 \times 10^4 cells per 35-mm dish and grown to confluency over a 3-day period. Fresh calf serum was then added to a final concentration of 20%. Thymidine uptake into the acid-soluble fraction of the cells was measured as described under “Experimental Procedure” using a 10-min incubation period. ■, 2 hours after serum addition; ○, 22 hours after serum addition. Main figure, reciprocal of uptake velocity versus reciprocal of thymidine concentration. This figure was constructed from data shown in the inset.

uptake by confluent 3T3 cells as a function of thymidine concentration 2 and 22 hours after adding fresh serum. These data were used to construct the Lineweaver-Burk plot shown in Fig. 5. As can be seen, uptake followed Michaelis-Menten kinetics at thymidine concentrations below about 5 \mu M, indicating that a saturable cell component was involved in transport. At higher concentrations, uptake was directly proportional to...
substrate concentration, demonstrating entry by passive diffusion. (Plagemann and Erbe (40) have recently reported Michaelis-Menten kinetics for thymidine uptake below 2 μM and simple diffusion above 2 μM by hepatoma cells growing in suspension culture.) $V_{\text{max}}$ and $K_m$ values were obtained from the plot of Fig. 5 and are shown in Table IV. As can be seen, the serum initiated increase in thymidine transport by 3T3 cells was accompanied by an increase in $V_{\text{max}}$ with practically no change in the $K_m$. This suggests that increased transport is a result of increased activity and/or amount of the same, rather than a different transport system.

Identical experiments were carried out on confluent 3T3TK- cells following treatment with fresh serum (Fig. 6 and Table IV). Uptake of thymidine by these cells also followed Michaelis-Menten kinetics below about 5 μM and simple diffusion above this concentration. These cells had a slightly higher $K_m$ and somewhat lower $V_{\text{max}}$ for thymidine uptake than 3T3 cells. However, like 3T3 cells, serum treatment of confluent 3T3TK- cells brought about an increase in the $V_{\text{max}}$ for thymidine uptake with no change in the $K_m$, suggesting activation and/or increase in the transport system that also takes up thymidine at the basal level.

**Concentration of Acid-soluble Thymidine-containing Compounds**

| TABLE IV Kinetic constants for thymidine uptake by confluent 3T3 and 3T3TK- cells 2 and 22 hours after addition of fresh serum |
| Cell line and time after fresh serum addition | $V_{\text{max}}$ (pmol/mg protein/5 min) | $K_m$ (μM) |
| 3T3, 2 hours | 63 | 0.48 |
| 3T3, 22 hours | 238 | 0.42 |
| 3T3TK-, 2 hours | 43 | 0.63 |
| 3T3TK-, 22 hours | 88 | 0.63 |

These values were obtained from the data shown in Figs. 5 and 6. Kinetic experiments indicated that they were taken up by different transport systems. In addition, the increased transport of thymidine represented a net increase in uptake by the cells. Measurements on confluent 3T3TK- cells demonstrated that addition of fresh serum stimulated uptake to a greater extent than efflux.

Although initiation of DNA synthesis is accompanied by an increase in thymidine transport, accurate measurements of the rate of DNA synthesis still can be made by following the incorporation of labeled thymidine. This conclusion is based on the data of Foster and Pardee (13) relating intracellular volume to total 3T3 cell protein.

**Table V** Concentration of acid-soluble thymidine-containing compounds in 3T3 and 3T3TK- cells as a function of thymidine concentration in the medium

| Thymidine concentration in medium | Intracellular concentration of acid-soluble thymidine-containing compounds |
|----------------------------------|-------------------------------------------------|
|                                  | 3T3 cells | 3T3TK- cells |
| 4 hours | 22 hours | 4 hours | 22 hours |
| 1.0 | 0.8 | 0.7 | 0.9 |
| 4.0 | 3.6 | 3.8 | 4.0 | 3.7 |

These results demonstrate that initiation of division of density-inhibited 3T3 cells by fresh serum brought about increased uptake of thymidine and deoxyribosine which closely coincident in time with initiation of DNA synthesis. This increased uptake was specific for pyrimidine deoxynucleosides, since transport of deoxyadenosine, deoxyguanosine, and orthophosphate did not change at the time of DNA synthesis. Although transport of thymidine and deoxyribosine increased in a similar manner, kinetic experiments indicated that they were taken up by different transport systems. In addition, the increased transport of thymidine represented a net increase in uptake by the cells. Measurements on confluent 3T3TK- cells demonstrated that addition of fresh serum stimulated uptake to a greater extent than efflux.

**Discussion**

These results demonstrate that initiation of division of density-inhibited 3T3 cells by fresh serum brought about increased uptake of thymidine and deoxyribosine which closely coincident in time with initiation of DNA synthesis. This increased uptake was specific for pyrimidine deoxynucleosides, since transport of deoxyadenosine, deoxyguanosine, and orthophosphate did not change at the time of DNA synthesis. Although transport of thymidine and deoxyribosine increased in a similar manner, kinetic experiments indicated that they were taken up by different transport systems. In addition, the increased transport of thymidine represented a net increase in uptake by the cells. Measurements on confluent 3T3TK- cells demonstrated that addition of fresh serum stimulated uptake to a greater extent than efflux.

Although initiation of DNA synthesis is accompanied by an increase in thymidine transport, accurate measurements of the rate of DNA synthesis still can be made by following the incorporation of labeled thymidine. This conclusion is based on the data of Foster and Pardee (13) relating intracellular volume to total 3T3 cell protein.
studies by Nordenskjöld et al. (26) which showed that increased uptake of thymidine by serum-stimulated mouse fibroblasts was paralleled by a similar increase in the pool size of TTP in cells grown in the absence of added thymidine. Thus, incubation of cells with labeled thymidine during this period would result in similar specific activities of the TTP pool.

Our studies on the mechanism of the increase in thymidine uptake led to the following conclusions. The increase was not a consequence of increased rates of DNA synthesis, since inhibiting DNA synthesis did not prevent the transport increase. Moreover, it did not require thymidine kinase, since a similar response occurred in 3T3 cells lacking this enzyme. Kinetic studies demonstrated that the transport increase was accompanied by an increase in $V_{\text{max}}$ with no change in $K_m$, indicating increased amounts and/or activity of the same rather than a new transport system. The transport increase was inhibited by cycloheximide, but further increased by actinomycin D, suggesting that the increase required the synthesis of protein(s) that might be subject to translational control (39). In addition, the increased uptake was not associated with the appearance of an active system for thymidine transport. Both stimulated and basal-level cells took up thymidine by facilitated diffusion below 5 $\mu$M and by passive diffusion above this concentration.

Even though 3T3 cells very rapidly phosphorylated thymidine to thymidine nucleotides, this appeared to have a small effect on the thymidine transport parameters we examined. Similar results were obtained with 3T3TK- cells which metabolized thymidine to TTP nucleotides, this appeared to have a large effect on the thymidine transport parameters. The transport increase in 3T3 cells which had been initiated with 10$^{-5}$ M levels of fresh serum, also brought about some very similar specific activities of the TTP pool.

The increase in thymidine and deoxycytidine uptake at the time of DNA synthesis suggests that increased pool sizes of these compounds or their derivatives might influence the initiation of DNA synthesis, since inhibiting DNA synthesis did not prevent the transport increase. Moreover, it did not require thymidine kinase, since a similar response occurred in 3T3 cells lacking this enzyme. Kinetic studies demonstrated that the transport increase was accompanied by an increase in $V_{\text{max}}$ with no change in $K_m$, indicating increased amounts and/or activity of the same rather than a new transport system. The transport increase was inhibited by cycloheximide, but further increased by actinomycin D, suggesting that the increase required the synthesis of protein(s) that might be subject to translational control (39). In addition, the increased uptake was not associated with the appearance of an active system for thymidine transport. Both stimulated and basal-level cells took up thymidine by facilitated diffusion below 5 $\mu$M and by passive diffusion above this concentration.

The increase in thymidine and deoxycytidine uptake at the time of DNA synthesis suggests that increased pool sizes of these compounds or their derivatives might influence the initiation of DNA synthesis. To test this possibility we added varying levels of deoxynucleosides ($5 \times 10^{-6}$ to $2 \times 10^{-8}$ M) individually and in combination to confluent 3T3 cells, and also to confluent 3T3 cells which had been initiated with low levels of fresh serum. We then measured the percentage of cells making DNA at various intervals by autoradiography, and mitotic cells by Giemsa stain. We could detect no significant and reproducible change in the timing or extent of DNA synthesis or mitosis.

In addition to these transport increases at the time of DNA synthesis, initiation by fresh serum also brings about some very early changes in uptake rates of other precursors. Large increases in uptake of uridine and phosphate (6) and also glucose (9) can be detected within 15 min. There is no increase in adenosine uptake within 30 min (6), and large decreases in amino acid uptake occur within 1 hour after serum addition (15), demonstrating that these early transport changes are also specific.

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