We have previously shown that 3,5,3′-triiodo-L-thyronine (L-T3) stimulates cell growth and a 4- to 8-fold increase in growth hormone mRNA in GH3 cells. These effects appear to be mediated by a thyroid hormone nuclear receptor with an equilibrium dissociation constant for L-T3 of 0.2 nM and an abundance of about 10,000 receptors per cell nucleus. In this report, we show that L-T3 exerts a pleiotropic effect on GH3 cells to rapidly (within 2 h) stimulate [3H]uridine uptake to a maximal value of 2.5- to 3-fold after 24 h. This results from an increase in the number of functional uridine “transport sites” as shown by studies documenting an increase in the apparent Vmax with no change in the Km, 17 μM. Although the labeling of the cellular uridine pool and pools of all phosphorylated uridine derivatives was increased by L-T3, there was no change in the relative amounts of the individual pools in cells incubated with or without hormone. The intracellular concentration of [3H]uridine was estimated to be similar to that of the medium, suggesting that facilitated transport mediates [3H]uridine uptake. That this increase in [3H]uridine transport was nuclear receptor-mediated is supported by the excellent correspondence of the L-T3 dose-response curve for [3H]uridine uptake and that for L-T3 binding to receptor. Finally, inhibition of protein synthesis by cycloheximide and RNA synthesis by actinomycin D demonstrated that the L-T3 effect required continuing protein and RNA synthesis. These results are consistent with an effect of the L-T3-nuclear receptor complex to increase uridine uptake in GH3 cells by altering the expression of gene(s) essential for the transport process.

Thyroid hormone has important effects on gene expression, cell replication, and differentiation and development (1). In several growth hormone-producing rat pituitary cell lines (GH3, GC, GH2), 3,5,3′-triiodo-L-thyronine (L-T3) stimulates growth hormone mRNA accumulation as well as cell growth (2-5). Abundant evidence indicates that these cellular responses are regulated by a chromatin-associated thyroid hormone receptor (1-6). Stimulation of growth hormone gene transcription by L-T3 is maximal within 1 h and parallels the kinetics of binding of L-[125I]T3 to nuclear receptors (2). After a lag period, L-T3 also stimulates cell replication (6). Hershko et al. (7) proposed that cells exhibit pleiotropic responses in which a set of unrelated metabolic events (e.g. amino acid, glucose, and nucleoside transport) change in concert with cell replication. If these changes are coordinately related to L-T3 stimulation of cell growth, these processes should be mediated by the same nuclear receptor which controls cell replication.

Segal and Gordon (8, 9) reported that L-T3 can rapidly stimulate deoxyglucose and uridine uptake in cultured chick embryo fibroblasts. Stimulation of deoxyglucose uptake during the first 6 h of L-T3 incubation was not blocked by inhibitors of RNA or protein synthesis. This suggested that L-T3 stimulation of membrane-related events could occur independently of a transcriptionally related process (8). However, the reported potency of different iodothyronine analogues paralleled that reported for responses thought to be mediated by the nuclear receptor (10). A similar iodothyronine analogue potency was subsequently described for 3-0-methylglucose uptake by rat thymocytes (11), a response which also was not blocked by cycloheximide. Although this occurred at concentrations several orders of magnitude greater than physiologic, iodothyronine binding studies suggested the existence of a membrane component having similar relative affinities for certain analogues as the nuclear receptor (11). These and other observations (12, 13) imply that the thyroid hormones can interact with plasma membrane receptors which directly regulate membrane transport events.

In this study we have examined the effects of L-T3 on [3H]uridine uptake by GH3 cells. L-T3 stimulates [3H]uridine uptake after a 1-h lag period, and the rate becomes maximal within 24 h of incubation. Analysis of the intracellular acid-soluble radiolabeled uridine, UMP, UDP, and UTP pools indicates that L-T3 stimulates the transport of uridine which is then phosphorylated to generate the uridine nucleotides. Stimulation of [3H]uridine transport by L-T3 in GH3 cells is totally dependent on RNA and protein synthesis. This observation along with the excellent parallelism between L-T3 nuclear receptor occupancy and [3H]uridine uptake indicates that this pleiotropic response reflects a membrane transport event that is modulated by the thyroid hormone nuclear receptor.

**EXPERIMENTAL PROCEDURES**

**Materials**—[5-3H]Uridine (40-60 Ci/mmol), L-3,5,3′[125I]T3 (1100 μCi/μg), and Aquasol were obtained from New England Nuclear. AG 1X-8 and AG 1X-10 resin (200-400 mesh) were purchased from BioRad. Ham’s F-10 culture medium, calf serum, fetal calf serum, and horse serum were obtained from Gibco. Calf serum was treated with AG 1X-8 resin to remove thyroid hormone as previously described (14). The nucleoside transport inhibitor 4-nitrobenzyl-6-thioinosine

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**EVIDENCE FOR REGULATION BY THE THYROID HORMONE NUCLEAR RECEPTOR**

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was purchased from Sigma. All other chemicals and reagents were from Sigma, Eastman, or Fisher Scientific.

**GH Cell Culture Conditions and Measurement of \([^3H]\)Uridine Uptake**—GH cells were cultured with Ham's F-10 medium supplemented with 2.5% fetal calf serum and 15% horse serum as previously described (3, 6). To study the effects of L-T3 on uridine uptake, the media was exchanged with Ham's F-10 medium containing 10% (v/v) thyroid hormone-depleted calf serum, and the cells were incubated for 48 h. This process was repeated one additional time. L-T3 was added to the cell cultures in 10–20 μl of the same medium to achieve the final concentrations indicated in the text. At various times after L-T3 incubation, uridine uptake was assessed by incubating the cells with \([^3H]\)uridine for 0.5–1 h as indicated. In some experiments the cells received cycloheximide (0.5 μg/ml) or actinomycin D (1 μg/ml) at the times indicated prior to \([^3H]\)uridine incubation. These compounds were prepared as 50-fold-concentrated stock solutions and added directly to the medium. After the incubation with \([^3H]\)uridine, the media were then removed and the cell monolayers were rapidly washed three times at 4 °C with chilled isotonic saline. One ml of 8% (w/v) trichloroacetic acid was then added to each monolayer to determine the trichloroacetic acid-soluble and precipitable uridine-radiolabeled pools. The trichloroacetic acid was removed and the residual cell material, which remains attached to the plastic surface, was solubilized with 0.4 N NaOH.

Aliquots of the trichloroacetic acid-soluble fraction and the 0.4 N NaOH fractions were analyzed using Aquasol and a liquid scintillation counter. A sample of the trichloroacetic acid-soluble fraction was also used for analysis of DNA (15) or protein (16). One million GH1 cells contain 10 μg of DNA and 100 μg of protein. We exclude the possibility that the trichloroacetic acid precipitable fraction represented incorporation into DNA, the fractions solubilized with 0.4 N NaOH were incubated for 2 h at 30 °C and then precipitated with 10% trichloroacetic acid (v/v). Less than 5% of the original trichloroacetic acid-insoluble radiolabeled material was recovered in the precipitated fraction indicating that over 95% of the radiolabel was incorporated into RNA.

**Separation of the Intracellular Radiolabeled Uridine Fractions**—In some experiments the trichloroacetic acid-soluble radiolabeled material was separated into uracil, uridine, UMP, UDP, and UTP using a Bio-Rad AG 1X-10 resin column as described by Lindsay et al. (17). The trichloroacetic acid was removed by four sequential extractions with 4 volumes of water saturated diethyl ether. The aqueous phase (0.2 ml) was reacted with 0.3 ml of 0.1 M KOH and 0.08 ml of 1.0 N NaOH to form a borate complex with uridine. The sample was then applied to a 0.7 × 2.5-cm column of AG 1X-10 resin and the column was eluted with 8 ml of the borate-free serum for 24 h. The fractions were then incubated with the indicated concentrations of L-T3 (30 μM) for 24 h at 37 °C. The cell monolayers were then chilled to 4 °C and harvested to isolate the nuclei as previously described (2, 18). The radioactivity in the nuclei was quantitated using a Packard gamma spectrometer at 55% efficiency followed by DNA determination. Nonspecific binding of L-[^3H]T3 to GH1 cell nuclei was estimated using 5 μM nonradioactive L-T3. This value, always less than 5% of total binding, was subtracted from results obtained using radioactive hormone alone.

**RESULTS AND DISCUSSION**

**Kinetics of Stimulation of Uridine Uptake and Incorporation into RNA by L-T3 in Cultured GH1 Cells**—The coordinate relationship of the cell uptake of amino acids, glucose, and nucleosides with L-T3 has been demonstrated and characterized for over a decade (7, 19–27). Stimulation of replication by a variety of distinct factors increases the cell accumulation of \([^3H]\)uridine and has been extensively studied in a variety of cell lines (7, 19, 20, 23, 26, 27). We have previously demonstrated that L-T3 increases the growth rate of GH1 cells (6). Therefore, we attempted to determine if L-T3 had a pleiotropic effect on the transport and/or metabolism of \([^3H]\)uridine. Fig. 1 illustrates the effect of 5 nm L-T3 on stimulating \([^3H]\)uridine uptake in GH1 cells into the trichloroacetic acid-soluble pool over 31 h of incubation. L-T3 increased the rate of accumulation of \([^3H]\)uridine into the trichloroacetic acid-soluble pool within 3 h, and this increased progressively to a maximal rate which was achieved within 24 h. Incorporation of \([^3H]\)uridine into RNA paralleled the change in accumulation of \([^3H]\)uridine into the trichloroacetic acid-soluble pool, and at each time point in the L-T3-incubated and the control cells approximately 95% of the total cell \[^3H\] radioactivity was incorporated into RNA (not illustrated). Therefore, we also corrected for the change in the trichloroacetic acid-soluble \([^3H]\)uridine nucleotide pool, L-T3 does not appear to stimulate total cell RNA synthetic rates.

**Analysis of the Trichloroacetic Acid-soluble \([^3H]\)Uridine and Phosphorylated \([^3H]\)Uridine Pools**—Evidence in a number of cell lines indicates that the rate-limiting step in the cellular accumulation of \([^3H]\)uridine is due to an increase in the rate of facilitated transport and not the phosphorylation of uridine (19, 22, 26, 27). That this is the case in GH1 cells is indicated in Table I. L-T3 stimulated an approximate 2-fold increase in total cell \([^3H]\)uridine accumulation and incorporation into RNA represented approximately 40% of the total cell radioactivity. The trichloroacetic acid-soluble radiolabeled material was separated into fractions representing uracil, uridine, UMP, UDP, and UTP. With the exception of uracil, the picomoles of \(^3H\) radioactivity in each fraction of the L-T3-incubated cells was approximately 2-fold greater than the control cells. In both the L-T3-incubated and the control cells each radiolabeled fraction represents the same percentage of the total trichloroacetic acid-soluble radiolabeled material (uridine, 2%; UMP, 22%; UDP, 16%; UTP, 60%). Although the levels of \([^3H]\) in the pools of uridine and in all of the phosphorylated uridine derivatives increase with L-T3 incubation, the ratio of the L-T3 to the control cell cultures remains the same for each fraction. This strongly argues that metabolism of uridine to UMP, UDP, and UTP is not responsible for the L-T3 mediated increase in uridine uptake by these cells.

Additionally, GH1 cells have an average diameter of 16 μm which can be used to calculate an average cell volume of about 2 × 10⁶ mm³. Based on the picomoles of \([^3H]\)uridine/10⁶ cells, and assuming that the cells are 80% water, we estimate that the intracellular \([^3H]\)uridine concentration in the L-T3 incubated cells is about 25–30 nm. This value is virtually identical to the extracellular \([^3H]\)uridine concentration used in the experiment of Table I (29 nm) suggesting that \([^3H]\)uridine enters the cell by facilitated transport.

**Influence of L-T3 on the Vmax and the Ks for Uridine Transport**—Table I suggests that L-T3 stimulates the accumulation of \([^3H]\)uridine into GH1 cells which is then rapidly phosphorylated to UMP, UDP, and UTP. This supports the notion that L-T3 increases the rate of \([^3H]\)uridine uptake either by stimulating an increase in the \(K_s\) for uridine transport or by increasing the number of transport sites. The \(K_s\) and \(V_{max}\) for uridine uptake in control cells and cells incubated with L-T3 for 6 h were examined (Fig. 2). L-T3 stimulated a 1.7-fold increase in the \(V_{max}\) while \(K_s\) for uridine uptake (17 μM) was identical to control values. This suggests that L-T3 stimulates \([^3H]\)uridine uptake by increasing in the number of functional transport units. Furthermore, the \(K_s\) for facilitated transport reported for a number of cell lines ranges from 6 to 80 μM (19, 26–29). These values are in good agreement with the \(K_s\) of 17 μM which we have observed in GH1 cells ± L-T3.

Uridine transport in some but not all cell lines can be
with diethyl ether, the acid-soluble radioactivity was then separated using trichloroacetic acid (w/v). After removing the trichloroacetic acid the acid-insoluble radioactivity. Each point represents the average of three cell cultures which showed less than ±3% variation.

**Fig. 2 (center).** Estimation of the $K_m$ and the $V_{max}$ for uridine uptake in L-T3 incubated and control cell cultures. GH$_1$ cells were incubated with (O) or without (●) 5 nM L-T3 for 6 h. $[^{3}H]$Uridine was then added (1 μCi/ml) along with various concentrations of nonradioactive uridine. After a 1-h incubation a sample of the medium was counted to determine the actual uridine concentrations which were calculated to be 8, 11, 15, 22, 40, 85, and 160 μM. The cells were washed and processed as described under "Experimental Procedures" to determine the acid-soluble radioactive fraction. $V$, pmol/h/10$^6$ cells. Each point represents the average of three cell cultures which showed less than ±5% variation.

**Fig. 3 (right).** Influence of cycloheximide and actinomycin D on the L-T3-stimulated and basal $[^{3}H]$uridine uptake in GH$_1$ cells. GH$_1$ cells were incubated ±5 nM L-T3 for 24 h. Cycloheximide (CH), 0.5 mm, was then added to one-third of the control and L-T3-treated cells while 1 μg/ml of actinomycin D (AMD) was added to a second set of cells. The remaining cells were maintained with or without L-T3 and served as controls. Thirty min prior to the times indicated in the figure the cells received 2 μCi/ml of $[^{3}H]$uridine. The acid-soluble radioactive fraction was then determined as described under "Experimental Procedures." O—O, control cells; ---●, 0.5 mm cycloheximide; O—O, 1 μg/ml actinomycin D; O—O, 5 nM L-T3; O—O, 5 nM L-T3 and 0.5 mm cycloheximide; O—O, 5 nM L-T3 and 1 μg/ml actinomycin D. Each point represents the average of three cell cultures which showed less than ±5% variation.

| TABLE 1 Analysis of the distribution of $[^{3}H]$uridine into acid-soluble and -insoluble fractions of GH$_1$ cells |
|---------------------------------------------------------------|
|                 | Control | L-T3 | L-T3/control |
| Radiolabeled component | pmol/10$^6$ cells (× 10$^6$) |
| Uracil | 1.1 | 1.2 | 0.99 |
| Uridine | 3.5 | 6.6 | 1.89 |
| UMP | 40.4 | 73.5 | 1.82 |
| UDP | 28.3 | 53.4 | 1.89 |
| UTP | 108.6 | 207.9 | 1.91 |
| Total nucleotide | 181.9 | 342.6 | 1.88 |
| RNA | 129.2 | 236.9 | 1.84 |

not be directly determined in GH$_1$ cells, the effect of L-T3 on the $V_{max}$ is consistent with an increase in the number of transporter units.

**Influence of Cycloheximide and Actinomycin D on Stimulation of $[^{3}H]$Uridine Transport by L-T3—A previous study in cultured chick embryo heart cells suggested that L-T3 could stimulate sugar transport even when RNA or protein synthesis was inhibited by actinomycin D or cycloheximide (8). To explore this we examined the influence of cycloheximide (0.5 mm) and actinomycin D (1 μg/ml) on uridine uptake in the trichloroacetic acid-soluble pool in cells first incubated for 24 h with L-T3 to stimulate steady state levels of $[^{3}H]$uridine uptake (Fig. 3). These concentrations of cycloheximide and actinomycin D inhibit protein synthesis by 95 and 20%, respectively (33), while actinomycin D inhibits RNA synthesis by greater than 95% (33). Cycloheximide incubation caused a first-order decay in the rate of $[^{3}H]$uridine uptake with a half-life of approximately 3 h in the L-T3-cultured cells. The relative amounts of UTP, UDP, UMP, and uridine in the radiolabeled trichloroacetic acid-soluble pool was not altered by cycloheximide incubation (data not shown).

Actinomycin D also elicited a decrease in the rate of uridine uptake in L-T3-incubated cells which after a 1-2-h lag period also decayed with a half-life of about 5 h. The decay of uridine uptake in the control cell cultures incubated with cycloheximide or actinomycin D (Fig. 3) both showed a half-life of greater than 15 h. The reason for the different half-lives in the control and L-T3 cultured cells is unclear but may indicate that L-T3 stimulates the synthesis of a distinct uridine transport system which has a similar $K_m$ as the control inhibited by 4-nitrobenzyl-6-thioinosine (NBMPR) which binds to the transporter and blocks the transport site (30). Thus, in those cells it is possible to measure the amount of transporter by the binding of $[^{3}H]$NBMPR (31). However, NBMPR did not inhibit the uptake of $[^{3}H]$uridine in GH$_1$ cells while $[^{3}H]$uridine transport in HeLa cells (known to respond to NBMPR (32)) was inhibited by this compound (data not shown). Although the $[^{3}H]$uridine transporter can...
cells. Alternatively, the transport system stimulated by L-T3 may be incorporated into a different membrane "environment" and therefore turns over more rapidly than in the control cell cultures.

To assess whether L-T3 directly activates the uridine transport system or if this regulation is mediated by stimulation of RNA and protein synthesis, we examined the influence of cycloheximide (0.5 mM) and actinomycin D (1 μg/ml) on the induction process. Cycloheximide (Fig. 4) completely inhibited the induction of uridine uptake by L-T3 to the same value as in the control cells with cycloheximide. Furthermore, addition of cycloheximide 4 h after L-T3 stimulation of uridine transport resulted in a reduction in the uridine transport rate to the same value as the control cells. Similar results were also obtained in a separate experiment performed with actinomycin D (Fig. 5).

In a study using a related cell line (GH4C1), Martin et al. (29) reported that thyrotropin-releasing hormone (TRH) induced a rapid 2- to 3-fold increase followed by a prolonged 40–50% decrease in [3H]uridine uptake. These changes were attributed to an effect of TRH on [3H]uridine phosphorylation (34). Although the rapid effect of TRH on [3H]uridine uptake was due to a change in the apparent Vmax rather than the K0n (34), there are two significant differences between our observations with L-T3 and those of Martin et al. (29). First, they observed a maximal effect within 30 min of TRH incubation. This is much more rapid than the effect of L-T3 in GH1 cells (Figs. 1, 4, and 5). Second, [3H]uridine uptake stimulated by TRH was not altered by cycloheximide incubation, whereas the effect of L-T3 in GH1 cells is inhibited (Figs. 3 and 4).

Comparison of the Level of Nuclear L-[32P]T3-Receptor Complexes to Stimulation of [3H]Uridine Uptake by L-T3—The above studies indicate that induction of uridine transport by L-T3 is mediated by a mechanism which is dependent upon RNA and protein synthesis. This supports the notion that this transport function is regulated by the thyroid hormone nuclear receptor which has been shown to be rate-limiting for transcriptional control of genes regulated by thyroid hormone (2). Further support for this conclusion is illustrated in Fig. 6. This study shows an excellent agreement between the rate of uridine transport 24 h after incubation with 0.1–5 nM L-T3 and the level of L-[32P]T3-receptor complexes present 24 h after incubation with L-[32P]T3 over the same concentration range.

Although abundant evidence indicates that the primary action of thyroid hormone is mediated at the transcriptional level by its nuclear receptor (2-5), several reports have suggested that L-T3 can increase membrane transport processes by a direct interaction with plasma membrane binding components (8–11). While this study was in progress Halpern and Hinkle (35) reported that L-T3 rapidly stimulated the accumulation of [3H]uridine in GH1 cells. The response, 1.5- to 2-fold, was maximal within 2 h and did not increase with further incubation. However, basal total cell [3H]uridine uptake was increased 100% by cycloheximide or decreased by 50% with 10 μg/ml actinomycin D. Therefore, it was not possible to resolve whether stimulation of [3H]uridine uptake by L-T3 was dependent on RNA and protein synthesis or to conclude that L-T3 acted at the cell surface as suggested for TRH stimulation of [3H]uridine uptake in GH1 cells (35).

Several lines of evidence suggest that L-T3 stimulation of [3H]uridine transport in GH1 cells is mediated at the nuclear level and does not reflect a direct action at the plasma membrane. First, Fig. 6 shows an almost exact correspondence between the dose-response curve for L-T3-receptor binding and L-T3 stimulation of [3H]uridine transport. Second, ongoing protein synthesis is necessary for the effect since the L-T3 response is rapidly inhibited by cycloheximide (Figs. 3 and 4). Supporting this observation are the results of Surks et al. (24) indicating that L-T3 stimulation of α-aminobutyric acid-soluble radioactivity was then determined as described under "Experimental Procedures." Each point represents the average of three cell cultures which showed less than ±2% variation.

Fig. 4 (left). Inhibition of L-T3 stimulation of [3H]uridine uptake by cycloheximide. At zero time some of the cultures received 5 nM L-T3 (●) while the others remained untreated as controls (O). Other cultures received 0.5 mM cycloheximide (CH) with (■) or without (□) 5 nM L-T3. A final group of cultures received 0.5 mM cycloheximide after a 4-h incubation, as indicated by the arrow, without (□) or with (■) 5 nM L-T3. Thirty min prior to the times indicated in the figure the cells received 1 μCi/ml [3H]uridine. The acid-soluble radioactivity was then determined as described under "Experimental Procedures." Each point represents the average of three cell cultures which showed less than ±2% variation.

Fig. 5 (right). Inhibition of L-T3 stimulation of [3H]uridine uptake by actinomycin D. The details of this experiment are similar to that described in the legend to Fig. 4 except that 1 μg/ml actinomycin D (AMD) and 2 μCi/ml of [3H]uridine were used. O, control cells; □, 1 μg/ml actinomycin D from zero time; ■, 5 nM L-T3; □, 5 nM L-T3 and 1 μg/ml actinomycin D from zero time and 5 nM L-T3 from zero time and 1 μg/ml actinomycin D after 4 h. Thirty min prior to the times indicated in the figure the cells received 2 μCi/ml of [3H]uridine. The acid-soluble radioactive fraction was then determined as described under "Experimental Procedures." Each point represents the average of three cell cultures which showed less than ±7% variation.

Fig. 6. Comparison of L-[32P]T3-receptor occupancy and stimulation of [3H]uridine uptake in GH1 cells. GH1 cells were incubated with the concentrations of L-[32P]T3 indicated while parallel cultures received the same concentrations of unlabeled L-T3. After 24 h the L-[32P]T3-incubated cells were used to quantitate L-[32P]T3-receptor levels and the results are expressed as femtomole of L-T3 bound/100 μg of cell DNA (O). The parallel flasks which received unlabeled L-T3 for 24 h were incubated for 1 h with 1 μCi/ml of [3H]uridine and the acid-soluble radioactive fraction (C) determined as described under "Experimental Procedures." Each point represents the average of three cell cultures which showed less than ±7% variation. The extent of "nonspecific" binding of L-[32P]T3, as determined by co-incubation with 5 μM L-T3, represented less than 5% of the total nuclear bound [32P] radioactivity.
acid transport in GC cells was dependent on protein synthesis. Additionally, iodothyronine analogue potency was found to parallel the relative analogue affinity for the thyroid hormone nuclear receptor (24). Finally, the actinomycin D-mediated inhibition of increased $[^3H]$uridine transport (Figs 3 and 5), under conditions where protein synthesis is only minimally inhibited, suggests that RNA synthesis is necessary for T3-mediated effect. Our results, along with the demonstrated ability of L-T3 to rapidly stimulate growth hormone gene transcription (2), suggest that the hormone-mediated increase in $[^3H]$uridine uptake is likely due to the regulated expression of genes involved in the transport process.

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