Effects of Nucleoside Transport Inhibitors on the Salvage and Toxicity of Adenosine and Deoxyadenosine in L1210 and P388 Mouse Leukemia Cells

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ABSTRACT

Incubation of deoxycoformycin-treated L1210 leukemia cells with dipyridamole or nitrobenzylthioinosine, inhibitors of nucleoside transport, enhanced the long-term incorporation of 2'-deoxyadenosine and adenosine into the nucleotide pool and the toxicity of 2'-deoxyadenosine for the cells. In contrast, 2'-deoxyadenosine uptake in deoxycoformycin-treated P388 leukemia cells, which was about 10 times greater than that in L1210 cells, was inhibited by dipyridamole and nitrobenzylthioinosine, and 2'-deoxyadenosine toxicity was not significantly affected by the transport inhibitors. P388 cells also were about 6 times more resistant to 2'-deoxyadenosine than were L1210 cells, in spite of the greater uptake of the nucleoside. We found that purine nucleoside transport in L1210 and P388 cells exhibited similar kinetic properties and sensitivity to dipyridamole and nitrobenzylthioinosine (both influx and efflux) and that the stimulation of 2'-deoxyadenosine uptake by the inhibitors in L1210 cells is not mediated at the level of its transport into the cells but rather reflects an enhanced intracellular net accumulation of deoxyadenosine nucleotides.

INTRODUCTION

Nucleoside salvage pathways in animal cells in their simplest form consist of two steps: the carrier-mediated transport of the nucleoside across the membrane, coupled with a simple, irreversible Michaelian phosphorylation within the cells (1-3). In the case of Ado and 2'-dAdo, an additional route consists of their deamination to Ino and dIno, respectively, phosphorylization of the latter, and salvage of the resulting Hyp. The non-mediated permeation of natural nucleosides is so slow, though it varies somewhat with their lipid solubility, that the effective salvage of a nucleoside depends on the functioning of the transport system. For example, a transport deficient variant of S49 mouse lymphoma cells (4) fails to grow in medium containing aminopterin, Hyp, and dThd, since it cannot salvage dThd.

The brush borders of epithelial cells of the kidney and intestine possess a Na+ dependent, concentrative nucleoside transport system (5, 6), but such a system has not been detected in erythrocytes, various tumor cells, hepatocytes, and numerous untransformed and transformed mammalian cell culture lines (1). The latter types of cells probably express only a single non-concentrative nucleoside transporter (1, 7, 8), which, however, may exist in the plasma membrane in two forms (9-11); one form is inhibited by nmolar concentrations of NBTI (nitrobenzylthioinosine) which correlates with the binding of NBTI to high affinity sites on the cell (Kd ~0.5 nM), whereas the other form lacks these binding sites and is inhibited only at μM concentrations of NBTI. The system, regardless of in which configuration, transports all natural pyrimidine and purine ribo- and deoxyribonucleosides with similar, though not equal, efficiency (1, 7, 8). However, with respect to purine ribo- and deoxyribonucleosides, this conclusion is largely based on the finding that they inhibit the transport of Urd and dThd in various types of cultured cells and human erythrocytes (1, 8, 12-14). Urd and dThd have been the favorite nucleosides for transport measurements because human RBC lack Urd and dThd kinases (12), appropriate variants lacking these enzymes are available for a considerable number of cell lines (1), and cultured cells can be sufficiently depleted of ATP to practically completely block the phosphorylation of Urd and dThd (1, 15). These cells also lack Urd and dThd phosphorolyases or their levels are so low as to not interfere with transport measurements. Thus, it is possible to measure the equilibration of these nucleosides across the membrane in metabolically inert cells.

Direct studies of Ado and dAdo transport, on the other hand, have been more problematic. Their deamination can be inhibited effectively by treatment with dCF, but it has been difficult to block their conversion to nucleotides either by genetic or biochemical approaches. Several studies have determined the kinetics of uptake4 of Ado in human RBC and cultured cells (13, 16-25), but in many studies two kinetic components in uptake were reported, and it was not clear whether the reported kinetic parameters pertained to Ado transport, a step in Ado metabolism, or a combination thereof. Even in cells in which Ado deamination and phosphorylation were greatly inhibited, Ado uptake appeared to be concentrative due either to non-specific binding or to residual conversion to nucleotides by direct phosphorylation or via adenosine, presumably resulting from the action of methylthioadenosine phosphorylase (26). Similar problems in interpretation apply to three recent reports which showed that the uptake of 2'-dAdo by Ado deaminase-deficient or inhibited human lymphoma cells (27) or mouse L1210 lymphocytic leukemia cells (28, 29) was stimulated or little affected, rather than inhibited, by NBTI and dipyridamole, another potent inhibitor of nucleoside transport (1, 7). The results raised the possibility that dAdo is transported by an alternate NBTI- and dipyridamole-resistant transporter (27) or that the accumulation of dAdo

1 This work was supported by USPHS Research Grants GM 24468 and AM 35211.
2 To whom requests for reprints should be addressed.
3 The abbreviations used are: Ado, adenosine; Ino, inosine; Hyp, hypoxanthine; dThd, thymidine; Urd, uridine; Ade, adenine; dCF, 2-deoxycoformycin; NBTI, 6-[4-nitrobenzyl(thio)]-9β,β-di-rubfuranylopyrimidine; IC50, concentration causing 50% inhibition.
4 "Uptake" denotes the total intracellular accumulation of radioactivity from exogenous labeled substrate regardless of metabolic conversions. "Transport" denotes solely the transfer of unmodified substrate across the cell membrane as mediated by a saturable, selective carrier.
nucleosides was stimulated by the transport inhibitors, perhaps by preferentially inhibiting the efflux of dAdo (29). To distinguish between these possibilities, we have determined the effect of dipyridamole and NBTI on the long term uptake of dAdo and Ado by dCF-treated L1210 and P388 cells, as well as on the influx and efflux of these purine nucleosides as measured by rapid kinetic techniques in ATP-depleted cells.

MATERIALS AND METHODS

Cell Cultures. Mouse L1210 and P388 cells were propagated in suspension culture in Eagle's minimum essential medium for suspension cultures supplemented with non-essential amino acids, sera, and extra d-glucose as described previously (30). For measuring the inhibition of cell growth by 2'-dAdo, the cells were seeded into 24-well tissue culture plates (about 1 x 10^5 cells/well) and incubated in a CO_2 incubator at 37°C for 3 days. The cells were then enumerated in a Coulter Counter.

The cell lines were examined periodically for Mycoplasma contamination by the Urd/uracil incorporation method (31). No contamination was detected.

Measurements of Uptake of Radiolabeled Substrates by Cells. Cells were collected from exponential phase cultures and suspended to 2-3 x 10^5 cells/ml in basal medium 42 (32). The suspension was supplemented with 25 μM dCF and after 5 min of incubation at 37°C, samples thereof were mixed with radiolabeled substrate as indicated in the appropriate experiments. The suspensions were incubated at 37°C, and at specified times the cells from samples of suspension were separated from the culture medium by centrifugation through an oil mixture as described previously (33). The cell pellets were analyzed for radioactivity. The radioactivity values were corrected for substrate trapped in the extracellular space of cell pellets, as estimated by use of [14C]inulin, and converted to pmol of substrate taken up/µl cell water on the basis of cell water values, determined experimentally using 3H_2O (34).

For efflux measurements, a suspension of 1-2 x 10^6 cells/ml was equilibrated with a specified concentration of radiolabeled substrate. Samples of the suspension were mixed using the dual syringe procedure at short time intervals in a ratio of 1:7.3 (opposite to that in influx measurements) with basal medium containing, where indicated, specified concentrations of transport inhibitors. The cells were separated from the medium by centrifugation through oil and analyzed for radioactivity.

RESULTS AND DISCUSSION

2'-dAdo Toxicity of L1210 and P388 Cells. We have compared the effect of various concentrations of dipyridamole and 2'-dAdo on the growth of dCF-treated L1210 and P388 cells. P388 cells were chosen for this comparison because they are also mouse tumor cells of lymphoid origin and have a similar size, growth properties, and nucleoside transport characteristics as L1210 cells (10). In this comparison, it was further of importance to rule out that any observed growth inhibition was due to the treatment with dipyridamole per se, since the latter is toxic, at higher concentrations, to L1210 and P388 cells (see Chart 1A, zero 2'-dAdo concentration) and other types of cultured mammalian cells. This toxicity is unrelated to an inhibition of nucleoside transport (12). The results in Chart 1A show that the presence of concentrations of dipyridamole that exhibited little, if any, toxicity by themselves (1, 4, and 10 μM) greatly potentiated the inhibition of growth of dCF-treated L1210 cells by various concentrations of 2'-dAdo. The results confirm those reported by Kang and Kimball (29). On the other hand, dipyridamole showed little synergism with 2'-dAdo in inhibiting the growth of P388 cells (Chart 1B). Furthermore, P388 cells were significantly more resistant to 2'-dAdo than were L1210 cells (IC_50 about 7 versus 40 μM 2'-dAdo).

The presence of 0.5 μM NBTI also potentiated the toxicity of 2'-dAdo for L1210 but not for P388 cells (data not shown). The effect was about equivalent to that observed with 2 μM dipyridamole. NBTI by itself did not affect the growth of either cell line.

Effects of Dipyridamole and NBTI on the Uptake of 2'-dAdo and Ado in L1210 and P388 Cells. Chart 2, A and B, illustrates time courses of uptake of [2,8-3H]2'-dAdo into total cell material by dCF-treated P388 and L1210 cells, respectively, in the presence of 2 and 10 μM dipyridamole and 500 nM NBTI. First, the results show that control P388 cells took up 100 times more 2'-dAdo than did L1210 cells in 2 hr of incubation at 37°C. Second, whereas in P388 cells, as one might expect, dipyridamole and NBTI inhibited the uptake of 2'-dAdo, both stimulated its uptake in L1210 cells. NBTI had relatively little effect on 2'-dAdo uptake in P388 cells when compared to dipyridamole, but this is not unexpected, since only about 80% of Urd transport of P388 cells is inhibitable by NBTI at concentrations up to 1 μM (9, 10), whereas dipyridamole at 20 μM inhibits transport >95% (10). However, the same is true for Urd transport in L1210 cells (9, 37).
SALVAGE OF Ado AND dAdo IN P388 AND L1210 CELLS

Chart 1. Effects of 2'-dAdo in combination with dipyridamole on the proliferation of L1210 (A) and P388 (B) cells. 24-well cultured plates were seeded with about 1 x 10^6 cells/well in 1 ml of growth medium supplemented with the indicated concentrations of dipyridamole (DIP) and 2'-dAdo plus 5 μM dCF. The plates were incubated at 37°C for 3 days, and the cells in each well were enumerated in a Coulter Counter. Control cultures of L1210 and P388 cells incubated with dCF alone contained 1.0 x 10^6 and 1.4 x 10^6 cells/well, respectively.

Chart 2. Effects of dipyridamole and NBTI on the uptake of [2,8-3H]2'-dAdo by P388 and L1210 cells (A and B, respectively) and its incorporation into acid-insoluble material (C). Samples of suspensions of about 1 x 10^7 BP388 or L1210 cells/ml of BM428 were supplemented with 20 μM dCF and 5 min later as indicated with 2 or 10 μM dipyridamole (DIP) or 500 nM NBTI plus 40 μM [2,8-3H]2'-dAdo (10 cpm/pmol). At the indicated times of incubation at 37°C, the cells from 0.5-ml samples of suspension were collected by centrifugation through an oil layer and were analyzed for radioactivity, and replicate samples were analyzed for radioactivity in acid-insoluble material. All points are averages of duplicate samples. The broken lines indicate the intracellular concentration of substrate equivalent to that initially in the medium.

Effects of Dipyridamole and NBTI on Purine Nucleoside Transport in L1210 and P388 Cells. We have measured the zero-trans influx of Ado and 2'-dAdo in ATP-deleted, dCF-treated cells at a substrate concentration of 500 μM. Under these conditions <10% of the intracellular substrate was phosphorylated at 3 min of incubation, allowing a reasonable approximation of the rate of transmembrane equilibration of unmodified substrate by the use of rapid kinetic techniques. Representative time courses of transmembrane equilibration of 2'-dAdo by L1210 cells in the presence of two concentrations of dCF 29. Chart 3 also shows that Ado uptake by L1210 cells was slightly stimulated by dipyridamole and NBTI, but far less than was 2'-dAdo uptake. The lesser effect, however, may simply be related to the fact that Ado uptake in untreated cells was already about 10 times greater than was 2'-dAdo uptake. In fact, Ado uptake ceased after about 2 hr of incubation (Chart 3A), because the medium had become practically depleted of substrate.

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10), and this fact therefore is unrelated to their different effects on 2'-dAdo uptake in the two types of cells.

The inhibition of 2'-dAdo uptake by the transport inhibitors in P388 cells was reflected by a similar inhibition of 2'-dAdo incorporation into acid-insoluble material (Chart 2C). The stimulation of dAdo uptake in L1210 cells had little effect on its incorporation into acid-insoluble material, but incorporation was very low (Chart 2C), and in another experiment (Chart 3B), the amount of 2'-dAdo incorporated into acid-insoluble material was transiently increased by the dipyridamole treatment. The reason for this difference is not known; the stimulation of 2'-dAdo incorporation into cell material by dipyridamole and NBTI was about the same in the two experiments, which demonstrated the reproducibility of the effect (compare Charts 2B and 34, right frame). Furthermore, chromatographic analyses of the acid-soluble pool of 2'-dAdo labeled L1210 cells showed clearly that the transport inhibitors stimulated the accumulation of 2'-dATP (Table 1). These results are in agreement with those reported by Kang and Kimball (29). Chart 3 also shows that Ado uptake by L1210 cells was slightly stimulated by dipyridamole and NBTI, but far less than was 2'-dAdo uptake. The lesser effect, however, may simply be related to the fact that Ado uptake in untreated cells was already about 10 times greater than was 2'-dAdo uptake. In fact, Ado uptake ceased after about 2 hr of incubation (Chart 3A), because the medium had become practically depleted of substrate.
SALVAGE OF Ado AND dAdo IN P388 AND L1210 CELLS

![Graph showing comparison of dipyridamole and NBTI on the uptake of Ado and 2'-dAdo](chart3.jpg)

Table 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>[3H]Ado (nmol/10^6 cells)</th>
<th>[3H]2'-dAdo (nmol/10^6 cells)</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>29.0</td>
<td>0.88</td>
</tr>
<tr>
<td>+10 µM dipyridamole</td>
<td>29.2</td>
<td>2.62</td>
</tr>
<tr>
<td>+0.5 µM NBTI</td>
<td>32.6</td>
<td>1.83</td>
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</table>

Our results overall indicate that the nucleoside transporters of L1210 and P388 cells possess similar kinetic properties and sensitivities to dipyridamole and NBTI, in agreement with previous results based on experiments with Urde as substrate (K, ~250 µM; V, ~20 pmol/µl cell water·s⁻¹; Ref. 10). Furthermore, no second dipyridamole- and NBTI-resistant purine nucleoside transport system specific for L1210 cells was detected. Our results contradict the suggestion that Ado and 2'-dAdo are transported by carriers that differ in NBTI sensitivity (27). The results are also inconsistent with the suggestion that dipyridamole may inhibit to a greater extent the efflux than the influx of 2'-dAdo in L1210 cells (29). This hypothesis seemed unlikely on the basis of the directional symmetry of the nucleoside carrier in these cells (1) and the rapid equilibration of this lipophilic substance across membranes. It has also been ruled out experimentally; dipyridamole inhibited about equally the influx of 500 µM 2'-dAdo from L1210 and P388 cells whether (data not shown) or not (Chart 6) they were ATP-depleted. The same was the case for NBTI (Chart 6). It follows that the enhancement of long term 2'-dAdo uptake by dipyridamole and NBTI in L1210 cells is not mediated at the transport step. Instead it seems to involve a stimulation of the net formation of dAdo nucleotides. This is also indicated by the finding that transport is not a limiting factor in the uptake of 2'-dAdo by L1210 cells.

Another experiment illustrates the shift from inhibition of 2'-dAdo transport to stimulation of uptake by dipyridamole in the overall uptake of 2'-dAdo in dCF-treated L1210 cells (Chart 7). Uptake during the first minute was inhibited by NBTI and dipyridamole; uptake during this interval reflects mostly transport. But beginning at about 2 min of incubation, 2'-dAdo uptake became stimulated greatly in the NBTI- and dipyridamole-treated cells. Since the rate of accumulation of dAdo nucleotides in L1210 cells was relatively low compared to the transport capacity of the cells, the inhibition of 2'-dAdo transport by dipyridamole or NBTI, which was >90% in the case of dipyridamole, was inconsequential as far as its conversion to nucleotides was concerned. This was not the case for P388 cells, which exhibited a much higher rate of conversion of 2'-dAdo to nucleotides. Inhibition of transport slowed 2'-dAdo phosphorylation, although not to the same extent (compare Charts 2 and 7), since the capacity even of these cells to transport 40 µM 2'-dAdo exceeded considerably their capacity to phosphorylate this substrate. That 2'-dAdo uptake in human lymphoma cells (27) is less sensitive to inhibition by dipyridamole and NBTI than is Ado uptake may be partially explained on the same basis, since Ado uptake was about 10 times higher than was 2'-dAdo uptake by these cells.
SALVAGE OF Ado AND dAdo IN P388 AND L1210 CELLS

Chart 4. Effect of dipyridamole (DIP) (A) and NBTI (B) on the zero-frans influx of 2'-dAdo in ATP-depleted, dCF-treated L1210 cells. The cells were depleted of ATP by incubation in glucose- and glutamine-free BME2B containing 5 mM KCN, 5 mM iodoacetate, and 25 μM dCF (about 2 × 10^6 cells/ml) at 37°C for about 10 min. Then samples of the suspension were supplemented with various concentrations of dipyridamole or NBTI (as indicated in Chart 5), and after at least 5 min of incubation at 25°C, the influx of 500 μM [2,8-3H]2'-dAdo (about 1 cpm/pmol) was measured by rapid kinetic techniques as described in "Materials and Methods." Only representative time courses of substrate equilibration are shown. Initial zero-frans entry velocities (v0) were estimated by integrated rate analysis.

Although our results indicate clearly that it is the net formation of intracellular dAdo nucleotides rather than 2'-dAdo transport into the cell that is stimulated by dipyridamole and NBTI in L1210 cells, further work is required to elucidate the mechanisms involved at the molecular level. The low net uptake of 2'-dAdo could reflect rapid and continuous degradation of deoxyadenosine nucleotides in these cells, and its stimulation by NBTI and dipyridamole could reflect the inhibition of such activity. Carson et al. (37) reported that the sensitivities of 21 human lymphoid cell lines to 2'-dAdo toxicity were inversely related to their soluble deoxyxynucleotidase activities. Such a relationship, however, cannot explain the difference in 2'-dAdo sensitivity between L1210 and P388 cells, since P388 cells are much more resistant to a 2'-dAdo than L1210 cells, in spite of their much greater capacity to take up the nucleoside. Furthermore, we could not detect any difference in the rate of turnover of dATP in L1210 and P388 cells (Chart 8). We labeled the dATP pool of both types of cells by treating them with dCF and then incubating them with 1 μM [3H]2'-dAdo in the presence of 5 μM dipyridamole at 37°C for 1 h. Under these conditions the two types of cells took up similar amounts of 2'-dAdo (see Chart 2), and >80% of the radioactivity in their acid-soluble pools was associated with dATP (Chart 8A). Then the cells were incubated in fresh medium without dAdo and monitored for cell-associated radioactivity. There was only a slow loss of radioactivity from the cells during 2 h of incubation at 37°C, which was, however, comparable in L1210 and P388 cells (Chart 8A). In both cultures, the radioactivity lost from the cells was recovered as 2'-dAdo (50–60%), dino plus Hyp (30–40%), and an unidentified component (about 4%) in the medium (data not shown). There was also a slow chase of radioactivity from the acid-soluble pool to acid-insoluble material, which was comparable in both types of cells (Chart 8A). The only difference we observed between L1210 and P388 cells was that the proportion of radioactivity in the soluble pool recovered in fraction III containing dAdo (but also Ado, dino, Ino, and Hyp) was greater in L1210 than P388 cells, both after the labeling period and the...
SALVAGE OF Ado AND dAdo IN P388 AND L1210 CELLS

Chart 6. Inhibition of 2'-dAdo efflux by dipyridamole and NBTI in L1210 (A) and P388 (B) cells. Suspensions of about 1.3 x 10^6 cells/ml of medium were treated with 50 μM dCF and then equilibrated with 500 μM [2,8-3H]2'-dAdo (4.5 cpm/pmol) at 37°C. The zero-frame exit of radiolabeled substrate into balanced salt solution or balanced salt solution containing, where indicated, 5 or 20 μM dipyridamole (DIP) or 1 μM NBTI was then measured at 25°C by rapid kinetic techniques as described in "Materials and Methods."

Chart 7. Comparison of the effects of dipyridamole and NBTI on the influx and phosphorylation of 2'-dAdo in intact L1210 cells at 25°C. Samples of a suspension of 3 x 10^7 dCF-treated (25 μM) L1210 cells/ml of BM42B were supplemented where indicated with 20 μM dipyridamole (DIP) or 0.5 μM NBTI and then the uptake of 40 μM [2,8-3H]2'-dAdo (10 cpm/pmol) at 25°C was measured by the rapid kinetic technique (2-60 s). Another portion of each of the suspensions was mixed with radiolabeled substrate and manually sampled in a comparable manner over longer intervals (1-8 min). The broken line indicates the intracellular concentration of substrate equivalent to that initially in the medium.

Chart 8. Turnover of dATP in L1210 and P388 cells. Suspensions of about 4 x 10^6 cells/ml of BM42B were supplemented with 20 μM dCF and 5 μM dipyridamole and 5 min later with 1 μM [2,8-3H]2'-dAdo (800 cpm/pmol). After 1 h of incubation at 37°C, the cells were collected by centrifugation, resuspended to the same density in fresh medium (0 time) and, at various times of further incubation at 37°C, the cells from 0.5-ml samples of suspension were collected by centrifugation through oil and were analyzed for radioactivity. Other 0.5-ml samples of suspension were analyzed for radioactivity in acid-insoluble material. All values in A are averages of duplicate samples and are expressed as a percentage of radioactivity associated with the cells at 0 time (about 4 x 10^6 cpm/0.5 ml of suspension). The acid-soluble pools were extracted from additional samples of cells and chromatographed with solvent 2B. Representative chromatograms are shown in B and C. Fraction I = dATP, dADP; II = dAMP; III = dAdo (Ado, Hyp, Ino, dino).

In view of the results in Chart 8, it seems more likely that the stimulation of 2'-dAdo uptake in L1210 cells by dipyridamole is at the level of intracellular phosphorylation of 2'-dAdo. For example, the low uptake of 2'-dAdo by L1210 cells and its stimulation by NBTI and dipyridamole could be due to some kind of inhibition of 2'-dAdo kinase activity which is somehow relieved by the treatment with the transport inhibitors. Regardless, since the stimulation of 2'-dAdo nucleotide accumulation is observed with two different inhibitors of nucleoside transport, one of which seems to be highly specific for the nucleoside transporter (NBTI), it seems likely that the effect is indirect and mediated through an inhibition of nucleoside transport. What mechanism is involved, however, is unclear at present.

The results with L1210 cells have additional interest in that...
they represent another example of a synergistic cytotoxic effect of a combination of substances, each of which alone exhibits relatively low or no cytotoxicity. It is also of interest that, in this case, the synergism seems to be relatively specific for a lymphoid tumor lacking T- or B-cell surface antigens which has been used as a laboratory model for acute lymphocytic leukemia of childhood.

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REFERENCES

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