Nucleobase Transporter-mediated Permeation of 2',3'-Dideoxyguanosine in Human Erythrocytes and Human T-lymphoblastoid CCRF-CEM Cells*


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Several 2',3'-dideoxynucleosides (ddNs), agents that inhibit the replication of human immunodeficiency virus and hepatitis B virus, enter mammalian cells by simple diffusion. In this report, we show that the membrane permeation of 2',3'-dideoxyguanosine (ddG) in human erythrocytes and CCRF-CEM cells, in contrast to that of other ddNs, is transporter-mediated. Inward fluxes of ddG in both cell types were inhibited by adenine, hypoxanthine, and acyclovir, but not by inhibitors of nucleoside transport (nitrobenzylthioinosine, dipyridamole, dilazep). Fluxes of ddG in human erythrocytes were attributable to a single, rate-saturable process (K_m, 380 ± 90 μM and V_max, 7.9 ± 0.8 pmol/s/μl cell water) that was competitively inhibited by adenine (K_i, 16 μM). These results showed that ddG entered human erythrocytes and CCRF-CEM cells by a transporter-mediated process that was also the basis for entry of purine nucleobases. In contrast, inward fluxes of 2,6-diaminopurine-2',3'-dideoxyriboside (ddDAPR), a prodrug of ddG, were not affected by purine nucleobases or nucleoside transport inhibitors in either cell type. Thus, the permeation properties of ddDAPR resembled those of 2',3'-dideoxyadenosine, a diffusional permeant (cell uptake is transporter-independent), and contrasted with those of ddG, the deamination product of ddDAPR. This study demonstrated that the nucleobase moiety of ddNs is an important determinant of membrane permeation.

Hepatitis B virus infection causes significant chronic infection in an estimated 300 million carriers worldwide. Increased incidence of cirrhosis and hepatocellular carcinoma are long-term consequences of the carrier state (1). There is no present effective antiviral therapy for acute or chronic infection with hepatitis B virus, although recent studies have reported the ability of purine ddNs (ddG, ddDAPR) to inhibit duck hepatitis B virus (2, 3). 2',3'-Dideoxyribosides of the physiological nucleobases and analogs thereof are also potent inhibitors of human immunodeficiency virus (4, 5). Blockade of viral replication by such agents has been correlated with the intracellular formation of nucleotide intermediates, which are presumed to interfere with the synthesis of viral or proviral DNA (6). On the basis of the current interest in ddNs as potent agents for treatment of these two important viruses, we have examined the mechanisms of membrane permeation of ddG and its prodrug, ddDAPR.

The importance of membrane permeation as an initial determinant of intracellular ddN anabolism and, thus, of antiviral activity, has been recognized in several recent studies aimed at characterizing cellular uptake mechanisms for ddNs (7–11). Physiological nucleosides and many analogs thereof enter mammalian cells by equilibrative, facilitated diffusion NT processes and by concentrative, Na+-dependent, secondary-active NT processes (12, 13). In some cell types, including human erythrocytes and human T-lymphoblastoid CCRF-CEM cells, nucleoside entry is mediated by an equilibrative NT process that is inhibited by NBMPR (14, 15), and designated the es NT system, according to the terminology of Belt and coworkers (16). That process is enantioselective, showing a dramatic preference for the physiological D-enantiomers of adenosine, uridine, and thymidine (13, 17), and discriminates against nucleosides that lack a 3'-hydroxyl group (18). Several ddNs, including AZT (7), d4T (8), d4T (9), and dA (10), which are modified at the 3' position and are more lipophilic than physiological nucleosides, are not substrates for the es NT system, but enter cells mainly by simple diffusion. The slow entry of ddC has been attributed to both simple diffusion and an inefficient interaction with NT processes (11).

In the present study, inward fluxes of several purine ddNs were measured in human erythrocytes and CCRF-CEM cells.

1 The abbreviations and trivial names used are: ddN, 2',3'-dideoxynucleoside; NT, nucleoside transport; NBMPR, 6-[(4-nitrobenzylthio)1H]-9-β-D-ribofuranosylpurine (nitrobenzylthioinosine); AZT, 3'-azido-3'-deoxythymidine; d4T, 3'-deoxythymidine; dF, 2',3'-dideoxy-3'-deoxythymidine (3'-deoxythymidin-2-ene); ddC, 2',3'-dideoxycytidine; dA, 2',3'-dideoxyadenosine; dG, 2',3'-dideoxyguanosine; acyclovir, 9-[2-(hydroxyethoxy) methyl]guanine; ddDAPR, 2,6-diaminopurine-2',3'-dideoxyriboside; RT, transport medium, RPMI 1640 medium without bicarbonate, containing 20 mM HEPES, pH 7.4; DPBS, Dulbecco's phosphate-buffered saline (22); dd, 2',3'-dideoxyinosine; ganciclovir, 9-[2-(hydroxy-1-hydroxyethylthoxy)methyl] guanine; desaclovir, 2-amino-9-[2-(hydroxyethoxy)methyl] purine.

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We show that ddG, in contrast to several other purine ddNs, entered cells by a mediated process shared by adenosine, hypoxanthine, and acyclovir, agents that are substrates for the purine nucleobase transporter of human erythrocytes (19-21). Nucleobase fluxes in those cells are mediated by a process that is independent of the NT system and is not affected by the NT inhibitors, NBMPR, dilazep, or dipyridamole (19, 20).

**EXPERIMENTAL PROCEDURES**

**Cells—** Human erythrocytes were recovered by centrifugation of blood collected in heparin-containing tubes, washed three times in 5-10 volumes of RT medium, and resuspended in that medium at a density of 2 × 10^6 cells/ml. CCRF-CEM cells were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum, in a humidified atmosphere of 5% CO_2/95% air at 37°C. The cultures were maintained at cell densities (less than 6 × 10^6 cells/ml) to ensure exponential growth. Prior to flux assays, CCRF-CEM cells were washed once in RT medium and resuspended at that medium at a density of 2 × 10^6 cells/ml.

**Determination of n-Octanol/Buffer Partition Coefficients—** Stock solutions, containing 10 μM [3H]ddN at a radioactive concentration of 100,000 cpm/ml, were prepared in DPBS. Triplicate 200-μl portions of stock solution were combined with equal volumes of n-octanol in microcentrifuge tubes, mixed vigorously several times on a vortex mixer, and re-mixed after standing for 30 min. Aqueous and n-octanol phases were separated by centrifugation (15,000 × g, 30 s) and the 3H concentration of each phase was measured by liquid scintillation counting. Partition coefficients were expressed as the ratio, [3H] ddN/n-octanol/[3H]ddN/medium.

**Measurement of Permeant Fluxes—** Time courses of permeant uptake were measured at 22 °C in cells in RT medium. Uptake intervals were initiated by the rapid addition of 100 μl of [3H]permant solution to an equal volume of cell suspension that was layered over 100 μl of a silicone oil/paraffin oil solution (density = 1.05 g/ml) in 1.5-ml microcentrifuge tubes, and ended by centrifugal pelleting of the cells under the oil layer, a procedure that increased the interval of cell exposure to permeant by 2 s (23). Addition of permeant and activation of the centrifuge were performed in response to metronome or stopwatch signals. In some experiments, permeant solutions (188 μl) were added to equal volumes of cell suspension in a series of replicate assay tubes at 1.5-s intervals by means of an automatic sample dispenser (Digiflex-CX Automatic Pipette, Model 33010; Micromedic Systems, Horsham, PA). In those experiments, the interval between permeant addition and centrifuge switch-on was recorded by electronic signaling to a stopwatch.

The [3H] content of cell pellets was determined as described previously (24). Intracellular water volume was measured as the difference between total pellet water volume, determined with 3H_2O, and the extracellular water space in cell pellets, determined with [14C]sucrose or [3H]polyethylene glycol. Values for cell-associated [3H] permeant were corrected for permeant trapped in the pellet extracellular water space.

Progress curves of permeant uptake by cells were fitted to uptake data as parabolas or by linear regression, in order to obtain initial slopes, which provided measures of unidirectional, inward fluxes.

**Materials—** [2',3'-H]ddDAPR (54 Ci/mmol) and [2',3'-H]ddA (30 Ci/mmol) were obtained from Moravek Biochemicals Inc., Brea, CA. Portions of those stocks served as substrates for the preparation of [2',3'-H]ddG and [2',3'-H]ddI, respectively, by deamination with adenosine deaminase (Sigma Type VI, from calf intestinal mucosa). [2',3'-H]hypoxanthine (20 Ci/mmol) was obtained from Moravek Biochemicals. All tritiated periments were purified by HPLC before use, by elution from a Whatman Partisil 10/ODS-3 M9 (25 cm) column with water/methanol mixtures. H_2O (100 μCi/ml) was from ICN Radiochemicals, Irvine, CA, and [U-14C]sucrose (499-671 μCi/mmol) and [1,2-3H]mannitol (2 μCi/μl) were from Du Pont Canada (New England Nuclear Products), Lachine, Que. ddA, ddG, and ddDAPR were prepared by Raylo Chemicals, Division of Teroxon Laboratories Ltd., Edmonton, AB.

**RESULTS**

**Time Courses of the Cellular Uptake of ddNs—** Fig. 1 shows progress curves of the uptake of ddG, ddA, ddDAPR, and ddI in CCRF-CEM cells in medium containing those agents at 10 μM concentrations. These data illustrate the relatively slow intracellular accumulation of the ddNs, which did not reach medium concentrations during the 10-s uptake intervals. Similarly, intracellular concentrations of ddG and ddDAPR in human erythrocytes were lower than medium concentrations after a 30-s uptake period (Fig. 2). These entry rates contrasted sharply with that of 10 μM adenosine, for which transmembrane equilibration occurred within 3 s in both cell types (not shown). The experiments of Fig. 1 also showed that the accumulation of ddG in CCRF-CEM cells exceeded that of the other purine ddNs during the 10-s interval. This unexpected result prompted the measurement of partition coefficients of ddNs and the characterization of inward ddN fluxes.

**n-Octanol/Buffer Partition Coefficients and Inward Fluxes of ddNs—** Oil/water partition coefficients of small solutes have been used as an index of lipophilicity, a property that correlates with the diffusional permeation of nonelectrolytes across cell membranes (26). Partition coefficients of purine ddNs, measured in n-octanol/DPBS mixtures, are shown in Table I. These data show that lipid solubilities of the 6-amino purine nucleosides, ddA and ddDAPR, were several-fold greater than those of the 6-oxypurine nucleosides, ddG and ddI, which were similar to that of thymidine (n-octanol/phosphate buffer partition coefficient, 0.064 (7)).

Unidirectional, inward fluxes of ddNs in erythrocytes and cell pellet water volume were determined with 3H_2O, and the extracellular water space in cell pellets, determined with [14C]sucrose or [3H]polyethylene glycol. Values for cell-associated [3H] permeant were corrected for permeant trapped in the pellet extracellular water space.

Progress curves of permeant uptake by cells were fitted to uptake data as parabolas or by linear regression, in order to obtain initial slopes, which provided measures of unidirectional, inward fluxes.
Figure 2. Time courses of ddG and ddDAPR uptake in human erythrocytes and the effects of hypoxanthine, adenine, and acyclovir. Intervals of permeant uptake were initiated by the manual addition of [3H]ddN solutions to cell suspensions (2 x 10^7 cells) in response to stopwatch signals, as described under “Experimental Procedures.” Radioactive nucleosides and test compounds were added simultaneously to cell suspensions. Flux intervals were terminated by centrifugal pelleting of cells through an oil layer. The data shown are means of three to six replicate determinations. ACV, acyclovir; Hyp, hypoxanthine.

Table I
n-Octanol/buffer partition coefficients and inward fluxes of ddNs in human erythrocytes and CCRF-CEM cells

Partition coefficients were determined in mixtures of n-octanol and DPBS, using the radiochemical method described under “Experimental Procedures.” The data shown are means of triplicate determinations. Inward fluxes of ddNs (10 μM) were determined as the initial slopes of 30-s progress curves of permeant uptake, as described under “Experimental Procedures.”

<table>
<thead>
<tr>
<th>Nucleoside</th>
<th>Partition coefficient</th>
<th>Human erythrocytes</th>
<th>CCRF-CEM cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>ddG</td>
<td>0.077</td>
<td>0.17 ± 0.03</td>
<td>0.36 ± 0.12</td>
</tr>
<tr>
<td>ddDAPR</td>
<td>0.31</td>
<td>0.23 ± 0.03</td>
<td>0.083 ± 0.043</td>
</tr>
<tr>
<td>ddI</td>
<td>0.056</td>
<td>0.053 ± 0.001</td>
<td>0.056 ± 0.022</td>
</tr>
<tr>
<td>ddA</td>
<td>0.50</td>
<td>0.86 ± 0.01</td>
<td>0.24 ± 0.19</td>
</tr>
</tbody>
</table>

* Mean ± S.D. from [n] experiments.
* Range.

CCR-F-CEM cells, determined from initial slopes of time courses of permeant uptake, are listed in Table I. We reasoned that if the flux behavior of the ddNs in erythrocytes was related to the partition coefficients of those substances, the high flux of ddG was paradoxical. Similarly, in CCRF-CEM cells, fluxes of ddA and ddI corresponded with the partition coefficients of those agents, whereas those of ddDAPR and ddG did not. These results suggested that fluxes of ddG were attributable to a process other than simple diffusion.

Effects of Nucleobases, NT inhibitors, and nucleosides on inward fluxes of ddG

Inward fluxes of 10 μM [3H]ddG were determined from time courses of permeant uptake, as described in the legend to Table I, in the presence of the agents listed below. [3H]ddG and test compounds were added simultaneously to cell suspensions. Control rates of ddG influx in the two cell types were 0.17 pmol/s/μl cell water (human erythrocytes) and 0.36 pmol/s/μl cell water (CCRF-CEM cells). Values shown are means from two experiments, each performed in triplicate.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Human erythrocytes</th>
<th>CCRF-CEM cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenine (1 mM)</td>
<td>9.6±4</td>
<td>0.73±4</td>
</tr>
<tr>
<td>Hypoxanthine (1 mM)</td>
<td>18±5</td>
<td>13±4</td>
</tr>
<tr>
<td>Acyclovir (1 mM)</td>
<td>23±5</td>
<td>19±5</td>
</tr>
<tr>
<td>NBMPR (5 μM)</td>
<td>105±7</td>
<td>101±7</td>
</tr>
<tr>
<td>Dipyridamole (10 μM)</td>
<td>99±5</td>
<td>89±5</td>
</tr>
<tr>
<td>Dilazep (10 μM)</td>
<td>96±5</td>
<td>89±5</td>
</tr>
<tr>
<td>Inosine (1 mM)</td>
<td>88±5</td>
<td>70±5</td>
</tr>
<tr>
<td>Formycin B (1 mM)</td>
<td>66±5</td>
<td>53±5</td>
</tr>
<tr>
<td>2'-Deoxyguanosine (1 mM)</td>
<td>25±5</td>
<td>31±5</td>
</tr>
<tr>
<td>+ NBMPR (5 μM)</td>
<td>42±5</td>
<td>56±5</td>
</tr>
</tbody>
</table>

* Flux significantly different from control flux (p < 0.05).
* Single experiment.

Table II
Effects of nucleobases, NT inhibitors, and nucleosides on inward fluxes of ddI

In contrast, potent NT inhibitors (NBMPR, dipyridamole, and dilazep) did not impair fluxes of ddG in either cell type, indicating that ddG was not recognized by the es NT system. Inosine and 3-(β-D-ribofuranosyl)pyrazolo[4,5-d]pyrimidin-7-one (formycin B) did not affect ddG fluxes significantly, whereas 2'-deoxyguanosine was a weak inhibitor. Inhibition types, suggesting that ddG entry was mediated by a nucleobase transporter. Of these three agents, adenine has the lowest Kᵣ for the nucleobase transporter in erythrocytes (19) and was the most potent inhibitor of ddG fluxes. In separate experiments (not shown), ddG (100 μM) reduced fluxes of [3H]hypoxanthine (25 μM) to 60% of the control value in CCRF-CEM cells. The finding that inward fluxes of ddG and hypoxanthine were mutually inhibitory supported the view that ddG permeation was nucleobase transporter-mediated.
of ddG fluxes by 2′-deoxyguanosine persisted when the assay mixture contained NBMPR, which ensured blockade of the nucleobase transporter-mediated entry of 2′-deoxyguanosine, suggesting that ddG and 2′-deoxyguanosine shared a common, non-es-mediated permeation process. The idea that entry of ddG and 2′-deoxyguanosine shared a common, nucleoside transporter-mediated entry of 2′-deoxyguanosine, whereas ddG, but not ddDAPR, was recognized by the nucleobase transporter.

Saturability of ddG Fluxes in Human Erythrocytes—Fig. 3 illustrates the concentration dependence of ddG fluxes in erythrocytes. Plotted are inward fluxes of ddG (measured as the rate of uptake between 3 and 5 s of permeant exposure) in cells suspended in media containing graded concentrations of ddG. When assay mixtures contained 2 mM adenine, a concentration sufficient to saturate the erythrocytic nucleobase transporter (19), inward ddG fluxes were not detectable at extracellular ddG concentrations of 1 mM or less, indicating that diffusion or other processes did not contribute to ddG entry. These results showed that ddG entered human erythrocytes by a single, saturable process, with a $K_m$ of 380 ± 90 μM and a $V_{max}$ of 7.9 ± 0.8 pmol/s/μl cell water (mean ± S.E.).

Inhibition of ddG Influx by Adenine—Fig. 4 shows a Dixon plot of the effects of graded concentrations of adenine on uptake of ddG, measured after the first 5 s of permeant exposure, in erythrocytes suspended in media containing graded concentrations of [3H]ddG. The data yielded a $K_i$ value of 16 μM for adenine, which is similar to the $K_m$ of adenine (13 μM (19)) for the nucleobase transporter in those cells.

Both the Dixon plot and a double-reciprocal plot of the data (inset) were consistent with a competitive mechanism of inhibition by adenine, supporting the view that adenine and ddG shared an entry process in human erythrocytes.

### DISCUSSION

This study has shown that ddG permeation in human erythrocytes and CCRF-CEM cells was mediated by a process shared with purine nucleobases, a conclusion that is supported by several observations. ddG fluxes were inhibited by purine nucleobases and acyclovir, substrates for the nucleobase transporter, but were unaffected by substrates and inhibitors of NT systems in those cells. In human erythrocytes, ddG fluxes were saturable, and attributable to a single process. The efficiency of ddG transport in human erythrocytes, expressed as $V_{max}/K_{max}$, was similar to that of acyclovir (21, but was about 10 times lower than that of hypoxanthine, guanine, or adenine (19). At 1 mM concentrations, fluxes of ddG were similar to diffusional fluxes of ddT (8), but were about 4-fold lower than diffusional fluxes of AZT (7), and about 18-fold higher than fluxes of dC (11).

The substrate specificity of the erythrocytic nucleobase transporter has been shown by Zimmerman and coworkers, to include purine nucleobases (19), as well as the acyclic guanosine analogues, acyclovir (21) and ganciclovir (27). The present study has shown for the first time that the nucleobase transporter can recognize a guanine 9-β-D-pentofuranoside

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**Fig. 3.** Concentration dependence of ddG influx in human erythrocytes. Inward fluxes of [3H]ddG were measured in suspensions of human erythrocytes (2 × 10⁷ cells) as the rate of ddG uptake between 3 and 5 s of permeant exposure. Flux assay mixtures were completed by the manual addition of permeant in response to metronome signals and terminated using an oil-stop method, as described under “Experimental Procedures.” Pooled data from four experiments are shown. Constants determined from these data were $K_m$ 380 ± 90 μM, and $V_{max}$, 7.9 ± 0.8 pmol/s/μl cell water.

**Fig. 4.** Competitive inhibition by adenine of ddG influx in human erythrocytes. Inward fluxes of [3H]ddG were measured in suspensions of human erythrocytes (2 × 10⁷ cells) as cell uptake of ddG after the first 5 s of permeant exposure, in the absence or presence of graded concentrations of adenine. Permeant solutions were added manually to cell suspensions in response to metronome signals, as described under “Experimental Procedures.” The data, which are means from two experiments, are presented as a Dixon plot, yielding a $K_i$ of 16 μM.

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**Table III**

Effects of nucleobases and NT inhibitors on inward fluxes of ddDAPR

<table>
<thead>
<tr>
<th>Agent</th>
<th>Inward flux of ddDAPR</th>
<th>% of control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Human erythrocytes</td>
<td>CCRF-CEM cells</td>
</tr>
<tr>
<td>Adenine (1 mM)</td>
<td>97</td>
<td>119</td>
</tr>
<tr>
<td>Hypoxanthine (1 mM)</td>
<td>97</td>
<td>79</td>
</tr>
<tr>
<td>NBMPR (5 μM)</td>
<td>127</td>
<td>98</td>
</tr>
<tr>
<td>Dipyridamole (10 μM)</td>
<td>100</td>
<td>95</td>
</tr>
</tbody>
</table>

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**TABLE III**

Membrane Transport of 2′,3′-Dideoxyguanosine 22275
lacking the 2′- and 3′-hydroxyl groups. The affinity of ddG for the nucleobase transporter (Ke, 380 μM) was lower than that of acyclovir (Ke, 260 μM (21)) but higher than that of ganciclovir (Ke, 890 μM (27)). Partial inhibition of ddG fluxes in human erythrocytes by 2′-deoxyguanosine in the present study suggested that 2′-deoxyguanosine may also be a weak substrate for the nucleobase transporter, and may, like ganciclovir (27), enter cells by both nucleobase transport and NT systems. In contrast, guanine 9-β-D-arabinofuranoside entered human erythrocytes via a low-affinity interaction with the NBMPR-sensitive NT system in these cells (28).

Other studies have shown that nucleobases did not significantly impair membrane fluxes of several ddNs, including ddT (8), ddA (10), and ddC (11) in human erythrocytes, and ddT in human lymphoid H9 cells (9). The failure of NBMPR to inhibit fluxes of ddA and ddT in CCRF-CEM cells suggested that entry of those agents was not nucleoside transporter-mediated (29). In the present study, the substantial fluxes of ddDAPR in human erythrocytes were not inhibited by nucleobases or NT inhibitors, suggesting that this agent behaved more like an analog of ddA (nonmediated entry) than of ddG. Structurally, ddDAPR differs from ddG by substitution of a 6-amino group for a 6-oxy group on the purine ring. Mahony and colleagues (21, 30) have noted the importance of the purine C-6 group in interactions with the nucleobase transporter, since acyclovir, a 6-oxypurine “acyclic nucleoside” analog, was a transporter substrate, whereas desciclovir, which lacks the 6-oxy substituent, interacted more weakly with the transporter and entered human erythrocytes mainly by simple diffusion. That view is supported in the present study through an apparent parallel between the membrane permeation properties of ddG and ddDAPR, and those of acyclovir and desciclovir, respectively.

Although characterizations of nucleobase transport in CCRF-CEM cells have not been reported, the present study suggests that ddG, hypoxanthine, adenine, and acyclovir shared a common transport process that is distinct from the NBMPR-sensitive, equilibrative NT system in those cells. As well, the lack of inhibition of ddDAPR fluxes by nucleobases or NT inhibitors in human erythrocytes was evident in CCRF-CEM cells. Noteworthy were differences between the apparently diffusional fluxes of ddDAPR in human erythrocytes and CCRF-CEM cells, which were 7-fold lower in the latter cells (Table 1). Fluxes of ddA were similarly lower in CCRF-CEM cells than in human erythrocytes (Table 1), suggesting that lipophilicity was a less important factor in the diffusional entry of ddNs in CCRF-CEM cells than in human erythrocytes.

In conclusion, this study has demonstrated the novel route of entry of an intact nucleoside analog, ddG, into human erythrocytes and CCRF-CEM cells by a nucleobase transporter-mediated process. Although nucleobase transporters have been described in only a few cell types (19, 20, 31–33), and are generally less well defined than are NT processes, transporter-mediated permeation of nucleobases is likely to occur in cells of many tissue types. The in vivo distributions and antiviral activities of ddG and ddDAPR may be affected significantly by the remarkably contrasting lipophilicities and membrane permeation properties of these agents.

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