Calcium-independent inhibition of glucose transport in PC-12 and L6 cells by calcium channel antagonists

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Calcium is the primary energy substrate used by the adult brain (24). The utilization of glucose by the brain is a dynamic process tightly coupled to neuronal activity (38). How neurons regulate glucose utilization is not known. In peripheral tissues, such as muscle and fat, glucose transport is rate limiting for glucose utilization (38). How neurons regulate glucose utilization is not known. In peripheral tissues, such as muscle and fat, calcium has been reported to be important for the regulation of glucose utilization. It is not known whether calcium regulates glucose transport in neurons.

Ardizzone, Timothy D., Xiao-Hong Lu, and Donard S. Dwyer. Calcium-independent inhibition of glucose transport in PC-12 and L6 cells by calcium channel antagonists. Am J Physiol Cell Physiol 283: C579–C586, 2002. First published March 13, 2002; 10.1152/ajpcell.00451.2001.—The goal of these studies was to determine whether different calcium channel antagonists affect glucose transport in a neuronal cell line. Rat pheochromocytoma (PC-12) cells were treated with L-, T-, and N-type calcium channel antagonists before measurement of accumulation of 2-[3H]deoxyglucose (2-[3H]DG). The L-type channel antagonists nimodipine, nifedipine, verapamil, and diltiazem all inhibited glucose transport in a dose-dependent manner (2–150 μM) with nimodipine being the most potent and diltiazem only moderately inhibiting transport. T- and N-type channel antagonists had no effect on transport. The L-type channel agonist l-BAY K 8644 also inhibited uptake of 2-[3H]DG. The ability of these drugs to inhibit glucose transport was significantly diminished by the presence of unlabeled 2-DG in the uptake medium. Some experiments were performed in the presence of EDTA (4 mM) or in uptake buffer without calcium. The absence of calcium in the uptake medium had no effect on inhibition of glucose transport by nimodipine or verapamil. To examine the effects of these drugs on a cell model of a peripheral tissue, we studied rat L6 muscle cells. The drugs inhibited glucose transport in L6 myoblasts in a dose-dependent manner that was independent of calcium in the uptake medium. These studies suggest that the calcium channel antagonists inhibit glucose transport in cells through mechanisms other than the antagonism of calcium channels, perhaps by acting directly on glucose transporters.

GLUCOSE is the primary energy substrate used by the adult brain (24). The utilization of glucose by the brain is a dynamic process tightly coupled to neuronal activity (38). How neurons regulate glucose utilization is not known. In peripheral tissues, such as muscle and fat, glucose transport is rate limiting for glucose utilization. In these tissues, glucose utilization could be regulated through changes in the number of glucose transporters (GLUTs) at the cell surface or by changes in the intrinsic activity of GLUTs. Recently, in efforts to study neuronal glucose metabolism, we found that many antipsychotic drugs inhibit glucose transport in rat pheochromocytoma (PC-12) cells (3, 11, 12). The mechanism through which these drugs inhibit glucose uptake has not been established; however, a role for dopamine receptors in this response has been ruled out (11). Some of the antipsychotic drugs, the diphenylbutylpiperidine type, are calcium channel antagonists (18), which might suggest the involvement of calcium channels in regulation of glucose uptake. In skeletal muscle and fat, calcium has been reported to be important for the regulation of glucose utilization. It is not known whether calcium regulates glucose transport in neurons.

Holloszy and Narahara (21) were the first to report that calcium could mediate an increase in glucose transport in muscle tissue preparations. Calcium has since been reported to be involved in the modulation of glucose transport stimulated by insulin in adipocytes and skeletal muscle (8, 26, 49). The effect of calcium channel antagonists on glucose transport in these tissue types has been controversial. Westfall and Sayeed (48) found that pharmacological modulation of intracellular calcium concentrations could alter basal and insulin-stimulated levels of glucose transport. Cartee et al. (7) found that L-type calcium channel antagonists could diminish stimulation of glucose transport by insulin in skeletal muscle while having no effect on basal transport at concentrations that did not block calcium influx through L-type calcium channels. The studies of Young and Balon (50) suggest that nifedipine inhibits glucose transport through calcium-mediated effects on the intrinsic activity of the transporter. Most of the studies involving calcium-mediated effects on glucose transport have primarily focused on compounds that affect the L-type calcium channel using peripheral tissues. The effects of the calcium channel antagonists on glucose transport in neuronal cells have not been investigated. In this study, we have examined the effects of antagonists of L-, T- and N-type calcium channels on basal glucose transport in model systems of neuronal and skeletal muscle tissues.

Calcium channel antagonists are widely used to treat a spectrum of disease states, including hyperten-
Most of the drugs exert their effects through blockade of L-type calcium channels in the vasculature to cause smooth muscle relaxation (16). L-type channels are found in skeletal, smooth, and cardiac muscle, endocrine cells, and neurons. Three different drug binding sites have been identified on the L-type calcium channels: the dihydropyridine, phenylalkylamine, and benzothiazepine binding sites (30). L-type calcium channel antagonists have been reported to prevent the increase in glucose transport elicited by insulin or contraction in skeletal muscle of rats (50). In addition, these drugs have been reported to cause profound hyperglycemia in overdose situations (2, 20, 37) and to exacerbate diabetic symptoms in humans (51). The hyperglycemia in these studies has generally been attributed to the effects of the drugs on insulin secretion (19). This study examines the effects of the calcium channel antagonists in a model cell culture system to determine whether these drugs modulate glucose transport independently of their effects on insulin secretion.

In addition to L-type calcium channels, neurons also express T- (41), P/Q- (40), R- (22), and N-type (34) calcium channels. These channels differ in their depolarization characteristics, function, and cellular location. The T-type calcium channels have been therapeutically targeted for the treatment of hypertension (45) and epilepsy (23). The N-type calcium channels have been suggested as possible targets for the treatment of chronic pain (4) and traumatic brain injury (47). Other than possible effects on insulin secretion (44), the role of these calcium channels in regulating glucose transport has not been investigated. These studies are the first to examine the possible contribution of calcium channels to the regulation of glucose transport in neuronal cells.

For these studies, PC-12 cells were used as a neuronal cell model system and rat L6 myoblasts were used as a model of a peripheral tissue. PC-12 cells express primarily GLUT3 at the cell surface but also GLUT1 and GLUT3 in intracellular vesicles (28, 42). L6 myoblasts express GLUT1, GLUT3, and very low levels of GLUT4 (6, 29); however, GLUT1 is the major isoform at the cell surface (29). Both cell types express L-type calcium channels (15, 33, 36). In addition, PC-12 cells also contain N- (33) and T-type calcium channels (15). The results of these studies demonstrate that the calcium channel antagonists inhibit glucose transport in two different cell types through a mechanism that is independent of these channels.

**MATERIALS AND METHODS**

**Reagents and drugs.** Nifedipine, nimodipine, d-verapamil, l-verapamil, dl/-verapamil, flunarizine, amiloride, methoxyverapamil, nimodipine metabolite, l-BAY K 8644, d-BAY K 8644, and o-conotoxin were purchased from Research Biochemicals International (Natick, MA). Poly-L-lysine (PLL), EDTA, and 2-deoxyglucose (2-DG) were obtained from Sigma Chemical (St. Louis, MO).

**Cell lines.** PC-12 cells were obtained from American Type Culture Collection (ATCC) and cultured in Dulbecco's modified Eagle's medium (DMEM) containing penicillin/streptomycin, 5% fetal bovine serum, and 10% equine serum as previously described (12, 13). L6 cells were obtained from ATCC and cultured in DMEM containing penicillin/streptomycin and 10% fetal bovine serum according to recommended procedures.

**Glucose uptake assay.** Glucose uptake was measured according to standard methods in our laboratory (3, 11–13). Briefly, PC-12 cells (1 × 10⁶ cells/ml) were incubated in tissue culture dishes coated with PLL (1 mg/ml) and allowed to attach for at least 1 h. Experiments using L6 myoblast cells were performed after overnight incubation of 3 × 10⁶ cells in tissue culture dishes that were not treated with PLL. The cells were then placed in 2-glucose-free DMEM (1.5 ml) containing 25 mM l-glucose in the presence of vehicle (DMSO), the desired drug concentrations, or 7 × 10⁻⁶ M cytochalasin B (to account for nonspecific background by blocking transport of glucose) for at least 15 min. 2-[3H]DG was added, and the dishes were allowed to incubate at room temperature for 5 min. For some experiments, cells were incubated with 3-O-[3H]methylglucose (3-[3H]OMG; 2 μCi/dish, 14 Ci/mmol; Amersham, Piscataway, NJ) for 1 min at room temperature. Uptake of the radiolabeled glucose analogs was terminated by rapid removal of the uptake medium followed by two washes with ice-cold PBS (pH 7.4). The cells were lysed in 0.1% sodium dodecyl sulfate, and radioactivity was determined in a liquid scintillation counter. To allow for comparison between experiments, we assayed total cell protein with the Pierce BCA Kit. Within an experiment, each condition was assayed in duplicate and each experiment was performed at least three times. Specific uptake of the radiolabeled glucose analogs was determined by subtracting the cytochalasin B counts from the counts obtained from the control and test conditions. The results represent an average of at least three experiments and are presented as the percent inhibition of glucose uptake with drug compared with control.

**Glucose sensitivity assay.** To examine whether the inhibition of glucose transport produced by these drugs is sensitive to substrate concentrations, glucose sensitivity assays were performed as previously described (3). Briefly, experiments were performed in the presence (+) or absence (−) of 5 mM 2-DG. For the (+)-2-DG condition, PC-12 cells were incubated in the presence (test) or absence (control) of drug and 5 mM 2-DG. For the (−)-2-DG condition, the cells were incubated in the presence (test) or absence (control) of drug without 2-DG. The cells were then placed in uptake medium, and the level of 2-DG (+ or −) was maintained as before. Uptake of trace amounts of 2-[3H]DG (2 μCi, 60 Ci/mmol) was measured over 5 min at room temperature. The percent inhibition of glucose uptake was determined by comparison of the vehicle and drug data from each condition (+2-DG and −2-DG). Glucose sensitivity was detected as a change in the inhibition of glucose transport between (−2-DG and +(−2-DG conditions).

**Calcium-independent inhibition of glucose transport.** Experiments were performed to determine whether the inhibition of glucose transport by the drugs was mediated through the antagonism of calcium entry into the cells. For these experiments, cells were incubated with vehicle (control) or drug (nimodipine and verapamil for PC-12 and nimodipine, verapamil, and diltiazem for L6) in the absence or presence of EDTA (4 mM). Uptake of 2-[3H]DG (0.5 μCi, 60 Ci/mmol) was measured over 5 min at room temperature. To confirm the EDTA data, we incubated PC-12 cells with vehicle (control) or nimodipine (20 μM) in uptake buffer consisting of PBS.
made with or without 0.9 mM CaCl2. The data are expressed as the percent inhibition of glucose transport caused by the drugs compared with the control conditions.

RESULTS

Chemical structures. Figure 1 shows the chemical structures of the drugs used in this study. The three classes of L-type calcium channel antagonists are represented by nimodipine, diltiazem, and racemic verapamil. Additional dihydropyridine compounds used in this study include nifedipine, nifedipine metabolites, d-BAY K 8644, and the L-type agonist l-BAY K 8644. The T-type calcium channel antagonists flunarizine and amiloride were also examined for effects on transport. The effect on transport of the N-type antagonist ω-conotoxin was examined as well.

Concentration-response curves. Previous studies have shown that various antipsychotic drugs can inhibit glucose transport in neuronal cells (11, 12). Among the most potent inhibitors were pimozide and fluphenazine, which also block L-type calcium channels. These data suggested that drugs which primarily block calcium channels might also affect glucose uptake. In the present study, calcium channel antagonists were tested for inhibition of glucose transport. PC-12 cells were allowed to attach to tissue culture dishes coated with PLL overnight. Most drugs were then tested for inhibition of glucose uptake over a range of concentrations (2, 20, 40, 60, and 100 μM). Because of a lower EC50 at the N-type calcium channels, ω-conotoxin was tested at 20, 100, and 200 nM. Cells were allowed to incubate with drug for 30 min before measurement of glucose uptake. Most of the drugs inhibited glucose transport in PC-12 cells in a concentration-dependent manner (Fig. 2, A and B). As determined from Fig. 2A, the approximate IC50 of d/-verapamil, l-verapamil, d-verapamil, and methoxyverapamil were 60, 75, 120, and 140 μM, respectively. The approximate IC50 values (Fig. 2B) for nimodipine, nifedipine, nifedipine metabolite, and d-BAY K 8644 were 15, 20, 130, and 30 μM, respectively. It is noteworthy that l-BAY K 8644, a calcium channel agonist, also inhibited uptake with an IC50 of ~70 μM. Figure 2C shows, for comparison, the representative drugs that bind to the three different sites on the L-type calcium channel along with amiloride and flunarizine. Diltiazem and amiloride are weak inhibitors of glucose transport. Flunarizine and conotoxin (Fig.

![L-type Channel Antagonists](image)

Fig. 1. Structures of the drugs used in this study. ω-Conotoxin is a polypeptide with the following sequence: CKSP*GSSCSP*TSYNCCRSCNP*YTKRCY, where P* is hydroxyproline. Nif, nifedipine.
2D) did not inhibit glucose uptake at the concentrations tested. Compounds that inhibited glucose accumulation in a concentration-responsive manner were chosen for further characterization.

These drugs could act on the transport or the phosphorylation of 2-DG to inhibit accumulation in cells. Immediately after transport into the cell, 2-DG is phosphorylated by hexokinases. To rule out effects of the drugs on hexokinase activity, we conducted some experiments using 3-[3H]OMG, which is not phosphorylated by hexokinases. Figure 3 demonstrates that nimodipine and verapamil inhibit the accumulation of 3-[3H]OMG in a dose-dependent manner. This finding suggests that the drugs inhibit the transport of glucose instead of its metabolism.

To examine whether the calcium channel antagonists could inhibit glucose transport in a cell model of a peripheral tissue, we conducted experiments in the L6 muscle cell line. L6 cells were placed in uptake medium in the absence or presence of nimodipine, nifedipine, verapamil, or diltiazem (2 and 100 μM for nimodipine and nifedipine and 20 and 100 μM for verapamil and diltiazem). As shown in Fig. 4, these drugs inhibited the accumulation of 2-[3H]DG in L6 cells in a dose-dependent manner.

Time course. The mechanism by which the drugs block glucose uptake is not known. A drug that acts at a very early time point could directly affect the glucose transport process. To begin to address this issue, we performed time course experiments to determine whether the response to the drugs had a rapid onset (Fig. 5). PC-12 cells were incubated with the various drugs (nimodipine and verapamil) for 1, 5, or 15 min before measurement of glucose transport. The drugs were used at the 40 μM concentration. Both of the drugs inhibited the accumulation of glucose equally at all time points, and there was no difference between the 15- and 30-min time points in terms of inhibition of glucose uptake. These data indicate that the drugs achieve maximum inhibition of transport very rapidly in this system.

Glucose sensitivity. Cytochalasin B (5) and the atypical antipsychotic drugs (3) have been shown to be
noncompetitive antagonists of glucose uptake into cells. To examine whether the ability of the calcium channel drugs to inhibit glucose transport was sensitive to glucose in the medium, we measured the uptake of trace amounts of 2-[3H]DG in the presence of drug and unlabeled 2-DG (5 mM). For comparison, the inhibition of 2-[3H]DG uptake was determined in the presence of drug without any unlabeled glucose. With the exception of nimodipine (40 μM), all drugs were tested at 100 μM (Fig. 6). In these experiments, the reduction of radiolabeled substrate uptake caused by the dilution with unlabeled 2-DG was accounted for by comparing the results obtained with the drugs to control (vehicle) data from their respective high or low 2-DG conditions. Under these conditions the inhibitory effects of the drugs were completely blocked in the presence of 5 mM 2-DG.

**Calcium dependence.** The inhibition of glucose transport by l-BAY K 8644, the calcium channel agonist, and the glucose-sensitive nature of inhibition by these drugs suggest that inhibition of transport may be mediated through mechanisms that are independent of effects on calcium channels. To determine whether the effects of the drugs were dependent on the influx of extracellular calcium, we measured uptake of 2-[3H]DG in PC-12 cells with nimodipine (40 μM) and verapamil (100 μM) in the absence or presence of 4 mM EDTA, a specific calcium-chelating agent. These experiments were also performed by using L6 cells with nimodipine, verapamil, and diltiazem (100 μM) (Fig. 7). The presence of EDTA in the uptake medium had no effect on the control condition or the inhibition of transport produced by these drugs. To confirm these findings, we performed glucose uptake assays in PC-12 cells with nimodipine in the uptake buffer made with or without calcium. The absence of calcium from the uptake buffer had no effect on the inhibition of glucose transport produced by these drugs.

**Fig. 5.** Time course for the inhibition of glucose transport. PC-12 cells were incubated with drug for 1, 5, or 15 min before measurement of 2-[3H]DG uptake. Nimodipine and racemic verapamil were used at 40 μM. Data are expressed as means ± SD of 3 experiments and represent percent inhibition of glucose transport by drugs compared with control conditions.

**Fig. 6.** Glucose sensitivity of drug effects. The ability of 2-DG (5 mM) to modulate the inhibitory effects of these drugs was examined by performing separate uptake assays in the presence or absence of unlabeled 2-DG. For each condition (with or without 5 mM 2-DG) uptake of trace amounts of 2-[3H]DG was measured in PC-12 cells in the presence of vehicle (control) or drug. Nimodipine and nifedipine were used at 20 μM, and l-verapamil was used at 40 μM. Data are expressed as means ± SD of at least 3 separate experiments for each condition and represent percent inhibition produced by drugs compared with control values. These data reveal significant (P < 0.01) attenuation of the inhibitory effects of the drugs by 5 mM 2-DG in the uptake medium as determined by Student’s t-test.

**Fig. 7.** Calcium-independent inhibition of glucose transport in PC-12 and L6 cells by calcium channel antagonists. PC-12 cells (A) were incubated with nimodipine (40 μM) and verapamil (100 μM), and L6 cells (B) were incubated with nimodipine (40 μM), verapamil (100 μM), and diltiazem (100 μM) for 30 min in the absence or presence of EDTA (4 mM). C: PC-12 cells were incubated with nimodipine (40 mM) in PBS made with or without calcium. Accumulation of 2-[3H]DG was measured over 5 min at room temperature. Data are expressed as means ± SD of at least 3 experiments for each condition. There are no significant differences between the calcium and calcium-free conditions.

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**CALCIUM-INDEPENDENT INHIBITION OF GLUCOSE TRANSPORT**

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DISCUSSION

Previously, the antipsychotic drugs pimozide and fluphenazine have been shown to potently inhibit glucose transport in PC-12 cells (11, 12). These same drugs are potent inhibitors of L-type calcium channels (18). Therefore, it was possible that the antipsychotic drugs might inhibit glucose transport by antagonism of calcium channels. We (3) have recently reported that the atypical antipsychotic drugs are noncompetitive antagonists of glucose transport in PC-12 cells, suggesting direct actions on GLUTs. However, these findings do not preclude the involvement of calcium channels in the regulation of glucose uptake in PC-12 cells.

Studies in muscle (48) and fat cells (43) suggest that calcium plays a significant role in regulating glucose utilization by altering rates of glucose transport. No previous studies have examined the role of calcium channels in regulating glucose transport in neurons. In this study, we examined the effects of antagonists of L-, T-, and N-type calcium channels on glucose transport in PC-12 and L6 myoblasts in an attempt to discern the relative contribution of these channels to glucose transport regulation. The findings reported here show that the L-type antagonists inhibit glucose transport into cells. A summary of various data in Table 1 reveals that there is a good correlation between the potencies of the drugs in assays of L-type calcium channel antagonism and their ability to block glucose transport. On the other hand, the N- and T-type antagonists did not inhibit glucose uptake. At first glance, these findings suggest that the drugs may interfere with glucose transport via antagonism of L-type channels. However, it is important to note that the drugs inhibited calcium channels at concentrations that were about three orders of magnitude lower than the concentrations needed to block glucose transport. In addition, we have shown that the L-type calcium channel agonist K 8644 inhibited glucose uptake and that the inhibition of transport by the drugs was sensitive to glucose in the uptake medium. The ability of these drugs to inhibit calcium channels is not affected by glucose. Finally, data showing that the drugs inhibit glucose transport in the absence of calcium in the uptake buffer provide evidence that these drugs act through mechanisms other than the inhibition of calcium channels, possibly through direct interactions with the GLUTs.

Previous studies have shown that the increases in glucose transport stimulated by insulin (8, 26, 49) or muscle contraction (21) are mediated by changes in intracellular calcium levels. Calcium can come from intracellular stores or pass through the plasma membrane from the extracellular fluid through calcium channels to increase cytoplasmic calcium concentrations. Khayat et al. (25) found that the rapid increase in glucose transport that results from mitochondrial uncoupling is dependent on calcium released from intracellular stores. On the other hand, studies with the calcium ionophore ionomycin have demonstrated that extracellular calcium is required for insulin stimulation of glucose transport in adipose tissue (8) and skeletal muscle (26). Several studies have reported that agonists and antagonists of L-type calcium channels can affect glucose transport in muscle (7, 8, 48, 50). Verapamil has been found to inhibit glucose transport in adipose tissue (8) and skeletal muscle (7). In addition, the dihydropyridine L-type antagonists inhibit glucose transport in skeletal muscle (7, 48, 50). We report here that verapamil and the dihydropyridine compounds also inhibit glucose transport in neuronal cells, suggesting that the mechanism for the inhibition of glucose transport by these drugs may be similar across multiple cell types. Furthermore, our data show that, in some cases, the calcium channel antagonists inhibit basal glucose transport independently of their effects on calcium channels. The calcium-independent inhibition of transport is consistent with the observations of Cartee et al. (7) that these drugs block glucose transport at concentrations that do not affect calcium channel activity. These data suggest that the drugs may act directly on GLUTs.

The calcium channel antagonists have been reported to bind to many proteins other than calcium channels. Schwartz et al. (35) reported that only a small fraction of dihydropyridine binding sites are functional calcium channels. The dihydropyridine and phenylalkylamine drugs have been reported to bind to α-adrenergic receptors (17), P-glycoprotein (32), σ1 receptors (31), the vesicular monoamine transporter (27), and the nucleoside transporter (39). Interestingly, binding to the nucleoside transporter was inhibited by increasing concentrations of nucleosides in the binding medium (39). We report here that increasing concentrations of glucose in the uptake medium block inhibition of glucose transport by the calcium channel antagonists. Furthermore, these drugs inhibit glucose transport equally well in either the absence or presence of calcium in the uptake medium. These data suggest that GLUTs should be added to the list of proteins that bind the dihydropyridine and phenylalkylamine drugs. In fact, we propose that these different proteins may share common structural features to form a promiscuous binding site such as those highlighted in a recent model of GLUT3 that is based on an ion channel protein (9). The summary in Table 1 supports the

<table>
<thead>
<tr>
<th>Drug</th>
<th>Calcium Channel (IC50), M</th>
<th>Glucose Transport (IC50), µM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Binding</td>
<td>Function</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>0.5 × 10^-9</td>
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</tr>
<tr>
<td>Nifedipine</td>
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<tr>
<td>Diltiazem</td>
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<td>4.0 × 10^-7</td>
</tr>
<tr>
<td>Flunarizine</td>
<td>1.7 × 10^-6</td>
<td>&gt;150</td>
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Calcium channel binding data were derived from binding competition assays with nifedipine and membranes from heart (14). Calcium channel function IC50 values were estimated from inhibition of smooth muscle constriction in response to depolarization (46). The IC50 values were chosen because the low potency of diltiazem made it difficult to estimate an IC50 in the glucose transport assay.
notion of pharmacological similarities in the drug binding sites of GLUTs and calcium channels. The evidence for the similarities includes both the data shown here, indicating that the drugs inhibit glucose transport and calcium channels with a similar rank ordering, and amino acid sequence homologies between GLUTs, calcium channels, and other transporters as reported elsewhere (10).

The L-type calcium channel antagonists are widely prescribed for the treatment of hypertension (16). Since the introduction of these drugs, there have been numerous reports of hyperglycemia in patients in overdose situations (2, 20, 37). In addition, the drugs have been reported to decrease insulin secretion in humans (19). On the basis of this finding, the hyperglycemic effects of these drugs in humans have been attributed to effects on insulin secretion. Abu-Jayyab et al. (1) reported that nifedipine-induced hyperglycemia in rats could be reversed by the administration of metformin but not glibenclamide. Thus the hyperglycemia may be mediated through mechanisms other than effects on insulin secretion (1). Our data suggest that these drugs could increase blood glucose concentrations through direct interference with glucose uptake. Recently, we have shown that nimodipine induced hyperglycemia in mice following acute administration of the drug (10). Cytochalasin B produced a similar response, suggesting that antagonism of GLUTs may be partly responsible for the hyperglycemia observed in overdose situations (10).

We are the first to report that the calcium channel antagonists can block the transport of glucose into a neuronal cell line. In addition, we have shown that inhibition of glucose transport by these drugs is glucose-sensitive and independent of calcium in the uptake medium. It would appear that the inhibition of glucose uptake is not mediated by antagonism of calcium channels. These findings provide evidence for some common features shared by GLUTs and calcium channels that may suggest an evolutionary link between GLUTs, other transporters (e.g., the nucleoside transporter), and calcium channels proteins.

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