INDUCTION OF HEPATIC CYTOCHROME P450 ISOFORMS BY NICARDIPINE AT THERAPEUTIC DOSES IN SPONTANEOUSLY HYPERTENSIVE RATS

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(Received December 20, 2006; Accepted December 28, 2006)

ABSTRACT — Nicardipine hydrochloride (Nic), a calcium channel antagonist, is used for the treatment of hypertension. In the present study, we estimated its effects on the levels and activities of hepatic cytochrome P450 isoforms in spontaneously hypertensive rats given p.o. with Nic at a dose of 0.5, 2.5, 5, or 12.5 mg/kg at 24-hr intervals for 14 days. Therapeutic effects on the development of hypertension were observed at doses of 5 and 12.5 mg/kg/day. Significant increases in the levels of mRNAs and enzyme activities of hepatic P450 isoforms, CYP1A1 and/or CYP1A2, by 14-day repetitive treatment with Nic were observed at lower therapeutic doses, whereas the increase in protein levels for CYP1A2 was observed at a higher therapeutic dose of 12.5 mg/kg/day. Likewise, the activities of hepatic CYP2B and CYP3A subfamily enzymes were increased by the 14-day-treatment of Nic only at a therapeutic dose (12.5 mg/kg/day), whereas their mRNA and protein levels were increased at lower therapeutic doses. To date, the dihydropyridine family, including Nic, has been believed to have inhibitory effects on the activity of various cytochrome P450 enzymes, especially human CYP3A4. However, the present findings demonstrate for the first time that Nic-repetitive treatments at a therapeutic dose result in significant increases in the expressions and activities of hepatic CYP1A, CYP2B, and CYP3A subfamily enzymes. Therefore, the effects of dihydropyridine family on cytochrome P450 enzymes have to be further validated to provide information on its safe and beneficial therapeutic application.

KEY WORDS: Nicardipine, Cytochrome P450, Hypertension, Drug therapy, Rat liver, CYP

INTRODUCTION

Most essential hypertensive patients develop complications such as cardiovascular disease, arteriosclerosis, and stroke, and are often given various kinds of drugs in combination with an anti-hypertensive drug. Drug-drug interactions resulting from such a combination of drugs sometimes expose these patients to a high risk of side effects or, conversely, might provide a lower therapeutic effect than expected (Carter, 2005).

As a cause of drug-drug interactions, drug-induced alterations of the levels and activity of drug-metabolizing enzymes, mainly cytochrome P450 (P450), would be considered. P450 consists of the superfamily enzymes, which show different substrate-specificities, and the expression level and/or activity of each enzyme are often affected by drug-treatment (Pichard et al., 1990; Chang et al., 1997; Michalets, 1998). Thus, drug-induced alterations of the enzymes result in changes in the metabolic fate and therapeutic effect of the drug(s) administered. Therefore, to predict the therapeutic effect of a drug, especially in a combination treatment with drugs, it is essential to determine the effects of the drugs on the expressions and activities of drug-metabolizing enzymes.

The dihydropyridine-type calcium channel blockers as well as nicardipine are commonly used as anti-hypertensive medications in the clinical treatment of hypertension. They are primarily substrates of P450 3A (CYP3A) subfamily enzymes, especially CYP3A4 in
humans, and then metabolized to pharmacologically inactive forms (Higuchi and Shiobara, 1980b; Guengerich et al., 1986; Guengerich, 1991). These drugs have been reported to inhibit the catalytic activities of these CYP3A subfamily enzymes, competitively or noncompetitively (Maenpaa et al., 1989; Pichard et al., 1990; Katoh et al., 2000; Ma et al., 2000; Nakamura et al., 2005). Recently, similar inhibitory effects of these drugs have also been indicated on other P450s, i.e. human CYP1A, CYP2D6, and CYP2C9 (Katoh et al., 2000; Ma et al., 2000; Nakamura et al., 2005). These findings suggest the possibility that use of these drugs might lead to augmentation of their own efficacy and efficacy of combined drugs, which are metabolized by those P450 subfamily enzymes. Meanwhile, we and other groups have recently revealed that several dihydropyridine-type anti-hypertensive drugs, including nicardipine, have the ability to induce the gene and protein expression of hepatic P450s, especially the CYP2B and CYP3A subfamily enzymes, in rats and mice (Zangar et al., 1999; Drocourt et al., 2001; Konno et al., 2003, 2004a, 2004b; Konno and Degawa, 2004; Cui et al., 2005). The results may also suggest that these drugs increase the net activities of the P450s in the liver through the transcriptional activation of their P450 genes and that their long-term treatments might reduce the therapeutic effects of themselves and/or the drugs in a combination treatment. It would therefore be important to accurately evaluate whether these drugs produce inhibitory and/or enhancing effect(s) on the P450s at a clinical level in an effort to provide effective and safe treatment. However, most studies on the inhibitory effects have been performed by estimation of the interaction between the drugs and P450 proteins in vitro. Studies regarding the induction of hepatic P450s were performed at high doses (more than 25 mg/kg body weight) of the drugs that seemed to be over-therapeutic (in humans, approximately 1 mg/kg/day).

In the present study, the spontaneously hypertensive rats (SHRs) (Okamoto and Aoki, 1963) were given nicardipine 14 times at several doses at 24-hr intervals, and therapeutic doses of nicardipine for hypertension were determined by estimating the decrease in systolic blood pressure (SBP) of the rats. The effects of nicardipine on the gene and protein expression levels and activities of hepatic CYP1A, CYP2B, and CYP3A subfamily enzymes were examined in those SHRs. The results revealed that repetitive treatment with nicardipine at a therapeutic dose leads to the induction of hepatic P450s in SHRs.

**MATERIALS AND METHODS**

**Materials**

Nicardipine hydrochloride (Nic) was purchased from Wako Pure Chemical, Osaka, Japan. The Nic (purity >98%) used was of the highest grade available.

**Animal treatments**

Male SHR/Izm strain rats (SHRs) were supplied by the Disease Model Cooperative Research Association, Japan, and used at 7 weeks of age. The rats were housed under controlled environmental conditions with free access to water and SP diet (Funabashi Nojo, Kanagawa, Japan) and with a 12-hr light/dark cycle. Experimental protocols were approved by the Animal Experimentation Ethical Committee at the University of Shizuoka. SHRs (each group, n=4) were administered p.o. with Nic (0.5, 2.5, 5, or 12.5 mg/kg body weight) dissolved in corn oil 14 times at 24-hr intervals or with a vehicle alone (corn oil, 3 ml/kg body weight).

**Measurement of systolic blood pressure**

The conscious SHRs administered with or without Nic for 2, 6, 10, or 14 days (Day 0 was the start date of administration) were restrained for 5 min using a temperature-controlled warming holder (37°C) before the systolic blood pressure (SBP) was measured. Their SBP-values were determined by the tail-cuff method using a programmed sphygmomanometer (UR-1000; Ueda Electric Works, Co., Tokyo, Japan), and the SBP-value of each rat was shown as the average of three recordings taken at 1-min intervals.

**RNA preparation and RT-PCR analysis**

The rats were sacrificed by decapitation 24 hr after the last (14th) treatment with Nic. Livers were rapidly removed, quickly frozen in liquid nitrogen, and stored at −80°C until processed for RNA preparation as described below. Total hepatic RNAs were prepared with ISOGEN (NipponGene, Toyama, Japan) and used for the evaluation of the gene expressions of P450s (CYP1A1, CYP1A2, CYP2B1, CYP2B2, CYP3A1, and CYP3A2) and ribosomal protein L27 (RPL27), an internal control. A portion (4 μg) of the total RNA was converted to cDNA by the use of poly d(N)6 primer (Amersham Pharmacia Biotech, Inc., Piscataway, NJ, USA) and Moloney murine leukemia virus reverse transcriptase (Gibco BRL, Gaithersburg, MD, USA) in an RT-reaction mixture (20 μl). PCR was performed in a total reaction mixture (25 μl) containing 0.8 μl of the RT-reaction mixture, 0.5 μM of each primer (forward
and reverse primers), and AmpliTaq Gold DNA polymerase (Perkin-Elmer, Norwalk, CT, USA). The primers and amplification conditions used are summarized in Table 1. PCR-products were separated by electrophoresis on a 2% agarose gel. The amount of separated PCR-product was densitometrically determined with a computer using Kodak 1D Image Analysis Software (Machintosh ID version 2.02) after being visualized by ethidium bromide staining under ultraviolet light, and was normalized to that of the RPL27 gene.

**Preparation of hepatic microsomes**
Liver was homogenized with three volumes (w/v) of 1.15% KCl in a Polytron homogenizer (Kinematica, Switzerland). Microsomes were prepared from the liver homogenates by differential centrifugations, as described previously (Degawa et al., 1989), and the amount of microsomal protein was assayed by the method of Lowry et al. (1951).

**Western blot analysis of P450s**
Western blot analysis was performed by the method described by Degawa et al. (1989). Briefly, each microsomal preparation (15 μg protein/lane for CYP1A and CYP3A, 30 μg protein/lane for CYP2B) solubilized with SDS was separated by SDS-polyacrylamide gel electrophoresis. The separated proteins were transferred from the gel to a nitrocellulose sheet and then immunostained by means of horseradish peroxidase-linked immunosorbent assay using 0.05% 3,3′-diaminobenzidine tetrachloride (Sigma-Aldrich, Tokyo, Japan) at 45 °C. The reaction mixture was centrifuged for 10 min at 2,500 × g, and the amount of resorufin formed in the supernatant was measured with a spectrofluorometer FL-500 (BioTek Instruments, Winooski, VT, USA) at excitation (530 nm) and emission (590 nm). Testosterone 6β-hydroxylation (TH) was determined as below. The reaction mixture (250 μl) consisted of 0.5 mg/ml microsomal protein, 0.2 mM testosterone, and an NADPH generating system (1.3 mM NADP+, 3.3 mM glucose-6-phosphate, 3.3 mM MgCl2, 0.4 unit/ml glucose-6-phosphate dehydrogenase) in 0.1 M potassium phosphate buffer (pH 7.4). The reaction was started by the addition of a 500 μM alkoxyresorufin (ethoxyresorufin, methoxyresorufin, pentoxyresorufin, or benzoxylresorufin; 5 μl) dissolved in dimethylsulfoxide, and 5 min later, stopped by the addition of cold ethanol (500 μl). The reaction mixture was centrifuged for 10 min at 2,500 × g, and the amount of resorufin formed in the supernatant was calculated by using a calibration curve of authentic 6β-hydroxytestosterone.

**Statistical analysis**
Statistical comparisons of the results were made using analysis of variance (ANOVA). Significant differences from the corresponding controls were analyzed by Dunnett’s test (Dunnett, 1964).
Table 1. The PCR primer sets used for the P450 genes.

<table>
<thead>
<tr>
<th>Target gene</th>
<th>Primer set</th>
<th>Reaction condition</th>
<th>Product size (bp)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A1</td>
<td>5'-TGACCTCTTTGGAGCT-3' (forward) 5'-TTGAGCCTCAGCAGAT-3' (reverse)</td>
<td>95 ºC, 60 sec, 50 ºC, 30 sec, 72 ºC, 120 sec</td>
<td>1050</td>
<td>Kim et al., 1991</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>5'-GATGAGAAGCAGTGGAAAGACC-3' (forward) 5'-AAAAAGAAAGGAGGAACAA-3' (reverse)</td>
<td>95 ºC, 60 sec, 50 ºC, 30 sec, 72 ºC, 120 sec</td>
<td>328</td>
<td>Gomez-Lechon et al., 1998</td>
</tr>
<tr>
<td>CYP2B1</td>
<td>5'-GCTCAAGTACCCCCATGTCCG-3' (forward) 5'-ATCAGTGATGGCATTTTACTGGCG-3' (reverse)</td>
<td>93 ºC, 60 sec, 54 ºC, 90 sec, 72 ºC, 60 sec</td>
<td>109</td>
<td>Omiecinski et al., 1990</td>
</tr>
<tr>
<td>CYP2B2</td>
<td>5'-CTTTGCTGGCAGTGAGACC-3' (forward) 5'-ATCAGTGATGGCATTTTACTGGCA-3' (reverse)</td>
<td>93 ºC, 60 sec, 54 ºC, 90 sec, 72 ºC, 60 sec</td>
<td>163</td>
<td>Omiecinski et al., 1990</td>
</tr>
<tr>
<td>CYP3A1</td>
<td>5'-GATGTTGAAATCAATGGTGTGT-3' (forward) 5'-TTTACGGGTAATGTTTGTTC-3' (reverse)</td>
<td>95 ºC, 60 sec, 60 ºC, 60 sec, 72 ºC, 120 sec</td>
<td>289</td>
<td>Oinonen and Lindros, 1995</td>
</tr>
<tr>
<td>CYP3A2</td>
<td>5'-AGTAGTGACGAATTCCGCAATAT3'-3' (forward) 5'-TCAGGATGATGTTTCCCT-3'(reverse)</td>
<td>95 ºC, 60 sec, 60 ºC, 60 sec, 72 ºC, 120 sec</td>
<td>252</td>
<td>Oinonen and Lindros, 1995</td>
</tr>
<tr>
<td>RPL27</td>
<td>5'-TTCAACGCGACAGTCAAGG-3' (forward) 5'-CATGGACTGTGGTCATGAG-3'(reverse)</td>
<td>95 ºC, 60 sec, 50 ºC, 60 sec, 72 ºC, 120 sec</td>
<td>234</td>
<td>Wool et al., 1990</td>
</tr>
</tbody>
</table>
RESULTS

Effects of Nic-repetitive treatments on systolic blood pressure

Male SHRs were treated p.o. with Nic at a dose of 0.5, 2.5, 5, or 12.5 mg/kg 14 times at 24-hr intervals. The systolic blood pressure (SBP) of the rats was measured over time from just before the onset of treatment (0 day) until 24 hr after the final treatment (14 days) (Fig. 1). Significantly increased SBP-values (increase of about 10 mmHg) in the control rats treated with vehicle alone were first observed 6 days after the onset of the experiment, and these levels were maintained until 14 days. Age-related increases in SBP-values are a well-known phenomenon in SHRs (Okamoto and Aoki, 1963; Fukuda et al., 2004). Thus the increase in SBP-values found in the control rats also seemed to be age-related. Such an age-related increase could hardly be suppressed by treatment with Nic at a dose of either 0.5 or 2.5 mg/kg/day. Meanwhile, treatments with Nic at doses of 5 and 12.5 mg/kg/day significantly suppressed the age-related increase in SBP-values. In addition, the SBP-values in the treatment at a dose of 12.5 mg/kg/day, but not 5 mg/kg/day, were lower than those immediately before the first treatment (at 0 day) throughout the treatment period.

Effects of Nic-repetitive treatments on gene expression of P450 isoforms

We examined the dose-effects of Nic on hepatic gene expression of several P450 isoforms in SHRs by the method of RT-PCR. Total hepatic RNAs were pre-

![Fig. 1. Therapeutic effects of Nic on the development of hypertension in SHRs. The rats (each group, n=4) were treated with Nic (0.5, 2.5, 5, or 12.5 mg/kg/day) at 24-hr intervals for 14 days, and their SBP-values were measured at the indicated periods. The symbols and bars represent the means and their standard deviations, respectively. Significantly different from the rats (0 day) just before the 1st Nic-treatment; * p < 0.05; ** p < 0.01, significantly different from the age-matched control rats; # p < 0.05, ## p < 0.01.](image-url)
pared from the rats 24 hr after the final treatment with Nic. Representative profiles of agarose gel electrophoreses for the RT-PCR products for the P450 mRNAs, CYP1A1, CYP1A2, CYP2B1, CYP2B2, CYP3A1, and CYP3A2, are shown in Fig. 2. The intensity of the band corresponding to CYP1A1 mRNA was significantly stronger even at a dose of 0.5 mg/kg/day Nic, approximately fourfold than at a dose of 0 mg/kg/day, and further stronger approximately fivefold at the doses of 2.5, 5, and 12.5 mg/kg/day (Fig. 3). Likewise, the intensities of the bands corresponding to CYP1A2, CYP2B1, and CYP2B2 mRNAs were also 2-4 times greater at doses over 0.5 mg/kg/day than those of the corresponding controls. The intensities of the bands corresponding to CYP3A1 and CYP3A2 mRNAs were significantly stronger at doses over 2.5 mg/kg/day, but not 0.5 mg/kg/day, approximately twice those of the corresponding controls.

Effects of Nic-repetitive treatments on P450 protein levels

To determine whether the increases in the expres-

![Fig. 2. Representative gene expression patterns of hepatic P450s in Nic-treated SHRs. The rats were treated with Nic (0.5, 2.5, 5, or 12.5 mg/kg/day) at 24-hr intervals 14 times and killed 24 hr after the last treatment. Hepatic total RNAs were extracted from the pooled livers removed from four rats in each experimental group and used for RT-PCR analysis. Each number on the right side of the photographs indicates the number of PCR cycles examined.](image-url)
Induction of Hepatic P450s by Nicardipine.

Expression levels of P450 genes by Nic-repetitive treatments lead to increases in the corresponding protein levels, we carried out Western blot analysis using hepatic microsomes of rats treated with Nic (Fig. 4). When anti-rat CYP1A1 monoclonal antibody APL-2 cross-reactive to CYP1A2 (Degawa et al., 1989; Konno et al., 2003) was used, only a single band, which was most likely to correspond to CYP1A2, was detected for

![Graphs showing dose effects of Nic on gene expression of hepatic P450s in SHRs.](image)

**Fig. 3.** Dose effects of Nic on the gene expression of hepatic P450s in SHRs. The rats were treated with Nic (0.5, 2.5, 5, or 12.5 mg/kg/day) at 24-hr intervals 14 times and killed 24 hr after the last treatment. Total hepatic RNAs were extracted from four individual rats in each experimental group and used for RT-PCR analysis. The number of PCR cycles used for each P450 gene is shown in Fig. 2. The values shown represent levels relative to the corresponding controls, and the closed circles and bars show means and their standard deviations, respectively. Significant differences from the corresponding controls; * p < 0.05, ** p < 0.01.
all treatments. Its density was stronger in the rats treated with Nic at a dose of 12.5 mg/kg/day than in the control rats (without Nic treatment). As for CYP2B proteins, a slight increase in the levels of CYP2B2 protein occurred in a dose-dependent fashion in the range of 2.5-12.5 mg/kg/day. Furthermore, a clear increase in the levels of CYP2B1 protein was observed, and the increase occurred in a dose-dependent fashion in the range of 2.5-12.5 mg/kg/day. Likewise, the levels of the CYP3A proteins were also dose-dependently increased in the range of 2.5-12.5 mg/kg/day.

Effects of Nic-repetitive treatments on microsomal P450 activities

Hepatic microsomal activities for ethoxyresorufin O-dealkylation (EROD), methoxyresorufin O-dealkylation (MROD), pentoxyresorufin O-dealkylation (PROD), benzyloxyresorufin O-dealkylation (BROD), and testosterone 6β-hydroxylation (TH), which are primarily catalyzed by CYP1A1/1A2 (specificity: 1A1>1A2), CYP1A2/1A1 (specificity: 1A2>1A1), CYP2B, CYP2B/CYP3A and CYP3A enzymes, respectively (Meehan et al., 1988; Namkung et al., 1988; Degawa et al., 1989; Chen and Eaton, 1991; Nerurkar et al., 1993), were examined in the rats after the 14-day-treatment with Nic at the indicated doses (Fig. 5). The EROD and MROD activities increased in a dose-dependent fashion. Significant increases were observed at doses of more than 2.5 mg/kg/day, and the levels increased approximately twofold over the corresponding control levels at a dose of 12.5 mg/kg/day of Nic. On the other hand, significant increases in the activities of PROD, BROD, and TH were observed only at a dose of 12.5 mg/kg/day of Nic.

DISCUSSION

We first determined the therapeutic doses of Nic for the hypertension of SHRs by temporally measuring the SBP of SHRs treated with Nic. Treatments with Nic at doses of 5 and 12.5 mg/kg/day, but at neither 0.5 nor 2.5 mg/kg/day, suppressed the age-related increase in SBP-values during the 2 to 14 days after the 1st Nic-treatment. It has already been reported that the metabolic rate of Nic is faster in rats than humans (Higuchi et al., 1980) and that the maximum plasma concentrations in rats (5 mg/kg/day) and humans (1 mg/kg/day) administered with Nic for 28 days are almost the same (Higuchi and Shiobara, 1980a). Nic ranging from 10 mg to 40 mg three times daily is usually prescribed for human patients. Therefore, 5-12.5 mg/kg/day of Nic seems to be reasonable as a therapeutic dose for the

![Fig. 4. Representative expression patterns of hepatic P450 proteins in Nic-treated SHRs. The rats were treated with Nic (0.5, 2.5, 5, or 12.5 mg/kg/day) at 24-hr intervals 14 times and killed 24 hr after the last treatment. Hepatic microsomes were extracted from the pooled livers removed from four rats in each experimental group and used for Western blot analysis.](image-url)
Induction of Hepatic P450s by Nicardipine.

hypertension of SHRs. However, the suppressive effects of Nic at doses of 5 and 12.5 mg/kg/day on the SBP were weakened 14 days after onset of the 1st Nic-treatment. One reason for this weakening may have been that Nic at these doses is not sufficient to suppress potentially age-related malignancy of hypertension based on the particular genetic factor(s) of SHR, or that the metabolic system for Nic is strengthened by Nic-repetitive treatment.

We next examined whether the gene and protein expression of hepatic P450 enzymes and their enzyme activities were changed in SHRs by the Nic-repetitive treatment. The results showed that the all parameters were significantly larger at Nic doses of 5 and/or 12.5 mg/kg/day than those of control rats. Therefore, it was concluded that Nic can augment the activities of the hepatic CYP1A, CYP2B and CYP3A subfamily enzymes through activation of their expression, even at therapeutic doses, as previously reported (Zangar et al., 1999; Drocourt et al., 2001; Konno et al., 2003, 2004a, 2004b; Konno and Degawa 2004; Cui et al., 2005). However, the correlativity was not necessarily seen among the increased ratios of mRNAs, proteins, and activities of the P450 enzymes. For example, although the gene expression levels and enzyme activities of CYP1A1 and CYP1A2 increased at lower doses (more than 0.5 mg/kg/day as for the gene expression and 2.5 mg/kg/day as for the enzyme activity), the increased expression of the CYP1A2 protein, but not the CYP1A1 protein, was observed only at a therapeutic dose of 12.5 mg/kg/day. Although the gene and protein expression levels of CYP2B and CYP3A subfam-

![Fig. 5](image-url)
ily enzymes were increased at doses of more than 0.5 or 2.5 mg/kg/day, hepatic microsomal activities of PROD, BROD, and TH, which are primarily mediated by the CYP2B, CYP2B/CYP3A and CYP3A subfamily enzymes, respectively, were increased only at a dose of 12.5 mg/kg/day. The difference between the increased ratios of mRNAs and proteins might be dependent on the posttranscriptional efficiency. It is hard to explain at this stage how the activities of the CYP1A1 and 1A2 enzymes were increased in a dose-dependent fashion in the range of 2.5-12.5 mg/kg/day, although the increase in CYP1A2 protein levels was detected only at 12.5 mg/kg/day. The reason that the increases in CYP2B and CYP3A enzyme activities were detected only at 12.5 mg/kg/day, although their protein expression was increased in a dose-dependent fashion, might be partly that Nic inhibits the catalytic activities of both proteins induced by Nic through competitive or noncompetitive mechanisms, as previously reported (Maenpaa et al., 1989; Pichard et al., 1990; Katoh et al., 2000; Ma et al., 2000; Nakamura et al., 2005).

In conclusion, we have demonstrated for the first time that Nic-repetitive treatments at a therapeutic dose for hypertension in SHRs result in significant increases in the gene and protein expression levels of hepatic P450s, CYP1A1, CYP1A2, CYP2B1, CYP2B2, CYP3A1, and/or CYP3A2, and their enzyme activities. To date, Nic as well as other dihydropyridine anti-hypertensive drugs has been believed to show inhibitory effects on the activity of CYP3A subfamily enzymes at high doses, generally indicating that high-dose treatment leads to side effects through increased AUC (area under the blood concentration-time curve) of itself and/or its combined drugs. However, our present results suggest the possibility that inhibition of the enzyme activities and induction of gene and protein expression in response to Nic-treatment occur at the same time. In other words, the efficacy of Nic (or other dihydropyridine drugs) and its combined drugs might depend on a balance of the inhibitory and inducing effects of Nic (or other dihydropyridine drugs) on P450 enzymes. Therefore, further studies on the drug-induced alterations of the expression of P450 isoforms would be necessary for effective and safe therapy with dihydropyridine anti-hypertensive drugs.

ACKNOWLEDGMENT

This work was supported in part by a Grant-in-Aid for Scientific Research (C) (no. 17590104, M.D. and K.N.) from Japan Society for the Promotion of Science.

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