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# Intervascular and stimulus selectivity of nitrendipine and related derivatives in KCl and prostaglandin $F_{2\alpha}$ precontracted porcine arteries

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**1** Dihydropyridine-type calcium entry blockers exhibit a different vasodilator potency depending on the arterial tissue (intervascular selectivity) as well as on the precontracting stimulus used (stimulus selectivity). In addition, the structure of their ester side chains seems to influence their activity.

**2** Vascular activity of nitrendipine and six related 3-ester side chain derivatives was investigated in isolated coronary, ulnar and basilar arteries of the pig following precontraction with KCl or prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$).

**3** After depolarization, all dihydropyridines exhibited a weak preferential action on coronary arteries. Bay E 6927 produced the strongest effect in all vessel types. By contrast, precontraction with $PGF_{2\alpha}$ resulted in a marked preferential action in basilar arteries, although higher concentrations of the dihydropyridines were required for half maximal vasorelaxation. In each case, ulnar arteries were less sensitive.

**4** Except with Bay O 5572, the most bulky substituted and least active derivative, only moderate differences were observed within the dihydropyridines studied. On the other hand, there was a pronounced increase in the ratios of the half maximal active concentrations required after precontraction of the vessels with $PGF_{2\alpha}$ compared to KCl (stimulus selectivity) following a limited prolongation of the 3-ester side chain up to an isopropyl-group.

**5** It is suggested that the observed shift in the intervascular selectivity after precontraction with $PGF_{2\alpha}$ is a consequence of different contractile mechanisms in the three vessel types studied. The degree of the stimulus selectivity may also depend on the structure of the dihydropyridines.

**Keywords:** Dihydropyridines; nitrendipine; structure; porcine isolated arteries; intervascular selectivity; stimulus selectivity; prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)

## Introduction

Calcium entry blockers of the dihydropyridine type are widely used in the treatment of cardiovascular diseases. On the molecular basis, their main target in the body are L-type calcium channels in the smooth muscles of the arterial system, although they also exhibit a definite influence on calcium channels of other tissues e.g. ventricular muscle (Godfraind *et al.*, 1986). In recent years several new dihydropyridines have been introduced with specific indications, that are based on a selective action of these drugs in different parts of the vascular system (intervascular selectivity). Thus nisoldipine has been described as acting preferentially in coronary arteries (Godfraind *et al.*, 1987,a,b). In addition, Kazda & Towart (1981) reported on the cerebrovascular selectivity of nimodipine, a drug with benefit in the management of cerebrovascular disorders following subarachnoidal haemorrhage (Gelmers *et al.*, 1985). On the other hand, Fricke & Ueckert (1988) demonstrated a particular cerebrovascular selectivity for nisoldipine in depolarized arteries, whereas nimodipine exhibited rather a predominant potency in coronary arteries. However, arterial depolarization as a widely used pharmacological model to study the effects of dihydropyridines reflects only in part the mechanisms responsible for arterial contraction (Bolton, 1979). Other mechanisms may be carried by receptor-mediated pathways. Investigations on dihydropyridines in isolated arteries precontracted with vasoactive agonists often revealed a reduced activity compared to that achieved in the same arteries precontracted by depolarization (Cauvin *et al.*, 1983). Such stimulus selective action has also been described for nitrendipine (Altura & Altura, 1984; Scriabine *et al.*, 1984). However, a comprehensive investigation on the intervascular and stimulus selectivity of dihydropyridines in different arteries of the same species is still lacking.

The present study was performed to investigate (1) if and to what degree nitrendipine displays intervascular and stimulus selectivity and (2) whether the intervascular selectivity depends on the stimulus used for precontraction of the different porcine arteries. In addition, we were interested in activity differences due to a modification of the chemical structure of nitrendipine. Therefore, six nitrendipine derivatives with a modified 3-ester side chain (cf. Figure 1) were included. The ester side chains of dihydropyridines have previously been found to have a direct influence on vasodilator activity (Bossert *et al.*, 1979; Fricke *et al.*, 1988).

## Methods

### *Preparation of vascular ring segments*

The experiments were performed on arterial vessels from 5–7 month old pigs (70–90 kg) obtained from the local slaughterhouse. The hearts, brains and forelegs were removed 10–30 min after death. Right coronary, ulnar and basilar arteries were rapidly dissected and flushed gently with cold oxygenated (95% $O_2$ + 5% $CO_2$) Krebs-Henseleit solution

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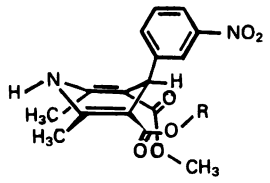
(pH 7.4) of the following composition: (mmol $l^{-1}$): $Na^+$ 123.07, $K^+$ 5.87, $Ca^{2+}$ 1.6, $Mg^{2+}$ 1.18, $Cl^-$ 124.78, $HCO_3^-$ 5.00, $H_2PO_4^-$ 2.36, $SO_4^{2-}$ 1.18 and glucose 5.05. After carefully removing all loosely adherent tissue, proximal parts of the arteries were cut into ring segments (3–4 mm) and mounted between stainless steel triangles in a 10 ml jacketed organ bath (37°C) as recently described (Fricke *et al.*, 1988). Previous experiments with KCl (60 mmol $l^{-1}$) revealed an optimal resting tension of 2.0 g for the coronary and ulnar arteries and 0.7 g for the basilar arteries. Destruction of the endothelium was achieved by carefully rubbing the luminal surface of the artery segments with a thin steel needle. To further prevent the influence of endothelium on the vasodilator activity of the dihydropyridines (Kojda *et al.*, 1990), all vessels were incubated with methylene blue (5–10 μmol $l^{-1}$) prior to the experimental procedure. Changes in arterial diameter were measured with an isotonic transducer (Fleck, Mainz, Germany) and recorded after amplification on a thermorecorder (Hellige Servomed, Freiburg, Germany) or on a digital point printing recorder (Linseis, Typ LPD 12, Selb, Germany). The contractile response of the artery rings was calculated from the observed changes in their diameter using the equation $W = m\ g\ s$, with W = work, m = tension, g = 9.81 m $s^{-2}$, s = change in diameter and is given in μJ as described previously (Kojda *et al.*, 1990). Mean values of KCl-induced (60 mmol $l^{-1}$) contractile work were 50.0 ± 1.5 μJ ($n = 53$); 2.6 ± 0.17 μJ ($n = 37$) and 37.7 ± 1.7 μJ ($n = 46$) and of $PGF_{2\alpha}$-induced contractile work were 55.8 ± 1.9 μJ ($n = 56$); 2.3 ± 0.08 μJ ($n = 54$) and 30.9 ± 2.1 μJ ($n = 46$) for coronary, basilar and ulnar arteries, respectively.

### *Organ bath experiments*

After an equilibration period of 1–2 h, reproducible and maximal contractions were induced by addition of KCl (60 mmol $l^{-1}$) or $PGF_{2\alpha}$ (50 μmol $l^{-1}$, in the case of basilar arteries 5 μmol $l^{-1}$). The different concentrations of $PGF_{2\alpha}$ used have been shown to elicit maximal contractions in the specific vessel types (Werner *et al.*, 1988). Nitrendipine and the six related derivatives shown in Figure 1 were added in a cumulative manner (0.1 nmol $l^{-1}$–100 μmol $l^{-1}$), in the course of which the volume of the applied drug solutions did not exceed more than 70 μl. The time intervals were chosen such as to allow a steady state of drug action indicated by a stable arterial tension. To prevent photodegradation of the dihydropyridines all experiments were carried out under sodium light. At the end of each concentration-response curve, all drugs were washed out by rinsing the artery segments several times with Krebs-Henseleit solution. In the case of $PGF_{2\alpha}$ precontracted coronary and ulnar arteries, 200 μmol $l^{-1}$ papaverine was added before the washout period to produce complete relaxation. Ulnar arteries in particular responded with a very slow reduction of tension following the washout period, so that baseline value was not achieved within 1 h. Such incomplete relaxation was not observed in $PGF_{2\alpha}$ precontracted basilar arteries or in depolarized vessels.




| | Substance | R | Mol. wt. | Volume |
|---|---|---|---|---|
| 1 | Bay A 4339 | $-CH_3$ | 346.3 | 20.0 |
| 2 | Nitrendipine | $-C_2H_5$ | 360.4 | 34.7 |
| 3 | Bay E 6927 | $-CH(CH_3)_2$ | 374.4 | 62.3 |
| 4 | Bay N 6391 | $-C(CH_3)_3$ | 388.4 | 65.3 |
| 5 | Bay I 1441 | $-CH_2-C_6H_5$ | 422.4 | 85.1 |
| 6 | Bay L 3501 | $-CH_2-C(CH_3)_3$ | 402.4 | 85.7 |
| 7 | Bay O 5572 | $-(CH_2)_7-CH_3$ | 444.5 | 171.7 |

**Figure 1** Chemical structure of nitrendipine and related 3-ester side-chain derivatives and their molecular weight (Mol. wt.). The calculated volumes of the 3-ester side-chains (see methods) are given in $Å^3$.

### *Statistical analysis*

Vasorelaxation due to treatment with the drugs is expressed as percentage of the maximal contractile response achieved with the vasoconstrictors used at the beginning of the experiments. The concentrations of the dihydropyridines for half maximal inhibition of KCl and $PGF_{2\alpha}$-induced vasoconstriction ($pD_2$ values) were calculated from the individual concentration-effect curves as proposed by Hafner *et al.* (1977). All data were analysed by one-way analysis of variance (ANOVA) with subsequent Student-Newman Keuls test (SAS PC Software 6.04, PROC ANOVA) and are expressed as mean values and standard error of the mean (s.e.mean) A $P$ value less than 0.05 was considered significant.

### *Sterical parameters*

The volumes of the different 3-ester side chains of nitrendipine and its derivatives (Figure 1) were approximately estimated by means of calculated data for the widths and length of various chemical substituents published by Verloop *et al.* (1976). These volume data correlated well with the lipophilicity of the dihydropyridines investigated, measured by high performance liquid chromatography (Kojda *et al.*, 1989).

### *Materials*

The chemicals (analytical grade) were purchased from Merck (Darmstadt, Germany) and dissolved in water. The dihydropyridines were generously provided by Bayer AG (Leverkusen, Germany) and dissolved in dimethylsulphoxide, which itself had no effect on the arterial tone up to a concentration in the organ bath of 1%.

## Results

### *KCl-stimulated arteries*

The sensitivity to KCl differed in the different vessel types examined. Concentrations for half maximal contractile response were in coronary 32.5 ± 1.3 mmol $l^{-1}$ ($n = 4$) and in ulnar arteries 33.4 ± 0.9 mmol $l^{-1}$ ($n = 5$), whereas in basilar arteries this concentration was significantly reduced to 24.8 ± 0.9 mmol $l^{-1}$ ($n = 4$; $P < 0.01$). Nitrendipine and all related 3-ester-side-chain derivatives inhibited concentration-dependently KCl-induced contractions of the different blood vessels. In coronary arteries Bay E 6927 was significantly more potent than nitrendipine and both compounds exhibited significantly higher $pD_2$ values than the other dihydropyridines (Table 1, $P < 0.05$). Except for Bay O 5572, which was the weakest drug, the differences in the potency of the compounds studied did not exceed one order of magnitude. A similar situation was observed in basilar and ulnar arteries, though the differences obtained in the potencies were rather more pronounced in basilar arteries (Tables 2 and 3). Contrary to the full relaxation induced by the dihydropyridines in coronary and basilar arteries, the reduction of tension at the end of each concentration-response curve in ulnar arteries

**Table 1** The vasodilator potencies of the 1, 4-di-hydropyridines examined (cf. Figure 1, NTD = nitrendipine) on porcine isolated coronary artery rings stimulated with KCl (60 mmol $l^{-1}$) or prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 50 μmol $l^{-1}$) expressed as the concentration producing half maximal response ($pD_2$) following cumulative drug application

| *Compound* | *$pD_2$ KCl* | n | *$pD_2$ $PGF_{2\alpha}$* | n |
|---|---|---|---|---|
| A 4339 | 7.49 ± 0.03 | 6 | 4.65 ± 0.04* | 8 |
| NTD | 8.25 ± 0.06 | 9 | 4.63 ± 0.10* | 11 |
| E 6927 | 8.53 ± 0.06 | 11 | 4.07 ± 0.07* | 8 |
| N 6391 | 7.71 ± 0.09 | 6 | 4.10 ± 0.06* | 6 |
| I 1441 | 7.71 ± 0.14 | 8 | 4.07 ± 0.07* | 8 |
| L 3501 | 8.02 ± 0.07 | 7 | 4.68 ± 0.08* | 7 |
| O 5572 | 5.93 ± 0.11 | 6 | <4.00 | 8 |

Mean values and standard error (s.e.mean) of *n* individual experiments are given in − log mol $l^{-1}$.
Significant differences, $*P<0.00001$.
Because of the very low activity of Bay O 5572 following $PGF_{2\alpha}$-precontraction, this $pD_2$-value is lacking.

was incomplete (percentage of persisting contraction following the drug sequence given in Figure 1: 26.4 ± 1.5; 12.2 ± 0.6; 16.4 ± 3.3; 31.8 ± 4.1; 17.1 ± 2.0; 16.8 ± 1.1 and 37.1 ± 0.5).

### *Prostaglandin $F_{2\alpha}$-stimulated arteries*

Apart from Bay O 5572, all dihydropyridines produced a distinct vasorelaxation in coronary and basilar arteries. However, compared to KCl-stimulation the calculated $pD_2$ values were shifted to much higher concentrations (Tables 1 and 2). In addition, treatment with the dihydropyridines did not abolish the contractions of the coronary arteries (percentage of persistent contraction following the drug-sequence given in Figure 1: 15.5 ± 1.7; 25.5 ± 2.7; 44.6 ± 2.7; 41.8 ± 3.4; 40.5 ± 3.9; 30.9 ± 3.5 and 99.6 ± 3.2). In ulnar arteries, only Bay A 4339, nitrendipine and Bay E 6927 produced relaxations of nearly 50% (percentage of persistent contraction following the drug-sequence given in Figure 1: 39.0 ± 2.7; 38.7 ± 2.9; 54.4 ± 3.1; 75.4 ± 2.9; 67.8 ± 4.5; 75.0 ± 4.0 and 82.0 ± 2.4). The corresponding $pD_2$-values are given in Table 3. As with the results obtained in KCl-stimulated arteries, Bay O 5572 was always the weakest drug tested. By contrast, the strongest potencies were shown by several dihydropyridines, which did not differ significantly from one another ($P<0.05$). Thus, in coronary arteries Bay A 4339, Bay L 3501 and nitrendipine and in basilar and ulnar arteries Bay A 4339 and nitrendipine were the most potent dihydropyridines (Tables 1 to 3).

In contrast to the results obtained after precontraction of the arteries with KCl and to the results with $PGF_{2\alpha}$-stimulated coronary and ulnar arteries, we found a significant linear correlation between the calculated $pD_2$ values of the dihydropyridines and the volume of their corresponding 3-ester-side-chain in $PGF_{2\alpha}$ precontracted basilar arteries (Figure 2).

### *Stimulus selectivity*

All dihydropyridines exhibited significant differences in potency ($P<0.05$) in coronary and basilar arteries depending on the precontraction method used (Tables 1 and 2). This effect was termed stimulus selectivity. The affinity ratios for each drug plotted in Figure 3 (stimulus selectivity ratios) demonstrate further that the observed reduction of vasodilator potency in $PGF_{2\alpha}$-stimulated arteries was also dependent on the structure of the dihydropyridines. In both arteries Bay E 6927 displayed maximal stimulus selectivity ratios, whereas those of Bay A 4339 were the least. Although it was not possible to consider the whole group of dihydropyridines, a similar tendency could be observed in ulnar arteries (Table 3).

### *Intervascular selectivity*

To quantify approximately the observed differences in potencies in the various vascular beds (intervascular selectivity) for each drug under both experimental conditions, a ratio was obtained between the calculated $pD_2$-values in coronary arteries and those obtained in basilar compared to ulnar arteries (intervascular ratios). A plot of these ratios (Figure 4) clearly demonstrates that the vasorelaxation induced by the dihydropyridines investigated in the specific vascular beds also depends on the stimulus used for precontraction. In arteries stimulated with KCl the dihydropyridines showed a coronary 'preference' (Figure 4a), whereas after arterial stimulation with $PGF_{2\alpha}$ this 'preference' was markedly shifted to basilar arteries (Figure 4b). In ulnar arteries, the vasodilator action of all the dihydropyridines studied was less pronounced.

## Discussion

Calcium entry blockers of the dihydropyridine type reduce the transmembrane calcium flux through distinct ion channels (Godfraind *et al.*, 1986). Voltage operated calcium chan-

**Table 2** The vasodilator potencies of the 1, 4-di-hydrophyridines examined (cf. Figure 1, NTD = nitrendipine) on porcine isolated basilar artery rings stimulated with KCl (60 mmol $l^{-1}$) or prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 5 μmol $l^{-1}$) expressed as the concentration producing half maximal response ($pD_2$) following cumulative drug application

| *Compound* | *$pD_2$ KCl* | n | *$pD_2$ $PGF_{2\alpha}$* | n |
|---|---|---|---|---|
| A 4339 | 7.29 ± 0.06 | 4 | 5.78 ± 0.03* | 8 |
| NTD | 8.05 ± 0.04 | 4 | 5.60 ± 0.07* | 12 |
| E 6927 | 8.42 ± 0.12 | 6 | 5.50 ± 0.08* | 6 |
| N 6391 | 7.17 ± 0.10 | 5 | 5.31 ± 0.04* | 8 |
| I 1441 | 7.46 ± 0.09 | 7 | 5.14 ± 0.06* | 8 |
| L 3501 | 7.48 ± 0.04 | 6 | 5.17 ± 0.07* | 6 |
| O 5572 | 5.79 ± 0.08 | 5 | 3.89 ± 0.09* | 6 |

Mean values and standard error (s.e.mean) of *n* individual experiments are given in − log mol $l^{-1}$.
Significant differences, $*P<0.00001$.

**Table 3** The vasodilator potencies of the 1, 4-di-hydropyridines examined (cf. Figure 1, NTD = nitrendipine) on porcine isolated ulnar artery rings stimulated with KCl (60 mmol $l^{-1}$) or prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 50 μmol $l^{-1}$) expressed as the concentration producing half maximal response ($pD_2$) following cumulative drug application

| *Compound* | *$pD_2$ KCl* | n | *$pD_2$ $PGF_{2\alpha}$* | n |
|---|---|---|---|---|
| A 4339 | 6.35 ± 0.05 | 7 | 4.24 ± 0.05* | 8 |
| NTD | 6.61 ± 0.04 | 7 | 4.38 ± 0.12* | 6 |
| E 6927 | 7.20 ± 0.07 | 7 | 3.82 ± 0.09* | 5 |
| N 6391 | 6.36 ± 0.05 | 7 | <3.80 | 9 |
| I 1441 | 6.53 ± 0.06 | 7 | <3.80 | 7 |
| L 3501 | 6.22 ± 0.11 | 7 | <3.80 | 6 |
| O 5572 | 4.86 ± 0.12 | 4 | <3.80 | 5 |

Mean values and standard error (s.e.mean) of *n* individual experiments are given in − log mol $l^{-1}$.
Significant difference, $*P<0.0001$).
Because of the very low activity of some drugs following $PGF_{2\alpha}$-precontraction, these $pD_2$-values are lacking.

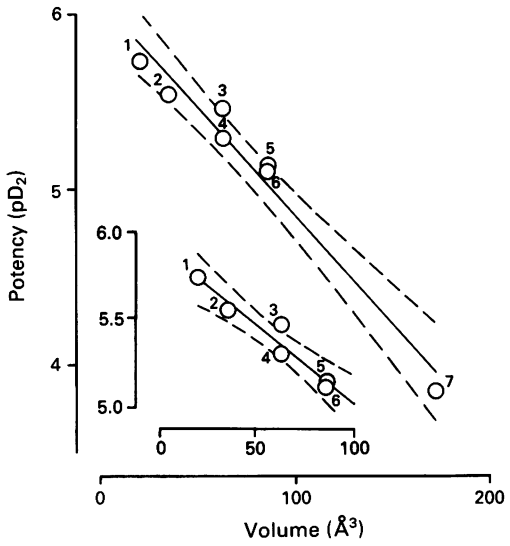



**Figure 2** Correlation between the vasodilator potency of the dihydropyridines examined in basilar arteries precontracted with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 5 μmol $l^{-1}$) and the calculated volume of their 3-ester side-chains (for numbers see Figure 1). Volumes are plotted against the $pD_2$ values ($r = 0.98$; $P < 0.05$). Inset: Same plot without Bay O 5572 (No 7; $r = 0.97$; $P < 0.05$).

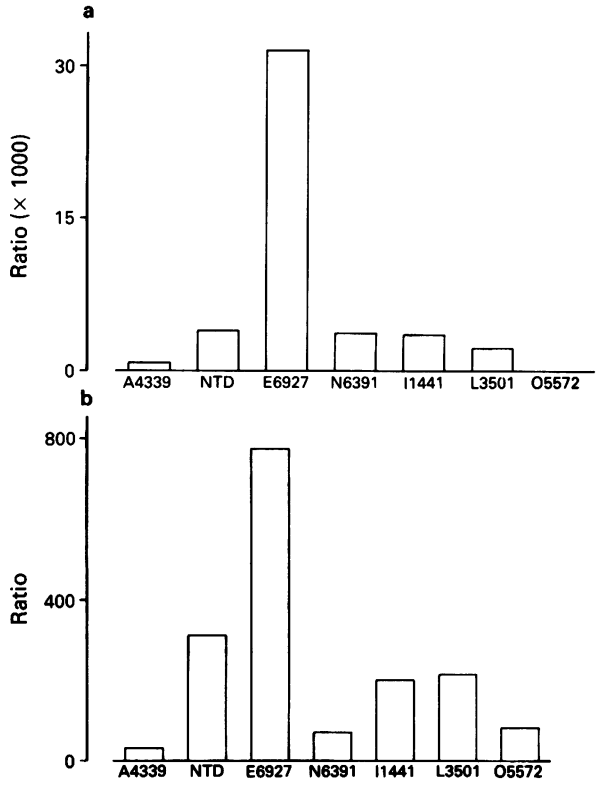



**Figure 3** Stimulus selectivity of the 1,4-dihydropyridines examined in porcine (a) coronary and (b) basilar arteries. Plotted are the ratios of half maximal effective molar concentrations (cf. Tables 1 and 2) observed following cumulative drug application in prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and KCl precontracted vessels. Because of the very low activity of Bay O 5572 in $PGF_{2\alpha}$ precontracted coronary arteries (Table 1) the ratio for this drug is lacking. Note the different ordinate scales.

nels (VOC's), which also exist in vascular smooth muscles (Bolton *et al.*, 1988), are activated by membrane depolarization e.g. by exposure to high potassium. Furthermore, the degree of such depolarization closely parallels the development of contraction e.g. in rat tail artery reaching maximal contraction at a membrane potential of − 20 mV achieved by 60 mmol $l^{-1}$ KCl (Neild & Kotecha, 1987). This concentration of KCl was also sufficient to induce maximal contractions in the different porcine arteries used here.

However, in preliminary experiments we found very similar half-maximal contractile concentrations of KCl in coronary and ulnar arteries, whereas in basilar arteries this concentration was significantly reduced (see Results). On the other hand, we observed only small differences in the $pD_2$ values of each dihydropyridine investigated in depolarized coronary and basilar arteries, but markedly reduced $pD_2$ values in depolarized ulnar arteries (Table 1 to 3; Figure 4a). These results indicate that the sensitivity of VOC's in vascular smooth muscles of porcine arteries to KCl may be separated from that to dihydropyridines.

However, Cauvin *et al.* (1983), summarizing the results of various studies on the activity of calcium entry blockers in isolated vessels, suggested a nearly constant sensitivity of

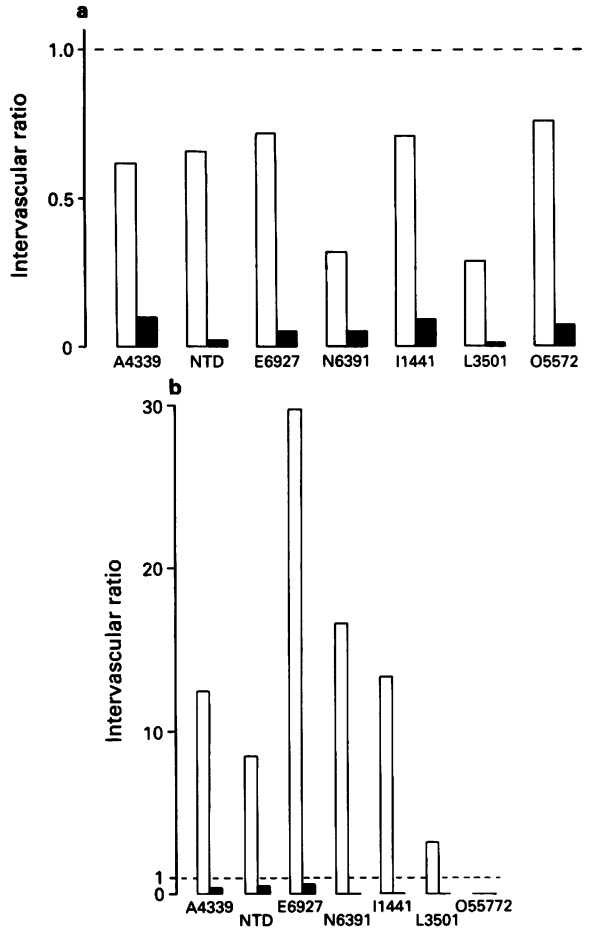



**Figure 4** Intervascular selectivity of the 1,4-dihydropyridines examined in porcine arteries precontracted with (a) KCl or with (b) prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). The ratios of the half maximal effective molar concentrations are plotted (cf. Table 1 to 3) following cumulative drug application in coronary arteries which were given a value of 1 (dotted line) relative to those obtained in basilar (open columns) and ulnar (solid columns) arteries. A selectivity for ulnar basilar vessels is expressed by a ratio-value exceeding 1, whereas a selective drug action in coronary arteries is indicated by a ratio-value lower than 1. Because of the very low activity of some drugs in $PGF_{2\alpha}$ precontracted coronary and ulnar arteries, these ratios are lacking.

VOC's to these drugs throughout the arterial system. Although our study supports this concept with respect to coronary and basilar arteries, the 10 fold reduced activity of all dihydropyridines investigated in depolarized ulnar arteries remains to be explained. In addition, 12.2–37.1% of the KCl-induced contractions in ulnar arteries were resistant to the action of nitrendipine and its derivatives even at the highest concentration used (see Results). By contrast, such concentrations completely abolished KCl-induced contractions in coronary and basilar arteries. Therefore we suggest a different distribution of various VOC-types in the arterial tree.

Besides the dihydropyridine-sensitive L-type-VOC's, Benham *et al.* (1987) demonstrated the existence of dihydropyridine-resistant T-type-VOC's in vascular smooth muscle. Furthermore some recent investigations show different vascular L-type-VOC's (Rosenberg *et al.*, 1986; Cruz *et al.*, 1987; Miller, 1987). A different distribution of dihydropyridine-resistant VOC's within the vascular system might also explain the previously described intervascular selectivity of dihydropyridines in various depolarized arteries (Gerthoffer *et al.*, 1987; Joulou-Schaeffer & Freslon, 1987; Fricke & Ueckert, 1988). Interestingly and in accordance with the results presented here, all authors reported a significantly greater vasodilator potency of dihydropyridines in cerebral compared to peripheral vessels.

The intervascular selectivity observed in the present study was not dependent on the different chemical structure of the dihydropyridines. Modification of the 3-ester-side-chain of nitrendipine improved the vasodilator potency only in the case of Bay E 6927, which was the most potent drug in every type of artery after stimulation with KCl (Tables 1 to 3). This result may possibly reflect a more pronounced affinity of Bay E 6927 for dihydropyridine-sensitive L-type-VOC's.

In a second series of experiments we examined the action of nitrendipine and its derivatives in the three vessel types following precontraction with $PGF_{2\alpha}$. This endogeneous prostaglandin has been described as a potent vasoconstrictor of (1) isolated pig (Yamamoto *et al.*, 1987) and human coronary arteries (Förstermann *et al.*, 1988), (2) isolated rat (Godfraind & Miller, 1983) and dog mesenteric arteries (Konishi *et al.*, 1981) and (3) isolated dog (Toda & Onoue, 1988), cat (Uski, 1985) and human cerebral arteries (Rose & Moulds, 1979). In addition, $PGF_{2\alpha}$ seems to be of pathophysiological relevance e.g. in the development of cerebral vasospasms following subarachnoid haemorrhage. Under these conditions the production of prostacyclin is reduced (Brandt *et al.*, 1981), whereas the concentrations in the cerebrospinal fluid of vasoconstrictor prostaglandins including $PGF_{2\alpha}$ increase up to 1 $\mu$mol $l^{-1}$ (Walker *et al.*, 1983; Rodriguez y Baena *et al.*, 1985). This concentration of $PGF_{2\alpha}$ is sufficient to elicit strong and stable contractions of human cerebral arteries (White & Robertson, 1987).

In $PGF_{2\alpha}$ precontracted porcine arteries all dihydropyridines investigated exhibited a vasodilator activity, which was strongly reduced compared to that after depolarization. A similar attenuation has been reported with nitrendipine in noradrenaline precontracted rabbit ear arteries (Scriabine *et al.*, 1984) and also in dog coronary and femoral arteries stimulated with 5-hydroxytryptamine or $PGF_{2\alpha}$ (Altura & Altura, 1984). Therefore $PGF_{2\alpha}$-induced vasoconstrictions probably involve mechanisms, which are insensitive to the action of dihydropyridines. Earlier studies revealed that such vasoconstrictions are mediated by a release of intracellular calcium as well as calcium influx from the extracellular space (Takayama, 1986; Santoian *et al.*, 1987). This calcium influx, possibly accompanied by loosely membrane-bound calcium (Uski, 1985), probably occur through both receptor-operated calcium channels (ROC's) and VOC's (Toda & Onoue, 1988). Dihydropyridines inhibit calcium influx through VOC's much more extensively than calcium influx through ROC's, whereas their influence on the release of intracellular stored calcium is a matter of controversy (Bolton, 1979; van Breemen *et al.*, 1979; Meisheri *et al.*, 1981; Godfraind *et al.*, 1986; Hurwitz, 1986). Therefore, the stimulus selectivity (KCl vs. $PGF_{2\alpha}$; Figure 3) of nitrendipine and its derivatives observed in the present study is possibly due to the involvement of calcium influx through ROC's and/or release of intracellular stored calcium following treatment with $PGF_{2\alpha}$.

The very low activity of the drugs studied in $PGF_{2\alpha}$-stimulated porcine coronary and ulnar arteries, which resulted in a high percentage of persisting contractions (see Results) even at the highest drug-concentration used (100 $\mu$mol $l^{-1}$), demonstrates a participation of contractile mechanisms with pronounced insensitivity to dihydropyridines. By contrast, all studied drugs except Bay O 5572, the least active derivative of all, completely abolished $PGF_{2\alpha}$-induced contractions in basilar arteries. Furthermore, the compounds exhibit a significant selective action in such vessels (intervascular selectivity, Figure 4b). Therefore, it seems likely that the enhancement of intracellular calcium concentration required for $PGF_{2\alpha}$-induced contraction in porcine basilar arteries is mainly due to a calcium influx from the extracellular space. In this respect the reduced potency of the dihydropyridines compared to depolarizing conditions points to an involvement of ROC's. The suggestion that different calcium influx pathways participate in $PGF_{2\alpha}$-induced vasoconstriction of basilar arteries is supported by the significant relationship between the chemical structure and the activity of the dihydropyridines (Figure 2), which has not been observed after depolarization. Furthermore, this result raises the question whether or not different calcium influx pathways display a different sensitivity to dihydropyridines depending on the structure of these compounds.

As indicated by the calculated stimulus selectivity ratios plotted in Figure 3, it might be supposed that the stimulus selectivity of dihydropyridines depends on the structure of their 3-ester side chain. Thus a limited prolongation from a methyl (Bay A 4339) to an isopropyl group (Bay E 6927) resulted in strongly increased stimulus selectivity ratios in each vessel type studied. In addition, this increase ensues from both an enhanced activity in depolarized as well as attenuated activity in $PGF_{2\alpha}$ precontracted arteries. These results suggest the possibility of developing dihydropyridines with defined stimulus-selectivity ratios. Such compounds could gain therapeutic value especially in the management of vascular disorders e.g. vasospastic angina or those following subarachnoid haemorrhage.

In brief, our study demonstrates that nitrendipine and six related 3-ester side chain derivatives display intervascular and stimulus selectivity within different arteries of the same species. After depolarization these compounds exhibited a weak preferential action in coronary arteries, whereas after precontraction with $PGF_{2\alpha}$ they predominantly relax basilar arteries. This shift in the intervascular selectivity seems mainly to be a consequence of different mechanisms, by which $PGF_{2\alpha}$-induced contractions are achieved in the different vessels. In addition, the magnitude of the stimulus selectivity, as expressed by the calculated stimulus selectivity ratios, might also be dependent on the chemical structure of the dihydropyridines

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