The 1,4-Dihydropyridine Nucleus: A Pharmacophoric Template Part 1. Actions at Ion Channels

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Abstract: The 1,4-dihydropyridine nifedipine is a prototypical example of the group of calcium channel blockers that also includes a number of second and third generation agents. These drugs enjoy substantial therapeutic prominence for their cardiovascular actions, including hypertension and angina. These actions are exerted at a specific member of the voltage-gated calcium channel family –the L-type channel. However, it is increasingly clear that the 1,4-dihydropyridine structure is a pharmacophoric template or "privileged structure" that, when appropriately substituted, can exert potent and selective actions at a diverse set of membrane receptors, including ion channels, G protein-coupled receptors and enzymes. This review will summarize the actions of 1,4-dihydropyridines at these receptors and advance the case that the 4-phenyl-1,4-dihydropyridine structure is a particularly versatile drug template. Part I of the review will summarize actions at ion channels and part II will summarize actions at other receptor systems.

Keywords: 1,4-dihydropyridines; nifedipine; ion channels; calcium channel blockers; receptors; G protein-coupled receptors.

1. INTRODUCTION

The calcium ion is a critical extra- and intra-cellular messenger that plays multiple roles in physiological stimulus-response coupling processes in addition to being a major structural component of bone and related skeletal appendices. Calcium is also a pathological species that can wreak cell death and destruction when its movements and concentrations are uncontrolled. Accordingly, the cell has multiple control loci at which movements and storage of calcium are controlled and these loci represent opportunities for therapeutic intervention by drugs [1].

Nifedipine [2,6-dimethyl-3,5-dicarbomethoxy-4-[2-nitro]phenyl-1,4-dihydropyridine is a first generation calcium channel blocker that interacts at a specific class of voltage-gated calcium channel – the L-type channel - to produce its cardiovascular effects, including the relief of hypertension and angina [2]. First introduced in 1975 nifedipine interacts at a discrete receptor site on the channel that is linked in complex allosteric relationships to other, and structurally quite distinct, calcium channel blocker binding sites [receptors] for the phenylalkylamine verapamil and the benzothiazepinone diltiazem (Fig. **1**). The receptor for 1,4-dihydropyridines has been localized to segments IIIS5, IIIS6 and IVS6 of the major α_1 subunit of the channel and some nine critical amino acid residues have been identified as constituting the binding domain [3-5].

The receptor site for nifedipine on the L-type class of calcium channel is shared not only by the 1,4-dihydropyridine antagonists of Figure **1**, but also by potent and structurally related 1,4-dihydropyridine activators, including Bay K 8644, that serve as vasoconstrictors, positive inotropic agents and secretagogues. The availability of extremely potent and structurally specific antagonist and activator ligands for this channel has raised the issue of the whether there exist endogenous regulatory species["endogenous ligands"] for which the 1,4-dihydropyridines are merely surrogate species. However, such species have not, despite much effort, been unambiguously identified [6].

The pharmacology and clinical applications of these agents have been reviewed on numerous occasions [*inter alia*, 2,7]. Nifedipine has now been joined in the clinical market place by several second- and third-generation 1,4-dihydropyridines including - amlodipine, felodipine, isradipine, nicardipine, nimodipine, nitrendipine, lacidipine and lercanidipine (Fig. **2**). These agents differ in detail in their overall pharmacological and pharmacokinetic characteristics, although they do share a fundamental similarity of action.

The L-type class of voltage-gated calcium channel that is of particular, although not exclusive, functional significance in the cardiovascular system is but one subtype of a large class of voltage-gated calcium channels [designated according to functional and pharmacological properties as L, T, N, P/Q and R; Table 1], and this class is itself a subclass of a "super family" of voltage-gated calcium, potassium and sodium channels that share significant structural and functional homology [8-11]. The L-type class of channel has itself several members designated $Ca_V1.1$ to $Ca_V1.4$ that differ in their expression characteristics and in their pharmacological sensitivity to 1,4-dihydropyridines [TABLES 2 and 3]. Although there is not yet available an adequate description of the subtype pharmacology of the

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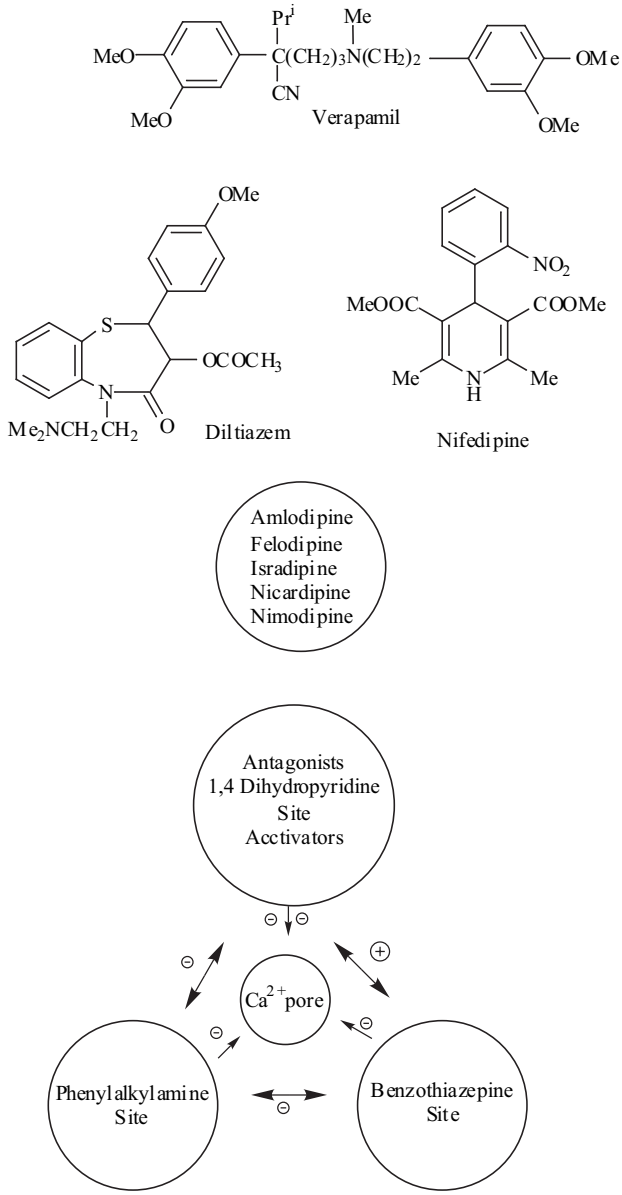


Fig. (1). Structural formulae of first generation calcium channel antagonists and second-generation 1,4-dihydropyridines (left). Organization of antagonist binding sites depicting distinct receptors for the three structurally distinct chemical classes linked allosterically to the gating machinery of the L-type voltage-gated channel.

channels listed in Table 1 current data do indicate clear differentiation by 1,4-dihydropyridines [Table 3]. These differences likely relate to sequence differences that produce both different 1,4-dihydropyridine receptor recognition characteristics and different voltage-dependent interactions with the resting, open and inactivated channel states [13].

It is scarcely surprising that there should exist subtype-specific differences in ligand recognition properties for the L-type calcium channel; such differences are extremely common for a large number of receptor types and subtypes and form a basis for the ultimate generation of truly subtype-specific agonists and antagonists. Additionally, the 1,4-

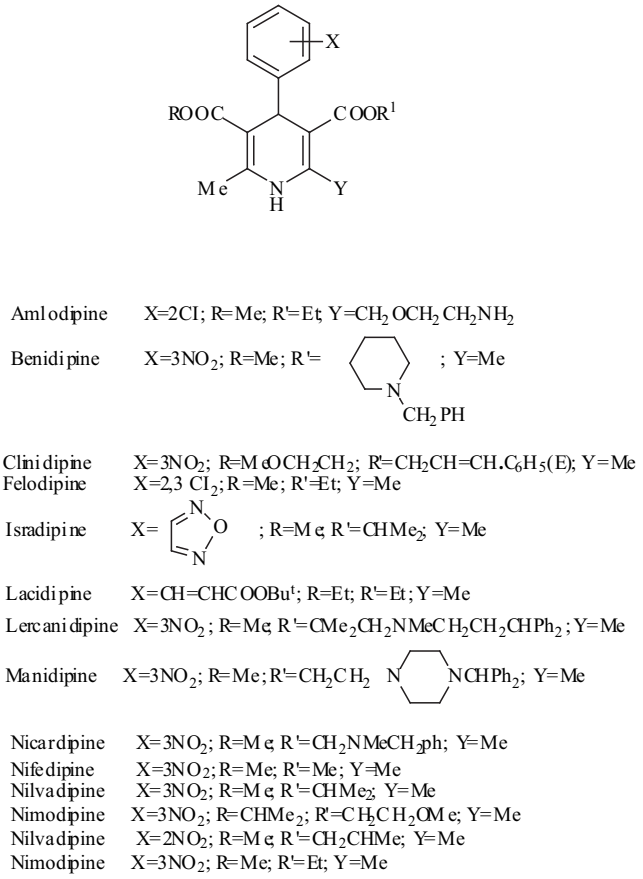


Fig. (2). Structural formulae of 1,4-dihydropyridine calcium channel antagonists.

dihydropyridine nucleus appears to be a particularly promiscuous structure interacting with a wide variety of channels and receptors, both related and unrelated. The 1,4-dihydropyridine nucleus is, in fact, an example of a "privileged structure"- a core structure that by appropriate molecular decoration can be directed to diverse pharmacological receptors.

That certain common chemical groupings are common in drugs of widely different biological activities has been widely recognized for many years [*inter alia* 14-16]. The term "privileged structure" was introduced by Evans *et al.* in their work on benzodiazepine-based drugs active at CCK-A receptors [17]. They argued that "*judicious modification of such structures could be a viable alternative in the search for new receptor agonists and antagonists"*. In a comprehensive review of peptidomimetic structures Wiley and Rich described some sixteen templates that shared a common property of possessing hydrophobic groups conformationally restricted to prevent intramolecular association [18]. This property ensures that the hydrophobic binding energies of these templates are available for interaction with receptor and are not dissipated through intramolecular stacking. The 4-phenyl-1,4-dihydropyridine structure was one of the listed templates.

The remainder of this review will focus on 1,4-dihydropyridines active at ion channels and Part II will focus

Table 1. Properties of Voltage-gated Calcium Channels

Property	L	T	N	P	Q	R
Conductance, pS [a]	~25	~8	~10-20	~9-19	16	—
Activation Threshold	High	Low	High	High	High	High
Deactivation Rate	Fast	Slow	Fast	Fast	Fast	Fast
Inactivation Rate	Slow	Fast	Moderate	Very slow	Moderate	Fast
Permeation	$Ba^{2+} > Ca^{2+}$	$Ba^{2+} = Ca^{2+}$	$Ba^{2+} > Ca^{2+}$	$Ba^{2+} > Ca^{2+}$	$Ba^{2+} > Ca^{2+}$	$Ba^{2+} = Ca^{2+}$
Function	E-C coupling CV system, smooth muscle, endocrine cells, some neurons	Cardiac SA node spiking, repetitive activity in neurons and endocrine cells, smooth muscle	Neuronal only ← Neurotransmitter release →	Neuronal only	Neuronal	Neuronal
Pharmacology [b]						
1,4-Dihydropyridines [activators/antagonists] (e.g. Bay K 8644/Nimodipine)	Sensitive	Insensitive	Insensitive	Insensitive	Insensitive	Insensitive
Phenylalkylamines (e.g. Verapamil)	Sensitive	Insensitive	Insensitive	Insensitive	—	Insensitive
Benzothiazepines (e.g. Diltiazem)	Sensitive	Insensitive	Insensitive	Insensitive	—	Insensitive
Benzimidazoles (e.g. Mibefradil)	Insensitive	Sensitive	—	—	—	—
ω-Conotoxin GVIA	Insensitive	Insensitive	Sensitive	Insensitive	Insensitive	Insensitive
ω-Conotoxin MVIIC	Insensitive	Insensitive	Sensitive	Sensitive	Sensitive	Insensitive
ω-Agatoxin IVA	Insensitive	Insensitive	Insensitive	Sensitive	Sensitive	Insensitive
ω-Agatoxin IIIA	Sensitive	Insensitive	Sensitive	Insensitive	Sensitive	Sensitive
Calciseptine	Sensitive (not skeletal muscle)	Insensitive	Insensitive	Insensitive	Insensitive	Insensitive
Calcicludine	Sensitive (not skeletal muscle)	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive
Cd^{2+} block	Potent	Weak	Potent	Potent	Potent	Potent
Ni^{2+} block	Weak	Potent	Weak	Intermediate	—	Potent

Footnotes

a ~l00 mM Ba^{2+} as charge carrier

b Sensitive refers to concentrations < 1 μM; insensitive refers to concentrations > 1 μM.

SA: Sino-atrial

on 1,4-dihydropyridines active at other classes of pharmacological receptors.

2. ACTIONS AT VOLTAGE-GATED CALCIUM CHANNELS

There are several principal subclasses of voltage-gated calcium channels that can be distinguished by functional, structural and pharmacological properties as well as by their localization [TABLE 1; 19]. In addition to their well-known and therapeutically useful applications at L-type channels, there is increasing evidence that 1,4-dihydropyridines are also active at other classes of calcium channel.

A. T-Type Calcium Channels

Dihydropyridines, as well as other structural classes of Ca^{2+} channel blockers have been examined in a number of preparations for their actions on low voltage-activated [T-type] Ca^{2+} currents. Early studies suggested insensitivity of T-type currents to both1,4-dihydropyridine antagonists and agonists [20-22], but more extensive studies are reported in Table 4 [23-40]. Although the data show generally low-affinity interactions there are a number of important caveats in the interpretation of the data. First, the 1,4-dihydropyridines used are those optimized principally for their actions at L-type currents. Second, the data are not directly comparable since they were obtained under a variety

Table 2. Classification of the 1,4-Dihydropyridine-sensitive L-type Calcium Channel

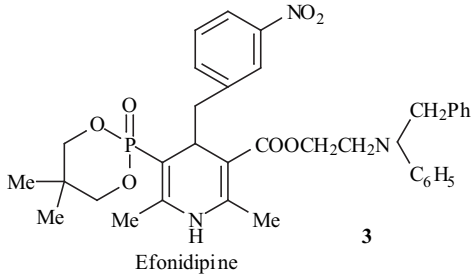
Name	Previous name	Splice variant	Tissue localization
$Ca_V1.1$	$a_1$skm	----	skeletal muscle
$\alpha_1 1.1$	$\alpha_1 S$		
$Ca_V1.2$	$\alpha_1 C$	$Ca_V1.2a$	heart
$\alpha_1 1.2$	rbC	$Ca_V1.2b$	smooth muscle
		$Ca_V1.2c$	brain, heart, pituitary, adrenal
$Ca_V1.3$	$\alpha_1 D$		brain, pancreas
$\alpha_1 1.3$	rbD		kidney, cochlea
$Ca_V1.4$	$\alpha_1 F$		retina
$\alpha_1 1.4$			

From Ertel *et al*. [11].

of different conditions [holding potential, charge carrier], the subtype of T current studied has, with rare exception, not been characterized and, of particular significance, the actions of the 1,4-dihydropyridines are voltage-dependent and thus the potencies measured depend very much on the membrane potential at which they are measured [41,42].

However, the data of Table 4 do reveal information of significance concerning 1,4-dihydropyridine action at T-type channels. In neuroblastoma-glioma hybrid cells there is clear evidence for a structure-function relationship among 1,4-dihydropyrididines at T-type channels distinct from that measured at L-type channels with niguldipine being some 2000 times more potent than nifedipine at T-type channels, but showing approximately equal activity at L-type channels [29]. Similar differential activity, albeit less marked, has been observed in cardiac tissue for amlodipine, felodipine and nifedipine [40]. Niguldipine exhibits a modest stereoselective interaction at T-type channels in atrial myocytes, consistent with a specific, rather than a non-specific, interaction [35]. Of interest, however, isradipine [PN 200 110] exhibits non-stereoselective interactions in atrial myocytes [34].

The influence of membrane potential on the comparative blocking potencies of 1,4-dihydropyridines at L- and T-type channels is shown very clearly in the work of Cohen *et al.* [34]. Felodipine interacts in voltage-dependent manner at both channel types and felodipine is actually more potent against inactivated T-type channels [K_D 13nM] than against non-inactivated L-type channels [K_D ~ 1000nM], although it is significantly more active at inactivated L-type channels [K_D < 1 nM]. Since, however, inactivation of L-type channels occurs at less negative membrane potentials than does T-type channel inactivation for most of the physiologically significant membrane potential range between –70 to –50mV felodipine is actually more potent at the T-type channel. Further evidence for the operation of distinct structure-activity relationships for 1,4-dihydropyridines at these two channel types is revealed by the comparable potency of felopdipine and isradipine at T-type channels and their significantly different potencies at the L-type channel in atrial myocytes [34]. Additionally, felodipine is significantly less active at the T-type channels of GH3 cells [34]. Efonidipine (Fig. **3**) has actions at both L- and T-type channels in the myocardium, and although it is more active at the L-type channel its selectivity of action is significantly less than for other 1,4-dihydropyridines – approximately 10-fold [43]. This property may underlie the significant negative chronotropic activity of this 1,4-dihydropyridine.



Efonidipine **3**

Fig. (3). Structural formulae of the 1,4-dihydropyridines efonidipine and PPK 5 and 12.

Novel 1,4-dihydropyridines containing a 2,6-disubstituted phenyl group with a pentadecyl group in the 6-position (Fig. **4**) have been shown to possess significant T:L channel selectivity [44]. In expressed channels with $\alpha 1_C$ or $\alpha 1_G$ subunits PPK 5 was 40-fold selective for the T channel at –80mV holding potential. Although this selectivity would certainly be reduced with increasing depolarization it is likely that significant T-selectivity would remain at –40mV. Several studies demonstrate that some nine amino

Table 3. Differential Interaction of 1,4-Dihydropyridines with L-Type Calcium Channel Subtypes

Drug	$Ca_V1.2a$	$Ca_V1.2b$	$Ca_V1.2a$	$Ca_V1.2b$	$Ca_V1.2a$	$Ca_V1.2b$
	K_D, nM (hp – 100mV)		K_D, nM (hp – 50mV)		K_I, nM (^{3}H-1,4-DHP)	
Nifedipine	47	10	6.9	3.7	2.9	1.9
Nisoldipine	2.1	0.56	0.33	0.15	0.16	0.08
(+)PN 200 110	15	2.2	0.82	0.46	0.41	0.19

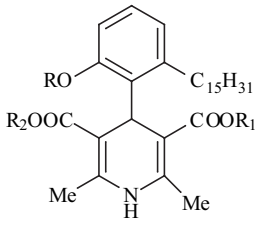
From Morel *et al*. [13].

Table 4. 1.4-Dihydropyridine Block of T-type Voltage-gated Calcium Channels

PREPARATION	DIHYDROPYRIDINE[a]									Reference
	1	2	3	4	5	6	7	8	9	
	IC_{50} or K_I, x 10^{-6}M									
Rat hypothalamic neuron				3.5	5.0	7.0				23
Rat amygdaloid neuron				2.5						24
Rat hippocampal CA1				1.6						25
Rat thalamic nucleus					2.6					26
Rat Meynert neurons				>3.0						27
Mouse dorsal root ganglion				2.0				>2.0	>2.0	28
Neuroblastoma-glioma				2.5	39	0.24	9.8			29
Adrenal glomerulosa								13.4 0.16[b]		30
Rat portal vein								0.05		31
Rat aorta				0.6						32
Canine atria								~10		33
GP atria myocytes				0.013					0.02[c]	34
GP atrial myocytes						0.018[d]				35
GP ventricle myocytes		~1.0								36
Human heart $Ca_V3.2$	5.7									37
Human thyroid tumor α_1H							10			38
Mouse spermatocyte					~10					39
Mouse spermatocyte					0.4					40
GH3 cells			0.7							30

Footnotes:a: 1 = Amlodipine; 2 = arandipine; 3 = felodipine; 4 = nicardipine; 5 = nifedipine; 6 = niguldipine; 7 = nimodipine; 8 = nitrendipine; 9 = PN 200 110. b = calculated affinities according to "modulated receptor" model [21] c = non-stereoselective effects of the (-) and (+) enantiomers d = stereoselective effects of niguldipine (+) > (-)

acid residues in the α_1 subunit determine 1,4-dihydropyridine binding at the L-type channel [*inter alia*, 45]. These residues are not conserved in T channels, indicating that the 1,4-dihydropyridine receptors are distinct in these distinct channel types and that the 4-phenyl-1,4-dihydropyridine nucleus is behaving as a privileged structure.



PPK5: $R=CHMe_2$; $R_1=Me$; $R_2=Me$
PPK12: $R=CH_2CH_3$; $R_1=CHMe_2$; $R_2=CH_2CH_3$

4

Fig. (4). 1,4-Dihydropyridines containing the 6-pentadecyl group and active at T-type channels.

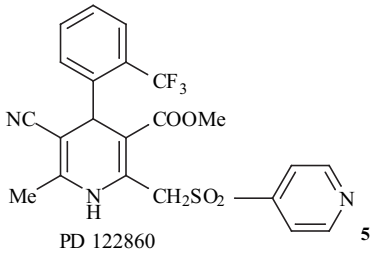
B.N-Type Calcium Channels

Actions of 1,4-dihydropyridines have also been reported in biochemical, electrophysiological and pharmacological preparations at N-type voltage-gated Ca^{2+} channels, although quite generally with little or no selectivity over actions at L-type channels [46-54]. In a comparative electrophysiological analysis of ten 1,4-dihydropyridines [amlodipine, benidipine, cilnidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine and nitrendipine] at cardiac L-type and sympathetic neuron N-type channels only cilnidipine exhibited selectivity for N-type channels with a selectivity ratio of 21 [50]. The selectivity ratios of other 1,4-dihydropyridines in these preparations ranged from 0.008 [nifedipine] to 0.43 [amlodipine]. In a variety of preparations the affinity of cilnidipine ranged between 10^{-6} and 10^{-7}M suggesting that it may serve as a lead structure for the development of more potent and more selective 1,4-dihydropyridine N-type Ca^{2+} channel antagonists. The ability of cilnidipine to interact at both L- and N-type channels may, together with its pharmacokinetic profile of slow onset and offset of action, contribute to the absence of reflex sympathetic stimulation seen during blood pressure reduction [50]. Additionally, cilnidipine has significant

antinociceptive actions also consistent with an *in vivo* action at neuronal N-type channels [51,53].

3. ACTIONS AT VOLTAGE-GATED SODIUM CHANNELS

Several early observations indicated that 1,4-dihydropyridines could serve as blockers of voltage-gated sodium channels, albeit with significantly lower potency [55-58]. Thus, Yatani and Brown observed that nitrendipine interacted with neonatal rat cardiac myocyte channels in voltage-dependent manner with a K_D value of approximately 1 uM: this voltage-dependent interaction parallels that seen with L-type cardiac Ca^{2+} channels, but with an approximately 1000-fold lower potency [56]. Voltage- and frequency-dependent effects of amlodipine have been measured in expressed human Na^+ channel α-subunits: amlodipine binds to the resting state with a K_D value of approximately 30uM, but exhibits a higher affinity for the inactivated state that depends on both holding potential and pulse duration [59].



PD 122860 **5**

Fig. (5). Structure of PD 122860.

This parallel between 1,4-dihydropyridine action at Na^+ and Ca^{2+} channels is further strengthened by the stereoselectivity of the enantiomers of PN 200 110 isradipine] where the (+)-enantiomer is some 10-fold more potent than the (-)-enantiomer, and by the enantiomer-selective actions of Bay K 8644 where the (-)-enantiomer is a Na^+ channel activator and the (+)-enantiomer is a channel blocker [57,58]. Interesting dual and approximately equipotent actions of the dihydropyridine PD 122860 [ethyl 5-cyano-1,4-dihydro-6-methyl-2-[(4-pyridinylsulfonyl)methyl]-4-[2-trifluoromethyl)phenyl]-3-pyridine carboxylate (Fig. **5**) have been reported whereby both enantiomers are sodium channel activators as revealed by their positive inotropic activities, but where Ca^{2+} channel antagonism resides dominantly in the (+)-enantiomer as revealed by radioligand binding and smooth muscle relaxant activities [Table 5; 60].

Table 5. Comparative Actions of 1,4-Dihydropyridines at Voltage-gated Calcium and Sodium Channels

Compound	[^{3}H]1,4-DHP Binding, IC_{50}, μM	Coronary resistance EC_{25}, μM	LV +dP/dT EC_{25}, μM
(+/-)- PD 122860	0.27	0.28	0.54
(+) - PD 122860	0.15	0.13	0.70
(-) - PD 122860	>10,000	1.6	0.89

Data from Haleen *et al*., [60].

4. ACTIONS AT POTASSIUM CHANNELS

Potassium channels constitute a large molecular group that is both functionally and structurally diverse. The broad groups include voltage-gated channels [delayed rectifier and A-type channels] whose individual subunits have six transmembrane sequences, Ca^{2+}-activated channels also with six transmembrane sequences, inward rectifier and ATP-sensitive channels with two transmembrane sequences, and a group of channels with four transmembrane sequences and two pores. The pharmacology of the potassium channel family is particularly diverse and complex. Useful discussions may be found in references 61 and 62. The 1,4-dihydropyridines have activity in several of the potassium channel subclasses [Table 6].

In the majority of the studies only one dihydropyridine has been examined and complete dose-response studies have not always been performed. Many of the activities reported for the large class of voltage-gated K^+ channels approximate the micromolar to high micromolar range. More interesting data are available for Ca^{2+}-activated K^+ channels where some structure-activity relationships are available and where activity in the submicromolar range becomes apparent [73-75]. Thus in a series of 1,4-dihydropyridines investigated by Ellory *et al.* [75] agents were characterized that were more potent at the Ca^{2+}-activated K^+ channel in human erythrocytes than against the L-type Ca^{2+} channel of smooth muscle [Table 7: FIGURE 6]. Niguldipine is a vasorelaxant that serves both as an L-type Ca^{2+} channel antagonist and as an activator of the $BKCa^{2+}$ channel [78,79]. This activity at the K^+ channel is stereoselective with the (+)-enantiomer being an activator and the (-)-enantiomer an antagonist. The EC_{50} value in vascular smooth muscle is approximately 2 x 10^{-8}M and niguldipine is thus a more potent ligand at K^+ channels than at Ca^{2+} channels.

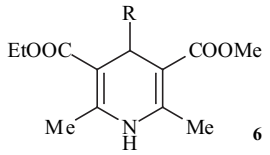


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Fig. (6). Structure of 1,4-dihydropyridines active at Na^+ channels. 1, R = cyclohexyl; 2, R = 4-nitrophenyl; 3, R = 4-phenyl.

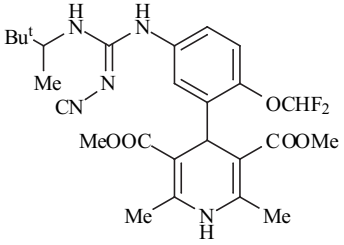

Fig. (7). Hybrid structure of 1,4-dihydropyridine and pinacidil moieties.

Table 6. Activities of 1,4-Dihydropyridines at Potassium Channels

Channel class	1,4-Dihydropyridine[a] IC_{50} x 10^{-6}M						
	1	**2**	**3**	**4**	**5**	**6**	**Ref**
Voltage-gated:							
K_V (heart)				16			63
K_V (Aplysia)		3-5					64
K_V (smooth muscle)	4.6						65
K_A (heart)	0.63b					7	66
K_A (adrenal)							667
K_V (plant)		5					68
K_V1.5 (heart)		18.6					69
		6.3c					
K_V (frog atria)	3						70
K_V(Shaker)	20-30	20-30	20-30			20-30	71
K_{IR}		265					72
K_V(r)		275					72
K_V(s)		360					72
Ca^{2+}-activated:							
Erythrocyte		4					73
						0.1	74,75
Cerebellar granule	1	>1	>>1		>1	>1	76
(B_{KCa2+})							
Kidney					6		77

a. 1,4-Dihydropyridine: 1 = Nicardipine; 2 = nifedipine; 3 = Nimodipine; 4 = nisoldipine; 5 = nitrendipiine; 6 = Bay K 8644 b. Order of activity: Nicardipine>nisoldipine>BayK 8644>nitrendipine>nifedipine c. The higher number refers to inhibition of peak current and the lower number to inhibition of steady-state current

Table 7. Activities of 1,4-Dihydropyridines at L-Type Ca^{2+}Channels and $K^+{}_{Ca}{}^{2+}$ Channels

	Ca^{2+} channel IC_{50}, M (smooth muscle)	**$K^+{}_{Ca}{}^{2+}$ channel IC_{50}, M (erythrocyte)**
1	3 x 10^{-7}	3.2 x 10^{-7}
2	1.2 x 10^{-6}	2.3 x 10^{-7}
3	2.6 x 10^{-8}	1.4 x 10^{-6}

Data from Ellory *et al*., [75]. Compounds are 4-substituted derivatives of (+/-)2,6-dimethyl-3-carbomethoxy-5-carboethoxy-1,4-dihydropyridine where the 4-substituent is: 1 = cyclohexyl; 2 = 4-nitrophenyl; 3 = phenyl.

Of particular interest are 1,4-dihydropyridines that serve as activators at the ATP-sensitive K^+ channel where glibenclamide and related agents serve as clinically useful antagonists [80-83]. ZM244085 (9-(3-cyanophenyl)hexahydro-1,8-acridinedione) is more potent on these channels in both binding and pharmacological assays with an EC_{50} value of approximately micromolar than it is on L-type Ca^{2+} channels in the same smooth muscle preparations. 1,4-Dihydropyridines that are actually hybrids of a 1,4-dihydropyridine nucleus with a pinacidil-like moiety also show both Ca^{2+} channel antagonistic and $K^+{}_{ATP}$ channel activating properties [83: Figure 7]. As shown by the data of Table 8 the structure activity-relationships are significantly different for the two channel types and it is possible to construct significantly selective 1,4-dihydropyridine $K^+{}_{ATP}$ channel activators.

Table 8. Activities of 1,4-Dihydropyridines at L-type Ca^{2+} Channels and $K^+{}_{ATP}$ Channels

1,4-Dihydropyridine	**Ca^{2+} channel IC_{50} M**	**$K^+{}_{ATP}$ channel IC_{50}, M**
Nifedipine	6.0 x 10^{-8}	> 10^{-5}
Pinacidil	> 10^{-4}	9.7 x 10^{-8}
Hybrid [Figure 7]	1.0 x 10^{-5}	6.2 x 10^{-6}

Data from Yagulpolskii *et al.* [83].

CONCLUSIONS

There are clearly adequate data to indicate that the actions of 1,4-dihydropyridines are not specifically confined to the L-type voltage-gated Ca^{2+} channel. It is clear also that where clinically available agents have been employed these non-L

type activities likely do not contribute significantly, save with one or two exceptions, to their cardiovascular profile. This is scarcely surprising since these agents have been developed through screening and selection processes designed to optimize cardiovascular actions that reflect dominant interactions at the L-type channel. However, there are sufficient data to indicate that the 4-phenyl-1,4-dihydropyridine structure does have significant actions at other classes of ion channel and that appropriate structural modification will likely lead to more selective drugs based on this template. The 4-phenyl-1,4-dihydropyridine structure is indeed a privileged molecule for ion channels.

REFERENCES

[1] Carafoli, E., Klee, C. [Editors]: Calcium as a Cellular Regulator, Oxford University Press, Oxford and New York, **1999**.

[2] Epstein, M. [Editor]: Calcium Antagonists in Clinical Medicine, 2nd Edition, Hanley and Belfus, Philadelphia, PA, **1998**.

[3] Peterson, B.Z., Tanada, T.M., Catterall, W.A. *J. Biol. Chem.* **1996**, *271*, 5293-5296.

[4] Hockerman, G.H., Petrson, B.Z., Sharp, E., Tanada, T.N., Scheuer, T., Catterall, W.A. *Proc. Nat. Acad. Sci. USA* **1997**, *94*, 14906-14911.

[5] Wappl, E., Mitterdorfer, J., Glossmann, H., Striessnig, J. *J. Biol. Chem.* **2001**, *276*, 12730-12735.

[6] Triggle, D.J. In, *The Calcium Channel: Structure, Function and Implications*, Eds. M. Morad, W. Nayler, S. Kazda and M. Schramm. Springer-Verlag, Berlin and Heidelberg, **1988**.

[7] Godfraind, T.M. *Pharmacol. Ther.* **1994**, *64*, 37-75.

[8] Catterall, W.A. *Ann. Rev. Biochem.* **1995**, *64,* 493-531.

[9] Hofmann, F., Lacinova, L., Klugbauer, N. *Rev. Biochem. Physiol.* **1999**, *139*, 33-88.

[10] Bergsmann, J.B., Wheeler, D.B., Tsien, R.W. In, *Pharmacology of Ionic Channels*, eds. M. Endo, Y. Kurachi and M. Mishina [Handbook of Experimental Pharmacology, volume 147, pp. 55-85] Springer-Verlag, Berlin and Heidelberg, **1999**.

[11] Ertel, E.A., Campbell, K.A., Harpold, M.M., Hofmann, F., Mori, Y., Perez-Reyes, E., Schwartz, A., Snutch, T.P., Tanabe,T., Birnbaumer, L., Tsien, R.W., Catterall, W.A. *Neuron* **2000**, *25*, 533-535.

[12] Triggle, D.J. In, *Calcium Antagonists in Clinical Medicine*, Ed. M. Epstein. 3rd Edition. Hanley and Belfus, Philadelphia, PA, **2002**.

[13] Morel, N., Burgi, V., Feran, O., Gomez, J.-P., Christen, M.-O, Godfraind, T. *Brit. J. Pharmacol.* **1998**, *125*, 1005-1012.

[14] Andrews, P.R., Lloyd, E..J. *Med. Res. Revs.* **1982**, *2*, 355-393.

[15] Ariens, E.J. *Med. Res. Revs.* **1987**, *7*, 367-387.

[16] Patchett, A.A., Nargund, R.P. *Ann. Rep. Med. Chem.* **2000**, *35*, 289-298.

[17] Evans, B.E., Rittle, K.E., Bock, M.G., DiPardo, RM., Friedinger, R.M., Whitter, W.L., Lindell, G.F., Veber, D.F., Anderson, P.S., Chang, R.S.L., Lotti, V.J., Cerino, D.J., Chen, T.B., Kling, P.J., Kunkel, K.A., Springer, JP., Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235-2246 .

[18] Wiley,R.A., Rich, D.H. *Med. Res. Revs.* **1993**, *13*, 327-384.

[19] Ertel, E.A., Campbell, K.P., Harpold, M.M., Hofmann, F., Mori, Y., Perez-Reyes, E., Schwartz, A., Snutch, T.P., Tanabe, T., Birnbaumer, L., Tsien, R.W., Catterall, W.A. *Neuron* **2000**, *25*, 533-535.

[20] Hess, P., Lansman, J.B, Tsien, R.W. *Nature* **1985**, *316*, 443-446.

[21] Fox, A.P., Nowycky, M.C., Tsien, R.W. *J. Physiol.* **1987**, *394*, 173-200.

[22] Hagiwara, N., Irisawa, H., Kameyama, M. *J. Physiol. 395*, **1988**, 233-253.

[23] Akaike, N., Kostyuk, P.G., Osipchuk, Y.V. *J. Physiol.* **1989**, *412*, 181-195.

[24] Kaneda, M., Akaike, N. *Brain Res.* **1989**, *497*, 187-190.

[25] Takahashi, K., Akaike, N. *J. Pharmacol. Exp. Therap.* **1991**, *256*, 169-175.

[26] Tarasenko, A.N., Kostyuk, P.G., Eremin, A.V., Isaev, D.S. *J. Physiol.* **1997**, *499*, 77-86.

[27] Rhee, J.-S., Ishibashi, H., Akaike, N. *J. Neurochem.* **1999**, *72*, 800-807.

[28] Richard, S., Diochot, S., Nargeot, J., Baldy-Moulinier, M., Valmier, J. *Neurosci. Lett.* **1991**, *132*, 229-234.

[29] Stengel, W., Jainz, M., Andreas, K. *Eur. J. Pharmacol.* **1998**, *342*, 339-345.

[30] Cohen, C.J., McCarthy, R.T., Barrett, P.Q., Rasmussen, H. *Proc. Nat. Acad. Sci. USA* **1988**, *85*, 2412-2416.

[31] Loriand, G., Mironneau, C., Mironneau, J., Pacaud, P. *J. Physiol.* **1989**, *412*, 333-349, .

[32] Kuga, T., Sadoshima, J.I., Tomoike, H., Kanaide, H., Akaike, N., Nakamura, M. *Circ. Res.* **1990**, *67*, 469-480.

[33] Bean, B.P. *J. Gen. Physiol.* **1985**, *86*, 1-30.

[34] Cohen, C.J., Spires, S., van Skiver, D. Block of *J. Gen. Physiol.* **1992**, *100*, 703-728.

[35] Romanin, C., Seydl, K., Glossmann, H., Schindler, H. *Pflug. Arch.* **1992**, *420*, 410-412.

[36] Masumiya, H., Tanaka, Y., Tanaka, H., Shigenobu, K. *Pharmacology* **2000**, *61*, 57-61.

[37] Perchenet, L., Benardeau, A., Ertel, E.A. *Naunyn-Schmied. Arch. Pharmacol.* **2000**, *361*, 590-599.

[38] Williams, M.E., Washburn, M.S., Hans, M., Urrutia, A., Brust, P.F., Prodanovich, P., Harpold, M.M., Stauderman, K.A. *J. Neurochem.* **1999**, *72*, 791-799.

[39] Santi, C.M., Darszon, A., Hernandez-Cruz, A. *Amer. J. Physiol.* **1996**, *271*, C1583-C1593.

[40] Arnoult, C., Villazz, M., Florman, H.M. *Mol. Pharmacol.* **1998**, *53*, 1104-1111.

[41] Hille, B. *J. Gen. Physiol.* **1977**, *69*, 197-313.

[42] Hondeghem, L.M., Katzung, B.G. *Ann. Rev. Pharmacol.* **1984**, *24*, 387-423.

[43] Masumiya, H., Shijuku, S., Tanaka, H., Shigenobu, K. *Eur. J. Pharmacol.* **1998**, *349*, 351-357.

[44] Kumar, P.H., Stotz, S.C., Paramasivappa, R., Reedle, A.M., Zamponi, G.W. *Mol. Pharmacol.* **2002**, *61*, 649-658.

[45] Wappl, E., Mitterdorfer, J., Glossmann, H., Striessnig, J. *J. Biol. Chem.* **2001**, *276*, 12730-12735.

[46] Jones, S.W., Jacobs, L.S. *J. Neurosci.* **1990**, *10*, 2261-2267.

[47] Uneyama, H., Takahara, A., Dohmoto, H., Yoshimoto, R., *Brit. J. Pharmacol.* **1997**, *122*, 37-42.

[48] Li, S.-N., Brater, M., Andreas, K. *Neurosci. Lett.* **1997**, *230*, 85-88.

[49] Li, S.-N., Brater, M., Andreas, K. *Acta Pharmacologica Sinica* **1999**, *20*, 117-120.

[50] Uneyama, H., Uchida, H., Konda, T., Yoshimoto, R., Aikake, N. *Eur. J. Pharmacol.* **1999**, *373*, 93-100.

[51] Muarakami, N., Nakagawasai, O., Fujii, S., Hosono, M., Hozumi, S., Esashi, A., Taniguchi, R., Okamura, T., Suzuki, T., Sasano, H., Yanagisawa, T., Tan-ano, K., Kisara, K. *Brain Res.* **2000**, *868*, 123-127.

[52] Murai, Y., Uneyama, H., Ishibashi, H., Takahama, K., Akaike, N. *Brain Res.* **2000**, *854*, 6-10.

[53] Murakami, M., Nakagawasi, O., Fujii, S., Kameyama, K., Murakami, S., Hozumi, S., Akisia, E., Taniguchi, R.,

Yanagisawa, T., Tan-no, K., Tadano, T., Kitamura, K., Kisara, K. *Eur. J. Pharmacol.* **2000**, *419*, 175-181.

[54] Hu, W.-Y., Fukuda, N., Su, J.-Z., Kanmatsuse, K. *J. Cardiovas. Pharmacol.* **2001**, *38*, 450-459.

[55] Kohlhardt, M., Haap, K. *Naunyn-Schmied. Arch. Pharmacol.* **1981**, *316*, 178-185.

[56] Yatani, A., Brown, A.M. *Circ. Res.* **1985**, *57*, 868-875,

[57] Yatani, A., Kunze, D.L., Brow, A.M. *Amer. J. Physiol.* **1988**, H140-H147.

[58] Kohlhardt, M., Fichtner, H., Herzig, J.W. *Naunyn-Schmied. Arch. Pharmacol.* **1989**, *340*, 210-218.

[59] Inoue, Y., Hisatome, I., Tsuboi, M., Ahmmed, G.u., Yatsuhashi, T., Uchida, K., Yamanouchi, Y., Santo, Y., Miale, J., Tanaka, Y., Hamada, T., Watanabe, M., Igawa, O., Yoshida, A., Shigemara, C., Makita, N., Sato, R. *Arzneim.-Forsch.* **1999**, *49*, 394-397.

[60] Haleen, S.J., Steffen, R.P., Sircar, I., Major, T.C., Taylor, M.D., Pugsley, T.A., Weishaar, R.E. *J. Pharmacol. Exp. Therap.* **1989**, *250*, 22-30.

[61] TiPS Nomenclature Supplement 2001. Alexander, S.P.H., Mathie, A., Peters, J.A. Editors. Trends in Pharmacological Sciences, **2001**.

[62] Watling, K.J. Editor. The SIGMA-RBI Handbook of Receptor Classification and Signal Transduction. 4th Edition. Sigma-RBI, Natick, MA, **2001**.

[63] Hume, J.R. *J. Pharmacol. Exp. Therap.* **1985**, *234*, 134-140.

[64] Nerbonne, J.M., Gurney, A.M. *J. Neuroscience* **1987**, *7*, 882-893.

[65] Terada, K., Kitamura, K., Kuriyama, H. *Pflug. Arch.* **1987**, *408*, 558-564.

[66] Gotoh, Y., Imaizumi, Y., Watanabe, M., Shibata, E.F., Clark, R.B., Gilews, W.R. *Amer. J. Physiol.* **1991**, H1737-H1742.

[67] Mlinar, B., Enyeart, J.J. *Mol. Pharmacol.* **1994**, *46*, 743-749.

[68] Thomine, S., Zimmerman, S., Van Duijn, B., Barbier-Brygoo, H., Guern, J. *FEBS Lett.* **1994**, *340*, 45-50.

[69] Zhang, X., Andersen, J.W., Fedida, D. *J. Pharmacol. Exp. Therap.* **1997**, *281*, 1247-122258.

[70] Richard, S., Charnet, P., Ouadid, H., Tiaho, F., Nargeot, J. *J. Mol. Cell Cardiol.* **1988**, *20*, 1133-1140.

[71] Avdonion, V., Shibata, E.F., Hoshi, T. *J. Gen. Physiol.* **1997**, *109*, 169-180.

[72] Zhabyeyev, P., Missan, S., Jones, S.E., McDonald, T.F. *Eur. J. Pharmacol.* **2000**, *401*, 137-1143.

[73] Kaji, D.M. *Amer. J. Physiol.* **1990**, *259*, C332-C339.

[74] Ellory, J.C., Kirk, K., Culliford, S.J., Nash, G.B., Stuart, J. *FEBS Letts.* **1992**, *296*, 219-221.

[75] Ellory, J.C., Culliford, S.J., Smith, P.A., Wolowyk, M.W., Knauss, E.E. *Brit. J. Pharmacol.* **1994**, *111*, 903-905.

[76] Fagni, L., Bossu, J.L., Bockaert, J. *Pflug. Arch.* **1994**, *429*, 176-182.

[77] Lopez-Burillo, S. Agapito-Serrano, M.T., Garay, R.P., Macias, J.F. *Eur. J. Pharmacol.* **1995**, *289*, 259-265.

[78] Klockner, U., Trieschmann, U., Isenberg, G. *Arzneim. Forsch.* **1989**, *39*, 120-126.

[79] Klockner, U., Isenberg, G. *Brit. J. Pharmacol.* **1989**, *97*, 957-967.

[80] Frank, C.A., Forst, J.M., Harris, R.J. Kau, S.T., Li, J.H., Ohnmacht, C.J., Smith, R.W., Trainor, D.A., Trivedi, S. *Bioorg. Med. Chem. Letters* **1993**, *3,* 2725-2726.

[81] Trivedi, S., Pottter-Lee, L., McConville, M.W. *et al.*, *Res. Comm. Mol. Path. Pharmacol.* **1995**, *88*, 137-151.

[82] Li, J.H. *Cardiovascular Drug Reviews* **2002**, *15*, 220-231.

[83] Yagulpolskii, L.M., Antepohl, W., Artunc, F., Handrock, R., Klebanov, B.M., Maletina, I.I., Marxen, B., Petko, K.I., Quast, U., Vogt, A., Weiss, C., Zibutel, J., Herzig, S. V.*J. Med. Chem.* **1999**, *42*, 5266-5271.