0031-6997/90/4201-0029$02.00/0
PHARMACOLOGICAL REVIEWS

Vol. 42, No. 1
Printed in U.S.A.

Drug- and Disease-Induced Regulation of Voltage-Dependent Calcium Channels

J. FERRANTE* AND D. J. TRIGGLE

Department of Biochemical Pharmacology, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York

I. Introduction

THE regulation of the number and function of receptors for hormones and neurotransmitters during cell development and growth by homologous and heterologous drug action and in disease states is a well-described phenomenon (35, 44). In homologous regulation a ligand regulates its own receptor, and in heterologous regulation the receptor is regulated by a ligand or process acting at a discrete receptor system. It has become increasingly evident that ion channels, such as the voltage-dependent calcium channel (VDCC),† are also subject to regulatory influences. These influences may be of a physiological, pathological, or pharmacological nature.

Three distinct types of VDCC (T, L, and N) have been described based on their electrophysiological properties and sensitivity to various pharmacological substances (124). Agents that interact selectively with L-type VDCCs consist of a group of compounds known as the organic calcium channel ligands. Drugs in this class include the 1,4-dihydropyridines (1,4-DHPs), phenylalkylamines, and the benzothiazepines of which nifedipine, verapamil, and diltiazem, respectively, may be regarded as prototypes. Both activator and antagonist ligands exist in the 1,4-DHP class; however, only the antagonists have been exploited clinically to treat hypertension and other cardiovascular disorders.

Membrane potential constitutes the primary signal to which VDCCs respond, activating and inactivating according to potential range and duration. However, these potential-dependent channels are also modulated in their activities by a variety of receptor-initiated events (42, 43, 65, 101, 113). These modulatory events include direct activation by intracellular messengers (cyclic adenosine 5′-monophosphate, cyclic guanosine 5′-monophosphate, inositol-1,4,5-trisphosphate), by protein kinase-mediated channel phosphorylation mediated by intracellular messengers, and by direct association with G proteins. The modulation of cardiac L-type calcium channels via phosphorylation through the cyclic adenosine 5′-monophosphate-dependent protein kinase A represents a relatively well-established example (11, 13, 55). However, it is clear that other signals may also be involved in the modulation of such calcium channels including 1,2-diacylglycerol and inositol-1,4,5-trisphosphate (79, 91) and that the modulation may be both positive and negative. Direct G protein control of ion channels has assumed considerable recent significance. Calcium channels appear to be likely candidates, together with potassium channels, for such direct control (10, 49). Thus, the α-subunit of the G_s protein appears to directly gate cardiac L channels in addition to its indirect control through the cyclic adenosine 5′-monophosphate cascade. Other classes of calcium channels, including the N channel, although less well investigated, are likely to be regulated also through such G protein interactions (66). This review will not focus on the details of these modulatory pathways because they are reviewed elsewhere. However, the regulation of calcium channel numbers and function by chronic drug and hormone action and during disease states may ultimately depend upon the impact of these modulatory pathways as they serve to control channel function.

Little is yet known about the mechanisms of drug- or

*To whom requests for reprints should be addressed: Department of Biochemical Pharmacology, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY 14260.

†Abbreviations: VDCC, voltage-dependent calcium channel; 1,4-DHP, 1,4-dihydropyridine.

disease-induced calcium channel regulation. However, several possibilities exist that parallel those described for other receptor systems. These drug-binding sites on the calcium channel may serve to regulate channel number and function in homologous and heterologous fashion, in a manner similar to that used by hormones and neurotransmitters. An alternative mechanism for calcium channel regulation may involve a role for calcium itself. Inactivation of calcium channels is dependent on both intracellular calcium and membrane potential (21, 54), and high-affinity-binding sites for calcium are thought to exist on calcium channels (1, 70, 124). Additionally, it has been demonstrated that, during myogenesis in cultured skeletal muscle cells, the appearance of high-affinity calcium channel-binding sites was prevented by a reduction of intracellular calcium (76).

It is probable that ion channels and cell surface receptors are regulated in similar fashion. Both groups are membrane proteins and as such their biogenesis involves protein synthesis and glycosylation in the endoplasmic reticulum, subsequent processing in the Golgi apparatus, storage in carrier vesicles, and membrane insertion (125). However, despite such common processing, there may be significant differences in mechanisms of regulation because hormone- or neurotransmitter-defined receptors have a corresponding physiological substrate, whereas an endogenous ligand for the 1,4-DHP-sensitive calcium channel remains to be identified (53, 122).

Considerable information concerning receptor turnover has been derived from studies of receptors for growth factors, polypeptide hormones, and serum proteins such as low-density lipoproteins (35, 107). These studies have been essential to our current understanding of the mechanisms involved in receptor regulation including the process of receptor-mediated endocytosis. This process has been described in some detail (35, 44, 72, 83). Initially, cell surface receptors bind ligands (e.g., hormones and low-density lipoproteins). These ligand-receptor complexes migrate into clathrin-coated pits which are internalized to form an endosome. Once inside the cell, the contents of the endosome become acidified, causing the ligand to dissociate from its receptor. The ligand is then transferred to and degraded in lysosomes while the receptor is recycled to the cell surface. Variations on this theme exist dependent upon the particular ligand-receptor complex, e.g., some receptors are internalized in the absence of ligand and there is not an absolute requirement for coated pits (35). However, it is clear that this general mechanism provides for changes in plasmalemmal receptor number which ultimately are a result of alterations in rates of receptor metabolism, i.e., synthesis, membrane insertion, internalization, recycling, and degradation (44, 72).

Receptor regulation can occur following either short- or long-term exposure to a ligand (45). Changes in receptor metabolism usually result from prolonged or persistent receptor stimulation. However, different mechanisms are responsible for receptor regulation which occurs within a short time. These mechanisms include modifications in coupling factors, membrane potential, the membrane lipid environment, receptor distribution, and phosphorylation state (45, 64). Thus, the mechanisms involved in receptor regulation are varied and dependent on the ligand, the receptor, and the extent and duration of receptor occupancy.

The type of ligand, agonist or antagonist, may dictate how a receptor system will be regulated. Generally, chronic administration of agonist or antagonist receptor ligands results in decreases (down-regulation) and increases (up-regulation), respectively, in ligand-binding densities (44, 83). Additionally, receptor regulation can be homologous or heterologous (44). These interrelationships of time of exposure, ligand nature, and mechanism(s) of desensitization are well illustrated with the β-adrenoceptor system. Both homologous and heterologous desensitization occur (38, 111, 112). During homologous desensitization, receptors move from the plasma membrane and are sequestered into the cytosolic fraction. Receptor phosphorylation mediated by the β-adrenergic receptor kinase is involved in this process: the phosphorylation of the agonist-occupied receptor results in uncoupling from G proteins and cytosolic sequestration (6). In heterologous desensitization, functional uncoupling of the receptors occurs mediated by several protein kinases in the absence of physical translocation of the receptor.

Many diseases, regardless of their origin (genetic, autoimmune, drug induced, or hormonally derived) are the result of alterations of receptor level or function. Thus, familial hypercholesterolemia is caused by defects in low-density lipoprotein- receptor expression, including the production of few or nonfunctional low-density lipoprotein receptors or receptors that fail to internalize (35). Myasthenia gravis, an autoimmune disorder, is due to the presence of antibodies specific for the nicotinic acetylcholine receptor of skeletal muscle (22). A decrease in myocardial β-adrenergic receptor number has been implicated in the pathophysiology of congestive heart failure (63, 102). Conversely, in hyperthyroidism, the number of cardiac β-adrenergic receptors is increased; additionally, changes in cardiac VDCCs have also been observed (39, 58). Receptor changes occur also as a result of chronic administration of drugs. Prolonged treatment with the β-adrenergic blocking agent propranolol can lead to an increase in β-receptor number in various tissues, which may contribute to the development of withdrawal symptoms if discontinuation of drug therapy is abrupt (63). However, β-adrenoceptor up-regulation is not an automatic consequence of antagonist exposure and in some systems β-adrenoceptor number decreases (48); this down-regulation may contribute to the pharmacological activity of these agents, but the underlying mechanism of action remains to be defined. Some antidepressant agents, including desipramine and desmethylimipramine, also produce a decrease in the number of β-adrenoceptors, and this is likely related to their mechanism of action (26, 30, 130). Thus, membrane receptor

or channel regulation has important therapeutic and pathological consequences.

Despite uncertainties about the mechanisms of calcium channel regulation, ample documentation exists of changes in channel number, ligand affinity, and/or function. The availability of radioligands, including the 1,4-DHP class of antagonists and activators, with high specificity for the VDCC, has made possible the study of expression of these channels during development, in various pathological states, and during chronic drug treatment. From these studies, calcium channels have been reported to be altered in diseases such as cardiomyopathy (126), myocardial ischemia (73, 77), and hypertension (12, 52), as well as during chronic drug administration with agents including reserpine (87), ethanol (20), and lead (98). The various factors that may alter the properties and turnover of VDCCs will be the focus of this review.

II. Channel Regulation by Drugs and Hormones

A. Homologous Regulation

The organic calcium channel antagonists are rapidly emerging as the most important group of compounds for the treatment of cardiovascular disorders. Furthermore, recent evidence suggests that these compounds have therapeutic value in other pathological states such as those involving smooth muscle hyperexcitability. Because the therapeutic application of these drugs is widespread, any long-term effects become important in terms of the potential development of tolerance, dependence, and withdrawal phenomena associated with their use. Several studies of the chronic administration of calcium channel ligands in vivo and in vitro have been reported (tables 1 to 6). In mice treated for 28 days with oral nifedipine and verapamil, there was a 40% reduction in 1,4-DHP-binding sites in membranes prepared from cer-

TABLE 1

*Regulation of Ca^{2+} channels: homologous regulation**

Treatment or condition	Species	Radioligand/ tissue	Effects			Reference
			K_D	B_{max}	Other	
28 d oral nifedipine, verapamil, and diltiazem	Mouse	Nitrendipine/ brain	NC	↓(40%) in nifedipine- and verapamil-treated mice; no change with diltiazem treatment	$^{45}Ca^{2+}$ uptake was decreased in the same brain areas of those mice treated with nifedipine or verapamil	82
20 d intravenous nifedipine	Rat	Nitrendipine/ heart and brain	NC	Brain, ↓(23%) Heart, ↓(49%)	[^{125}I]Iodocyanopindolol binding decreased; B_{max} decreased, 65% in brain, 62% in heart	33
14 d oral nifedipine	Rat	Nitrendipine/ heart	NC	NC	[^{3}H]Dihydroalprenolol binding unchanged	81
7–21 d nitrendipine	Rat—Spontaneously hypertensive (SHRSP) Salt-sensitive (S/Jr)	Nitrendipine/ heart	NC	S/Jr, ↑(55%) SHRSP, ↑(33%)	High salt also increased B_{max}	31
5 d nifedipine and (S) Bay K 8644		PN200-110/ PC12 cells	NC	Nifedipine, ↑(29%) (S) Bay K 8644, ↓(24%)		118
4 wk verapamil	DOCA/NaCl/ Rat	/Heart			Verapamil-treated rats had a lower systolic blood pressure, a greater sensitivity to norepinephrine, and a similar sensitivity to isoproterenol compared to controls	120
5 wk nitrendipne	Human	/Vascular smooth muscle			Antihypertensive effect of nitrendipine was associated with reductions in pressor responses to norepinephrine but not to angiotensin II	114

* Abbreviations: NC, no change; SHRSP, spontaneously hypertensive stroke-prone rats.

TABLE 2

*Regulation of Ca^{2+} channels: heterologous regulation**

Treatment or condition	Species	Radioligand/ tissue	Effects			Reference
			K_D	B_{max}	Other	
β-Adrenergic receptors						
10 d ISO	Rat	Nitrendipine/ heart	NC	NC		33
Chronic administration receptor antagonists and/or nifedipine	Human	Iodohydroxybenzylpindolol/heart	β-Adrenergic antagonists Nifedipine Propranolol and nifedipine		K_D NC ↑(27%) ↑(59%) B_{max} ↑(46%) ↑(52%) ↑(65%)	40
6 wk verapamil	Rat	Dihydroalprenolol/ heart	NC	NC	Cardiac stores of NE decreased 77%	78
1 wk verapamil	Human	Iodocyanopindolol/ lymphocyte			Increase in ISO-stimulated adenylate cyclase activity, a decrease in the IC_{50} for ISO inhibition of iodocyanopindolol binding, and a decrease in plasma NE levels	23
Chronic administration of ISO and alprenolol	Chick	Nitrendipine/ skeletal muscle	ISO ↑(300%) Alprenolol ↓(72%)	ISO ↑(200%) Alprenolol ↓(62%)	Short-term treatment with ISO and other agents which elevate cyclic AMP enhanced $^{45}Ca^{2+}$ influx	109
24 h ISO	Chick	PN 200-110/ skeletal muscle	NC	NC		84
α-Adrenergic receptor						
6 d phenylephrine	Rat	Nitrendipine/ heart	NC	↓(32%)	[^{3}H]prazosin, B_{max} ↓(39%) [^{3}H]dihydroalprenolol, B_{max} ↓(31%)	32
Muscarinic receptors						
23 d atropine and 14 d diisopropyl phosphorofluoridate	Rat	Nimodipine/ brain	NC	NC		33
Morphine-tolerant animals	Mouse	Nitrendipine/ brain	NC	↑(60%)		88
3 d morphine	Rat	Nimodipine/ brain	NC	↑(20%)	Ca^{2+} channel antagonists reduced naloxone-precipitated withdrawal in morphine-tolerant mice and rats	90
Morphine-dependent animals	Rat	/Brain			Verapamil and nimodipine reduced the behavioral expression of the morphine abstinence syndrome	9
Prolactin						
4 d nimodipine, Bay K 8644, verapamil, and diltiazem		GH3 cells			Verapamil, diltiazem, and nimodipine decreased prolactin synthesis; Bay K 8644 increased prolactin synthesis	41
Dopamine receptors						
18 d nimodipine and flunarizine	Rat	Spiroperidol/ brain	Nimodipine Flunarizine		K_D (↑88%) (↑159%) B_{max} (↑61%) (↑114%)	36
Nicotinic acetylcholine receptors						
48 h D600, nisoldipine, and Bay K 8644	Chick	α-Bungarotoxin/skeletal muscle	D600 (0.5 μM), Nisoldipine, (23 nM)	K_D NC NC	Bay K 8644 had no effect on binding	B_{max} ↑(50%) ↑(50%)	119

* Abbreviations: NC, no change; ISO, isoproterenol; NE, norepinephrine.

TABLE 3
*Regulation of Ca^{2+} channels: hormonal regulation**

Treatment or condition	Species	Radioligand/ tissue	Effects			Reference
			K_D	B_{max}	Other	
21 d insulin (10 μg)	Human	PN200-110/ muscle	NC	↑(250%)		17
Thyroid						
5 d thyroxine; hyperthyroid state	Rat	Nitrendipine and iodocyanopindolol/heart and vascular smooth muscle	NC	Nitrendipine ↓(42%)	Iodocyanopindolol ↑(36%)	39
30 d Propylthiouracil; hypothyroid state				↑(26%)	↓(23%)	
2 d triiodothyronine (10 nM)	Chick	PN200-110/ heart	NC	↑(67%)		58
Estrogen						
4 d estrogen	Rat	Nitrendipine/ uterine smooth muscle	NC	↑(96%)	Increased $^{45}Ca^{2+}$ influx	3
Chronic estrogen or estrogen and progesterone	Rat	Nitrendipine and Bay K 8644/uterine smooth muscle	NC	B_{max} for Bay K 8644 binding was lower in progesterone-dominated rats than in estrogen dominated		104
4 d estrogen, progesterone, or estrogen plus progesterone treatment	Rat	Nitrendipine/ uterine smooth muscle	↓(38%) ↓(42%)	Estrogen NC Estrogen + progesterone NC		50

* Abbreviation: NC, no change.

ebral cortex, caudate nucleus, and hippocampus (82). Additionally, there was a corresponding decrease of calcium uptake in these same brain areas. Chronic treatment of rats with intravenous nifedipine for 20 days resulted in a decrease in 1,4-DHP binding in both heart and brain (33). However, rats treated with lower doses of nifedipine for a shorter time (14 days) failed to show any changes in nifedipine binding to ventricular membranes, suggesting that dose and duration of treatment are important factors (81). In contrast to these reports, up-regulation of 1,4-DHP sites following a 21-day combined high-salt and nitrendipine treatment was reported in cardiac membranes from stroke-prone spontaneously hypertensive rats (SHRs) and salt-sensitive Dahl rats (31). A recent report showed up- and down-regulation of 1,4-DHP-binding sites following chronic administration of calcium channel antagonist and activator, respectively, in PC12 cells (118). These latter observations differ from those obtained in vivo and may be due in part to the lack of compensatory mechanisms (e.g., rebound sympathetic activity) that operate only in vivo.

B. Heterologous Regulation by Calcium Channel Drugs

Changes associated with chronic treatment with calcium channel ligand are not limited to those on VDCCs but may overlap with other receptor systems in heterologous fashion. Studies have demonstrated that chronic treatment with calcium antagonist can alter β-adrenoceptors. Chronic administration of nifedipine, with or without β-receptor antagonists, to patients with heart disease prior to cardiac bypass surgery, resulted in increased β-adrenergic receptor numbers in atrial tissue (40). Conversely, in rats treated chronically with nifedipine, decreased β-adrenergic receptor numbers were observed in the heart and brain (33). There was no change in β-adrenoceptor density in rats given verapamil for 6 weeks (78). However, there was a reduction in cardiac norepinephrine levels. The differences between these results may represent the differences between human and animal models. It is clear, however, that more studies are needed to examine the relationship between long-term calcium antagonist treatment and β-adrenoceptor expression.

Prolactin synthesis was reduced following chronic treatment with the calcium channel antagonist nimodipine and enhanced by the agonist Bay K 8644 in a pituitary cell line (41). Furthermore, there were corresponding changes in prolactin messenger ribonucleic acid levels with each treatment. Thus, it was concluded that calcium channel ligands, acting at VDCCs, regulate prolactin synthesis by an effect on prolactin messenger ribonucleic acid.

Eighteen-day administration of the calcium antagonists nimodipine and flunarizine to rats significantly increased the number of dopamine-receptor sites in rat striatum (36). Evidence that alterations in the expression

TABLE 4
*Regulation of Ca^{2+} channels: neuronal lesions**

Treatment or condition	Species	Radioligand/ tissue	Effects					Reference
			K_D		B_{max}		Other	
6-Hydroxydopamine								
6-hydroxydopamine induced lesions	Rat	Nitrendipine/ brain	NC		↑(14–23%) in hippocampus only			7
6-hydroxydopamine induced lesion	Rat	Nitrendipine or DHA/ heart	Nitrendipine NC	DHA NC	Nitrendipine ↑(31%)	DHA ↑(28%)		117
6-hydroxydopamine induced lesions	Rat	Nitrendipine/ brain	NC		NC			105
6-hydroxydopamine	Chick	Nitrendipine/ heart	NC		↑(35%)			92
Reserpine								
3 d reserpine	Chick	Nitrendipine/ skeletal muscle	↓(78%)		↓(36%)			109
5 d reserpine	Rat	Nitrendipine/ smooth muscle	NC		↑(169%)		[^{3}H]prazosin, K_D ↓(53%) B_{max} ↑(79%)	87
Chronic reserpine administered once every 5 d for 25 d	Rat	Nitrendipine/ brain	NC		NC			105
4 d reserpine	Rat	Nimodipine/ heart	NC		↓(22%)		Increased β-adrenergic receptor density in ventricle and brain	89
Kainic acid								
Kainic acid-induced lesions	Rat	Nitrendipine/ brain	NC		NC			7
Kainic acid-induced lesions	Rat	Nitrendipine/ brain	NC		↓(76%)			105
Kainic acid-induced lesions	Rat	Nimodipine/ brain	NC		↓(43%)		Dopamine receptor density (58%)	115
Colchicine								
Colchicine-induced lesions	Rat	PN200-110/ brain			Gyrus dentatus (molecular layer)	↓(90%)		14
					Hippocampus:			
					s. oriens,	↓(55%)		
					s. lucidum	↓(54%)		
Denervation	Rat and chick	Nitrendipine/ skeletal muscle	NC		Rat skeletal muscle 11 d postdenervation	↑(200%)		108
					Chick skeletal muscle 15 d postdenervation	↑200%)		

* Abbreviations: NC, no change; DHA, dihydroalprenolol.

of nicotinic acetylcholine receptors are controlled by intracellular calcium concentrations was shown in a study in which chronic treatment of cultured chick myotubes with calcium antagonist, which will inhibit cellular calcium entry through VDCCs, resulted in an increase in α-bungarotoxin-binding sites (119). Interestingly, chronic treatment with a calcium channel agonist, Bay K 8644, did not alter α-bungarotoxin binding.

Other studies suggest that chronic administration of calcium antagonist influences other receptors in a heterologous fashion as indicated by reactivity changes. Thus, chronic treatment of deoxycorticosterone/NaCl rats (a hypertensive rat model) with verapamil resulted in a lower systolic blood pressure and an increased α-adrenergic responsiveness in aortic contractility; however, the decreased β-adrenergic responsiveness which is

TABLE 5
*Regulation of Ca^{2+} channels: chronic treatments**

Treatment or condition	Species	Radioligand/ tissue	Effects				Reference
			K_D		B_{max}	Other	
Lead							
Lead	Rat	Nitrendipine/ brain	NC		↑(48%)		99
Lead	Rat	Nitrendipine/ brain	NC	Cortex	↑(25%)		98
			NC	Striatum	↑(54%)		
			NC	Hippocampus	NC		
Alcohol							
7 d ethanol	Rat	Nimodipine/ brain	NC		↑(50%)		20
4 d ethanol (150 mM)		PN 200-110/ PC12 cells	NC		↑(41%)	Net $^{45}Ca^{2+}$ uptake and sensitivity to in vitro ethanol were increased posttreatment	116
40 min ethanol	Rat	Nitrendipine/ brain	NC	Cortex	↑(36%)	B_{max} returns to normal 4 h posttreatment; the K_D is decreased 8 h posttreatment but returns to control levels at 36 h	97
			NC	Hippocampus	↑(33%)		
			NC	Striatum	↑(52%)		
6 d ethanol (200 mM)		Nitrendipine/ PC12 cells	NC		↑(92%)	Increased $^{45}Ca^{2+}$ uptake	75
25 d ethanol	Rat	Nitrendipine/ brain	NC		↑(52%)	Increased B_{max} was observed in the absence of Ca^{2+}	69
NaCl							
21 d NaCl	Rat SHR/ SP; R/ JR; S/JR	Nitrendipine/ heart	NC		Brain ↑(46%) Heart ↑(65%)	Salt loading increased blood pressure in SHR/ SP and S/JR	31
14 d NaCl	Rat	Nitrendipine/ treatment glomerulosa cell membranes	NC		B_{max} was higher in rats on a NaCl-restricted diet	Nitrendipine binding in vascular and uterine smooth muscle was unchanged	106
Potassium							
Chronic depolarization with high K^+ (4 d)		Nitrendipine/ PC12 cells	NC		↓(45%)		15
Chronic depolarization with high K^+ (3 d)		Nitrendipine/ PC12 cells	NC		↓(50%)	Decreased Ca^{2+} influx	16
Ca^{2+}							
Calcium	Chick	PN 200-110/ skeletal muscle				Calcium is necessary during myogenesis for the expression of dihydropyridine receptors	76
ECS							
25–30 d ECS	Cat	Nitrendipine/ brain	NC	Cortex	↑(45%)		8
			NC	Hippocampus	NC		
			↓(33%)	Cerebellum	NC		
10 d once/d	Rat	Nitrendipine/ brain	NC	Cortex	↑(19%)		8
			NC	Hippocampus	↓(11%)		
Cholesterol							
1–3 d mevinolin	Chick	Nitrendipine/ heart	NC		NC	Activation of Ca^{2+} channels by high K^+, isoproterenol, or Bay K 8644 was absent in mevino-	93

TABLE 5—Continued

Treatment or condition	Species	Radioligand/ tissue	Effects			Reference
			K_D	B_{max}	Other	
					lin-treated cells compared to control cells; Ca^{2+} channel-binding density did not change, but the channels had become nonfunctional	
Cholesterol	Human	/Erythrocyte			There was a direct correlation between $^{45}Ca^{2+}$ influx and the cholesterol content of the membrane; cholesterol-rich membranes enhanced Ca^{2+} influx through the channel, whereas cholesterol depletion reduced influx	68

* Abbreviations: NC, no change; ECS, electroconvulsive shock.

normally observed was prevented (120). Evidence for a direct interaction of verapamil with β-adrenergic receptors was observed in a study in which verapamil was administered to humans for 1 week. The results showed an increase in isoproterenol-stimulated adenylate cyclase activity, a decrease in the IC_{50} for isoproterenol inhibition of iodocyanopindolol binding, and a decrease in plasma norepinephrine levels in lymphocytes extracted from these subjects (23). In another study the effect of long-term nitrendipine treatment on systemic pressor responses to norepinephrine and angiotensin II was documented in humans. It was found that pressor responses to norepinephrine, but not to angiotensin II, were reduced in those subjects receiving nitrendipine (114). However, it is unknown whether this decrease in the pressor effect of norepinephrine is due to alterations in adrenergic receptors.

C. Heterologous Regulation

L-type VDCCs may be regulated following the chronic administration of agents other than calcium channel ligands. It is known that a number of neurotransmitters and hormones alter calcium channel function by activation of protein kinases via second-messenger pathways involving either cyclic adenosine 5′-monophosphate or diacylglycerol (94). Accordingly, coregulation with other receptor systems known to affect these pathways might be anticipated. For example, in primary cultures of chick myotubes treated for 37 hours with isoproterenol (10 μM), there was an increase in the K_D and B_{max} values for nitrendipine binding (109). Chronic administration of alprenolol in vivo exhibited the opposing effects of reductions in both K_D and B_{max} values for nitrendipine binding (109). In contrast to these findings, 10-day isoproterenol treatment in rats did not alter 1,4-DHP binding in heart membranes (33). Similarly, 24-h isoproterenol treatment of cultured chick myotubes did not change the binding constants for the 1,4-DHP, PN200–110 (84). The effects of long-term occupancy of other receptor systems including α-adrenergic, muscarinic, and opioid, on calcium channel expression have also been examined. Six-day administration of the α-adrenergic agonist phenylephrine to rats resulted in a decrease in the number of cardiac nitrendipine receptors (32). This change was accompanied by decreases in α_1 and β-adrenergic receptor densities (32). However, chronic treatment with the muscarinic antagonist, atropine, or with diisopropylphosphorofluoridate, an inhibitor of acetylcholinesterase, which increase and decrease, respectively, quinuclidinyl benzilate binding to muscarinic receptors, did not change binding of the 1,4-DHP, nimodipine, in brain (33).

There is evidence that analgesics such as morphine inhibit calcium channel function (37). Prolonged morphine administration has been shown to increase the number of 1,4-DHP-binding sites in a time- and dose-dependent fashion in discrete brain areas (88, 90). This effect was reversible when the drug was removed. In contrast, Pillai and Ross (85) demonstrated a decrease in nimodipine binding in the cortex and cerebellum subsequent to morphine treatment. It was also observed that calcium antagonists reduce naloxone-precipitated withdrawal signs in mice and rats (9, 90). Thus, changes in VDCCs following chronic morphine administration may

TABLE 6
*Regulation Ca^{2+} channels: disease states**

Treatment or condition	Species	Radioligand/ tissue	Effects				Reference
			K_D		B_{max}	Other	
Hypertension							
Hypertension	Rat, SHR (24 wk old)	Nitrendipine/ heart	↑(55%)		↑(43%)		12
Hypertension	Rat, SHR (16 wk old)	Nitrendipine/ heart			↑(45%)	[^{3}H]Prazosin, B_{max} ↓(42%)	110
Hypertension	Rat, SHR (10 wk old)	Nitrendipine/ heart and brain	NC NC	Heart Brain	NC ↑(57%)		52
Hypertension	Rat, SHR (4, 6, 10, 15 wk old)	Nitrendipine/ brain	NC NC NC	Striatum Thalamus Hippocampus	↑(21–40%) ↑(28–40%) ↑(21–34%)		51
Hypertension	Rat	Nitrendipine/ brain (brain-stem)	NC		↓(56%)	Nitrendipine binding in left ventricular tissue and cerebral cortex was unchanged	62
Hypertension	Rat (WKY) (SHR)	/Vascular smooth muscle cells				Ca^{2+} current in vascular muscle cells from SHR had a proportionally greater L current (62% of total) than T current when compared with WKY rats	103
Ischemia							
Ischemia	Rat 60 min hypoxia	Nitrendipine/ heart	NC ↓67%)	High-affinity site Low-affinity site	↓(74%) ↓(52%)		77
Ischemia (hypoxic and reoxygenated heart)	Guinea pig 30 min hypoxia	Nitrendipine/ heart	NC		↓(73%)		73
Ischemia	Rat	Verapamil/ heart	↓(54%) ↓(54%)	High-affinity site Low-affinity site	↓(83%) ↓(72%)		19
Ischemia	Gerbil	Nitrendipine/ brain	↓(62%) NC ↓(48%)	Unilateral ligation Left frontal cortex Right frontal cortex Bilateral ligation Whole frontal cortex	↓(63%) ↓(52%) ↓(26%)		56
Ischemia	Rat	PN200-110/ brain (hippocampus)		↑(64%)	↑(62%)		71
Cardiomyopathy							
Cardiomyopathy	Hamster (30, 60, and 90 d old)	Nitrendipine desmethoxyverapamil/ heart, brain, skeletal and smooth muscle	NC ↑(89%) ↑(200%) ↓(23%) NC NC NC	Brain, nitrendipine D888-high-affinity site low-affinity site Heart, nitrendipine D888-high affinity site Skeletal muscle, nitrendipine Smooth muscle, nitrendipine	↑(60%) ↑(163%) ↑(124%) ↑(90%) ↑(100%) ↑(53%) ↑(93%)	Increased $^{45}Ca^{2+}$ uptake in brain synaptosomes	126

TABLE 6—Continued

Treatment or condition	Species	Radioligand/ tissue	Effects			
			K_D	B_{max}	Other	Reference
Cardiomyopathy	Hamster (4–6 mo old)	Nitrendipine/ heart	NC	↑50%)		27
Cardiomyopathy	Hamster (4 mo old)	Nitrendipine/ heart	NC	↑(50%)		28
Hypertrophy	Rat	Nitrendipine/ heart	NC		Hypertrophied left ventricle contained an increased number of total Ca^{2+} channels compared to controls	74
Cardiomyopathy	Rat				Cardiac Ca^{2+} current is increased in myocytes from rats with myocardial hypertrophy	57
Cardiomyopathy	Hamster	PN200-110/ heart	NC	NC		4
Dystrophic cardiac muscle	Hamster (50–60 d old)	Nitrendipine/ heart	NC	NC		46
Cardiomyopathy	Hamster	Nitrendipine/ heart	NC	NC		47
Cardiomyopathy	Human	Nitrendipine/ heart	NC	↑(162%)		29
Cardiomyopathy	Human	PN200-110/ heart	Undetermined	↑(33%)	[^{3}H]Saxitoxin and [^{125}I]cyanopindolol binding were unchanged	128
HOCM or MVD	Human	Nimodipine, PN200-110, dihydroalprenolol/heart			Binding site density for nimodipine correlated significantly with the density of β-adrenoceptors in HOCM patients but not in those with mitral valve disease; B_{max} for nimodipine binding was > in HOCM patients than in patients with MVD	25
Muscular dystrophy						
Muscular dystrophy	Human	Nitrendipine/ skeletal muscle	NC	NC		18
Muscular dysgenesis						
Muscular dysgenesis	Mouse	/Skeletal muscle			Myotubes prepared from embryos of mice with muscular dysgenesis lacked contractile activity and had action potentials not followed by after-hyperpolarizations	100

TABLE 6—Continued

Treatment or condition	Species	Radioligand/ tissue	Effects				Reference
			K_D		B_{max}	Other	
Muscular dysgenesis	Mouse	PN200-110/ skeletal muscle and heart	NC			Decrease in diaphragm, limbs, and tongue skeletal muscle; no change in cardiac muscle	86
Muscular dysgenesis	Mouse	/Skeletal muscle				Mice with muscular dysgenesis have skeletal muscle which lacks a slow Ca^{2+} current	5
Muscular dysgenesis	Mouse	/Skeletal muscle				Absence of the α-1 subunit of the 1,4-DHP receptor in dysgenic muscle	60
Lambert-Eaton syndrome							
Lambert-Eaton syndrome	Bovine	/Adrenal chromaffin cells				IgG antibodies from patients with Lambert-Eaton syndrome reduced VDCC by 40%; Ca^{2+} channel activation and elementary channel activity were not altered	59
Parkinson's disease							
Parkinson's disease	Human	Nitrendipine/ brain	NC	Caudate nucleus	↓(49%)		80
			NC	Putamen	↓(44%)		
			NC	Substantia nigra	↓(55%)		

* Abbreviations: NC, no change; HOCM, hypertrophic obstructive cardiomyopathy; MVD, mitral valve disease.

play a role in the development of tolerance and physical dependence to opioid analgesics.

D. Hormonal Regulation

VDCCs are subject also to hormonal regulation. For instance, 21-day treatment with insulin resulted in an increase in the density of 1,4-DHP-binding sites in cultured human muscle (17). Thyroid status also influences the expression of VDCCs. Chronic treatment of cultured chick ventricular cells with thyroid hormone is reported to produce an increase in calcium channel density which correlated with an increase in 1,4-DHP-sensitive calcium uptake (58). The number of β-adrenergic receptors was also elevated, a finding that has been previously documented in a number of systems (129). In contrast, heart membranes from rats made hyperthyroid by 5-day treatment with thyroxine showed a decrease in the number of VDCCs which was also associated with an increase in β-adrenoceptor density (39). In this same study hypothyroid animals showed the opposite effect, an increase in VDCCs and a decrease in β-adrenoceptors. The binding of nitrendipine has been reported to be identical in uterine smooth muscle from estrogen- or progesterone-dominated rats (104). However, in other studies a decrease in the K_D value for nitrendipine binding in uterine membranes from rats treated with estrogen alone or estrogen plus progesterone was reported (50). An increase in calcium channel density with an insignificant change in the K_D value for nitrendipine binding was observed in uterine smooth muscle of rats treated chronically with estrogen (3). Additional studies of the influence of estrogen on calcium channel expression and function in uterine smooth muscle are clearly needed.

III. Channel Regulation by Lesions, Chronic Treatments, and Disease

A. Neuronal Lesions

It has been suggested that calcium may have an important role in neuronal outgrowth (2, 67). Electrophysiological evidence has shown that functional VDCCs are more abundant in growth cones than in neuritic processes (2). Other studies have demonstrated that an optimum level of intracellular calcium must be achieved to support neuronal growth because both reduced or excessive intracellular calcium will inhibit growth (67). Agents

such as 6-hydroxydopamine, colchicine, and kainic acid which induce neuronal lesions have been shown to modulate 1,4-DHP-binding sites. Thus, 6-hydroxydopamine increased the number of nitrendipine-binding sites in rat hippocampus but not in cerebral cortex, striatum, cerebellum, or brainstem (7). This effect was not observed with kainic acid or with reserpine (an amine-depleting agent). Similarly, increased numbers of nitrendipine-binding sites were demonstrated in rat heart following 6-hydroxydopamine treatment (117). This increase in 1,4-DHP number was accompanied by a 28% increase in β-adrenoceptors. In another study, no change was observed in nitrendipine binding following 6-hydroxydopamine or reserpine treatment; however, kainic acid treatment resulted in a dramatic loss of nitrendipine-binding sites in the caudate nucleus (105). Likewise, following intrastriatal injection of kainic acid to rats, there was a reduction in both 1,4-DHP and dopamine receptors in rat striatum (115). Evidence for coregulation of 1,4-DHP receptors and other receptor systems has been demonstrated following chronic reserpine treatment in rats. Thus, in rat smooth muscle there were increases in 1,4-DHP-binding sites and α_1-adrenergic receptors following administration of reserpine for 5 days (87). In contrast, Ramkumar and El-Fakahany (89) demonstrated a decrease in 1,4-DHP-receptor sites and an increase in β-adrenergic receptor density in rat ventricles following 4 days of treatment with reserpine. The density of 1,4-DHP-binding sites was reduced significantly following the destruction of hippocampal granule cells by colchicine, suggesting that this brain region contains a high density of L-type VDCCs (14). In skeletal muscle, an increase in nitrendipine-binding sites was observed subsequent to surgical denervation (108). Chronic reserpine administration produced a decrease in both K_D and B_{max} values for nitrendipine binding in the same tissue (109). Conversely, reserpine was shown to have no effect on nitrendipine binding in chick heart, whereas 6-hydroxydopamine treatment resulted in a 35% increase in 1,4-DHP-binding sites (92). These results suggest that innervation is important for the normal maintenance of VDCCs.

B. Chronic Treatments

Chronic treatment of animals or cells with ethanol or lead results in increases in 1,4-DHP-binding sites. Initial studies showed that lead treatment in vivo induced a 48% increase in the B_{max} for nitrendipine binding in rat striatum (99). Further studies demonstrated that this effect occurred only in certain brain regions, i.e., in cortex and striatum but not hippocampus (98). Ethanol, an agent known to inhibit calcium influx following acute treatment, has been shown to increase brain 1,4-DHP-binding sites in vitro and in vivo when administered chronically (20, 69, 75, 97, 116). It has been suggested that this effect may be responsible for the development of physical dependence to ethanol (20, 75).

NaCl restriction in rats resulted in a higher B_{max} for nitrendipine binding in adrenal glomerulosa cells but not in vascular or uterine smooth muscle (106). In another study, salt loading increased the number of cardiac and brain 1,4-DHP receptors in SHRs (31). Furthermore, the increase in receptor number was enhanced when nitrendipine was added to the high-salt regimen.

VDCCs are likely regulated by changes in intracellular calcium concentrations. Chronic depolarization of PC12 cells with elevated potassium induced a reduction in nitrendipine-binding sites with a corresponding decrease in calcium influx (15, 16). This effect has also been observed in a primary culture of chick neural retina cells (24). This regulation might be due to changes in intracellular calcium because VDCCs serve as a pathway for calcium entry into cells. However, it was demonstrated that the initial elevation of intracellular calcium following depolarization returns to normal with prolonged depolarization of PC12 cells (16). Thus, factors other than persistent elevation of intracellular calcium may be responsible for the observed down-regulation of 1,4-DHP-binding sites with chronic depolarization.

The effects of electroconvulsive shock on neuronal 1,4-DHP-binding sites were examined in two animal models (8). In cats given daily electroconvulsive shock for 25–30 days, there was an increase in the B_{max} value for nitrendipine binding in the cortex, a decrease in the value for K_D nitrendipine in the cerebellum with no changes observed in either receptor numbers or affinities in the hippocampus. Increased and decreased nitrendipine-binding site density was observed in the cortex and hippocampus, respectively, of rats subjected to chronic electroconvulsive shock treatment. The significance of these changes is not well understood. However, it was suggested that the alteration in nitrendipine binding in cat cerebellum may play a role in the development of tolerance to electroconvulsive shock, which is observed in cats.

Several studies have documented changes in calcium channel activity as a consequence of alterations in cellular or membrane cholesterol. Chronic treatment of cultured avian cardiac cells with mevinolin, an agent that depresses de novo cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, resulted in the uncoupling of excitation from contraction in these cells (93). This treatment decreased calcium current, but there were no corresponding reductions of 1,4-DHP-binding sites. In another study, calcium influx in human erythrocytes correlated with the cholesterol content of the membrane (68). Thus, in membranes with elevated cholesterol levels there was an enhancement of calcium influx and in those depleted of cholesterol there was a decreased influx. The relationship of these changes to the arterial structure and reactivity

changes in atherosclerosis has been reviewed elsewhere (123).

C. Disease States

The observation that changes in 1,4-DHP-binding sites occur in hypertensive rats has led some workers to suggest that alterations in VDCCs might reflect functional changes in these animals and play a role in the etiology of hypertension. Increases in the K_D and B_{max} values for [^{3}H]nitrendipine binding were observed in heart membranes from 24-week-old SHRs but not in 9-week-old SHR relative to normotensive controls (12). Similarly, Sharma et al. (110) found an increase in cardiac nitrendipine sites in older (16-week) SHRs; however, no changes were reported in 1,4-DHP binding in heart membranes from 10-week-old SHRs (51, 52). In the latter studies, an increase of binding site numbers was observed in brain membranes. In contrast to these findings in the brain, a selective decrease in the B_{max} for nitrendipine binding in membranes from brainstem, but not cerebral cortex or heart, was observed in deoxycorticosterone/NaCl hypertensive rats (62). Further studies are clearly necessary to document the relevance of any such changes to hypertension. However, Rusch and Hermsmeyer (103) have shown in venous muscle cells from 1- to 3-day-old rats that, although total cell calcium current was not different between normotensive controls and SHRs, the proportion of current carried by L channels was greater (62%) in SHRs than in normotensive control rats (42%).

There is evidence that chronic ischemia influences the binding of calcium channel antagonists. Thus, high- and low-affinity-binding sites for nitrendipine were detected in rat myocardial sarcolemmal fragments. Following 60 min of ischemia by occlusion of coronary flow, a reduction in the B_{max} of both high- and low-affinity sites was observed (77). A decrease in the value for the low-affinity, but not the high-affinity, site was also shown. However, the significance of the low-affinity-binding sites for 1,4-DHPs is not known (53). Additionally, ischemia has been found to reduce the K_D and B_{max} values of rat cardiac [^{3}H]verapamil-binding sites (19). In cardiac membranes from guinea pig hearts made hypoxic and then reoxygenated, there was a significant decrease in [^{3}H]nitrendipine-binding sites (73). Interestingly, in hearts that were made only hypoxic and not reoxygenated, there was no change in [^{3}H]nitrendipine binding compared to controls. Cerebral ischemia has also been shown to modulate 1,4-DHP binding in the brain. For example, in gerbils, either unilateral or bilateral carotid occlusion resulted in changes in [^{3}H]nitrendipine binding to cerebral membranes (56). Bilateral occlusion decreased both K_D and B_{max} values. Unilateral occlusion resulted in decreased site density in right frontal cortex and increased affinity and decreased number in left frontal cortex. However, changes in channel number and affinity in unilaterally occluded animals were greater in the contralateral hemisphere than in the ischemic hemisphere. This suggests that factors other than ischemia may contribute to the changes associated with this treatment. In contrast, it was demonstrated that 60-min occlusion of the right carotid resulted in a significant increase in K_D and B_{max} values for [^{3}H]PN200–110 binding in rat hippocampus from the right hemisphere but not the left hemisphere (71). This effect appeared to be region selective because no changes were observed in the cortex or striatum.

A number of studies have demonstrated that calcium channels are increased in hypertrophied cardiac muscle (27, 28, 61, 74, 126). [^{3}H]1,4-DHP and [^{3}H]-desmethoxyverapamil-binding sites were increased in heart and brain of Syrian cardiomyopathic hamsters (Bio 14.6) which serve as a model for human hypertrophy (126, 127). Additionally, there were increases in nitrendipine binding in skeletal and smooth muscle. A corresponding increase of $^{45}Ca^{2+}$ uptake into brain synaptosomes was also observed, but this may represent Ca^{2+} influx through 1,4-DHP-insensitive Ca^{2+} channels (95). In another model, cardiac hypertrophy was induced by aortic stenosis. In these rats the number of 1,4-DHP-binding sites per left ventricle was increased either 5 days or 3 weeks postsurgery (74). Furthermore, it has been demonstrated that calcium current is increased in myocytes from hypertrophied rat heart (57). Some reports indicate that calcium channels are unaltered in cardiac tissue from cardiomyopathic hamsters (4, 46, 47) . No significant changes in 1,4-DHP binding were found in cardiac tissue from 35- to 41-day-old myopathic hamsters (TO 53:58 strain) relative to control hearts (4). In addition, the number of [^{3}H]nitrendipine-binding sites in cardiac muscle membranes from 60-day-old dystrophic Syrian hamsters (CHF 146) and Bio 14.6 were not significantly different from genetically matched controls (CHF 148 and F1B) (46, 47). A resolution of the discrepant conclusions from these several reports is awaited. It is likely that strain differences contribute: additionally, differences in the ages at which measurements were made and the use of membrane preparations versus homogenates are also likely important determinants. Most significantly, however, recent reports have shown increases in 1,4-DHP-binding sites in tissue from hypertrophied human heart (29, 128). In another investigation involving human tissue evidence for receptor coregulation was demonstrated. In this study the number of 1,4-DHP-binding sites correlated significantly with the density of β-adrenoceptors in patients with hypertrophic obstructive cardiomyopathy (25). Additionally, the B_{max} value for 1,4-DHP binding was higher in patients with hypertrophic obstructive cardiomyopathy than in patients with mitral valve disease.

Embryonic dysgenic mice represent another model of a muscular disorder. This abnormality is due to a recessive, lethal gene and is characterized by the absence of normal skeletal muscle development (34, 100). It has been shown that myotubes prepared from embryos of

mice with this mutation lack contractile activity and have action potentials not followed by after-hyperpolarization as observed in normal skeletal muscle (100). Also, the fast and slow calcium current is significantly diminished in dysgenic skeletal muscle. Ultrastructural abnormalities as well as dramatic decreases in 1,4-DHP-binding sites were observed in skeletal muscle of dysgenic mice but not in cardiac muscle (86). This is in agreement with electrophysiological data demonstrating that the slow calcium current in mutant mice is abolished in skeletal muscle cells but not in cardiac cells (5). The implication that this disease is due to a mutation of the calcium channel was challenged in a study that demonstrated that coculture of dysgenic myotubes with normal spinal cord neurons restores calcium channel activity, contraction, and normal muscle ultrastructure (96). These results suggested that normal nerve cells supply a factor that is lacking in the mutant muscle cells. However, it has now been shown that microinjection of an expression plasmid carrying complementary deoxyribonucleic acid encoding the 1,4-DHP receptor for rabbit skeletal muscle into dysgenic skeletal muscle cells restored both excitation-contraction coupling and 1,4-DHP-sensitive calcium current (121). These latter results indicate that the structural gene for the skeletal muscle 1,4-DHP receptor is altered in muscular dysgenesis and that the 1,4-DHP receptor is both a voltage sensor and channel component. The observation that a 1,4-DHP-receptor defect is responsible for this disease is consistent with a recent finding that the α_1-nonglycosylated subunit of the 1,4-DHP receptor is absent in dysgenic mice (60). Thus, it was suggested that the presence of this subunit is necessary for excitation-contract ion coupling.

Other diseases suggested to be associated with changes in calcium channel function or expression include Lambert-Eaton myasthenic syndrome and Parkinson's disease. Lambert-Eaton myasthenic syndrome is a neuromuscular autoimmune disorder characterized by impaired evoked release of acetylcholine from the motor nerve terminal (59). It has been shown that immunoglobulin G antibodies from patients with Lambert-Eaton myasthenic syndrome reduce VDCCs by 40% (59). This modification of calcium channel function may underlie the alteration in transmitter release observed in this syndrome. A decrease in [^{3}H]nitrendipine-binding sites was demonstrated in various brain areas of patients with Parkinson's disease (80). The B_{max} for nitrendipine binding was reduced in the caudate nucleus, substantia nigra, and putamen with no change in the affinity. It was suggested that this loss of 1,4-DHP-binding sites may be a consequence of the degeneration of nigral dopamine neurons which is characteristic of this disease.

IV. Conclusions

Substantial documentation of alterations in L-type VDCCs exists in the literature. The concept of channel regulation has important therapeutic and pathophysiological implications, because chronic drug exposure that induces changes in VDCCs may lead to the development of tolerance and dependence, and observations that VDCCs are dysfunctional or present in abnormal numbers may underlie the etiology of certain disease states. This knowledge is invaluable and will help lead to the development of new drugs and drug therapy regimens designed to circumvent potential therapeutic problems and provide an alternate approach to obviate and treat disease that is directed at the channel or receptor system involved.

REFERENCES

1. ALMERS, W., MCCLESKEY, E. W., AND PALADE, P. T.: A non-selective cation conductance in frog muscle membrane blocked by micromolar external calcium ions. J. Physiol. **353:** 565–583, 1984.
2. ANGLISTER, L., FARBER, I. C., SHAHER, A. AND GRINVALD, A.: Localization of voltage-sensitive calcium channels along developing neurites: their possible role in regulating neurite elongation. Dev. Biol. **94:** 351–365, 1982.
3. BATRA, A.: Increase by oestrogen of calcium entry and calcium-channel density in uterine smooth muscle. Br. J. Pharmacol. **92:** 389–392, 1987.
4. BAZAN, E., SCHWARTZ, A., GARDNER, S., WELLS, J. W., SOLE, M. J., AND JOHNSON, C. L.: Receptors for calcium channel antagonists in cardiomyopathy. Fed. Proc. **46:** 3125, 1987.
5. BEAM, K. G., KNUDSON, C. M., AND POWELL, J. A.: A lethal mutation in mice eliminates the slow calcium current in skeletal muscle cells. Nature (Lond.) **320:** 168–170, 1986.
6. BENOVIC, J. L., MAYOR, F., STANISZEWSKI, C., LEFKOWITZ, R. J., AND CARON, M. G.: Purification and characterization of the β-adrenergic receptor kinase. J. Biol. Chem. **262:** 9026–9032, 1987.
7. BOLGER, G. T., BASILE, A. S., JANOWSKY, A. J., PAUL, S. M., AND SKOLNICK, P.: Regulation of dihydropyridine calcium antagonist binding sites in the rat hippocampus following neurochemical lesions. J. Neurol. Res. **17:** 285–290, 1987.
8. BOLGER, G. T., WEISSMAN, B. A., BACHER, J., AND ISAAC, L.: Calcium antagonist binding in cat brain tolerant to electroconvulsive shock. Pharmacol. Biochem. Behav. **27:** 217–221, 1987.
9. BONGIANNI, F., CARLA, V., MORONI, F., AND PELLEGRINI-GIAMPIETRO, D. E.: Calcium channel inhibitors suppress the morphine-withdrawal syndrome in rats. Br. J. Pharmacol. **88:** 561–567, 1986.
10. BROWN, A. M., AND BIRNBAUMER, L.: Direct G protein gating of ion channels. Am. J. Physiol. **254:** H401–410, 1988.
11. BRUM, G., FLOCKERZI, V., HOFMANN, F., OSTERRIEDER, W., AND TRAUTWEIN, W.: Injection of catalytic subunit of c-AMP-dependent protein kinase into isolated cardiac myocytes. Pfluegers Arch. **398:** 147–154, 1983.
12. CHATELAIN, P., DEMOL, D., AND ROBA, J.: Comparison of [^{3}H]nitrendipine binding to heart membranes of normotensive and spontaneously hypertensive rats. J. Card. Pharmacol. **6:** 220–223, 1984.
13. COHEN, P.: Protein phosphorylation and hormone action. Proc. R. Soc. Lond. Biol. Sci. **234:** 115–144, 1988.
14. CORTES, R., SUPAVILAI, P., KAROBATH M., AND PALACIOS, J. M.: The effects of lesion in the rat hippocampus suggest the association of calcium channel blocker binding sites with specific neuronal population. Neurosci. Lett. **42:** 249–254, 1983.
15. DELORME, E. M., AND MCGEE, R.: Regulation of voltage-dependent Ca+ channels of neuronal cells by chronic changes in membrane potential. Brain Res. **397:** 189–192, 1986.
16. DELORME, E. M., RABE, C. S., AND MCGEE, R.: Regulation of the number of functional voltage-sensitive Ca+ channels on PC12 cells by chronic changes in membrane potential. J. Pharmacol. Exp. Ther. **244:** 838–843, 1988.
17. DESNUELLE, C., ASKANAS, V., AND ENGEL, W. K.: Insulin increases voltage-dependent Ca^{2+} channels in membranes of aneurally cultured human muscle. Neurology **36** (suppl. 1): 171–172, 1986.
18. DESNUELLE, C., RENAUD, J. F., DELPONT, E., SERRATRICE, G., AND LAZDUNSKI, M.: [^{3}H]Nitrendipine receptors as markers of a class of putative voltage-sensitive Ca^{2+} channels in normal human skeletal muscle and in muscle from Duchenne muscular dystrophy patients. Muscle Nerve **9:** 148–151, 1986.
19. DILLON, J. S., AND NAYLER, W. G.: [^{3}H]Verapamil binding to rat cardiac sarcolemmal membrane fragments: an effect of ischaemia. Br. J. Pharmacol. **90:** 99–109, 1987.
20. DOLIN, S., LITTLE H., HUDSPITH, M., PAGONIS, C., AND LITTLETON, J.: Increased dihydropyridine-sensitive calcium channels in rat brain may underlie ethanol physical dependence. Neuropharmacology **26:** 275–279, 1987.
21. ECKERT, R., AND CHAD, J. E.: Inactivation of Ca^{2+} channels. Prog. Biophys. Mol. Biol. **44:** 215–267, 1984.
22. ENGEL, A. G.: Myasthenia gravis and myasthenic syndromes. Ann. Neurol. **16:** 519–534, 1984.
23. FELDMAN, R., PARK, G. D., AND LAI, C.: The interaction of verapamil and

norverapamil with β-adrenergic receptors. Circulation **72:** 547–554, 1985.
24. FERRANTE, J., AND TRIGGLE, D. J.: unpublished observations.
25. FERRY, D. R., AND KAUMANN, A. J.:Relationship between β-adrenoceptors and calcium channels in human ventricular myocardium. Br. J. Pharmacol. **90:** 447–457, 1986.
26. FINBERG, J. P.: Antidepressant drugs and down-regulation of presynaptic receptors. Biochem. Pharmacol. **36:** 3557–3562, 1987.
27. FINKEL, M. S., MARKS, E. S., PATTERSON, R. E., SPEIR, E. H., STEADMAN, K. A., AND KEISER, H. R.: Increased cardiac calcium channels in hamster cardiomyopathy. Am. J. Cardiol. **57:** 1205–1206, 1986.
28. FINKEL, M. S., MARKS, E. S., PATTERSON, R. E., SPEIR, E. H., STEADMAN, K. A., AND KEISER, H. R.: Correlation of changes in cardiac calcium channels with hemodynamics in Syrian hamster cardiomyopathy and heart failure. Life Sci. **41:** 153–159, 1987.
29. FINKEL, M. S., PATTERSON, R. E., ROBERTS, W. C., SMITH, T. D., AND KEISER, H. R.: Calcium channel binding characteristics in the human heart. Am. J. Cardiol. **62:** 1281–1284, 1988.
30. FISHMAN, P. H., AND FINBERG, J. P.: Effect of the tricyclic antidepressant desipramine on β-adrenergic receptors in cultured rat glioma C6 cells. J. Neurochem. **49:** 282–289, 1987.
31. GARTHOFF, B., AND BELLEMANN, P.: Effects of salt loading and nitrendipine on dihydropyridine receptors in hypertensive rats. J. Cardiol. Pharmacol. **10** (suppl. 10): S36–S38, 1987.
32. GENGO, P., BOWLING, N., WYSS, V. L., AND HAYES, J. S.: Effects of prolonged phenylephrine infusion on cardiac adrenoceptors and calcium channels. J. Pharmacol. Exp. Ther. **244:** 100–105, 1988.
33. GENGO, P., SKATTEBOL, A., MORAN, J. F., GALLANT, S., HAWTHORN, M., AND TRIGGLE, D. J.: Regulation by chronic drug administration of neuronal and cardiac calcium channel, beta adrenoceptor and muscarinic receptor levels. Biochem. Pharmacol. **37:** 627–633, 1988.
34. GLUECKSOHN-WAELSCH, S.: Lethal genes and analysis of differentiation. Science (Wash. DC) **142:** 1269–1276, 1963.
35. GOLDSTEIN, J. L., BROWN, M. S., ANDERSON, R. G. W., RUSSELL, D. W., AND SCHNEIDER, W. J.: Receptor-mediated endocytosis: concepts emerging from the LDL receptor system. Annu. Rev. Cell Biol. **1:** 1–39, 1985.
36. GOVONI, S., DI GIOVINE, S., MORESCO, R. M., BATTAINI, F., AND TRABUCCHI, M.: Effect of chronic calcium antagonist treatment on dopamine recognition sites in rat striatum. Neurosci. Lett. **87:** 173–177, 1988.
37. GUERRERO-MUNOZ, F., CERRETA, K. V., GUERRERO, M. L., AND WAY, E. L.: Effect of morphine on synaptosomal Ca^{2+} uptake. J. Pharmacol. Exp. Ther. **209:** 132–136, 1979.
38. HARDEN, T. K.: Agonist-induced desensitization of the β-adrenergic receptor-linked desensitization of the β-adrenergic receptor-linked adenylate cyclase. Pharmacol. Rev. **35:** 5–32, 1983.
39. HAWTHORN, M., GENGO, P., WEI, S. Y., RUTLEDGE, A., MORAN, J. F., GALLANT, S., AND TRIGGLE, D. J.: Effect of thyroid status on β-adrenoceptors and calcium channels in rat cardiac and vascular tissue. Naunyn-Schmiedebergs Arch. Pharmacol. **337:** 539–544, 1988.
40. HEDBERG, A., KEMPF, F., JOSEPHSON, M. E., AND MOLINOFF, P.: Coexistence of beta-1 and beta-2 adrenergic receptors in the human heart: effects of treatment with receptor antagonists or calcium entry blockers. J. Pharmacol. Exp. Ther. **234:** 561–568, 1985.
41. HINKLE, P. M., JACKSON, A. E., THOMPSON, T. M., ZAVACKI, A. M., COPPOLA, D. A., AND BANCROFT, C.: Calcium channel agonists and antagonists: effects of chronic treatment on pituitary prolactin synthesis and intracellular calcium. Mol. Endocrinol. **2:** 1132–1138, 1988.
42. HOCKBERGER, P., AND SWANDULLA, D.: Direct ion channel gating: a new function for intracellular messengers. Cell. Mol. Neurobiol. **7:** 229–236, 1987.
43. HOFMANN, F., NASTAINCZYK, W., ROHRKASTEN, A., SCHNEIDER, T., AND SIEBER, M.: Regulation of the L-type calcium channel. Trends Pharmacol. Sci. **8:** 393–398, 1987.
44. HOLLENBERG, M. D.: Examples of homospecific and heterospecific receptor regulation. Trends Pharmacol. Sci. **6:** 242–245, 1985.
45. HOLLENBERG, M. D.: Biochemical mechanisms of receptor regulation. Trends Pharmacol. Sci. **6:** 299–302, 1985.
46. HOWLETT, S. E., AND GORDON, T.: Calcium channels in normal and dystrophic hamster cardiac muscle: [^{3}H]nitrendipine binding studies. Biochem. Pharmacol. **36:** 2653–2659, 1987.
47. HOWLETT, S. E., RAFUSE, V. G., AND GORDON, T.: [^{3}H]Nitrendipine binding sites in normal and cardiomyopathic hamsters: absence of a selective increase in putative calcium channels in cardiomyopathic hearts. Cardiovasc. Res. **22:** 840–846, 1988.
48. HUGHES, R. J., MAHAN, L. C., AND INSEL, P. A.: Certain β-blockers can decrease β-adrenergic receptor numbers. II. Down-regulation of receptor number by alprenolol and propranolol in cultured lymphoma and muscle cells. Circ. Res. **63:** 279–285, 1988.
49. IMOTO, Y., YATANI, A., REEVES, J. P., CODINA, J., BIRNBAUMER, L., AND BROWN, A. M.: Alpha-subunit of Gs directly activates cardiac calcium channels in lipid bilayers. Am. J. Physiol. **255:** H722-H728, 1988.
50. ISHII, K., KANO, T. AND ANDO, J.: Calcium channel, Ca^{2+} mobilization, and mechanical reactivity of estrogen- and progesterone-treated rat uterus. Jpn. J. Pharmacol. **41:** 47–54, 1986.
51. ISHII, K., KANO, T., ANDO, J., AND YOSHIDA, H.: Binding of [^{3}H]nitrendipine to cardiac and cerebral membranes from normotensive and renal, deoxycorticosterone/NaCl and spontaneously hypertensive rats. Eur. J. Pharmacol. **123:** 271–278, 1986.
52. ISHII, K., KANO, T., KUROBE, Y., AND ANDO, J.: Binding of [^{3}H]nitrendipine to heart and brain membranes from normotensive and spontaneously hypertensive rats. Eur. J. Pharmacol. **88:** 277–278, 1983.
53. JANIS, R. A., SILVER, P. J., AND TRIGGLE, D. J.: Drug action and cellular calcium regulation. Adv. Drug Res. **16:** 309–591, 1987.
54. KALMAN, D., O'LAGNE, P. H., ERXLEBEN, C., AND ARMSTRONG, D. L.: Calcium-dependent inactivation of the dihydropyridine-sensitive calcium channels in GH3 cells. J. Gen. Physiol. **92:** 531–548, 1988.
55. KAMEYAMA, M., HESCHELER, J., HOFMANN, F., AND TRAUTWEIN, W.: Modulation of calcium current during the phosphorylation cycle in guinea pig heart. Pfluegers Arch. **407:** 123–128, 1986.
56. KENNY, B. A., KILPATRICK, A. T., AND SPEDDING, M.: Changes in [^{3}H] nitrendipine binding in gerbil cortex following ischaemia. Br. J. Pharmacol. **89:** 858P, 1986.
57. KEUNG, E. C., BERG, R., AND KATZUNG, B. G.: Calcium current is increased in single myocytes from hypertrophied rat myocardium. Circulation **76** (suppl 4): 329, 1987.
58. KIM, D., SMITH, T. W., AND MARSH, J. D.: Effect of thyroid hormone on slow calcium channel function in cultured chick ventricular cells. J. Clin. Invest. **80:** 88–94, 1987.
59. KIM, Y. I., AND NEHER, E.: IgG from patients with Lambert-Eaton syndrome blocks voltage-dependent calcium channels. Science (Wash. DC) **239:** 405–408, 1988.
60. KNUDSON, C. M., CHAUHAUDHARI, N., SHARP, A. H., POWELL, J. A., BEAM, K. G., AND CAMPBELL, K. P.: Specific absence of the alpha-1, subunit of the dihydropyridine receptor in mice with muscular dysgenesis. J. Biol. Chem. **264:** 1345–1348, 1989.
61. KUO, T. H., JOHNSON, D. F., TSANG, W., AND WIENER, J.: Photoaffinity labeling of the calcium channel antagonist receptor in the heart of the cardiomyopathic hamster. Biochem. Biophys. Res. Commun. **148:** 926–933, 1987.
62. LEE, H. R., WATSON, M., YAMAMURA, H. I., AND ROESKE, W. R.: Decreased [^{3}H]nitrendipine binding in the brainstem of deoxycorticosterone-NaCl hypertensive rats. Life Sci. **37:** 971–977, 1985.
63. LEFKOWITZ, R. J., CARON, M. G., AND STILES, G. L.: Mechanisms of membrane-receptor regulation: biochemical, physiological, and clinical insights derived from studies of the adrenergic receptors. N. Engl. J. Med. **310:** 1570–1579, 1984.
64. LEVITAN, I. B.: Phosphorylation of ion channels. J. Membr. Biol. **87:** 177–190, 1985.
65. LEVITAN, I. B.: Modulation of ion channels in neurons and other cells. Annu. Rev. Neurosci. **11:** 119–130, 1988.
66. LIPSCOMBE, D., KONGSAMUT, S., AND TSIEN, R. W.: Alpha-adrenergic inhibition of sympathetic neurotransmitter release mediated by modulation of N-type calcium channel gating. Nature (Lond.) **340:** 639–642, 1989.
67. LIPTON, S. A., AND KATER, S. B.: Neurotransmitter regulation of neuronal outgrowth, plasticity, and survival. Trends Neurosci. **12:** 265–270, 1989.
68. LOCHER, R., NEYSES, L., STIMPEL, M., KUFFER, B., AND VETTER, W.: The cholesterol content of the human erythrocyte influences calcium influx through the channel. Biochem. Biophys. Res. Commun. **124:** 822–828, 1984.
69. LUCCHI, L., GOVONI, S., BATTAINI, F., PASINETTI, G., AND TRABUCCHI, M.: Ethanol administration in vivo alters calcium ion control in rat striatum. Brain Res. **332:** 376–379, 1985.
70. LUCHOWSKI, E., YOUSIF, F., TRIGGLE, D. J., MAURER, S. C., SARMIENTO, J. G., AND JANIS, R. A.: Effects of metal cations and calmodulin antagonists on [^{3}H]nitrendipine binding in smooth and cardiac muscle. J. Pharmacol. Exp. Ther. **230:** 607–613, 1984.
71. MAGNONI, M. S., GOVONI, S., BATTAINI, F., AND TRABUCCHI, M.: L-Type calcium channels are modified in rat hippocampus by short-term experimental ischemia. J. Cereb. Blood Flow Metab. **8:** 96–99, 1988.
72. MAHAN, L. C., MCKERNAN, R. M., AND INSEL, P. A.: Metabolism of alpha- and beta-adrenergic receptors in vitro and in vivo. Annu. Rev. Pharmacol. Toxicol. **27:** 215–235, 1987.
73. MATUCCI, R., BENNARDINI, F., SCIAMMARELLA, M. L., BACCARO, C., STENDARDI, I., FRANCONI, F., AND GIOTTI, A.: [^{3}H]Nitrendipine binding in membranes obtained from hypoxic and reoxygenated heart. Biochem. Pharmacol. **36:** 1059–1062, 1987.
74. MAYOUX, E., CALLENS, F., SWYNGHEDAUW, B., AND CHARLEMAGNE, D.: Adaptational process of the cardiac Ca^{2+} channels to pressure overload: biochemical and physiological properties of the dihydropyridine receptors in normal and hypertrophied rat hearts. J. Cardiol. Pharmacol. **12:** 390–396, 1988.
75. MESSING, R. O., CARPENTER, C. L., DIAMOND, I., AND GREENBERG, D. A.: Ethanol regulates calcium channels in clonal neural cells. Proc. Natl. Acad. Sci. USA **83:** 6213–6215, 1986.
76. NAVARRO, J.: Dihydropyridine [^{3}H]PN200–110 binding and myogenesis in intact muscle cells in vitro. J. Neurochem. **46:** 1166–1169, 1986.
77. NAYLER, W. G., DILLON, J. S., AND MCKELVIE, M.: An effect of ischemia on myocardial dihydropyridine binding sites. Eur. J. Pharmacol. **115:** 81–89, 1985.
78. NAYLER, W. G., DILLON, J. S., STURROCK, W. J., AND BUCKLEY, D. J.: Effect of chronic verapamil therapy on cardiac norepinephrine and β-adrenoceptor density. J. Cardiovasc. Pharmacol. **12:** 629–636, 1988.
79. NELSON, M. T., STANDEN, N. B., BRAYDAY, J. F., AND WORLEY, J. F., III:

Noradrenaline contracts arteries by activating voltage-dependent calcium channels. Nature (Lond.) **336:** 382–384, 1988.

80. NISHINI, N., NOGUCHI-KUNO, S. A., SUGIYAMA, T., AND TANAKA, C.: [^{3}H] Nitrendipine binding sites are decreased in the substantia nigra and striatum of the brain from patients with Parkinson's disease. Brain Res. **377:** 186–189, 1986.
81. NISHIYAMA, T., KOBAYASHI, A., HAGA, T., AND YAMAZAKI, N.: Chronic treatment with nifedipine does not change the number of [^{3}H]nitrendipine and [^{3}H]dihydroalprenolol binding sites. Eur. J. Pharmacol. **121:** 167–172, 1986.
82. PANZA, G., GREBB, J. A., SANNA, E., WRIGHT, A. G., JR., AND HANBAUER, I.: Evidence for down-regulation of ^{3}H-nitrendipine recognition sites in mouse brain after long-term treatment with nifedipine or verapamil. Neuropharmacology **34:** 1113–1117, 1985.
83. PASTAN, I. H., AND WILLINGHAM, M. C.: Journey to the center of the cell: role of the receptosome. Science (Wash. DC) **214:** 504–509, 1981.
84. PAUWELS, P., VAN ASSOUW, H. P., AND LEYSEN, J. E.: Depolarization of chick myotubes triggers the appearance of [^{3}H]PN200–110 binding sites. Mol. Pharmacol. **32:** 785–791, 1987.
85. PILLAI, N. P., AND ROSS, D. H.: International Symposium on Calcium Antagonists, New York City, Feb 10–13, 1987.
86. PINCON-RAYMOND, M., RIEGER, F., FOSSET, M., AND LAZDUNSKI, M.: Abnormal transverse tubule system and abnormal amount of receptors for Ca^{2+} channel inhibitors of the dihydropyridine family in skeletal muscle from mice with embryonic muscular dysgenesis. Dev. Biol. **112:** 458–466, 1985.
87. POWERS, R. E., AND COLUCCI, W. S.: An increase in putative voltage-dependent calcium channel number following reserpine treatment. Biochem. Biophys. Res. Commun. **132:** 844–849, 1985.
88. RAMKUMAR, V., AND EL-FAKAHANY, E. E.: Increase in [^{3}H]nitrendipine binding sites in the brain in morphine-tolerant mice. Eur. J. Pharmacol. **102:** 371–372, 1984.
89. RAMKUMAR, V., AND EL-FAKAHANY, E. E.: Selective reduction in the density of [^{3}H]nimodipine binding sites in rat ventricular tissue following reserpine treatment. Pharmacologist **28:** 113a, 1986.
90. RAMKUMAR, V., AND EL-FAKAHANY, E. E.: Prolonged morphine treatment increases rat brain dihydropyridine binding sites: possible involvement in development of morphine dependence. Eur. J. Pharmacol. **146:** 73–83, 1988.
91. RANE, S. G., AND DUNLAP, K.: Kinase C activator 1,2 oleoylacetylglycerol attenuates voltage-dependent calcium current in sensory neurons. Proc. Natl. Acad. Sci. USA **83:** 184–188, 1986.
92. Renaud, J. F., Kazazoglou, T., Schmid, A., Romey, G., and Lazdunski, M.: Differentiation of receptor sites for [^{3}H]nitrendipine in chick hearts and physiological relation to the slow Ca^{2+} channel and to excitation-contraction coupling. Eur. J. Biochem. **139:** 673–681, 1984.
93. RENAUD, J. F., SCHMID, A., ROMEY, G., NANO, J.-L., AND LAZDUNSKI, M.: Mevinolin, an inhibitor of cholesterol biosynthesis, drastically depresses Ca^{2+} channel activity and uncouples excitation from contraction in cardiac cells in culture. Proc. Natl. Acad. Sci. USA **83:** 8007–8011, 1986.
94. REUTER, H.: Calcium channel modulation by neurotransmitters, enzymes and drugs. Nature (Lond.) **301:** 569–574, 1983.
95. REYNOLDS, I. J., WAGNER, J. A., SNYDER, S. H., THAYER, S. A., OLIVERA, B. M., AND MILLER, R. J.: Brain voltage-sensitive calcium channel subtypes differentiated by ω-conotoxin fraction GVIA. Proc. Natl. Acad. Sci. USA. **83:** 8804–8807, 1986.
96. RIEGER, F., BOURNAUD, R., SHIMAHARA, T., GARCIA, L., PINCON-RAYMOND, M., ROMEY, G., AND LAZDUNSKI, M.: Restoration of dysgenic muscle contraction and calcium channel function by co-culture with normal spinal cord neurons. Nature (Lond.) **330:** 563–566, 1987.
97. RIUS, R. A., BERGAMASCHI, S., DIFONSO, F., GOVONI, S., TRABUCCHI, M., AND ROSSI, F.: Acute ethanol effect on calcium antagonist binding in rat brain. Brain Res. **402:** 359–361, 1987.
98. RIUS, R. A., GOVONI, S., AND TRABUCCHI, M.: Regional modification of brain calcium antagonist binding after in vivo chronic lead exposure. Toxicology **40:** 191–197, 1986.
99. RIUS, R. A., LUCCHI, L., GOVONI, S., AND TRABUCCHI, M.: In vivo chronic lead exposure alters [^{3}H]nitrendipine binding in rat striatum. Brain Res. **322:** 180–183, 1984.
100. ROMEY, G., RIEGER, F., RENAUD, J. F., PINCON-RAYMOND, M., AND LAZDUNSKI, M.: The electrophysiological expression of Ca^{2+} channels and of apamin sensitive Ca^{2+} activated K^+ channels is abolished in skeletal muscle cells from mice with muscular dysgenesis. Biochem. Biophys. Res. Commun. **136:** 935–940, 1986.
101. ROSENTHAL, W., AND SCHULTZ, G.: Modulations of voltage-dependent ion channels by intracellular signals. Trends Pharmacol. Sci. **8:** 351–354, 1987.
102. RUFFOLO, R. R., JR., AND KOPIA, G. A.: Importance of receptor regulation in the pathophysiology and therapy of congestive heart failure. Am. J. Med. **80** (suppl. 2B): 67–72, 1986.
103. RUSCH, N. J., AND HERMSMEYER, K.: Calcium currents are altered in the vascular muscle cell membrane of spontaneously hypertensive rats. Circ. Res. **63:** 997–1002, 1988.
104. RUZYCKY, A., CRANKSHAW, D. J., AND TRIGGLE, D. J.: Ca^{2+} channel ligand activities in uterine smooth muscle: influence of hormonal status. Can. J. Physiol. Pharmacol. **65:** 2085–2092, 1987.
105. SANNA, E., HEAD, G. A., AND HANBAUER, I.: Evidence for a selective localization of voltage-sensitive Ca^{2+} channels in nerve cell bodies of corpus striatum. J. Neurochem. **47:** 1552–1557, 1986.
106. SCHIEBINGER, R. J., AND KONTRIMUS, K.: Dietary intake of sodium chloride in the rat influences [^{3}H]nitrendipine binding to adrenal glomerulosa cell membranes, but does not alter binding to vascular smooth muscle membranes. J. Clin. Invest. **76:** 2165–2170, 1985.
107. SCHLESSINGER, J., SCHREIBER, A. B., LIBERMANN, T. A., LAX, I., AVIVI, A., AND YARDEN, Y.: Polypeptide-hormone-induced receptor clustering and internalization. *In* Cell Membranes, Methods and Reviews, ed. by Elson, Frazier and Glaser, pp. 117–149, chapter 4, Plenum Press, New York, 1983.
108. SCHMID, A., KAZAZOGLOU, T., RENAUD, J. F., AND LAZDUNSKI, M.:Comparative changes of levels of nitrendipine-sensitive Ca^{2+} channels, of tetrodotoxin-sensitive Na^+ channels and of ouabain-sensitive (Na^+-K^+)-ATPase following denervation of rat and chick skeletal muscle. FEBS Lett. **172:** 114–118, 1984.
109. SCHMID, A., RENAUD, J. F., AND LAZDUNSKI, M.: Short-term and long-term effects of beta-adrenergic effectors and cyclic AMP on nitrendipine-sensitive voltage-dependent Ca^{2+} channels of skeletal muscle. J. Biol. Chem. **260:** 13041–13046, 1985.
110. SHARMA, R. V., BUTTERS, C. A., AND BHALLA, R. C.: Alterations in the plasma membrane properties of the myocardium of spontaneously hypertensive rats. Hypertension **8:** 583–591, 1986.
111. SIBLEY, D. R. AND LEFKOWITZ, R. J.: β-Adrenergic receptor-coupled adenylate cyclase: biochemical mechanisms of regulation. Mol. Neurobiol. **1:** 121–154, 1987.
112. SIBLEY, D. R., AND LEFKOWITZ, R. J.: Biochemical mechanisms of β-adrenergic receptor regulation. ISI Atlas Sci. Pharmacol. **2:** 66–70, 1988.
113. SIEGELBAUM, S. A., AND TSIEN, R. W.: Modulation of gated ion channels as a mode of transmitter action. Trends Neurosci. **6:** 307–313, 1983.
114. SIMON, G., AND SNYDER, D.: Altered pressor responses in long-term nitrendipine treatment. Clin. Pharmacol. Ther. **36:** 315–319, 1984.
115. SKATTEBOL, A., HRUSKA, R. E., HAWTHORN, M., AND TRIGGLE, D. J.: Kainic acid lesions decrease striatal dopamine receptors and 1,4-dihydropyridine sites. Neurosci. Lett. **89:** 85–89, 1988.
116. SKATTEBOL, A., AND RABIN, R. A.: Effects of ethanol on $^{45}Ca^{2+}$ uptake in synaptosomes and in PC12 cells. Biochem. Pharmacol. **36:** 2227–2229, 1987.
117. SKATTEBOL, A., AND TRIGGLE, D. J.: 6-Hydroxydopamine treatment increases β-adrenoceptors and Ca^{2+} channels in rat heart. Eur. J. Pharmacol. **127:** 287–289, 1986.
118. SKATTEBOL, A., TRIGGLE, D. J., AND BROWN, A. M.: Homologous regulation of voltage-dependent Ca^{2+} channels by 1,4-dihydropyridines. Biochem. Biophys. Res. Commun. **160:** 929–936, 1989.
119. SMILOWITZ, H., SMART, E., BOWIK, C., AND CHANG, R. J.: Regulation of the number of alpha-bungarotoxin binding sites in cultured chick myotubes by a 1,4-dihydropyridine calcium channel antagonist. J. Neurol. Res **19:** 321–325, 1988.
120. SMITH, C. D., AND KATOVICH, M. J.: Effects of chronic verapamil treatment on the development of DOCA/NaCl hypertension in rats. Pharmacologist **27:** 161, 1985.
121. TANABE, T., BEAM, K. G., POWELL, J. A., AND NUMA, S.: Restoration of excitation-contraction coupling and slow calcium current in dysgenic muscle by dihydropyridine receptor complementary DNA. Nature (Lond.) **336:** 134–139, 1988.
122. TRIGGLE, D. J.: Endogenous ligands for the Ca^{2+} channel: myths and realities. *In* The Calcium Channel: Structure, Function and Implications, ed. by M. Morad and W. G. Nayler, pp. 549–563. Springer-Verlag, Berlin, 1988.
123. TRIGGLE, D. J.: Calcium antagonists in atherosclerosis: a review and commentary. Cardiovasc. Drug Rev. **6:** 320–335, 1989.
124. TSIEN, R. W., HESS, P., MCCLESKEY, E. W., AND ROSENBERG, R. L.: Calcium channels: mechanisms of selectivity, permeation, and block. Annu. Rev. Biophys. Biophys. Chem. **16:** 265–290, 1987.
125. VERNER, K. AND SCHATZ, G.: Protein translocation across membranes. Science (Wash. DC) **241:** 1307–1313, 1988.
126. WAGNER, J. A., REYNOLDS, I. J., WEISMAN, H. F., DUDECK, P., WEISFELDT, M. L., AND SNYDER, S. H.: Calcium antagonist receptors in cardiomyopathic hamster: selective increases in heart, muscle, brain. Science (Wash. DC) **232:** 515–518, 1986.
127. WAGNER, J. A., WEISMAN, H. F., SNOWMAN, A. M., REYNOLDS, I. J., WEISFELDT, M. L., AND SNYDER, S. H.: Alterations in calcium antagonist receptors and sodium-calcium exchange in cardiomyopathic hamster tissues. Circ. Res. **65:** 205–214, 1989.
128. WAGNER, J. A., SAX, F. L., WEISMAN, H. F., PORTERFIELD, J., MCINTOSH, C., WEISFELDT, M. L., SNYDER, S. H., AND EPSTEIN, S. E.: Calcium-antagonist receptors in the atrial tissue of patients with hypertrophic cardiomyopathy. N. Engl. J. Med. **320:** 755–761, 1989.
129. WILLIAMS, R. S., AND LEFKOWITZ, R. J.: The effect of thyroid hormone on adrenergic receptors. *In* Molecular Basis of Thyroid Hormone Action, ed. bt J. H. Oppeheimer and H. H. Samuels, pp. 325–349, Academic Press, New York, 1983.
130. WOLFE, B. B., HARDEN, T. K., SPORN, J. R., AND MOLINOFF, P. B.: Presynaptic modulation of beta adrenergic receptors in rat cerebral cortex after treatment with antidepressants. J. Pharmacol. Exp. Ther. **207:** 446–457, 1978.