Therapeutic Potential of Voltage Gated Calcium Channels

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Abstract: Voltage-gated Calcium channels (VGCCs) play important roles in neurotransmitter release, excitation-contraction coupling, hormone secretion, and a variety of other physiological processes. Currently, there exist ion channel therapeutics for anxiety, epilepsy, hypertension, insomnia and pain. There is limited amount of study in this area despite their relevance to human disease and VGCCs remain considerably underexploited. The present review mainly focuses on calcium channel blockers (CCBs), especially for L-type channels and T-type channels, and therein lie some of the opportunities and advantages associated with VGCCs as drug targets.

Key Words: Calcium, Voltage gated channel, L-type channel, T-type channel, dihydropyridine.

INTRODUCTION

Ion channels are embedded transmembrane proteins that allow the passage of charged particles (ions) by formation of a concentration gradient between the extracellular and intracellular contents. They form one of the mechanisms by which cells respond to informational inputs. Ion channels are of different types and is distinguished based on the sequence similarity, gating mechanism and ion selectivity. There are mainly three types of ion channels- (i) voltage gated channels, (ii) ligand gated channels and (iii) mechanically gated channels. Voltage gated channels open or close in response to changes in the charge (measured in Volts) across the plasma membrane. For example, the influx of calcium ions into the cell occurs by opening of voltage-gated calcium channels (VGCCs) leading to excitation-contraction coupling in cardiac and skeletal muscle fibers. These ion channels are the target for calcium channel blockers (CCBs). The structure of α_1 subunit forms the ion conducting pore along with several modulating auxiliary subunits. Major subtypes of VGCC include L-type ($Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$, $Ca_v1.4$), P and Q-type ($Ca_v2.1$), N-type ($Ca_v2.2$), R-type ($Ca_v2.3$) and T-type ($Ca_v3.1$, $Ca_v3.2$, $Ca_v3.3$). Other examples include voltage gated sodium channels and voltage gated potassium channels. In the voltage gated sodium channels an impulse passes down a neuron, the reduction in the voltage opens sodium channels in the adjacent portion of the membrane. This allows the influx of Na^+ into the neuron and thus the continuation of the nerve impulse [1-6].

Ligand gated channels open or close in response to the binding of a small signaling molecule or "ligand". Some ion channels are gated by extra cellular ligands; some by intracellular ligands. In both cases, the ligand is not the substance that is transported when the channel opens. The binding of neurotransmitter acetylcholine opens sodium channels in certain synapses and other examples of ligand gated channels include the nicotinic acetylcholine receptor, 5HT3 serotonin receptor, glutamate-gated receptors, GABA-A receptors and ATP-gated P2X receptors. Mechanically gated channels under physiological conditions permit an orderly movement of ions across cell membranes and contribute both to cellular signaling processes and to the maintenance of cellular homeostasis (e.g. stretch receptors) [5].

Ion channels contribute to or drive various disease processes from achalasia and arrhythmias to xerostomia and vertigo under pathological conditions. Currently there exists ion channel therapeutics for anesthesia, anxiety, epilepsy, hypertension, insomnia, pain and excellent opportunities for ion channel therapeutic modulation in, affective disorders, allergic disorders, autoimmune diseases, contraception, incontinence and stroke [1].

LITERATURE REVIEW

Calcium is the most common signal transduction element in cells. Stimulation of cells can lead to increase in intracellular concentrations of calcium [2]. Calcium, an ubiquitous secondary messenger, regulates a wide range of cellular processes, such as mediating the constriction and relaxation of blood vessels, nerve impulse transmission and secretion of harmones [3]. Various molecular structures are involved in the regulation of calcium, like voltage gated calcium channels (VGCCs), receptor operated calcium channels, calcium pumps (ATPases), Na+/Ca++ -exchanger, stretch operated or leaky channels.

VOLTAGE GATED (OR DEPENDENT) CALCIUM CHANNELS

Voltage Gated Calcium Channels (VGCCs) are large multi-subunit, macromolecular machines that control calcium entry into cells in response to membrane potential changes [4]. They constitute one of a group of superfamily of ion channels including sodium and potassium channels showing sequence, topological and functional similarity [5]. Permitting the entry of calcium in response to membrane depolarization, these channels serves multiple functions, viz muscle contraction, hormone and neurotransmitter release,

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cell motility, cell growth and regulation, cell damage and death and finally cell survival.

The diversity of VGCCs has been extensively studied using electro-physiological, biochemical, pharmacological and molecular biology techniques. Mainly there are two classes of channels: (i) those that respond to small changes in the resting membrane potential, or low voltage-activated (LVA), and (ii) those that require stronger depolarization to open, or high-voltage-activated (HVA). Indeed HVA opens at membrane potential around –30mV whereas LVA gets activated at around –50mV [6]. Based on the pharmacological studies further categorization of the HVA family into L-, N-, P-, Q- and R- has been done and is presented in Table **1**. L-type channels are responsible for long lasting current, large sustained conductance, inactivate slowly, widespread in cardiovascular system, responsible for plateau phase (slow inward current) of action potential, may trigger release of internal Ca^{2+}, sensitive to calcium channel blockers (CCBs). N-, P-, Q- and R-type channels are present most notably in neurons, initiating neurotransmission and are not very sensitive to the CCBs but blocked by polypeptide toxins from snail and spider venoms (Table **1**). T-type channels form the tiny and transient current, structurally similar to L-type channels; inactivate rapidly, expressed throughout the body, including nervous tissue, heart, kidney, smooth muscle and many endocrine organs. They have been implicated in variety of physiological processes including smooth muscle contraction, cardiac pacemaker activity, growth regulation, neuronal firing, harmone secretion, myoblast fusion and fertilization.

STRUCTURE OF VOLTAGE GATED CALCIUM CHANNELS

Voltage Gated Calcium Channels (VGCCs) have been characterized biochemically as complex proteins composed of four or five distinct subunits i.e. it is a hetero-multimer composed of α_1, α_2-δ, β and γ subunits.

The α_1 subunit, the largest hydrophobic subunit of 190 to 250 kDa is the major functional unit of the channel; it incorporates the conduction pore, the voltage sensor and gating apparatus, and known sites of channel regulation by second messengers, drugs, and toxins [7,8]. It is organized as four homologous domains (I–IV) with each having six transmembrane segments (S1–S6). Each third and fourth amino acid of the S4-segments contains a positive arginine or lysine, which most likely represents the voltage sensor of the channel [8]. The pore loop between transmembrane segments S5 and S6 in each domain determines ion conductance and selectivity. Three amino acids change in the pore loops of domains I, III, and IV will convert a sodium channel to calcium channel. The calcium channel pore is exquisitely calcium selective due to the key negatively charged residues, usually glutamate, in each pore loop. In the three-dimensional arrangement of α_1 subunit, four glutamate residues are located centrally in the calcium channel and create a part of the channel pore (P-region). In the middle of the pore, a Ca^{2+} can bind, which is then shifted into the cell after binding of a second Ca^{2+} in the pore region. The pharmacological and electrophysiological diversity of calcium channels arises primarily from the existence of multiple α_1 subunit, although the auxiliary subunits described below, modulate the properties of the

Table 1. Types of Calcium Channels, Activation Threshold, Subunit Genes, Along with the Calcium Channel Blockers, Tissue Expression and Disease Cause

Types of Calcium Channel/ Activation Threshold	Calcium Channel α_1 Subunit Genes	Calcium Channel Blockers	Tissue Expression	Disease Cause
L-type/High	$Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$, $Ca_v1.4$ (α_{1C}, α_{1D}, α_{1S}, α_{1F})	Dihydropyridines (e.g. nicardipine), phenylalkylamines (e.g. verapamil) and benzothiazepines (e.g. diltiazem) Calcicludine (from snake, *Dendroaspis angusticeps*)	neurons, endocrine, skeletal muscle, cardiovascular system	cardiac disorders
P-and Q-type/ High	$Ca_v2.1$ (α_{1A})	ω-agatoxin IVA (from spider, *Agelenopsis aperta)* ω-conotoxin MVIIC (from marine cone snail, *Conus magus*) ω-conotoxin GVIA (from marine cone snail, *Conus geographus*`)	neurons	epilepsy, migraine symptoms
N-type/High	$Ca_v2.2$ (α_{1B})	ω-conotoxin MVIIA (from marine cone snail, *Conus magus*), Prialt® synthetic version ω-conotoxin CVID (from marine cone snail, *Conus catus*)/ AM336 synthetic version	neurons	pain
R-type/ High	$Ca_v2.3$ (α_{1E})	SNX-482 (from tarantula, *Hysterocrates gigas*	neurons	diabetes symptoms
T-type/Low	$Ca_v3.1$, $Ca_v3.2$, $Ca_v3.3$ (α_{1G}, α_{1H}, α_{1I})	Nickel Ethosuximide, zonisamide, mibefradil and kurotoxin	neurons, smooth muscle, sinoatrial node	arrhythmias, epilepsy, pain, fertility?

channel complex. There are ten α_1 subunits: $Ca_v1.1$-1.4, formerly α_{1C}, α_{1D}, α_{1S} and α_{1F}; $Ca_v2.1$-2.3, formerly α_{1A}, α_{1B} and α_{1E}; $Ca_v3.1$-3.3, formerly α_{1G}, α_{1H} and α_{1I}.

The gene $\alpha_2\delta$ form two subunits α_2 and δ, which is the product of the same gene and have a combined molecular weight of 170 kDa. The δ subunit is associated with the α_1 subunit and is the connecting element to the extracellular α_2 subunit. There are four $\alpha_2\delta$ genes. The δ subunit have a single transmembrane region with short intracellular portion and helps anchoring the protein in the plasma membrane. It is supposed that the α_2-δ association which is disulphide linked, modulates ligand binding either by a direct contribution to the dihydropyridine binding site or by altering the drug binding site on α_1. Also the $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits are the binding site for gabapentin and pregabalin, anticonvulasant drugs used in the treatment for neuropathic pain.

β subunit is an intracellular membrane-associated guanylate kinase protein (55 kDa), having guanylate kinase (GK) domain and an Src homology 3 (SH3) domain. Apart from this it also have variable N- and C- terminus as well as connecting variable and flexible HOOK region. The GK domain of β subunit interacts with the α-interaction domain of α_1 subunit and regulates the voltage gated channel activity. However, the complete molecular mechanism of this action is still unclear. The crystal structure studies revealed recently a highly conserved 18 amino acid region interaction between the hydrophobic groove of the GK domain and α-interaction domain (AID), which is the high-affinity binding site in the pore-forming α_1 subunit. The study also confirmed the dual role of the β-subunit i.e. in chaperoning the channels to the plasma membrane and modulating the gating properties [9,10].

γ subunit is composed of four transmembrane spanning helices. There are 8 genes (γ1- γ8) for gamma subunits. The γ1 subunit a 33 kDa glycoprotein is found in skeletal muscle VGCC complexes. Although these auxiliary subunits modulate the properties of the channel complex and does not affect trafficking. The pharmacological and electrophysiological diversity of calcium channels arises primarily from the existence of multiple α_1 subunits. However other γ subunits: γ_2, γ_3, γ_4 and γ_8 are mainly associated with alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptors.

MECHANISM OF ACTION OF VOLTAGE GATED CALCIUM CHANNELS

In contractile cells, voltage gated calcium channels **(**VGCCs) are particularly important because they allow influx of extracellular Ca^{2+} which is essential for muscle contraction and maintenance of tension. Arterial tone, which underlies the maintenance of peripheral resistance in the circulation, is a major contributor to the control of blood pressure. The contractile force of arterial smooth muscle is regulated by the intra-cellular concentration of Ca^{2+}. The calcium calmodulin complex so formed, converts the enzyme myosin light chain kinase to its active form. The latter phosphorylates the myosin light chains, thereby initiating the interaction of myosin with actin. While transient contractions of vascular smooth muscle appear to involve release of Ca^{2+} from intracellular stores by inositol trisphosphate and possibly by Ca^{2+} itself, however maintained contraction depending upon the long-term balance between the entry of external Ca^{2+} and its extrusion from the cell [11,12]. Calcium channels have received a great deal of attention in vascular smooth muscle and it is one of the important route for entry of Ca^{2+} into the cell, others being IP_3 mediated stretch operated. It is the entry of calcium into these cells followed by the sequence of physiological events that causes the heart to contract and arteries to narrow i.e. affects arterial vasoconstriction and vasorelaxation, which ultimately influences systemic blood pressure [11].

Calcium channel blockers (CCBs) are a class of drugs that block this entry of calcium into the muscle cells of the heart and the arteries. In doing so CCB's decrease contraction of heart and dilate the arteries. This causes decreased peripheral smooth muscle tone, decreased systemic vascular resistance ultimately leading to decreased blood pressure.

CHEMICAL CLASSIFICATION OF CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (CCBs) are a heterogeneous, mature group of drugs that inhibit inward calcium channel current to a variable degree in different tissues including vascular smooth muscle, myocardium, sinus and AV nodes. They are exorbitantly used in treating patients with stable angina pectoris, hypertension, variant angina etc. The CCBs are one of the seven principal classes of antihypertensive agents– the others being α-blockers, ß-blockers, ACE inhibitors, AII antagonists, aldosterone antagonists and diuretics [13].

Five major classes of CCBs are known with diverse chemical structures: a) phenylalkylamines: verapamil, b) dihydropyridines: nifedipine, c) benzothiazepines: diltiazem, d) diarylaminopropylamine ethers: bepridil, e) benzimidazole-substituted tetralines: mibefradil (T-type channel blocker). The chemical structure of representative drugs from each class is presented in Fig. (**1**), showing basic differences among them. This CCBs also have relative selectivity towards cardiac versus vascular L-type calcium channels. Some of them are also known as first (I), second (II) and third (III) generation CCBs. All first generation CCBs, nifedipine and diltiazem, block L-type calcium channels, and is classified as dihydropyridine or non-dihydropyridine agents which belongs to phenyalkylamines or benzothiazepines classes. The second and third generation CCBs are either slow release or long acting formulations of the first generation CCBs (e.g. amlodipine or felodepine) [14].

SITES OF ACTION OF CALCIUM CHANNEL BLOCKERS

Like other voltage-gated ion channels, calcium channels exist in at least three different states. A resting state stabilized at negative potentials (such as the resting potentials of most electrically excitable cells) which is a closed state (most stable) from which the channel can open. The open state (unstable, when the membrane is depolarized) is induced by depolarization. Channels do not stay open indefinitely because they are "turned off" during prolong depolarization by transition into an inactivated state (shift from open

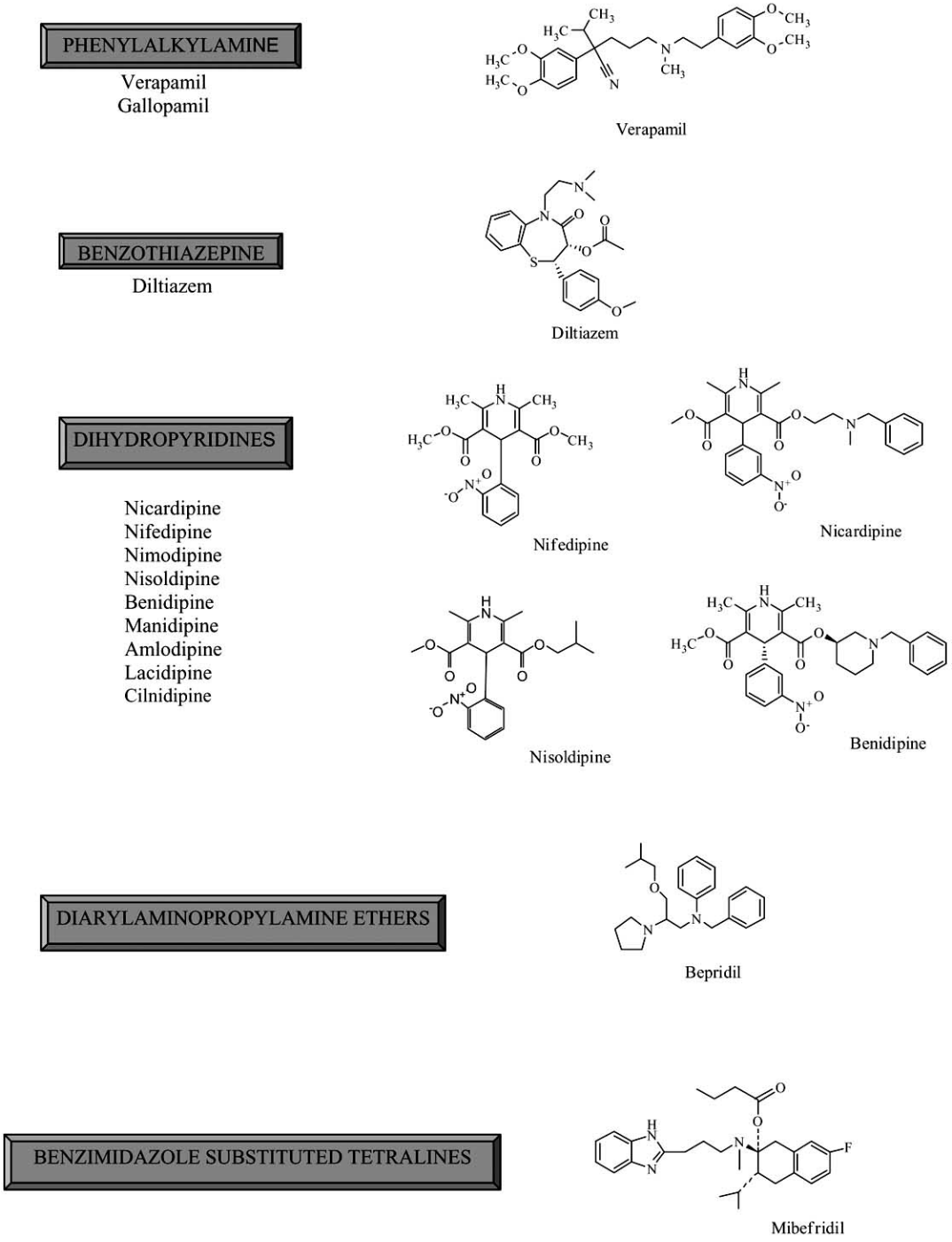

Fig. (1). Different classes of Calcium Channel Blockers.

conformation at hyperpolarized potential). Once the cell repolarizes inactivated channels return to the resting state and are now again available for opening. CCBs inhibit calcium flux mainly by "allosterically" stabilizing the inactivated closed state. By delaying its transition to the resting state after repolarization, some blockers can also increase the refractory period of these channels.

The pharmacology of the three families of calcium channel is quite distinct. Table **1** shows the different types of calcium channels, activation threshold, subunit genes, along with the tissue expression, disease cause and its blockers. The Ca_V1 channels are the molecular targets of organic CCBs, used widely in the therapy of cardiovascular diseases. These drugs are thought to act at three separate, but allosterically coupled, receptor sites [15]. Phenylalkylamines are intracellular pore blockers, which are thought to enter the pore from the cytoplasmic side of the channel and block it. Their receptor site is formed by amino acid residues in the S6 segments in domains III and IV, in close analogy to the local anesthetic receptor site on sodium channels [16]. Dihydropyridines are different in that they can be channel activators or inhibitors and therefore are thought to act allosteri-

cally to shift the channel toward the open or closed state, rather than by occluding the pore. Their receptor site includes amino acid residues in the S6 segments of domains III and IV and the S5 segment of domain III. The dihydropyridine receptor site is closely apposed to the phenylalkylamine receptor site and shares some common amino acid residues. Diltiazem and related benzothiazepines are thought to bind to a third receptor site in close proximity to S6 of domain III and IV, but the amino acid residues that are required for their binding overlap extensively with those required for phenylalkylamine binding.

In contrast to the situation with the development of different small molecule CCBs for Ca_V1 channels i.e. L-type; therapeutic potential of other channels such as P-, Q-, N-, R- and T-type remains considerably underexploited. The Ca_V2 family of calcium channels (P-, Q-, N-, R-type) are relatively insensitive to dihydropyridine CCBs, but are specifically blocked by peptide toxins from spiders and marine snails [17]. The $Ca_V2.1$ channels are blocked specifically by ω agatoxin IVA from funnel web spider venom. The $Ca_V2.2$ channels are blocked specifically by ω conotoxin GVIA and related cone snail toxins. The $Ca_V2.3$ channels are blocked specifically by the synthetic peptide toxin SNX-482 derived from tarantula venom. These peptide toxins are potent blockers of synaptic transmission because of their specific effects on the Ca_V2 family of calcium channels. The Ca_V3 family of calcium channels (T-type) are insensitive to dihydropyridines and the spider and cone snail toxins [2]. The organic CCBs, mibefradil is somewhat specific for T-type versus L-type calcium currents (3- to 5-fold). The peptide kurtoxin inhibits the activation gating of $Ca_V3.1$ and $Ca_V3.2$ channels [18].

Earlier CCB drugs were developed clinically by a process of trial and error i.e. animal model and cell based testing of the compound or in vitro biochemical assays. Computer aided drug design of CCBs forms an alternative approach and become fruitful only when the target structure active sites are known. The present bottleneck in this area is the lack of experimental model structure of VGCCs, to know the drug binding sites for its rational design [13]. Various in silico methods like 2D-QSAR, 3D-QSAR, ANN, combinatorial QSAR approach and pharmacophore mapping techniques have been employed in order to circumvent this problem even when the receptor structure is not known [13-14, 20-28]. Reviewing all the aspects of in silico model in detail is beyond the scope of this mini-review article.

BENEFITS AND SIDE EFFECTS OF CALCIUM CHANNEL BLOCKERS

The benefits of taking CCBs include: a) haemodynamics not effected: no impairment of physical work capacity, b) cerebral perfusion is maintained: compatible with intense mental activity thereby no sedation, c) Not contraindicated in asthma and angina patients, d) renal perfusion not effected, d) male sexual function not effected, e) no deleterious effect on plasma lipid profile, uric acid level and electrolyte balance.

The therapeutic use of this synthetic CCBs is often limited by the appearance of unwanted side effects. For instance, dihydropyridines can initiate reflex tachycardia in response to peripheral vasodilatation and can exert proischaemic effects. They also induce ankle edema, headache, and flush. Verapamil and diltiazem can exert negative chronotropic and dromotropic actions with prolonged atrioventricular conduction. Furthermore, L-type CCBs can reduce the contractility of the heart muscle. The potential for negative inotropic action is inherent to their mechanism of action, and their propensity for neurohormonal activation and can entail dangerous consequences in patients with limited left ventricular function. The combined therapy of diltiazem/ verapamil and β-receptor blockers can engender well known complications like atrioventricular block or bradycardia. Non-dihydropyridines drug-drug interactions study shown that patients treated with beta-blocker depress cardiac electrical and mechanical activity and therefore the addition of a CCB augments the effects of beta-blockade.

CURRENT STATUS OF L-TYPE CALCIUM CHANNEL BLOCKERS

The classical calcium channel blockers (CCBs) dihydropyridines (nifedipine), phenylalkylamines (verapamil), benzothiazepines (dilitiazem) all fall into the category of L-type calcium channel antagonists. A large number of L-type CCBs are available, some of them are presented in Table **1** and Fig. (**1**) respectively.

NEED FOR T-TYPE CALCIUM CHANNEL BLOCKER

Focusing on one of the ion channel therapeutics, hypertension, a pathophysiological condition wherein the blood pressure is chronically elevated and prevalence of which is pandemic, it has been found that VGCC blockers forms one of the exorbitantly used class of drug. However, the side effects like negative inotropism, reflex tachycardia, ankle edema and toxic drug-drug interaction produced by the available drugs are resented, leaving a room for improvement. T-type voltage gated calcium channels (VGCCs) which though have been implicated in pathogenesis of hypertension, epilepsy, neuropathic pain, cancer etc. but for which only a limited progress has been made till date in the quest to identify both selective and non-toxic T-type CCBs [2, 19]. T- type VGCCs are validated targets for use in hypertension, selective inhibitors of which (e.g. mibefradil, kurtoxin) are devoid of above mentioned adverse effects and thus entices academia and industries.

The adverse effects of L-type CCBs like negative inotropism, reflex tachycardia, negative chronotropic and dromotropic actions with prolonged atrioventricular conduction, ankle edema and constipation, the need for safe and selective drugs devoid of these effects was taken seriously. Mibefradil (Posicor or Ro 40-5967), devoid of such adverse effects, was launched in the market in 1997. The beneficial pharmacological and hemodynamic actions were consequence of its pharmacological selectivity for T-type over L-type calcium channels and its functional selectivity for the vasculature over the myocardium [29,30]. However, mibefradil was withdrawn from the market after fatal drug interactions which involved increased plasma concentrations of co-administered drugs, including other CCBs, beta blockers,

digoxin, cyclosporine, simvastatin, erythromycin and tacrolimus [31]. This toxic manifestations were attributed to the multiplicity of pathways inhibited by mibefradil, including metabolism by key cytochrome P450 enzymes like CYP 2D6 and CYP 3A4, responsible for the metabolism of a variety of drugs and drug transport by the drug efflux transporter P-gp. CYP 3A4 and P-gp in enterocytes contribute to reducing systemic availability of drugs administered orally and enjoys considerable overlap of substrates, such that inhibition of both systems would result in a substantial increase in plasma drug concentrations and patient exposure to drug with toxic effect. Thus, the dual inhibition of CYP 3A4, CYP 2D6 and P-gp have toxic outcomes which ultimately lead to withdrawal of mibefradil on 8th June, 1998 [32]. The current status of CCBs can be described as, that though several drugs have reached the public front acting on L-type channel, but none for T-type channel, since the withdrawal of mibefradil. However many molecules based on piperazinylalkylisoxazole skeleton [33] and 3,4-dihydroquinazoline skeleton [25] are being reported to be putative blockers for the same.

CURRENT STATUS OF T-TYPE CALCIUM CHANNEL BLOCKERS

Unlike the large number of L-type calcium channel antagonists that are available, selective T-type blockers are not commercially available. Since the withdrawal of first selective T-type calcium channel antagonist, mibefradil a benzimidazolyl-substituted tetraline derivative, no drug belonging to this class has been launched; but many molecules based on piperazinylalkylisoxazole skeleton [33], 3,4-dihydroquinazoline skeleton [19] are being reported to be putative blockers for the same. Antiproliferative activity of the T-type calcium channel blockers is their ability to block the influx of calcium involved in cell cycle regulation has also been reported e.g. VCP11177 [34]. Therefore compounds targeting these channels can be promising in the field of cancer, where the cell cycle is aberrant. In recent studies both N- and T-type calcium channels are reported to be particularly attractive molecular targets for the discovery and development of new analgesic drugs [35].

ONGOING AND FUTURE PROSPECTIVE ON CALCIUM CHANNEL BLOCKERS

In general, new calcium channel blockers (CCBs) should combine the following desired properties: a) selectivity, b) nontoxic, c) high bioavailability, d) long half-life, allowing once-a-day dosing, e) lack of negative inotropism, f) absence of reflex stimulation of the neuro hormonal axis. Also well studied L-type channel blockers do have limitations and are all antagonists class showing cardiovascular effect. Exceptions include the drugs pregabalin, gabapentin and a peptide toxin ziconotide for the relief of chronic neuropathic pain. The multiple calcium channel pathways effecting during neuronal disorders such as pain and ischemic stroke is a daunting task ahead for the researchers to find out ligands interacting at multiple sites or targeting the specific pathway to block the entire scenario. Other channels such as T-, N-, P-, Q-, R-type channels are of therapeutic interest targeting epilepsy, pain, fertility and diabetes.

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