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Prolonged Administration of Various Calcium Channel Blocker Drugs Jeopardizes the Homeostasis of Our Body, Though They Are Life Saving

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Abstract

In this paper, our study sought to clarify some factors that describe a comprehensive approach of a biofeedback paying regards to homeostasis of human body. A biofeedback system involves a sensory organ and an appropriate stimulus. The stimulus is mediated through organs derived from specific biosensors. Homeostasis is the set of processes by which constant or static conditions are maintained within the internal environment of a of a subject and therefore a homeostat is a controller involved in maintaining homeostasis. Calcium channel blockers are a class of drugs and natural substances with effects on many excitable cells of the body, like the muscles of the heart, smooth muscles of the vessels or neuron cells. The main action of the Calcium channel blockers is to reduce the blood pressure. It is for this action that it is used in individuals with hypertension. Most important fact is that, sodium ions are also driving force in Antiports that extrude Calcium ions from a variety of cells. The Sodium-Calcium exchanger sends Calcium ion out of the cell in exchange for the entry of three Sodium ions. This Antiporter is extremely important in maintaining the cytosolic Calcium ion level in many cells of our body. So, Calcium channel blocker drugs, though they are lifesaving, but prolonged administration of those drugs jeopardizes homeostasis of our body with the development of several side effects like dizziness, headache, fluid deposition in limbs, constipation and impaired reflex in vasoconstriction as well as vasorelaxation. Though now-a-days, several diuretic drugs are used simultaneously with those hypertensive drugs to avoid deposition of fluids in the body, but such sort of concept as well as practice fails to give relief to a patient from impaired vasorelaxation which in turn may develop several chronic disorders associated with vasoconstriction in different parts of our body.

Keywords: Biofeedback, Homeostasis, Antiport, Calcium channel blocker drugs

Introduction

The goal of Scientific cultivation in any area / platform of Nature is to maintain a stainless equilibrium and obviously that should be in favour of Natural Homeostasis. As we are also part of Nature and that is why we should be much careful on our different approaches of scientific cultivations that would generate such yields, which are always in favour of mankind in order to obtain**,** maintain & upgrade a fruitful civilization. This paper describes regarding the biofeedback on long-term administration of calcium channel blocker drugs in human systems that appears to be causal factor of jeopardizing the homeostasis of human body. Most calcium channel blockers decrease the force of contraction of the myocardium (muscle of the heart). This is known as the negative ionotropic effect of calcium channel blockers. It is because of the negative ionotropic effects of most calcium channel blockers that they are avoided (or used with caution) in individuals with cardiomyopathy. Many calcium channel blockers also slow down the conduction of electrical activity within the heart, by blocking the calcium channel during the plateau phase of the action potential of the heart. This is known as a negative dromotropic effect. It causes a lowering of the heart rate and may cause heart blocks, which is known as the negative chronotropic effect of calcium channel blockers. The negative chronotropic effects of calcium channel blockers make them a commonly used class of agents in individuals with atrial fibrillation or flutter in whom control of the heart rate is an issue. Calcium channel blockers work by blocking L-type voltage-gated calcium channels (VGCCs) in muscle cells of the heart and blood vessels. Voltage-dependent calcium channels (VDCC) are a group of voltage-gated ion channels found in excitable cells (neurons, glial cells, muscle cells, etc.) with a permeability to the ion Ca^{2+}.This prevents calcium levels from increasing as much in the cells when stimulated, leading to less muscle contraction. In the heart, a decrease in calcium available for each beat results in a decrease in cardiac contractility. Voltage-dependent calcium channels are formed as a complex of several different subunits: α_1, $\alpha_2\delta$, β_{1-4}, and γ[1,2,3,4,5]. The α_1 subunit forms the ion conducting pore while the associated subunits have several functions including modulation of gating. But, if we do consider the subsequent effects of prolonged administration of such calcium channel blocker drugs paying regards to membrane transport system of our body, extensive study shows that, that jeopardizes the homeostasis of our body, though they are surely life saving for certain events.

Methods of Analysis

It has been reported as well as strongly established that the main action of calcium channel blockers is to decrease the blood pressure. It is for this action that it is used in individuals with hypertension. The calcium signalling pathway has been well studied from KEGG (Kyoto Encyclopedia of Genes and Genomes) PATHWAY which is a collection of manually drawn pathway maps representing our knowledge on the molecular interaction and reaction networks of various things. Extensive *in silico* study was carried on the nature of membrane transport involving several ions associated with calcium transportation in and out of the membrane and we have also used Pfam database for domain analysis of the components of VDCCs.

Results

We found as most important fact is that, Sodium ions are also driving force in Antiports that extrude Calcium ions from a variety of cells. The Sodium-Calcium exchanger sends $Ca+^{2}$ ion out of the cell in exchange for the entry of three Na+ ions. This Antiporter is extremely important in maintaining the cytosolic $Ca+^{2}$ level in many cells of our body. As a result, any sort of blockade in these specified ion channels causes an imbalance in the transport systems involving specified ions to them. Therefore, imbalanced transport, if sustained for prolonged period, though may be required for certain course of time, automatically generates a vulnarable effect in the integral system of our body, followed by several side effects which are really unwanted for us.

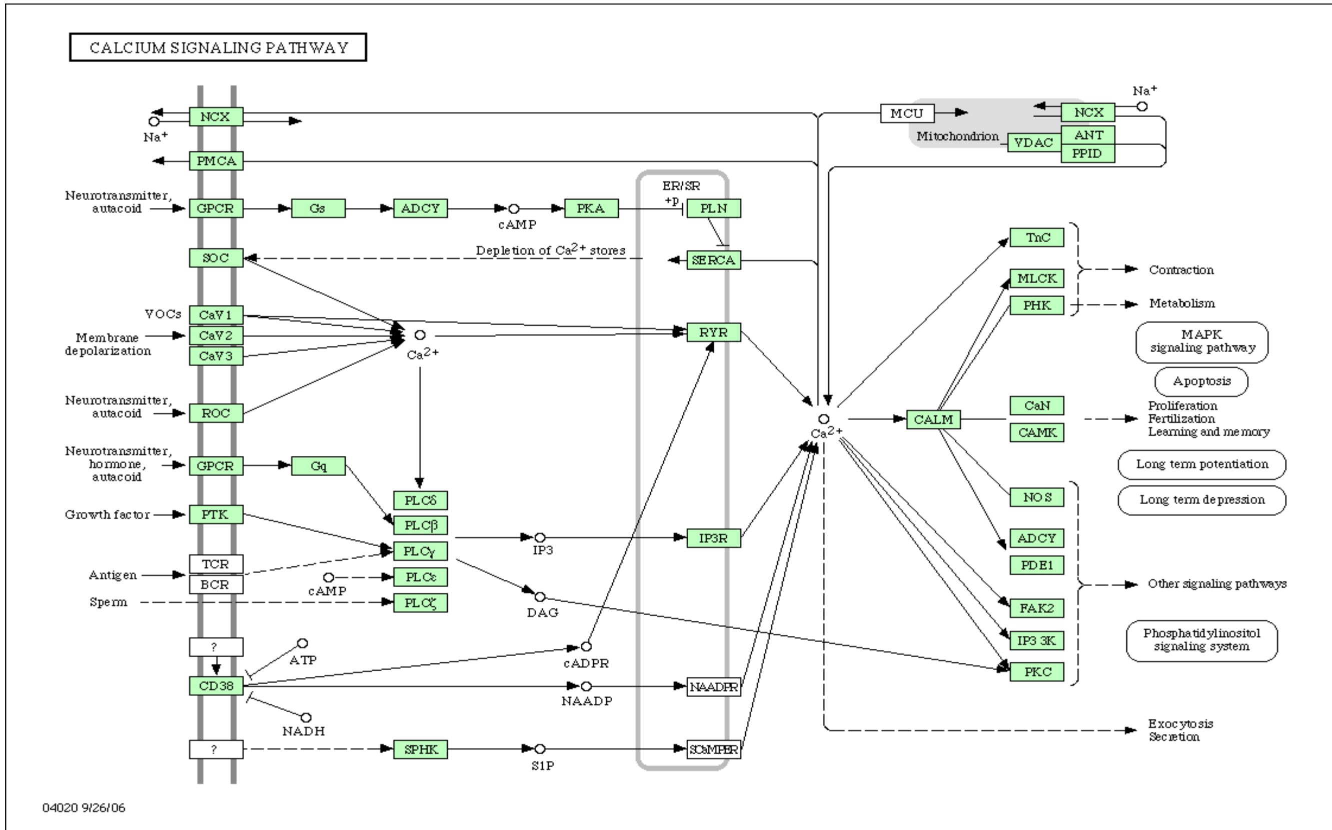
Discussion

Voltage-dependent calcium channels (VDCC) are a group of voltage-gated ion channels found in excitable cells (neurons, glial cells, muscle cells, etc.) with a permeability to the ion Ca^{2+} [2]. At physiologic or resting membrane potential, VDCCs are normally closed. They are activated at depolarized membrane potentials and this is the source of the "voltage-dependent" epithet. Activation of particular VDCCs allows Ca^{2+} entry, which permits the release of neurotransmitters and hormones, muscular contraction, excitability of neurons, and gene expression. Voltage-dependent calcium channels are formed as a complex of several different subunits: α_1, $\alpha_2\delta$, β_{1-4}, and γ. The α_1 subunit forms the ion conducting pore while the associated subunits have several functions including modulation of gating [3]. There are several different kinds of high-voltage-gated calcium channels (HVGCCs). They are structurally homologous among varying types; they are all similar, but not structurally identical. In the laboratory, it is possible to tell them apart by studying their physiological roles and/or inhibition by specific toxins. High-voltage-gated calcium channels include the neural N-type channel blocked by ω-conotoxinGVIA, the R-type channel (R stands for **R**esistant to the other blockers and toxins) involved in poorly-defined processes in the brain, the closely-related P/Q-type channel blocked by ω-agatoxins, and the dihydropyridine-sensitive L-type channels responsible for excitation-contraction coupling of skeletal, smooth, and cardiac muscle and for hormone secretion in endocrine cells. The α_1 subunit pore (~190 kDa in molecular mass) is the primary subunit necessary for channel functioning in the HVGCC, and consists of the characteristic four homologous I-IV domains containing six transmembrane α-helices each. The α_1 subunit forms the Ca^{2+} selective pore, which contains voltage-sensing machinery and the drug/toxin-binding sites. A total of ten α_1 subunits that have been identified in humans [2]. The $\alpha_2\delta$ gene forms two subunits α_2 and δ (which are both the product of the same gene). They are linked to each other via a disulfide bond and have a combined molecular weight of 170 kDa. The α_2 is the extracellular glycosylated subunit that interacts the most with the α_1 subunit. The δ subunit has a single transmembrane region with a short intracellular portion, which serves to anchor the protein in the plasma membrane. There are 4 $\alpha_2\delta$ genes. Co-expression of the $\alpha_2\delta$ enhances the level of expression of the α_1 subunit and causes an increase in current amplitude, faster activation and inactivation kinetics and a hyperpolarizing shift in the voltage dependence of inactivation. Some of these effects are observed in the absence of the beta subunit, whereas, in other cases, the co-expression of beta is required. The intracellular β subunit (55 kDa) is an intracellular MAGUK-like protein (Membrane-Associated Guanylate Kinase) containing a guanylate kinase (GK) domain and an SH3 (src homology 3) domain. The guanylate kinase domain of the β subunit binds to the α_1 subunit I-II cytoplasmic loop and regulates HVGCC activity. There are four known isoforms of the β subunit. The γ1 subunit is known to be associated with skeletal muscle VGCC complexes, but the evidence is inconclusive regarding other subtypes of calcium channel. The γ1 subunit glycoprotein (33 kDa) is composed of four transmembrane spanning helices. The γ1 subunit does not affect trafficking, and, for the most part, is not required to regulate the channel complex. However, γ_2, γ_3, γ_4 and γ_8 are also associated with AMPA glutamate receptors.

When a smooth muscle cell is depolarized, it causes opening of the voltage-gated, or L-type, calcium channels. Depolarization may be brought about by stretching of the cell, agonist-binding its G protein-coupled receptor (GPCR), or autonomic nervous system stimulation. Opening of the L-type calcium channel causes infux of extracellular Ca^{2+}, which then binds calmodulin. The activated calmodulin molecule activates myosin light-chain kinase (MLCK), which phosphorylates the myosin in thick filaments. Phosphorylated myosin is able to form crossbridges with actin thin filaments, and the smooth muscle fiber (i.e., cell) contracts via the sliding filament mechanism.

From the detailed discussion above it is clear that, where ever may be the point of blokage of calcium channels, transport system works in the more or less same way.

The following is the general schema for Calcium Signalling Pathway found from KEGG:



As we know that, Many calcium channel blockers also slow down the conduction of electrical activity within the heart [6, 7], by blocking the calcium channel during the plateau phase of the action potential of the heart, prior to that, let us discuss about the cardiac action potential and it looks like as follows:

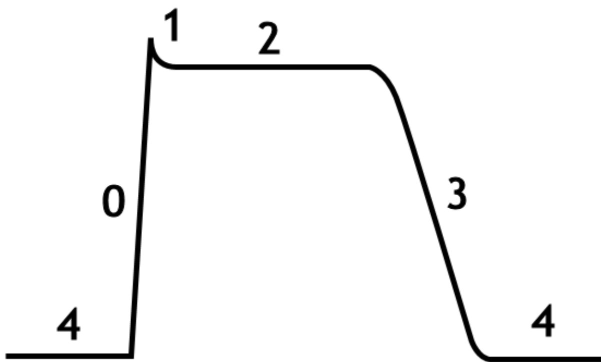


Fig: The Cardiac Action Potential has five phases

The standard model used to understand the cardiac action potential is the action potential of the ventricular myocyte. The action potential has 5 phases (numbered 0-4). Phase 4 is the resting membrane potential, and describes the membrane potential when the cell is not being stimulated.

Once the cell is electrically stimulated (typically by an electric current from an adjacent cell), it begins a sequence of actions involving the influx and efflux of multiple cations and anions that together produce the action potential of the cell, propagating the electrical stimulation to the cells that lie adjacent to it. In this fashion, an electrical stimulation is conducted from one cell to all the cells that are adjacent to it, to all the cells of the heart.

Phase 4 is the resting membrane potential. This is the period that the cell remains in until it is stimulated by an external electrical stimulus (typically an adjacent cell). This phase of the action potential is associated with diastole of the chamber of the heart.

In addition to stimulus from adjacent cells, certain cells of the heart have the ability to undergo *spontaneous depolarization*, in which an action potential is generated without any influence from nearby cells. This is also known as cardiac muscle automaticity. *Phase 0* is the rapid depolarization phase. The slope of phase 0 represents the maximum rate of depolarization of the cell and is known as V_{max}. This phase is due to the opening of the fast Na^+ channels causing a rapid increase in the membrane conductance to Na^+ (G_{Na}) and thus a rapid influx of Na^+ ions (I_{Na}) into the cell; a Na^+ current.

The ability of the cell to open the fast Na^+ channels during phase 0 is related to the membrane potential at the moment of excitation. If the membrane potential is at its baseline (about -85 mV), all the fast Na^+ channels are closed, and excitation will open them all, causing a large influx of Na^+ ions. If, however, the membrane potential is less negative, some of the fast Na^+ channels will be in an inactivated state insensitive to opening, thus causing a lesser response to excitation of the cell membrane and a lower V_{max}. For this reason, if the resting membrane potential becomes too positive, the cell may not be excitable, and conduction through the heart may be delayed, increasing the risk for arrhythmias.

Phase 1 of the action potential occurs with the inactivation of the fast Na^+ channels. The transient net outward current causing the small downward deflection of the action potential is due to the movement of K^+ and Cl^- ions, carried by the I_{to1} and I_{to2} currents, respectively. Particularly the I_{to1} contributes to the "notch" of some ventricular cardiomyocyte action potentials.

It has been suggested that Cl^- ions movement across the cell membrane during Phase I is as a result of the change in membrane potential, from K^+ efflux, and is not a contributory factor to the initial repolarisation ("notch").

This "plateau" phase of the cardiac action potential is sustained by a balance between inward movement of Ca^{2+} (I_{Ca}) through L-type calcium channels and outward movement of K^+ through the slow delayed rectifier potassium channels, I_{Ks}. The sodium-calcium exchanger current, $I_{Na,Ca}$ and the sodium/potassium pump current, $I_{Na,K}$ also play minor roles during phase 2.

During phase 3 of the action potential, the L-type Ca^{2+} channels close, while the slow delayed rectifier (I_{Ks}) K^+ channels are still open. This ensures a net outward current, corresponding to negative change in membrane potential, thus allowing more types of K^+ channels to open. These are primarily the rapid delayed rectifier K^+ channels (I_{Kr}) and the inwardly rectifiyng K^+ current, I_{K1}. This net outward, positive current (equal to loss of positive charge from the cell) causes the cell to repolarize. The delayed rectifier K^+ channels close when the membrane potential is restored to about -80 to -85 mV, while I_{K1} remains conducting throughout phase 4, contributing to set the resting membrane potential.

At this, though our purpose for reduction of vesoconstriction is apparently solved, but there are so many musculatures, which are in requirement of vesoconstriction in order to maintain different physiological performences in favour of homeostasis of our body. So, with the long term use of such calcium channel blocker drugs generates impared activity/reflex in both of the phenomenoa vesoconstriction as well as vesodialatation. And we find its reflection in fluid deposition in limbs, dizziness and constipation in most of the patients suffering from hypertension followed by administration of several calcium channel blocker drugs [8].

Recently, different types of diuretics drugs [9, 10] are found to be administrated to drain up deposited water from the body, they do work well accordingly, but can not recover the impared activity of those musculature which are really victim of such maladministration of drugs.

Conclusion

The Antiport involving sodium & calcium ions in between I.C.F & E.C.F jeopardizes the homeostasis of our body in prolonged administration of several calcium channel blocker drugs, though they are life saving. These drugs reduces blood pressure, but prolonged administration of these drugs generates several side effects, rather to say, impaired activity of several musculature in different portions of our body and thereby jeopardizes the human homeostasis.

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