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PROTEIN-PROTEIN INTERACTION FOR THE ACTIVITY OF TRPP2 CHANNELS AND MEMBRANE AND CYTOSKELETAL REGULATION: PHYSIOLOGICAL AND MATHEMATICAL MEDICINE

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ABSTRACT

Physiological medicine provides general clinical understanding of the disordered conditions and their management. Whereas the other aspect relates to the biophysical and mathematical medicine that provides the subtle mechanisms or the theoretical philosophy of medicine. The biophysical and mathematical concepts, principles and mechanisms lead to the real understanding of the science and art of medicine. There are pertinent biophysical concepts for understanding the transient receptor potential polycystin-2 (TRPP2) or polycystin-2 (PC2) channels, e.g., Goldman-Hodgkin-Katz (GHK) equations for determining membrane potential, Boltzmann equation for model gating probabilities, and Nernst equation for determining equilibrium potential of a single ion. Protein-protein interaction for the activity of TRPP2 channels and membrane and cytoskeletal regulation are quite hot topics. More innovative approaches involve with the newer findings that PC2 interacts with cytoskeleton especially in primary cilia of kidney cells and forces and dynamics are modelled. In cytoskeletal abnormalities, PC2 mutations cause disordered conditions, e.g., polycystic kidney disease (PKD). The structures in cytoskeleton e.g. a): actin, tropomyosin-1 (TM-1) and alpha-actinin in interaction with PC2 for stabilizing the normal structure and functions of cells, b): for the regulation of PC2 channel activity, the actin by conformational changes modulates PC2 for permitting the cells to have the sense for responding to the physical forces, c): interaction of microtubules with PC2 leading to the regulation of proteins in microtubules for the mechanosensation and the occurrence of cytoskeletal link to endoplasmic reticulum, d): triggering of the calcium influx via PC2 by a complex of PC1 and PC2 in primary cilium membrane, that causes the calcium signal to control various cellular functions. Despite continual research efforts, it still could not be understood how polycystins interact and work in normal and disordered functions e.g., cyst formation. The cyst formation in fact is a dysregulated repair process, and polycystins seem involved in regulating the repair processes. Further research would uncover the mechanism reversing the cyst formation and cystic diseases. It is, hence, hoped for the novel therapeutic approaches. The current article explores the role of protein-protein interaction for the activity of TRPP2 channels and membrane and cytoskeletal regulation in normal cellular functions and disordered conditions. At quite subtle level, the physiological or clinical medicine, and the mathematical medicine or the medicine based on theoretical philosophical interpretations merge and provide a common mechanism of understanding the normal and disordered conditions.

Key Words: Protein-protein interaction, transient receptor potential polycystin-2 (TRPP2) channels, membrane and cytoskeletal regulation, physiological and mathematical medicine

INTRODUCTION

Physiological medicine provides general clinical understanding of the disordered conditions and their management. Whereas the other aspect relates to the biophysical and mathematical medicine that provides the subtle mechanisms or the theoretical philosophy of medicine. The biophysical and mathematical concepts, principles and mechanisms lead to the real understanding of the science and art of medicine. There are pertinent biophysical concepts for understanding the transient receptor potential polycystin-2 (TRPP2) or polycystin-2 (PC2) channels. Goldman-Hodgkin-Katz (GHK) equations for determining membrane potential, Boltzmann equation for model gating probabilities, and Nernst equation for determining equilibrium potential of a single ion are employed.

Membrane potential is calculated using Goldman-Hodgkin-Katz (GHK) equation:

$I=g(Vm-Eeq)$

Where I, g, Vm and Eq respectively are current, conductance, membrane potential and equilibrium potential.

The equilibrium potential (E) is calculated using the Nernst equation:

$E=RT/zF$ ln $[ion]/[ion]_{in}$

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Where R, T, z, F, $[ion]_{out}$ and $[ion]_{in}$ respectively represent gas constant, absolute temperature, charge of ion, Faraday's constant, extracellular concentration and intracellular concentration.

Hodgkin-Huxley model provides kinetics of the voltage-gated channels:
$Dx/dt=\alpha(V)(1-x)-\beta(V)x$

Where $\alpha(V)$ and $\beta(V)$ represent the voltage-dependent transition rates between open and closed states.

To explain the open channel probability, the Boltzmann equation is used:
$P=1/1+e^{q(V-V_{1/2})/kT}$

Where P, V, $V_{1/2}$, q, k and T respectively represent probability of open state, membrane potential, half activation potential, charge change associated with activation, Boltzmann's constant and absolute temperature.

The human ciliopathies affected by monogenic disorders have comprehensively been studied (Dalgaard and Nørby, 1989; Hussain, 1990a,b,c; Sutters and Germino, 2003; Yasmeen *et al*., 2008; Harris and Torres, 2009; Yasmeen *et al*., 2009; Boletta and Caplan, 2025; Buqaileh *et al*., 2025), along with pathophysiological perspectives (Beebe, 1996; Hussain and Hussain, 1998; Yoder *et al*., 2002; AbouAlaiwi *et al*., 2009; Yin *et al*., 2010; Yoshimura and Sokabe, 2010; Borghol *et al*., 2025).

Transporting the ions across the semipermeable membranes is the major function of ion channels that is studied by using electrophysiological techniques (patch clamp/ planar lipid bilayer) (Lal *et al*., 2018). The polycystin-1 and polycystin-2 mutations in ADPKD involves the interaction of C-terminals and the regulation occurs via the cytosolic regions for cell proliferation/differentiation (Behn *et al*., 2010).

The mechanist concepts are derived typically from Hodgkin-Huxley or Markov state conditions that reveal the ion channel conformational changes, though differences exist between models and discrepancy-based reality termed models due to rate of transition and related abstracted assumptions and conformation states (Lei and Mirams,2021).

For voltage gated channels, the ion channels are usually modelled (Lei and Mirams,2021) as:
closed $\alpha(V)\rightleftharpoons\beta(V)$open

Where the V is membrane voltage, and transition rates mentioned between the open state and closed state are α and β

The x-open probability of the gate is described as:
$Dx/dt=f(x,V)$
$\beta(V)=A\beta\exp(B\beta V)$

The neural networks are expressed as:
$y=N(x;\Theta)=WM+1\circ(hM\circ WM)\circ\cdots\circ(h1\circ W1)(x)$
The Θ, and $\circ$, respectively represent parameters of the network weights, and operator composition.

The Hodgkin and Huxley model was applied later by Beattie *et al.* (2018) by modelling the current with the standard Ohmic presentation (Lei and Mirams, 2021) as:
$I=g\cdot a\cdot r\cdot(V-E)$
Considering g, a and r respectively as maximal conductance, Hodgkin-Huxley-style activation gate, and inactivation gate. The E is reversal potential for potassium ion current (Nernst potential) calculated as
$E=RT/zF \ln([K+]o/[K+]i)$

The ion channel modeling with neural network was employed as:
$dxdt=N(V,x)$
N(V, x) shows neural network that taking voltage V and state x as inputs.
$dxdt=f(x,V)+N(V,x)$
$f(x, V) = \alpha(1 - x) - \beta x$ present any other gate model.

In voltage clamp experiments, current model was generalized (Lei and Mirams, 2021) for Hodgkin-Huxley current model for state space estimation as:
$I=g\cdot\prod k(xk)^{nk}\cdot(V-E)$
The k distinct gating variables xk, integer power nk, and g, E as constants.

Two procedures are used to estimate state space of the gate xi. The current derivative is approximated (Lei and Mirams, 2021) as:

$Dxi/dt|I(xi,V)=1/nixi^{(ni-1)}\prod k\neq I\ xk^{nk}(1/(V-E)(1/g\ dI/dt-\prod k\ xk^{nk}dV/dt)-\sum j\ njxj^{(nj-1)}dxj/dt\prod k\neq j\ xk^{nk})$
In NN-f model, T serves as number of data points and loss function for NN-d model is represented as:
$Ld(\Theta)=1/TT\sum t=1(da/dt|t-f(xt,Vt)-N(xt,Vt;\Theta)^2$

Non-selective calcium permeable TRPP2 (transient receptor potential) channel containing six domains (Anyatonwu and Ehrlich, 2005) causes PKD by PKD2 mutations (Montalbetti *et al*., 2007) whereas the TRPP3 that is potentiated by alpha actinin (Li *et al*., 2007) regulates pH sensitive action potentials of central spinal canal neurons and sour taste. Prevalence of ADPKD in US was found in the range of 5-15% (Ćelić *et al*., 2012; Wang *et al*., 2012; Chebib *et al*., 2025). The pkd1 & pkd2 genes cause PKD a type of ciliopathy leading to renal failure of progressive form that suggests conducting further studies for the management of PKD and kidney cysts (Buqaileh *et al*., 2025; Chebib *et al*., 2025).

Though the mutations in PKD2 gene expressed in Xenopus oocytes identified PC2 after its reconstitution in lipid bilayer, the genetic model for PC2 by cloning of DmPC2 or Drosophila PC2 showed the confirmation of PC2 channels (Venglarik *et al*., 2004). Regulation of PC2 from the cytoplasmic side of the channel was suggested and the mechanism of cyst formation was elucidated (Gonzalez-Perrett *et al*., 2001, 2002) and PC2 was detected later by patch clamp electrical recording in reconstituted lipid bilayer (Li *et al*., 2004).

The primary cilia were initially considered as nonmotile hair like microtubular structures. Later they were found to have in isolated form the current recording of ion channels that indicated that primary cilia contain necessary apparatus to respond for mechanical stimulation/fluid flow and must contain the ion channels (Raychowdhury *et al*., 2005).

It was investigated that PC2 in kidney regulates the processes via making interactions with microtubular ciliary system comprising sensory processes (Li *et al*., 2006; Montalbetti *et al*., 2007). It was documented that PC2 in human placental syncytiotrophoblast (hST) manufactured at term has actin and other cytoskeletal components that help regulating the PC2 functions (Montalbetti *et al*., 2007). PC2 has mainly been studied in primary cilium and the ADPKD (Cantero and Cantiello, 2011). It has been investigated that quite abundant Enormous PC2 expression by hST emphasizes the pregnancy related role PC2 (Montalbetti *et al*., 2008). Electrical properties of the PC2 were found to be affected by Lithium (Li^+) (Cantero and Cantiello, 2011).

Regarding the Ca2+ transport via PC2 channels, the theoretical calcium permeability of pore was determined (Cantero and Cantiello, 2013) as:
$P_{Ca}=V\text{pore}/t_{Ca}$
The Ca^{2+} permeability coefficient is represented by P_{Ca}

The J_{Ca}, was obtained that agrees with the boundary condition in the maximal Calcium permeability PmaxCa, estimated by Läuger (1976).

The current review article explains the protein-protein interactions for the activity of TRPP2 channels via membrane and cytoskeletal regulation. The physiological and mathematical background of the activity of PC2 and related diseases have been elaborated. Hopefully, the future studies would unravel the intricate aspects of protein-protein interaction processes regulated interactively by membrane and cytoskeletal systems in physiological and disordered conditions.

PC2 AND MEMBRANE INTERACTION

The in vivo pore size of PC2 channels provided potential information about its leakage for calcium from endoplasmic reticulum (Anyatonwu and Ehrlich, 2005). The presence of phospholipids and high PC2 associated calcium transport produces cluster formation of channels and oscillating current (Velázquez *et al*., 2023). There are a variety of ways PC2 interacts with membrane. It may interact to lipids in membrane/ lipid bilayer and modulates the functions involving the protein-protein interaction that is modelled for interactions e.g., potential of mean force (PMF):
$PMF(r)=-k_BTln(P(r))$
P(r) serves for the probability of system with distance r between the protein and the lipid.

For having information for how PC2 can deform the lipid membrane, free energy of deformation is obtained by:
$F_{el,q}=\pi k_cR(\ldots)+\text{constant}$
Kc and R respectively are bilayer bending modulus and radius for protein
For more complicated systems, $\tilde{c}_0$ can be determined as:
$\tilde{c}_0=c_0+\sum v_\alpha/v_0\,(\partial c_0/\partial \ln S_\alpha)$

where $\tilde{c}_0$, v_α and S_α respectively represent spontaneous membrane curvature, volume deviation of q_α, and area/ lipid molecule. Lipid interactions of ciliary membrane PC2 Channel explain the roles of lipids in regulation and organization of the ciliary membranes (Wang *et al*., 2020). Intrinsic mechanosensitive nature of PC2 resulting from external forces were revealed by atomic force microscopy (AFM) along with lipid bilayer procedures (Lal *et al*., 2018). The quartz crystal microbalance (QCM) provided opportunity to have information of the interaction of lipid bilayer with the C-terminal end of PC1 & PC2. It was found that PC2 V-terminal forms trimers in the solution condition and binds to PC2 C-terminal (Behn *et al*., 2010).

PROTEIN-PROTEIN INTERACTION AND CYTOSKELETAL REGULATION

The PC2 forms interaction with PC1 for the regulation of calcium levels and for sensing the mechanical forces that can be explained by:

$I=N\times i\times P_o$

Where N, I and P_o respectively are total active channels, current in a single channel, and open probability, and

$P_o=t_o/T$

t_o and T respectively are total time of open state and total observation time.

Applying these concepts revealed that PC2 is controlled by PC2 binding domain in intracellular side of fibrocystin (Kim *et al*., 2008). A variety of techniques comprising immunofluorescence, co-immunoprecipitation, yeast two-hybrid, pull-down, dot blot overlay and lipid bilayer setup showed that cytoskeletal proteins including mainly the alpha actin bind with PC2 (C and N terminals) for adhesion, proliferation, migration, other channel regulatory activities (Li *et al*., 2005), and have Ca^{2+} regulated PC2 activities in hST (Cantero and Cantiello, 2015).

The filamin have significant inhibitory effect on the functions of PC2 in the presence of calcium but no effect in the absence of calcium (Cantero and Cantiello, 2015). The structural binding and functional actions of PC2 through its N- & C- termini associate with C terminal in filamin (Wang *et al*., 2012). The PC2 was affected by gelsolin at quite a low concentration of intracellular calcium whereas it was enhanced by profilin both in the presence or absence of calcium (Cantero and Cantiello, 2015).

Studies employing the Goldman-Hodgkin-Katz equation and absolute rate theory manifested the clinical and pharmaceutical effects of lithium on ciliary length, PC2 blockage and change in the electrical properties of PC2 (Cantero and Cantiello, 2011). A common mechanism for the role of calcium signaling PC2 in various organisms was revealed by fluorescence microscopy, immunohistochemistry and lipid bilayer techniques (Kaja *et al*., 2012).

Immunocytochemistry, immunohistochemistry, electron microscopy, biophysical techniques and lipid bilayer electrophysiological applications showed high expression electrophysiological properties of PC2 found in nucleus, endoplasmic reticulum, Golgi bodies and other organelles in various tissues (Kaja *et al*., 2011). The investigation of the interaction of PC2 with fibrinogen via K1FB3 motor subunit of kinesin 2 provided the association of ADPKD and ARPKD (Wu *et al*., 2006).

PC2 was found inhibited by ROS (reactive oxygen species) for calcium to be transported in term hST (Montalbetti *et al*., 2008) and disordered cation transference in mother and fetus in pregnancy occurred. The microtubular structures were found quite potential in the regulation of ion channel transport activity (Montalbetti *et al*., 2007).

The cellular and histological techniques provided interesting information about the hST apical structures e.g. colocalization of PC2 and tubulin (Montalbetti *et al*., 2007). A potential aspect about the interaction of PC2 and microtubular system was found involving the effect of colchicine, tubulin, guanosine triphosphate, and taxol on hST reconstituted bilayers with PC2 activity (Montalbetti *et al*., 2007) as indicated earlier (Montalbetti *et al*., 2005) by using Immunofluorescence that the colocalization of PC2 and actin occurs in the vicinity of membrane revealing that the physical forces acting upon the cells regulate PC2 through actin and other sensory cytoskeletal system. It was noted that hST cytoskeletal system controls the increased function of PC2 by K1F3A protein, and this interaction is important for placenta related transport of ions (Montalbetti *et al*., 2007).

A report revealed that ion channel reconstitution in primary cilia has high density for PC2 and two other channel proteins (Raychowdhury *et al*., 2005). It was found that PC2 controls primary ciliary microtubules and microtubular system controls PC2 (Li *et al*., 2006). The disordered Ca^{2+} signaling and loss of ryanodine receptor 2 regulation was found to occur in heart in response to PC2 and its mutations (Anyatonwu *et al*., 2007). The number and EF hand associated domains for calcium binding sites regulate calcium levels for necessary functions of PC2 (Kuo *et al*., 2014). It was revealed that PC2iv did not show sensitivity for the regulation of Ca^{2+} (Cantero and Cantiello, 2013) that showed that controlling sites are not intrinsic to PC2, and Ca^{2+} microdomain is mainly found through the control of PC2 in hST (Cantero and Cantiello, 2013). The NMR and small angle x-ray scattering served for the measurement of interatomic distance clarified that channel opening & closing was controlled by conformational changes produced by calcium in the PC2 C terminal tail, and PC2 was controlled by conformational changes in the cytoplasmic tail of the PC2 that proceed to channel pore area (Ćelić *et al*., 2012).

The interaction and role of cytoskeleton and cytoskeletal proteins for the regulation of PC2 in normal and disordered processes can be explained by understanding cytoskeletal mechanics. The structure and contractility of network can be explained by modeling the cytoskeletal remodeling, e.g., actin cytoskeleton in response to the effect of mechanical stimuli. The cytoskeletal force generation can be modelled by calculating the total force magnitude (F). The continuum mechanics models are developed by applying the concepts of, linear momentum, conservation of mass and angular momentum to understand the cellular behavior.
Considering the conservation of linear momentum, it is:
$d/dt\int_V \rho \upsilon_k dV = \int_S \tau_k dS + \int_V \rho b_k dV$
Considering the conservation of angular momentum, it is:
$d/dt\int_V \epsilon_{ijk} x_j \rho \upsilon_k dV = \int_S \epsilon_{ijk} x_j \tau_k dS + \int_V \epsilon_{ijk} x_j \rho b_k dV$

where: ρ, υ_k, V, S, τ_k, b_k, and ϵ_{ijk} respectively are mass density, velocity component, volume, surface, traction stress vector component, body force component and permutation symbol.

Force generated by cytoskeletal polymers/ filaments, e.g., microtubules is modelled by thermodynamic principles, based on free energy change of polymerization (ΔG) for maximal force (F) generated as:
$F = -kT/l \ln(c/c_{cr})$

Where k, T, l, c and c_{cr} respectively represent Boltzmann constant, absolute temperature, length of single monomer, solution concentration of the monomer, and critical concentration of polymerization.

CONCLUSIONS

Highly innovative approaches uncover that PC2 interacts with cytoskeleton especially in primary cilia of kidney cells and forces and dynamics are modelled. In cytoskeletal disorders, PC2 mutation causes polycystic kidney disease (PKD). The structures in cytoskeleton is related to, a): actin, tropomyosin-1 (TM-1) and alpha-actinin in interaction with PC2 for stabilizing the normal structure and functions of cells, b): the regulation of PC2 channel activity, the actin by conformational changes modulates PC2 for permitting the cells to have the sense for responding to the physical forces, c): interaction of microtubules with PC2 tht leads to the regulation of proteins in microtubules for mechanosensation and the occurrence of cytoskeletal link to endoplasmic reticulum, d): triggering of the calcium influx via PC2 by a complex of PC1 and PC2 in primary cilium membrane, that causes the calcium signal to control various cellular functions.

Despite continual research efforts, it still could not be clearly understood how polycystins interact and work in normal and disordered functions e.g., cyst formation. This aspect is highly emphasized since the cyst formation in fact is a dysregulated repair process, and polycystins seem involved in regulating the repair processes. It is, hence, hoped for the novel therapeutic approaches. Physiological medicine provides general clinical understanding of the disordered conditions and their management. Whereas the other aspect relates to the biophysical and mathematical medicine that provides the deep-seated subtle mechanisms or the theoretical philosophy of medicine. Hopefully, further research will uncover the mechanisms of diseases involving conventional physiological medicine as well as the mathematical medicine.

DEDICATION

The author dedicates this article to the loving memory of his highly intellectual mentor and his first postdoc mentor, Dr. W. McIntyre Burnham, former Emeritus Professor, Department of Pharmacology and Toxicology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada. The author carried out his postdoctoral fellowship program under the supervision of Prof (Emeritus) W. McIntyre (Mac) Burnham in Jan-Dec 1995. The author learned Experimental Neurology/ Epileptology, Kindling Model of Complex Partial Seizures, Amygdala Electrophysiology, Psychophysiology and Neuropsychophamacology under the guidance of Prof. Burnham.

Dr. Burnham was born in Chicago (July 1, 1939). He completed an honours B.A. in Experimental Psychology at Cornell University (1962) and Ph.D. in Physiological Psychology at McGill University (1971), followed by post-doctoral training in Neurophysiology at the Montreal Neurological Institute (1971-1974) with Prof. Pierre Gloor.

Professor Willets McIntyre (Mac) Burnham (1939-2024) B.A., Ph. D.- a renowned neuropsychopharmacologist, and a former Emeritus Professor, Department of Pharmacology and Toxicology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada.

Mac made seminal contributions to the field of convulsive disorders/epilepsy and continuously pursued research on anticonvulsant drugs and potential therapies for epilepsy. He had over 250 scientific publications and mentored over 30 graduate and post-graduate trainees. In recent years his research work focused on ketogenic diet and cannabinoids as therapeutical approaches for treatments of epilepsy. In addition to his scientific work, Mac was heavily engaged with patient organizations, patient advocacy groups and he strived to find improved treatment for patients suffering from epilepsy. Some of this work was done in his capacity as president of Epilepsy Canada (2011-2013) and Epilepsy Ontario (1995-1998, 2000-2009).

Mac received many honours and awards during his career, including The Queen's Golden Jubilee Medal Government of Canada (2002), the Honorary Pioneer Award from Epilepsy Canada (2004) and the Ontario Volunteer Service Award Government of Ontario (2005). As a dedicated educator, he was also recipient of the Sustained Excellence and Innovation in Life Sciences Education from the Faculty of Medicine of University of Toronto (2021).

Mac passed away on Tuesday February 20th, 2024. He is remembered as a kind and generous colleague and friend as well as an exceptional educator and mentor to his colleagues, trainees and students.

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