Your Name

Instructor Name

Course Number

Date

Review Article on “Sodium Calcium Exchanger”

**Introduction**

 The sodium-calcium exchanger is recognized as an important form of protein that plays a vital role in the overall body functioning. The practical idea of the sodium-calcium exchanger is defined as an antiporter membrane protein that is considered to successfully eliminate the element of calcium from cells. It is worthy to mention that the stored energy in the form of electrochemical incline of sodium ensures the proper functioning of this form of protein. The approach of sodium-calcium exchanger also identified with the denotation of Na+/Ca2+ exchanger,exchange protein, or the facet of NCX. The primary function of this protein is established as its role in removing calcium from body cells. There is extensive former research work that is conducted to examine the accurate functioning of the protein of sodium-calcium exchanger. A detailed review of these related research studies is a vital step to better apprehend the actual operations of the sodium-calcium exchanger as a protein. This review article focuses to critically examine different functional dimensions of sodium-calcium exchanger by considering relevant research studies on the topic.

**Discussion**

 The feature of the sodium-calcium exchanger established its position as the protein comprised of the domain of the antiporter membrane.

*Ion-exchange mechanism of sodium calcium exchanger*

 It is necessary to consider that sodium-calcium exchangers play a vital role in the human body. They function as a membrane transporter to maintain a specific level of homeostasis of cytosolic in the human body. Jun Liao et al. (2012) made a study to examine the functional features of Na+ /Ca2+ exchanger. According to Liao, sodium-calcium exchanger has the potential to exchange both Na+ and Ca2+ with a high turnover rate. The exchanger reaction of sodium-calcium exchanger is bidirectional, while the entire process of ion-exchange is electro-genic. Liao et al. determined that the sodium calcium exchanger reaction is based on the chemical gradient of both calcium and sodium ions. Dysfunctions of sodium-calcium exchanger are associated with post ischemic brain damage, arrhythmia, or cardiac hypertrophy as it plays essential roles in homeostasis of calcium ion. Results of Liao et al. concluded that a highly active sodium-calcium exchanger is yielded by the removal of the intracellular regulatory domain. It indicates that the functional unit for ion transport is constituted in a trans-membrane portion of sodium-calcium exchanger. In addition to this, Chin et al. (1993) illustrated in their study that two highly conserved homologous sequence motifs are included in a sodium-calcium exchanger. These motifs are vital in the process of ion bonding and translocation in the human body. The generation of the structural model of inward-facing conformation is only possible with the help of NCX\_Mj structural and functional features. Chin et al. suggested that inward-facing model should maintain equable ion accessibility and symmetry due to bidirectional ion exchange and symmetry of NCX\_Mj.

*Sodium Calcium Exchange and Contraction of the Heart*

 Michela Ottolia, Natalia Torres, John H. B. Bridge, Kenneth D. Philipson, and Joshua I. Goldhaber in their study examined the significance of sodium calcium exchanger in the contraction of the heart. Ottolia et al. illustrated that sodium-calcium exchanger has a vast impact on contractility as is the dominant Ca efflux mechanism. Ottolia et al. made extensive research in order to understand the influence of sodium-calcium exchanger (NCX) on the heart’s contractility. With the help of various pathophysiological and physiological conditions, the researchers tried to examine NCX influence. In order to understand this issue, there is a need to evaluate the relationship of excitation contraction coupling with the sodium-calcium structure. In this regard, Ottolia et al. consider the cardiac isoform of sodium-calcium exchanger (NCX). A critical examination of NCX indicates that it is a plasma membrane protein that has a critical function of binding and transporting both calcium and sodium across the plasma membrane. The authors have illustrated that NCX is regulated allosterically with the help of intracellular calcium rather than only moving calcium across the sarcolemma membrane. However, it is unclear whether or not sodium calcium exchanger accumulates as dimers in the plasma membrane. Ottolia et al. in his immunolocalization study identified that the entire surface of the membrane is comprised of a number of sodium calcium exchangers.

It is also be found on the t-tubules or transverse tubular sarcolemma due to its higher density within the t-tubules. In accordance with the results of Ottolia et al., electrogenic transportation occurs as 3 sodium ions are transported for each calcium ion during NCX transport. While NCX has the ability to operate in a bidirectional fashion it includes forward and backward modes. In exchange for sodium influx, the exchanger expels out calcium from myocyte in the forward mode. On the other side, sodium is extruded in the reverse mode. Giladi et al. tried to figure out the relationship between sodium and calcium. The authors found that sodium and calcium gradients are more likely to influence the mode of NCX operation across the cell membrane. In accordance with the findings of Giladi et al., calcium removal function is applicable in the forward mode of NCX. The removal function of calcium voltages is less as compared to the equilibrium potential. It has been observed by Giladi et al. that through L-type calcium channels (LCCs) the calcium enters the cell during the cardiac contraction relaxation cycle. Ryanodine receptors are then triggered by this calcium in order to allow that calcium to release into the cytoplasm from the sarcoplasmic reticulum (SR). In addition to this, the results of Ottolia et al. indicated that contractile force is generated when calcium releases into the cytoplasm. The gain of excitation contraction (EC) coupling refers to the relationship between calcium current generation and release flux of SR calcium. Giladi et al. also suggested that SR Ca release is unlikely to correlate with changes in the gain of excitation-contraction. It is demonstrated by the researchers that changes in gain merely reflect about the alterations in the efficiency of calcium current at activating the release of SR Ca. The removal of Ca from the cytoplasm results in myocyte relaxation.

 It has been observed that dysfunction characteristics of systolic heart failure are associated with the SR Ca depletion, which is a consequence of depressed SR Ca ATPase (SERCA) function (Weber et al., 2003). According to Weber et al., SR Ca stores and contractility in heart failure, which results in increased expression of NCX. According to Ottolia et al., the accumulation of Ca in the SR does not require the actual Ca influx via NCX. Due to this particular reason, it can be assumed that the burden of Ca removal is shifted to SERCA as the thermodynamic drive for Ca efflux through NCX reduces. A number of studies suggest that the inotropic effect of digoxin is possible through NCX. However, these studies only rely on the non-selective NCX blockers (Giladi et al.). Inconsistent experimental results are generated due to the poor selectivity of NCX blockers. Giladi et al. tried to prove the effectiveness of NCX in the inotropic effect of digoxin by using an NCX knockout (KO) mouse. The researchers concluded that “global knock-out of NCX (NCX−/−) is embryonic lethal”. Still, it is possible to load these heart tubes with Ca indicator fura-2. For this particular purpose, Ottolia et al. loaded heart tubes with Ca indicator fura-2, which indicates normal regional contraction by Ca transients despite a poorly developed SR. Calcium transients in wild type heart tubes are increased due to the application of cardiac glycoside ouabain that ultimately results in Ca overload.



Figure: Effects of ouabain on Ca transients in embryonic heart tubes isolated from wild type and NCX−/− mice

 Ottolia et al. effectively demonstrated that “NCX is highly necessary for the effect of ouabain on Calcium transients. In addition to this, Giladi et al. also concluded that the action of cardiac glycosides requires sodium calcium exchanger. In accordance with the findings of Giladi et al., Ottolia et al., also indicated that SR Ca load can be easily influenced by NCX and it has a tendency to impact the efficiency of EC coupling.

# *Role sodium-calcium exchanger in the digestive system*

Liao et al (2019) stated that the sodium-calcium exchanger is considered as the NCX family, which is a protein family. The reason for this consideration is that, human cardio and nervous system functioning in pathological and physiological processes. NCX plays a vital role in the human body which is being functioned with the help of body organs and mechanisms. Each organ and mechanism play a vital role in the proper functioning of the body. Cellular signals are also major functions happening inside bodies. One of the important cellular signals in the human body is Ca2+, while this controls various dysfunction and abnormal regulations leading to diseases (Liao et al.). The human digestive system is considered to be an important function for a reason that it helps to break nutrients from the food, which humans consume into micro parts, so that the body absorbs them and utilizes energy for cell repairing, body growth, and functioning. According to Liao et al, in the human digestive system, the functioning of NCX has got attention for the purpose that it is always active in the process of healing injuries in gastric mucosal and gastric ulcers. Furthermore, it is also stated by Liao et al that the NCX family helps to control the increase in acute pancreatitis, digestive cancer, and absorptions in the intestine. Liao et al, in their article, mentioned the importance of NCX for the esophagus, pancreas, and intestine.

## *NCX and esophagus*

In the article by Liao et al. it is stated that, there is a special muscular portion in the digestive tracts which is called the esophagus. Transportation of food is carried out through pharynx to stomach with the help of Esophagus and transportation depends on the muscular contractions. NCX is vital for muscular relaxation and contractions in lower esophageal smooth muscle and this depends on the concentrations of Ca2+. According to the clinical studies by Liao et al. they have presented that smoking may result in enhanced functioning of the NCX family by allowing Ca2+ to enter and it also results in the pathogenesis of esophageal squamous cell carcinoma.

## *NCX and pancreas*

Liao et al stated that pancreatitis is the main cause which develops abdominal problems, and higher levels of Ca2+ leads to hyperkalemia and pancreatic cancer. NCX plays the role of arbitrator in pancreatic cancer and this is possible when NCX starts mediating the higher levels of cytoplasmic Ca2+. The role of NCX is considered to be responsible for the efflux of Ca2+ from human cells.

# *Sodium-calcium exchanger: influence of metabolic regulation on ion carrier interactions*

The major role of the sodium-calcium exchanger is to excrete Ca2+ concentrations from cells whether they are human or animal cells (Dipolo and Beaugé). This article by Diplo and Beague (2006) stated the role and distribution of sodium-calcium exchanger in human and animal cells and tissues. Diplo and Beague discussed the inter-linkages and relationships that resulted due to sodium-calcium exchange. Inter-linkages and relationships are created between ions and metabolic modulations. Diplo and Beague furthermore emphasized the modulations, which only take place at special sites in proteins and they are located at extra- intra-, and transmembrane domains of the proteins. Higher concentrations of Ca2+ from a cell can be removed with the help of two methods that include sodium-calcium exchange and Ca-pump. Furthermore, Diplo and Beague stated in their article that, sodium-calcium does not require any external functions, however, the importance of phosphoarginine is dramatically noticed. In this article, Diplo and Beague also concluded in their article that the regulations of phosphoarginine are important for the active sodium-calcium exchange.

# *Sodium-calcium exchange: its physiological implications*

Sodium-calcium exchange is considered as a reversible transporter that is held responsible for the mediation of Ca2+ entry in parallel of different ions in the cells (Blaustein and Lederer). Article by Blaustein and Lederer (1999), mainly studied the mammals, while most of the NCX has been found in the frog, squid, lobster, and Drosophila. There are a number of NCX variants being identified that are responsible for the leveling of functional differences. When Na+ concentrations are increased they also increase Ca2+ concentrations. While a sodium-calcium exchange mediates these higher concentrations in Ca2+. Blaustein and Lederer stated about the role of calcium that is it more suitable for the signaling of functions in the body cells of both humans and animals. The main critical feature in the cytosol is the slow diffusion of Ca2+, while cytosol is considered to be an aqueous component in the cytoplasm. Various organelles and particles are supposed to be suspended within the cytoplasm of the cell. Blaustein and Lederer in their article described the importance and features of sodium-carbon exchange. They stated that to extrude higher levels of Ca2+, a maximum turnover rate of the sodium-carbon exchanger is important and it does not influence negatively on the mammalian cells.

# *Role of sodium-carbon exchange in excitation-contraction coupling*

Blaustein and Lederer also studied the role of sodium-carbon exchange in excitation-contraction coupling. Sodium-carbon exchange influences higher amounts of Ca2+ in myocytes and it may enter Ca2+ into cells under several conditions. As stated by Blaustein and Lederer, sodium-carbon is responsible for indirect control over the stores of Ca2+. It is responsible for the purpose that it has a dominancy during the extrusion mechanism of Ca2+, however, it can be visually observed that sodium-carbon exchange also transports Ca2+ from the cell to outside.

# *Role of sodium-carbon exchange in vascular smooth muscle*

According to Blaustein and Lederer, the direct function of sodium-calcium exchange in vascular smooth was originally presented 25 years ago. It was also studied that the direct function of the sodium-carbon exchanger is to modulate the smooth muscles and it also influences the signaling and tension growth of Ca2+. The reason for the influence is that sodium-carbon exchange is the source through which the Na+ pump is inhibited in the driving of Ca2+into cells. Blaustein and Lederer further mentioned that the précised roles of sodium-carbon exchanger in vascular smooth muscle are not that much studied to deduce a major role in vascular smooth muscle.

*Sodium Calcium Exchanger and Airway Smooth Muscle*

 It is highly necessary to consider the significance of the airway smooth muscle (ASM) in the human body. It is an extensive constituent of the respiratory system and its muscular behavior is more likely to influence respiratory physiology. Ricardo Espinosa-Tanguma, Paola Algara-Suárez, Rebeca Mejía-Elizondo and Víctor Saavedra-Alanís made explicit research in order to determine the importance of sodium-calcium exchanger in ASM. According to Espinosa-Tanguma et al., the contractility of ASM is associated with the concentration of calcium ion in NCX. Sensitization and concentration of calcium ion determine the contractility of ASM. Calcium ion plays a vital role in ASM due to its cytosolic calcium ion concentration. Espinosa-Tanguma et al. demonstrated that the contractility, phenotype, and proliferation of ASM are regulated by cytosolic calcium ion concentration. Due to this particular reason, it can be illustrated that the alterations in ASM calcium homeostasis are linked with the pathologies, such as, asthma. Espinosa-Tanguma et al. suggested that ASM cell interacts with lymphocytes, epithelium, and nerve terminals. Hence, with the suggestion of Espinosa-Tanguma et al., it is safe to say that the modification in ASM calcium ion homeostasis is associated with asthma and chronic obstructive pulmonary disease. The sensitization of Ca ion and elevation in cytosolic Ca ion induce ASM contraction. Marinelli et al. (2014) indicated that phosphorylation and De-phosphorylation are two key events during the smooth muscle contraction. The type 1 myosin phosphatase (MLCP) and calcium ion catalyze these reactions.

Marinelli et al. concluded that relaxation or contraction of smooth muscle occurred by the balance of the activity of MLCP and calcium ion. These findings by Marinelli et al. indicate that the relaxation of airways smooth muscles is associated with de-phosphorylation, while non-linear and variable relationships occurred by the coupling between force and phosphorylation. Espinosa-Tanguma et al. illustrated that contraction and remodeling of smooth muscle cells are also possible by calcium ion, as it is a vital messenger in this regard. Espinosa-Tanguma et al. also concluded that the concentration of calcium ion in smooth muscle cell varies from human to human. Normally, it ranges from 100 to 200nM. It is notable to mention that the concentration of intracellular calcium ion is mainly possible with the help of NCX. Espinosa-Tanguma et al. suggested that the calcium ion and sodium ion transmembrane ionic gradient are responsible for the direction of sodium ion in exchange for calcium ion. Likewise, Marinelli et al. also concluded that membrane potential is also responsible for the direction of Na+ in exchange for Ca2+. According to the findings of Marinelli et al., it is evident that NCX transport a huge amount of calcium ion in certain pathological conditions such as cardiac arrhythmia, ischemia reperfusion injury, and hypertension. In order to diminish high blood pressure, the blockers of the reverse mode of sodium calcium exchangers are highly effective. Marinelli et al. demonstrated that these blockers are also effective to reduce the tissue damage and to abolish cardiac arrhythmias. Impressive results of NCX blockers ensure their viability in the therapeutic management of various respiratory diseases.

**Conclusion**

 To conclude the above discussion about the roles and functions of sodium calcium exchangers, it is observed that NCX plays a vital role in controlling and modifying contractility in the cardiac myocyte. A critical examination indicates that SR Ca load is influenced by NCX. The efficiency of EC coupling is impacted by NCX due to the depletion of calcium from the dyadic cleft. Furthermore, a highly active sodium calcium exchanger is generated by the elimination of intracellular directing dominion, which indicates that the functional unit for ion transport is founded in a trans-membrane portion of NCX. In addition to this, during NCX transport, it has the ability to operate in a bidirectional fashion. Increased expression of NCX is associated with the SR Ca stores and contractility in heart failure.

**Works Cited**

Blaustein, Mordecai P., and W. Jonathan Lederer. “Sodium/Calcium Exchange: Its Physiological Implications.” Physiological Reviews, vol. 79, no. 3, July 1999, pp. 763–854. physiology.org (Atypon), doi:10.1152/physrev.1999.79.3.763.

Chin, T. K., et al. "The effect of exchanger inhibitory peptide (XIP) on sodium-calcium exchange current in guinea pig ventricular cells." *Circulation research* 72.3 (1993): 497-503.

Dipolo, Reinaldo, and Luis Beaugé. “Sodium/Calcium Exchanger: Influence of Metabolic Regulation on Ion Carrier Interactions.” Physiological Reviews, vol. 86, no. 1, 2006, pp. 155–203.

Espinosa-Tanguma, Ricardo, et al. "The Role of Sodium-Calcium Exchanger in the Calcium Homeostasis of Airway Smooth Muscle." *Current Basic and Pathological Approaches to the Function of Muscle Cells and Tissues-From Molecules to Humans*. IntechOpen, 2012.

Giladi, Moshe, et al. "Dynamic distinctions in the Na+/Ca2+ exchanger adopting the inward-and outward-facing conformational states." *Journal of Biological Chemistry* 292.29 (2017): 12311-12323.

Liao, Jun, et al. "Structural insight into the ion-exchange mechanism of the sodium/calcium exchanger." *Science* 335.6069 (2012): 686-690.

Liao, Qiu-Shi, et al. “Roles of Na+/Ca2+ Exchanger 1 in Digestive System Physiology and Pathophysiology.” World Journal of Gastroenterology, vol. 25, no. 3, Jan. 2019, pp. 287–99. www.wjgnet.com, doi:10.3748/wjg.v25.i3.287.

Marinelli, Fabrizio, et al. "Sodium recognition by the Na+/Ca2+ exchanger in the outward-facing conformation." *Proceedings of the National Academy of Sciences* 111.50 (2014): E5354-E5362.

Ottolia, Michela, et al. "Na/Ca exchange and contraction of the heart." *Journal of molecular and cellular cardiology* 61 (2013): 28-33.

Weber, Christopher R., et al. "Dynamic regulation of sodium/calcium exchange function in human heart failure." *Circulation* 108.18 (2003): 2224-2229.