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Advanced Therapeutic Strategies for Antimalarial and Antibacterial Drug Development through Lactate and Nitrite Transport

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Abstract

Malaria remains a foremost health problem following the emergence and spread of plasmodium falciparum and that is resistance to most of antimalarial drugs. The biochemical and physiological integrity of parasites and intra-cellular erythrocytes is depending on efflux of lactic acid. Lactate comes into erythrocytes by free diffusion of the undissociated acid, transport on specific H+ monocarboxylate transporter and exchange with other ions. L-lactate transport is transported by monocarboxylate transporter (MCT) and plasmodium falciparum formate nitrite transporter (PfFNT), which is novel target for antimalarial drugs. On the other hand, cytoplasmic nitrate reduction carried out export of nitrite, re-import of nitrite to facilitate reduction into ammonia. NADH-dependent nitrite reductase (NirBD) and cytochrome c nitrite reductase (NrfA) both promote conversion of nitrite to ammonia in cytoplasm and periplasm respectively. Encounter of Nitrogen reactive species by bacteria is caused by transported nitrite via interacting with Fe-S containing proteins, heme-containing proteins, free thiols, and DNA. Here we briefly review mechanism of lactate transport and nitrate transport, summarize their role as antimalarial and antibacterial development which provide new hopes for global health problems.

Keywords: Lactate transport; Monocarboxylate transporter (MCT); Antimalarial; nitrate; Nitrite transport; Antibacterial

Introduction

Malaria is a mosquito-borne infectious disease of human caused by protist Plasmodium known as malarial parasite belongs to phylum Apicomplexa [1]. It is widespread in tropical and subtropical regions, including much of sub-Saharan Africa, but also in Southeast Asia and South America becoming global health problem [2,3]. The multiplication of malarial parasites within red blood cells can supply malarial disease. There are five species of Plasmodium which may cause malaria including Plasmodium falciparum, Plasmodium vivax, Plasmodiu ovale, Plasmodium malariae, and Plasmodium knowlesi. There is a one more species that cause malarial disease is Plasmodium wallikeri. Plasmodium vivax is the most prevalent species and Plasmodium falciparum is the most virulent species [4]. The life cycle of the malarial parasite (Plasmodium) is complicated and involves two hosts like humans and female Anopheles mosquito. The disease is transmitted to human when an infected Anopheles mosquito bites a person and injects the malarial parasites (sporozites) into blood. Severe diseases are mostly caused by Plasmodium falciparum, which may lead to coma and death [5]. In human body organs like kidney, liver, red blood cells (erythrocytes), heart and skeletal muscles contains lactate dehydrogenase. Lactate dehydrogenase (LDH) is a hydrogen transfer enzyme belongs to the class of oxidoreductases and it is found in the cytoplasm of most of the cells in the body. LDH enzyme is mainly activate in substrate-binding pocket site [6,7]. Elevated LDH level in kidney, erythrocytes, skeletal muscles, liver and heart can cause myocardial infarction, renal infarction and hemolysis. Lactate dehydrogenase also known as lactic acid dehydrogenase which catalyzes conversion of pyruvate

to lactate with regeneration of NADH to NAD+ [8,9]. Lactate dehydrogenase may also have capability to reversible conversion of lactate to pyruvate through oxidation process with the help of co-enzyme Acetylpyridine dinucleotide (APAD). The catalytic conversion of pyruvate to lactate in presence of Plasmodium falciparum lactate dehydrogenase enzyme (pfLDH), is important to malarial parasite for energy generation based on glycolysis. Hence the Plasmodium falciparum lactate dehydrogenase enzyme is being as a molecular target for antimalarial [10]. P. falciparum lactate dehydrogenase (PfLDH) is essential for the anaerobic lifestyle of Plasmodium and a possible drug target. As above mentioned, the parasite cause malaria, like that bacteria cause various bacterial diseases. Microorganism including bacteria, yeast, moulds and viruses can infect to human which are available in the environment. Because of the rapid growth of bacterial infection and high resistance to antibiotic by microorganism there is need to develop new drug treatment for various bacterial diseases. The formate-nitrite transporter members play key role in antibacterial development. Formate, nitrite and hydrosulphide are monovalent anions that is metabolite of bacterial respiration within anaerobic mixed-acid fermentation. The metabolite like formate ($HCOO^-$) and nitrite ($NO2^-$) are released in the absence of oxygen. The FNT members are found in bacteria, archaea, fungi and protists. The pathogenic parasites and fungi like Toxoplasma gondii, Candid. albicans, Aspergillus fumigatus and Aspergillus flavus may consist of FNT members. In malaria Plasmodium falciparum formate-nitrite transporter (PfFNT) can able to transport lactate that is necessary to parasite. The main focus of this article in on the structural characteristic and mechanism of LDH, lactate transport, role of lactate transport for antimalarial development, whereas structure and mechanism of FNT, nitrate and nitrite transport for antibacterial development.

Structural Characteristic Lactate Dehydrogenase (LDH)

LDH is consist of tetrameric isoenzymes that contains two different types of subunits [11-14]. Heart contain Subunit-H and Muscle contain Subunit-M, these both are two different types of subunit which can form tetramer [15-23]. The 5 tetrameric isoenzyme expressed as LDH-1 to LDH-5 and structure of each isoenzymes are different in different tissues. LDH-1 mainly consists of four heart subunit (4-H) and found in heart, erythrocytes, renal tissue as well as in the brain. LDH-2 subunit found in reticuloendothelial system and contains 3 heart and 1 muscle subunit (3H1M). LDH-3 subunit has two heart and two muscle subunits (2H2M) which are located in lungs. Isozyme LDH-4 predominate in kidney consist of one heart and three muscle subunits (1H3M) and also present in placenta and pancreas. Last isoenzyme LDH-5 having four muscle subunits (4M) which are found in liver, skeletal muscle and hepatocytes (Figure 1).

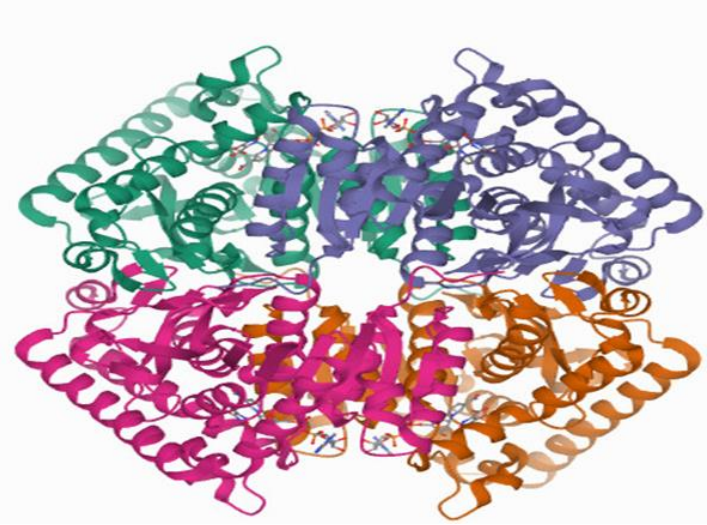

Figure 1: *Structure of lactate dehydrogenase (LDH).*

Mechanism of LDH

When parasite level increased in red blood cell, then it is known as blood stage parasites which is actively produce glucose as a primary source of energy and metabolic steps involved in the conversion of glucose to lactate and pyruvate under anaerobic and aerobic conditions respectively via glycolysis process. Energy production, intracellular pH and osmotic stability required by parasite is managed by lactate transport and glucose uptake. Lactate dehydrogenase is tetrameric enzyme which is responsible for the anaerobic conversion of NADH to NAD+ (Figure 2).

The General reaction carried out by LDH is as follows:

Pyruvate + NADH + H+ → Lactate + NAD+

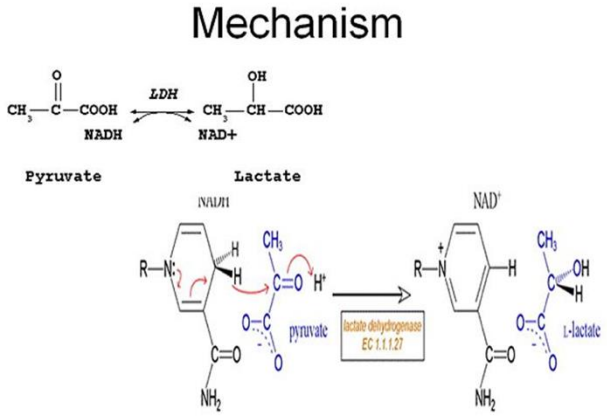

Figure 2: *Mechanism of LDH: from Jasper lactate final, Proteopedia, life in 3D.*

In first step NADH mainly interacts with enzyme in the presence of LDH leads to formation of LDH-NAD+-lactate and LDH-NADH-pyruvate complexes. Therefore, NAD+ regenerated after

detachment of pyruvate from enzyme. The rate limiting step in this reaction is the rate of dissociation of NADH. Released NAD+ by anaerobic respiration of P. falciparum is an important electron acceptor in glycolysis. In the aerobic condition, NAD+ produced through glycolysis, the citric acid cycle, and the electron transport chain. The glucose is metabolized into CO2 and H2O to get greater amount of adenosine triphosphate (ATP). Production of ATP is essential for anabolic and homeostatic processes. On the other hand, in anaerobic condition pyruvate fermentation process occurred for regenaration of NAD+. This process is followed by removal of electron from NADH to release NAD+. Thus pyruvate converted to lactate with regenartion of NAD+ from NADH and this process helpful for survival of malarial parasite [24-26]. Direct shifting of hydride ion from donor carbon of the cofactor NADH to substrate carbon of acceptor pyruvate is responsible for lactate production through H+ symport mechanism. Lactate dehydrogenase also able to carried out reversible conversion of lactate to pyruvate via oxidation reaction process. The reverse reaction is essential for body to utilize the remaining energy present in the lactate. In a condition where oxygen supply is in a smaller amount, the enzyme LDH provide an oxygen to manage homeostasis. Also LDH having significant role in cellular respiration and this enzyme regulated by substrate. PfLDH plays significant role in energy production via glycolysis. Biochemical functioning, growth, and development of plasmodium falciparum mainly depends upon this enzyme that may supply energy to it. Inhibitions of PfLDH enzyme resulting into parasites death. Therefore, this enzyme need to be target for antimalarial development.

Lactate transport

The biochemical and physiological integrity is depending on efflux of lactic acid. Intracellular parasite as well as host erythrocytes contain lactate. Intracellular parasite encapsulated in vacuole in which lactate get entered and then export to erythrocyte cytosol by leaving this vacuole. Lactic acid interaction with lactate anion and proton to promote metabolism of glucose in plasmodia and transports out of the cytoplasm. This process essential in managing parasite's energy flux and pH homeostasis [27-29]. The lactate transported plasma membrane of cell includes, hepatocyte, skeletal muscles, cardiac myocytes, blood brain barrier, pancreatic cell and tumour cell [30-35]. The protein transporter which promote efflux of lactate that present in intraerythrocyte malarial parasite is plasmodium falciparum formate nitrite transporter (PfFNT). Plasmodial lactate transporter, PfFNT comes under microbial formate nitrite transporter (FNT) family and FNT is structurally not related to monocarboxylate that transport lactate. But as like lactate transport, FNT also able to transport other monocarboxylate. PfFNT having a high capacity to symport lactate/proton. L-lactate that is the end product of glycolysis process which is carried across plasma membrane. Parasite growth increases when malarial parasite infects to red blood cell and propagate rapidly. L-lactate transport is rapid, non-saturating, and insensitive which can be transported by monocarboxylate transporter (MCT) also that is located at parasite surface. Lactate comes into erythrocytes by three ways including a free diffusion of the undissociated acid, transport on specific H+ monocarboxylate transporter and exchange with other ion. Monocarboxylate transporters (MCTs) play significant role as a carrier of monocarboxylate like L-lactate, pyruvate, and the ketone bodies. MCT promote exchange of one carboxylate with other. Both MCT and lactate receptor GPR81 having affinity towards lactate. Lactate is end product of glycolysis process which is transported across plasma membrane via protein linked monocarboxylate belong to family MCT as well as solute carrier (SLC16). There are distinct isoforms of MCT present in brain namely: MCT-1, MCT-2 and MCT-4. MCT-1 is found in vascular endothelial cells, ependymocytes. MCT-2 present in neuron as well as found in liver, kidney and testis, while MCT-4 located at astrocytes. Microglia contain both MCT-1 and MCT-2. There are also some other isoforms are present such as MCT-3, MCT-8 and MCT-10 but MCT-8 and MCT-10 are not linked to protein and not involved in lactate transport. MCT-8 mainly responsible for specific thyroid hormone transport. SLC5 solute carrier family contain sodium-linked monocarboxylate which can also responsible for transport system and to carried out endothelial monocarboxylate transport.

All this isoform of monocarboxylate transporter play essential role to transport lactate are as follows:

MCT 1- Monocarboxylate transporter-1 is protein encoded by SLC16A1 gene. It is proton-linked which influx or efflux lactic acid based on some criteria including the prevailing intracellular and extracellular substrate concentrations and the pH gradient across the plasma membrane. Thus, MCT1 have an ability to transport L-lactate across the plasma membrane.

MCT 2- It is proton coupled monocarboxylate transporter has SLC16A7 gene. This transporter having high-sensitivity to hypoxia, intracellular pH, and, to lactate. It is carried out rapid transport process and promote uptake of lactate which is neccesary respiratory fuel in oxidation.

MCT 3- This is also known as SLC16A8 and located in retinal pigment epithelium and choroid plexus epithelia. This transporter having important function to transport lactate produced through glycolysis to outside of the retina.

MCT 4- It is also proton coupled transporter encoded by SLC16A3. MCT-4 play important role in active transport, export of lactate and metabolism of lactate in skeletal muscle.

The major facilitator superfamily (MFS) having 12 transmembrane helices (TMs) fixed in two six-helix bundles which is attached with long intracellular loop. C and N-termini of MFS are intracellularly situated and this family also contain MCT. TM6 and TM7 attached

by intracellular loop and TM8 that is arginine residue also involved in MFS. The function of TM8 is too binding of carboxylate group of monocarboxylate. MCT-4 show less affinity toward L-lactate but involved in lactate transport. MCT-1 and MCT-2 (SLC16A7) both are significantly responsible for uptake of L-lactate, but MCT-2 show more affinity as compared to MCT-1 (SLC16A1). The L-lactate based on transmembrane proton gradient also transported via SfMCT. Attachment site for proton is important for cotransportation of L-lactate and proton. Positively charged amino acid influence the transport of L-lactate. In the basic medium positive charge is reduced and because of this there are some changes occurred in proton and L-lactate transport process. The bacterial lactate transporter (sfMCT) also transport lactate and it is having higher affinity to lactate than pyruvate and ketone bodies.

Role of lactate transport

Lactate transport is necessary for various reasons. Lactate transport mainly involved efflux or influx of lactic acid that is present in intracellular parasite. Due to that the acid load occurred in cytosol after entry of lactate into it. Because of lactate production ATP generated in plasma membrane of parasite. Malarial parasite may require energy which is generated by glycolysis in the form of ATP, that's why malarial parasite dependent on glycolysis for energy. This lactate transport has another significant part in osmoregulation. Each glucose molecule gives two lactate molecules that regulate constant osmotic pressure in parasite. In the absence of lactate pyruvate produce as a metabolic end product. Inhibitions of lactate and pyruvate results into retention and accumulation of both lactate and pyruvate, thus finally cause cell death. Oxidation-reduction reaction process balanced by lactate transporter. P. falciparum in which single mitochondrion present depends on conversion of pyruvate to lactate and Generation of NAD+ from NADH. So greater amount of glucose produced by glycolysis. Plasma membrane having greater ability to export lactate. Balance between H+ accumulation and H+ removal is important for maintenance of cellular pH homeostasis. Sarcolemma containing transporter may help to this process. Lactate which essential in cellular respiration can transport through sarcolemma membrane. H+/lactate co-transporter having greater ability for removal of H+ as compared to Na+-H+ exchanger or bicarbonate dependent transport. Lactate-H+ cotransport mechanism is medium for transport of lactate. This system is less susceptible to internal pH. More H+ removal occurred when more lactate is produced. On the other hand, when internal pH is less as well as in absence of lactate, the NA+-H+ exchanger system has been worked. Since as like other functions lactate also play role in muscle pH regulation. Acidosis occurred in malaria is mainly caused by Lactate.

Effect of High-Level Lactate in Malaria

As we all know that, the lactate is very important for parasite which needed energy production conjointly show their varied action or impact in protozoal infection. Lactate chiefly show their activity at blood brain barrier (BBB). In tight junction of endothelium of cerebral micro vessels and capillaries BBB is situated. In the first step lactate comes into endothelial cells and spreading at interstitial space after transported by MCT. Thus lactate binding with GPR81 receptor site to control cAMP. Increased lactate influx from blood to brain, whereas effluence of lactate from brain to blood occurred during normal lactate level (43). Inflated lactate level will cause convulsions in cerebral protozoal infection. Stroke, meningitis, neuromyelitis optica yet as brain tumour might be also caused by brain MCT (2). Elevated lactate mainly related to parasitized erythrocyte. Pyruvate and lactate level increased to cause hyperlactatemia, anoxia, hyper metabolism and lactic acidosis (40). Generally, it is less in brain and cerebrospinal fluid. Severe anaemia caused because of deficiency of oxygen in tissue. Throughout this host cell promote metabolic transfer and glucose metabolism (41). Therefore, lactate produced in greater amount by muscle cell, red blood cells, brain and alternative tissues. So, additional lactate accumulate leads to lactic acidosis. Lactic acidosis may cause disruption of acid/base balance (pH) that resulting into muscular weakness, rapid breathing, nausea, vomiting, sweating, and in severe case coma. Due to accumulation of lactate there is conjointly depletion of hepatic and renal clearance of lactic acid (42). Myocardial infarction, renal infarction and haemolysis also caused by elevated lactate level attributable to increased lactate dehydrogenase catalyst in tissue. It was believed that the elevated lactate levels during sepsis is due to inappropriate oxygen supply which increase lactate production.

Antimalarial Development

The molecular target for antimalarial development is PfLDH enzyme and lactate transport process. On the basis of that further process is carried out to develop new drug for treatment of malarial disease. For that mainly the mechanism of transport as well as substrate selectivity must be known. Generally, these are belonging to biochemical and biophysical properties and site of action of targeted molecule is also important. Malarial parasite changes the function of erythrocyte and insert the plasmodial membrane protein into red blood cell membrane. So, transport protein should be selectively targeted (44). The following steps significantly involved in antimalarial development:

A) Inhibition of PfLDH B) Inhibition of PfFNT C) Inhibition of MCT and GPR81 lactate receptor

Inhibition of PfLDH

Lactate dehydrogenase from plasmodium falciparum considered to be important for energy production which is necessary to malarial

parasite. Glucose is main source of energy that is supplied to intraerythrocyte parasite via host and sugar transporters (34). PfLDH may not be directly target for antimalarial. This enzyme having their active site on which residue is present. This is unique binding site for NADH generated with lactate production that is important to new antimalarial by inhibition of PfLDH. Binding with NADH in substrate binding pocket to form complex and substituting the position of that cofactor to become inhibitor for glycolytic enzyme. If considered to act on active site of PfLDH for inhibition of lactate production from pyruvate, resulting into no production of energy. Expected to block the ATP generation by subsequent inhibition of LDH enzyme. ATP production is important for fast replicating intraerythrocyte parasite. The blockage of LDH enzyme by any compound is done by different action. Whenever the ATP production is stopped due to enzyme inhibition leads to blocking of parasite survival. Therefore, lack of energy and ATP supply to malarial parasite there is subsequent parasite death occurred. Breakdown of erythrocytes hemoglobin occurred in food vacuole of malarial parasites to form hematin. Single food vacuole found in plasmodium falciparum and this food vacuole is important active site for drug action. This digestive vacuole is lysosome like organelle in which detoxification of heme also included. Hemazoin produced in the form of globin and pigment from hematin that is degraded products of hemoglobin. This process is essential for parasite survival. Inhibition of hemazoin formation cause production of free radical and inhibition of globin hydrolysis. There is a protonation and ion trapping, active uptake, and binding to specific receptor of food vacuole will included. Hemazoin formation blocked by binding with NADH and competiting with PfLDH to form complexes and due to that the hemazoin polymerization will stopped. Also quite toxicity can get inhibited.

Inhibition of PfFNT

Plasmodium falciparum formate nitrite transporter which act as transporter protein that separate out lactate from malarial parasite. This protein transporter found in parasite surface and food vacuole. Interaction between lactate anion and proton followed by the PfFNT transport mechanism. Affinity of the lactate anion, proton shifting as well as transport of the neutral lactic acid through lipophilic active sites are main step involved in mechanism of PfFNT transporter. PfFNT also carried out the H+ coupled with lactate. So any compound which supposed to inhibit transport of lactate through biological membrane by other transporter may also inhibit lactate transport by PfFNT protein transporter and cause inhibition of H+ coupled with lactate that is H+/lactate transport system. Some conditions expected to involve during inhibition of H+/lactate co-transporter such as glycolysis process may not be continued and not to produce lactate as well as no effect of this transporter system on pH should be necessary. Slight cytosolic acidification may be produced and they prevent electrogenic anion transport [36]. The complete mechanism of PfFNT is not clear but due to inhibition of H+/lactate transporter, lactate and pyruvate transport across parasite plasma membrane get inhibited and lactate accumulate inside the cell. Infected red blood cell and parasite can have swelled. Therefore, resulting into killing of malarial parasite and inhibition of PfFNT is essential target for new antimalarial drug production.

Inhibition of MCT and GPR81 lactate receptor

Inhibition mainly depends on carrier-mediated transport. MCT present in some organ like brain, retina, endothelial cells in the form of their isoforms and GPR81 lactate receptor also found in similar manner. GPR81 receptor is 7-transmembrane, G-protein coupled orphan receptor. This is highly found in fat cells but in kidney, intestine and brain present at low level. Lactate transport mainly balanced into and out of brain by MCT1 and GPR81 receptor which is mostly act in endothelial cells. And also important for pathogenesis of malaria. Highly spreading of lactate from the brain acts on the receptor. So, lack of receptors is mainly resistant to malarial pathogenesis and their growth. Blocking the action of MCT leads to reduced lactate level as well as their transport. When influx of lactic acid in inhibited then its action at endothelial luminal side, on brain parenchyma also stopped by GPR81 receptor. Inhibition of MCT1 consistently effect on transport moment. Thus, intracellular lactate increased but extracellular lactate decreased as well as lactate uptake get reduced [37,38]. Since intracellular lactate is greater as compared to extracellular [39-43].

Structure of Formate-Nitrite Transporter (FNT)

Five FNT protein having crystal structure with three subfamilies like FocA, HSC and NirC. These all structures are identical exhibiting a homopentamer [44,45]. Molecular mechanism of FNT mainly depends upon its three dimensional structure. Tetrameric aquaporin and aquaglyceroporin are a part of FNT structure that belongs to Major Intrinsic Protein (MIP) superfamily. FNT containing hour-glass helical fold that consists of six transmembrane helical such as TM1-TM6. Among these TM2 and TM5 both are located in middle of transmembrane. Ω-loop formed by linking between TM2a and TM2b whereas TM5a and TM5b attached to form S-loop [46,47]. Pseudo two-fold symmetry aligned to plane of membrane containing two halves including the N-terminal (TM1-TM3) and C-terminal (TM4-TM6) halves. Interconnection of five protomer leads to formation of stable pentamer. Cytoplasmic and periplasmic sides responsible for opening of central pore region. Histidine residue also situated at cytoplasmic site while periplasmic site having four residues. The cytoplasmic slit and central constriction site are narrow

constriction region of FNT members and these are made up of hydrophobic residues. The Phe residue between TM2a (Phe-75) and TM5a (Phe-202) both may have combined to produce central constriction site that including S-loop containing His (His-209) and also as TM5 (Ala-212) containing an Ala residue. TM2a (Leu-79) and Ω-loop (Leu-89) having Leu residues, TM4 (Val-175) consists of a Val and remaining one residue is Thr present in Ω-loop (Thr-91) may create another one constriction. Ω-loop containing Thr-91 travel after opening of channel while during this narrow region supposed to be released. As like central constriction, cytoplasmic slit also produced by using Phe residue such as Leu-79 (TM2a), Leu-89 (Ω-loop), Val-175 (TM4) and TM4 (Asn-172) containing Asn.

Mechanism of FNT

Formate-nitrite transporter is membrane protein responsible for transport of monovalent polyatomic substrate anions like formate, nitrite and hydrosulfide [48]. The mechanism for proteins of the FNT family have not been extensively characterized. The anion attaching in the pore is energetically react with protonation of a histidine which is situated centrally. The histidine may protonate an anion. Thus this mechanism responsible for export and import of substrates, with or without proton co-transport. There are three steps expected to be involved in FNT mechanism including: 1) Electrostatic interaction of substrate anion with FNT. 2) Dielectric transfer of substrate acidity and passage of proton resulting into neutralization by decreasing acidity. 3) This neutral substrate anion transfers through lipid soluble constrictions.

Transport Process in Bacteria

Nitrate transport

Nitrate is source of nitrogen that is required by organisms like bacteria, fungi, yeast. In bacteria, there are some enzymes are responsible for nitrate reduction including periplasmic nitrate reductase (NAP) which having active site at cytoplasm. Membrane bound nitrate reductase (NAR) and cytoplasmic assimilatory nitrate reductase (NAS) both also having active site in cytoplasm. Therefore, there is transport process of nitrate do not have other particular mechanism process. Nitrite may transport to cross cytoplasmic membrane when it enters at active site of these enzymes. Active transport of nitrate is important step of nitrate absorption. Nitrate uptake mechanism mainly done by nitrate/proton symporter with the help of two main membrane protein namely NarK and NarU [49-53].

Nitrite transport

Nitrite synthesized by two ways: first one is the reduction of nitrate and another one is oxidation of nitrogen monoxide that is also known as nitric oxide (NO) and export through NirC.

Nitrate (NO_3) → Nitrite (NO_2) (by using catalyst nitrite reductase)

$2NO + O_2$ → $2NO_2$ (via oxidation)

Nitrite is a product of nitrate reduction in the presence of nitrite reductase. Cytoplasmic membrane act as barrier for nitrite passive diffusion. By viewing nitrate is essential, so that for its transport process across the membrane certain transporter must be known. There are three transporters namely NarK, NarU and NirC used for transport of nitrite. Cytoplasmic nitrate reduction carried out export of nitrite, re-import of nitrite to facilitate reduction into ammonia. NarK is less active as compared to NirC. Reduction of nitrate into nitrite mainly characterized by nitrite reductase containing nitrate reductases A and Z that is present in cytoplasm and a periplasmic nitrate reductase. NADH-dependent nitrite reductase (NirBD) and cytochrome c nitrite reductase (NrfA) both promote conversion of nitrite to ammonia in the cytoplasm and periplam respectively. NarK and NarU that facilitate nitrite transport comes under major facilitator superfamily (MFS). NarK further categorized into NarK1 (nitrate/proton symporters) and NarK2 (nitrate/nitrite antiporters). FNT family having remaining transporter protein that is NirC which carried out passive transport of nitrite. NirC is important for uptake of anion via proton symport, also essential in export and import of nitrite. Decomposition occurred with production of ammonia or ammonium compounds especially by the action of bacteria like E. coli and this process is done by imported nitrite.

Antibacterial Development

Antibacterial will need to be developed to reduce resistance of microorganisms to drug and apply for treatment purpose. New drug development essentially based on FNT mechanism, transport process of nitrite. Bacterial metabolism may have done with the help of FNT members by transporting formate, nitrite and hydrosulfide. Generally, NirC is carried out the transport of nitrite that mainly related to virulence factor and function of NirC is to permit pathogens to enter into macrophage containing food vacuole. Intracellular bacteria stop the production of nitric oxide by converting nitrite into ammonia and nitrite uptake is done. Therefore, due to blockage of nitric oxide formation there is antimicrobial activity will have produced. NirC is expected to be important target for new antimicrobial production because it is having significant role in pathogenesis of bacteria and it is not found in mammals. Growth of bacteria are going to be inhibited to produce antibacterial that is carried out by sodium nitrite that play against some bacteria like Pseudomonas aeruginosa and this inhibition process was conducted under aerobic as well as anaerobic conditions. Encounter of Nitrogen reactive species by bacteria is caused by nitrite via interacting with Fe-S-containing proteins, heme-containing proteins, free thiols, and DNA. On the basis of NO production and NO-independent mechanisms this

process can worked out. Nitrite may prevent oxygen uptake in bacteria, thus NO independent is stopped. Bacterial respiration is important for aminoglycoside whereas bonding between nitrite and aminoglycoside is essential for potential antimicrobial action of nitrite [54,55]. Antimicrobial activity occurred due to production of NO, deactivation of protein and inhibition of bacterial respiration. Nitrite that inhibit growth of bacteria in absence of oxygen that may also produce energy [56]. Nitric oxide (NO) which oxidized to form nitrite helpful in cure of infection caused by bacteria. Antimicrobial activity of NO will be conducted by facilitation of growth, immune cell function and killing of bacteria via interacting with DNA, lipid and proteins. Immunoregulatory and antimicrobial activity essential for treatment of disease and these characteristics are present in NO. NO play role in production of antimicrobial by generating reactive nitrogen and oxygen substrates via reacting with oxygen and superoxide. These reactive nitrogen and oxygen species may cause changes in DNA to prevent enzyme function. Thus, resulting into antimicrobial action of NO. Antimicrobial activity or property of nitric oxide also highly depends on chemical modification of DNA [57].

Conclusion

In conclusion, overlooking on the aim of this article to seek out particular targeted molecule for development of new drug. Lactate mainly influence the malarial parasite by its transportation. Lactate transport may act as significant support to parasite that may be dependent on it. Specific protein component belong to FNT family and other transporters are taking important part in lactate transport and these transporters are namely Plasmodium falciparum formate nitrite transporter, monocarboxylate transporter. For transport of lactate there is primarily production of lactate from pyruvate is vital and during this step LDH enzyme taking significant role. Lactate produced with generation of ATP and energy production that is much important and this produced lactate may have transported to play role in maintenance of homeostasis, osmoregulation and also in regulation of redox reaction. As like targeted active site where drug will be going to act, also specific molecule will be targeted that can liable for increasing disease condition. Another one is nitrate and nitrite transport also administered on the basis of particular transporter process and protein molecule such as NarK and NarU for nitrate transport and NirC for nitrite transport. Nitrite transporter protein involving both export and import of nitrite.

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Conflict of Interest

Author do not have any conflict of interest to declare.

References

1. Wirth JD, Boucher JI, Jacobowitz JR, Classen S, Theobald DL. Functional and structural resilience of the active site loop in the evolution of plasmodium lactate dehydrogenase. Biochemistry. 2018; 57: 6434-6442.
2. Mariga ST, Kolko M, Gjedde A, Bergersen LH. Lactate transport and receptor actions in cerebral malaria. Front Neurosci. 2014; 8: 125.
3. Gbotosho GO, Happi CT, Folarin O, Keyamo O, Sowunmi A, Oduola AJ. Rapid detection of lactate dehydrogenase and genotyping of plasmodium falciparum in saliva of children with acute uncomplicated malaria. Am J Trop Med Hyg. 2010; 83: 496-501.
4. Menkin-Smith L, Winders WT. Malaria (Plasmodium Vivax). StarPearls publishing, Treasure Island (FL); 2020.
5. Penna-Coutinho J, Cortopassi WA, Oliveira AA, França TC, Krettli AU. Antimalarial activity of potential inhibitors of plasmodium falciparum lactate dehydrogenase enzyme selected by docking studies. PLoS ONE. 2011; 6.
6. Farhana A, Lappin SL. Biochemistry, lactate dehydrogenase (LDH). StarPearls publishing, Treasure Island (FL). 2020.
7. Ahed JA, Nawaf AMA. Lactate Dehydrogenase: Physiological roles and cli implications. Am J Biomed Sci Res. 2019; 3: 415-416.
8. Abdul A, Hussein S, Ali ZQ, Noree ZM. Lactate dehydrogenase as an indicator of liver, muscular and cancer diseases. J Coastal Life Medicine. 2015; 3: 543-546.
9. Garba IH, Ubom GA. Total serum lactate dehydrogenase activity in acute Plasmodium falciparummalaria infection. Singapore Med J. 2005; 46: 632-634.
10. Nwazue NR. Dehydrogenases in health and disease. Intech Open; 2012.
11. Papadopoulos NM. Clinical applications of lactate dehydrogenase isoenzymes. Ann Clin Lab Sci. 1977; 7: 506-510.
12. Rabiu S, Umar RA, Hassan SW, Umaru MA. Characterization and inhibition studies of lactate dehydrogenase isolated from chicken muscles by aqueous and ethanolic leaves extracts of allium sativum and Gossypium arboretum. Int J Chem Tech Res. 2013; 5: 322-341.
13. Pineda JRE, Callender R, Schwartz SD. Ligand binding and protein dynamics in lactate dehydrogenase. Biophys J. 2007; 93: 1474-1483.
14. Bittar PG, Charnay Y, Pellerin L, Bouras C, Magistretti PJ. Selective distribution of lactate dehydrogenase isoenzymes in neurons and astrocytes of human brain. Cereb Blood Flow Metab. 1996; 16: 1079-1089.
15. Alam A, Neyaz MK, Ikramul Hasan S. Treat Exploiting unique structural and functional properties of malarial glycolytic enzymes for antimalarial drug development. Malar Res. 2014.
16. Hapuarachchi SV, Cobbold SA, Shafik SH, Dennis ASM, McConville MJ, Martin RE, et al. The malaria parasite's lactate transporter PfFNT is the target of antiplasmodial compounds identified in whole cell phenotypic screens. PLoS Pathog. 2017; 13.
17. Wiwanitkit V. Plasmodium and host lactate dehydrogenase molecular function and biological pathways: implication for antimalarial drug discovery. Chem Biol Drug Des. 2007; 69: 280-283.
18. Parra-Bonilla G, Alvarez DF, Al-Mehdi A, Alexeyev M, Stevens T. Critical role for lactate dehydrogenase A in aerobic glycolysis that

sustains pulmonary microvascular endothelial cell proliferation. Am J Physiol Lung Cell Mol Physiol. 2010; 29: 513-522.

19. Singh R, Bhardwaj V, Purohit R. Identification of a novel binding mechanism of Quinoline based molecules with lactate dehydrogenase of Plasmodium falciparum. J Biomol Struct Dyn. 2020; 1-9.
20. Holm-Bertelsen J, Bock S, Helmstetter F, Beitz E. High-level cell-free production of the malarial lactate transporter PfFNT as a basis for crystallization trials and directional transport studies. Protein Expression and Purification. 2016; 126: 109-114.
21. Kanaani J, Ginsburg H. Transport of lactate in Plasmodium falciparum -infected human erythrocytes. J Cellular Physiology. 1991; 149: 469-476.
22. Halestrap AP. The Monocarboxylate Transporter Family—Structure and Functional. IUBMB Life. 2012; 64: 1-9.
23. Adams MJ, McPherson A, Rossmann MG, Schevitz RW, Smiley IE, Wonacott AJ. Structure and Mechanism of Lactate Dehydrogenase. Pyridine Nucleotide-Dependent Dehydrogenases. 1970; 157-174.
24. Jialal I, Sokoll LJ. Clinical utility of lactate dehydrogenase: A historical perspective. Am J Clin Pathol. 2015; 143: 158-159.
25. Akagawa M, Minematsu K, Shibata T, Kondo T, Ishii T, Uchida K. Identification of lactate dehydrogenase as a mammalian pyrroloquinoline quinone (PQQ)-binding protein. Sci Rep. 2016; 6.
26. Cameron A, Read J, Tranter R, Winter VJ, Sessions RB, Brady RL, et al. Identification and activity of a series of azole-based compounds with lactate dehydrogenase-directed anti-malarial activity. The J Biological Chemistry. 2004; 279: 31429-31439.
27. Bosshart PD, Kalbermatter D, Bonetti S, Fotiadis D. Mechanistic basis of L-lactate transport in the SLC16 solute carrier family. Nat Commun. 2019; 10.
28. Kirk K. Membrane transport in the malaria-infected erythrocyte. Physiol Rev. 2001; 81: 495-537.
29. Golldack A, Henke B, Bergmann B, Wiechert M, Erler H, Soares AB, et al. Substrate-analogous inhibitors exert antimalarial action by targeting the Plasmodium lactate transporter PfFNT at nanomolar scale. PLoS Pathog. 2017; 13.
30. Elliott JL, Saliba KJ, Kirk K. Transport of lactate and pyruvate in the intraerythrocytic malaria parasite, Plasmodium falciparum. Biochem J. 2001; 355: 733-739.
31. Atchade PS, Doderer-Lang C, Chabi N, Perrotey S, Abdelrahman T, Akpovi CD, et al. Is a Plasmodium lactate dehydrogenase (pLDH) enzyme-linked immunosorbent (ELISA)-based assay a valid tool for detecting risky malaria blood donations in Africa? Malar J. 2013; 12: 279.
32. Juel C, Halestrap AP. Lactate transport in skeletal muscle role and regulation of the monocarboxylate transporter. J Physiol. 1999; 517: 633-642.
33. Ashley EA, Phyo AP. Drugs in development for malaria. Drugs. 2018; 78: 861-879.
34. Nigussie D, Beyene T, Shah NA, Belew S. New targets in malaria parasite chemotherapy: A review. Malaria Contr Elimination. 2015.
35. Poole RC, Halestrap AP. Transport of lactate and other monocarboxylates across mammalian plasma membranes. Am J Physiol. 1993; 264: 761-782.
36. Helmstetter F, Arnold P, Hoger B, Petersen LM, Beitz E. Formate–nitrite transporters carrying nonprotonatable amide amino acids instead of a central histidine maintain pH-dependent transport. J Biol Chem. 2019; 294: 623-631.
37. Bola BM, Chadwick AL, Michopoulos F, Blount KG, Telfer BA, Williams KJ, et al. Inhibition of monocarboxylate transporter-1 (MCT1) by azd3965 enhances radio sensitivity by reducing lactate transport. Mol Cancer Ther. 2014; 13: 2805-2816.
38. Ranganathan P, Shanmugam A, Swafford D, Suryawanshi A, Bhattacharjee P, Hussein MS, et al. GPR81, a cell-surface receptor for lactate, regulates intestinal homeostasis and protects mice from experimental colitis. J Immunol. 2018; 200: 1781-1789.
39. Hoque R, Farooq A, Ghani A, Gorelick F, Mehal WZ. The Anti-inflammasome effect of lactate and the lactate GPR81-Receptor in pancreatic and liver inflammation. Gastroenterology. 2014; 146: 1763-1774.
40. Kingston HW, Ghose A, Rungpradubvong V, Herdman MT, Plewes K, Ishioka H, et al. Does reduced oxygen delivery cause lactic acidosis in falciparum malaria? An observational study. Malar J. 2019; 18: 97.
41. Casals-Pascual C, Kai O, Lowe B, English M, Williams TN, Maitland K, et al. Lactate levels in severe malarial anaemia are associated with haemozoin-containing neutrophils and low levels of IL-12. Malar J. 2006; 5: 101.
42. Genderen P, van der Meer IM, Consten J, Petit PC, Gool T, Overbosch D. Evaluation of plasma lactate as a parameter for disease severity on admission in travelers with plasmodium falciparum malaria. J Travel Med. 2005; 12: 261-264.
43. Bergersen LH. Lactate transport and signaling in the brain: potential therapeutic targets and roles in body–brain interaction. J Cereb Blood Flow Metab. 2015; 35: 176-185.
44. Meier A, Erler H, Beitz E. Targeting channel and transporters in protozoan parasite infection screenshot. Front Chem. 2018; 6: 88.
45. Waight AB, Czyzewski BK, Wang DN. Ion selectivity and gating mechanisms of FNT channels. Curr Opin Struct Biol. 2013; 23: 499-506.
46. Mukherjee M, Vajpai M, Sankararamakrishnan R. Anion-selective Formate/nitrite transporters: taxonomic distribution, phylogenetic analysis and subfamily-specific conservation pattern in prokaryotes. BMC Genomics. 2017; 18: 560.
47. Wiechert M, Beitz E. Mechanism of formate–nitrite transporters by dielectric shift of substrate acidity. EMBO J. 2017; 36: 949-958.
48. Atkovska K, Hub J. Energetics and Mechanism of Permeation across FNT Channels. Biophysical J. 2015; 108: 441.
49. Corbett Y, Alessandro SD, Parapini S, Scaccabarozzi D, Kalantari P, Zava S, et al. Interplay between Plasmodium falciparum haemozoin and L-arginine: implication for nitric oxide production. Malar J. 2018; 17: 456.
50. Rycovska A, Hatahet L, Fendler K, Michel H. The nitrite transport protein NirC fromSalmonella typhimuriumis a nitrite/proton antiporter. Biochim Biophys Acta. 2012; 1818: 1342-1350.
51. Lu W, Schwarzer NJ, Du, J, Gerbig-Smentek E, Andrade SL, Einsle O. Structural and functional characterization of the nitrite channel NirC from Salmonella typhimurium. Proc Natl Acad Sci USA. 2012; 109: 18395-18400.
52. Moir JW, Wood NJ. Nitrate and nitrite transport in bacteria. Cell Mol Life Sci. 2001; 58: 215-224.

53. Jia W, Tovell N, Clegg S, Trimmer M, Cole JA. Single channel for nitrate uptake, nitrite export and nitrite uptake by Escherichia coli NarU and a role for NirC in nitrite export and uptake. Biochem J. 2009; 417: 297-304.
54. Aichi M, Yoshihara S, Yamashita M, Maeda S, Nagai K, Omata T. Characterization of the nitrate-nitrite transporter of the major facilitator superfamily (the nrtp gene product) from the cyanobacterium nostoc punctiforme strain ATCC 29133. Biosci Biotechnol Biochem. 2006; 70: 2682-2689.
55. Zemke AC, Gladwin MT, Bomberger JM. Sodium nitrite blocks the activity of aminoglycosides against pseudomonas aeruginosa biofilms. Antimicrob Agents Chemother. 2015; 59: 3329-3334.
56. Zemke AC, Shiva S, Burns JL, Moskowitz SM, Pilewski JM, Gladwin MT, et al. Nitrite modulates bacterial antibiotic susceptibility and biofilm formation in association with airway epithelial cells. Free Radic Biol Med. 2014; 77: 307-316.
57. Schairer DO, Chouake JS, Nosanchuk JD, Friedman AJ. The potential of nitric oxide releasing therapies as antimicrobial agents. Virulence. 2012; 3: 271-279.
58.