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ABC TRANSPORTERS: AT BLOOD BRAIN INTERCONNECTION AND THEIR FUNTION IN VARIOUS NEUROLOGIAL AND METABOLIC DISEASES

Sachin Kumar*, Pranav Gupta and Sarabjot Singh

Department of Pharmaceutical sciences, School of Pharmacy, Delhi Pharmaceutical Sciences and Research University, New Delhi, India.

***Corresponding Author: Sachin Kumar**

Department of Pharmaceutical sciences, School of Pharmacy, Delhi Pharmaceutical Sciences and Research University, New Delhi, India.

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ABSTRACT

BBB is commonly considered as a mechanism for protecting the brain from undesirable activities resulting from substances in the blood and keeping up brain homeostasis by means of observing the section or efflux of compounds. ATP Binding Cassette (ABC) transporters structure an exceptional group of layer proteins, described by homologous ATP-binding, and enormous, multispanning transmembrane domains. ATP-binding cassette (ABC) group of transporters including P-glycoprotein (P-GP) and breast cancer-related protein (BCRP), broadly communicated in the luminal layer of the micro vessel endothelium and in the apical film of the choroids plexus epithelium, assume significant parts in the capacity of BBB. Nonetheless, these transporters are easily altered by certain diseases. ABC transporters have been affirmed to be closely related to the pathogenesis of infections, for example, metabolic sicknesses and Alzheimer's disease dependent on their transport abilities. In recent years, there have been numerous epidemiological and clinical studies that have indicated the useful impacts of organic compounds, for example, Verapamil, Berberine, Fascalpsyn, Oleocanthal and some more, on these neurological pathologies. In spite of the fact that these compounds follow up on an alternate objective to fix the illness headway yet as of late, the function of these compounds has been recognized as a modulator of different ABC Transporters Likewise, the necessary remedial impacts in neurological issues can be accomplished by safe medication conveyance into brain parenchyma. Yet, because of an intense barricade arrangement of BBB through ABC transporters, the transportation of drug is controlled. This review gives a general overview of the human ABC transporters, their structure, their demeanor, limitation and fundamental mechanism of action. Then we shortly deal with the role of ABC Transporters in several neurological and metabolic diseases. Besides, we featured some human ABC carriers as focuses of helpful therapeutic in medication, including atherosclerosis and other metabolic disorders, and also in Alzheimer's disease.

KEYWORDS: ABC transporters, BBB, Alzheimer's disease, Diabetes, Amyloid β peptide.

INTRODUCTION

Neurodegeneration is principally showed by continually repeating reformist loss of structural integrity and typical functioning of the neuronal cells, prompting practical and mental afflictions. This primarily influences senior people and happens during Numerous Neurodegenerative Diseases (NDDs) including, Alzheimer's Disease (AD), Parkinson's Disease (PD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and Epilepsy. The causative variables related with the degenerative cycle of central nervous system (CNS) are inadequately seen, however, mounting bit of confirmations recommend that ATP-binding cassette (ABC) carriers may add to such obsessive events in the cerebrum. These carriers are basically restricted to the outside of mind endothelial cells of the cerebrum parenchyma furthermore, Blood-Brain Barrier (BBB) and are principally responsible for managing the homeostasis of CNS. ABC transporters have a place with one of the biggest and most antiquated protein superfamilies' and are profoundly preserved among species and all through development. ABC transporters are transmembrane proteins that transport lipids, sterols, metabolic squanders, and helpful medications across intra-and extracellular layers. These vehicle measures are ATP-driven and can, accordingly, be coordinated against a solute's focus angle. ABC (ATP-binding cassette) proteins structure one of the biggest protein families, and individuals from this family are found in all living life forms from organisms to people. The wide-spread presence of these proteins with a generally monitored structure and capacity proposes a crucial job. ABC transporters (ABCB1/MDR1, ABCC1/MRP1, ABCG2) shows a broad articulation profile, giving a cell safeguard instrument all through the creature. The tissue dispersion of these three significant multidrug opposition proteins is covering yet

extraordinary. ABCC1 articulation is high in all tissues, it is raised in lung and the testis, and diminished in the liver. MDR1 is exceptionally communicated in tissues with pharmacological hindrance work, for example, the blood-mind obstruction, and the choroid plexus. Ongoing reports have exhibited that ABCG2 is exceptionally communicated in the placenta, liver, digestive system and in different immature microorganisms. In tissues where distinctive multidrug transporters are available, the subcellular limitation of these proteins can be a segregating highlight. ABCB1/MDR1 shows luminal articulation in enraptured cells, for example epithelial cells of the digestive tract and the proximal tubules of kidney, or the canalicular layers of hepatocytes. Conversely, MRP1 in enraptured cells is limited exclusively in the basolateral layer.

Diabetes mellitus (DM) is an progressive metabolic illness, which builds up various perceived large scale and microvascular difficulties identified with endothelial dysfunction. Direct harm to little veins, especially by hyperglycemia, is showed by endothelial dysfunction, decreased perfusion, unusual endothelial cell expansion, and expanded vessels porousness. Type 2 DM patients display comparative microvascular harm inside the CNS which may bring about expanded frequency of intellectual disintegration, vascular dementia, lacunar infarcts, hemorrhages and Alzheimer's illness (AD). This diabetes actuated mind microvascular entanglements have sickening outcomes in brokenness of the BBB. DM is additionally connected with changes in ABC transport capacities in the cerebral micro vessels. Under diabetic conditions, the trustworthiness of BBB is undermined and molecules that are ordinarily limited to the blood may enter the parenchyma prompting sensational changes in cerebral structure and capacity.

The current article sums up and features the gathering proof in the writing which depict the role of ABC transporters in various metabolic and neurodegenerative diseases.

Structure of Abc Transporter

The overall structure of an ABC transporter contains of four utilitarian domains in which two NBDs (Nucleotide Binding Domains) and two TMDs (Transmembrane Domains). The NBDs are ties with ATP and trigger their hydrolysis that thusly supplies the driving energy needed for the vehicle. Furthermore, TMDs give a passage to substrate development across lipid bilayers.[1]

The NBDs are classified into seven highly conserved motifs as given below.[2]

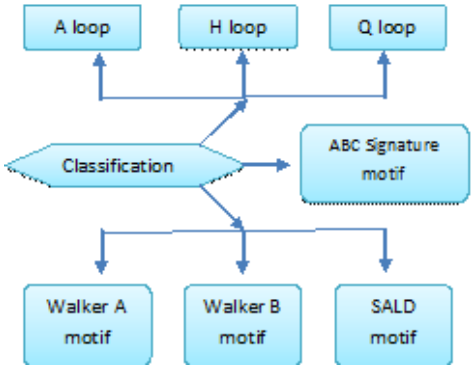

Fig. 1: Classification of NBDs.

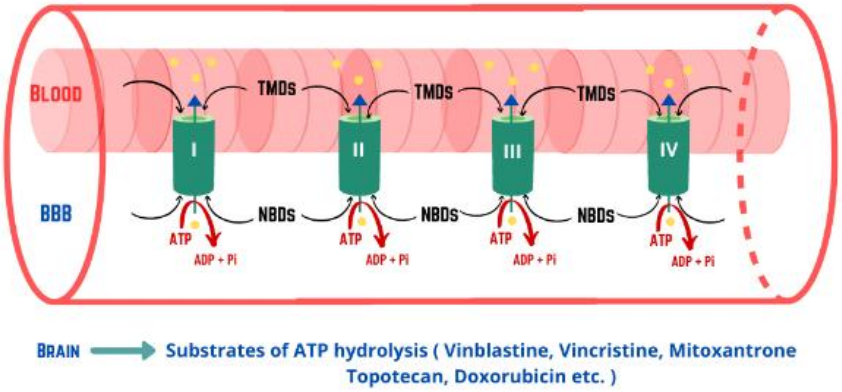

Fig.2. Most general structure of ABC (ATP Binding Cassette) transporters : Where I, II, III and IV represents ABCA, ABCB, ABCC and ABCG transporter respectively. And TMDs (Transmembrane domains); NBDs (Nucleotide binding domains); ATP(Adenosine triphosphate) and BBB (Blood-brain barrier)

The motifs are construct with explicit amino acid residues which exceptionally distinguish the ABC transporters from other ATP-binding proteins.[3] While NBDs are profoundly preserved among members, TBDs are fundamentally more dissimilar, generally involving exceptional arrangements of membrane crossing helices among various ABC carriers or transporters.[4] ABC transporters classified so far can be divided into exporters and importers with the importers further partitioned into two classes (I and II), contingent upon subtleties of their structure and mechanism. The connected group of energy-coupling factor (ECF) transporters (now and then alluded to as class III ABC importers) is architecturally and functionally more particular. Despite the fact that, TMDs need prominent arrangement similitude among individuals, they do share a run of the mill collapsing design inside certain gatherings of ABC transporters dependent on which they can be assembled into four classes: (a) type I, (b) type II, (c) type III ABC exporters (associated with inundation exercises) and (d) ABC exporters (engaged with efflux capacities). NBDs have saved nucleotide binding and hydrolysis motifs, including a Walker A motif that connects the a-and b-phosphates, a Walker B motif which contains a preserved glutamate, a switch area with a saved histidine, and a signature motif that cooperates with the g-phosphate.[5] Each ATPase site is shaped from Walker A, Walker B and change motifs from one NBD, and the signature motif from the second NBD. Following ATP hydrolysis and phosphate discharge, the signature motif separates and the dimer dissociates. In eukaryotes, the four domains that make up the ABC structure are typically encoded as combination proteins that can be in this manner organized either as a single polypeptide including all the subunits (full transporters), or as dimers of two polypeptide chains. Under typical physiological conditions, ABC transporters embrace two unique compliances during each synergist cycle that achieves substrate stacking and substrate conveyance.[4,5]

As per the "ATP switch model", this conformational exchanging is directed by the arrangement and separation of a NBD dimer, the energy for which is determined by ATP binding and hydrolysis.[7] Further, the model likewise recommends that the binding of a substrate to TMDs actually increase the affinity of NBDs for two ATP molecules. The chemical energy delivered during NBD dimerization after ATP restricting is thusly changed over into versatile conformational energy that is moved to TMDs along these lines authorizing them to shift back and forth between the two key situations for substrate transport over the film.[8] Afterward, ATP hydrolysis discharges inorganic phosphate (Pi) and ADP that triggers the destabilization and separation of the NBD dimer, permitting the TMDs to re-visitation of their basal arrangement, indeed set for another vehicle cycle.[9,10]

Abc Transporters At Blood Brain Interface & In Various Metabolic Diseases

ABC Transporters are closely associated with metabolic disorders as they play an essential role in maintaining lipid homeostasis. Anomalies/abnormalities in ABC transporters can lead to accumulation of excess free cholesterol that results in toxicity for adipocytes and macrophages. This promotes the Unfolded Protein Response (UPR) which initiates apoptosis through the Endoplasmic Reticulum.[19] Recent studies illustrate the role of ABCA1 and ABCG1 transporters in metabolic diseases in detail.

METABOLIC SYNDROME

Metabolic syndrome is a group of metabolic diseases which is identified by high blood sugar level, high blood triglyceride level, increased waist circumference, high blood pressure and low high density lipoprotein - cholesterol levels. Chen WM et al.[20] stated that abnormalities in the functioning of ABCA1 transporter can induce metabolic syndrome and ABCA1 expression in macrophages is further inhibited by hyperglycemia through post transcriptional regulation. Also, people suffering from metabolic syndrome are at a higher risk of developing cardiovascular disease or/and type 2 diabetes mellitus.

Diabetes

Diabetes Mellitus (or diabetes) is a metabolic disorder which results in high blood sugar levels (i.e. hyperglycemia). Insulin is the main hormone secreted from endocrine level and regulates the glucose level in blood.[18] Thus, any defect in insulin hormone becomes one of the major reason which leads to diabetes mellitus. It can be of following types:

- **Type 1:** It is insulin dependent Diabetes Mellitus and is also called as juvenile diabetes mellitus. In this, the cells which synthesise insulin are destroyed due to which insulin is not produced, thus, causing hyperglycaemia.
- **Type 2:** It is no – insulin dependent Diabetes Mellitus (DM) or maturity onset diabetes. In this, insulin is produced by body but the cells in the body due not respond to it as effectively as it once did.
- **Type 3:** It is called secondary insulin and usually occurs due to pancreatectomy (removal of pancreas by surgery), drugs and some other reasons.

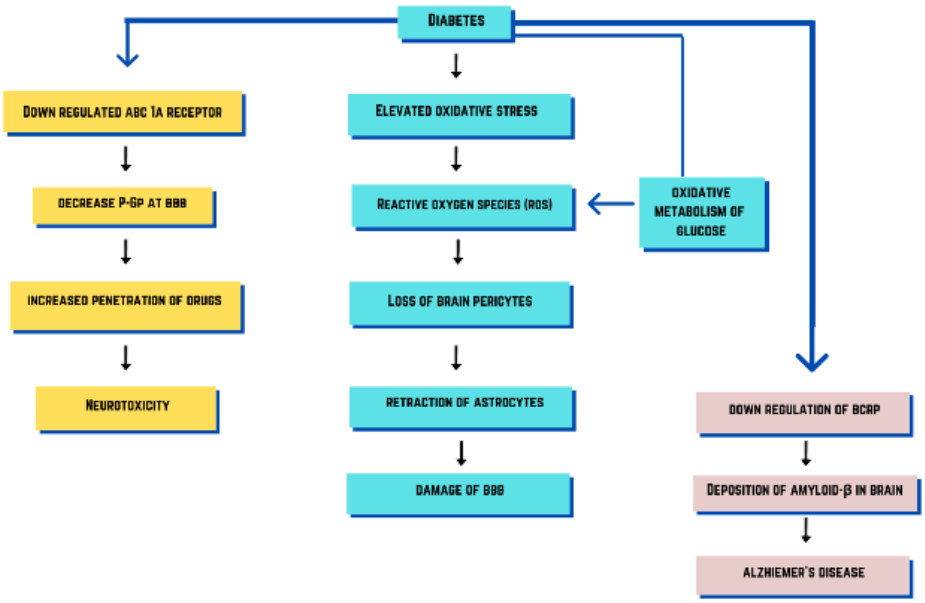

Fig.3. conceivable relationships between diabetes, Blood brain barrier (BBB) and alzheimer's disease

Gestational Diabetes: It occurs in women during pregnancy in which body becomes less sensitive to insulin and hence, leads to increase in the sugar level of blood. However, it does not occur in all of the women and generally resolves after giving birth.[19]

Role of ABC transporters in Diabetes: ATP-binding cassette (ABC) family of transporters including P-glycoprotein (P - GP) and breast cancer - related protein (BCRP), which are widely expressed in the luminal membrane of the micro - vessel endothelium and also in the apical membrane of the choroids plexus epithelium, plays very important roles in the function of Blood Brain Barrier (BBB).[19] The changes in ABC transporter in DM are as follows:

Treatment: We know that DM occurs due to low level of insulin (or insulin resistance), thus, the main aim is to increase its levels which can be done by using drugs such as:

- Metformin[17]
- Sodium – Glucose Cotransporter 2 (SGLT2) inhibitors
- Glucon – Like – Peptide – 1 (GLP1) inhibitors

Though the proper treatment of diabetes is still under consideration. But all the above discussion can lead to an increase in insulin level due to which BBB would not damage, P – GP levels would remain normal (which would decrease neurotoxicity) and BCRP levels would also remain normal[16] (which prevents Aβ deposition and, hence, prevents AD) remain normal (which prevents Aβ deposition and, hence, prevents AD).

Stargardt Disease

Stargardt disease (STGD1) is an autosomal recessive retinopathy, which is caused by mutations in the retina-specific ATP-binding cassette transporter (*ABCA4*) gene. It is a disorder of retina which is inherited and can typically cause vision loss during childhood or adolescence, though in some forms vision loss would not be seen until childhood. Stargardt disease is also known as Stargardt macular dystrophy, juvenile macular degeneration, or fundus flavimaculatus. The infection causes reformist harm — or degeneration — of the macula, which is a little region in the focal point of the retina that is answerable for sharp, straight - ahead vision.

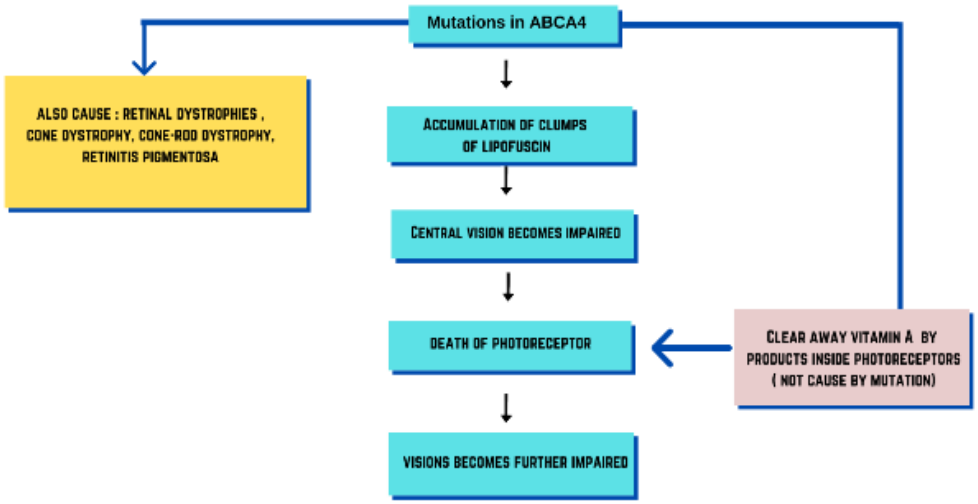

Fig.4. Mutation in ABCA4 transporter and its consequences

The symptoms observed in Stargardt Disease are not constant i.e. they are changed in every patient, but often very slow loss of vision is seen in both the eyes. People might see white, black or grey spots in the centre of vision or it would take more time for the eyes to adjust when moving from light to dark environments and vice – versa. Their eyes become more sensitive to bright light and some people also develop colour blindness later in the disease. Individuals with a prior beginning of infection will in general have more quick vision misfortune. Vision misfortune may diminish gradually from the outset, at that point intensify quickly until it levels off.

Role of ABC Transporter in Stargardt Disease: It is known that retina consists two light – sensing cells called photoreceptors. These are: -

1. **Rods –** They are found in the outer retina and help us see in dim and dark light.
2. **Cones -** They are found in the macula and help us see fine visual detail and colour.

Together they both functions to detect light and convert it into electrical signals, which are then "seen" by the brain. Vitamin – A rich diet is very important for healthy vision because they make photoreceptors. But they also produce some Vitamin – A byproduct (such as N-retinylidene - PE) which have harmful effects and plays an important role in the Stargardt Disease.

Treatment: Currently there is no treatment of STGD1 disease but scientists are working to find new mutations in *ABCA4* gene and other genes that can contribute to STGD1.[14,15] However, doctors recommend the patients to follow few steps such as:-

- Wear dark glasses and hats to reduce the formation of lipofuscin.
- Normal amount of Vitamin A should be taken as higher amounts can lead to increased formation of lipofuscin.
- Counselling and Occupational Therapy are also important.

Tangier Disease

Tangier disease (TD) is a lipoprotein digestion problem which is uncommon and is portrayed biochemically by a practically complete nonattendance of plasma High - Density Lipoproteins (HDL), and clinically by liver, spleen, lymph hub and tonsil extension alongside fringe neuropathy in kids and youths, and, incidentally, cardiovascular infection in grown-ups.

The main characteristics of TG is exhausted HDL levels in plasma, increased TG levels, the deposition of sterol in tissue macrophages and also, an increase in susceptibility to Coronary Heart Disease (CHD). The extremely low HDL levels are detected in the childhood only, but the more prevalent feature is the enlargement of tonsils which take an orange – yellow color due to deposition of cholesterol in lympho– monocytes cells. Patients may likewise show asymptomatic hepatosplenomegaly, lymph hub broadening, and stomach torment. Cholesterol aggregation is likewise seen inside the rectal mucosa and at times, sickliness is additionally watched. The TD is due to mutations in *ABCA1* gene (9q31) [14], which fail to mediate lipid efflux or nascent HDL formation but have elevated TG secretion. The disease is also called by the names of ABCA1 Transporter Deficiency, Analphalipoproteinemia and defective ABCA1 Transporter.

Role of ABC Transporter in Tangier Disease: As discussed above, mutations in ABCA1 Transporters causes TD. These genes provide instructions that that releases cholesterol and phospholipids from cells. These

substances are used to make HDL, which transport them to liver.

Treatment: The TD still does not have any treatment. Scientists are trying to experiment on new mutations in ABCA1 genes to treat the disease.[14] However, following precautions can be taken by the patients of TD:

- Tonsillectomy can be done in case of enlargement of tonsils.
- A low fat – diet can lead to reduction in cholesterol level, reduces liver enlargement and prevents atherosclerosis.
- Low Density Lipoprotein (LDL) - lowering drugs (such as Lovastatin, Fluvastatin, Pitavastatin etc.) are required in patients with overt signs of carotid atherosclerosis or cardiovascular disease.
- Treatments improving cell cholesterol efflux by HDL (for example reconstituted HDL, CETP inhibitors) may lessen neuropathic and cardiovascular inconveniences.

Dubin Johnson Syndrome

Two scientists named Dubin and Johnson told about a new clinic - pathological entity consisting of chronic idiopathic jaundice and presence of some unidentified pigments in the liver. Dubin Johnson Syndrome (DJS) is a rare, autosomal recessive, benign disorder which can cause an increase of conjugated bilirubin in the plasma. The main effect observed in this disease is the black liver which occurs due to deposition of a pigment, which is similar to melanin. This defect mainly occurs because of defect in the ability of the hepatocytes to secrete the conjugated bilirubin in the bile. The disease does not show any symptoms and generally requires no treatment. However, the patients suffering from DJS can show non – pruritic jaundice during their teenage years.

Role of ABC Transporters in Dublin Johnson Syndrome: DJS occurs by the mutations in ATP binding cassette subfamily C member (ABCC2) gene. The ABCC2 gene gives instructions for producing a protein called Multidrug Resistance Protein - 2 (MRP2) that works as a transporter protein. The MRP2 protein is involved in the transport of substances out of cells and is essential for the secretion of conjugated bilirubin out of the hepatocytes into the bile duct system for its excretion. An exemplary component of DJS is the inversion of the proportion of the results produced during amalgamation of heme. The degrees of urinary coproporphyrin l levels are more noteworthy than coproporphyrin lll. In any case solid individuals, the ratio of coproporphyrin lll to coproporphyrin l is about 3.5:1.[13]

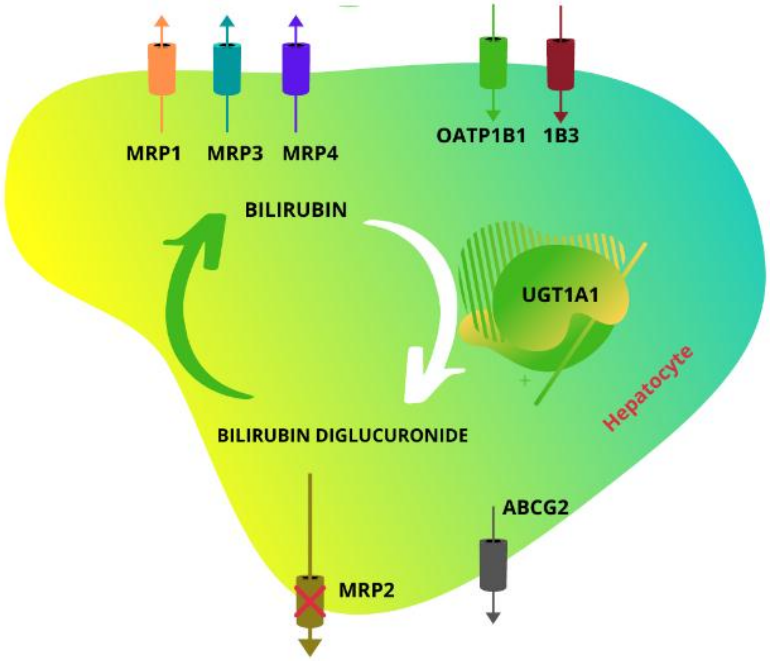

Fig.5. Normal deposition of bilirubin involves its transportation to the liver where a sugar molecule viz glucuronic acid is conjugated.

Treatment: As discussed earlier, DJS is a benign disease which does not leads to fibrosis or in the development of cirrhosis, and requirement of treatment is nill. The only importance of diagnosing DJS is to eliminate the possibility of some other disorders that can lead to hepatic injury and diagnose those which are treatable. Phenobarbital and Ursodeoxycholic Acid are therapeutic for significant cholestasis that occurs in neonatal DJS.[13]

The bilirubin is converted into water soluble compound (i.e. bilirubin digiglucoride) that can be easily excreted in feces. This conversion is catalyzed by enzyme bilirubin – UDP – glucuronosyltransferase (UGT1A1). After

conjugation, bilirubin diglucuronide is excreted out of the hepatocytes into bile canaliculi for transport to the gall bladder. DJS results from the mutations that occur in the gene encoding of bile canalicular.

Adrenoleukodystrophy

Adrenoleukodystrophy (ALD) is one of the rare genetic conditions which results in the build - up of very long chain fatty acids (VLCFAs) in the brain. When accumulation of VLCFAs occur, they destroy the protective myelin sheath present around nerve cells (that is responsible for brain function). What's more, we realize that without the myelin sheath, the nerves can at this point don't transfer data to and from the brain.

The ALD usually begin showing symptoms between the ages of 4 and 10. Most common symptoms being behavioral problems, withdrawal / aggression, poor memory and difficulty in reading & writing & understanding speech. But it must be treated properly and if not treated, condition can worsen causing vision problems, seizures, difficulty swallowing, deafness, poor coordination and inability to speak or respond.

Role of ABC Transporters in Adrenoleukodystrophy: The *ABCD1* gene contains instructions for creating a protein known as X-linked adrenoleukodystrophy protein or ALDP. This is a transporter protein which helps in transportation of fat molecules called VLCFAs into structures called peroxisomes. Peroxisomes are small membrane-bound structures within the cytoplasm of cells that play a vital role in numerous biochemical processes in the body. VLCFAs are then metabolized. Since this is a lack of ALDP, the vehicle and, eventually, the breakdown of VLCFAs are upset and, therefore, these greasy particles aggregate in the tissues of the body.

ALD is an X - linked recessive condition which is caused by a mutation in the *ABCD1* gene on the X chromosome. Because a female has two X chromosomes, if she inherits the faulty gene, then she still has another X chromosome to offset the mutation. In any case, since males just have one X chromosome, the quality variation from the norm causes the sickness. With every pregnancy, female ALD transporters have a 25 percent (1 out of 4) possibility of having a transporter girl and a 25 (1 out of 4) percent possibility of having a child influenced with the illness.

Treatment: The treatment is very important because no treatment can lead to very serious problems. Some of the treatment options are as discussed below:

1. Stem Cell Transplant: It is the only effective treatment option for cerebral ALD. It involves a procedure in which the patient receives blood stem cells from a genetically matched donor. The main purpose is to provide healthy stem cells that produce the protein lacking in ALD. However, it is very difficult to find the genetically matching donor and also have a very high risk of infection.

Gene Therapy: This therapy is still under test and has an advantage that there is no need of donor. In this, the patient's own blood stem cells are being removed and then treated in the laboratory with a vector (which is a non-infectious virus) that is used to get the quality that makes the ALD protein (ABCD1 quality) into the cell. The cells containing the vector are then given back to the patient by an intravenous (IV) infusion. When these new cells grow, divide and make new cells in the body, they will have the *ABCD1* genes which now are capable of breaking down the VLFCAs, the cause which were responsible for ALD.

OBESITY

Obesity is one of the most common and serious metabolic disease with at least 2.8 million people dying each year as a result of being obese/overweight. Generally, more than 50% of the total cholesterol of the body is accumulated in the adipose tissues of an obese adult.[21] A decrement in the ABCA1 expression in visceral adipose tissues is linked with obesity.[22] Due to higher concentration of cholesterol on adipose tissue membranes, adipocyte ABCA1 transporter plays an essential role in modulating adipocyte lipogenesis and lipid accumulation. Activities of lipogenic transcriptional factors PPARγ and SREBP1 can be inhibited by ABCA1 transporter which results in the decrement of the total cholesterol levels of the body.[23] Mouse models have proven that obesity is caused due to lack of adipocyte-specific ABCA1 transporter. Also, these mice models without adipocyte-specific ABCA1 transporter showed a decrement in the levels of the most active form of adiponectin and high molecular weight adiponectin.[22] Moreover, a down regulation of G protein pathway suppressor 2 (GPS2) seen in type 2 diabetes mellitus and obese patients further confirms ABCA1 repression in obesity and type 2 diabetes mellitus.[24] R219K and I883M are the two single nucleotide polymorphisms (SNPs) of the ABCA1 gene which are found to be closely linked with susceptibility to obesity. The SNP I883M of the ABCA1 gene plays a protective role whereas the SNP R219K of the ABCA1 gene increases the susceptibility and phenotype severity.[21]

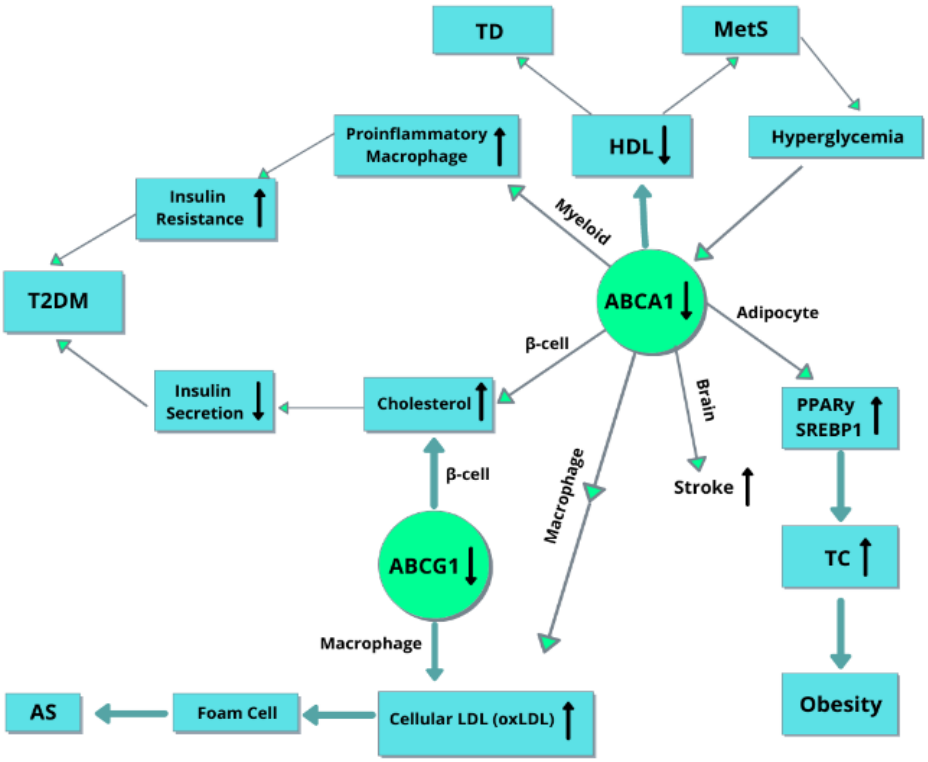

Fig.6. The relationship between ABC Transporters and metabolic diseases

Atherosclerosis

The uptake and metabolism of macrophage mediated cholesterol is linked with the initiation and development of atherosclerosis in focal areas of the arterial sub endothelial space.[24] The formation of the foam cells, lipid-laden macrophages, is the beginning step of atherosclerosis. Macrophage expression of ABCA1 and ABCG1 inhibits the development of foam cells.[25] Anomalies in macrophage ABCA1 and ABCG1 expression leads to less cholesterol efflux and excess uptake of modified low density lipoprotein (LDL), especially oxidized LDL, which further results in development of foam cells.[26,27] It's been proven that ABCA1 C69T polymorphism is linked with higher atherosclerosis risk.[28] One of the major mechanisms through which high density lipoprotein (HDL) shields against atherosclerosis is Reverse cholesterol transportation (RCT) but the atheroprotective effect of ABCA1 is not completely dependent on RCT.[26,41] It's interesting to know that myeloid cell ABCA1 increases the hepatic very low density lipoprotein (VLDL) triglyceride secretion and plasma VLDL/LDL ratios, which lessens the atheroprotective effect and results in minimal increase in atherosclerosis.[29] Reports shows that ABCG1 transporter is essential for aiding the development of advanced atherosclerotic lesions by inducing the necrotic core of the atherosclerotic plaque.[30] Instability in lipid-rich plaques can lead to thrombosis, cardiac arrest and death. Davis W et al.[19] stated that instability in lipid-rich plaques in macrophages can be reduced by ABCA2 transporter. Cholesterol-induced toxicity can lead to intracellular lipid-rich plaques which can be eliminated by ABCA2 transporter as they modulate cholesterol trafficking from the late endosome/ lysosomal membrane compartment (LE/LY) to the ER in cells. ABCA1 and ABCG1 expression can be affected by many factors. Sortilin is closely linked with hyperlipidemia and atherosclerosis risk. Oxidized LDL upregulates macrophage sortilin expression in both concentration and time-dependent manners. Sortilin can bind with ABCA1 to enhance its lysosomal degradation and hence inhibits the expression of macrophage ABCA1.[31] Moreover, psychological stress factors such as corticotropin-releasing hormone (CRH) can also lead to atherosclerosis. CRH activates CRH receptor 1 (CRHR1)-induced phosphorylation of protein kinase B (Akt) which inhibits ABCA1 expression and results in stress-related atherosclerosis.

STROKE

One of the key targets of the transcription factor Liver X receptor (LXR) is the ABCA1 gene. Activation of LXR results in anti-inflammatory and neuroprotective effects in animal ischemic stroke models. Lack of brain ABCA1 results in increment in blood brain barrier (BBB) leakage, white matter axonal damage and functional deficits after stroke. Upregulation of matrix metalloproteinase-9 and concomitant reduction of

insulin-like growth factor 1 may also further contribute to brain ABCA1 deficiency– induced BBB and white matter axonal damage in the ischemic brain.[32] Moreover, Li Q et al.[27] stated that polymorphisms in ABCG1 could decrease the ischemic stroke in a hypertriglyceridemic population with atherothrombotic stroke

Role of Abc Transporters In Neurological Diseases

In AD brain, changes in the ABC transporter-encoding genes can cause the ABC transport framework to work unusually that bring about the agglomeration of poisonous Aβ peptides in the CNS, causing synaptic misfortune and memory shortages.[45] Contrariwise, completely practical ABC transporters forestall the accumulation of poisonous Aβ plaques in the mind, either legitimately by means of dynamic vehicle of Aβ over the BBB or by implication by directing Aβ blend and additionally corruption in the cerebrum.[46] Because of the part of ABC transporters in both neuroprotection and neurodegeneration, it would be of prime enthusiasm to scientists to comprehend the nitty gritty usefulness of these carriers in AD science. There are in excess of 40 different sorts of ABC carriers in people, out of which, just 9 (ABCA1, ABCA2, ABCA5, ABCA7, ABCB1, ABCC1, ABCG1, ABCG2 and ABCG4) have been accounted for to have a function in AD pathophysiology. Collection of poisonous Aβ peptides in the CNS is one of the prime foundations for quickening AD-connected memory deficiencies.[47] End of these peptides from CNS is needed for the ordinary homeostasis of the mind, which can be accomplished by the typical working of ABC transporters. It is presently broadly acknowledged that, any modifications or insufficiency in these carriers because of loss of useful transformation adverse effects CNS.

ABCB1

For example, ABCB1 distortion has been known to assume a function in the development of poisonous plaques because of Aβ growth in the brain. In expansion, ABCB1 additionally bolsters the cycle that achieves Aβ disposal from the synapses.[48] An ongoing report by Brukmann et al. seen that ABCB1 inadequacy in a transgenic murine model of AD disables the Aβ evacuation measure and can prompt intraparenchymal cerebral amyloid angiopathy.[49] A reformist decrease of ABCB1 levels is commonly seen in cerebrum micro vessels during typical maturing, and in connection, it has been accounted for that poisonous Aβ peptides moderate ABCB1 downregulation at the BBB mainly by two instruments. Initially, by interfacing with a protein called Receptor for Advanced Glycation End Products (RAGE) that thus summons the atomic factor kappa beta (NF-κβ) flagging pathway, which encourages ABCB1 downregulation. What's more, besides, by a ubiquitination and proteasome-subordinate corruption component that achieves ABCB1 downregulation.[48,50,51]

ABCC1

Additionally, ABCC1 downregulation has been accounted for to build the Aβ levels in the brain of amyloid-β antecedent protein (AβPP) or presenilin-1(PS-1) transgenic mice that brought about a checked increment of Aβ plaques. Unexpectedly, these impacts are not brought about by the strange articulation of AβPP handling compounds or Aβ corruption proteins, yet are an outcome of the decrease in the ABCC1-interceded Aβ transport across cerebrum narrow endothelial cells (BCECs), as was set up as of late in another in vitro model.[52,53] Further, another investigation expressed that monomeric Aβ advances the arrival of astrocyte-got glutathione from the synapses by instigating ABCC1 articulation. This achieves a decrease in the defensive cell reinforcement impact of glutathione, chiefly because of Aβ oligomerization and furthermore because of a diminishing in ABCC1 levels in AD mouse models as amyloid pathology advances.[54]

ABCA7

Further, the AD-risk minor G allele of ABCA7 SNP rs3752246 has been appeared to manage the declaration of a changed type of ABCA7, where an insufficiency in myristoylation mutilates the ordinary capacity of the protein in this manner bringing about an upgraded βsecretase activity and resulting Aβ creation.[55] Several other ABCA7 hereditary variations, expected to be pernicious to the coding protein and that could prompt ABCA7 loss of-work have now been distinguished in a few AD cases.[56] In view of this, analysts and researchers advocate that ABCA7 variations, for example, SNP rs3764650 are the helpless locus for the AD and consequently could of restorative centrality.[57] Actually, SNP rs3764650 influences the pathways associated with cholesterol homeostasis that thus is engaged with AβPP preparing and creation of Aβ.[58]

ABCA1

ABCA1, in spite of the fact that not being directly involved engaged with Aβ transport over the BBB, is in reality a central determinant of amyloid pathology. Hereditary affiliation and utilitarian investigations emphatically exhort that ABCA1 may incline to AD predominantly by an Apo lipoprotein E4 (APOE4)-related hindrance of Aβ leeway over the BBB and by acceptance of Aβ fibrillation. On the opposite, ABCA1 can prevent AD by concealment of Aβ creation and by encouraging Apo lipoprotein E2(APOE2)- related proteolytic debasement of cerebral Aβ.[59]

ABCA2

Further, the association among ABCA2 and AD has been proposed simply by a predetermined number of reports. One of these investigations recommends that ABCA2 controls AβPP digestion by upregulating AβPP mRNA and protein articulation levels, and by inciting β-secretase that expands the degree of emitted Aβ in cell culture models. Predictable with the above discovering, ABCA2 knockdown has been appeared to cause a

decline in Aβ age both in vitro and in vivo frameworks, because of diminished β-secretase preparing of AβPP. Furthermore, two late investigations have recognized a hereditary variation of ABCA2, the SNP rs908832 that might be connected with increased danger of both inconsistent and no sporadic types of the AD. The T allele of this ABCA2 SNP that is overexpressed in irregular AD cases, is related with elevated cholesterol levels in the CSF, and may legitimately or by implication include APOE and ABCA1.[60-64] Consequently, both ABCA1 and ABCA2 might be considered as potential helplessness qualities, which could connect lipid homeostasis to AD pathogenesis.

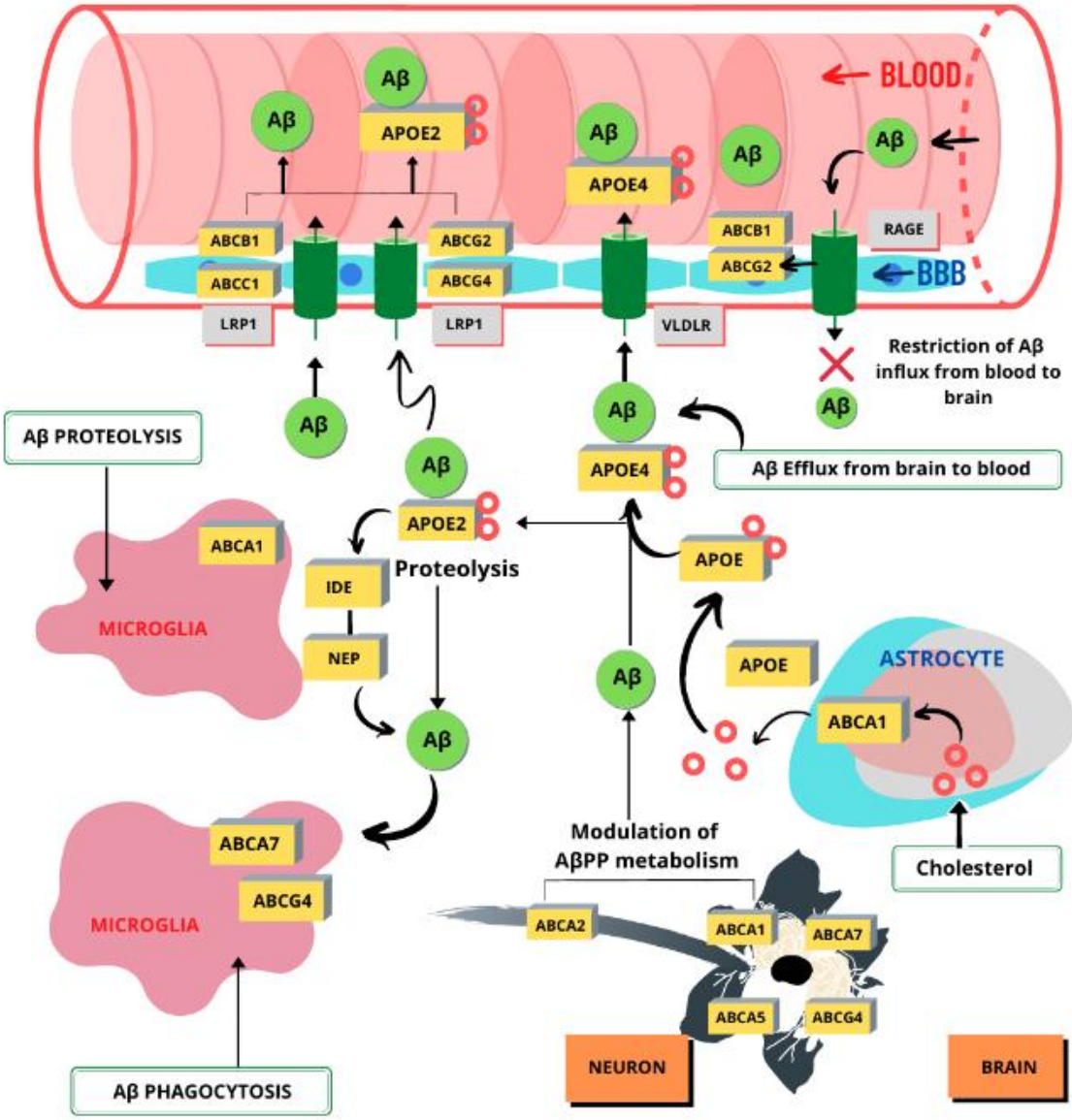

Fig.7. Interference between ABC transporters and cerebral Aβ levels. The interlink between Aβ levels in the brain and ABC transporters action is rising, as these transporters are answerable for delivering poisonous Aβ from the mind to the fundamental course to safeguard the cerebrum from poisonous affronts.

ABCG1

Further, the useful information accessible with respect to the inclusion of ABCG1 in the AD is clashing. One lot of scientists advocate that ABCG1 and AβPP co-expression in vitro model upsurges the degree of discharged Aβ to a great extent by advancing the accessibility of AβPP as a substrate for the amyloid genic handling pathway. This association recommends that the ABCG1-intervened guideline of AβPP dealing potentially aids AD advancement.[65] Notwithstanding, the other arrangement of specialist's advocate that the job ABCG1 in the AD is actually neuroprotective in light of the fact that ABCG1

essentially decreases Aβ creation in AβPP communicating cells.[66,67] Consistent with the statement, a few investigations have detailed that the presence of ABCG1 manage or confine β-secretase movement as well as changes its restriction in the lipid pontoon miniature spaces, where the greater part of its action happens. By and large, these discoveries recommend that ABCG1 can be either neuroprotective or could have a hindering impact in AD.[66]

ABCG2

In like manner, ABCG2 assumes a key part in redox homeostasis and aggravation, and a few investigations have set up that ABCG2 misfortune firmly identifies with diminished glutathione levels, expanded cell lipid peroxidation, DNA oxidation and provocative quality articulation in AD mice models.[68] ABCG2 mRNA and protein articulation are heartily upregulated in AD patients and furthermore as cerebral amyloid stores in AD mouse models.

ABCG4

In conclusion, ABCG4 mRNA and protein articulation is discernibly upregulated in microglial cells and relates with Aβ trouble in the mind of AD patients.[69,70] As like ABCG1, ABCG4 can have defensive impacts in the AD by advancing Aβ leeway, produced through proteolytic corruption and phagocytosis.

Diabetes Mellitus

Diabetes mellitus related diverse deciding elements including, insulin obstruction, insulin insufficiency, and micro vascular pathogenesis, alongside other key factors, for example, AGEs, insulin development factor-1 (IGF-1) and changing development factor-β1 (TGF-β1), have likewise been accounted for to be engaged with ABC transporters and BBB interruption to cause Aβ collection because of diminished Aβ efflux and expanded Aβ inundation from mind to blood.[71] Anyway these carriers have been associated with AD headway because of Aβ collection however these are additionally occupied with Aβ leeway as a result of its debasement by means of proteolytic corruption, phagocytosis, and end through BBB.

Above all, these carriers are likewise answerable for delivering poisonous Aβ peptides from the cerebrum to blood. There are a few components that have been accounted for to be associated with the expulsion of cerebral Aβ, which incorporates Aβ debasement by means of protease, for example, neprilysin (NEP) and insulin-corrupting catalyst (IDE), phagocytosis of harmful Aβ by microglia and astrocytes, Aβ leeway by the perivascular lymphatic seepage framework, Aβ freedom through the brain ISF/CSF and mass stream into the circulation system, and ultimately, transcytosis of Aβ over the BBB intervened by the LRP1. In addition, Aβ efflux to the fringe blood or foundational course is additionally determined with a particular goal in mind by the ABC transporters, which helps in the vehicle of harmful Aβ peptides from the neurons.[72,73]

In any case, explicit systems by which ABC transporters send out Aβ peptides from neurons and efflux them over the BBB endothelium is as yet hazy. There are a few proposed functions of ABC transporters in the control of brain Aβ levels have been uncovered up until now.

1). ABCA1, ABCA5, ABCA7, ABCG4 and ABCA2:

The ABC carriers including, ABCA1, ABCA5, ABCA7, and ABCG4 have been engaged with stifling AβPP proteolysis to create Aβ in the neuronal cells, while ABCA2 expands Aβ creation [60, 66, 74-76]. ABCA7 forestalls Aβ age and amyloid pathology by adjusting the degrees of Sterol Regulatory Element-restricting Protein 2 (SREBP2), that balance a record factor for βsecretase.[77]

2) LRP1

Further, Aβ efflux over the BBB by ABC transporters is done in participation with the LRP1 complex. LRP1 essentially tweaks Aβ endocytosis from the mind ISF into BCECs followed by Aβ transcytosis from a luminal side to the luminal side of the BBB.

3) ABCB1, ABCC1, ABCG2 and ABCG4

ABC transporters, for example, ABCB1, ABCC1, ABCG2, and ABCG4 convey across Aβ from the apical film of BCECs into the foundational dissemination.[78,79] Most prominently, both ABCB1 and ABCG2 specifically limit the apical-to-basolateral porousness of BCECs to circling poisonous Aβ peptides that are shipped by RAGE through the BBB into the CNS by siphoning it back to the fringe blood. Further, ABCA1 can regulate the APOE levels and their lipidation express that thus may influence the Aβ leeway measure over the BBB. Ongoing examinations have uncovered that free Aβ is endocytosed all the more rapidly by the LRP1 mind boggling when contrasted with the APOE-bound Aβ, while, lapidated APOE4/Aβ buildings are disguised rather gradually by means of Very Low Density Lipoprotein Receptor (VLDLR) when contrasted with the lapidated APOE2/Aβ edifices by the LRP1complex.[78,79]

4) Phagocytosis

In spite of the fact that the functions of ABC transporters are limited chiefly because of the arrival of harmful Aβ peptide from neurons to the fundamental course, the transporters likewise assume a key part in the phagocytosis of Aβ peptides after its proteolytic debasement by proteolytic catalysts, for example, NEP and IDE.

For example, ABCA1 interceded APOE2 lipidation helps in the proteolytic corruption of dissolvable Aβ inside the cerebrum by microglial NEP or extracellular IDE [80]. Furthermore, ABCA7 and ABCG4 additionally invigorate the cleansing of cerebral harmful Aβ by

helping microglial phagocytic movement and hence keep up ordinary working of the cerebrum.[81,82] Further, the cross-talk between ABC carriers and cerebral Aβ levels in AD mind has been portrayed in Fig. (7). Taken inside and out, it is presumed that ABC transporters are having both neuroprotective just as obsessive ramifications to the mind.

Table 1: Drugs modulating ABC Transporters expression for the treatment of several diseases.

S.No	Drugs	Target	Effects	Disease	Reference
1.	Progestrone	ABCA2	Alleviates cholesterol induced toxicity in macrophages	Atherosclerosis	[19]
2.	Co-enzyme Q10	ABCG1	Increase RCT & promotes macrophage cholesterol efflux	Atherosclerosis	[63]
3.	Diosgenin	ABCA1	Inhibits MiR-19b expression & enhances cholesterol efflux	Atherosclerosis	[56]
4.	Dihydrogen	ABCA1	Increases HDL anti atherosclerotic function	Metabolic syndrome, Atherosclerosis	[61]
5.	Metformin	ABCG5, ABCG8	Upregulate macrophage RCT, facilitate excretion of excess cholesterol into bile	Cardiovascular	[62]
6.	Triptolide	ABCA1	Reduces the secretion of inflammatory factors	LPS-induced ALI	[57]
7.	Cilostazol	ABCA1	Ameliorate hepatic steatosis	Dyslipidemia	[58]
8.	Paeonal	ABCA1	Represses foam cell formation	Atherosclerosis	[60]
9.	Hydrogen sulfide	ABCA1	Ameliorate intracellular lipid accumulation in HepG2 cells	Atherosclerosis	[59]
10.	Statins	ABCA1	Decreases Akt phosphorylation	Atherosclerosis, obesity	[53]
11.	Verapamil	ABCB1	Neuroprotective effect	AD	[42,83]
12.	Berberine	ABCB1	Neuroprotective effect	AD	[42,83]
13.	α- tocopherol	ABCB1	Promotes Aβ clearance	AD	[84]
14.	Hypericumperforatum	ABCB1	Decrease Aβ accumulation	AD	[86]
15.	Facalpsym	ABCB1	Induces ABCB1 activity	AD	[91]
16.	Rivastigmine	ABCB1 & LRP1	Decrease both the number 4 & size of amyloid plaques	AD	[92]
17.	Oleocanthal	ABCB1 & LRP1	Hasten Aβ clearance from the brain	AD	[43]
18.	1 α, 25-dihydroxytitamin D	ABCB1	Counteracts the brain Aβ accumulation	AD	[88,89,90]
19.	Pregnenolone-16 α-carbonitrile	ABCB1 & ABCG2	Reduces cerebral Aβ levels	AD	[44,85]
20.	Rifampicin	ABCB1	Reduces cerebral Aβ levels & attenuates cognitive decline in patients	AD	[87]

NIEMANN – PICK TYPE C DISEASE

ABCA2 mRNA articulation is raised in Niemann-Pick Type C and familial hypercholesterolemia fibroblasts. Niemann-Pick Type C sickness is a neurological problem of teenagers because of autosomal-latent transformations in it is possible that one or both Niemann-Pick-2 (NPC2) and NPC1 qualities, which, as ABCA2, are confined to the LE/LY compartment.[93] Cholesterol exit from the LE/LY requires the coordinated activity of both NPC2 and NPC1 to convey free cholesterol from the lumen to the restricting layer of the LE/LY, where it deals to other intracellular compartments, e.g., Golgi mechanical assembly, endoplasmic reticulum, by vesicular and nonvasicular mechanisms.[94–96] Freak NPC1 fibroblasts have a deformity in the conveyance of LDL-got free cholesterol from the LE/LY prompting cholesterol aggregation inside this compartment.[97,98] Notwithstanding cholesterol collection, different lipids including sphingomyelin, glycosphingolipids and sphingosine likewise gather in the LE/LY.[99,100] The declaration of the LDLR and the cholesterol engineered qualities are likewise raised in freak NPC1 fibroblasts. Fibroblasts from Familial Hypercholesterolemia (FHC) patients need practical LDL receptors that are needed for LDL take-up from the plasma.[101] We guessed that in refined cells, diminished conveyance of LDL-FC to the endoplasmic reticulum in NPC1 fibroblasts or diminished take-up of LDL in FHC fibroblasts would emulate sterol hardship and initiate cholesterol sequestration and result in enactment of ABCA2 articulation. Human fibroblasts from typical, FHC and NPC1 patients were refined in complete medium and

following RNA seclusion, ABCA2 articulation was estimated by Northern blotch. ABCA2 articulation was raised in NPC1 and FHC fibroblasts contrasted with ordinary fibroblasts. These examinations were critical in that they spoke to the main reports that demonstrated sterol hardship and ABCA2 articulation in cells with hereditary deformities in cholesterol take-up and exit from the LE/LY. These outcomes are additionally predictable with the consequences of analyses portrayed above, where ABCA2 articulation was raised in cells refined in LPDS containing medium (sterol hardship).

CONCLUSION

In summary, due to the complex structures of ABC transporters its complete mechanism of action in neurological and metabolic disorders is obscure. The ABC transporters which incorporates P - GP and BCRPs at BBB assumes significant function in the transportation of essential compounds through BBB. In view of the current information we have, the P - GP and BCRPs viz ABC Transporters can be both useful and dangerous for us. On one hand, ABC assists with moving and get out excess substances and, subsequently, prevents neurotoxicity yet then again, they can likewise add to cerebrum confusions. Yet, the explanation we are not satisfactory about the working is that we don't have the clear idea about the specific mechanism of action of these transporters yet. For instance, how diabetes influence ABC carriers in cerebrum is as yet indistinct viz we don't know the specific systems by which the infections and harms to BBB happens. Along these lines, a superior comprehension of the functioning of ABC transporter in human brain is critical to comprehend the impacts of illnesses in mind and particularly, to build up a more secure and proficient measurement to treat a significant number of the diseases in human body. In this report we have proposed: (1) Structure of ABC transporters (2) Role of ABC transporters in neurological infections (3) Role of ABC transporters in a few metabolic sicknesses (3) Drugs focusing on ABC transporters for the therapy of these illnesses.

There are various ABC carriers, in which explicit transformations cause serious acquired infections. These are for the most part common remedial focuses in medication and in the current audit we just in a matter of seconds highlight a portion of these objective proteins. On account of the deadly acquired infection, cystic fibrosis, the most incessant transformation in the ABCC7/CFTR protein causes a misprocessing of the protein, along these lines any technique helping the correct handling and confinement of this freak variation is of significant interest. Significant changes in the ABCC8/SUR1 protein cause an extreme hyperinsulinemia infection in early stages, and at present the main treatment for this condition is the evacuation of insulin-delivering pancreatic islands. Regulation of ABCC8 and the connected K channel may fundamentally improve current medicines for different types of diabetes. It's a given, that on account of each particular carrier, disregarding the overall essential structure and instrument, explicit methodologies are needed for such turns of events.

ABBREVIATIONS

MDR = Multidrug resistance
LDL-C =Low-density lipoprotein-cholesterol
AS = Atherosclerosis
HA = Hyperalphalipoproteinemia
CAD = Coronary artery disease
TD = Tangier disease
FT = Full-transporter
HT = Half-transporter
SBPs = Substrate-binding proteins
RCT = Reverse cholesterol transportation
T2DM = Type 2 diabetes mellitus
HLCs = Hepatocyte-like cells
TG =Triglyceride
LPS = Lipopolysaccharide
LXRs = Liver X receptors
RXR = Retinoid-X-receptor
PPARs = Peroxisome proliferator-activated receptors
NF-Kb = Nuclear factor kappa-light-chain-enhancer of activated B cells
GPS2 = G protein pathway suppressor 2
ARF6 = ADP-ribosylation factor 6
RDS = Respiratory distress syndrome
NKT = Natural killer T
CYP450 = Cytochrome P450;
MRP1 = Multidrug resistance protein 1
TGN = Trans-Golgi network
ERC = Endosomal recycling compartment
PP = Protoporphyria
EPP = Erythropoietin protoporphyria
BLI = Bioluminescence imagine
MiRNAs = MicroRNAs
30-UTR = 30-untranslated region
SNPsm = Single nucleotide polymorphisms
AIS = Acute ischemic stroke
MAP K1 = Mitogen-activated protein kinase 1
LPP = Lipoma-preferred partner
CNS = Central Nervous System
NDDs = Neurodegenerative Diseases
AD = Alzheimer's Disease
PD = Parkinson's Disease
ABC = ATP-Binding Cassette
BBB = Blood-Brain Barrier
LDL = Low-Density Lipoprotein
LRP1 = LDL Receptor Related protein 1
AβPP = Amyloid-β Precursor Protein
NVU = Neurovascular Unit
ATP = Adenosine Triphosphate
ADP = Adenosine Diphosphate
ALS = Amyotrophic Lateral Sclerosis
MDR = Multidrug Resistance
NBDs = Nucleotide-Binding Domains
TMDs = Transmembrane Domains

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