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An Update on Role of Bile Acids in Neurological Functions and Neurodegenerative Diseases: A Narrative Review

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ABSTRACT

Having previously reviewed the role of Bile Acids (BAs) in obesity, NAFLD/NASH/HCC and crosstalk of Gut Microbiome in numerousbody disorders here we further attempted to assess part of BAs in normal brain physiology and in different Neurodegenerative Diseases (NDD). BAs constitute significant physiological molecules which apart from modulating nutrient absorption as well as metabolism in peripheral tissues influence neuromodulatory actions in the Central Nervous System (CNS). The formation of bile acids takes place basically from cholesterol in the liver by the canonical as well as alternate pathwaysor in the brain started by the neuron particular sterol Cholesterol-24 hydroxylase (CYP46A1) modulated pathway. Circulating BAs possess the capacity of crossing the Blood Brain Barrier (BBB) and thus gaining entry into the CNS via passive diffusion orthrough BAs transporters. Brain BAs act in the CNS via activationof membrane or nuclear receptors or influence the working of the neurotransmitter receptors. Indirect signal might be further given to the CNS through the Farsenoid X Receptor (FXR) based Fibroblast growth factor 15/19 (FGF15/19) pathway or the takeda G Protein Coupled (GPC) bile acid receptor 5 (TGR5) based Glucagon Like Peptide 1(GLP) pathway. In case of pathological situations, changes in BAs have been observed to probably aid in the pathogenesis of different neurological diseases. Of greater significance is the supplementationof hydrophilic amidated Ursodeoxycholic Acid (UDCA) or Tauroursodeoxycholic Acid (TUDCA) have been corroborated to illustrate therapeutic advantagesby hampering the neuroinflammatory reactions, apoptosis, Oxidative Stress (OS), Endoplasmic Reticulum (ER) stress, mitochondrial protection or work in the form of probable chaperone for correction of misfolding of proteins in the treatment of different neurological diseases.This yields opportunity of utilization of UDCA along with TUDCA in the treatment of different neurodegenerative diseases inclusive of Alzheimer'sdisease; Parkinson's disease, Huntingtons disease, Amyotrophic Lateral sclerosis,and prion disease.

Keywords

Bile Acids (BAs), Cholesterol metabolism, Neurodegenerative diseases, Ursodeoxycholic Acid (UDCA), Tauroursodeoxycholic Acid (TUDCA)

Introduction

Bile Acids (BA) are basically cholesterol obtained acidic steroids which are generated from cholesterol in liver, with storage in gall bladder followed by liberation into Gastrointestinal Tract (GIT), with regards to postprandial nutrient absorption, reabsorption with effectiveness from the intestines with ultimate return back to liver. This key motion which is named enterohepatic circulation aids in in sustenance of homeostasis [1,2]. Apart from nutrient reabsorption BA further work in the form of the steroid hormones for glucose, lipids along with energy metabolism by binding in addition to activation of different nuclear receptors for instance Farsenoid X Receptor [FXR] or Takeda G Protein Coupled (GPC) bile acid receptor 5 (TGR5). Previously we have reviewed the etiopathogenesis of both obesity, DM, next earlier endeavours to elucidate the association of GM dysbiosis alongwith microbial metabolites alterations in NAFLD/NASH/HCC where we studied bile acid metabolism and further we reviewed the detailed Bile Acids (BA) metabolism in various Cancers [3-6]. What is of maximum significance is the presence of BA in the brain in case of both physiological along with pathological situations has assumed considerable significance that highlights how examination of interactions amongst Central Nervous System (CNS), Peripheral Nervous System (PNS) along with its part in controlling brain working. Hence the aim of this review is concentration on generation, connection of BA amongstperiphery in addition to brain, physiological part of CNS by direct/in direct pathways as well as pathogenic or conferring protection part in case of Neurological conditions.

Methods

We conducted a narrative review utilizing the Pubmed search engine on, Bile Acids (BA using the MeSH terms Bile Acids (BA), Farsenoid X receptor [FXR], Takeda G protein Coupled (GPC) bile acid receptor 5 (TGR5), Cholic Acid (CA), Chenodeoxycholic Acid (CDCA), Ursodeoxycholic Acid (UDCA), Tauroursodeoxycholic Acid (TUDCA), CYP7A, CYP8B1, CYP46A1, 24(S)-Hydroxycholesterol (24-OHC), brain metabolism macrophage polarization, Alzheimer's disease, Parkinson's disease, Huntingtons disease, Amyotrophic Lateral sclerosis,

prion disease, (UDCA/TUDCA) treatment in neurodegenerative diseases from 1990's till date in August 2023.

Results

We found a total of 7050 articles out of which we selected 147 articles for this review. No Meta analysis was done.

Bile Acids (BA) Metabolism in Periphery in Addition to Brain

The circulating BA pool constitution comprises of primary BA's generated in liver along with secondary BA's conversion by particular Gut Microbiota (GM). Furthermore,the brain obtained BA adds to the BA pool. A connection amongst circulating BA or BA metabolic intermediate amongst periphery in addition to brain is existent by passive diffusion or BA transporters regarding crossing the Blood Brain Barrier (BBB). It is mainly formed along with circulated in periphery in addition to brain by the following the way highlighted in Figure 1 [7].

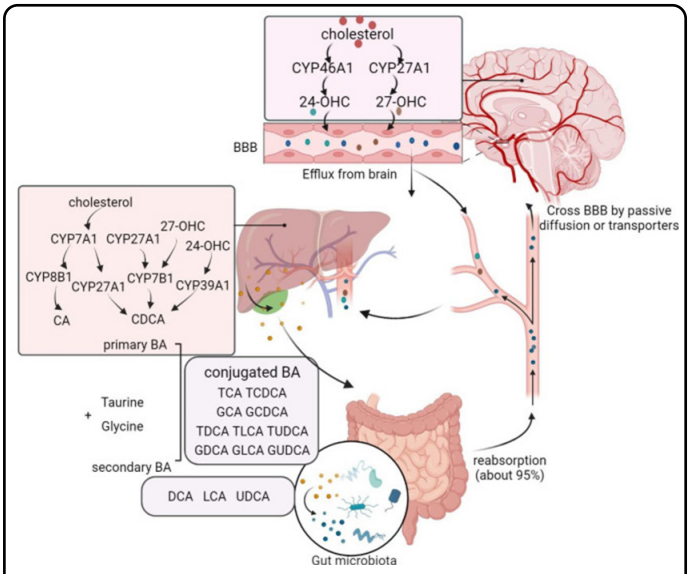

Figure 1: Courtesy ref no-7-Metabolism and circulation of bile acids in periphery and brain. The catabolism of cholesterol to primary Bile Acids (BA) in liver by two pathways, involving the critical enzymes cholesterol 7α-hydroxylase (CYP7A1) and sterol 12α-hydroxylase (CYP8B1) in the classical pathway to form Cholic Acid (CA), and sterol 27-Hydroxylase (CYP27A1) and oxysterol 7α-hydroxylase (CYP7B1) in the alternative pathway to synthesize Chenodeoxy Cholic Acid (CDCA). The neural cholesterol clearance pathway is initiated by CYP46A1 to form 24(S)-Hydroxycholesterol (24-OHC) from cholesterol. 24-OHC subsequently crosses the BBB, and is metabolized by CYP39A1 in the liver to synthesize CDCA. The brain 27-OHC converted by CYP27A1 might also cross the BBB and is metabolized by CYP7B1 in the liver. The primary BA are converted to conjugated forms with glycine or taurine. Then, primary BA are further converted to the secondary BA metabolized by the gut microbes. After re-absorption through passive diffusion or bile acid transporters, about 95% of BA are reabsorbed in the ileum and returns to enterohepatic circulation. A small amount of BA in the systemic circulation can be taken up into the brain by passive diffusion or by active transport through the Blood Brain Barrier (BBB).

Bile Acids (BA) Metabolism in Liver Along with Iintestine

Cholesterol catabolism to primary BA's takes place in periphery basically in the liver by the utilization of canonical pathway in addition to the alternate pathway [3]. The initiation of canonical pathway takes place by cholesterol hydroxylation at 7th position by CYP7A1 for generation of 7-α-Hydroxy Cholesterol (7-α-OHC). Subsequent to epimerization of 7-α-OHC through 3-β Hydroxysteroid Dehydrogenase type 7 (HSD3B7), the formed 7-α-hydroxy-cholesten-3-one either gets hydroxylated by sterol 12-α-hydroxylase (CYP8B1) which is followed by catalysis by aldo-keto-reductase family 1 members D1 (AKR1D1) along with aldo-keto-reductase family1 member C4 (AKR1C4) to generate 5-β-cholestan-3α,7α 12α-triol or catalysis by AKR1D1 or AKR1C4 in case of lack of CYP8B1. The steroid side chain of 5-β-cholestan-3α,7α, 12α triol as well as 5-β-cholestan-3α,7α-diol undergo oxidation by sterol 27-Hydroxylase (CYP27A1) for the production of Cholic Acid (CA) as well as Chenodeoxycholic Acid (CDCA) respectively [8]. The initiation of alternate pathway takes place on cholesterol hydroxylation at 27th position by CYP27A1 for production of 27-α-Hydroxy Cholesterol (27-α-OHC). Subsequently, 27-α-OHC undergoes more metabolism by CYP7B1 for production of 3-β-7-α-di hydroxy 5-cholestanoic acid for further transformation to CDCA. CA along with CDCA portray 2 primary bile acids. Specifically the maximum part of CDCA undergoes transformation to α-Muricholic Acid (α-MCA) along with β-Muricholic Acid (β-MCA) in case of mice by cytochrome P4502C70 (CYP4502C70) [9]. Elimination of hydroxyl group from CA along with CDCA get catalysis through Gut Microbiota (GM) into Deoxycholic Acid (DCA) as well as Lithocholic Acid (LCA) production takes place respectively [10]. In case of mice LCA might further be transformed into Ursodeoxycholic Acid (UDCA) followed by 7-α-hydroxylase to Hydroxydeoxycholic Acid (HDCA) further by 6 α hydroxylase or to Murideoxycholic Acid (MDCA) by 6-β-hydroxylase [11]. In case of humans 7-β-Hydroxysteroid Dehydrogenase (7-HSDH) work for catalysis of little quantities of CDCA to UDCA) [11]. Furthermore primary bile acid get transformed into conjugated BAs basically through glycine in case of humans or taurine (in case of mice) by Bile Acid CoA Synthase (BACS) along with bile acid CoA: Amino Nacyl Transferase (BAAT) [1].

The conjugated BA's Taurocholic Acid (TCA), Glyco Cholic Acid (GCA), Taurourochenodeoxycholic Acid (TCDCA) in addition to Glycochenodeoxy Cholic Acid (GCDCA). In mice the development of tauro-α (α-MCA) or tauro-β (β-MCA) along with Tauroursodeoxycholic Acid (TUDCA) are further present. The generated conjugated BA's might be transported by Bile Salt Export Protein (BSEP) in addition to Multidrug Resistance Protein 2 (MRP 2) from the hepatocytes into canaliculi that is followed by to the gall bladder for the generation of bile. Subsequent to food consumption; the nutrientspresent (specifically fat along with protein) in the stomach stimulate the emptying of gall bladder with liberation into the duodenum. This is followed by further transformation to the main secondary BA's, metabolized by the GM [12]. The main secondary BA's are inclusive of DCA, UDCA LCA, Hyocholic Acid (HCA), Hyodeoxycholic Acid (HDCA), MDCA in addition to ω-MDCA. The unconjugated BA's along with certain glycine conjugated BA's possess the capacity of reabsorption via passive diffusion in the jejunum as well as colon. Approximately maximum of BA's (95%) have the requirement of active reabsorption through the Apical Sodium dependent Bile Acid Transporting (ASBT) in the ileum. Approximately (95%) of BA's get reabsorbed in the ileum as well as is returned back to liver through Sodium-Taurocholate-Co transporting Peptide (NTCP) in addition to Organic Anion Transporting Polypeptides (OATPs) modulated BA's reuptake from the portal vein circulation [13]. Approximately 5% of BA's excretion takes place

via faeces. Thereby organizational homeostasisof BA'soccurs via enterohepatic circulation by dynamic generation, transportation as well as reuptake events.

Initiation of BA's generation by CYP27A1 in liver aids in greater than 70% of BA's biogeneration [14]. The initiation of alternate pathways by CYP7A1 is implicated in 25-30% of BA's produced in rodents; however just 5-10% BA's pool in humans. Recentlyit has been revealed that BA's quantities in CYP27A1-/- CYP27A1-/- mice displayed diminished quantities in plasma (45.9%), liver (60.2%), gall bladde (76.3%), small intestine (88.7%), colon (93.6%), in contrast to the wild kind mice [15]. In addition to that in female mice double knockout mice apparently illustrated greater quantitiesof reduced BA's [16], further confirmed with regards to presence of BA's formation in other tissuesin aiding in BA's homeostasis.

Brain Obtained Bile Acids (BA) Generation

Maximum enrichment of cholesterol exists in the brain having approximately 20% of full quantities of cholesterol [17]. Cholesterol is a constituent in the cellular membrane, myelin, synapses as well as generation of dendrites, along with is a precursor of steroid hormone; apart from impacting neuronal physiology in the generation in addition to adult stage [18]. Generation of cholesterol in the brain is independent of its production in periphery in view of Blood Brain Barrier (BBB) effectiveness in avoidance of its exchanging of the cholesterol existent in the circulatory system. Noticeably, the neural cholesterol clearance pathway takes place by transforming into BA's gives a main excretion manner in brain for ensuring the balance of escalated cholesterol.

Brain obtained Bile Acids (BA) generation pathway has the requirement of neuronal particular as well as rate limiting enzyme. Sterol Cholesterol-24-Hydroxylase (CYP46A1) expression takes place in variable brain areas for instance cerebral cortex, hippocampus, frontal lobe ,caudate nucleus, amygdala has placement entirely in the brain [18]. In brain BA generation takes place by oxidation of cholesterol to 24 (S)-hydroxy cholesterol whose catalysis takes place by CYP46A1. Apart from cholesterol S-OHC possesses the capacity of crossing the Blood Brain Barrier (BBB) as well as undergo passive diffusion into the systemic circulation to be followed by bioconversion by oxysterol-7-α-hydroxylase II (CYP39A1) in the liver resulting in the generation of CDCA [20]. Thereby the brain obtained BA generation implicates the earlier stages of cholesterol clearance in brain, transportation of 24 S-OHC from the BBB toward the periphery with following generation in the liver.

Via the aiding CYP46A1 modulated pathways the total BA generation is minimal, the transformation of cholesterol into 24 S-OHC represents the maximum significant cholesterol clearance pathways in the CNS. CYP46A1 deficiency might result in dysfunctional 24-S-OHC formation in the CNS that results in decreased brain in addition to serum 24-S-OHC quantities as well as deficiencies in cognitive function inclusive of spatial, associative along with motor learning [21]. A separate study further has demonstrated that knockout of CYP46A1 expression in the striatum replicated Huntingtons disease phenotype with spontaneous striatal neuron degradation as well as motor deficiencies [22]. Nevertheless, knockout of CYP46A1 genes resulted in approximately 40% diminished brain cholesterol excretion, pointing to other routes of cholesterol elimination from the brain which is independent of CYP46A1 presence also [21].

CYP7A1 expression takes place throughout the body. Continuous influx of 27 OHC produced by CYP7A1 in addition to metabolites with regards to this oxysterol from extrahepatic sources into the liver for further transformation into BA. CYP7A1 along with CYP7B1 are further expressed in the brain might be pointing that primary bile acids might be formed in the brain as well [23]. By utilization of mouse model 27 OHC escalated 12 times in the brain [23]. 27 OHC possesses the capacity of crossing the BBB followed by pacey depletion of 27 OHC in the brain for getting metabolized into a steroid acid , 7-α-hydroxy-3 oxo-4-cholestanoic acid that might further cross the BBB ,thereby gaining entry into the circulation [24]. Mice having the CYP7A1-/- illustrated reduction in the BA pool size along with escalation of cholestanol in the brain [25]. As per the expression of CYP7A1 in the brain appears to be working in a different manner for elimination of cholesterol. Furthermore, CYP7B1 in the brain is implicated in neurosteroid metabolism by catalysis of 27-OHC Hydroxylation, Dehydroepiandrosteron (DHEA), as well as pregnenolone [20,26]. In toto working of CYP7A1 in addition to CYP7B1 in the brain is probably for depletion of cholesterol; however if they aid in BA generation in the brain needs further validation.

Interactions of BA amongst CNS along with Periphery

Persistence of flow of knowledge amongst the brain along with peripheral tissues is significant in sustenance of physiological functions. Specifically circulating metabolites working in the form of the connecting bridge amongst the gut along with brain has sought escalating interest. In the gut lumen the dihydroxylation of the primary bile acids gets guided by restricted quantities of microbes which are a part of the Firmicutes phylum which is followed by deconjugation of glycine along with taurine from the sterol core of conjugated BA gets catalyzed by various microbial species inclusive of *Lactobacillus, Clostridium, Bifidobacterium* Bacteroides which express functional enzymes Bile Salt Hydrolases (BSH) [27]. Furthermore, certain other BA conversions for instance oxidation/reduction reactions along with hydroxyl group epimerization might get catalysis by Gut Microbiota (GM) inclusive of *Actinobacterium Proteobacteria, Bacteroides Firmicutes Clostridium, Eubacterialis spp, Ruminococus spp* [28,29].The microbiota encoded conversions ultimately form secondary bile acids aiding in the intestinal bacterial constitution in addition to the full BA pool size [30]. With the escalation of validation of key communication amongst the GM along with working of the brain or the neurological situations, thegut microbial metabolites BA are most likely to be linked in the form of a significant connection channels in the gut-brain-axis [31].

Recently, the existence of numerous primary in addition to secondary bile acids metabolites have been observed expressed in the brain in case of physiological conditions. Different studies have illustrated that variable BAs spp inclusive of conjugated as well as unconjugated BAs are observed in brain metabolomic profiles of human as well as rodents [32-35]. In a prior study 3 protein bound unconjugated BAs inclusive of CA, CDCA along with DCAwere isolated in the rat brain cytoplasmic fraction [32].

With the utilization of high sensitivity as well as high resolution Mass Spectrometry (MS), 20 BAs collectively have been isolated in rat brain metabolome, maximum of which had not been earlier revealed [33]. By contrasting BAs constitution in addition to quantities in the brain along with plasma of humans as well as mouse samples, variable BAs profiles have been isolated in brain tissues inclusive of the frequent BAs (CDCA, CA, LCA, TCA, DCA) human particular BAs (CDCA, GCA, GDCA, GCDCA, TUDCA, UDCA) in addition to mouse particular BAs (TUDCA, β-MCA, Ω-MCA) [35]. The isolated BAs metabolites in the brain are comprised of primary BAs generated in the liver, secondary BAs transformed by intestinal microbiota. Thereby there is requirement of direct interaction of BA amongst CNS along with periphery.

Direct origination of brain BA pool size from systemic circulation is feasible.It has been pointed that unconjugated BAs might get transported across the BBB as well as gain entry into the brain at minimal quantities by passive diffusion mainly based in their hydrophobic characteristics [36]. For instance UDCA illustrates the capacity of penetration of experimental BBB model via utilization of concurrent monolayer of human brain microvascular endothelial cells in a time based way [37]. Quantities of brain CA, CDCA, as well as DCA positively associates withserum quantities in addition to intraperitoneal deuterium labelled CA, as well as CDCA got well determined in rat brain [38]. Regarding conjugated BAs, BAs conjugation with glycine along with taurine possessed the capacity of escalating amphipathicity (amphipathic molecules represent chemical substances possessing both polar/non-polar (apolar) parts in their structure (derived from Greek, amphis-both and pathy-suffering/feeling) as well as their solubility, that ensures their impermeability for crossing the cell membranes. Variable BAs transporters have been observed to be expressed in the CNS inclusive of MRP2, BSEP, NTCP in the choroid plexus [39], OATPs in brain capillary endothelial cells [40], ASBT in the hypothalamus [41], yielding the mode behind the neuronal uptake of conjugated BAs from periphery into the CNS by expressing BA transporters. Nevertheless, direct validation of in vivo BAs transport crossing the BBB their transporters is currently absent. Recently it has been displayed that variable endogenous BAs, particularly the tauro conjugated spp. like TDCA, TCA, TUDCA, TαMCA TβMCA possessed the capacity of reaching the hypothalamus pacily with transitory escalation of 30-60’ subsequent to physiological feeding at the initiation of the dark phase of mice [42]. Akin to that orally delivered BAs mix possessing the sodium salt of taurocholic acid, glycocholic acid, deoxycholic acid as well as cholic acid possessed the capacity of reaching the hypothalamus very fast. Overall transportation of BAs might take place across the BBB by passive diffusion or uptake by transporters that is associated with their conjugated or unconjugated forms.

The intactness of BBB along with permeability possess sensitivity to BAs quantities, whose modifications/injury is feasible by escalated quantities of exposure to BAs. Aberrantly greater quantities of sodium deoxycholate along with taurochenodeoxycholate working in the form of robust detergents which might injure the lipid layers of the BBB, whereas just minimal escalation of BAs quantities might result in modifications of the BBB permeability in an indistinct manner [43]. Furthermore, CDCA as well as DCA acid possess the capacity of disturbing endothelial tight junctions by enhancement of occluding phosphorylation in a Rac1 based way which results in escalation of permeability of the BBB [44]. Thereby peripheral BAs possess the capacity of gaining entry into the brain with ease in view of escalated BAs quantities in systemic circulation or in view of disrupted BBB permeability in case of pathological situations, that is in agreement with numerous displayed aberrant BA profiles in brain tissues or in Cerebrospinal Fluid (CSF) in neurological conditions [45].

The Physiological Working of BA in CNS

It has been broadly revealed that BAs work in the form of signaling molecules in case of non nervous systems by activation of different nuclear or membrane receptors. FXR as well as TGR5 portray 2 of the maximum evaluated BA receptors. Apart from these 2 receptors, further receptors also get activated by BA; for instance Liver X Receptor-A (LXR–α), Glucocorticoid Receptor (GR), Pregnane X Receptor-A (PXR), Vitamin D-Receptor (VDR), Sphingosine-1-Phosphate Receptor-2-Receptor (SIPR2) respectively [46]. Despite, the observation of these receptors in the brain, asssessment has not been done till now if BAs impact neurological working directly via these receptors. Recently it has been displayed that functional FXR receptors are observed in mouse along with human brain [47,48]. With the utilization of FXR knockout mice, FXR signaling disrupted the balance amongst Gamma Amino Butyric Acid (GABA) to Glutamate (Glu) in the hippocampus in addition tocerebellum along with dysfunctional cognitive function as well as motor coordination [49]. Nevertheless, direct validation with regards to confirmation of BAs activated FXR signaling in controlling brain working needs further evaluation . Recently ,a separate study has verified that postprandial BAs possessed the capacity of gaining entry into the brain as well as control satiety in reaction to physiological feeding [42]. Peripheral or centrally delivered BAs mix or TGR5 particular BA mimetic (INT-777) might possess an anorexogenic actions through activation of TGR5 in the orexogenic Agouti Related Protein (AgRP)/Neuropeptide Y (NPY) neurons in the hypothalamic arcuate nucleus [42].

Certain studies further observe the neurological working of BA is produced via impacting the working of neurotransmitter receptors for instance, N-Methyl-D-Aspartate (NMDA) receptors, GABA type A (GABAA) receptor. The NMDA receptor, mirrors an ionotropic glutamate receptor, that possesses significant part regarding synaptic function connection by resulting in Ca2+ influx by activating calmodulin which stimulates CaMKII, mitogen activated protein kinase (MAPK), CREB in addition to Phosphatidyl Inositol 3–Kinase (PI3K) pathways [50]. The GABA A receptor portrays a ligand gated chloride ionic channel whose activation results in influx of chloride ions leading to neurons hyperpolarization as well as neurotransmission hampering [51]. Endogenous neurosteroids portray robust modulators of NMDA receptor along with GABA A receptor [52]. Akin to that, CDCA as well as CA acid possessed the capacity of blockade of GABA A in addition to NMDA receptor, with CDCA possessing greater robustness of reduction of the firing of hypothalamic neurons along with synchronization of the networks actions by antagonization of the NMDA receptor along with GABA A

receptor [53]. GABA works to stimulate sleep through binding to GABA A receptors which get expressed in the histaminergic neurons as well as repression of histaminergic neurons present in the Tuberomammilary Nucleus (TMN) of the hypothalamus [54]. UDCA further possesses the capacity of blockade of GABA A receptor on TMN neurons for dishampering of the histaminergic system which works to facilitate wakefulness at the time of active period of day in case of wild mice [55]. Furthermore, TUDCA was verified to escalate the proliferation,self renewal in addition to neuronal talk with Neural Stem Cells (NSCs) [56]. Adult neurogenesis takes place in 2 particular areas inclusive of subgranular zone(SGZ) of the hippocampal Dentate Gyrus (DG) as well as Sub Ventricular Zone (SVZ) of the lateral ventricles. TUDCA possessed the capacity of influencing postnatal NSCs fate by selectively stimulating SVZ obtained NSCs proliferation along with neural differentiation; however, not of the DG obtained NSCs [57]. Intracerebroventricular delivered TUDCA in adult rats considerably escalated NSCs proliferation along with neural differentiation in SVZ areas [57]. Thereby these observations confirmed that BAs influence the neurological working of neurotransmitter receptors that get expressed in the local brain areas.

Apart from direct actions stimulated by BAs in brain, peripheral BAs might further indirectly convey the signal to the CNS through FXR based Fibroblast growth factor 15/19 (FGF) 15/19 pathways or TGR5 based glucagon like peptide 1 (GLP) pathway [58]. Mouse FGF 15 in addition to itshuman orthologue FGF 19 portray hormone like enterokines basically produced by ileum that are under transcriptional regulation of BAs activated FXR. In the intestine, BAs whose absorption takes place by enterocytes possess the capacity of activation of nuclear receptors FXR well as resulting in generation of FGF 15/19 [59]. Liberation of FGF 15/19 into the portal vein takes place for influencing its hampering actions on BAs generation or control glucose along with lipid metabolism [60]. Of maximum significance is that FGF 19 has the capacity of crossing the BBB along with having germane stability in the brain [61]. Fibroblast Growth Factor Receptor (FGFR) 4 expression-the major receptors for FGF 15/19 have been observed in the hypothalamus along with medial habenacular nucleus [62]. Intriguingly, the orexogenic AgRP/NPY neurons placed in the hypothalamic arcuate nucleus possess the capacity of reacting to FGF 19 delivered by both intraperitoneal as well as intracerebroventricular injection in mice [63]. The central actions of FGF 19 decrease hypothalamic AgRP/NPY neurons actions along with result in improvement of glucose metabolism as well as glucose homeostasis [62,63]. A separate study has corroborated that TCA gavage had the capacity of escalating transcriptional FGF 15 expression in the ileum in addition to result in improvement of oral glucose tolerance in case of obese mice. Furthermore, mice having FGFR 1 deficiency in particular in AgRP/NPY neurons generate elimination of reacting to TCA, implying thereby that FGFR 1 is imperative for modulating the advantageous actions over glucose tolerance [64]. Overall FGF 15/19 signaling in the CNS is intricately correlated with energy in addition to glucose tolerance. Nevertheless,one key query which still is there is if escalation of circulating FGF 15/19 stimulated by intestine BAs is enough to evoke a considerable action in the CNS at the time of normal physiological situations.

In the intestine, activation of TGR5 by BAs in the enteroendocrine L cells possess the capacity of leading to the liberation of GLP-1 that portrays a gut hormone having the capacity of conveying BAs signal from the intestine to the other body areas [65]. Intestinal GLP-1 might be of gaining entry into the brain through the systemic circulation or via the vagal nerve [66]. The expression of GLP-1occurs in different tissues inclusive of CNS as well as vagal neurons [67]. GLP-1 has the capacity of crossing the BBB or convey the signal through the vagal afferents from the GIT to the CNS [68,69]. Through the vagal-brain stem- hypothalamic pathway peripheral GLP-1 has the capacity of impacting numerous brain areas in addition to sequentially hampering actions on food consumption along with enhanced satiety perception [66,70]. Noticeably, it was feasible to inactivate GLP-1 very fast by the enzyme Dipeptidyl Peptidase-4 (DPP-4) that gets expressed in the endothelial membrane of the capillaries along with plasma. Thereby greater probability exists with regards to intestinal BAs might be signaling to the brain through GLP-1 pathway conveyed via the vagal nerve instead of crossing the BBB through the systemic circulation [71]. Nevertheless, the precise repercussions along with how much BAs aid in these signaling routes is the requirement for future research.

Generally, BAs might be impacting a neuromodulatory action in the CNS through the membrane or nuclear receptors or influencing the working of neurotransmitter receptors.

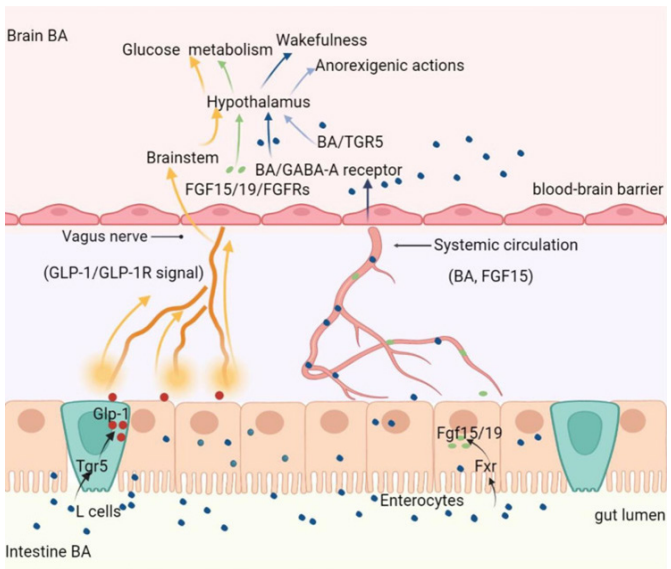

Figure 2: Courtesy ref no-7-Bile acids signal to the central nervous system (CNS). Bile Acids (BA) in the intestinal lumen can signal to the CNS via the direct pathway or indirect pathway. Bile acids in the intestine escape the enterohepatic circulation, reach the systemic circulation, and cross the Blood-Brain Barrier (BBB) to interact with receptors in the brain. BA in the CNS could exert an anorexigenic effect via activating TGR5 in the hypothalamic arcuate nucleus or block GABA A receptor on Tuberomammillary Nucleus (TMN) of the hypothalamus to promote wakefulness. BA taken up by enterocytes can activate the nuclear receptor FXR to promote FGF15/19 production. FGF15/19 is released by the enterocytes, enters the systemic circulation, and cross the BBB to interact with FGF receptors in the brain. The central effects of FGF15/19 are involved in glucose metabolism and energy homeostasis. TGR5 activation by BA in enteroendocrine L-cells triggers GLP-1 production. GLP-1 could interact with GLP-1 receptors expressed on afferent terminals of the vagal nerve present in the lamina propria and portal vein. The vagal nerve projects to the brainstem, from where projections are further directed toward other brain regions. GLP-1 is believed to exert its inhibitory effect on food intake and energy homeostasis via the vagal-brainstem-hypothalamic pathway.

Peripheral BAs connection with the CNS takes place through the systemic circulation directly gaining entry into the brain or indirectly via the FXR-FGF 15/19 pathway or TGR5-GLP-1 pathway. Figure 2 which illustrates pathways of BAs signal to the CNS.

Working of BA in Neurological Conditions

The cytotoxic characteristics of BAs have key association with their hydrophobicity. The extent of hydrophobicity of unconjugated bile acids would be UDCA<CA<CDCA DCA<LCA. On conjugating them with glycine or taurine they become hydrophilic amidated kinds. On hydrophobic unconjugated bile acids getting retained might result in damage to the hepatocytes which implicates the interference with cell membranes, facilitating Reactive Oxygen Species (ROS) generation, result in mitochondrial impairment, induction of Endoplasmic Reticulum (ER) stress leading to apoptosis as well as necrosis [72]. Noticeably, the hydrophilic BAs, UDCA in addition to its taurine conjugated TUDCA have gained attention with regards to their lesser toxicity possess the characteristics of protection against cholestatic liver disease by escalation of antioxidant actions as well as hampering apoptosis. Different BAs, metabolites in the diseased brain further display that BAs are associated with the pathogenesis of neurological disorders, or work in the form of protective factors for relief of symptoms in certain neurological diseases.

BA Metabolites in Neurological Disorders: The Robust Probable Pathogenic Factors

Hepatic Encephalopathy (HE), a robust inimical complication of acute as well as chronic liver failure has a presentation of impairment of brain which encompasses a broad spectrum of neurological in addition to psychiatric aberrations varying from mild cognitive dysfunction to considerable disorientation,confusion along with coma [73]. Serum BAs have been acknowledged to escalate in situations where liver injury is present for instance in acute as well as chronic liver conditions. Significantly changed bile acid profilesin brain or CSF has been further corroborated in patients of HE or experimental models.The blood quantities of overall BAs as well as in particular conjugated BAs wereconsiderably elevated in cirrhosis patients with HE in contrast to cirrhosis patients without HE or healthy subjects as controls [74]. BAs quantities in CSF illustrated a greater escalation of GUDCA (93 times) as well as GCA (241 times) in HE patients [75]. In case of rat brain where HE induction took place subsequent to ligation of bile duct, substantial enhancement of the toxic Lithocholic Acid (LCA) (84.7% of overall BAs), whereas LCA was lacking in controls [76]. Utilization of Azoxymethane (AOM) injections, stimulated HE mice model have illustrated escalation of BAs quantities in brain tissues as well [48]. Moreover, TCA was isolated tobe particularly escalated in the cortex of AOM stimulated HE mice [77]. Additionally, through delivery of a BA sequestrant alias cholestyramine to AOM stimulated HE mice,there was a reduction of circulating as well brain BAs quantities. On the other hand, CA or DCA feeding further were inimical for AOM stimulated neurological decrease, pointing that BAs spp aid in the neurological decrease in HE [48]. The modes behind how Bas stimulate neurological decrease has further been worked out, that implicate FXR along with SIPR2 signaling [48,77]. Particularly, their observation was that activation of cortical SIPR2 by escalated TCA quantities stimulated microglial activation; thereby sequentially result in neuroinflammation in the AOM stimulated HE mice [77]. Overall, their observations pointed to the escalation of BAs pool size in the brain works in the form of a systemic pathogenic aiding to the impairment of brain in HE.

Alzheimer's Disease (AD): Alzheimer's Disease (AD) portrays, an accelerated degenerative disease resulting in dementia in elderly age having the properties of neuropathoological alterations inclusive of aggregated beta amyloid (A beta) plaques in addition to Neurofibrillary Tangles (NFT), astrogliosis, microglial activation along with remarkable neuronal death [78]. At present the changed BA constitution are of escalating problem in experimental models along with mild cognitive dysfunction or AD patients. In plasma of amnesic mild cognitive dysfunction or patients of AD the quantities of certain BAs inclusive of DCA, LCA, GDCA, or GUDCA, have been reported to be significantly escalated in contrast to age matched controls [79]. A different study further revealed significantly lesser quantities of serum CA or brain, TCA in case of AD patients in contrast to cognitively elder adults [26]. In case of Amyloid Precursor Protein α (APPα) APP/PSI mice model of AD; there is a probability of disruption of quantities as well as constitution of brain BAs at the time of generation of AD pathology. Greater serum CA, greater LCA, in addition to, lesser TMCA in the brain were determined in 6 months old APP/PSI mice whereas quantities of brain CA,TMCA, βMCA, ΩMCA, TCA along with TUDCA were reduced in 12 months old APP/PSI mice [26]. Noticeably, the changed BA metabolites as well as the ratios of secondary bile acids vis primary bile acids were further observed to be correlated with brain structural along with functional dysfunction in AD. Dependent on the brain transcriptomics as well as metabolomics of postmortem AD samples greater GCDCA/CA in addition to secondary BA's (DCA, LCA, TDCA as well as GDC) were isolated in patients of AD in contrast to cognitively normal subjects [80]. Akin to that escalated quantities of secondary BA's (DCA, GDCA as well as TDCA) in serum along with escalated DCA: CA ratio in serum as well as brain was observed to be intricately correlated with cognitive decrease [81]. Utilization of targeted metabolomic profiling, the correlation of Serum dependent BA metabolites with neurodegeneration biomarkers in addition to structural alterations of AD were isolated. Greater GCDCA: CA quantities had a correlation with greater amyloid getting deposited [82]. Greater quantities of primary GCDCA, secondary BA's (GLCA, as well as TLCA) were associated with greater CSF p-tau values. Escalated quantities of primary GCDCA, secondary BA's (GLCA, as well as TLCA) in addition to ratios of secondary BA's to primary BA's (TDCA: CA, GDCA: CA as well as GLCA: CDCA) had a significant correlation with decreased cortical thickness as well as hippocampal volume. Overall, their observations gave a newer insight for illustrating that escalated quantities of secondary cytotoxic BA's as well as their ratios with primary BAs have an intricate correlation with the pathogenesis of AD. The existence of secondary cytotoxic BAs in the brain further robustly pointed to the significance of gut- brain axis in addition to gut microbiome in the physiological alterations in AD. Taken together these present observations verified the thought that circulating along with brain BAs might be aiding in the

pathogenesis of AD.

Parkinson's Disease (PD): Parkinson's Disease (PD) illustrates the 2nd commonest neurodegenerative diseases with presentation in the form of a propagating motor worsening having the properties of Dopaminergic (DA) neurons demise in addition to accrual of intracytoplasmic α-synuclein possessing Lewy bodies in the substantia nigra [83]. In case of studies performed in clinical PD patients as well as surgical rodents models of PD changes in BA metabolism was found. Escalation of unconjugated BA's (CA as well as DCA) along with conjugated BA's were observed in plasma of patients of PD in contrast to healthy controls, that further might be ameliorated by levodopa [83]. Asssessment of BAs in PD patients further displayed an escalation in appendix (of DCA as well as LCA) in addition to in ileum (LCA) germane to controls [84]. Conducting metabolic profiling of CSF from people impacted by sporadic along with genetically susceptible (LRRK2) to PD, BA metabolism was further isolated in the form of the main influenced biochemical pathways, in particular the abnormal quantities of GDCA, TCA, as well as GUDCA [85]. Using rodents PD model by stereotactic unilateral injection of human α-synuclein fibrils, 3 BAs were observed inclusive of (ΩMCA, TUDCA in addition to UDCA) were observed to be downregulated in serum of prodrome phase of PD in contrast to healthy controls [86]. By utilization of quantities of the 3 BAs in combination of logistic regression,these prodromal mice were differentiated from control mice with greater precision subsequent to cross corroboration. Thereby these outcomes emphasize the probability of BAs in the form of biomarkers for anticipation of PD in its early stage along with probably the propagation of PD.

Huntingtons Disease (HD): Huntingtons Disease (HD) portrays an inherited autosomal dominant neurodegenerative disease, whose presentation is motor, behavioral as well as cognitive impairments in the form of clinical symptoms [87]. The expansion of CAG repeats in the exon 1 of Huntingtin gene on chromosome 4 stimulates neuronal elimination in the striatum as well as result in synaptic impairment. At present clinical in addition to animal dependent research still don't validate the correlation of BAs profiles in the pathogenesis of HD. Nevertheless, recent observations pointed to changed cholesterol homeostasis in the pathophysiology of HD [88]. Despite, no description of BA quantities in the brain along with circulating systems, CYP46A1 expression in addition to quantities of CYP46A1 expression in addition to 24 S-OHC metabolites have been observed to be decreased in the plasma of HD patients [89] along with brain of the different Yeast Artificial Chromosome (YAC) mice (possessing propagating escalating CAG repeats) along with knock-in mouse models [89]. The way revealed previously reduction of CYP46A1 expression in the putamen of HD patients as well as in the striatum of R6/2 mice (a mouse model of HD) in addition to striatal Huntingtons disease cells lines (by transfection of mutant Huntingtin gene) [22]. Knockout of CYP46A1 expression in the mouse striatum stimulated generation of spontaneous striatal neurodegeneration that had a correlation with aberrant balance along with motor coordination.On restoring CYP46A1 in the striatum of R6/2 mice, led to reduced neuronal atrophy in addition to improvement of motor deficiency. This study corroborates the neuroprotective part of CYP46A1 in HD. Thereby these outcomes indicate that the dysfunctional brain obtained BA formation might aid in HD pathology.

Cerebrotendinous Xanthomatosis (CTX): Cerebrotendinous Xanthomatosis (CTX) represents an occasional neurodegenerative condition which takes place secondary to an autosomal recessive mutation in the CYP46A1 gene, illustrates infants originating diarrhea,juvenile onset cataracts, young adult initiation of tendon xanthomas, propagating neurological impairment etc. [90]. The neurological propagation inclusive of maximum frequent corticospinal tracts aberrations (weakness, hyperreflexia, spasticity,ataxia, cognitive impairment as well as gait problems) in addition to lesser frequent aberrations (convulsions, psychiatric, as well asspeech alterations) [91]. CYP27A1 deficiency resulted in dysfunctional capacity of transformation of cholesterol into CDCA, resulting in accrual of cholesterol as well as plasma cholestanol (precursor of CDCA) in tendon, artery along with brain [92]. Despite, there is scarcity of involvement of BA metabolites in the CTX brain, replacing CA as well in part CDCA delivery is done for reduction of the accrued cholesterol in addition to improvement of symptoms in CTX [93]. Nevertheless, with regards to improvement of neurological symptomsof CTX, the age at which diagnosis in addition to CDCA initiation is done is intricately correlated with the prognosis [94]. Despite, no clarification exists with regards to the molecular modes behind the actions of the CDCA on the neuropathological phenotypes in the CTX cases, the dysfunctional BA formation as well as decreased CDCA basically aid in CTX pathology along with neurological impairment.

Working of BA in treatment of neurological conditions: the neuroprotective part UDCA along with its taurine conjugation obtained Tauroursodeoxycholic Acid (TUDCA) are both believed to be hydrophilic BAs [95]. Currently, just UDCA has got acquisition of US FDA approval regarding treatment of primary biliary cirrhosis [5,6]. Utilization of UDCA along with TUDCA in the form of a substance for treatment of neurological conditions is now believed to be attractive for stimulation of anti–neuroinflammatory reactions, hampering apoptosis, diminish Oxidative Stress (OS), mitochondrial protection, or might be working in the form of a chaperone for correction of misfolding of proteins.

The anti–neuroinflammatory actions: Neuroinflammation takes place as a reaction to inimical stimuli, along with damage at the time of infection, traumatic brain injury, or neurological diseases. Its properties are activation as well as proliferation of microglia/astrocytes which gets followed by liberation of proinflammatory mediators [96]. Escalating studies have corroborated the presence of neuroinflammation in aiding in the pathogenesis of neurological conditions [97].

UDCA possess the capacity of impacting the anti–neuroinflammatory actions by repression of microglial activation as well as proinflammatory cytokines generation. A previous study illustrated that UDCA has the effectiveness of hampering proinflammatory cytokines Interleukin-1β (IL-1β) along with Nitric Oxide (NO), stimulated by Amyloid beta 42 (A beta42) or Lipopolysaccharides (LPS) in rats microglial cells [98]. Moreover, UDCA was observed to hamper the breakdown of IκB kinase-β (IKappaB) for blockade of genes implicated in expression of nuclear factor κB (NFκB) based genes involved in

inflammation commonly reduced glial activation in A beta 42 in BV-2-microglial cells [99]. Thereby UDCA works to abrogate the formation of the proinflammatory mediators inactivation of NFκB in microglia for hampering neuroinflammation. Furthermore, in 1-Methyl-4-Phenyl,1,2,3,6-Tetrahydropyridine (MPTP) stimulated mouse model of PD, treatment with UDCA reduced the quantities of Tumor Necrosis Factor alpha (TNFα) IL-6,IL-1β, in addition to IFN-γ as well as avoided MPTP stimulated degeneration of DA neurons, whose mode associated with the hampering of phosphorylation of c-Jun-N-Terminal Kinase (JNK) as well as p38MAPK against neuroinflammation [100].

TUDCA's anti-inflammatory characteristics further have been validated in different pathological situations. In an animal model of acute neuroinflammation TUDCA particularly diminished microglial activation in the hippocampus, Monocyte Chemoattractant Protein 1 (MCP1), Vascularcell Adhesion Molecule [VCAM]-1), whose requirement is present for microglial migration in addition to blood monocyte invasion to the CNS inflammation area [101]. TUDCA's molecular modes behind influencing anti-inflammatory actions was diminished nitrite generation via transcriptional hamperingof inducible Nitric Oxide Synthase (iNOS), along with hampering of proinflammatory stimulated NFκB activation of glial cells [101]. Moreover, TUDCA possessed an extra modes in impacting anti-inflammatory actions via activation of transforming growth factor beta (TGF-β) in mouse brain [102]. Yanguas Cansas Netal [103], further verified that TUDCA resulted in biasing of the microglial phenotype to anti-inflammatory one in vitro as well as in vivo. By binding the bile acid receptors GPBAR/TGR-5, TUDCA resulted in escalated cAMP quantities in microglial cells leading to induction of anti-inflammatory biomarkers whereas decreasing proinflammatory biomarkers [103].

Akin to that TUDCA treatment ameliorated dysfunctional behaviour with effectiveness, reverted downregulated TGR-5, mitigated microglia lactivation, avoided neuroinflammation by hampering NFκB signaling for decreasing proinflammatory cytokines (TNFα, IL-6,IL-1β,) along with escalates anti-inflammatory cytokine (IL-10) in the hippocampus [104].

TUDCA further illustrated amelioration of secondary neuroinflammation resulting from primary traumatic brain injury . Spinal Cord Injury (SCI), a robust kind of trauma/damage that takes place to the spinal cord, having the properties of complete/incomplete spinal motor as well as sensory impairment [105]. In view of the irreversibility of the event of the primary damage resulting from original mechanical injury, the following, secondary damage which takes place in view of ischaemia along with edema has the requirement of considerable botheration along with resolve. Resident microglia in addition to haematogenous macrophages work in the form of crucial stimulators for inciting the inimical inflammatory reactions subsequent to SCI. TUDCA dependent anti-inflammatory treatment recently has illustrated promise with regards to efficiency in SCI therapy. TUDCA further possessed the capacity of reducing proinflammatory med inclusive of NO, TNFα, IL-1β, Cyclooxygenase-2 (COX-2), as well as iNOS in LPS stimulated BV-2-microglial cells, RAW264.7 macrophages in addition to Bone Marrow-Obtained Macrophages (BMDM's) [106]. Concurrently, in SCI in rats, TUDCA treatment aided in the restoration of the damaged area in addition to aiding in the polarization of macrophages/microglia towards M2, kinds for diminishing inflammatory response by repression of inflammatory factors (iNOS, CD68, as well as CD86) [106]. Furthermore, TUDCA abrogated PKM2 pathway of microglial activation in proinflammatory microglia as well as hampered the expression of IL-6, IFN-β, along with high mobility group AT-hook2 (MGA2) in the centre of the lesion [107]. Utilization of injectable hydrogel possessing TUDCA, further significantly diminished the inflammatory quantities of cytokines (TNFα, IL-1β, IL-6, IFN-γ) as well as repressed the phosphorylation of extracellular signal–Regulated Kinase (ERK), JNK in addition to p38 in the MAPK pathway in the damaged Spinal cord segments [108]. Moreover, TUDCA was validated to facilitate the differentiation of BMDM's obtained M2 macrophages. Additionally, transplantation of TUDCA inducing M2 phenotype macrophages in SCI rats model reduced proinflammatory cytokines ((TNFα, IL-1β, IL-6) in addition to enhanced anti-inflammatory cytokine (IL-4) that associates with hampering of phosphorylation of ERK, JNK in addition to p38 in the MAPK pathway [109]. Nevertheless, a recent study verified that TUDCA just diminished neuroinflammation along with resulted in improvement of autonomic as well as motor working in the subacute phase however does not support long term functional recovery in the chronic phase of SCI rats model [110]. Thereby these outcomes illustrated apparently TUDCA gives part protection possessing therapeutic significance in the reducing of secondary neuroinflammation resulting from primary traumatic brain injury.

TUDCA possessed the capacity of ameliorating chronic neuroinflammation by hampering astrocytoses or microglial activation in neurodegenerative diseases inclusive of AD, PD, Multiple Sclerosis (MS), retinitis pigmentosa.In case of AD deposition of amyloid beta resulted in remarkable microglioses as well as astrocytoses which surround the influenced region. TUDCA supplementation had the capacity of attenuation of activation of glial cells in APP/PSI mice [111]. Akin to that one more study illustrated that TUDCA treatment possessed the capacity of abrogating remarkable microglioses as well as astrocytoses in the hippocampus along with frontal cortex in APP/PSI mice, in addition to reduction of proinflammatory cytokines(in particular TNFα [112]. In case of a MPTP stimulated PD mouse model, TUDCA hampered astrocyte in addition to microglial activation [113,114,]. Furthermore, TUDCA ameliorated expression of IL-1β along with enhanced the anti-inflammatory protein ANXA1 expression in the cortex [114]. In case of chronic demyelinating MS repressed quantities of circulating BAs metabolites were observed in numerous cohorts of adult in addition to Paediatric MS pts in contrast to controls by utilization of metabolomics patients [115]. Of greater significance TUDCA supplementation possessed the capacity of blockade of neurotoxic polarization of astrocytes in addition to proinflammatory polarization of microglia, decreased innate immune cells infiltration along with the robustness of behavioural as well as pathological alterations in Experimental Autoimmune Encephalomyelitis (EAE) animal model of MS which abrogated neuroinflammation by the actions of TUDCA on G Protein Coupled (GPC) bile acid receptor 5 (GPBAR) [115]. Heritable neurodegenerative retinitis pigmentosa model, TUDCA proved to be of advantage through

anti-inflammatory actions by reduction in numbers in addition to activation of microglial cells [116]. TUDCA treatment further possessed the capacity of escalating phagocytosis of photo receptors outer segments of by retinal pigment epithelium cells through activation of Mer Tyrosine Kinase (MerTK) receptor [117]. Thereby these outcomes overall illustrated that TUDCA treatment ameliorated chronic neuroinflammation in case of neurodegenerative conditions.

The anti–apoptotic actions: Animal model as well as cell line studies displayed that apoptosis appears to possess key part in the propagation of neurological conditions [118]. The anti apoptotic actions of UDCA/ TUDCA have been substantially evaluated as well as their properties assessed in *in vitro* studies on cultured neuronal cells in addition to *in vivo* studies on animal disease models.

The emblem of AD pathological alterations are implicated in deposition of amyloid plaques in addition to neurofibrillary tangles. The neuroprotective actions of UDCA/TUDCA in hampering apoptosis have been validated in amyloid β treated neuronal cells in addition to in vivo studies on transgenic model of AD. In case of in vitro studies, apoptosis induction by A beta incubation in primary rat neurons or differentiated rat neuronal like PC12 cells was avoidable by UDCA/ TUDCA [119]. Akin to that the anti–apoptotic actions of TUDCA were further observed in in vitro familial model of AD by expression of the APP with Swedish mutation or by dual mutated human APP along with PSI in mouse neuroblastoma cells [120]. Moreover, mitochondrial apoptotic pathway disturbance was observed to be a key process in UDCA/TUDCA hampering of A beta stimulated apoptosis. UDCA along with TUDCA with greater effectiveness attenuated A beta stimulated mitochondrial membrane permeabilization followed by liberation of cytochrome c in isolated neuronal mitochondria. Additionally, A beta exposure guided mitochondrial disturbance, structural alteration inclusive of mitochondrial membrane redox status, lipid polarity as well as interfered with protein motion might be practically abrogated by TUDCA treatment [155]. Of greater significance TUDCA's anti–apoptotic actions might be impacted by disrupting the upstream signal of mitochondrial apoptosis. TUDCA possessed the capacity of amelioration of A beta stimulated apoptosis via hampering of JNK nuclear localization, caspase-2 activation, disturbing E2F1/p53/Bax apoptotic pathway, diminishing nuclear fragmentation in addition to caspase-2 and 6 activation as well as modulates p-53, Bcl2 along with Bax or stimulating phosphatidyl inositol 3–kinase (PI3K) based survival signaling pathway [119,120,123]. A separate study observed that TUDCA facilitated Mineralocorticoid Receptors (MR) getting disassociated from its cytoplasmic chaperone hsp 90 which was followed by MR nuclear translocation in addition to transactivation for avoidance of A beta stimulated neuronal apoptosis. Apart from that TUDCA has been illustrated to mitigate the toxic downstream actions of A beta by hampering the quantities of apoptosis along with caspase-3 activation as well as ameliorating the caspase-3 cleavage of tau into a toxic spp in primary rat cortical neurons [124]. Taking into account in vivo studies TUDCA supplementation possessed the capacity of abrogating amyloidogenic Amyloid Precursor Protein (APP) processing, decreasing A beta getting deposited in hippocampal in addition to prefrontal cortex for avoidance of spatial, recognition,circumstantial memory deficiencies APP/PSI mice [111,125].

The major properties of PD are comprised of propagating demise of Dopaminergic (DA) neurons in the substantia nigraarea of brain. Application of TUDCA reduced the quantities of apoptotic cells as well as promoted the survival of DA neurons in the serum free in vitro situations. Akin to that prior treatment with TUDCA possessed the capacity of improvement of survival in addition to working of nigral transplants in a rat model rat model of PD [126].

In case of mouse model of HD, TUDCA has been illustrated to lead to repression of liberation of cytochrome c, reduced caspase activation, hamper DNA fragmentation as well as decreased thevolume and quantities of striatal damages, leading to escalated neuronal survival in addition to improvement of sensorimotor,locomotor deficiencies. In the case of 3-nitrolpropionic acid (3NP) stimulated model of HD, TUDCA significantly decreased the 3NP modulated cell demise in cultured striatal neurons in addition to apoptosis along with damages in 3NP delivered rats [127]. In case ofR6/2 transgenic mouse model of HD, Systemically delivered TUDCA resulted in diminished striatal atrophy, reduced striatal apoptosis, lesser as well as smaller ubiquitinated intranuclear inclusions along with improvement of sensorimotor as well as locomotor capacity [128].

Regarding, apoptosis represents a significant process in the secondary damages subsequent to original traumatic brain injury. TUDCA possessed the capacity of reduction of extent of damage, repress apoptosis through upregulation of anti–apoptotic factor Bcl2 or hampering the expression of pro apoptotic factors (Bax, caspase 3, caspase 12) [129]. The probably modes behind TUDCA repressing apoptosis might be implicating activation of autophagy by escalating the expression of autophagy correlated transformation of the microtubule correlated protein 1A/1B light chain 3B (Beclin1 LC3BIL/I) or hampering of the Endoplasmic Reticulum (ER) stress correlated factors (IRE1, phosphorylation of eukaryotic initiation factor-2 alpha (p-eIF2α), C/EBP-Homologous Protein (CHOP) c-Jun-N-Terminal Kinase (JNK), (ATG6, Grp78, Erdj4) [130].

Amyotrophic Lateral Sclerosis (ALS) portrays the commonest adult initiating motor neurons diseases where selectively propagation of inimical sequelae in addition to depletion of neurons working stability in the brain along with spinal cord [131, rev by us 132]. Gene mutations inclusive of Superoxide Dismutase-1 (SOD1), Chromosome 9 Open Reading Frame 72 (C9orf72), TDP43 (RNA binding protein), Fused Protein In Sarcoma (FUS) etc. are correlated with ALS pathogenesis. Subsequent to good absorption UDCA possesses the capacity of crossing the BBB along with reduce the rate of propagation of ALS [133]. Akin to that a slower propagation in ALS cases in addition to postponed muscle's denervation in an hSOD1 G93A mouse model of ALS were further found subsequent to delivery of TUDCA [134]. Nevertheless, probable modes behind the effectiveness in part of UDCA or TUDCA,even now has requirement of remarkable validation in future. Intriguingly, GUDCA, glycine conjugated UDAC further apparently hampers apoptosis in a frequently utilized in vitro model of ALS utilizing the motor neurons like

NSC34 which carries hSOD1 G93A mutation. GUDCA, treatment had avoidance in altering mitochondrial dynamic characteristics as well as apoptosis by decreasing quantities of caspase-9 which suggested the attractive anti–apoptotic actions of GUDCA, for reducing disease initiation along with propagation of ALS [135].

The antioxidant actions: There is robust involvement of mitochondrial impairment along with OS in PD in addition to asssessment of antioxidant actions of TUDCA have been basically evaluated in PD. As was previously revealed with TUDCA treatment avoidance of MPTP stimulated reduction of Dopaminergic (DA) neurons, quantities of Adenosine Triphosphate (ATP), mitochondrial working [136]. Furthermore, TUDCA resulted in improvement of mitochondrial numbers as well as working by avoiding 1-Methyl-4-Phenyl Pyridinium (MPP+) stimulated generation of ROS along with elimination of ATP in mouse cortical neurons. Additionally, TUDCA possessed the capacity of impacting neuroprotective actions in a Parkin based way by aiding in mitochondrial stabilization in addition to modulation of mitophagy for conferring protection against mitochondrial impairment along with OS [137]. These findings pointed that clearance of impaired mitochondria might be significant antioxidant as well as pro survival approach of TUDCA in PD treatment.

Nuclear factor erythroid-2-related factor-2 (Nrf2), a nuclear controller of cellular redox status is responsible for activation of transcription of antioxidant enzyme Hemeoxygenase-1 (HO1), as well as Glutathione Peroxidase (GPx). TUDCA might be conferring protection from MPP+ stimulated as well as intracytoplasmic α-synuclein stimulated OS by activation of Nrf2 in human neuroblastoma SH-SY5Y cells. Furthermore, the assessment of antioxidant stress actions of TUDCA was performed in PD mice model which was treated with MPTP in vivo. Prior treatment with TUDCA resulted in avoiding reduction of ATP quantities, facilitated activation of AMP-Activated Protein Kinase (AMPK), sustenance of escalated quantities of antioxidant enzyme HO1, as well as Parkin [114]. The findings were that TUDCA treatment escalated the expression of Nrf2, Nrf2 stabilizer DJ1 in addition to antioxidant enzymes HO1, as well as GPx [138]. Specifically TUDCA conferred protection against dopaminergiccell elimination in nigro striatal axis in MPTP stimulated neurodegeneration PD mice model, which implicates dysfunctional ROS formation, modulation of JNK action along withactivation of AKT prosurvival pathway [139].

The Hampering of Endoplasmic Reticulum (ER) Stress

Endoplasmic Reticulum (ER) stress possesses the properties of Unfolded or mis folded proteins in the ER lumen in addition to the onset of a stepwise event of Signal Transduction known as Unfolded Proteins Response (UPR). TUDCA might be working in the form of a molecular chaperone for abrogating ER stress in addition to avoidance of UPR impairment in ER stress correlated diseases for instance hepato biliary conditions, obesity, diabetes mellitus [140]. Intriguingly, UPR further gets activated in neurodegenerative tauopathies like AD. TUDCA has further been illustrated to avoidhyperphosphorylation of tau proteins hampering of UPR in human neuroblastomacell lines [141]. Furthermore, TUDCA delivery to a transgenic mouse model of familial of familial amyloidotic polyneuropathy possessed the capacity of decreasing transthyretin toxic collection which in turn reduced apoptotic as well as oxidative biomarkers that are frequently correlated with transthyretin deposition [142]. Thereby these outcomes overall verified that UPR is the probable mode behind the neuroprotective actions of TUDCA in AD.

Prion disease portrays a class of occasional in addition to a neurodegenerative disease without any cure, possessed the properties of abnormal conformational transformation in addition to generation of aggregates of cellular Prion protein (PrPC) into the disease correlated ''scrape'' isoform (PrPSc) [143]. Utilization of UDCA/TUDCA treatment has been made for targeting as well as postponing protein collection; mode behind Prion disease; however the effectiveness illustrates complicated sequelae. Cortez M, et al. [144], have validated the neuroprotective actions of UDCA/TUDCA along with hampering the generation of aggregates in Prion disease. For instance UDCA/TUDCA considerably diminished PrP transformation in chronically as well as acutely infected cells cultured reduced depletion of neurons in Prion infected cerebellar slice cultures. Lesser dosage UDCA treatment in early stage possessed the capacity of prolongation of incubation periods, decrease astrocytoses, escalating survivaltime in Prion infected male mice however not inthe female mice [144]. Akin to that lesser dosage of TUDCA treatment in chow 7 days post inoculation illustrated protective actions by escalating incubation periods as well as escalated phosphorylated eukaryotic translation Initiation Factor (eIF2) quantities. Nevertheless, Utilization of greater quantities UDCA/TUDCA did not offer any advantages. postponing of treatment with greater quantities UDCA/TUDCA is inefficacious or might even yield greater inimical sequelae as well [145]. At present no clarification exists with regards to the total misfolded proteins-reducing or ER stress attenuating actions of UDCA /TUDCA with absence of remarkable validation in Prion disease along with otherneuropathological situations.

The Molecular Modes of Bile Acid at Intracellular Organelles and Mitochondria Level

Recently KIiriyama Y as well as Nochi H [146] explained how Bile Acids work at the intracellular organelles and Mitochondria level in case of neurodegenerative diseases Mitochondria portray intracellular organelles which possess a double membrane comprising of an inner as well as outer membranes along with work in the event of cellular ATP generation. They are implicated in variable in addition to different cellular functions, inclusive of apoptosis, controlling of intracellular calcium quantities, as well as metabolism of glucose, fatty acids, along with amino acids. Mitochondria maintain a functional population by recurrence of fusion along with fission to deplete impaired mitochondria, as well as mitochondrial impairment is implicated in different kinds of diseases. The equilibrium amongst fission along with fusion have a key part in mitochondrial quality regulation. The fusion of mitochondria results in an exchange of mitochondrial DNA (mtDNA) as well as metabolites amongst damaged along with healthy mitochondria to prevent the accrual of injured substances into one mitochondrion. Mitochondrial fusion takes place when the Outer Mitochondrial Membranes (OMM) of two mitochondria fuse with each other as well as with the inner mitochondrial membranes. Mitofusin (MFN) has a key part in the fusion of the outer membrane. Additionally, Optic

Atrophy 1 (OPA1) possesses a key part in the fusion of the inner membrane. MFN is a dynamin-like GTPase that comprises of two isoforms, namely, MFN1 as well as MFN2. Despite both isoforms possess significant parts in the tethering along with fusion of OMMs, the tethering activities of MFN1 are higher in contrast to those of MFN2. Thereby, MFN1 is the major tethering isoform for the fusion of OMMs. MFN2 is placed on the mitochondria- correlated Endoplasmic Reticulum (ER) Membrane (MAM), along with it connects mitochondria to the ER, bringing Ca^{2+} influx from the ER to the mitochondria [rev in 146]. Mitochondrial fission tends to isolate injured DNA and metabolites in mitochondria. Dynamin-Related Protein 1 (DRP1) is the main controller of mitochondrial fission. DRP1 generates a ring-like structure comprised of multimer at mitochondrial fission areas of the OMM as well as results in the constriction and scission of mitochondria. The activity of DRP1 is controlled by post-translational modifications, such as phosphorylation, ubiquitination, sumoylation, S-nitrosylation, and O-GlcNAcylation]. Glycocholic Acid (GCA), Taurocholic Acid (TCA), Glycochenodeoxycholic Acid (GCDCA), as well as Taurochenodeoxycholic Acid (TCDCA) are abundant in the mitochondria of the liver of healthy subjects. Nevertheless, most BAs are toxic to mitochondria at high quantities along with can results in lead to a reduction in mitochondrial membrane potential. In comparison, Tauroursodeoxycholic Acid (TUDCA) facilitate escalated mitochondrial biogeneration along with confer protection against mitochondrial impairment. Furthermore, peroxisome proliferator-activated receptor γ coactivator 1α, nuclear respiratory factor 1, and mitochondrial transcription factor A are related to mitochondrial biogeneration. TGR5 activation induces these molecules as well as facilitates the functional gain and biogeneration of mitochondria. Thereby, drugs which activate TGR5, inclusive of BA, may be potential therapeutic agents for neurodegenerative diseases. It has been recently reported that DCA, CDCA, and their taurine conjugates activate MFN2 by binding directly to MFN2, facilitating mitochondria-to-mitochondria fusion as well as mitochondria-to-ER fusion in THP-1 cells that are differentiating into macrophages (Figure 3). DCA along with CDCA at physiological conditions (5 μM)) facilitate the fusion amongst mitochondria, causing an escalated formation of ATP. In comparison, DCA along with CDCA with cholestatic conditions (100 μM) escalate the fusion amongst the mitochondria as well as the ER, resulting in Ca^{2}+ influx from the ER to the mitochondria, the activation of NLRP3 inflammasome as well as pyroptosis, in addition to innate immunity. Furthermore, CA as well as UDCA antagonize the actions of DCA as well as CDCA on the GTPase activity of MFN2. The sites where mitochondria along with ER contact are called mitochondria-associated membranes or mitochondria-associated ER Membranes (MAMs) along with a correlation amongst MAMs and neurodegenerative diseases has been pointed. MAMs are initiation areas of autophagosome generation. Furthermore, knockdown of MFN2 incites dysfunctional autophagy. In comparison overexpression of MFN2 results in the induction of autophagy. Moreover, it is key tosustain a balance amongst mitochondrial fusion along with fission to support both mitochondrial as well as cellular function, in addition to mitochondrial structural alterations are correlated with neurodegenerative diseases.In view of MFN2 has a key part in regulating mitochondrial structure, MFN2 is related to neurodegenerative diseases [146].

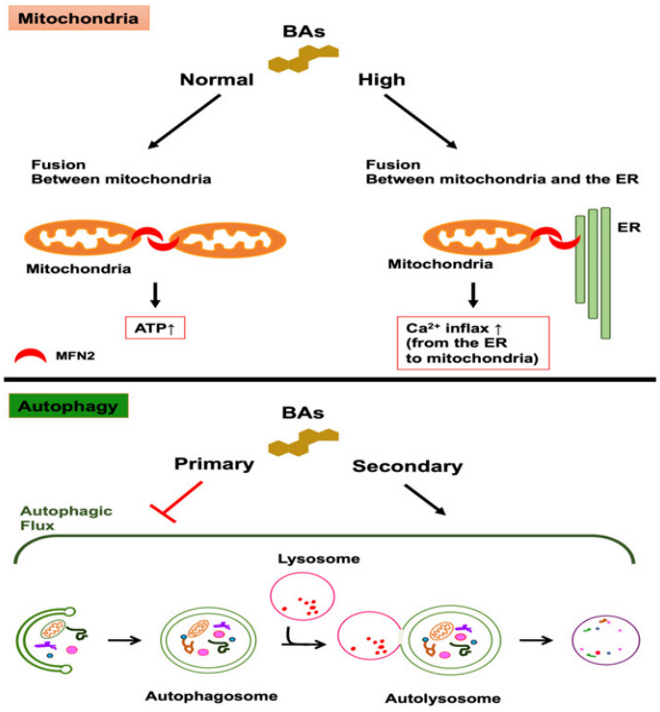

Figure 3: Courtesy ref no- 146- The effects of Bile Acids (BAs) on mitochondria and autophagy. The effects of BAs on mitochondria: DCA, CDCA, and their taurine conjugates activate MFN2 by binding directly to MFN2, promoting mitochondria-to-mitochondria fusion and mitochondria-to-ER fusion. These BAs, at normal concentration, promote the fusion between mitochondria, leading to the generation of ATP. By contrast, these BAs, at high concentration, promote the fusion between the mitochondria and the ER, leading to Ca2+ influx from the ER to the mitochondria. The effects of BAs on autophagy: secondary BAs (DCA and UDCA) induce autophagy and primary bile acids (CA, CDCA, and TCA) inhibit autophagy by preventing the formation of autolysosomes. In addition, the activation of TGR5, a receptor for secondary bile acids, leads to the activation of autophagy. By contrast, the activation of FXR, a receptor for primary bile acids, leads to the inhibition of autophagy.

Innovative Modes of How G-M-B Axisis Implicated in Cognition-Role of Bile Acids

Cognitive function in humans on the complicated along with crosstalk amongst numerous body systems, inclusive of the Hypothalamic-Pituitary-Adrenal (HPA) axis. The gut microbiota, which vastly outnumbers human cells in addition to possess agenetic potential that exceeds that of the human genome, have a key part in this crosstalk. The Microbiota-Gut-Brain (MGB) axis is a bidirectional signalling pathway whichworks via neural, endocrine, immune, along with metabolic pathways. Of the main neuroendocrine systems reacting to stress is the HPA axis thatgenerates glucocorticoids such as cortisol inhumans as well as corticosterone in rodents. Precise quantities ofcortisol are imperative for normal neurodevelopment as well as working, along with cognitive events for instance learning along with memory, as well as studies have illustrated that microbes modulate the HPA axisright through life. Stress can significantly impact the MGB axis through the HPA axis in addition to other pathways. Animal research hasadvanced our insight of these modes as well as pathways, resulting in an archetypical shift in conceptual thinking about the influence of the microbiota on

human health and disease. Preclinical along with human trials are at present ongoing for estimating the manner these animal models translate to humans. Inthis review article, Ruschetal [147], summarized the present information regarding the association amongst the gut microbiota, HPA axis, in addition to cognition, as well as providede anoverview of the major observations along with conclusions in this wide field (Figure 4, Figure 5 and Figure 6).

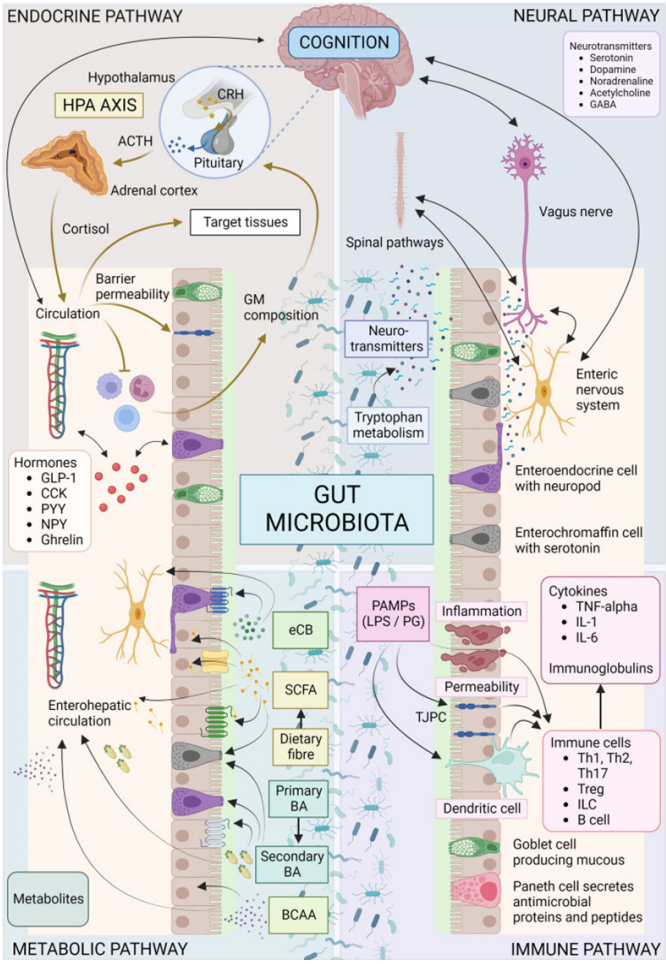

Figure 4: Courtesy ref no-147-Overview of microbiota-gut-brain axis. Bidirectional communication mechanisms of the MGB axis include endocrine, neural, metabolic and immune system pathways. The hypothalamic-pituitary-adrenal axis is a major neuro-endocrine system responding to stress with the release of Corticotrophin-Releasing Hormone (CRH) from the hypothalamus, and the subsequent release of ACTH from the pituitary, then cortisol from the adrenal cortex. Cortisol reaches target tissues through the circulation, modulates the immune system, and impacts on GM composition and gut permeability. The GM in turn is able to influence the stress response (for e.g., the HPA axis can be activated in response to increased circulating cytokines subsequent to bacterial translocation). Various GM and enteroendocrine cell interactions result in the release of hormones that work locally or on target tissues such as the brain, via the circulation. The vagus nerve, enteric nervous system, and spinal pathways provide rapid neural communication routes, while neurotransmitters or their precursors can be produced or metabolized by microbes. Metabolites such as SCFA, BA and eCB may be produced or modified by microbes and bind specific cell receptors in the gut or they may be absorbed into circulation and affect target tissues. Microbes and their products may interact with the immune cells with downstream pro-inflammatory or anti-inflammatory effects. ACTH, Adrenocorticotropic hormone; BA, bile acid; BCAA, branched chain amino acids; CCK, cholecystokinin; CRH, corticotropin-releasing hormone; eCB, endocannabinoid; GABA, γ-aminobutyric acid; GLP-1, glucagon-like peptide 1; GM, gut microbiota; HPA, hypothalamic-adrenal-pituitary; IL, interleukin; ILC, innate lymphoid cells; LPS, lipopolysaccharide; PYY, Peptide YY; NPY, neuropeptide Y; PAMP, Pathogen-associated molecular pattern; PG, peptidoglycan; SCFA, short chain fatty acid; Th, T helper cell; TJPC, tight junction protein complex; T reg, regulatory T cell; TNF-α, tumor necrosis factor-α. Figure created with BioRender.com.

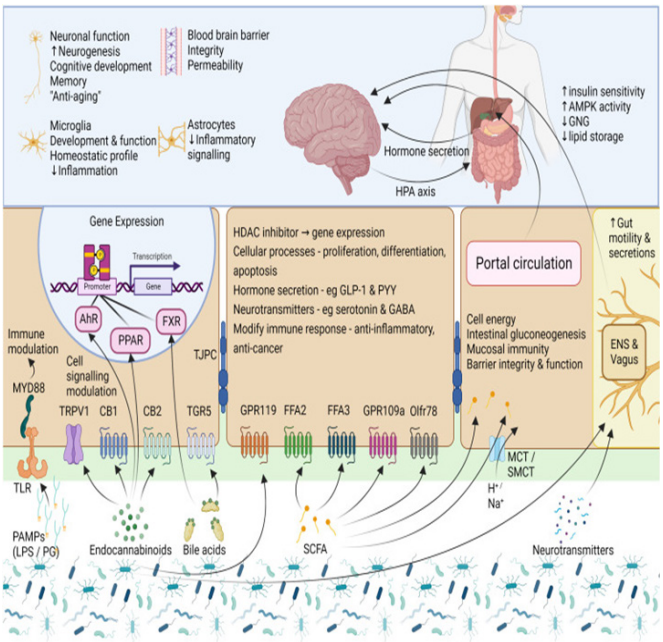

Figure 5: Courtesy ref no-147-Signalling mechanisms–microbial products, metabolites, and neurotransmitters. Cells of the gut express a variety of receptors which are able to sense and transmit signals from the intestinal lumen and mucosa. To communicate, the GM uses factors which include several microbial products, eCBs, BAs, SCFAs, and neurotransmitters. PAMPs, such as LPS and PG, are small molecular microbial motifs that are recognized by TLRs, while this signal is transferred to intracellular signaling pathways (for e.g., immune cell activation) by MYD88. The eCB system is not limited to the activity of CB1 and CB2, and eCBs can also interact with other GPCRs, TRPV1, and the nuclear receptors PPAR-α and PPAR-γ. To modulate gut function, BAs interact with two main receptors, the GPCR named TGR5, and the nuclear receptor FXR. In the gut, SCFAs can activate FFA2, FFA3, GPR109a and Olfr78, but may also enter the cell via transporters or via passive diffusion where they modulate the activity of several enzymes and transcription factors or provide a source of energy for the cell. Small amounts of SCFAs are taken up into circulation where they may be transported to target tissues such as the liver, pancreas and brain. The binding of these GM-derived molecules with their respective receptors leads to the activation of cellular signaling pathways which then leads to alterations in cellular activity and gene expression, with downstream effects on host physiological processes. AhR, aryl hydrocarbon receptor; AMPK, AMP-activated protein kinase; BA, bile acid; CB1 and CB2, cannabinoid receptor type 1 and 2; eCB, endocannabinoid; ENS, enteric nervous system; FFA2 and FFA3, free fatty acid receptor 2 and 3; FXR, farsenoid X receptor; GABA, γ-aminobutyric acid; GLP-1, glucagon-like peptide 1; GNG, gluconeogenesis; GPR119 and GPR109a, G-protein coupled receptor 119 and 109a; HDAC, histone deacetylase; LPS, lipopolysaccharide; MCT, monocarboxylate transporter; MYD88, Myeloid differentiation primary response 88; Olfr78, Olfactory receptor 78; PAMP, Pathogen-associated molecular pattern; PG, peptidoglycan; PPARα/γ, peroxisome proliferator-activated receptors α/γ; PRRs, pattern recognition receptors; PYY, Peptide YY; SCFA, short chain fatty acid; SMCT, sodium-dependent monocarboxylate transporter; TGR5, Takeda G protein-coupled receptor 5; TJPC, tight junction protein complex; TLR, toll-like receptor; TPRV1, transient receptor potential cation channel subfamily V member 1. Figure created with BioRender.com.

Conclusions

Thus here we have summarized the recent observations regarding emphasizing the interaction amongst brain as well as periphery in addition to neurological functions of BA in case of

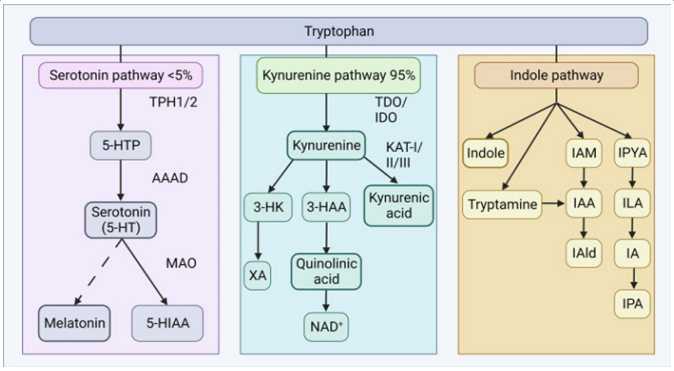

Figure 6: Courtesy ref no-147-Tryptophan metabolism. Tryptophan metabolism occurs via the serotonin or kynurenine pathways to produce bioactive products. In the serotonin pathway, tryptophan is converted to 5-HTP by TPH1 in enterochromaffin cells, or TPH2 in neurons of the ENS or CNS. AAAD converts 5-HTP to serotonin, which can be further metabolized to melatonin, via a series of steps. The vast majority of tryptophan is, in fact, utilized in the kynurenine pathway, where tryptophan is converted to kynurenine by TDO in the liver (majority), or ubiquitously via IDO (including gut, brain, liver). Kynurenine can be converted to kynurenic acid by the KAT enzymes, quinolic acid and further NAD+, or XA. In the indole pathway, microbes of the gut metabolize tryptophan into indole and indole derivatives. 3-HAA, 3-hydroxyanthranilic acid; 3-HK, 3-hydroxykynurenine; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine; 5-HTP, 5-hydroxytryptophan; AAAD, aromatic amino acid decarboxylase; IA, anholocyclic acid; IAA, indole-3-acetic acid; IAAld, indole-3-acetaldehyde; IAld, indole-3-aldehyde; IAM, indole-3-acetamide; IDO, indoleamine 2,3-dioxygenase; ILA, indole-3-lactic acid; IPA, indole-3-propionic acid; IPYA, indole-3-pyurvic acid; KAT, kynurenine aminotransferase; MAO, monoamine oxidase; NAD+, nicotinamide adenine dinucleotide; TDO, tryptophan 2,3-dioxygenase; XA, xanthurenic acid. Figure created with BioRender.com.

physiological along with pathological situations. At the time of physiological conditions, the existence of BA metabolites in addition to receptors as well as transporters possess a part directly in the neurological functions in the brain. BA work in the form of the significant steroid hormones for impacting neuromodulatory actions in the CNS via activation of membrane or nuclear receptors or influence the working of the neurotransmitter receptors. The interaction amongst brain as well as periphery the interaction amongst brain as well as periphery might take place via connection through system circulation directly gaining entry into the brain or indirect pathway modulated through the FXR- FGF15/19 pathway or TGR5- GLP-1 pathway. Nevertheless, considerable actions whichget directly stimulated by BA in the brain in particular in postprandial escalation of circulating BA still there is requirement for evaluation. Taking into account the indirect pathway, BAs aid in the generation of FGF15/19 via activation of the FXR generation in enterocytes or the formation of the GLP-1 via activation of the TGR5 in the enteroendocrine L-cells in the intestine. Nevertheless, greater studies are further needed for verifying if escalation of FGF15/19 is enough for influencing considerable actions via the existence of FGFRs in the CNS. In view of greater quantities of postprandial GLP-1 in the lamina propria of the intestine, there is greater probabilityof signaling through TGR5- GLP-1 pathway to the CNS through the vagus nerve existent in the lamina propria. Nevertheless, the precise repercussions as well as the manner by which BAs aid in the signaling to CNS continues to be an enigmatic area for future research.

BAs work in the form work in the form of the etiological modulators which correlate the pathogenesis of different neurological diseases, validating BAs in the form of the of probable biomarker with regards to prognosis of diseases. In view of the complicated nature of BA metabolites in constitution in addition to biochemical characteristics, the manner of ascertaining the precise workingof particular BAmetabolites or thefull mannerby which changed BA profiles aid in the pathogenesis of different neurological diseases still requires to be resolved. Of greater significance is the supplementation of hydrophilic amidated UDCA or TUDCA have been corroborated to illustrate therapeutic advantages by hampering the neuroinflammatory reactions, apoptosis, OS, Endoplasmic Reticulum (ER) stress, mitochondrial protection or work in the form of probable chaperone for correction of misfolding of proteins in the treatment of different neurological diseases.The neuroprotective part of UDCA, in particularof TUDCA promise to be attractive approaches in the treatment of neurological diseases. Greater insight with regards to BA signaling in addition to its actions in the brain would aid in innovative inventions along with approaches for tackling these disabling diseases in future.

References

1. Chiang JYL, Ferrell JM. Bile Acids as metabolic regulators and nutrient sensors. *Annu Rev Nutr.* 2019;39(4):175-200.

2. Ciaula AD, Garruti G, Baccetto RL, et al. Bile Acid physiology. *Ann Hepatol.* 2017;16(Suppl.1:s3-105.):s4-s14.

3. Kaur KK, Allahbadia GN, Singh M. MUtilization of Clostridium Species as Probiotics as an Alternative to the Conventional Probiotics like Lactobacillus rhamnosus /Bifidobacterium-How Far is it Feasible-A Systematic Review. *JEndocrinol.* 2021;5(1):1-12.

4. Kaur KK. Delivered a talk on 30th September on 'Advantages and Limitations of utilizing Clostridium species as Probiotics-A Sytematic Review'' in a webinar held by Gastroenterology conference on 30th September 2021.

5. Kaur KK, Allahbadia GN, Singh M. Mode of Actions of Bile Acids in Avoidance of Colorectal Cancer Development and Therapeutic Applications in Treatment of Cancers-A Narrative Review. *J Pharm Nutr Sci.* 2022;12:1-19.

6. Kaur KK, Allahbadia GN, Singh M. An update on the Association of Gut-Liver Axis with Gut Microbiome Dysbiosis Correlated NAFLD along with NAFLD- HCC with Potential Therapeutic Approaches:a systematic review. *J Hepatol Gastroint Dis.* 2022;8(6):1-9.

7. Xing C, Huang X, Wang D, et al. Role of Bile Acids signaling in neuromodulation under physiological and pathological conditions. *Cell Biosci.* 2023;13(1):125.

8. Russell DW. The enzymes, regulation, and genetics of bile acids synthesis. *Annu Rev Biochem.* 2003;72(7):137-174.

9. Takahashi S, Fatumi T, Masuo Y, et al. Cyp2c70 is responsible for the species difference in bile acid metabolism between mice and humans. *J Lipids Res.* 2016;57(12):2130-2137.

10. Hoffmann AF, Hagey LR. Bile Acids chemistry, patho chemistry, biology, pathobiology and therapeutics. *Cell Mol Life Sci.* 2008;65(16):2461-2483.

11. Eggert T, Bakonyl D, Hummel W. Enzymatic routes for the synthesis of ursodeoxycholic acid. *J Biotechnol.* 2014;191(12):11-21.

12. Dawson PA, Karpen SJ. Intestinal transport and metabolism of bile acids. *J Lipids Res.* 2015;56(6):1085-1099.

13. Dawson PA. Hummert M, Haywood J, et al. The heteromeric organic solute transporter alpha beta, Ost alpha Ostbeta is an ileal basolateral bile acid transporter. *J Biol Chem.* 2015;280(8):6960-6968.

14. Shwarz M, Russell DW, Dietschy JM, et al. Marked reduction in bile acids synthesisin cholesterol -7 α hydroxylase- deficient mice does not lead to diminished tissue cholesterol turnover or hypercholesterolemia. *J Lipids Res.* 1998;39(9):1833-1843.

15. Rizzolo D, Buckley K, Kong B, et al. Bile Acid homeostasis in a cholesterol -7 α hydroxylase and sterol 27α hydroxylase double knockout mouse model. *Hepatology.* 2019;70(1):389-402.

16. Rizzolo D, Kong B,Taylor RE, et al. Bile Acid homeostasis in mice deficient in Cyp 7a1 and Cyp 27a1. *Acta Pharm Sin B.* 2021;11(12):3847-3856.

17. Bjorkhem I, Meaney S. Brain cholesterol:long secret life behind a barrier. *Arterioscler Thromb Vasc Biol.* 2004;24(5):806-815.

18. Zhang J, Liu Q. Cholesterol metabolism and homeostasis in the brain. *Protein Cell.* 2015;6(4):254-264.

19. Lund EG, Gulleyard JM, Russell DW. cDNA cloning of Cholesterol -24hydroxylase,a mediator of cholesterol homeostasis in the brain . Proc NatlAcad Sci USA 1999; 96(3):7238-7243.

20. Bjorkhem I, Andersson U, Ellis E, et al. From brain to bile: evidence that conjugation and omega hydroxylation are important for elimination of 24 Shydroxy cholesterol (cerebrosterol) in humans. *J Biol Chem.* 2001;276(40):37004-37010.

21. Lund EG, Xie C, KottiT, et al. Knockout of Cholesterol -24hydroxylase gene in mice reveals a brain specific mechanismof cholesterol turnover. *J Biol Chem*. 2003;278(25):22980-22988.

22. Bloussicault L, Alves S, Lamaziere A, et al. CYP46A1, the rate limiting enzymefor cholesterol degradation ,is neuroprotective in Huntingtons disease. *Brain.* 2016;139(Pt3):953-970.

23. Ali Z, Heverin M, Olin M, et al. On the regulatory role of side chain hydroxylated oxysterols in the brain:lessons from CYP7A1transgenic and Cyp 27a1(-/-)mice. *J Lipids Res.* 2013;54(4):1033-1043.

24. Meaney S, Heverin M, Panzenboeck U, et al.Novel route for elimination of brain oxysterols across the blood brain barrier : conversion into 7--α- hydroxy-cholesten-3-oxo-4 cholestenoic acid. *J Lipids Res.* 2007;48(4):944-951.

25. Bavner A,Shafaati M, Hansson M, et al. On the mechanism of accumulation of cholestanol in the brain of mice with disruption of sterol 27α hydroxylase. *J Lipids Res.* 2010;51(9):2722-2730.

26. Wu Z, Martin KO, Javitt NB, et al. Structure and function of human oxysterol 7α-hydroxylase cDNAs and gene CYP7B1. *J Lipids Res.* 1999;40(12):2195-2203.

27. Ridlon JM, KangDJ, Hylemon PB. Bile salts biotransformations byhuman intestinal bacteria. *J Lipids Res.* 2006;47(2):241-259.

28. Ridlon JM, KangDJ, Hylemon PB.Consequence of bile salts biotransformations by intestinal bacteria. *Gut Microbes.* 2016;7(1):22-39.

29. Molinero N, Ruiz L, Sanchez B, et al. Intestinal bacteriainterplay with bile acid and cholesterol metabolism: implications on host physiology. *Front Physiol.* 2019;10(3):185.

30. Saylin SI, Wahlstorm A, Felin J, et al. Gut microbiotaregulates bile acid by reducing the levels of tauroβmuricholic acid, a naturally occurring FXR antagonist. *Cell Metab.* 2013;17(2):225-235.

31. Park J, Kim CH. Regulation of commonneurological disorders by gut microbial metabolites. *Exp Mol Med.* 2021;53(12):1821-1833.

32. Mano N, Goto T, Uchida M, et al. presence of protein unconjugated bile acids in the cytoplasmic fractionof rat brain. *J Lipids Res.* 2004;45(2):295-300.

33. Baloni P, Funk CC,Yan J, et al. Metabolic network analysis reveals altered bile acids synthesis and metabolism in Alzheimer'sdisease. *Cell Rep Med.* 2020;1(8):100138

34. Zheng SX, Chen T, Zhao A, et al. The brain metabolome of male rats across the lifespan. *Sci Rep.* 2016;6(4):24125.

35. Pan X, Elliot CT, McGuinness B, et al. Metabolomic profiling of bile acids in Clinical and experimental samples of Alzheimer'sdisease . *Metabolites.* 2017;7(2):28.

36. Kitazawa T, Terasaki T, SuzukiH, et al. Efflux of taurocholic acid across the blood brain barrier:interactions with cyclic peptides. *J Pharmacol Exp Ther.* 2018;367:373-388.

37. Palmela I, Correia L, Silva RF, et al. Hydrophilic bile acidsprotect human blood brain barrier endothelial cells from disruption by unconjugated bilirubin:an in vitro study. *Front Neurosci.* 2015;9:80.

38. Higashi T, Watanabe S, Tomaru K, et al. Unconjugated bile acids in rat brain: analyticalmethod based on LC/ESI -MS/MS with chemical derivatization andestimation of their origin by comparison to serum levels. *Steroids.* 2017;125:107-113.

39. Choudhari S, Cherrington NJ, Li N, et al. Constitutive expression of xenobiotic and endobiotic transporter mRNAs in the choroid plexus of rats. *Drug Metab Disp.* 2003;31(11):1337-1345.

40. OseA, Kusuhara H, Endo C, et al. Functional characterization of organic anion transporting polypeptide 1a4 in the uptake and efflux of drugs across blood brain barrier. *Drug Metab Disp.* 2010;38(1):168-176.

41. Nizamudiditnov D, De Morrow S, McMillin M, et al. Hepatic alterations are accompanied by changes to the bile acids expressing neurons in the hypothalamus after traumatic brain injury. *Sci Rep.* 2017;4(1):40112.

42. Perino A, Velasquez-Villegas LA, Bresconi N, et al. Central anorexogenic actions of bile acids are mediated by TGR5. *Nat Med.* 2021:3(5):595-603.

43. Greenwood J, Adu J, Davey AJ, et al. The effectsof bile salts on the permeability and ultrastructure of the perfused energy depleted rat blood brain barrier. *J Cereb Blood Flow Metab.* 1991;11(4):644-655.

44. Quinn M , McMillin M, Galindo C, et al. Bile acid signaling is

permeabilize the blood brain barrier after bile duct ligation in rat via Rac1 dependent mechanisms . *Dig Liver Dis.* 2014;46(6):527-534.

45. Grant SM, DeMellowS. Bile acids signaling in Neurodegenerative and neurological disorders. *Int J Mol Sci.* 2020;21(17):5982.

46. Schaap FG, Trauner M, Janett PL. Bile acid receptors as targets for drug development. *Nat Rev Gastroenterol Hepatol.* 2014;11(1):55-67.

47. Huang F, WangT, HuW, et al. Identification of Farsenoid X receptors in brain neurons. *FEBS Lett* 2016; 590(18):2233-2243.

48. McMillin M, Frampton G, Quinn M, et al. Bile acids signaling is involved in the neurological decline in a murine model of acute liver injury. *Am J Pathol.* 2016;186(2):312-323.

49. Huang F, Wang T, Lan Y, et al. Deletion of mouse FXR gene disrupts multiple neurotransmitter systems and altersneurobehaviour. *Front Behav Neurosci.* 2015;9(3):70.

50. de Oca Balderas PM. Flux-independent NMDAR signaling , molecular mediators, cellular functions and complexities. *Int J Mol Sci.* 2018;19(12):3800.

51. Cicek S. Structure dependent activity of natural GABA A receptor modulator. *Molecules.* 2018;23(7):1516.

52. Liao WL, Heo GY, Dodder NG, et al. Quantification of cholesterol metabolizingP450s CYP27A1 and CYP46A1 in neural tissues reveals a lack of enzyme product correlations in human retina but not in human brain. *J Proteome Res*. 2011;10(1):241-248.

53. Schubring SR, Fleischer W, Lin JS, et al. The bile chenodeoxycholate is a steroid potent antagonist at NMDA and GABA (A) receptors. *Neurosci Lett.* 2012;506(2):322-326.

54. Xie JF, Fan K, Wang C, et al. Inactivation of tuberomammilary nucleus by GABA (A) receptors agonist promote slow wave sleepin freely moving rats and histamine treated rats. *Neurochem Res.* 2017;42(8):2314-2325.

55. YanovskyY, Schubring SR, YaoQ, et al. Waking actions of Ursodeoxycholic Acid (UDCA) involves histamine and GABA A receptor block. *PLOS ONE*. 2012;7(8):e42512.

56. Xavier JM, Morgado AL, Rodriques CM, et al. Tauroursodeoxycholic acid increases neural stem cell pool and neuronal conversation by regulating mitochondrial cell cycle reterograde signaling. *Cell Cycle.* 2014;13(22):3576-3580.

57. Soares R, Ribeiro FF, Xapelli S, et al. Tauroursodeoxycholic acid enhances mitochondrial biogenesis, neural stem cell pool and early neurogenesis in adult rats. *Mol Neurobiol.* 2018;55(5):3725-3738.

58. Mertens KL, Kalsbeek A, Soeters MR, et al. Bile acids signaling pathways from the enterohepatic circulation to the central nervous system. *Front Neurosci.* 2017;11(11):617.

59. Kliewer SA, Mangelsdorf DJ. Bile acids as hormones: the FXR- FGF 15/19 pathway. *Dig Dis.* 2018;33(3):327-331.

60. Gadaleta RM, MoschettaA. Metabolic messengers: Fibroblast growth factor 15/ 19. Nat Metab. 2019;1(6):588-594.

61. Hschou H, Pan W, Kastin AJ. Fibroblast growth factor 19 entry into brain. *Fluid Barriers CNS*. 2013;10(1):32.

62. Ryan KK, Kohli R, Gutteirez-Aquilar R, et al. Fibroblast growth factor-19 actions in the brain reduces food intake and body weight and improves glucose tolerance in malerats. *Endocrinology.* 2013;154(1):9-15.

63. Marcelin G, Jo YH, LiX, et al. Central actions of FGF19 reduces hypothalamic AgRP/ NPY neurons activity and improves glucose metabolism. *Mol Metab.* 2014;3(1):19-28.

64. Liu S, Marcelin G, Blouet C, et al. A gut- brain axis regulating glucose metabolism mediated by bile acids and competitive Fibroblast growth factor actions in the hypothalamus. *Mol Metab.* 2018;8:37-50.

65. Brighton CA,Rievaz J,Kuhre RE,Glass LL,S K,Holst JJ,etal. Bile Acids trigger GLP-1 release predominantly by accessing basolaterally located G protein coupled bile acid receptor 5. *Endocrinology.* 2015;156(11):3961-3970.

66. Ruttiman EB, Arnold H, Hillebrand JJ, et al. Intrameal hepatic portal and intraperitoneal infusions of glucagon like peptide 1 reduce spontaneous meal size in the rat by different mechanisms. *Endocrinology.* 2009;150(3):1174-1181.

67. Cork SC, Richards JE, Holt MK, et al. Distribution and characterization of glucagon like peptide 1 receptor expressing cells in the mouse brain. *Mol Metab*. 2015;4(10);718-731.

68. Kastin A, AkerstromV, PanW. Interactions of glucagon like peptide 1(GLP-1) with the blood brain barrier. *J Mol Neurosci.* 2002;18(1-2):7-14.

69. Borgmann D, Cigliieri E, Biglari N, et al. Gut- brain communication by distinct sensory neurons differently controls feeding and glucose metabolism. *Cell Metab* 2021;33(7):1466-1482.

70. Punjabi M, Arnold H, Ruttiman EB, et al. Circulating glucagon like peptide 1(GLP) inhibit eating in malerats by acting in the hind brain without avoidance. *Endocrinology.* 2014;155(5):1690-1699.

71. Holst JJ. The physiology of glucagon like peptide 1. *Physiol Rev.* 2007;87(4):1409-1439.

72. Perez MJ, Briz O. Bile acid induced cell injury. *World J Gastroenterol.* 2009; 15(14):1677-1689.

73. Rose CF, Amodio P, Bajaj JS, et al. Hepaticencephalopathy:novel insights into classification, pathophysiology and therapy. *J Hepatol.* 2020; 73(6):1526-1547.

74. Xie G, Wang X, Jiang R, et al. Dysregulated bile acid signaling contributes to the neurological impairment in murine models of acute and chronic liver failure. *E Bio Medicine*. 2018;37(11):294-306.

75. Wiess N, Hilaire PBS, Colsch B, et al. Cerebrospinal fluid metabolomics highlights dysregulation of energy metabolism in overt hepatic encephalopathy. *J Hepatol.* 2016;65(6):1120-1130.

76. Tripodi V, Contin M, Fernandez-MA, et al. Bile acid content inrat brain of common duct ligated rats. *Ann Hepatol.* 2012;11(6):930-934.

77. McMillin M, Frampton G, Grant S, et al. Bile acid mediated sphingosine-1- phosphate receptor-2- receptor signaling promotes neuroinflammation during hepatic encephalopathy in mice. *Front Cell Neurosci.* 2017;11:191.

78. Lane CA, Hardy J, Scott JM. Alzheimer's disease. *Eur J Neurol.* 2018; 25(1):59-70.

79. Marksteiner J, Blasko I, Kemmler G, et al. Bile acid quantification of 20 plasma metabolites identifies lithocholic acid as a putative biomarker in Alzheimer'sdisease. *Metabolomic.* 2018;14(1):1.

80. Rose KA, Stapleton G, Dott K, et al. Cyp7b, a novel brain cytochrome P450catalyzes the synthesis of neurosteroid 7 α hydroxy Dehydroepiandrosterone and 7 α hydroxy pregnenolone. *Proc NatlAcad Sci USA.* 1997; 94(10):4925-4930.

81. Mahmoudian Dehkordi S, Arnold M, Nho K, et al. Altered bile acid profiles associates with cognitive impairment in Alzheimer'sdisease-an emerging role for Gut Microbiome. *Alzheimer's Dement.* 2019;15(1):76-92.

82. Nho K, Kuider Paisley A, Mahmoudian Dehkordi S, et al. Altered bile acid profiles in mild cognitive impairment and Alzheimer'sdisease: relationship to Neuroimaging and CSF biomarkers. *Alzheimer's Dement.* 2019;15(2):232-244.

83. Shao Y, Li T, Liu Z, et al. Comprehensive metabolic profiling of Parkinson's disease by liquid chromatography-mass spectrometry. *Mol Neurodegener.* 2021;16(1):4.

84. Li P, Killinger BA, Ensink E, et al. Gut Microbiota dysbiosis is associated with elevated bile acids in Parkinson's disease. *Metabolites.* 2021;11(1):29.

85. Yilmaz A, Ugur Z,Ustun I, et al. Metabolic profiling of CSF from people suffering from Sporadic andLRRK2 Parkinson's disease:a pilot study. *Cells.* 2020;9(11):294.

86. Grahams SF, Rey NL, Ugur Z, et al. Metabolic profiling of bile acids in an experimental model of prodromal Parkinson's disease. *Metabolites.* 2018;8(4):71.

87. McColgan P, Tabrizi S. Huntingtons disease: a clinical review. *Eur J Neurol.* 2018; 25(1):24-34.

88. Kacher R, Mounier C, Caboche J, et al. Altered cholesterol homeostasis in Huntingtons disease. *Front Aging Neurosci.* 2022;14:797220.

89. Leoni V, Long JD, Mills JA, et al. Group-P-Hs: plasma245-hydroxy cholesterol correlation with biomarkers of Huntingtons disease progression. *Neurobiol Dis.* 2013;55:37-43.

90. Verrips A, Van Englen BG, Wevers RA, et al. Presence of diarrhoea and absence of tendon xanthomas in patients with cerebrotendinous xanthomatosis. *Arch Neurol.* 2000;57(4):520-524.

91. Wong JC, Walsh K, Hayden D, et al. Natural history of neurological abnormalities in cerebrotendinous xanthomatosis. *J Inherit Metab Dis.* 2018;41(4):647-656.

92. Nie S, Chen G, Cao X, et al. Cerebrotendinous xanthomatosis: a Comprehensive review of pathogenesis, Clinical manifestations, diagnosis and management. *Orphanet J Rare Dis.* 2014; 9:179.

93. Koyama S, Sekijima Y, Ogura M, et al. Cerebrotendinous xanthomatosis: molecular pathogenesis, Clinical spectrum, diagnosis and diseasemodifying rx. *J Atheroscler Thromb.* 2021; 28(9):905-925.

94. Stelten BML, Lycklama ANG, Hendricks E, et al. Long term MRI finding in patients with cerebrotendinous xanthomatosis treated with chenodeoxycholic acid. *Neurol.* 2022;99(13):559-566.

95. Khalaf K ,Tornese P, Cornese A, et al. Tauroursodeoxycholic acid: a potential therapeutic tool in neurodegenerative diseases. *Transl Neurodegener.* 2022;11(1):33.

96. Matias I, Morgado J, Gomes FCA. Astrocytesheterogeneity: impactto brain aging and disease. *Front Aging Neurosci.* 2019;11:59.

97. Stephenson J, Nutrina E, van der Walk, et al. Inflammation in CNS neurodegenerative diseases. *Immunology.* 2018;154(2):204-9.

98. Joo SS, Kang HC, Won TJ, et al. Ursodeoxycholic acid inhibits proinflammatory repertoire, IL-1β and nitric oxide in rats microglia. *Arch Pharmacol Res.* 2003;26(12):1067-1073.

99. Joo SS, Won TJ, Lee DL. potential role of suppression of nuclear factor κappa B in microglial cell line(BV-2). *Arch Pharmacol Res.* 2004;27(9):954-960.

100. Jiang C, Shen T, Li K, et al. Protective effects of ursodeoxycholic acid against Oxidative stress and neuroinflammation through Mitogen Activated Protein Kinase (MAPK) in MPTP induced Parkinson's disease. *Clin Neuropharmacol.* 2022;45(6):168-174.

101. Yanguas Cansas N, Barreda Manso N, et al. Tauroursodeoxycholic acid reduces glial activation in an animal model of acute neuroinflammation. *J Neuroinflammat.* 2014;11:50.

102. Yanguas Cansas N, Barreda Manso N, Perez Rial S, et al. TGF- beta contributes to the TUDCA anti-inflammatory effects of Tauroursodeoxycholic acid in an animal model of acute neuroinflammation. *Mol Neurobiol.* 2017;54(9): 6737-6749.

103. Yanguas Cansas N, Barreda Manso N, et al. TUDCA,anagonist of bile acid receptors GPBAR/TGR-5 with anti-inflammatory effects in microglial cells. *J Cell Physiol.* 2017;232(8):2231-2245.

104. Wu X, Liu C, Chen L, et al. Protective effects of tauroursodeoxycholic acid on lipopolysaccharide induced conitive impairment and neurotoxicity in mice. *Int Immunopharmacol.* 2019;72:166-175.

105. Sweis R, Biller J. Systemic complications of spinal cord Injury. *Curr Neurol Neurosci Rep.* 2017;17(2):8.

106. Kim SJ, Ko WK, Jo MJ, et al. Anti-inflammatory effects of tauroursodeoxycholic acid in RAW264.7 macrophages, Bone marrow-derived macrophages, BV-2 microglial cells and spinal cord Injury. *Sci Rep.* 2018;8(1):3176.

107. Romero Ramirez L, Garcia-Rama C, Wu S, et al. Bile Acids attenuate PKM2 pathway microglial activation in proinflammatory microglia. *Sci Reports.* 2022;12(1):1459.

108. Han GH, Kim SJ, Ko WK, et al. Injectable hydrogel containing tauroursodeoxycholic acid for anti - neuroinflammatory therapy after spinal cord Injury in rats. *Mol Neurobiol.* 2022;57(10):4007-4017.

109. Han GH, Kim SJ, Ko WK, et al. Transplantation of tauroursodeoxycholic acid transplantation of inducing M2 phenotype macrophages promote an anti-neuroinflammatory effect and functional recovery after spinal cord Injury in rats. *Cell Prolif.* 2021:54(6):e13050.

110. Wu S, Garcia-Rama C, Romero Ramirez L, et al. Tauroursodeoxycholic acid reduces neuroinflammation but

does not support long term functional recovery of rats with spinal cord Injury. *Biomed.* 2022;10(7):1501.

111. Nunes AF, Amaral JD, Lo AC, et al. TUDCA, a bile acid, attenuates amyloid precursor protein processing and amyloid beta deposition in APP/PSI mice. *Mol Neurobiol.* 2012;45(3):440-454.

112. Dionisio PA, Ribeiro MF, Lo AC, et al. Amyloid beta pathology is attenuated by tauroursodeoxycholic acid treatment in in APP/PSI mice after disease onset. *Neurobiol Aging.* 2015;36(1):228-240.

113. Cuevas E, Burks R, Raymick J, et al. Tauroursodeoxycholic Acid (TUDCA) is neuroprotective in a chronic mouse model of Parkinson's disease. *Nutr Neurosci.* 2022;25(7):1374-1391.

114. Mendes MI, Rosa AI, Carvalho AN, et al. Neurotoxic effects of MPTP on mouse cerebral cortex : modulation of neuroinflammation as aneuroprotectivestrategy. *Mol Cell Neurosci.* 2019;96: 1-9.

115. Bhargava P,Smith MD, Mische L, et al. Bile Acids metabolism is altered in Multiple Sclerosis and supplementation ameliorates neuroinflammation. *J Clin Investig.* 2020;130(7):3467-3480.

116. Noailles A, Fernandez-Sanchez L, Lax P, et al. Microglial activation in a model of retinal degeneration and TUDCA neuroprotective effects. *J Neuroinflammat.* 2014;11:186.

117. Murase H, Tsuruma K, Shimazawa M, et al. TUDCA promotes phagocytosis by retinal pigment epithelium via MerTK activation. *Invest Ophthalmol Vis Sci.* 2015;56(4):2511-2518.

118. Radi E, Formichi P, Battisti C, et al. Apoptosis and Oxidative stressin neurodegenerative diseases. *J Alzheimer' Dis.* 2014;42(Suppl3):125-152.

119. Viana RJ, Ramalho RM, Nunes AF, et al. Modulation of amyloid beta peptide induced toxicity through inhibition of JNK nuclear localization and caspase-2 activation. *J Alzheimer' Dis.* 2010; 22 (2):557-568.

120. Ramalho RM, Boralho PM, Castro RE, et al. Tauroursodeoxycholic acid modulates p-53 mediated apoptosisin Alzheimer's disease mutant neuroblastoma cells. *J Neurochem*. 2006;98(5):1610-1618.

121. Rodriques CM, Sola S, Brito MA, et al. Amyloid beta peptide disrupts mitochondrial membranelipid and protein structure: protective role of tauroursodeoxycholic acid. *Biochim Biophys Res Commun.* 2001;281(2):468-474.

122. Sola S, Castro RE, Laires PA, et al. Tauroursodeoxycholic acid prevents amyloid beta peptide induced neuronal death via a phosphatidyl inositol 3-kinase dependent signaling pathway. *Mol Med.* 2003;3(9-12):226-234.

123. Sola S, Amaral JD, Boralho PM, et al. Functional modulation of nuclear steroid receptors by tauroursodeoxycholic acid reduces amyloid beta peptide induced apoptosis. *Mol Endocrinol.* 2006;20(10):2292-2303.

124. Ramalho RM, Viana RJ, Low WC, et al. Bile Acids and apoptosis modulation: an emerging role in experimental Alzheimer'sdisease. *Trends Mol Med.* 2008;14(2):54-62.

125. Lo AC, Callaerts-Vegh Z, Nunes AF, et al. Tauroursodeoxycholic Acid (TUDCA) supplementation prevents cognitive impairment and amyloid deposition in APP/PSI mice. *Neurobiol Dis.* 2013;50:21-29.

126. DuanWM, Rodriques CM, Zhao LR, et al. Tauroursodeoxycholic acid improves the survival and function of nigral transplants in a rat model of Parkinson's disease. *Cell Transplant.* 2002;11(3):195-205.

127. Keene CD, Rodriques CM,Eich T, et al. A bile acid protects against motor and cognitive deficits and reduces striatal degeneration in the 3-nitrolpropionic acid model of Huntingtons disease. *Exp Neurol.* 2001;171(2):351-360.

128. Keene CD, Rodriques CM, Eich T, et al. Tauroursodeoxycholic acid,a bile acid is neuroprotective in a transgenic model of Huntingtons disease. *Proc Natl Acad Sci USA.* 2002;99(16):10671-10676.

129. Dong Y, Miao L, Hei L, et al. Neuroprotective effects and impact on caspase-12 expression of tauroursodeoxycholic acid after spinal cord Injury in rats. *Int J Exp Pathol.* 2015;8(12):15871-15878.

130. Chang Y,Yang T, Ding H, et al. Tauroursodeoxycholic acid protects rats spinal cord neurons after mechanical injury through regulating neuronal autophagy. *Neurosci Lett.* 2022;776(2):136578.

131. Hulisz D. Amyotrophic Lateral sclerosis: disease state overview. *Am J Manage Care.* 2018;24(15Suppl):S320-S326.

132. Kaur KK,Allahbadia GN, Singh M. A Comprehensive Update on the Etiopathogenesis of Amyotrophic Lateral Sclerosis with Specific Emphasis on Gut Microbiota (GM), Enteric Nervous System (ENS) and Associated Crosstalk of Astrocytes, GM, Muscle with Mitochondrial Melatonergic Pathway-A Narrative Review. *Int J Neurobiol.* 2023;5(2):158.

133. Min JH, Hong YH, Song JJ, et al. Oral solubilized ursodeoxycholic acid therapy in Amyotrophic Lateral sclerosis:a randomizedcrossover trial. *J Korean Med Sci.* 2012;27(2):200-206.

134. Thams S, Lowry ER, Larraufi MH, et al. A stemcells screening platform identifies compounds that desensitizes motor neurons to Endoplasmic Reticulum (ER) stress. *Mol Ther.* 2019;27(1):87-101.

135. Vaz AR, Cunha C, Gomes C, et al. Glyco Ursodeoxycholic Cholic Acid(GCDCA) reduces Matrix Metalloproteinase-9 and caspase-9 in a cellular model of superoxide dismutase-1 neurodegeneration. *Mol Neurobiol.* 2015;51(3):864-877.

136. Rosa AI, Duarte Silva S, Silva-Fernandez A, et al. Tauroursodeoxycholic acid improves motor in a mouse model of Parkinson's diseas. *Mol Neurobiol.* 2018;55(12):9139-9155.

137. Rosa AI, FonsecaI, Nunes MJ, et al. Novel insight into the antioxidant role of tauroursodeoxycholic acid in experimental models of Parkinson's disease. Biochem J Biochim Biophys Acta *Mol Basis Dis.* 2017;1863(9):2171-2181.

138. Moreira S, FonsecaI, Nunes MJ, et al. Nrf2 activation by tauroursodeoxycholic acid in experimental models of Parkinson's disease. *Exp Neurol.* 2017;295:77-87.

139. Castro-Caldas M, Carvalho AN, Rodriquez E, et al. Tauroursodeoxycholic acid prevents MPTP induced dopaminergiccell death in a mouse model of Parkinson's disease. *Mol Neurobiol.* 2012;46(2):475-486.

143. Zattoni M, Legname G. Tackling prion disease:a review of patent landscape. *Exp Opin Ther Pat.* 2021;31(12):1097-1115.

144. Cortez M, Campeau J, Norman G, et al. Bile acids reduce prion conversion, reduce neuronal loss andprolong male survival in models of prion disease . *J Virol*. 2015;89(15):7660-7672.

145. Norman G, Campeau J, Sim VL. High doses and delayed treatment with Bile acid is ineffective in RML prion infected mice. *Antimicrob Agents Chemother.* 2018;62(8):e00222-e00318.

146. Kliriyama Y, Nochi H. Bile Acid Role of Microbiota Bile Acids in the regulation of intracellular organelles and neurodegenerative diseases. *Genes (Basel).* 2023;14(4):825.

147. Rusch JA, Layden BT, Dugas LR. Signaling cognition: the GutMicrobiota and hypothalamo-pituitary-adrenal axis. Front *Endocrinol (Lausanne).* 2023;14:1130689.