

Neurological Functions of Bile Acids

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Bile acids (BA) are amphipathic steroid acids synthesized from cholesterol in the liver. They act as detergents to expedite the digestion and absorption of dietary lipids and lipophilic vitamins. BA are also considered to be signaling molecules, being ligands of nuclear and cell-surface receptors, including farnesoid X receptor and Takeda G-protein receptor 5. Moreover, BA also activate ion channels, including the bile acid-sensitive ion channel and epithelial Na⁺ channel. BA regulate glucose and lipid metabolism by activating these receptors in peripheral tissues, such as the liver and brown and white adipose tissue. Recently, 20 different BA have been identified in the central nervous system. Furthermore, BA affect the function of neurotransmitter receptors, such as the muscarinic acetylcholine receptor and γ -aminobutyric acid receptor. BA are also known to be protective against neurodegeneration.

bile acids

Alzheimer's disease

Parkinson's disease

Huntington's disease

ALS

1. Introduction

Bile acids (BA) are synthesized from cholesterol in the liver and are a significant component of bile. They are stored in the gallbladder and released into the small intestine after a meal. BA are amphipathic steroid acids and are known as indispensable detergents, expediting the digestion and absorption of dietary lipids and lipophilic vitamins by forming micelles in the small intestine. Recently, they have also been considered to be signaling molecules. They are now recognized as ligands of farnesoid X receptor (FXR), a nuclear hormone receptor, and Takeda G-protein receptor 5 (TGR5), a G-protein-coupled receptor (GPCR) that is also known as G protein-coupled bile acid receptor 1 (GPBAR1) [1].

Bile salt composition of a variety of vertebrate species is validated. Bile salts include C₂₇ bile alcohols, C₂₇ bile acids, and C₂₄ bile acids. C₂₄ bile acids exist in all vertebrates, although C₂₇ bile alcohols and C₂₇ bile acids exist in fish, amphibians, reptiles, and birds [2]. 5 α -C₂₇ bile alcohol sulfates are considered as the first ancestral bile salts. 5 α -cyprinol sulfate is 5 α -C₂₇ bile alcohol sulfate and activates FXR from the frog and the zebrafish, but not from the human and the mouse. In contrast, taurochenodeoxycholic acid (TCDCA) and lithocholic acid (LCA) activate FXR from the human and the mouse, but not from the frog and the zebrafish. Thus, the structure of FXR may be changed to adapt to bind species-specific bile salts [3].

2. Neurological Functions of BA

Twenty different BA and their receptors have been identified in the brain, implying that BA have physiological and pathophysiological roles in this tissue (Figure 2), and indeed, many studies of their physiological roles in the brain have been reported.

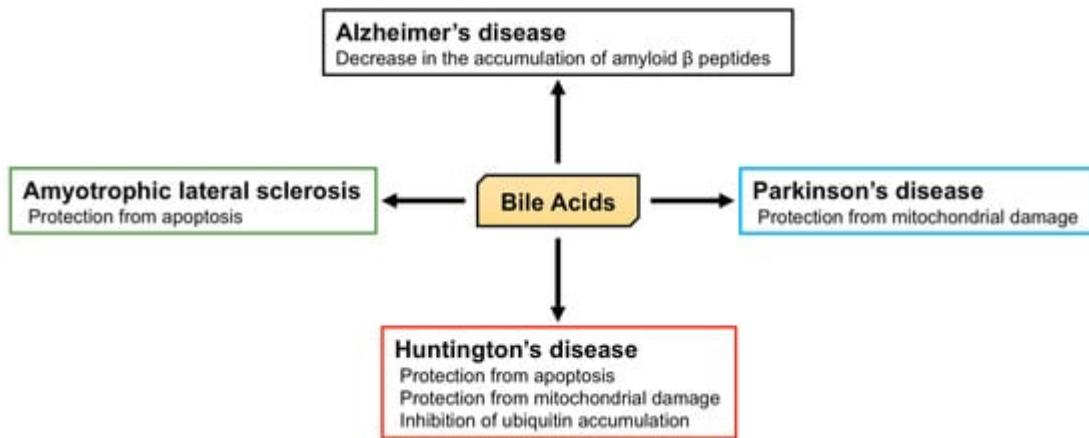


Figure 2. Protective functions of bile acids (BA) against neurodegeneration. BA are known to prevent the accumulation of amyloid β peptides in Alzheimer's disease; protect against mitochondrial damage in Parkinson's disease; protect against apoptosis, mitochondrial damage, and ubiquitin accumulation in Huntington's disease; and protect against apoptosis in amyotrophic lateral sclerosis.

2.1. The Role of BA in the Brain

BA affect the functioning of the receptors for several neurotransmitters, including M_2 and M_3 muscarinic acetylcholine receptors, γ -aminobutyric acid (GABA) type A ($GABA_A$) receptors, and N-methyl-D-aspartate (NMDA) receptors. TCA, GDCA, and TDCA activate the M_2 receptor, while DCA activates the M_3 receptor. M_2 receptors are distributed throughout the brain and are crucial for cognitive function. However, M_3 receptors are localized to neurons, which project to regions such as the hippocampus and substantia nigra, although they are also expressed at low levels throughout the brain. Thus, BA may affect cognitive function, memory, and learning [4]. NMDA receptors are ionotropic glutamate receptors that are activated by the simultaneous binding of both glutamate and D-serine or glycine [5][6]. Their activation causes Ca^{2+} influx, which can induce long-term potentiation and long-term depression. Therefore, appropriate NMDA receptor activation is important for learning and memory [7]. In contrast, the $GABA_A$ receptor is an ionotropic GABA receptor that is a ligand-gated chloride ion channel. The activation of $GABA_A$ receptor causes an influx of chloride ions, leading to the hyperpolarization of neurons and the inhibition of neurotransmission [8]. CDCA, DCA, and CA block both $GABA_A$ and NMDA receptors [9]. Histaminergic neurons in the tuberomammillary nucleus (TMN) of the hypothalamus play an important role in arousal and wakefulness [10] and express $GABA_A$ receptors; thus, the suppression of histaminergic neuronal activation in the TMN by GABA induces sleep [11]. Conversely, UDCA increases arousal by blocking $GABA_A$ receptors on TMN neurons [12]. Moreover, a recent study has demonstrated that TUDCA can induce neurogenesis in adult rats [13]. Adult neurogenesis is the process of generating new functional neurons that are added to the adult brain and occurs in two specific regions: The subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus and the subventricular zone (SVZ), located in the walls of the lateral ventricles. Neural stem cells (NSCs) in the SGZ of

adult mammals generate neurons in the DG. NSCs in adult human SVZ may produce functional neurons in the striatum by migrating there. In contrast, NSCs in adult rodent SVZ may produce functional neurons in the olfactory bulb [14]. In the rat, TUDCA increases the proliferation and neural differentiation of NSCs in the SVZ, but not in the DG [13].

2.2. The Role of BA in Neurodegenerative Diseases

Alzheimer's disease is characterized by memory loss, dementia, and morphological changes in the brain and is a common progressive neurodegenerative disease. The main pathological feature of the brains of patients with Alzheimer's disease is the accumulation of amyloid β peptides and tangles of tau protein [15]. The processing of amyloid precursor protein (APP) by β and γ secretases generates amyloid β peptide [16][17] and the γ secretase complex includes presenilin 1 (PS1), which is associated with the maturation of V-ATPase, responsible for the acidification of lysosomes. PS1 dysfunction, thus, leads to an impairment in lysosomal acidification and function [18][19]. The accumulation of amyloid β peptides is relevant to the dysfunction of both APP and γ secretase, and APP/PS1 double knockout mice, which express both mutated human APP and PS1, are used as a model of Alzheimer's disease. Interestingly, TUDCA reduces the accumulation of amyloid β peptides in the hippocampus and frontal cortex and rescues memory deficits in APP/PS1 double knockout mice [20][21]. In humans, plasma CA concentrations in patients with Alzheimer's disease are significantly lower than those in control subjects, and the TCA concentration in the brain of patients with Alzheimer's disease is also significantly lower [22]. In contrast, the plasma concentration of LCA, a secondary BA, is significantly higher in patients with Alzheimer's disease than in controls [23]. Furthermore, it has been shown that the ratio of DCA (secondary BA) to CA (primary BA) in serum is significantly higher in Alzheimer's patients [24]. These studies indicate the relationship between BA and Alzheimer's disease, and the importance of the brain-gut-microbiome axis. However, morphological and functional abnormalities in mitochondria have also been identified in patients with Alzheimer's disease [25][26]. In fibroblasts from Alzheimer's disease patients, the mitochondrial membrane potential (MMP) is lower, and there is mitochondrial elongation. Dynamin-related protein 1 (DRP1) plays an important role in mitochondrial fission and is essential for mitochondrial quality control [27]. Although the expression of DRP1 is lower in fibroblasts from Alzheimer's disease patients, UDCA increases its expression [28].

Parkinson's disease is another common progressive neurodegenerative disease that is characterized by tremors, muscle stiffness, loss or impairment of voluntary movements, slowness of movement, and postural instability [29]. Mutations in phosphatase and tensin homolog-induced putative kinase 1 (PINK1) and parkin are found in early-onset Parkinson's disease and are important in the progression of Parkinsonism [30][31][32][33]. PINK1 and parkin initiate mitophagy and nuclear dot protein 52 kDa (NDP52), and optineurin are essential for this process [34][35]. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone treatment have been widely used in the creation of a model of Parkinson's disease. Both toxins inhibit complex I in mitochondria, leading to neuronal mitochondrial damage and Parkinsonism [36][37]. However, TUDCA protects neurons from MPTP-induced oxidative stress and neurotoxicity in the midbrain and striatum of mice [38]. TUDCA induces nuclear factor erythroid 2-related factor 2 (Nrf2) expression and reduces the generation of reactive oxygen species, and indeed, this anti-oxidant effect of TUDCA may be Nrf2-dependent [39]. Moreover, TUDCA ameliorates clinical signs induced by MPTP, such as the

increase in swimming latency, foot-dragging, and tremors. In addition, TUDCA inhibits the loss of dopaminergic neurons and reduces the loss of MMP and mitochondrial mass elicited by MPTP [40]. Furthermore, TUDCA increases the expression of PINK1, parkin, and the ratio of LC3-II/IC3-I, implying that TUDCA induces mitophagy [41]. In addition, in the rotenone-induced rat model of Parkinson's disease, UDCA ameliorates abnormalities in the mitochondria of striatal neurons, such as irregular swelling and loss of cristae [42].

Huntington's disease is an autosomal dominant inherited neurodegenerative disease caused by a CAG trinucleotide expansion encoding polyglutamine (polyQ) at the N-terminus of Huntingtin (HTT). Huntington's disease is characterized by motor dysfunction, cognitive decline, and psychiatric disturbances [43][44]. Chemical and genetic models of Huntington's disease have been studied [45][46]. Firstly, 3-nitropropionic acid (3-NP) is an inhibitor of succinate dehydrogenase (complex II) in mitochondria and induces degeneration of the caudate-putamen, which is also present in Huntington's disease [45]. 3-NP treatment is associated with swelling of striatal mitochondria, abnormal mitochondrial membrane structure, and apoptosis. However, TUDCA prevents mitochondrial damage and apoptosis and ameliorates the sensorimotor deficits induced by 3-NP [47]. Secondly, R6/2 transgenic mice possess a genomic fragment containing exon 1 of the human *Huntingtin* gene, which carries 144 CAG repeats, and are the most widely used model of Huntington's disease [46][48]. In these mice, TUDCA prevents the striatal apoptosis and cerebral and striatal atrophy [49]. The accumulation of HTT and ubiquitin are also symptoms of Huntington's disease, and ubiquitin is recruited to polyglutamine-expanded HTT fragments [50]. TUDCA reduces the accumulation of ubiquitin in the striatum of R6/2 transgenic mice and ameliorates their sensorimotor deficits [49].

Amyotrophic lateral sclerosis (ALS) is a progressive and ultimately fatal disease that is characterized by the degeneration of both upper and lower motor neurons, leading to muscle weakness, atrophy, and paralysis [51]. Impairments in superoxide dismutase 1 (SOD1), C9ORF72, TAR DNA-binding protein of 43 kDa (TDP-43), and fused in sarcoma (FUS) are molecular features of this disease [52]. Transgenic mice that carry the glycine 93 to alanine mutation of human SOD1 (hSOD1^{G93A}) are the most studied model of ALS [53]. NSC-34 cells carrying hSOD1^{G93A} also represent a useful model of ALS-affected motor neurons [54]. Glycoursodeoxycholic acid (GUDCA) prevents the apoptosis of NSC-34 cells carrying hSOD1^{G93A} [55], and clinical trials of the use of TUDCA in patients with ALS have shown an improvement in muscle function and survival time, without adverse effects [56].

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