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REVIEW

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Bilirubin metabolism: delving into the cellular and molecular mechanisms to predict complications

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Abstract

Bilirubin is a metabolic product of heme, and an increase in its level may be toxic to the body. It may be conjugated or unconjugated. Encephalopathy is caused by unconjugated bilirubin has the ability to pass through the blood-brain barrier, entering the central nervous system. Conjugated forms of bilirubin result in biliary obstruction and a change in urine colour due to a decrease in excretion. Excessive hemolysis can result from hereditary and autoimmune diseases, deficient RBC membranes, enzyme deficiency, and hemoglobin structural anomalies. In this review, we summarize all the possible mechanisms and complications regarding bilirubin. Cellular and molecular functions and mechanisms of bilirubin are explained, followed by several complications viz neurotoxicity, auditory dysfunction, and nephrotoxicity. The cause of bilirubin-induced neuronal cell damage is likely due to the elevated levels of unconjugated bilirubin in plasma, mitochondrial, and endoplasmic reticulum (ER) membranes. These disruptions in the membranes could lead to harmful effects such as neuronal excitotoxicity, energy failure in mitochondria, or an increased concentration of calcium within the cells. At the cellular level, bilirubin exerts its toxic effect by disturbing the normal functioning of neuronal cells. Bilirubin's presence can cause certain inflammatory responses, resulting in the activation of proinflammatory cytokines. Additionally, research has demonstrated that bilirubin can negatively affect auditory abilities. It disrupts the integrity of auditory pathways, resulting in auditory dysfunction and potentially causing long-term hearing impairments in infants affected by it. In conclusion, a comprehensive understanding of the complications associated with unconjugated bilirubin in neonates is essential for improving clinical management and outcomes. Understanding the cellular and molecular pathophysiology of high bilirubin may lead to a new therapeutic approach.

Keywords Bilirubin encephalopathy, Auditory disfunction, Cellular and molecular mechanism, Unconjugated bilirubin, Kernicterus, Jaundice, Hyperbilirubinemia

Background

Bilirubin is an end of heme breakdown of erythrocyte hemoglobin and typically produces about 80% of bilirubin; the remaining 20% is formed by heme-containing enzymes. When the serum total bilirubin level exceeds 5 mg/dl, it is known as neonatal hyperbilirubinemia. This condition affects newborns with hemolytic anemia who have a bilirubin level of 25–30 mg/dL.

Unconjugated bilirubin accumulation in the body can be caused by increased bilirubin activity, diminished liver excretion, or increased enterohepatic circulation of the pigment. Since unconjugated bilirubin is insoluble in water and unable to be eliminated through urine (known as acholuric jaundice). It may penetrate the central nervous system and breach the blood-brain barrier, causing encephalopathy. Conjugated (direct) hyperbilirubinemia

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is caused by the reflux of direct or conjugated bilirubin into the bloodstream as a result of biliary obstruction. Conjugated bilirubin, or indirect bilirubin, is water soluble and can be eliminated in the urine, darkening its colour (choluric jaundice). Until the 1980s, when its antioxidant action was discovered, bilirubin was thought to be a harmful by-product linked with the potentially fatal disorders of neonatal hyperbilirubinemias, acute hepatitis, and cirrhosis. Bilirubin has antioxidant properties and can effectively remove peroxyl radicals, preventing lipid and lipoprotein oxidation, particularly LDL-C peroxidation. This ability may contribute to the prevention of atherosclerotic plaque development and its associated clinical complications [1–3].

Types of jaundice

1. Pre-hepatic jaundice brought by the breakdown of erythrocyte.
2. Hepatic jaundice, which results from the liver's improper elimination and metabolism of bilirubin.
3. Hepatic jaundice based on bile duct blockage [4].

Pathophysiology

Excessive breakdown of heme occurs due to hemolysis, which can be caused by various hereditary and autoimmune diseases that result in deficient red blood cell membranes (such as hereditary spherocytosis), enzyme deficiencies (such asG6PD), and abnormalities in hemoglobin structure. OATP1A1 is a specific transporter found in the liver that is responsible for carrying negatively charged substances, such as bilirubin. If OATP1A1 activity is reduced, it can lead to unconjugated hyperbilirubinemia. Studies have connected genetic variations in OATP1A1 to malfunction. Bilirubin is prevented from returning to the plasma by binding with ligandin in liver cells. Within the cells, enzymes called UGT's convert bilirubin into monogluconide and digluconide conjugated bilirubin. The specific UGT1A1 is an important UGT type for the glucuronidation of bilirubin. The primary transporter that excretes conjugated bilirubin is MRP2, while there are other types of transporters present on the membrane of the liver as well. Bacteria convert conjugated bilirubin to urobilinogen, which is eventually converted into urobilin, in the terminal of the intestines. Before being removed by urine, some urobilinogens are reabsorbed into the bloodstream (Fig. 1) [5].

Athetoid cerebral palsy is one type of cerebral palsy associated with, hearing loss or impairment, impairment of upward gaze, and primary tooth enamel dysplasia are the traditional outcomes of excessive neonatal hyperbilirubinemia, which are also linked with abnormalities in the globus pallidus and subthalamic nucleus, auditory, and oculomotor brainstem nuclei [6].

Newborns are more susceptible to jaundice compared to adults. However, if it occurs in adults, it can be fatal. The condition can be caused by either excessive production of bilirubin or the liver's inability to eliminate it due to various factors such as liver or bile duct inflammation, hemolytic anemia, bile duct obstruction, cholestasis, and Gilbert's syndrome. It can also lead to other severe symptoms like psychosis, lethargy, convulsions, coma, or even death. Liver disease is a significant contributor to illness and death globally. Several risk factors for newborn jaundice include preterm birth, race, medications, living at high altitudes, polycythemia, blood type incompatibility, mode of delivery, and maternal diabetes [7]. Neonatal hyperbilirubinemia can be defined as a blood total bilirubin level greater than 5 mg/dl (86 mol/L). Neonatal hyperbilirubinemia is caused by high production due to increased rate of RBC breakdown and limited ability to eliminate it by the baby. The generation of bilirubin occurs at higher rates in newborns than in adulthood, particularly in preterm infants. The ability of newborns to conjugate bilirubin is restricted, and unconjugated bilirubin is not easily removed from them. Coupling these drawbacks causes physiological jaundice, or high blood bilirubin concentrations, in the first few days of life in fully developed neonates, which is followed by a drop to values typically found in adults during the following few weeks [8]. The amount of unattached or "free" unbound bilirubin (Bf) and the level of hydrogen ions (pH) in the circulation determines the likelihood that bilirubin may induce neurological damage. Age, infection or sepsis, and hemolysis, particularly Rh isoimmunization, are additional important neuronal susceptibility risk factors for kernicterus. Preterm delivery, sepsis, and other neonatal inflammatory diseases may decrease albumin's capacity to bind bilirubin [9].

Hyperbilirubinemia effects according to cellular basics

Excessive amounts of free bilirubin (UCB), can suppress the brain's defensive mechanisms [8]. Kernicterus induces yellow staining in the basal ganglia, particularly the globus pallidus and subthalamic nucleus. The oculomotor system, vestibular nuclei, and auditory structures (cochlear nucleus, inferior colliculus, and superior olivary complex) exhibit increased sensitivity. Additionally, the Purkinje cells in the cerebellum and the CA2 region of the hippocampus are especially susceptible locations [9]. If chronic bilirubin encephalopathy is left untreated, initially reversible symptoms (hypotonia, lethargy, poor sucking, and auditory evoked potentials) can lead to the accumulation of free bilirubin in particular focal areas

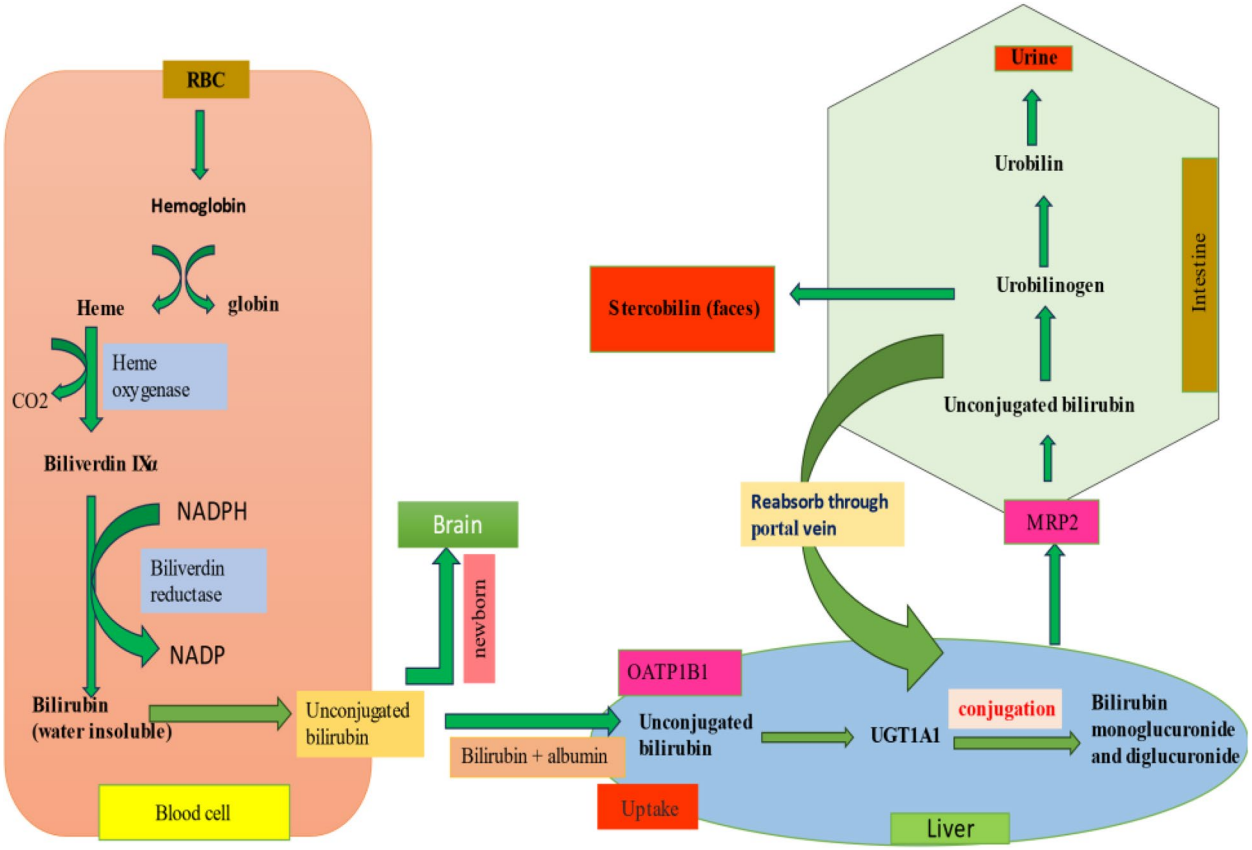

Fig. 1 Catabolism of bilirubin

of the central nervous system (CNS), resulting in permanent neurologic damage [10]. Bilirubin-IXa (Z, Z), which can exist as a charged dimer or as bilirubin acid, is the main bilirubin isomer in humans. The presence of intramolecular hydrogen bonds in the acid form causes it to be almost undissolved in water, whereas the inclusion of eight water-friendly groups in the dianion configuration provides some water solubility at neutral pH. The hydrophobic bilirubin-IX isomer of bilirubin causes negative consequences, but the soluble in water isomers are benign and nontoxic [11–14]. More bilirubin could enter the brain if the blood-brain barrier was broken. Radiation, hypoxia, hyperosmolality, and hypercarbia have all caused such openings. Bilirubin appears to enter the brain largely as a free molecule in respiratory acidosis (hypercarbia). In hyperosmolality, both albumin-bound and unbound bilirubin entrance seem to be connected to the disruption of the BBB (Fig. 2) [15–18].

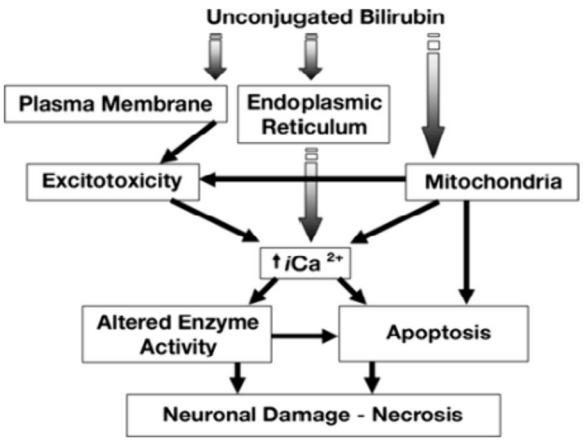

Fig. 2 Pathophysiology of bilirubin-induced neuronal damage [19]

Hyperbilieubemia complications on molecular basics

Bilirubin effects on neuronal excitotoxicity

In the CNS, glutamate is an excitatory neurotransmitter of the NMDA receptor, which is essential for normal neuronal function, but bilirubin interferes with the blocking of the NMDA receptor and also inhibits the ion channel activity. This shows that UCB may obstruct nerve conduction and interfere with neuroexcitatory signals, particularly in the auditory nerve. The high affinity of UCB for neuronal membranes causes a

conformational change in the NMDA receptor, resulting in an open and activated NMDA receptor-ion channel complex [19]. Even a little exposure to free-form bilirubin can prevent a steady expansion of synaptic transmission in the hippocampus, a critical element regulating the processes of memory and learning. UCB has considerable negative impacts on the nervous system [20]. UCB also produces synaptotoxicity, which has been linked to increased inhibitory synaptic transmission. The production of synaptophysin and SNAP-25, two proteins that contribute to synaptic formation and neurotransmitter release, has been discovered to be decreased by UCB. As a result, UCB has been shown to trigger presynaptic degeneration while maintaining postsynaptic neurons. The N-methyl-d-aspartate (NMDA) receptor-mediated excitatory procedure, which provides the intracellular Ca2+ increase necessary for nNOS activation, is another mechanism by which UCB-induced neuronal damage occurs. Indeed, UCB has been demonstrated to increase glutamate's extracellular concentration by increasing the flow of it, especially from developing neurons, which causes the overstimulation of NMDA receptors. Furthermore, extended UCB exposure reduced presynaptic transmitter release while impairing postsynaptic NMDA receptor function [8].

Protein kinase C activity is inhibited by UCB. This process is crucial in preserving synaptic function, which is brought about by calcium ions entering the plasma membrane of the post-synaptic neuron by a high-conductance cation channel. In addition to glutamate binding to NMDA receptors in the membrane cleft, membrane depolarization also causes this channel to open. This causes NMDA overstimulation and excitotoxicity of receptors. Excitotoxicity, which is brought on by a higher intake of sodium, calcium, chloride ions, and water, causes the expansion of neuronal cells and ultimately cell death by both apoptosis and necrosis. The direct contact of UCB with nerve cell membranes, which results in higher oxidative damage, the permeability of membranes, and reduced order in lipids and proteins, may be the cause of the potential disruption of cell equilibrium [20]. In addition to its strong affinity for the membrane, which causes it to depolarize fast and inhibits the Na+K+ATPase, bilirubin has effects on brain electrical activity. It interferes with the presynaptic terminal's ability to make, consume, maintain, and release neurotransmitters. Upon inhibiting astrocyte absorption, glutamate release rises. Through glutamate receptors in downstream neurons, excess glutamate leads to excitotoxin. Plasticity of synapses is hampered by bilirubin. It causes post-synaptic neuron excitation in developing neurons and improves transmission at GABAergic synapses [21].

Bilirubin effects on mitochondrial disfunction

Before apoptosis, there were indicators of poor mitochondrial metabolism and membrane disruptions, such as altered lipid polarity and flow, protein ordination, and oxidative status. Increased lipid polarity indicates the effect on cell membranes. Bilirubin interacted directly with mitochondria, affecting membrane lipid and protein characteristics, redox status, and cytochrome C concentration, and bilirubin-induced apoptosis may be mediated in part by physical changes in the mitochondrial membrane. Thus, high bilirubin concentrations (100 M) resulted in early necrosis, but low-to-moderate doses (0.66–25 M) primarily resulted in delayed apoptosis [22]. The establishment of a multi-protein pore complex that is susceptible to cyclosporin A or non-specific damage to the lipid structure of the mitochondrial membrane can both lead to increased permeability of the membrane. It is thought that when cytochrome c enters the cytosol, it causes the creation of a multi-protein assembly that starts the proteolytic activation of caspases, which are cellular death enzymes [23]. Cytochrome c is released when the transmembrane potential of the mitochondria is lowered by unconjugated bilirubin. While Bcl-2, an apoptosis inhibitor, is deactivated by the translocation of Bax, an apoptosis promoter, to the mitochondrial membrane, certain ion channels are formed in the membranes. This is an extra procedure that aids in cytochrome c release. Caspase 9 is activated when cytosolic cytochrome c interacts with the protein known as apoptotic protease activating factor-1 (Apaf-1). Caspase 9 then cleaves and activates pro-caspase-3, leading to the commencement of the cell death program, commonly known as the apoptosis cascade [24].

Bilirubin effects on calcium level

It is obvious that bilirubin ultimately leads to abnormal intracellular calcium levels, probably as a consequence of a combination of the following factors,

Increased transmembrane Ca2+ influx
Ca2+ release from intracellular reserves
Reduced intracellular Ca2+ buffering capacity

regardless of the type of event that is taking place, be it excitotoxicity, an actual relationship between the plasma and cellular membranes, a direct impact on the endoplasmic reticulum, or energy depletion.

After being established, heightened levels of intracellular calcium through second messenger pathways can trigger various enzyme systems such as lipases, endonucleases, and proteases. This, in turn, can lead to the production of free radicals, ultimately resulting in cell

death through either apoptosis or necrosis [19]. A rise in intracellular Ca2+ ([Ca2+]) is essential for starting the subsequent steps that lead to bilirubin-induced neurodegeneration. The inflow of calcium through voltage-gated calcium channels and the absorption of intracellular calcium that has been stored are both involved in the rise in calcium levels brought on by bilirubin. In Ca2+ and calmodulin-dependent activities, bilirubin increased voltage-gated calcium currents through high voltage-activated P/Q-type calcium channels [21]. Bilirubin has been demonstrated to affect synapsin phosphorylation at both the CAMP-dependent and calcium-dependent sites. As a result, characterizing bilirubin's effects on neuronal phosphorylation systems could contribute to resolving some of bilirubin's neurotoxic effects. CaM kinase II influences neurotransmitter production and release, as well as, neuroskeletal components, calcium-dependent ion current and receptor-gated ion channels [25].

Bilirubin effects on the nucleus

Oxidative stress, which prevents the cell cycle from progressing and results in DNA damage, contributes to the beginning of cell death brought on by bilirubin [26]. Jaundice with high TSB levels is thought to be genotoxic. It is probable that the long-term repercussions of neonatal hyperbilirubinemia could include potential genetic or carcinogenic ramifications later in life because DNA strand breaks have the potential to result in carcinogenic and mutagenic outcomes. Recent studies have shown that UCB lowers the presence of decreased glutathione while simultaneously boosting the oxidized disulfide form, causing a decrease in glutathione levels in neurons and splenocytes. Exposure to UCB increases superoxide radical anion generation in neutrophils [27, 28].

Bilirubin impacts the endoplasmic reticulum and golgi complex

The creation, retracting, and transport of proteins, as well as cellular reactions to stress and calcium concentration regulation, are all controlled by the endoplasmic reticulum. The presence of expanded vacuoles and larger vesicles generates kernicterus in the Golgi complex [27, 29]. After being exposed to UCB, astrocytes developed ER and mitochondrial abnormalities. Endoplasmic reticulum stress is caused by the accumulation of unconjugated bilirubin (UCB) inside the cell and has been demonstrated to increase the expression of several associated genes. Caspases 2 and 12 in the ER can either start or trigger apoptotic cell death [27]. Initially recognized as the primary protease in mitochondria, caspase-2 is now known to be activated by both calpain and caspase-3, triggering caspase-9 in the process [30]. A few genes that UCB activates also suggest a potential function in autophagy, a mechanism that is thought to help slow down cell development [31, 32].

Cellular mechanism of bilirubin

It has been demonstrated that UCB is present at the cellular level in neurons, neuronal functions, and microscopic glia and that it causes neuronal death, demyelination, and gliosis. It has been proven to inhibit neuronal arborization and to cause microglia and astrocytes to generate pro-inflammatory cytokines [8]. UCB causes neuron and glial cell destruction, as well as lesions in more vulnerable brain locations, potentially leading to permanent CNS dysfunction [33]. While glial cells are essential for maintaining brain networks, facilitating neuronal migration through development, and forming myelin, neurons are highly specialized for analyzing signals and communication (Fig. 3) [34, 35].

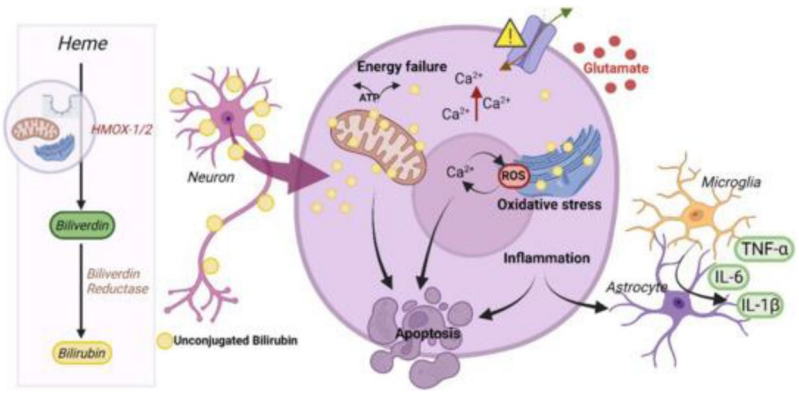

Fig. 3 Molecular mechanism involved in BIND induced neurotoxicity [36]

Bilirubin's effects on neurons

Bilirubin completely adheres to cell walls, particularly myelin-rich membranes, making neurons the primary target of bilirubin toxicity. Bilirubin totally binds to cell membranes, especially myelin-rich membranes, making neurons the principal target of bilirubin toxicity. Cell migration and synapse development may be impaired as a result of altered cell proliferation. Bilirubin causes protein oxidation, lipid peroxidation, decreased cellular glutathione content, increased lactate dehydrogenase levels, and nitric oxide release (via neuronal nitric oxide synthase activation via N-methyl-d aspartate receptor activation). Thus, sequence of neuronal damage may be bilirubin-induced oxidative stress and mitochondrial alterations. Bilirubin's main effects on neurons are decreased oxygen consumption and increased calcium and caspase-3 release, which results in apoptosis [36, 37]. For the transmission and processing of cellular impulses neurons are highly specialized to perform a variety of activities in various areas of the CNS [28]. Axonal connections are often lost as a result of CNS injury, which results in cell death and neuronal failure. The transfer of mitochondria to precise places in neurons allows optimal nerve cell activity [27]. Glial cells and immature neurons are more susceptible to the free form of bilirubin than mature ones according to several investigations [21]. They produce greater ROS, protein oxidation, and lipid peroxidation than astrocytes and are more sensitive to unconjugated bilirubin produce death, most likely due to reduced glutathione storage [27]. Due to interaction with unconjugated bilirubin which impairs neurogenesis, leads to neurotic atrophy, and causes cell death through apoptosis and necrosis, all of which are made worse by accompanying hypoxia, is particularly harmful to developing neurons. The impact results in a rapid and irreversible loss of neuronal protection, as well as a decrease in the number of synapses and dendritic spines. Cells also remain sensitive and become more susceptible to repeated toxic shocks [8].

Effects of bilirubin in astrocytes

Astrocytes, the most popular kind of glia, which are closely connected with astrocyte development. Like microglia, astrocytes can play a toxic or protective role in the nervous system, with the lifespan of neurons decreased, and their vulnerability to neurotoxic agents is increased by the release of inflammatory agents ATP, glutamate, cytokines, and unstable radicals. Indeed, astrocyte disruption has been identified as a major contributor to neuronal dysfunction. In response to UCB, extracellular glutamate concentration rises, usually in developing astrocytes, and this rise in concentration appears to be produced by UCB inhibition by its absorption, which is greater in glial cells compared to neurons [8]. Microglia and astrocytes are crucial in the activation of inflammatory responses and oxidative damage. In response to UCB stimulation, IL-1beta, TNF-alpha, NF-B, and MAPK pathways have been shown to serve significant functions in cytotoxicity and cytokine production, which led to UCB-induced neurotoxicity [31]. Astrocytes can release transmitters like ATP and glutamate which lead to the constant control of local cerebral blood flow as well as the adaptability of Brain terminals [27, 38, 39]. Astrocytes participate in glutamate uptake, they may neutralize its toxic effect, prevent overactivation of microglia, boost immunological responses, and reduce myelin regeneration [27, 40]. because astrocyte dysfunction has become increasingly important in the aetiology of CNS diseases [41].

Effects of bilirubin in oligodendrocyte

Prenatally and postnatally, oligodendrocyte precursor cells (OPCs) constitute a copious source of developing cells with the ability to mature into myelin-producing oligodendrocytes (OLGs). OLGs have to keep constant contact with axons in order to regulate OPC growth, differentiation, and myelination, which decreases myelin formation and axonal function due to OPC and OLG damage, thus interfering with neuronal connectivity and function. OLGs are mature glial cells in the spinal cord and brain that myelinate axons [34]. UCB cytotoxicity to OLGs reduced OLG viability with increasing apoptotic cell death NO generations and increasing apoptotic cell death. In fact, kernicterus causes demyelination in most cases [27, 42–44]. Furthermore, UCB appears to preferentially bind to myelin, and white matter problems appear to precede grey matter injury in severely jaundiced infants [27, 45]. UCB exhibits a rapid increase in ER stress characteristics, including Ca2+ release, calpain, activation of JNK1/2, and the production of ROS, mitochondrial dysfunction, apoptosis, and necrosis [46]. Furthermore, UCB retards OPC development, increasing the amount of immature (NG2 +) cells while decreasing OLGs (MBP +) [27].

Effect of bilirubin in microglia

Microglia has been linked to neurogenesis, post-lesional tissue healing, and "synaptic stripping". It plays a substantial role in synaptic refinement throughout postnatal maturation, microglia have the potential to be regarded as an additional target for hyperbilirubinemia protection [8, 47]. Microglial activation might result in neurotoxic effects and influence whether the damage is temporary or permanent. When microglia are exposed to UCB, they produce TNF, IL-1, and IL-6, as well as glutamate. About 10-20% of all glial cells are microglia, which are

more commonly found in the basal ganglia, substantia nigra and hippocampal [48, 49]. Activating microglia with unconjugated bilirubin at an early stage enhances their phagocytic capabilities, subsequently leading to the development of an inflammatory profile. Additionally contributing to neuronal death, damage persistence, and inflammatory cytokine production is microglial phagocytosis [27]. Changes in brain homeostasis cause changes in microglia motility and morphology [33]. The interaction of UCB with microglia initially affects defensive processes involved with the expression nuclear factor kappa B (NF-B) and of mitogen-activated protein kinases (MAPKs) as well as enhanced phagocytosis and the subsequent generation of pro-inflammatory cytokines. Tumor necrosis factor-alpha (TNF-)and Interleukin-1 (IL-1) as well as other cytokines involved in homeostasis or neuroinflammation and illness, are produced by microglia [34]. TNF- and interleukin-1 secretion enhanced matrix metalloproteinases 2 and 9 action (Fig. 4) [33].

Bilirubin response to inflammatory mediators

Chronic neuroinflammation has come to be seen as a major risk factor for CNS damage in premature infants. Severe systemic inflammation-related conditions such as sepsis, necrotizing enterocolitis, and the maternal inflammatory response syndrome are all related to increased bilirubin toxicity [50]. It has been shown that UCB causes oxidative stress, p38MAPK, and GSH depletion activation in splenocytes, among other internal and extrinsic pathways. Systemic pro-inflammatory mediators eventually activate microglia, which leads to neuronal death, inflammation, and BBB rupture, of the nervous system. This alteration disturbs the delicate equilibrium of neuroglial interaction components, impairing memory, neurogenesis, neuronal plasticity, and neuritic arborization as well as synaptic transmission. The inflammatory response has also been demonstrated to impact dopaminergic neurons' sensitivity to subsequent environmental pollutants, which has been associated with neurological disorders. As a result, the combination of inflammation and hyperbilirubinemia can cause functional dysregulation and even neurodegeneration, resulting in disruption of nerve terminal activity and synaptic loss. Furthermore, by acting on endothelial cells, inflammatory cytokines may enhance blood-brain barrier permeability [27]. Pro-inflammatory production of cytokines, as well as the presence of NOS and ROS, can impair nerve terminal efficiency, which can result in UCB breakdown and a loss of synaptic connections. Normal brain function normally involves very small amounts of COX-1, however after brain damage, many cell types quickly produce COX-2, the responsive variant.COX2 is activated by pro-inflammatory stimuli and has been implicated as a defense reacting to glutamate imbalance, preferably in neurons. LPS (Lipopolysaccharides) has been demonstrated to considerably increase PGES-1 (prostaglandin E synthase-1) in microglia and by activating both constitutive and inducible COX (Cyclooxygenase) isoforms, PGE2 is released from astrocytes [8].

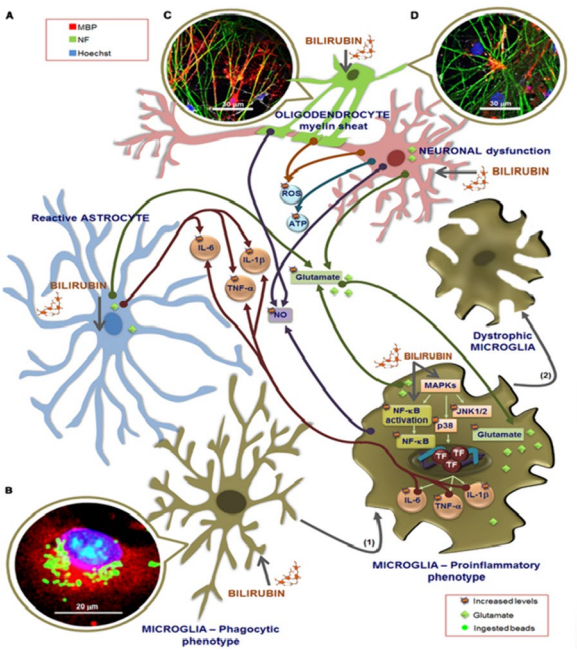

Fig. 4 Cellular mechanisms involved in glial cells and neurons after interacting with bilirubin [8]

Bilirubin induces auditory dysfunction

The exterior and inside hair cells of the auditory system appear to be unaffected by bilirubin; however, the cell structures of the auditory nerve within the spiral ganglia may be disturbed. The auditory system's brainstem auditory nuclei appear to be its most responsive region. The thalamus and the brain's auditory circuitry don't seem to be altered [10]. The auditory nuclei, superior olivary complex, and inferior colliculi are only a few of the auditory processing area of the brain stem that exhibits a heightened vulnerability to the negative consequences of bilirubin-induced neurodegeneration. Due to bilirubin's preference for bigger myelinated neurons, the spiral ganglia and auditory nerve may be susceptible, although maybe to a lesser extent. Both cerebral and peripheral (VIIIth cranial nerve) auditory functions are affected. There are no obvious abnormalities in the inner ear parts of the central auditory system, which includes the ventral and dorsal cochlear nuclei, superior olivary complex, lateral lemniscus nuclei, and inferior colliculus Hearing impairment has been observed in cases with auditory neuropathy spectrum disorder, as shown by behavioural

audiograms with varying degrees of severity ranging from usual to moderate too serious and profound. Dysarthria, dystonia, and anomalies in the movement of the speech apparatus are common in children with kernicterus, which can make it difficult for them to communicate vocally [51].

Genetic disorder associated with hyperbilirubinemia

Crigler-Najjar syndrome

It is a condition marked by persistent discoloration of the skin, mucous membranes, and sclera. It is a rare genetic disorder that has the potential to cause elevated bilirubin levels without hemolysis. The conversion of bilirubin to uridine diphosphate glucoronosyl transferase-1 and its elimination are both caused by mutations in the UGT1A1 gene, which codes for this enzyme [2]. There are two distinct kinds of Crigler-Najjar syndrome: type I, which is distinguished by a nearly complete absence of enzyme activity and the presence of noticeable symptoms; and type II, which is characterized by limited enzyme activity and less noticeable symptoms. Encephalopathy, which results in coloration in many basal ganglia regions including the globus pallidus, subthalamic nuclei, and cranial nerve nuclei, can be caused by both CNS types 1 and 2 [52]. Unconjugated hyperbilirubinemia is commonly caused by neonatal jaundice and Gilbert syndrome [53].

Gilbert syndrome

It is an inherited disorder marked by slight, persistent unresolved hyperbilirubinemia without hemolysis or other signs of liver injury. Lack of UGT1A1 activity is often associated with another problem since UGT1A1 activity usually decreases to 10–35% from normal and bile pigments show a distinctive rise in bilirubin monoglucuronides. According to a review of bilirubin kinetics data, people with Gilbert's syndrome (GS) might suffer from deficiencies in bilirubin absorption and conjugation [54].

Conclusion and recommendation

Bilirubin is a toxic by product of heme metabolism and exists in conjugated and unconjugated forms. The complications associated with bilirubin include hepatic encephalopathy, auditory dysfunction, skeletal muscle damage, extrapyramidal symptoms like athetosis and chorea, visual abnormalities including gaze palsies, abnormalities in dentition, extrapyramidal symptoms like athetosis and chorea, visual abnormalities including gaze palsies, abnormalities in dentition, etc. Detailed study of cellular and molecular mechanisms of bilirubin production, circulation, and metabolism provides new drug targets, especially for damage caused by bilirubin on brain cells, ear damage, etc. It is clear that bilirubin presents a toxicity risk to preterm infants. Currently, phenobarbital and other pharmaceutical treatments are used to manage this condition. However, a multifaceted approach involving advanced pharmaceutical interventions, gene therapy, in silico modeling, nanotechnology, stem cell therapy, and bilirubin-binding agents holds promise for the management of bilirubin-related disorders in the future.

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