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BIOCHEMISTRY OF HEPATIC DETOXIFICATION: BIOTRANSFORMATION (PHASE I–II) ENZYME SYSTEMS, OXIDATIVE STRESS, AND ITS ASSOCIATION WITH HYPERBILIRUBINEMIA

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Abstract. The liver is the main organ that detoxifies foreign chemicals and endogenous metabolites through biotransformation. This process includes Phase One functionalization reactions and Phase Two conjugation reactions, followed by transporter mediated excretion into bile or blood. Phase One reactions, driven largely by the cytochrome P450 monooxygenase system, introduce or expose polar groups through oxidation, reduction, or hydrolysis. However, cytochrome P450 activity can generate reactive intermediates and reactive oxygen species when electron transfer is inefficient, promoting oxidative stress and cellular damage. Phase Two reactions generally reduce toxicity by conjugating metabolites with highly polar groups via enzyme families such as uridine diphosphate glucuronosyltransferases, sulfotransferases, glutathione transferases, N acetyltransferases, and methyltransferases, thereby increasing water solubility and facilitating elimination. Hyperbilirubinemia is closely linked to detoxification because bilirubin requires hepatic uptake, glucuronidation by uridine diphosphate glucuronosyltransferase family one member A one, and biliary secretion. Oxidative stress can impair detoxification enzymes and transporters and modify gene expression through redox sensitive signaling pathways, including nuclear factor erythroid two related factor two, which alters antioxidant and detoxification capacity. Together, Phase One and Phase Two metabolism, antioxidant defenses, and bilirubin handling form an integrated biochemical network that explains many clinical manifestations of liver dysfunction, particularly oxidative injury and hyperbilirubinemia.

Keywords. Liver detoxification; Biotransformation; Cytochrome P450 monooxygenase system; Oxidative stress; Hyperbilirubinemia; Heme oxygenase

БИОХИМИЯ ПЕЧЁНОЧНОЙ ДЕТОКСИКАЦИИ: ФЕРМЕНТНЫЕ СИСТЕМЫ БИОТРАНСФОРМАЦИИ (I–II ФАЗЫ), ОКИСЛИТЕЛЬНЫЙ СТРЕСС И ЕЁ СВЯЗЬ С ГИПЕРБИЛИРУБИНЕМИЕЙ

Аннотация. Печень является главным органом, обеспечивающим обезвреживание ксенобиотиков и эндогенных метаболитов посредством биотрансформации. Этот процесс включает реакции функционализации первой фазы и реакции конъюгации второй фазы, после чего продукты выводятся с участием транспортных белков в желчь или кровь. Реакции первой фазы, в основном опосредованные монооксигеназной системой

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цитохрома P450, вводят или раскрывают полярные группы за счёт окисления, восстановления или гидролиза. Однако при неэффективной передаче электронов активность цитохрома P450 может приводить к образованию реактивных промежуточных метаболитов и активных форм кислорода, что усиливает окислительный стресс и повреждение клеток. Реакции второй фазы обычно снижают токсичность, поскольку метаболиты конъюгируются с высокополярными группами при участии семейств ферментов, таких как уридиндифосфат-глюкуронозилтрансферазы, сульфотрансферазы, глутатион-трансферазы, N-ацетилтрансферазы и метилтрансферазы, что повышает водорастворимость и облегчает выведение. Гипербилирубинемия тесно связана с детоксикацией, поскольку метаболизм билирубина требует печёночного захвата, глюкуронирования с участием уридиндифосфат-глюкуронозилтрансферазы семейства 1, член A1, и секреции в желчь. Окислительный стресс может нарушать работу ферментов и транспортёров детоксикации, а также изменять экспрессию генов через редокс-чувствительные сигнальные пути, включая ядерный фактор, родственный эритроидному 2, что влияет на антиоксидантную защиту и детоксикационный потенциал. В совокупности метаболизм первой и второй фаз, антиоксидантные системы и обмен билирубина образуют единую биохимическую сеть, объясняющую многие клинические проявления дисфункции печени, прежде всего окислительное повреждение и гипербилирубинемию.

Ключевые слова. Детоксикация печени; Биотрансформация; Монооксигеназная система цитохрома P450; Окислительный стресс; Гипербилирубинемия; Гемоксигеназа.

JIGAR DETOKSIKATSIYASINING BIOKIMYOSI: BIOTRANSFORMATSIYA (I–II FAZA) FERMENT TIZIMLARI, OKSIDLOVCHI STRESS VA GIPERBILIRUBINEMIYA BILAN BOG‘LIQLIGI

Annotatsiya. Jigar ksenobiotiklar va endogen metabolitlarni biotransformatsiya orqali zararsizlantiradigan asosiy organdir. Bu jarayon birinchi fazadagi funksionallashtirish reaksiyalari va ikkinchi fazadagi kon’yugatsiya reaksiyalarini o‘z ichiga oladi hamda keyinchalik hosil bo‘lgan mahsulotlar tashuvchi oqsillar yordamida o‘t suyuqligi yoki qonga chiqarilib, organizmdan yo‘qotiladi. Birinchi faza reaksiyalari asosan sitoxrom P450 monooxygenaza tizimi orqali amalga oshib, oksidlanish, qaytarilish yoki gidroliz yo‘li bilan molekulalarda qutbli guruhlarni paydo qiladi yoki ochib beradi. Biroq elektronlar uzatilishi samarasiz bo‘lganda sitoxrom P450 faolligi reaktiv oraliq metabolitlar va reaktiv kislorod shakllarini hosil qilishi mumkin, bu esa oksidlovchi stressni kuchaytirib, hujayra shikastlanishiga olib keladi. Ikkinchi faza reaksiyalari odatda toksiklikni kamaytiradi, chunki metabolitlar yuqori qutbli guruhlar bilan kon’yugatsiyalanadi; bu jarayonda uridin difosfat-glyukuronoziltransferazalar, sul’fotransferazalar, glutation-transferazalar, N-atsetiltransferazalar va metiltransferazalar kabi ferment oilalari ishtirok etadi. Natijada suvda eruvchanlik oshadi va chiqarib yuborish osonlashadi. Giperbilirubinemiya detoksikatsiya bilan chambarchas bog‘liq, chunki bilirubin almashinuvi jigar tomonidan ushlab olinishi, uridin difosfat-glyukuronoziltransferaza oilasi 1, A1 a’zosi ishtirokida glyukuronidlanishi va o‘tga sekretsiya qilinishini talab etadi. Oksidlovchi stress detoksikatsiya fermentlari va tashuvchilar faoliyatini buzishi hamda genlar ekspressiyasini redoksga sezgir signal yo‘llari, jumladan eritroid 2 ga o‘xshash yadro omili orqali o‘zgartirishi mumkin; bu antioksidant himoya va detoksikatsiya salohiyatiga ta’sir qiladi. Umuman olganda, birinchi va ikkinchi faza

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metabolizmi, antioksidant tizimlar va bilirubin almashinuvi jigar disfunksiyasining ko‘plab klinik ko‘rinishlarini, ayniqsa oksidlovchi shikastlanish va giperbilirubinemiya holatlarini tushuntirib beradigan yagona biokimyoviy tarmoqni tashkil etadi.

Kalit so‘zlar. Jigar detoksikatsiyasi; Biotransformatsiya; Sitoxrom P450 monooxygenaza tizimi; Oksidlovchi stress; Giperbilirubinemiya; Gem oksigenaza.

Introduction. Hepatic detoxification is a biochemical and physiological process by which the liver transforms lipophilic compounds into more water soluble products that can be eliminated. Substrates include medications, dietary chemicals, environmental toxicants, bile acids, steroid hormones, bilirubin, and metabolic by products. The classical framework divides detoxification into Phase One biotransformation and Phase Two biotransformation reactions, followed by transporter mediated excretion into bile or blood for renal elimination. Phase One biotransformation often increases chemical reactivity by producing electrophilic intermediates and oxidants, whereas Phase Two biotransformation typically neutralizes and solubilizes intermediates via conjugation using endogenous cofactors. Detoxification capacity is strongly dependent on redox homeostasis, because oxidants generated during metabolism must be balanced by antioxidant defenses. Bilirubin metabolism is a prototypical endogenous detoxification pathway: unconjugated bilirubin is hydrophobic and potentially neurotoxic at high levels, while conjugation increases water solubility and enables biliary elimination. Therefore, impairments in bilirubin uptake, conjugation, secretion, or bile flow can produce hyperbilirubinemia, and these impairments frequently overlap with oxidative stress and hepatocellular injury.

Methods. This work is a narrative literature review. The synthesis integrates established biochemical principles of hepatic biotransformation with peer reviewed review literature on Phase One and Phase Two metabolism, oxidative stress in liver disease, and bilirubin metabolism. The focus is on mechanistic relationships among enzyme systems, redox homeostasis, transporter mediated excretion, and biochemical patterns of unconjugated and conjugated hyperbilirubinemia. No new experimental data were generated.

Results. Phase One biotransformation introduces or exposes polar functional groups by oxidation, reduction, or hydrolysis. The cytochrome P450 monooxygenase system is the central Phase One enzyme system and is a major source of oxidant generation due to imperfect coupling during electron transfer. Additional Phase One systems include flavin containing monooxygenases, alcohol dehydrogenases, aldehyde dehydrogenases, monoamine oxidases, and carboxylesterases. Phase Two biotransformation conjugates substrates using polar donors to increase solubility and reduce reactivity. Key Phase Two enzyme families include uridine diphosphate glucuronosyltransferases, sulfotransferases, glutathione transferases, N acetyltransferases, and methyltransferases. Transporter mediated excretion is required to complete detoxification; impaired bile flow or transporter dysfunction promotes intrahepatic retention of conjugated metabolites and can worsen oxidative and inflammatory injury. Oxidative stress develops when oxidant formation exceeds antioxidant defenses such as glutathione, superoxide dismutase, catalase, and glutathione peroxidases, causing lipid peroxidation and protein dysfunction that can reduce detoxification efficiency. Hyperbilirubinemia results from increased bilirubin production, decreased hepatic uptake, impaired glucuronidation by uridine diphosphate glucuronosyltransferase family one member A

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one, or impaired excretion due to cholestasis. Unconjugated hyperbilirubinemia is associated with reduced uptake or conjugation, while conjugated hyperbilirubinemia is associated with impaired secretion or bile flow.

Discussion. Phase One and Phase Two biotransformation represent complementary biochemical functions. Phase One increases polarity but may bioactivate compounds into reactive intermediates and generate oxidants. Phase Two generally detoxifies these intermediates through conjugation and relies heavily on adequate cofactor supply, enzyme capacity, and intact redox balance. Oxidative stress links directly to biotransformation because oxidants can be produced during Phase One metabolism and because antioxidant resources, especially glutathione, are also required for conjugation and protection against electrophiles. When oxidative stress persists, glutathione depletion and lipid peroxidation products create additional detoxification burden and can damage enzymes and transporters, thereby worsening clearance of xenobiotics and endogenous metabolites. Bilirubin handling is a clinically important example of these principles: conjugation by uridine diphosphate glucuronosyltransferase family one member A one is a Phase Two biotransformation step that prevents accumulation of hydrophobic bilirubin. In cholestasis, retention of bile acids and conjugated organic anions increases oxidative and inflammatory signaling, which can impair transporter function and mitochondrial energy production, contributing to conjugated hyperbilirubinemia. Redox sensitive transcriptional control, especially via nuclear factor erythroid two related factor two, can induce antioxidant and detoxification genes and is broadly protective, yet in specific injury contexts it may coincide with altered heme metabolism and bilirubin dynamics. Overall, hyperbilirubinemia can be interpreted as an integrated biochemical signal reflecting disturbances in uptake, conjugation, excretion, and redox homeostasis.

Conclusion. Hepatic detoxification is an integrated network consisting of Phase One biotransformation, Phase Two biotransformation, transporter mediated excretion, and antioxidant defense. Phase One biotransformation is driven mainly by the cytochrome P450 monooxygenase system and can generate oxidants and reactive intermediates. Phase Two biotransformation, mediated by uridine diphosphate glucuronosyltransferases, sulfotransferases, glutathione transferases, N acetyltransferases, and methyltransferases, typically neutralizes reactivity and increases solubility, enabling elimination. Oxidative stress arises when oxidant production exceeds antioxidant defenses and can impair detoxification enzymes and transporters while depleting glutathione, weakening both redox protection and conjugation capacity. Hyperbilirubinemia is closely linked to detoxification because bilirubin requires hepatic uptake, glucuronidation by uridine diphosphate glucuronosyltransferase family one member A one, and biliary excretion; disruption at any step produces unconjugated or conjugated hyperbilirubinemia. Understanding the biochemical coupling between biotransformation and redox balance supports clearer interpretation of liver dysfunction and informs rational prevention of toxin and drug related injury.

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