Energy change in the formation of conjugated bilirubin: A possible responsive mechanism for liver cell pathology

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ABSTRACT

Bilirubin is formed when red blood cells die and their hemoglobin is broken down within the macrophages into heme and globins. In the liver, bilirubin is conjugated with UDP-glucuronate, making it water-soluble diglucuronide. Concerning this conjugation, a molecule of bilirubin reacts with two molecules of glucuronic acid. However, the nature of this energy-consuming reaction in the formation of conjugated bilirubin has never been reported, and this can be important for its potential implication in hyperbilirubinemia. In this work, the author calculated the energy required by conjugated-bilirubin formation per molecule. The energy required for complex formation is -22 kCal/mol. The nature of this energy-producing reaction can be a good explanation. Increased energy delivery in conjugated hyperbilirubinemia in liver disease might be a responsive mechanism to hepatic damage.

Key words: Energy. Bilirubin. Conjugation.

INTRODUCTION

Bilirubin is the degraded product of heme (1). Bilirubin is formed when red blood cells die and their hemoglobin is broken down within the macrophages to heme and globins (1). The heme is further degraded to Fe^2+, carbon monoxide and bilirubin via the intermediate compound biliverdin (1). Since bilirubin is poorly soluble in water, it is carried to the liver and bound to albumin (1). In the liver, bilirubin is conjugated with UDP-glucuronate, making it a water-soluble diglucuronide. Conjugated bilirubin is excreted into the bile and passed into the intestine where it is further metabolized, which gives feces their brown color (2,3).

Concerning the glucuronide conjugation, a molecule of bilirubin (Fig. 1) reacts with two molecules of glucuronic acid. The reaction occurs between an OH group of propionic acid, a part of the bilirubin molecule, and a CH group of each glucuronic acid, which results in conjugated bilirubin. This process is energy-dependent and occurs against a concentration gradient (2). However, the nature of this energy-consuming reaction in the formation of conjugated bilirubin has never been reported, and this can be important for its potential implication in hyperbilirubinemia. In this work the author calculated the energy required by conjugated bilirubin formation per molecule.

MATERIALS AND METHODS

Quantum chemical analysis for bonding energy

This is a calculation-based study. The quantum chemical analysis for the reaction was performed according to the classic bonding theory (4). Basically, bond breaking takes in energy and bond forming gives out energy. The methodology is similar to recent reports (5,6). Briefly, the conjugation pathway for bilirubin was analyzed for both the bond breaking and bond forming parts. Calculations for the energy change within the pathway were performed. The energy required for complex formation in the pathway was calculated. A descriptive statistical analysis was used in this work.

RESULTS

Concerning the pathway, the bond breaking and bond forming parts are presented in table I. The corresponding en-
In laboratory medicine, bilirubin fractions are measured by: a) the direct diazo reaction; b) high-performance liquid chromatography (HPLC); c) direct spectrophotometry; and d) enzymatic methods (9). Because the measurement of conjugated bilirubins is clearly more helpful than that of direct bilirubin in the differential diagnosis of jaundice, direct diazo methods should be replaced by methods specific for conjugated bilirubin (9).

Although bilirubin is a widely used test in clinical pathology, the exact energy change in the physiological conjugation of bilirubin has never been clarified. The conjugation reaction in the formation of bilirubin is a type of covalent bond formation. Here the author calculated the bonding energy of the reaction and found that the reaction is a type of "energy-producing reaction". This finding implies several consequences in clinical medicine.

Physiologically, conjugation gives out an amount of energy to the external environment, the liver cell. Under physiological conditions, this energy might be suitable for the hepatic environment, but this might be increased in the pathological condition. Indeed, impaired or defective excretion of bilirubin, reduced glutathione, and other organic anions from hepatocytes can be seen in the conjugated hyperbilirubinuria rat model (10). Granato et al. found that the antiapoptotic effect of bilirubin associated with its antioxidant properties indicates that hyperbilirubinemia may have a protective role in liver disease (11). The nature of this energy-producing reaction can be a good explanation. Increased giving out of energy during conjugated hyperbilirubinemia in liver disease can be a responsive mechanism to hepatic damage in liver conditions.

**DISCUSSION**

Bilirubin, the oxidative product of heme in mammals, is excreted into the bile after its esterification with glucuronic acid to polar mono- and di-conjugated derivatives (7,8). The accumulation of unconjugated and conjugated bilirubin in the serum is caused by several types of hereditary disorders (7,8). Jaundice in an adult patient can be caused by a wide variety of benign or life-threatening disorders (7). Organizing the differential diagnosis by prehepatic, intrahepatic, and posthepatic causes may help make the work-up more manageable (7). Prehepatic causes of jaundice include hemolysis and hematoma resection, which lead to elevated levels of unconjugated (indirect) bilirubin (7). Intrahepatic disorders can lead to unconjugated or conjugated hyperbilirubinemia (7). The conjugated (direct) bilirubin level is often elevated by alcohol, infectious hepatitis, drug reactions, and autoimmune disorders. Posthepatic disorders also can cause conjugated hyperbilirubinemia (7).

![Fig. 1. Diagram showing the molecule of bilirubin (*the arrow indicates the two P (propionic) molecules undergoing the conjugation reaction).](image-url)

REFERENCES