Central Asian Journal of Medicine

Volume 2020 | Issue 4 Article 10

1-4-2021

ROLE OF THE MONOOXYGENASE SYSTEM IN THE DEVELOPMENT OF ACUTE PANCREATITIS

Lobarkhon U. Alimbekova
Tashkent Medical Academy, Tashkent, Uzbekistan

Rixsi A. Sabirova
Tashkent Medical Academy, Tashkent, Uzbekistan

Djakhongir X. Tursunov
Tashkent Medical Academy, Tashkent, Uzbekistan

Aziza X. Aslanova
Tashkent Medical Academy, Tashkent, Uzbekistan

Central Asian Journal of Medicine

ROLE OF THE MONOOXYGENASE SYSTEM IN THE DEVELOPMENT OF ACUTE PANCREATITIS

Lobarkhon U. Alimbekova, Rixsi A. Sabirova, Djakhongir X. Tursunov, Aziza X. Aslanova

Tashkent medical academy

ABSTRACT

The article clarifies role of the monooxygenase system in the development of acute pancreatitis. Authors determine cytochrome P-450 possesses unique properties that ensure the maintenance of chemical homeostasis in physiological and pathological states of the internal organism medium. The liver is the main organ supporting physico-chemical homeostasis, detoxification of endogenously formed and exogenously introduced xenobiotics into the body. But there is also extrahepatic metabolism of foreign compounds. The intestine plays an important role in this process. Endogenous intoxication syndrome disrupts metabolism and reduces the functional activity of natural detoxification systems, in particular by inhibiting the liver's monooxygenated detoxification system.

Key words: monooxygenase system, homeostasis, cytochrome P-450, oxidative-reducing enzymes, endogenous intoxication, pathogenesis

INTRODUCTION

Nowadays, researchers have shown an interest in inter-system and inter-branch relationships at the level of cell activity, especially in bodies responsible for the functioning of the whole organism, the maintenance of its homeostasis at pathological conditions arising in fact, internal or external causes. Because of their particular structural and functional position and liver values, hepatocytes are of primary interest as they are constantly attacked by endogenous and exogenous xenobiotics. The liver parenchyma has the ability to counteract all these

threats. The functional activity of hepatocytes is determined by the solidity of enzymes of the monooxygenase system [1].

The microsomal monooxygenase (MMO) system is present in the endoplasmic reticulum (ER) of most animal tissues. The highest P-450 microsomal cytochromes are found in liver cells, but they also function in the lungs, kidneys, the brain of the smooth muscles of blood vessels, the intestinal epithelium, the mucous membrane of the nose, the mammary gland and other tissues. MMO catalyzes the oxidation of foreign compounds (drugs, carcinogens and other xenobiotics) just like a number of endogenous substrates (hormones, steroids, fatty acids, prostaglandins, etc.). Microsomal cytochromes P-450 - are the main metabolic drugs in the human body. Hence researchers' keen interest in drug discovery mechanisms, undesirable effects and interdrug interactions. The MMO system can metabolize a large number of different substrates due to multiple forms of cytochrome P-450 with different substrate specificity [14].

Cytochrome P-450 possesses unique properties that ensure the maintenance of chemical homeostasis in physiological and pathological states of the internal organism medium. The first is the ability to catalyze oxidation reactions of a variety of chemical compounds. In addition, his enzymes are involved in the metabolism of many endogenous substances (steroids, bile and fatty acids, prostaglandins, leukotrienes, biogenic amines, etc.). Second, when foreign compounds are introduced into the body, the monooxygenase system is activated - P-450 cytochrome in liver cells is increased and enzymatic reactions are enhanced. Third, cytochrome P-450 is represented by a large number of different isoforms induced by various compounds [4].

With the participation of cytochrome P-450 during xenobiotic monoxification, reactive metabolites are formed that implement specific effects. At the same time, toxic products are eliminated from the body by means of conjugation reactions. Regardless of the damaging factor, one of the first links in the chain of pathological disorders (toxogenesis) is the membrane-mediating effect. It inhibits the functioning of the cascade of microsomal and mitochondrial

enzymes involved in the maintenance of cell homeostasis, its repair and the elimination of xenobiotics (or their metabolites). The next step - disrupts cell energy formation, then creates a surplus of free radicals, which triggers two typical integral mechanisms of cell damage and death: hypoxic and free-radical necrobiosis. Such a vicious circle does not allow hepatocytes to implement the mechanism of natural cytoprotection [3].

It is generally accepted that, in microsomal NAD(P)H-specific liver redox chains, the cytochrome b5 is an intermediate carrier of electrons between the P-450 flavor and cytochrome. The main feature of the oxygenase system containing cytochrome-P450 is its intracellular localization. [19].

The cytochrome P-450-containing liver mono-oxygenase system (P-450-hydroxylase) is at the top of the evolutionary ladder. All of its components are actually related to membrane proteins. Due to their wide specificity, microsomal monooxygenases are able to oxidize non-polar compounds with a completely different chemical nature. In this way they perform a key function - decomposition of xenobiotic hydrophobic toxicants and their removal from the body [17].

NADPH-P450 - The reductase belongs to a large family of oxidoreductases. Typical members of this family, in addition to NADPH-P-450 reductase, are synthase nitrooxide (NOS), flavocytochrome P-450BM3, and methionine synthase reductase (MSR). The proteins of this family are characterized by the presence of two flavinase-binding domains associated with Flavinadeninucleotide (FAD) and Flavinmononucleotide (FMN). Each flap coenzyme fulfils its role. FAD accepts two electrons from NADP*H (two reducing equivalents) and immediately transfers them to FMN [15]. The FMN transmits the reduction equivalents to the cytochrome P-450 in turn, one after the other [18]. Precise protein-protein and/or interdomain interactions are necessary for rapid and specific electron transport in multi-protein or multi-domain oxidative-reducing enzymes. Thus, precise control of the association and dissociation of domains or proteins is key for rapid and controlled electron transfer [11]. NADPH-P450 reductase is a multidomain protein, and its function requires certain inter-molecular and inter-domain

interactions. Precise and specific interactions between the FMN and FAD domains within the molecule, and between the FMN domain and the cytochrome P450 are necessary for electron transport, which provides the catalytic function of the cytochrome P-450 [7].

Let us remind that besides NADP*H-dependent reduction of cytochrome P-450 in microsomal monooxygenated cytochrome system P-450 there is another supplier of electrons - cytochrome b5. This protein performs a number of other non-electron transfer functions. Consider this protein in more detail. Cytochrome b5 (CYB5B) is a small (about 15 kDa) protein containing heme as a prosthetic group. In mammalian cells, there are two isoforms of the cytochrome b5 with a general structure (similar order of structure and identical placement of polypeptide chains), but coded by different genes. They play a variety of intracellular localizations: the membrane of the endoplasmic reticulum contains the microsomal isoform (CYB5A) and the external membrane of the mitochondria contains the mitochondrial (CYB5B) [20].

Analysis of available mammalian genome data has shown that all CYB5 contains 134 amino acid residues. A comparison of CYB5A amino acid sequences in mammals showed an identity of 84-97%. The CYB5B isoform and contains 146 amino acid residues, the identity of the primary CYB5B sequences in mammals was 63-65%. The primary structures of the two CYB5 isoforms are similar: a pairwise comparison of full-size CYB5A and CYB5B rats showed only 49% identity [9].

Despite their common structure, CYB5 isoforms exhibit different physico-chemical properties and affect P-450 (CYP) activity in different ways. These differences are due to the structure of the hydrophilic domain CYB5. It is shown to have a more rigid structure and is thus more resistant to chemical and thermal denaturation. However, it is less effective with redox partners than the CYB5B [10] isoform. Cytochrome b5 has long been known to activate some P-450 cytochrome monooxygenase reactions, but the mechanism of this effect remains controversial. In recent years, researchers have clarified this problem by

identifying three ways in which b5 cytochrome effects on the functional activity of P-450: 1) direct, CPR-independent, transfer of two necessary electrons from NADP-cytochrome b5-reduction to P-reduction450; 2) Second electron transmission on the cytochrome P-450, whose hemic iron is in oxyferrous state; 3) Allosteric stimulation of P-450 activity not associated with electron transfer.

The results of the study showed that each of these techniques can work in a natural environment. Cytochrome b5 is also involved in lipid biosynthesis, acting as an electron donor for at least three individual microsomal desaturations that synthesize unsaturated fatty acids. These acids are necessary to ensure membrane fluidity and also serve as precursors for peanut acid and eicosanoid signal molecules. Cytochrome b5 is also important for the biosynthesis processes of plasmalgen and sterols, and is also a donor of electrons for desaturation enzymes involved in catalyzing the synthesis reactions of these compounds. Cytochrome b5 is associated with endoplasmic reticulum, as is its electron donor, NADH-cytochrome-b5reductase. The addition of NADH to the suspension of the liver microscope enhances the functional metabolism of the medicinal substances, indicating the involvement of b5 reduction/ cytochrome b5 in P-450-mediated reactions [12]. The cytochrome b5 is known to recover easily in the presence of NADPH [16]. On this basis, it can be assumed that cytochrome P-450-reductase can also be used as an electron donor for cytochrome b5, which was also confirmed in vitro using purified protein preparations [13]. These studies linked the cytochrome b5 to the monooxygenase system of P-450 microsomal cytochromes. Questions emerged about the role and mechanisms of cytochrome b5 on the metabolism of medicinal substances [8].

Data from numerous studies carried out in Russia and other foreign countries make it possible to assert that one of the main biochemical processes determining the individual response of the organism to xenobiotics (including medicinal substances) is a biotransformation with the predominant participation of a large family of cytochromes P-450, conjunction enzymes and transport proteins [5].

The liver is the main organ supporting physico-chemical homeostasis, detoxification of endogenously formed and exogenously introduced xenobiotics into the body. But there is also extrahepatic metabolism of foreign compounds. The intestine [6] plays an important role in this process.

One of the complex pathogenic links and severe clinical manifestations of acute pancreatitis is endogenous intoxication, which contributes to the development of polyorgan insufficiency syndrome in acute destructive pancreatitis. Unidentified toxic protein-based substances - so-called low and medium molecular mass (BSM) - contribute significantly to the pathogenesis of pancreatogenic endotoxicity. They are formed by the aggressive action of proteases on the protein structures of the organism.

Pathological changes in the body at EC depend on the balance of two opposite processes: the rate at which endotoxins are produced and released into the blood, on the one hand, and their detoxification, the body's protective systems and treatment measures, on the other. The state of the natural detoxification system affects the survival of the organism in the event of generalized infection. Three interconnected functional systems are known to protect the internal environment from the damaging effects of various exogenous and endogenous toxic factors: 1) monooxygenase; 2) immune; 3) excretion. Despite the development and widespread introduction into clinical practice of various methods of intracorporeal detoxification of the body (peritoneal dialysis, hemo-, plasma-, lymph-phosphorption, plasmapheresis, etc.)Endotoxicity, as the leading pathogenetic factor of toxic shock, remains the leading cause of death in pancreatogenic peritonitis patients.

Endogenous intoxication syndrome disrupts metabolism and reduces the functional activity of natural detoxification systems, in particular by inhibiting the liver's monooxygenated detoxification system. In pancreathology, it is generally believed that as soon as hepatocellular insufficiency develops during OD, clinical signs of polyorgan insufficiency immediately appear. A sharp decline in the detoxification potential of the liver increases the generalized effect of toxins on the

body and consequently leads to the development of multi-organ insufficiency, which is generally the cause of death [3].

CONCLUSION

Research has showed that pancreatitis is a polytheological acute aseptic inflammation of the pancreas. Its main cause is the activation of digestive enzymes produced by the pancreas. In the pathogenesis of acute pancreatitis special role is given to enzymes of monooxygenase system: cytochromes P-450 and b5, whose main function is detoxification of xenobiotics. When cytochrome function is impaired, xenobiotics are reduced and acute pancreatitis develops. A detailed study of the functioning of the mono-oxygenase system of an organism will help to create new methods of treatment and prevention of acute pancreatitis.

REFERANCES

1. Ashurova O.Yu. Aktivnost' monooksigenaznoy i nitrergicheskoy sistem v mikrosomakh pecheni pri deystvii na organizm induktorov i ingibitorov lekarstvennogo metabolizma// Nauka i innovatsii – sovremennyye kontseptsii. Sb. nauch. statey po itogam raboty Mezhdunar. Nauch. foruma. M., 2020. - S. 60-64.

2. Myshkin V.A., Yenikeyev D.A. // Trudy V Vseross. Nauchn.-prakt. konf. s mejdunar. uchastiyem «Voprosy patogeneza tipovykh patologicheskikh protsessov». Novosibirsk, 4-5 aprelya 2013. – S. 81-84.

3. Meloshkin A.V. Patogeneticheskiye osnovy sovershenstvovaniya lechebnykh programm detoksikatsionnoy terapii pri ostrom peritonite: diss. kand. med. nauk – Saransk: 2017 – 6s.

4. Petrosyan E.A., Sergiyenko V.I., Rykunova V.Ye. Biotransformatsiya kseno- i endobiotikov pri peritonite. Eksper. i klin. gastroenterologiya. 2017;(2):92-96.

5. Rakitskiy V.N., Yudina T.V. Antioksidantnyy i mikroelementnyy status organizma: sovremennyye problemy diagnostiki // Vestn. RAMN. 2005.-№3.-S.33-36;

6. Sivkov A.S., Paukov S.V., Ruvinov YU.V., Kukes I.V. Individual'naya bezopasnost' farmakoterapii pri otsenke aktivnosti izofermenta tsitokhroma R-450 3A4 (SUR3A4) // Klin.med. – 2010. - №2. – S. 61 – 67.

7. Yablokov Ye.O., Gnedenko O.V. Mol'nar A.A Ivanov A.S. Usanov S.A. Archakov A.I. Molekulyarnoye uznavaniye mezhdu belkami v P-450-zavisimykh

monooksigenaznykh sistemakh» //Mater. IV s"yezda biofizikov Rossii, 20-26 avgusta 2012, N/Novgorod, Rossiya, 2012 S.325.

8. Yablokov Ye.O. Molekulyarnoye uznavaniye, affinnost' i termodinamika belok-belkovykh vzaimodeystviy v tsitokhrom p450- zavisimykh monooksigenaznykh sistemakh: diss. kan. med. nauk: M.: 2014 -30 s.

9. Altuve A., Silchenko S., Lee K.H., Kuczera K, Terzyan S., Zhang X, Benson D.R., and Rivera M., Probing the differences between rat liver outer mitochondrial membrane cytochrome b5 and microsomal cytochromes b5. //Biochemistry 40 (2001) 9469-83.

10. Perret A., and Pompon D., Electron shuttle between membrane-bound cytochrome P450 3A4 and b5 rules uncoupling mechanisms // Biochemistry 37 (1998) 11412-24.

11. Bashir Q, Scanu S, Ubbink M. FEBS J. 2011; 278:1391–1400. [PubMed: 21352493]

12. Correia MA, Mannering GJ. DPNH synergism of TPNHdependent mixed function oxidase reactions // Drug Metab Dispos 1973;1:139–149.

13. Enoch HG, Strittmatter P// J. Biol. Chem. 1979; 254:8976–8981. [PubMed: 113406]

14. Ingelman-Sundberg M. (2005) Toxicol. Appl. Pharmacol., 207. P. 52-56

15. Iyanagi T, Mason H.S. //Biochemistry. 1973; 12:2297–2308. [PubMed: 4145653]

16. Oshino N., Imai Y., Sato R. A function of cytochrome b5 in fatty acid desaturation by rat liver microsomes // J. Biochem (Tokyo) 1971;69:155–167

17. Hall P., Gustafsson I.A. (Ed.) // Biochemistry, Biophysics and Regulation of Cytochrome P-450, Elsevier/North-Holland Biomed Press, Amsterdam. 1980 – P. 461-477

18. Roman L.J., Masters B.S. Textbook of Biochemistry with Clinical Correlations. Devlin, TM., editor; Mowat CG, Gazur B, Campbell LP, Chapman SK // Arch. Biochem. Biophys. 2010; 493:37–52.

19. Structural–functional organization of cytochrome P-450 containing monooxygenase and some aspects of modeling Author links open overlay panel M.S.Gordeziani, T.G.Varazi, M.V.Pruidze Durmishidze Institute of Biochemistry and Biotechnology of Agricultural University of Georgia, 240, David Agmashenebeli Alley, Tbilisi, 0159, Georgia

20. Yu Y., Yamasaki H., Kita K., and Takamiya S., Purification and molecular characterization of a novel b5-type cytochrome of the parasitic nematode, Ascaris suum //Arch Biochem Biophys 1996. - №328- P. 165-72