EFFECT OF SELECTED FIBRATES ON LIVER BRANCHED-CHAIN α-KETOACID DEHYDROGENASE COMPLEX

MALGORZATA KNAPIK-CZAJKA, JERZY JASKIEWICZ, IZABELA CYGANEK, MALGORZATA TYSZKA-CZOCHARA, RENATA FRANCIK
Department of Analytical Biochemistry, Faculty of Pharmacy, Collegium Medicum, Jagiellonian University, 30-688 Kraków, Poland

Branched-chain α-ketoacid dehydrogenase (BCKDH) catalyzes the oxidative decarboxylation of branched-chain α-ketoacids, the rate-limiting step of the catabolic pathway of branched-chain aminoacids. BCKDH activity is subject to covalent regulation catalyzed by a specific kinase (BK) and a specific phosphatase. It has been preliminarily established that, at the molecular level, hypolipidemic drugs, clofibrate and clofibric acid derivatives activate transcriptional factors called peroxisome proliferator activated receptors. It was proved that clofibrate, affecting the activities of both BK and BCKDH, stimulates branched-chain amino acid oxidation. Therefore, it is conceivable that other fibrates affect BCKDH activity. The effect of bezafibrate and fenofibrate on the activity of rat liver BCKDH was studied.

Wistar male rats were fed a low-protein diet (8% protein) supplemented with 0.5% bezafibrate and fenofibrate ad libitum for 14 days. The control group was kept on a low-protein diet without any drug. Feeding rats a diet deficient in protein is known to increase the activity of BK and cause the inactivation of BCKDH.

BCKDH and BK activities were assayed spectrophotometrically. BCKDH protein subunit content and the expression of BK protein and BK mRNA were determined using Western and Northern blot analyses, respectively. Both the actual and total activities of BCKDH were significantly higher, while BCKDH kinase activity was lower in rats kept on a diet supplemented with fibrates than in those from the low-protein group. An increase occurred in E1α, E1β and E2 (BCKDH subunits) protein expression in all the rats fed with fibrates. The expression of BK protein and BK mRNA in rats fed a diet with fibrates was significantly lower than in the control group.

To conclude, fibrates affect both BCKDH and BCKDH kinase activities at all transcriptional levels.