ALTERATION OF LIVER DRUG METABOLISM BY INTRACEREBROVENTRICULAR ADMINISTRATION OF LIPOPOLYSACCHARIDE

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Hepatic cytochrome P450s are monooxygenases consisting of several isozymes. These enzymes play a key role in the metabolism of endogenous compounds such as steroid hormones, biliary salts and fatty acids and exogenous substances such as drugs, carcinogens and other chemical pollutants. Recently, it has been reported that P450s are decreased in the acute phase of the inflammatory process. Considering the administration of drugs for diseases, it is important therapeutically to understand the mechanism of the regulation of P450s which metabolize drugs in the acute phase of this process. It has also been reported that the brain regulates a number of physiological responses in the liver at the time of inflammation. However, it is not clear whether contents of P450s are regulated by the brain in the acute phase of the inflammatory process. The purpose of this study is to clarify whether the brain is involved, in any way, in the regulation of hepatic P450s in this acute phase. The effect of intracerebroventricular (i.c.v.) administration of lipopolysaccharide (LPS) on total P450 content in rat liver was examined and I found that the content of P450 was markedly decreased. To determine whether this response was caused by activation of the CNS, the effect of intraperitoneal (i.p.) administration of LPS was compared with that of i.c.v. at the same dose. At a dose of 0.1 μg, total P450 content was significantly decreased by i.c.v. but not by i.p. administration of LPS. By measuring the P450-dependent drug metabolizing activities and by Western blot analysis, it was found that P450 1A1, 2B1/2, 2C11, and 3A were decreased by LPS i.c.v. administration at 24 hours but not by i.p. administration. These results suggest that the brain regulates the level of P450 isozymes and their activities in the acute phase of the inflammatory process. The levels of P450 2D1 and 2E1 were not changed by i.c.v. administration of LPS, indicating that the brain regulation of P450 isozymes and their activities is P450 isozyme-selective.