T1 and T2 relaxation times of LEC rat livers in the pre-, acute- and chronic-hepatic phases, and showed that the shortening of both times due to an excess amount of paramagnetic irons were observed in the liver of acute phase. The theoretical calculation of the MR signal intensities using the measured T1 and T2 relaxation times indicated that their imaging might be possible under the condition of TR/TE=2,000ms/20ms that the parameter-weighted index of proton density was largest. In fact, the clear-cut MR image showing hepatitis as hyperintense regions in the livers of the acute-phase was obtained under this condition. The further application of this high-magnetic field MRI to the livers of 50– and 116–week-old rats showed hyperintense regions around the hepatic veins in 50–week-old rat and those throughout the hepatic lobe in 116–week-old rat. These hyperintense regions might be assumed as HCC in LEC rats.

Finally, MRI combining a Bruker 7.05 T superconducting magnet and the extremely strong gradient coil (3.5 mT/cm) was carried out to visualize the topographical structure of mouse brain. Imaging condition was TR/TE=3,000ms/10.4ms, which was more favorable for imaging than TR/TE=2,000ms/20ms since the contribution of proton-density weighting to MRI signal intensity under this condition was greater than that under the TR/TE=2,000ms/20ms. As expected, the resolution of MRI was comparable to that of the histological sections. The white matter was distinguished from the gray matter in some regions of the brain. Coronal sections of the brain also showed that the hippocampal CA1–CA3 regions were distinguishable from the other regions. These results suggested that the high-magnetic field MRI might be a useful tool for studying diseases in animal models like rats and mice.

Alterations in levels of hepatic microsomal cytochrome P450 isozymes following intracerebroventricular injection of bacterial lipopolysaccharide in rats

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To investigate the effect of central inflammation due to bacterial infection such as meningitis on the activities of hepatic cytochromes P450 (CYPs), rats were injected intracerebroventricularly (icv) with 0.1 μg of bacterial lipopolysaccharide (LPS). The LPS icv injection significantly decreased the total P450 contents (by 30% of the levels of control rats treated with saline icv), the contents of CYP1A (48%), 2B (54%), 2C11 (37%) and 3A (40%) and related drug metabolizing activities, 7–ethoxycoumarin O-deethylation (ECOD ; 36%), imipramine N-demethylation (IMND ; 41%) and erythromycin N-demethylation (ERND ; 33%) in liver microsomes 24 hrs after the treatment. In contrast, intraperitoneal (ip) injection of LPS at the same dose as icv (0.1 μg) did not significantly affect the hepatic microsomal contents of total P450 or the content of each individual CYP isozyme and its activity. CYP2D protein and the activity of imipramine 2–hydroxylase (IMOH) were not significantly decreased by LPS injection regardless of the route of administration. The inhibitory effects of 0.1 μg icv-LPS on total P450 contents were almost equal to those of 10 μg ip-LPS. As low as 0.01 μg of icv-LPS significantly decreased

the activity of imipramine N-demethylase, while ip injection at this dose did not cause any effect on CYP catalyzed reaction. Therefore, the LPS icv injection resulted in CYP isozyme-selective inhibition at an ineffective dose when injected ip. It is suggested that a central inflammation like meningitis differentially decreases the levels of hepatic CYP isozymes and that the central action of LPS may be involved in this down-regulation.

Next, the possible involvement of the sympathetic nervous and adrenocortical systems in the down-regulation of CYP isozymes by icv-LPS was investigated using rats with surgical or chemical sympathetecomy or adrenalectomy. The norepinephrine (NE) content in the liver in rats with surgical hepatic sympathetectomy was reduced by 88% as compared with that of sham-operated rats that received icv-saline and 85% as compared with that of sham-operated rats that received icv-LPS, indicating that hepatic denervation was successful. The NE content in the liver in rats chemically sympathetectomized by two ip injections of 6–hydroxydopamine (40 mg/kg/time) 1 and 2 days before icv injection was reduced by 82% in icv-saline-treated and by 74% in icv-LPS-treated groups as compared with that in rats pretreated with ip-saline. These results indicate that sympathetic NE terminals were effectively removed. Intracerebroventricular LPS decreased the total P450 content and the activities of CYP dependent drug metabolism, ethoxyresorfin O-deethylase (EROD), pentoxyresorfin O-depentylase (PROD), IMND and ERND activities after 24 hrs in both sympathetectomized rats and non-denervated rats. Adrenalectomy (ADX) reduced the level of corticosterone in serum by 81% compared to sham-operated rats, indicating that adrenalectomy was successful. ADX did not inhibit the decrease in the total P450 content and the metabolism of these drugs induced by icv-LPS, but more profoundly emphasized the inhibitory effect of icv-LPS than the sham-operation did. These results suggest that the sympathetic nervous systems both directly and indirectly innervating the liver do not participate in the primary mechanism of the decrease in the activities of CYP isozymes in rat liver microsomes induced by icv-LPS and that the adrenal glands, especially the adrenocortical system, play a suppressive role in the decrease in CYP isozymes caused by icv-LPS.

Finally, we examined the gene expression of CYP2C11, the total P450 contents, the CYP2C11–dependent activity of IMND and microsomal contents of CYP2C11 apoprotein 10 hr after icv or ip injections of LPS. Intracerebroventricular injection of LPS significantly decreased the level of CYP2C11 mRNA (to 63% of saline icv control), the total P450 contents (to 70% of saline icv control), and the IMND activity (to 74% of saline icv control) in rat liver. But the significant decrease in apoprotein of CYP2C11 by icv injection of LPS was not observed at this time. In contrast, ip injection of LPS at the same dose as icv did not significantly affect these parameters. Since CYP is a heme protein, using the same rat liver microsomes, the activity of heme oxygenase (HO) was also measured. The HO activity was increased to 166% by icv injection of LPS and 135% by ip injection of LPS compared to corresponding saline controls. It is suggested that icv injection of LPS down-regulates the expression of CYP2C11 at transcriptional level and that the decrease in CYP2C11 mRNA is involved in the decreased level of CYP2C11 by icv injection of LPS in rat liver. The increase in heme degradation by icv-LPS may affect the content of the functional CYP2C11 isozyme.