10) Utilization of SHR in the detection of cardiotoxicity

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It is well known that such myocardial damage as myocardial necrosis or fibrosis, as well as myocardial hypertrophy often occur in spontaneously hypertensive rats (SHR) following elevations in blood pressure. As these changes are similar to those in the hypertensive human heart, SHR appear to be suitable animal models for the study of cardiomyopathy. In an experimental study involving administration of large doses of isoproterenol, it was reported that compared to normotensive Wistar Kyoto rats (WKY) it was easy to induce lethal heart failure in SHR. (Wexler, B.C.: Cardiovasc. Res. 13: 450-458, 1979) In this study we examined whether or not SHR can be used in the detection of weak cardiotoxicity resulting from the use of drugs such as tegafur, an antitumor agent.

Male SHR, WKY and Wistar rats were obtained from Aburahi Lab. (Shionogi Co., Ltd.) at 10 weeks of age. Tegafur was administered intravenously (150 mg/kg/day) for five consecutive days. Systolic blood pressures, heart rates, plasma GOT and LDH levels were determined just before the first and again after the last administration. The rats were killed the day after the final dose of tegafur and the hearts processed for light microscopic examination with H-E and PTAH staining. LDH and SDH were also histochemically examined using fresh frozen sections after the methods of Mori and Nachlas, respectively. The PTAH-stained sections were used in measuring the areas of the myocardial lesions with an image analysis system (Kontron MOP-20, GMBH).

In all three strains, experimental group mean body weights decreased, with that of SHR being more pronounced than that of WKY or Wistar rats. Systolic blood pressures and heart rates for SHR and WKY also dropped markedly after the fifth day of the experiment. Plasma GOT and LDH activities did not elevate after administration of tegafur. Some of SHR suffered from hydrothorax, indicating cardiac failure. Histological examinations revealed focal necrosis or dissolution of myocytes, sometimes with mononuclear cell infiltration, mainly in the subepicardial layer of the ventricular walls in both SHR and WKY. LDH and SDH, mitochondrial marker enzymes, did not detected histochemically in the affected areas. Such lesions were widely spread out through both ventricular wall. Through image analysis it was ascertained that cardiac lesions are more prominent in SHR, both in the number of necrotic foci as well as in total necrotic area, than they are in WKY. In comparison, no such changes were observed in the experimental group Wistar rats.

In our previous experiment, cardiotoxicity of tegafur, a derivative of 5-FU, was detected in dog heart. However, no report is found on cardiotoxicity of tegafur in rat heart. In the present study, focal myocardial necrotic lesions were recognized in SHR heart after administration of tegafur and more severe than that in WKY heart. Although the mechanisms of cardiotoxicity in SHR are still unclear, these results suggest that SHR are prone to cardiomyopathy and therefore are a useful animal for the detection of weak cardiotoxicity of certain drugs.