COMPARISON OF PHARMACODYNAMICS BETWEEN CARVEDILOL AND METOPROLOL IN RATS WITH ISOPROTERENOL-INDUCED HEART FAILURE
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In the Carvedilol or Metoprolol European Trial (COMET), carvedilol was shown to be superior to metoprolol in terms of mortality reduction in patients with heart failure. However, some researchers criticized the fact that heart rate reduction as an indicator of the beta-blocking effect differed between the carvedilol and metoprolol treatment groups in the trial. The aim of the present study, therefore, was to compare the suppression of cardiac hypertrophy and beta-adrenoceptor density between carvedilol and metoprolol in rats with isoproterenol-induced heart failure at a similar heart rate. Isoproterenol (8 mg/kg/day) was infused continuously for 2 weeks using an osmotic mini-pump (model 2ML4, Alzet, Direc; Cupertino, CA) in order to induce experimental heart failure. Then, metoprolol (33.3 mg/kg/day) or carvedilol (10 mg/kg/day) was infused continuously with isoproterenol (8 mg/kg/day) for 4 weeks. Body weight, heart weight, heart rate, brain natriuretic peptide, and beta-adrenoceptor density in lymphocytes and the left ventricular membrane were determined. The beta-adrenoceptor density was determined by radioreceptor assay using [3H]CGP12177. Heart rate and heart weight were significantly increased 1.15-fold and 1.3-fold, respectively, in comparison with rats that received water. Treatment with carvedilol or metoprolol significantly attenuated the increase in heart rate. Heart weight was decreased significantly by carvedilol but not to a significant degree by metoprolol. There was no significant difference in heart weight between the carvedilol and metoprolol groups.

RELATIONSHIP BETWEEN THE ANTINOCICEPTIVE EFFECT OF ST JOHN'S WORT AND PLASMA AND BRAIN CONCENTRATION OF HYPERFORIN
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St John’s wort (SJW, Hypericum perforatum) has been reported to exert not only antidepressant effect but also anti-inflammatory effect. However, there is little information of the relationship between pharmacological effects of SJW and plasma and brain concentrations of hyperforin considered as a major active constituent in the extract of SJW. The aim of this study was to evaluate the antinociceptive activity of SJW extract in relation to the plasma and brain concentrations of hyperforin. SJW extract (300 mg/kg) was orally administrated to male ICR mice, and blood and brain samples were collected until 12 h after the oral administration. Plasma and brain concentrations of hyperforin were determined by liquid chromatography/tandem mass spectrometry. The formalin test was performed to evaluate the antinociceptive activity of SJW extract. At 1 and 3 h after oral administration, the plasma concentrations of hyperforin in mice were 303 ± 131 nM and 118 ± 19 nM, respectively. On the other hand, the brain concentration of hyperforin in mice at 3 h after administration was 1.7-fold higher than that 1 h. In the formalin test, SJW extract reduced significantly paw licking/biting time in first and second phase at 3 h after the administration compared with the vehicle treated mice. These results suggest that the antinociceptive effect of SJW extract is responsible for the increased brain concentration of hyperforin.