bral infarct dog without ECG changes in the early stage showed second degree atrio-ventricular block 1 week after occlusion. It disappeared after atropin injection. Serum catecholamine increased in the early stage but showed normal level 1 week after occlusion. Heart rate and Aortic pressure unchanged. It is suggested that the changes of ECG on the experimental canine cerebral ischemia models may occur due to the increase of catecholamine (sympathicotonia) and vagotonia after cerebral artery occlusion.

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VASOSPASTIC EFFECTS OF 15-HPETE AND 15-HETE ON CEREBRAL ARTERIES

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The mechanisms of cerebral vasospasms are still unknown. Cyclooxygenase and lipoxygenase products of arachidonic acid have strong vascular actions in respect to vasoconstriction and relaxation. We purified 15-HPETE and 15-HETE to examine their vascular effects in vitro and in vivo.

15-HPETE was chemically synthesized by the incubation of arachidonic acid with soybean lipoxygenase. After ether extraction, 15-HPETE was purified by TLC and further by HPLC. 15-HETE was made by the reduction of 15-HPETE with sodium borohydride. The purities of 15-HPETE and 15-HETE were 96 and 99%, respectively. 15-HPETE and 15-HETE produced concentration-related contraction of isolated canine cerebral arterial strips. The maximum contraction was about 70% of the contraction induced by 30 mM KCl. The ED₅₀ values of 15-HPETE and 15-HETE were $1.50 \pm 0.08 \times 10^{-6}$ M and $1.99 \pm 0.44 \times 10^{-6}$ M, respectively. Aspirin enhanced 15-HPETE induced cerebral vasoconstriction by about 20% and NDGA inhibited the contraction by about 50%. Nicardipine prevented contraction by about 80%. ³H-Arachidonic acid was metabolized to 6-keto-PGF_{1α} and HETE(s) by isolated canine cerebral arteries analyzed by TLC. 15-HPETE and 15-HETE inhibited the production of 6-keto-PGF_{1α} significantly and 15-HPETE enhanced HETE(s) production significantly. Intracisternal injection of 15-HPETE caused canine cerebral vasoconstriction in vivo. 15-HETE, which induced vasoconstriction in vitro, led to no significant change in cerebral arteries after intracisternal injection up to 5 hours.

These results suggest that 15-HPETE and 15-HETE constrict cerebral arteries by inhibiting PGI₂ production, enhancing the production of vasoconstrictive lipoxygenase products in addition to their direct action. Peroxide moiety or 15-series leukotrienes may be responsible for the cerebral vasospasms in vivo.

Chairman

350-354 H. Tanaka, *Kagoshima*
355-359 K. Murata, *Maebashi*

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PLASMOCID INDUCED CARDIOMYOPATHY IN RATS

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We studied the effect of plasmocid on the myocardium in rats. Wistar strain rats were divided into two groups and given either normal saline or plasmocid intraperitoneally, at a dose of 30 mg/kg body weight. They were sacrificed 30 days after the injections. Light microscopic observations revealed myocardial degeneration, atrophic muscle fiber and myocardial fibrosis in the rats treated with plasmocid. Electron microscopic observations showed mitochondriosis, degenerated mitochondria, dilated sarcoplasmic reticulum, separation of intercalated disk and increased collagen fibers in the rats treated with plasmocid. We also studied the direct effect of plasmocid on the myocardium using Langendorff method. Ultrastructural changes were observed in the myocardium perfused with plasmocid solution (5×10^{-5} M) for 30 minutes. Furthermore, contractile force was reduced obviously after 8 minutes' perfusion with plasmocid solution (10^{-4} M).

In conclusion, plasmocid directly causes myocardial changes, which last for 30 days or more in rats at the dose of 30 mg/kg body weight.

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ALTERATIONS IN CARDIAC [³H]NITRENDIPINE BINDING IN PATHOGENESIS IN CARDIOMYOPATHY OF SYRIAN HAMSTERS (BIO 14.6)

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The cardiomyopathic Syrian hamster develops heart failure following genetic cardiac hypertrophy, which can be prevented with the calcium antagonist verapamil. To elucidate the role of Ca channel activity in pathogenesis of hamster CM, we determined the changes in binding of [³H]nitrendipine, a radioactive Ca antagonist, to the cardiac membranes in three stages of the development in CM of Syrian hamsters.

In preliminary study, we characterized [³H]-nitrendipine binding in rat cardiac membrane. [³H]nitrendipine binding was specific and saturable, and showed K_d of 0.280 ± 0.063 nM and B_{max} of 98.8 ± 13.2 fmol/mg protein in rat cardiac membrane. The binding of [³H]nitrendipine was not influenced with 10^{-4} M of norepinephrine, prazosin or yohimbine. Diltiazem increased the [³H]nitrendipine binding 18% in 10^{-4} M. Verapamil showed biphasic inhibition of [³H]nitrendipine binding, suggesting the heterogeneous interaction to the [³H]nitrendipine binding site of Ca channel.

The [³H]nitrendipine binding at 1.4 nM to the cardiac membranes of Bio 14.6 and their age-matched Golden hamster (control) were as follows.

stage	age in days	control	Bio 14.6
pre-hypertrophy	65-75	58.3 ± 9.2	91.7 ± 6.6*
hypertrophy	160-170	57.5 ± 5.9	51.6 ± 6.4
heart failure	220-230	43.3 ± 4.0	30.2 ± 2.6*

mean ± SE, *p < 0.05 vs control, fmol/mg protein

These results indicate that Ca channels increase in the pre-hypertrophic stage and this increase may be involved in the development of myocardial injury and hypertrophy. In contrast, Ca channels were decreased in the heart failure stage. Thus, we conclude that alterations in Ca channels play an important role in pathogenesis of cardiomyopathy.

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ALTERATIONS OF SARCOLEMMA Ca²⁺ TRANSPORT ACTIVITIES IN CARDIOMYOPATHIC SYRIAN HAMSTER

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Previous studies have indicated that various membrane systems such as sarcoplasmic reticulum, mitochondria and sarcolemma (SL), which are involved in handling intracellular Ca^{2+} , became defective at different stages of disease in the UM-X7.1 strain cardiomyopathic hamster. The present studies were undertaken to examine changes of SL Ca^{2+} transport activities at different stages in myopathic hamster. Myopathic and control hamsters at 40, 120 and 280 days of age were employed for the examination of heart sarcolemmal Na^{+} - Ca^{2+} exchange and Ca^{2+} -pump activities. Na^{+} -dependent Ca^{2+} uptake activities were significantly depressed in myopathic animals at 120 and 280 days of age in comparison to the control values. No difference in Na^{+} -induced Ca^{2+} release activities was found between control and experimental sarcolemmal vesicles. Ca^{2+} -pump activities (ATP-dependent Ca^{2+} binding and Ca^{2+} stimulated Mg^{+} ATPase activities) were depressed in the experimental animals at 120 and 280 days of age. Similarly, alterations in the SL Na^{+} -dependent Ca^{2+} uptake and Ca^{2+} -pump activities were seen upon treating the control hamsters with 40 mg/Kg isoproterenol for 24 hr.

It is therefore suggested that a depression in the sarcolemmal Ca^{2+} transport activities may contribute to the development of intracellular Ca^{2+} overload in the genetically determined cardiomyopathy in hamsters and such a defect may be due to excessive amount circulating catecholamines in these disease.

-353- THE ROLE OF CARDIAC ADRENERGIC RECEPTORS IN CARDIOMYOPATHIC BIO 14.6 SYRIAN HAMSTERS

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To elucidate the role of sympathetic nerve activity in cardiomyopathy, we studied the changes of cardiac adrenergic receptors in cardiomyopathic BIO 14.6 Syrian hamsters (BIO) by verapamil treatment. To verapamil treated BIO, verapamil (10 mg/kg/day, i.p.) was administered from 21th day old to 27th day old and then verapamil (20 mg/kg/day, i.p.) was administered for 6 weeks. Cardiac membranes were obtained from ventricles of nontreated BIO aged 10–12 weeks, verapamil treated BIO, saline treated BIO and age-matched golden healthy hamsters (G.H.H.), respectively. The α_1 - and β -adrenoceptors were identified utilizing [^{125}I] HEAT and [^{125}I] CYP respectively.

Bmax of [^{125}I] HEAT and [^{125}I] CYP were larger in non-treated BIO than G.H.H., whereas Kd did not change. Bmax of [^{125}I] CYP significantly decreased in verapamil treated BIO than saline treated BIO. However Bmax of [^{125}I] HEAT in verapamil treated BIO did not change and it was larger than that of G. H. H.. These results indicate that α_1 - and β -adrenoceptors increase in non-treated BIO but β -adrenoceptor of verapamil treated BIO do not increase.

Treatment of young BIO with verapamil prevented the myocytolytic necrosis leading to scar formation and reactive hypertrophy. We suggest that α_1 -adrenoceptor may play an important role in pathogenesis of BIO, whereas the increase of β -adrenoceptor may be secondary to myocardial hypertrophy.

-354- IMMUNOLOGICAL STUDY IN IDIOPATHIC CARDIOMYOPATHY-LYMPHOCYTE SUBSETS AND NK CELL FUNCTION

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The role of immunity has been discussed in the pathogenesis of dilated cardiomyopathy (DCM). The purpose of the present study is to evaluate the immunological conditions determined by lymphocyte subsets and NK cell activity in 12 patients (pts) with DCM, 11 ischemic heart diseases (IHD) and 13 normal controls (NC).

T cell and Ty cell were identified using the double rosette formation method. T cell subsets and NK cell were investigated using monoclonal antibodies (OKT4, OKT8, Leu7, Leu11a). NK cell functional assay was performed by ^{51}Cr releasing method using the cultured K562 cells as target.

The peripheral lymphocyte counts and the percentage of Ty cells were significantly lower in pts with DCM than IHD and NC ($p < 0.01$). The percentage of T cells, B cells, OKT4 and OKT8 positive cells was not statistically different among the three groups. NK cell functional activity in DCM and IHD pts tested were frequently attenuated ($25.6 \pm 5.0\%$ in DCM, $29.5 \pm 4.8\%$ in IHD, $36.1 \pm 3.8\%$ in NC). In addition, recombinant interleukin 2 (rIL2) enhanced NK cell activity in all pts with DCM with one exceptional case. Since we could not observe the production of interferon γ induced by rIL2 and the serum inhibitory factors to NK cell function in our assay, it might be suggested that DCM pts had a low IL2 production and/or the reduced numbers with defective function of NK cell.

Our results showed the possibility that an imbalance in cellular immune reactions partly explain the pathogenesis of DCM.

-355- SPONTANEOUSLY OCCURRING HYPERTROPHIC CARDIOMYOPATHY IN THE RAT

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Gross anatomic and microscopic findings of the heart that was arrested at end diastole were compared between 8-wk-old normotensive Wistar rats, 7-wk-old SHR, and the 8-wk-old rats we have been maintaining by selective inbreeding.

In the 20 male Wistar rats, heart wt to body wt ratio (mean $\pm$ SD) was 3.77 ± 0.27 and septum to free wall ratio in thickness was 0.97 ± 0.06 . In