We reviewed the concept that de-differentiation is a mechanism of electrical remodeling in diseased hearts, referring to our data on 1) differential changes in action potential duration (APD) and transient outward current (I_o) of cultured ventricular myocytes of newborn rats and 2) changes in APD, I_o and its gene expression in hypertrophied adult rat ventricles. The latter changes associated with progression of the hypertrophy appeared in the reverse order of those in newborn rats. Gene switching of ionic channels to de-differentiation was concluded to be essential for electrical remodeling of the diseased hearts.

Introduction
It is suspected that de-differentiation is a mechanism of remodeling of the diseased myocardium associated with ventricular hypertrophy, congestive failure and ischemic heart disease (1-2). Therefore, although such a mechanism may play an important role in electrical remodeling in diseased hearts, we can not find any paper to propose this concept.

We have investigated postpartum-developmental changes in electrophysiologic properties of cultured rat ventricular myocytes, focussing on developments of action potentials, transient outward channel current (I_o) and its channel gene expression (3-4). In this paper, we aimed to correlate these developmental changes with those observed in ventricular myocytes cultivated under hypoxic condition or isolated from hypertrophied ventricles.

I. Hypoxia inhibits postpartum-developmental changes in action potentials and ion channels of cultured ventricular myocytes
To prove the hypothesis that a sudden step-up of oxygen tension (three times higher than fetal stage) after birth is essential for postnatal...
shortening in action potentials and augmentation of \( I_{\text{to}} \) channel currents, we compared these electrophysiologic properties between the myocytes cultivated in normoxic (\( O_2 \geq 100 \text{ mmHg} \)) and hypoxic (\( \leq 60 \text{ mmHg} \)) mediums (Figure 1)(5). After 10 days of cultivation under normoxia, the action potential duration (APD) was shortened (APD\(_{80} \): 122.1 ± 8.4 ms) similar to that recorded in the ventricular myocytes isolated freshly from the neonatal rats growing for a corresponding number of days, whereas under hypoxia it remained unchanged [APD\(_{80} \): 182.4 ± 28.8 ms, \( p<0.05 \) (vs. normoxia)]. Similarly, \( I_{\text{to}} \) density increased markedly (189-265% at voltages levels of -20 to +50 mv) under normoxia, but remained unchanged under hypoxia. Furthermore, kinetics of \( I_{\text{to}} \) density under hypoxia reverted to those obtained at peripartum stage.

II. Stage-dependent changes in APD and \( I_{\text{to}} \) density in rats with monocrotaline-induced right ventricular hypertrophy

In monocrotaline (MCT) induced right ventricular hypertrophy of the rat, action potential duration of the left ventricular myocytes prolonged in association with progression of right ventricular hypertrophy (6). Figure 2 compares action potentials of ventricular myocytes isolated from rats on day 14 and 28 after MCT injection of controls. Action potential duration (APD\(_{90} \)) measured at 90% repolarization was prolonged significantly (APD\(_{90} \) of control vs MCT-treated rats on day 28: 28.3 ± 0.2 vs 49.1 ± 8.4 msec, \( p < 0.05 \)) in myocytes of the hypertrophied right ventricle while it remained unchanged in those of the left ventricle. \( I_{\text{to}} \) density of the hypertrophied ventricular myocytes was reduced to 56% of control (\( p < 0.05 \)) without significant changes in activation and inactivation kinetics.

III. Downregulation of voltage-gated K⁺
channels in hypertrophied rat ventricles

We investigated changes in voltage-gated K+ channel gene expression in its hypertrophied right ventricular cells with MCT-treated rat mRNA levels of Kv1.2, Kv1.5, Kv 2.1, Kv4.2 and Kv 4.3 α - subunits were measured by ribonucleic protection assay (7). The expression levels of Kv 1.2 and Kv 1.5 channels in the hypertrophied ventricular cells of MCT-treated rats on day 28 were decreased significantly [Kv 1.2 (control vs. MCT): 1.0 ± 0.12 vs. 0.4 ± 0.13 (arbitrary units), p <0.05; Kv 1.5 1.0 ± 0.05 vs. 0.24 ± 0.03, p <0.01], but those of Kv 1.4 remained unchanged. The Kv 2.1 mRNA expression level was reduced markedly [Kv 2.1 (control vs. MCT): 1.0 ± 0.02 vs. 0.42 ± 0.05, p <0.05]. Figure 3 shows changes of mRNA expression in Kv 4.2 channel, one of the most likely candidates for I_{Na} in adult rat ventricles, in the hypertrophied right ventricle.

Expression levels of Kv 4.2 were markedly decreased in MCT rats on day 28 [Kv 4.2 (control vs. MCT): 1.0 ± 0.08 vs. 0.19 ± 0.05, p <0.01]. In the mean time, Kv 4.3 mRNA expression levels were also decreased but not so significant as those of Kv 4.2 [Kv 4.3 (control vs. MCT): 1.0 ± 0.05 vs. 0.55 ± 0.12, p <0.05].

Conclusion

As far as rat ventricular muscle is concerned, prolongation of ventricular recovery process in diseased hearts can be explained by de-differentiation induced-genetic downregulation of the I_{Na} channel which determines APD of the adult rat. Downregulation of voltage-gated K+ channels such as LQT1 and LQT2 channels by gene switching due to de-differentiation may play an essential role in the ventricular repolarization delay in diseased human hearts. However, a detailed analysis should be performed to reveal which K+ channels predominantly determine APD of the human ventricles.
Figure 3  Kv 4 mRNA expression in the right ventricles of control and MCT-treated rats on day 28 after infection. A: Kv 4.2 mRNA was measured by ribonuclease protection assay. Cyclo, cyclophilin mRNA as internal control. B: average amounts of Kv 4.2 are presented as ratio to internal control. Long axis: Kv4.2 mRNA (arbitrary unit). Significantly different from control. ※※p <0.01 [Reproduced from Reference 7]

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