Does Dopamine Act on Myocardial Cells?

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We examined the electrophysiological effects of dopamine on the single myocardial cells isolated from the rat and rabbit heart. Dopamine at a concentration of 1 or 10 μM did not affect the L-type Ca$^{2+}$ current (I_{Ca}) or the transient outward current (I_{TO}) in rat ventricular, rabbit atrial, ventricular, and sinoatrial node cells. It did not induce any detectable change in the action potential configuration of the rabbit ventricular cells either. We conclude that dopamine does not directly act on myocardial cells at least in terms of the electrophysiological properties. (Hypertens Res 1995; 18 Suppl. I: S157–S159)

Key Words: dopamine, myocardial cell, calcium current, transient outward current, action potential

Dopamine is a precursor of epinephrine and nor-epinephrine in the adrenal cortex or nerves, and is itself one of important neurotransmitters. This catecholamine has been widely used for the treatment of heart failure because of its potent positive inotropic and chronotropic effects on the heart (1). However, dopamine can act as a substrate for the catecholamine synthesis in the adrenal cortex or peripheral nerves. In addition, numerous tissues including nerves have dopaminergic receptors. Therefore, dopamine may affect the cardiac activity indirectly by causing a release of catecholamines from the adrenal cortex and peripheral nerves. The direct effects of dopamine on the myocardium has not been clarified so far, since the results of previous studies using isolated tissues, as well as in situ models, could have been modified by the catecholamines released from the nerve endings or adrenal cortex. In the present study, we first measured the tissue dopamine concentration in WKY and SHR heart to clarify whether or not dopamine plays any role under pathological conditions. Then, we examined the electrophysiological effects of dopamine on single cells isolated from the rat and rabbit heart. Voltage clamp experiments were focussed on the L-type Ca$^{2+}$ current (I_{Ca}) and transient outward current (I_{TO}), because these currents are very sensitive to β and α adrenoceptor stimulation, respectively.

Methods

Catecholamine Measurement

The heart of WKY and SHR at 10 weeks of the age was quickly excised, and the right and left ventricles were homogenized with perechloric acid. The catecholamine concentrations in the supernatant were measured with the high performance liquid chromatography.

Cell Isolation

Single myocytes were isolated from rats at 8 weeks of the age or rabbits weighing 2.5–3 kg as previously described (2).

Electrical Measurement

The whole-cell patch-clamp method was employed to record the action potentials and membrane currents in the isolated single cells. The action potentials were recorded in a current clamp mode. The extracellular solution contained in mM, NaCl 142, KCl 5.4, NaH$_2$PO$_4$ 1, CaCl$_2$ 1.8, MgCl$_2$ 1, HEPES 5 and glucose 10 (pH = 7.4 adjusted by NaOH), and the intrapipette solution contained in mM, K-aspartate 80, KCl 20, CaCl$_2$ 0.5, MgCl$_2$ 1, K$_2$-ATP 5, Na$_2$-phosphocreatine 5 and HEPES 5 (pH = 7.2 adjusted by KOH). The extracellular solution for I_{Ca} measurement contained in mM, NaCl 100, CsCl 20, CaCl$_2$ 1.8, MgCl$_2$ 1, tetraethylammonium 30, glucose 10, and HEPES 5 (pH = 7.4 adjusted with CsOH). The internal solution contained in mM, Cs-aspartate 80, CsCl 20, tetraethylammonium 20, CaCl$_2$ 0.3, MgCl$_2$ 1, EGTA 10, K$_2$-ATP 5, Na$_2$-phosphocreatine 5 and HEPES 5 (pH = 7.2). Test pulses were applied from a holding potential of −40 mV to 0 mV. The solutions for I_{TO} were the same as those for the current clamp experiments. 0.1 mM CdCl$_2$ was added to the extracellular solution to eliminate the contamination of I_{Ca}. Test pulses were applied from −120 to +30 mV. The nystatin-permeabilized method was used for I_{Ca} measurement in sinoatrial node cell to maintain the intracellular signal transduction intact (2). The pipette electrode contained in mM, KCl 140, NaCl...
6, HEPES 5 (pH = 7.2), and nystatin was dissolved at a concentration of 400 μg/ml. K⁺ currents were blocked by 1.3 mM BaCl₂.

**Results**

In the catecholamine measurement study, we found that the tissue concentration of dopamine was significantly higher in SHR heart than in WKY (p< 0.05 with Student's t test). It was 22.0 ± 4.7 ng/g (mean ± SD, n=11) for SHR and 13.2 ± 3.9 ng/g for WKY (n=11) in the right ventricle, and 14.5 ± 3.1 ng/g for SHR and 9.6 ± 2.4 ng/g for WKY in the left ventricle.

Fig. 1A shows action potentials in a rabbit ventricular cell. Dopamine at a concentration of 10 μM did not affect the height of plateau or duration of the action potential. Fig. 2B shows the effect of dopamine on the I_{TO}, which is a predominant repolarization current in rabbit and human cardiac cells (3, 4). In line with the results of the action potential experiments, dopamine did not affect the I_{TO}. In Fig. 1C, the sinoatrial cell was first exposed to 2 μM isoproterenol, which doubled the I_{Ca}. An additional application of acetylcholine reversed the stimulatory effect. On the other hand, dopamine did not affect the I_{Ca} in the sinoatrial node cell either (Fig. 1D). The absence of dopaminergic effect on I_{Ca} was observed also in rat (both SHR and WKY) and rabbit ventricular cells (data not shown).

**Discussion**

The present results have shown that 1) the tissue dopamine concentration is increased under some pathological conditions such as myocardial hypertrophy, but 2) dopamine itself does not seem to exert a direct action on isolated myocardial cells. Recently, we reported that the sensitivity to β adrenergic stimulation is significantly lower in the SHR heart than in the control (WKY) one (5). Therefore, the increased dopamine activity could be a result from an enhanced catecholamine synthesis in response to the impaired sensitivity to adrenergic stimulation in the SHR heart.

In this study, we did not observe any distinctive effect of dopamine on I_{Ca} or I_{TO} in rabbit and rat heart cells. The former current has been known to be very sensitive to β adrenergic stimulation, and plays pivotal roles in pacemaking and tension development in the myocardium. On the other hand, α adrenergic stimulation reportedly exerts the ino-
tropic effect by inhibiting the I_{TO} and prolonging the action potential duration (6). Therefore, our present results are in sharp disagreement with the previous view that an application of dopamine in situ produces strong positive inotropic and chronotropic effects via β and α adrenoceptor stimulation (1). The intravenously injected dopamine may act as a substrate for the catecholamine synthesis in the adrenal cortex or peripheral nerves. Otherwise, the dopaminergic receptor stimulation in these tissues may trigger a release of catecholamines. However, it may be argued that the enzymatic cell isolation procedures have caused a degradation of dopaminergic receptors on the myocardial sarcolemma. Further studies including the dopaminergic receptor assay would be necessary on the myocardial cells isolated in different manners.

References