BIBLID: ISSN 0253-9756 Acta Pharmacologica Sinica 中国药理学报 1996 Sep; 17 (5): 435-438

Effects of dopexamine on heart function of isolated hypoxic rabbit heart and in comparison with fenoldopam and procaterol[1]

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KEY WORDS dopamine agonists; dopexamine; fenoldopam; procaterol; left ventricular function; coronary circulation; anoxia

AIM: To study the effects of dopexamine hydrochloride (Dop) on heart functions and coronary flow (CF) of normal and hypoxic isolated perfusing heart and compare the effects of Dop with those of fenoldopam hydrochloride (Fen) and procaterol hydrochloride (Pro). **METHODS:** The isolated rabbit normal and hypoxic hearts were perfused with Krebs-Henseleit (K-H) solution via aorta at 37 ± 0.5 ℃. The drug were added into the K-H solution. **RESULTS:** Dop increased the CF, left ventricular contractile function ($+dp/dt_{max}$ etc) and heart rate (HR) in normal heart; Fen increased the heart function more potently, but increased the CF to a lesser degree than Dop did, whereas the effects of Pro was the least. In simple hypoxic group, at 30 min of perfusion, the $+dp/dt_{max}$ and CF decreased by 66 ± 4 % and 48.1 ± 1.0 %, respectively. Dop remarkably attenuated the decreases in both CF and heart function during hypoxia as it decreased the $+dp/dt_{max}$ by 32.0±2.4 % and CF by 28±3 %. Fen was less potent than Dop in attenuating the diminution of CF, while Pro was the least effective. **CONCLUSION:** Dop has a better prospect in the treatment of ischemic heart disease in view of its dual action of increasing CF and inotropism.

Dopexamine hydrochloride (Dop) is a novel dopamine receptor agonist at both dopamine-1 (DA_1) receptors and β_2-adrenoceptors. Unlike dopamine, it has little, if any, β_1-adrenergic activities and does not stimulate α-adrenoceptors[1,2]. It improved the heart function by reducing afterload and mild positive inotropism without significant increase in myocardial oxygen consumption[3-5]. It improved the oxygen supply by increasing coronary flow[6]. These suggested the potential benefit of Dop in the treatment of myocardial ischemia. Dop had anti-arrhythmic action during myocardial ischemia[7]. But little is known regarding its effects on heart function in ischemic heart. To verify the overall anti-ischemic action of Dop, we evaluated its effects on heart function in isolated hypoxic rabbit heart and compared it with those of fenoldopam hydrochloride (Fen, DA_1 receptor agonist) and procaterol hydrochloride (Pro, β_2-adrenoceptor agonist).

MATERIALS AND METHODS

Dop (Fisons Pharmaceuticals, UK), Fen (SK&F 82526-J, SmithKline Beecham, USA), Pro (Sigma, USA).

Isolated rabbit heart preparation Rabbits of either sex weighing 2.7 ± *s* 0.3 kg were anesthetized with sodium pentobarbital 40 $mg \cdot kg^{-1}$ iv and heparinized (200 $IU \cdot kg^{-1}$ iv). The heart was excised into cold (4 ℃) Krebs-Henseleit (K-H) solution. After cessation of contraction, the heart was cleaned of fat and periadventitial tissue and mounted on a Langendorff apparatus via aortic catheter. K-H solution aerated with 95 % O_2 + 5 % CO_2, 37 ± 0.5 ℃, pH 7.4, was used for perfusion. The composition of K-H solution was ($mmol \cdot L^{-1}$): NaCl 118.0, KCl 4.74, KH_2PO_4 0.93, $MgSO_4$ 1.2, $NaHCO_3$ 24.0, $CaCl_2$ 1.25, and glucose 10.0.

Measurements Isovolumetric contractions were obtained by a latex balloon filled with fluid inserted in the left ventricle via the left atrium. The following primary and derived variables were monitored on a polygraph through a short fluid-filled silicone tube connected to the balloon and attached to a pressure transducer: peak left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), maximal rate of rise of ventricular pressure ($+dp/dt_{max}$), maximal rate of decline of ventricular pressure ($-dp/dt_{max}$), and heart rate (HR). Coronary flow was measured continuously with an in-line flow probe connected to an electromagnetic blood flowmeter (MFV-1200, Japan).

[1] Project supported by the Shanxi Natural Science Foundation, № 3439207.
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Received 1995-01-11 Accepted 1996-04-25

Experimental protocol The hearts were randomly divided into 2 groups: (1) normal group ($n=24$), including control group ($n=6$) and normal + drug group ($n=18$, for each drug $n=6$). In control group, no drug was added to the K-H solution. In control + drug group, an infusion of K-H solution containing Dop, Fen or Pro at the doses of 15 μmol·L^{-1}, 150 μmol·L^{-1}, 1.5 mmol·L^{-1}, 15 mmol·L^{-1}, was performed successively at intervals of a minimum of 15 min. Recordings were made 5 min after dosing. (2) hypoxic group ($n=24$), including simple hypoxic group ($n=6$), and hypoxia + drug group ($n=18$, for each drug $n=6$). In simple hypoxic group, the heart was perfused with K-H solution bubbled with 95 % N_2 + 5 % CO_2 at a low rate of 50 % normal flow rate (12.8 ± 1.7 mL·min^{-1} for 30 min. In hypoxia + drug group, the test drugs were given at 10 min and 25 min respectively, after hypoxia. Recording was made after each dosing.

Data analysis Data were expressed as $\bar{x} \pm s$. Within each group, differences were analyzed using a paired t test. Among the groups, the effects were compared using ANOVA.

RESULTS

Effects on heart function of normal heart All variables were maintained constant during 60-min perfusion with K-H solution in normal control group. Various concentration of Dop (15 and 150 μmol·L^{-1}, 1.5 and 15 mmol·L^{-1}) increased the LVSP, $\pm dp/dt_{max}$, CF, and HR in a dose-dependent manner. At 1.5 mmol·L^{-1}, Dop increased the $+dp/dt_{max}$ from 82 ± 12 to 126 ± 19 kPa, CF from 13.0 ± 1.9 to 17.0 ± 2.5 mL·min^{-1} and HR from 157 ± 23 to 184 ± 23 beat·min^{-1}. Fen was slightly more potent than Dop in increasing the $+dp/dt_{max}$ and HR ($P<0.05$ *vs* Dop), but it was significantly less potent than Dop in increasing CF ($P<0.05$ *vs* Dop, Tab 1). The effects of Pro were the least potent ($P<0.05$ *vs* Dop, $P<0.05$ *vs* Fen).

Effects on heart function of hypoxic heart In simple hypoxic group, the LVSP, $+dp/dt_{max}$ and HR decreased, while the LVEDP increased remarkably during 30 min of hypoxic and low flow rate perfusion. At 30 min, the $+dp/dt_{max}$ decreased by − 66 ± 4 % and the LVEDP increased by + 370 ± 43 % *vs* control. In hypoxia + Dop group, These changes were greatly reduced as compared to simple hypoxic group with the $+dp/dt_{max}$ being decreased only by − 32.0 ± 2.4 % and the LVEDP increased only by + 142 ± 19 % at 30 min perfusion. In comparison, Fen was comparatively more effective ($P<0.05$ *vs* Dop),

Tab 1. Effects of dopexamine hydrochloride (Dop), fenoldopam hydrochloride (Fen), and procaterol hydrochloride (Pro) on heart function in isolated rabbit heart 5 min after dosing. $n=6$, $\bar{x} \pm s$. $^bP<0.05$. $^cP<0.01$ *vs* control; $^eP<0.05$, $^fP<0.01$ *vs* Dop; $^hP<0.05$ *vs* Fen.

	Control	15 μmol·L^{-1}	Control	150 μmol·L^{-1}	Control	1.5 mmol·L^{-1}	Control	15 mmol·L^{-1}
Left ventricular systolic pressure (kPa)								
Dop	8.3 ± 1.1	10.0 ± 1.8^b	8.4 ± 1.2	10.9 ± 1.8^b	8.3 ± 1.1	11.6 ± 1.9^c	8.4 ± 1.1	12.6 ± 2.0^c
Fen	8.4 ± 1.1	10.6 ± 2.0^{be}	8.4 ± 1.0	11.6 ± 2.0^{be}	8.4 ± 1.1	12.1 ± 2.0^{ce}	8.4 ± 1.2	13.4 ± 2.2^{ce}
Pro	8.4 ± 1.1	9.9 ± 1.0^b	8.3 ± 1.1	10.4 ± 1.7^{beh}	8.4 ± 1.1	10.9 ± 1.8^{beh}	8.4 ± 1.1	11.6 ± 1.9^{beh}
$+dp/dt_{max}$ (kPa·s^{-1})								
Dop	82 ± 13	101 ± 17^b	81 ± 13	117 ± 18^b	82 ± 12	126 ± 19^c	81 ± 14	132 ± 21^c
Fen	82 ± 14	105 ± 19^{be}	82 ± 14	124 ± 20^{be}	81 ± 13	134 ± 20^{ce}	81 ± 14	143 ± 24^{ce}
Pro	82 ± 10	100 ± 13^{bh}	82 ± 11	112 ± 15^{beh}	81 ± 11	117 ± 16^{beh}	82 ± 12	126 ± 19^{beh}
Coronary flow (mL·min^{-1})								
Dop	12.9 ± 1.8	15.2 ± 2.1^b	12.8 ± 1.8	15.7 ± 2.4^c	13.0 ± 1.9	17.0 ± 2.5^c	12.9 ± 2.0	20.6 ± 2.7^c
Fen	12.7 ± 1.6	14.1 ± 2.0^{be}	12.9 ± 1.5	15.1 ± 1.7^{be}	12.8 ± 1.7	16.2 ± 2.3^{be}	12.8 ± 1.9	16.7 ± 2.2^{be}
Pro	12.9 ± 1.4	13.7 ± 1.6^{be}	12.9 ± 1.9	14.6 ± 2.1^{beh}	13.0 ± 1.6	15.4 ± 1.8^{bfh}	13.0 ± 2.1	16.0 ± 2.1^{bfh}
Heart rate (beats·min^{-1})								
Dop	157 ± 24	173 ± 26^b	157 ± 22	178 ± 24^b	157 ± 23	184 ± 23^b	156 ± 21	188 ± 21^b
Fen	157 ± 22	177 ± 22^{be}	157 ± 26	186 ± 27^{be}	157 ± 22	196 ± 29^{ce}	155 ± 24	195 ± 30^{ce}
Pro	157 ± 25	172 ± 20^b	157 ± 21	174 ± 20^{beh}	157 ± 20	178 ± 19^{beh}	157 ± 23	180 ± 22^{beh}

whereas Pro was less effective than Dop in attenuating the changes in heart functions ($+dp/dt_{max}$ and LVEDP) induced by hypoxia ($P<0.05$ *vs* Hypoxia + Dop, $P<0.05$ *vs* Hypoxia + Fen, Tab 2).

Tab 2. Effects of dopexamine hydrochloride (Dop), fenoldopam hydrochloride (Fen), and procaterol hydrochloride (Pro, 1.5 mmol·L^{-1}) on heart function of hypoxic isolated rabbit heart. $n=6$, $\bar{x}\pm s$. **$^{b}P<0.05$, $^{c}P<0.01$ *vs* control; $^{e}P<0.05$, $^{f}P<0.01$ *vs* Hypoxia; $^{h}P<0.05$ *vs* Hypoxia + Dop; $^{k}P<0.05$ *vs* Hypoxia + Fen.**

Hypoxia +	Control	Hypoxia time/min 15	30
Left ventricular systolic pressure (kPa)			
−	8.3±1.2	4.1±0.6^{c}	3.8±0.6^{c}
Dop	8.5±1.2	5.8±0.9^{be}	5.5±0.7^{be}
Fen	8.1±1.6	6.6±1.5^{bfh}	6.1±0.9^{bfh}
Pro	8.4±1.1	5.2±0.4^{behk}	4.5±0.5^{behk}
$+dp/dt_{max}$ (kPa·s^{-1})			
−	82±13	37±5^{c}	36±5^{c}
Dop	82±14	57±8^{be}	52±8^{be}
Fen	82±18	63±15^{bfh}	59±10^{bfh}
Pro	81±11	51±5^{behk}	46±6^{behk}
Left ventricular end-diastolic pressure (kPa)			
−	0.24±0.03	0.96±0.11^{c}	1.13±0.18^{c}
Dop	0.25±0.04	0.58±0.06^{be}	0.60±0.13^{be}
Fen	0.24±0.04	0.48±0.04^{bfh}	0.51±0.08^{bfh}
Pro	0.24±0.03	0.75±0.08^{behk}	0.81±0.13^{behk}
Heart rate (beats·min^{-1})			
−	156±25	85±15^{c}	84±13^{c}
Dop	157±20	102±12^{be}	97±19^{be}
Fen	154±37	121±18^{bfh}	110±20^{bfh}
Pro	156±34	95±29^{behk}	89±20^{behk}

Effects on the coronary flow of hypoxic heart

In simple hypoxic group, at 30 min of perfusion, the CF decreased by −48.1±1.0 % *vs* control. Dop, Fen, and Pro iv in the same doses of 1.5 mmol·L^{-1} decreased the CF by −28±3 %, −39.9±2.0 %, and −45±4 %, respectively, showing Dop to be the most potent agent in attenuating the decrement of CF caused by hypoxia (Tab 3).

Tab 3. Coronary flow (mL·min^{-1}) after dopexamine hydrochloride (Dop), fenoldopam hydrochloride (Fen) and procaterol hydrochloride (Pro, 1.5 mmol·L^{-1}) on hypoxic isolated rabbit heart. $n=6$, $\bar{x}\pm s$. **$^{b}P<0.05$, $^{c}P<0.01$ *vs* control; $^{e}P<0.05$, $^{f}P<0.01$ *vs* hypoxia; $^{h}P<0.05$ *vs* hypoxia + Dop.**

Hypoxia +	Control	Hypoxia time/min 15	30
−	12.8±2.2	6.4±1.1^{c}	6.6±1.0^{c}
Dop	13.1±2.4	9.3±1.5^{bf}	9.3±1.2^{bf}
Fen	12.5±1.4	7.8±0.7^{ceh}	7.5±0.8^{ceh}
Pro	13.0±2.0	7.3±1.2^{ceh}	7.1±1.0^{ceh}

DISCUSSION

In the present study, it was shown that while Dop enhanced the myocardial contractility and HR to a moderate degree, it increased the CF considerably in normal isolated heart. In contrast to this, Fen was more potent than Dop in increasing the myocardial contractility and especially the HR, it was, however, much less potent than Dop in increasing CF. The effects of Pro on all these variables were the smallest among 3 agents. In our results, Dop also significantly improved the heart dysfunction caused by hypoxia albeit slightly less potent than Fen did. However, it was the most potent one in reducing the decreasing extent of CF caused by hypoxia. Pro was the most ineffective in improving both CF and heart function during hypoxia.

The above-mentioned pharmacological profiles of the 3 agents may be explained by their characteristic receptor actions. Both DA_1 receptor and β_2-adrenoceptor mediate vasodilation. Therefore, Dop as a combined agonist acting at both DA_1- and β_2-receptors, can be expected to be more potent in increasing CF. This is in line with our previous findings[8] that Dop is by far more potent than Fen and Pro in increasing myocardial nutritional flow. The cardiac β_2-adrenoceptor agonistic activity of Dop may account for its mild inotropic and chronotropic activities[9]. Fen has a potent β_1-adrenergic stimulating action especially at larger doses[10] and hence is the most potent one in increasing inotropic and chronotropic actions among 3 agents. Pro, being a simple β_2-adrenoceptor agonist, shows only slight coronary vasodilating action and positive inotropic effect.

In *in vivo* conditions, it would be expected that Dop, by virtue of its powerful effects on reducing afterload, may be more effective in increasing heart function. Although Dop is less

potent than Fen in positive inotropic action as shown in this study, its relative lack of β_1 stimulation and a larger coronary vasodilating action may be potentially beneficial in the treatment of ischemic heart disease.

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435-438

多培沙明对离体兔缺氧心功能的影响及其与非诺多泮和丙卡特罗效应的比较

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关键词 多巴胺激动剂；多培沙明；非诺多泮；丙卡特罗；左心室功能；冠脉循环；缺氧

目的：研究多培沙明(Dop)对离体兔心功能(HF)和冠脉流量(CF)的影响，并与非诺多泮(Fen)和丙卡特罗(Pro)的效应做对比 **方法**：用 Krebs-Henseleit(K-H)液经主动脉灌流心脏. 药剂加到 K-H 液中. **结果**：Dop 使正常心脏 CF，左室肌收缩功能(+dp/dt_{max}等)和心率均显著增加.. Fen 增加 HF 作用较强，但增加 CF 作用不如 Dop. Pro 对各指标作用最小. 单纯缺氧组，在 30 min 时，其+dp/dt_{max}和 CF 分别较对照降低 66±4 % 和 48.1±1.0 %. Dop 能显著减轻缺氧心脏 CF 与 HF 的变化，使+dp/dt_{max}和 CF 仅降低 32.0±2 4 %和 28±3 %. Fen 减轻 CF 变化的作用不如 Dop. 而 Pro 的作用最小 **结论**：Dop 根据其增加 CF 和正性肌力作用特性，对缺血性心脏病的治疗可能有较好的前景.

R972 R96P.4