Cardiovascular Functions and Dopamine: Mechanism of Action in Adult Male Anesthetized Balady Rabbits

Enas A. Hamed,[1] Emtethal M Moustafa,[1] Nashwa A Abd El-Mottalib[1]
[1]Department of Physiology, Faculty of Medicine, Assiut University, Assiut, Egypt

ABSTRACT

This study aimed to elucidate mechanism(s) that mediate dopamine regulation of cardiovascular system (CVS) functions. Forty eight adult male anesthetized Balady rabbits (4 experiments, 8 groups, 6 animals each) were included. Experiment I assessed the effect of intravenous (iv) dopamine infusion (0.1, 1, 4 and 12 µg/kg/min) on diastolic (DBP), systolic (SBP), mean blood pressure (MBP), heart rate (HR), cardiac contractility (CC) and renal sympathetic nerve activity (RSNA). Experiment II assessed the effect of dopamine infusion on ventricular sarcomere length. Experiment III confirmed the contribution of dopamine receptor subtype(s). Experiment IV evaluated adrenergic receptors involved in dopamine's action. Mean BP, CC, HR and RSNA were recorded by physiograph. At low dopamine infusion rate DBP, MBP, CC and RSNA were decreased; while sarcomere length and A:I ratio were increased. At high dopamine infusion rate DBP, SBP, MBP, HR and CC were increased while; sarcomere length and A:I ratio were decreased. D_1-like receptor activation decreased MBP; while D_2-like receptor activation decreased MBP, CC, and RSNA. Both D_1-and D_2-like receptors blockade attenuated hypotensive response, whereas CC was abolished by D_2 receptor blockade. Mean BP, HR and CC were not changed after D_1- and D_2-like receptors blockade, but decreased after D_1- and D_2 like receptors activation. Low dopamine infusion into animals pre-treated with α-adrenoceptor blockade (reserpine) or β-adrenoceptor blockade (propranolol) decreased MBP and CC whereas, with high dopamine infusion, the HR and CC were increased after α-adrenoceptor blockade and MBP was increased after β-adrenoceptor blockade. From this study, we can conclude that dopamine elicits biphasic effect on CVS. Low dopamine doses acts via stimulation of D_1- and D_2- like receptors. With increasing dose, actions occur via stimulation of α- and β-adrenergic receptors. Normal endogenous dopamine may not alter basal cardiovascular functions.

INTRODUCTION

Dopamine (DA) is an endogenous catecholamine that serves not only as a precursor for norepinephrine and epinephrine but also as a neurotransmitter. Dopamine is involved in a wide variety of physiological processes both in central nervous system (CNS) and in peripheral tissues and organs[(1)]. In the mammalian brain, DA controls a variety of functions including locomotors activity, cognition, food intake and endocrine regulation. This catecholamine also plays multiple

roles in the periphery as a modulator of cardiovascular functions (CVS), catecholamine release, hormone secretions, vascular tone, renal functions and gastrointestinal motilities[2].

Dopamine exerts its physiological actions via α- and β-adrenergic receptors as well as via specific dopaminergic receptors, a class of cell surface receptors coupled to G-proteins. Dopaminergic receptors have been classified into two families (D_1-like and D_2-like) based on biochemical, pharmacological and molecular cloning studies. In mammals, two D_1-like receptors (D_1 and D_5) have been cloned and linked to stimulation of adenyl cyclase stimulate phospholipase C[3]. Three D_2-like receptors have been cloned (D_2, D_3 and D_4) and linked to inhibition of adenyl cyclase[2]. All the mammalian dopamine receptors initially cloned from the brain, have been found to be expressed outside CNS, in such sites as the heart, blood vessels, carotid body, kidney, adrenal gland, parathyroid gland, gastrointestinal tract, vascular smooth muscle, and on the terminals of postganglionic sympathetic nerves[4,5,6].

It is evident from forgoing studies on the multiple dopamine receptors that activation and /or blockade of them can lead to pronounced changes in cardiovascular functions. Indeed, rodents with genetic hypertension and human with essential hypertension are associated with a defective dopamine production and/or dopamine receptor functions[2,7]. Moreover, dopamine receptor blockade is associated with the development of hypertension in saline-loaded rats. Finally, inhibition of dopamine synthesis outside CNS accelerates hypertension development in spontaneously hypertensive rats[8].

The present study was designed to determine the possible receptor subtype(s) which mediate the effect of dopamine in regulation of some cardiovascular functions as arterial blood pressure (ABP), heart rate (HR) and cardiac contractility (CC). Also, to study the possible association between dopamine and sympathetic nervous system on affecting cardiovascular functions.

MATERIALS & METHODS

Animals.

This investigation was carried out on 48 adult male Balady rabbits, weighing (1.2 - 1.5 kg) divided into 8 groups, 6 animals each. On arrival, animals were caged individually in room temperature with natural light-dark cycle with free access to water and commercial rabbit food. This study was carried out on 4 experiments at the same period each day (8-10 am). After one week of acclimatization, rabbits were randomly assigned into the studies. After termination of the experimental protocols, all animals were scarified. The surgical and experimental procedures were carried out according to "Guideline on Experiments on Animal" at Faculty of Medicine, Assiut University and approved by Ethical Committee.

Reagents.

Dopamine (3-hydroxytyramine hydrochloride) was purchased from Fluka Company [Buchs, Switzerland]; reserpine, SCH-23390 and metochlopramide from Sigma Aldrich [Seelze, Germany]; urethane from Aldrich Chemical Company [Wis., USA]; heparin from Pharmacia

Pharmacuticals [Cairo, Egypt]; SKF-38393 and bromocriptine from ICN Biomedicals Inc. [Ohio, USA] and propranolol from Macclesfeild [Cheshire, UK].

Surgical Preparation.

The surgical technique was done according to steps described by Muhlbauer et al. (9). Rabbits were anesthetized through intraperitoneal (ip) injection of urethane (600 mg/kg). The trachea was exposed by blunt dissection and intubated with a short cannula to insure free airways during experiments. One catheter was inserted into right jugular vein for iv infusion of the drugs via its connection to the syringe pump (Cole-Parmer, 74900-00-05, Cole-Parmer Instrument Company, USA) and another catheter into left common carotid artery for ABP recording and blood sampling. Heparin (0.25 ml) was injected iv through the catheter to prevent intracatheter clotting. Following surgical preparation, animals were allowed to reach steady state condition defined by stable ABP and HR which achieved within 15 min.

Study protocol.

In Experiment I, two groups of rabbits (Groups 1 and 2) were used. After the steady state conditions reached, a baseline period (control) of 30 min was performed. During the control period the animals received iv infusion of 0.9 % sterile sodium chloride solution (vehicle) at a rate of 0.02 ml/min delivering approximately 0.6 ml solution throughout the experiment. After completion of baseline period, infusion was switched to dopamine in 4 doses. Group (1) received iv infusion of dopamine at a rate of 0.1 and 1 µg/kg/min with 15 min interval delivering approximately 0.6 ml (0.02 ml/min) throughout the experiment for each dose. Group (2) received iv infusion of dopamine at a rate of 4 and 12 µg/kg/min with 15 min interval delivering approximately 0.6 ml (0.02 ml/min) throughout the experiment for each dose. Arterial BP, HR and CC were recorded before (baseline), at 1, 15 and 30 min during dopamine infusion (experimental period) and at 15 min after termination of infusion (recovery period). Renal sympathetic nerve activity (RSNA) was recorded before (baseline) and at 30 min during dopamine infusion at rates of 1 and 12 µg/kg/min (preferred effective low and high doses respectively).

In experiment II, 3 groups of rabbits (Groups 3-5) were used. Group 3 (control group) received iv infusion of normal saline at a rate of 0.02 ml/min for 30 min; groups (4 and 5) received iv infusion of dopamine at a rate of 1 and 12 µg/kg/min for 30 min successively. After infusion termination, specimens from left ventricle were taken and prepared for electro-microscopic examination. Sarcomere length (µm) and ratio of A: I band were measured.

In experiment III, two groups (6 and 7) of rabbits were used. Animals of group (6) received iv infusion of SKF-3839 (5 µg/kg/min for 15 min), a selective agonist of D_1-like receptor (10). After a rest period of 15 min, the same animals received iv infusion of 1µg/kg/min dopamine 20 min after a previous administration of SCH-23390 (50 µg/kg, ip), a selective antagonist of D_1-like receptor[11]. After an additional 15 min rest period, rabbits received iv infusion of 12 µg/kg/min dopamine 20 min after previous administration of SCH-23390 (50 µg/kg, ip). Animals of

group (7) received iv infusion of bromocriptine (1µg/kg/min for 15 min), a selective agonist of D_2-like receptor[12]. After a rest period of 15 min, the same animals received iv infusion of 1µg/kg/min dopamine 20 min after a previous administration of metoclorpramide (15 mg/kg, ip), a selective antagonist of D_2-like receptor[13]. After an additional 15 min rest period, rabbits received iv infusion of 12 µg/kg/min dopamine 20 min after previous administration of metoclorpramide (15 mg/kg, ip). Arterial BP, HR, CC and RSNA were recorded before (baseline) and 15 min during D_1- and D_2-like receptor agonist and antagonism treatment.

*In experiment IV***,** one group (Group 8) was used. Animals of this group received iv infusion of 1 and 12 µg/kg/min dopamine for 15 min with 15 min interval, 20 min after previous administration of reserpine (α-adrenoceptor blockade, 3 mg/kg, ip)[14]. After a rest period of 15 min, the same animals received iv infusion of 1 and 12 µg/kg/min dopamine for 15 min with 15 min interval, 20 min after previous administration of propranolol (β-adrenoceptor blockade, 1 mg/kg, sc)[15]. Arterial BP, HR and CC were recorded before (control) and at 15 min during dopamine infusion.

Arterial BP was recorded by EM 75/No 4403" pressure transducer that convert ABP to a proportional electrical signals. Signals were amplified using "Strain Gauge Coupler Fc 137" of physiograph [Harvard Apparatus Limited, 50-8622, Kent, UK]. Systolic (SBP) and diastolic blood pressure (DBP) of the animal were recorded. Mean BP was calculated as DBP + [1/3 (SBP - DBP)][16]. Electrocardiogram (ECG) was recorded using [Fx 2111 Electrocardiograph Cardimax]. HR was registered with "Fc123 ECG coupler" connected to the physiograph. Heart isometric contractility was monitored by means of a photoelectric force transducer [E & M Physiograph Myograph, Houston TX, USA] connected to a heart clips at apex of the ventricles. The amplitude of contractions in mm is used as an index of cardiac contractility. Renal nerve traffics were recorded after their stimulation with micro electrodes connected to stimulator cable [electronic stimulator, SEN 3201]. Renal nerve signals were magnified with Harvard coupler apparatus [50-6360]. Renal SNA was recorded according to the method described by Thoren & Ricksten[17]. The amplitude of bursts (mm) and frequency (rate/min) were used as an index of sympathetic nerve activity. Samples from ventricular tissues of the rabbits were prepared for electro-microscopic examination.

Statistical analysis.

The statistical analysis was performed using Prism software version 3. Data were expressed as mean +/- standard error (SE). For inter-group comparison, analysis with two-sided paired Student's "t" test or one way ANOVA test was carried out as appropriate. Differences between results were considered statistically significant when *P*- value was less than 0.05.

RESULTS

Tables (1) and Figures (1 and 2) summarize the effect of intravenous dopamine infusion (0.1, 1, 4 and 12 µg/kg/min) on ABP (mmHg), HR (beat/min) and CC (mm) respectively in adult male rabbits. From these

tables it is clear that at dose 1 µg/kg/min, a significant decrease was observed in DBP (P <0.05, P <0.01 *and* P <0.01) and MBP (P <0.05, P <0.001 and P <0.001) compared with baseline level at 1, 15 and 30 min during infusion respectively. While, at dose 12 µg/kg/min, a significant increase was observed in DBP (P <0.05), SBP (P <0.01), and MBP (P <0.01, P <0.001 and P <0.001) compared with baseline level at 1, 15 and 30 min during infusion successively.

Heart rate was significantly increased at 15 and 30 min during iv dopamine infusion at doses of 4 µg/kg/min (P <0.05) and 12 µg/kg/min (P <0.05) (Table 2; Figures 1 and 2). Cardiac contractility at 1, 15 and 30 min during dopamine infusion showed a significant decrease with a dose of 1 µg/kg/min (P <0.05, P <0.01 and P <0.01 respectively) but a significant increase was observed with a dose of 12 µg/kg/min (P <0.05, P <0.01 and P <0.01 successively). Whereas, at a dose of 4 µg/kg/min, a significant increase in CC was observed at 15 and 30 min only (P <0.05) (Table 3; Figures 1 and 2).

Intravenous infusion of dopamine at a dose of 1 µg/kg/min led to a significant decrease in frequency and amplitude (P <0.001) of RSNA and a significant increase in sarcomere length and A:I ratio (P <0.01). While, iv infusion of dopamine at a dose of 12 µg/kg/min led a to decrease in sarcomere length and A:I ratio (P <0.05) (Table 4, Figures 3-6).

Activation of D_1-like receptor by intravenous SKF-38393 infusion resulted in a significant decrease in MBP (P <0.01). Whereas, activation of D_2 receptors by iv bromocriptine infusion resulted in a significant decrease in MBP, CC and frequency and amplitude of RSNA (P <0.05, P <0.01, P <0.001 and P <0.001 respectively) (Table 5).

Administration of D_1-like antagonist SCH-23390 alone didn't cause any significant change in the levels of MBP, HR and CC compared with baseline levels. Intravenous dopamine infusion after SCH-23390 pre-treatment at a dose of 1µg/kg/min led to a significant decrease in the MBP and CC (P <0.05, P <0.01), meanwhile, at dose 12 µg/kg/min led to significant increase in MBP, HR and CC (P <0.01, P <0.05 *and* P <0.01 successively) compared to control level. Administration of D_2-like receptor antagonist metoclopramide alone didn't cause any significant change in the levels of MBP, HR and CC compared with baseline levels. Intravenous dopamine infusion after metoclopramide pre-treatment led to a significant decrease in the MBP (P <0.05), while, 12 µg/kg/min led to a significant increase in the MBP, HR and CC (P <0.01) compared to control level (Table 6).

After reserpine pre-treatment, iv dopamine infusion at a rate of 1 µg/kg/min led to a significant decreased in MBP and CC (P <0.05 and P <0.01 respectively), while at dose of 12 µg/kg/min led to significant increased in HR and CC (P <0.05, P <0.01 successively) compared with the pre-injected dopamine (control) levels and after propranolol pre-treatment, iv dopamine infusion at a rate of 1 µg/kg/min led to a significant decreased in MBP and CC (P <0.01), while at a dose of 12 µg/kg/min led to significant increase in MBP (P <0.05) compared to control level (Table 7).

Table (1): The effect of intravenous dopamine infusion (0.1, 1, 4, 12 µg/kg/min) on arterial blood pressure (mmHg) in adult male rabbits.

Dose	Variables	Diastolic Pressure (mmHg)					Systolic Pressure (mmHg)					Mean Blood Pressure (mmHg)				
		Base	Time (min)			Rec.	Base	Time (min)			Rec.	Base	Time (min)			Rec.
			1	15	30			1	15	30			1	15	30	
0.1	Mean	76.00	75.17	76.50	74.00	76.67	103.30	101.80	100.80	102.70	103.30	85.11	84.06	84.61	83.56	85.56
	±SE	±3.13	±2.34	±2.14	±3.00	±2.77	±3.33	±2.51	±3.27	±1.76	±3.08	±2.58	±2.14	±2.51	±2.55	±2.52
	P value		P >0.05	P >0.05	P >0.05	P >0.05		P >0.05	P >0.05	P >0.05	P >0.05		P >0.05	P >0.05	P >0.05	P >0.05
	%Change		1.09↓	0.66↑	2.63↓	0.88↑		1.45↓	2.42↓	0.58↓	0.00		1.23↓	0.59↓	1.82↓	0.53↑
1	Mean	74.00	63.33	52.83	58.50	78.67	105.20	104.20	97.50	97.17	100.00	84.39	76.94	67.72	71.39	85.78
	±SE	±3.65	±1.52	±3.83	±2.75	±2.62	±2.59	±1.72	±1.71	±1.64	±0.52	±3.21	±1.35	±2.84	±1.86	±1.63
	P value		***P*<0.05**	***P*<0.01**	***P*<0.01**	P >0.05		P >0.05	P >0.05	P >0.05	P >0.05		***P*<0.05**	***P*<0.001**	***P*<0.001**	P >0.05
	%Change		14.42↓	28.61↓	20.95↓	6.31↑		0.95↓	7.32↓	7.60↓	4.94↓		8.83↓	19.75↓	15.40↓	1.65↑
4	Mean	79.33	82.67	87.83	86.17	84.67	110.00	106.30	109.17	115.50	115.30	89.56	90.56	95.11	95.94	94.89
	±SE	±3.71	±7.51	±5.78	±3.66	±3.49	±5.16	±8.01	±4.52	±4.11	±4.22	±3.56	±7.48	±5.26	±1.79	±5.04
	P value		P >0.05	P >0.05	P >0.05	P >0.05		P >0.05	P >0.05	P >0.05	P >0.05		P >0.05	P >0.05	P >0.05	P >0.05
	%Change		4.21↑	10.71↑	8.62↑	6.73↑		3.36↓	0.75↓	5.00↑	4.82↑		1.12↑	6.20↑	7.12↑	5.95↑
12	Mean	79.33	90.83	94.50	94.50	86.67	110.00	128.70	138.70	136.80	116.00	89.56	103.4	109.20	108.60	96.44
	±SE	±3.33	±1.94	±2.68	±1.89	±2.62	±5.63	±7.67	±7.33	±8.04	±6.22	±3.06	±3.43	±3.69	±3.26	±3.35
	P value		***P*<0.05**	***P*<0.05**	***P*<0.05**	P >0.05		***P*<0.01**	***P*<0.01**	***P*<0.01**	P >0.05		***P*<0.01**	***P*<0.001**	***P*<0.001**	P >0.05
	%Change		14.50↑	19.12↑	19.12↑	9.25↑		16.97↑	26.06↑	24.39↑	5.45↑		15.45↑	21.93↑	21.26↑	7.68↑

SE : Standard Error.

↓ : Percent decrease, ↑: Percent increase.

Base: Baseline. Rec: Recovery

Significance versus base level using one way ANOVA test

Table (2): The effect of intravenous dopamine infusion (0.1, 1, 4, 12 µg/kg/min) on heart rate (beat/min) in adult male rabbits.

Dose	Variables	Baseline	Time (min)			Recovery
			1	15	30	
0.1 (µg/kg/min)	Mean ± SE	285.00±8.94	285.80±11.72	280.00±9.31	281.70±10.14	283.3±12.02
	P value		*P* >0.05	*P* >0.05	*P* >0.05	*P* >0.05
	%Change		0.28 ↓	1.75 ↓	1.16 ↓	0.60 ↓
1 (µg/kg/min)	Mean ± SE	285.80±8.80	278.30±11.38	276.70±7.60	277.50±9.29	285.00±7.64
	P value		*P* >0.05	*P* >0.05	*P* >0.05	*P* >0.05
	%Change		2.62 ↓	3.18 ↓	2.90 ↓	0.28 ↓
4 (µg/kg/min)	Mean ± SE	283.30±8.43	285.00±10.88	321.70±8.33	326.70±12.56	281.70±9.10
	P value		*P* >0.05	***P* <0.05**	***P* <0.05**	*P* >0.05
	%Change		0.60 ↑	13.55 ↑	15.32 ↑	0.56 ↓
12 (µg/kg/min)	Mean ± SE	284.20±8.98	290.00±3.65	328.3±11.95	320.0±10.33	288.30±6.01
	P value		*P* >0.05	***P* <0.05**	***P* <0.05**	*P* >0.05
	%Change		2.04 ↑	15.54 ↑	12.61 ↑	1.44 ↑

SE: Standard Error,

↓: Percent decrease, ↑: Percent increase.

Significance versus baseline level using one way ANOVA test.

Table (3): The effect of intravenous dopamine infusion (0.1, 1, 4, 12 µg/kg/min) on cardiac contractility (mm) in adult male rabbits.

Dose	Variables	Baseline	Experimental Period (min)			Recovery
			1	15	30	
0.1 (µg/kg/min)	Mean ± SE	30.83±3.71	30.17±4.21	28.50±4.16	28.83±4.36	31.67±4.21
	P value		*P* >0.05	*P* >0.05	*P* >0.05	*P* >0.05
	%Change		2.14 ↓	8.18 ↓	6.49 ↓	2.72 ↑
1 (µg/kg/min)	Mean ± SE	32.50±2.90	21.83±4.58	19.00±3.11	20.67±2.70	29.83±3.50
	P value		***P* <0.05**	***P* <0.01**	***P* <0.01**	*P* >0.05
	%Change		32.83 ↓	41.54 ↓	36.40 ↓	8.22 ↓
4 (µg/kg/min)	Mean ± SE	30.83±3.56	33.67±3.78	38.67±1.89	38.00±2.13	31.83±3.65
	P value		*P* >0.05	***P* <0.05**	***P* <0.05**	*P* >0.05
	%Change		9.21 ↑	25.43 ↑	23.26 ↑	3.24 ↑
12 (µg/kg/min)	Mean ± SE	29.00±3.54	35.67±1.98	39.50±2.55	39.33±2.96	30.17±0.75
	P value		***P* <0.05**	***P* <0.01**	***P* <0.01**	*P* >0.05
	%Change		23.00 ↑	36.21 ↑	35.62 ↑	4.03 ↑

SE : Standard Error.

↓: Percent decrease, ↑: Percent increase.

Significance versus baseline level using one way ANOVA test.

Table (4): Effect of intravenous dopamine infusion (1 and 12 µg/kg/min) on sympathetic nerve activity, sarcomere length and A:I ratio in adult male rabbits.

Animal's number	Sympathetic Nerve Activity						Sarcomere Length (µm)				A:I ratio	
	Frequency (rate/min)			Amplitude (mm)								
	Baseline	Dopamine (µg/kg/min)		Baseline	Dopamine (µg/kg/min)		Baseline	Dopamine (µg/kg/min)		Baseline	Dopamine (µg/kg/min)	
		1	12		1	12		1	12		1	12
1	36.00	33.00	33.00	22.00	13.00	20.00	2.10	2.70	1.80	1.90	2.20	1.50
2	42.00	30.00	36.00	21.00	18.00	18.00	2.25	3.10	2.10	2.20	2.70	1.80
3	45.00	36.00	39.00	20.00	15.00	17.00	2.30	3.10	1.90	1.64	2.66	1.30
4	42.00	27.00	42.00	19.00	14.00	19.00	2.00	2.60	1.60	1.80	2.50	1.55
5	36.00	30.00	39.00	21.00	12.00	20.00	2.50	3.20	1.50	2.40	3.00	2.00
6	39.00	33.00	36.00	22.00	16.00	21.00	2.20	2.20	2.20	2.35	2.80	1.85
Mean ±SE	40.00 ±1.48	31.50 ±1.28	37.50 ±1.28	20.83 ±0.48	14.67 ±0.88	19.17 ±0.60	2.23 ±0.07	2.82 ±0.16	1.85 ±0.11	2.05 ±0.13	2.64 ±0.11	1.67 ±0.11
P value		***P* <0.001**	P >0.05		***P* <0.001**	P >0.05		***P* <0.01**	***P* <0.05**		***P* <0.01**	***P* <0.05**
%Change		21.25 ↓	6.25↓		29.75↓	7.97↓		26.46 ↑	17.04 ↓		28.76 ↑	18.54 ↓

SE: Standard Error.

↓: Percent decrease, ↑: Percent increase.

Significance versus baseline level using one way ANOVA test

Table (5): Effects of D1- and D_2-like receptor activation on mean arterial blood pressure, heart rate, cardiac contractility and sympathetic nerve activity in adult male rabbits.

Variables		Mean Blood Pressure (mmHg)		Heart Rate (beat/min)		Cardiac Contractility (mm)		Sympathetic Nerve Activity			
								Frequency (rate/min)		Amplitude (mm)	
		Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment
SKF-38393	Mean ± SE	86.33 ±2.80	72.00 ±3.19	288.30 ±6.54	285.00 ±4.28	34.17 ±2.68	32.83 ±2.65	40.00 ±1.48	39.00 ±1.10	20.83 ±0.48	19.50 ±0.56
	P value		***P*<0.01**		*P* >0.05		*P* >0.05		*P* >0.05		*P* >0.05
	%Change		16.60 ↓		1.14 ↓		3.92 ↓		2.50 ↓		6.39 ↓
Bromocriptine	Mean ± SE	89.75 ±3.03	75.33 ±3.46	291.70 ±3.07	280.00 ±6.83	33.50 ±2.95	24.50 ±3.81	40.00 ±1.48	33.00 ±1.10	20.83 ±0.48	15.00 ±0.89
	Significance		***P*<0.05**		*P* >0.05		***P*<0.01**		***P*<0.001**		***P*<0.001**
	%Change		15.97 ↓		4.01 ↓		26.86 ↓		17.50 ↓		27.99 ↓

SE: Standard Error.

↓: Percent decrease

Significance versus baseline level using Paired two-sided Student "t-test".

Table (6): Intravenous dopamine infusion (1and 12 µg/kg/min) after pre - treatment with D_1-like (SCH-23390) and D2-like (metoclopramide) receptor blockers on mean arterial blood pressure, heart rate and cardiac contractility in adult male rabbits.

Variables		Mean Blood Pressure (mm Hg)				Heart Rate (beat /min)				Cardiac Contractility (mm)			
		Baseline	Antagonist (Control)	Dopamine (µg/kg/min)		Baseline	Antagonist (Control)	Dopamine (µg/kg/min)		Baseline	Antagonist (Control)	Dopamine (µg/kg/min)	
				1	12			1	12			1	12
SCH-23390	Mean ±SE	85.17 ±2.37	86.35 ±2.41	74.17 ±3.58	115.00 ±3.39	288.30 ±6.54	290.00 ±5.16	285.00 ±4.28	331.7 ±11.38	34.17 ±2.68	33.50 ±2.31	20.83 ±1.08	40.00 ±2.85
	Significance		*P* >0.05	***P*** **<0.05**	***P*** **<0.01**		*P* >0.05	*P* >0.05	***P*** **<0.05**		*P* >0.05	***P*** **<0.01**	***P*** **<0.01**
	%Change		1.39 ↑	14.12 ↓	33.18 ↑		0.59 ↑	1.72 ↓	14.37 ↑		1.96 ↓	39.01 ↓	19.40 ↑
Metoclopramide	Mean ±SE	82.57 ±2.88	83.33 ±3.65	70.83 ±3.93	105.00 ±2.19	291.70 ±3.07	293.30 ±2.11	296.7 ±4.94	343.3 ±14.53	33.50 ±2.95	33.00 ±2.71	32.83 ±2.61	41.17 ±1.33
	Significance		*P* >0.05	***P*** **<0.05**	***P*** **<0.01**		*P* >0.05	*P* >0.05	***P*** **<0.01**		*P* >0.05	*P* >0.05	***P*** **<0.01**
	%Change		0.92 ↑	14.92 ↓	26.00 ↑		0.55 ↑	1.16 ↑	17.05 ↑		0.15 ↓	0.52 ↓	24.70 ↑

SE : Standard Error.

↓: Percent decrease, ↑: Percent increase.

P: Significance versus baseline level using Paired two-sided Student "t-test"; *P significance versus control using one way ANOVA test.

Table (7): Effect of intravenous dopamine infusion (1and 12 µg/kg/min) after pre-treatment with α-adrenergic receptor blocker (reserpine) and β-adrenergic receptor blocker (propranolol) on mean arterial blood pressure, heart rate and cardiac contractility in adult male rabbits.

Variables		Mean Blood Pressure (mm Hg)			Heart Rate (beat /min)			Cardiac Contractility (mm)		
		Control	Dopamine (µg/kg/min)		Control	Dopamine (µg/kg/min)		Control	Dopamine (µg/kg/min)	
			1	12		1	12		1	12
Reserpine	Mean ± SE	83.12± 3.15	71.11±3.09	82.42±2.52	288.30±7.92	291.70±7.92	330.00±7.30	38.17±1.70	27.50±1.67	44.33±2.04
	Significance		***P* <0.05**	*P* >0.05		*P* >0.05	***P* <0.05**		***P* <0.01**	***P* <0.01**
	% Change		14.45 ↓	0.84 ↓		1.18 ↑	14.45 ↑		35.24 ↓	16.14 ↑
Propranolol	Mean ± SE	82.67±2.31	69.00±2.39	94.52±3.96	260.00±5.77	256.70±7.60	256.70±5.58	36.33±1.28	26.67±2.43	33.83±0.60
	Significance		***P* <0.01**	***P* <0.05**		*P* >0.05	*P* >0.05		***P* <0.01**	*P* >0.05
	% Change		16.54 ↓	14.33 ↑		1.27 ↓	1.27 ↓		26.62 ↓	6.88 ↓

SE: Standard Error.

Significance versus control using one way ANOVA test.

↓: Percent decrease, ↑: Percent increase.

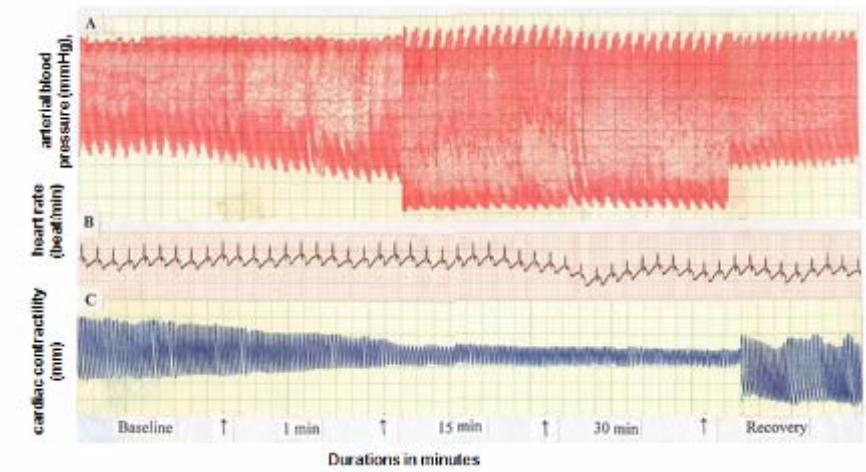

Figure (1): Recording of arterial blood pressure (A), heart rate (B) and cardiac contractility (C) responses to intravenous dopamine infusion at a rate of 1 µg/kg/min in adult male rabbits.

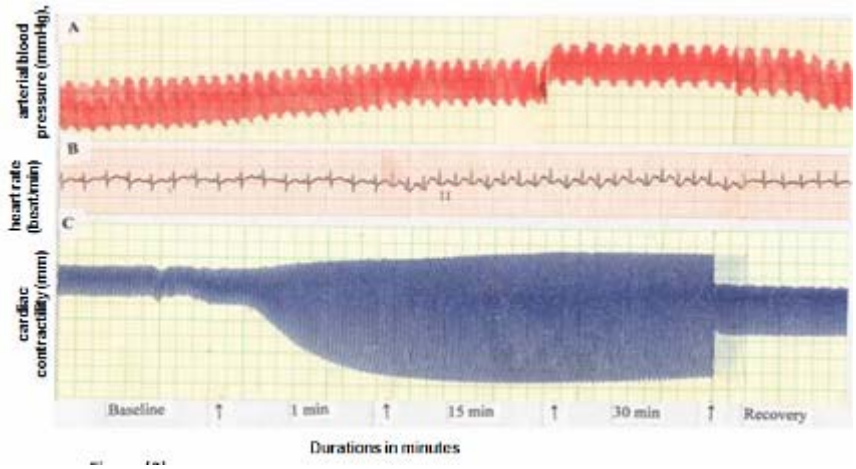

Figure (2): Recording of arterial blood pressure (A), heart rate (B) and cardiac contractility (C) responses to intravenous dopamine infusion at a rate of 12 µg/kg/min in adult male rabbits.

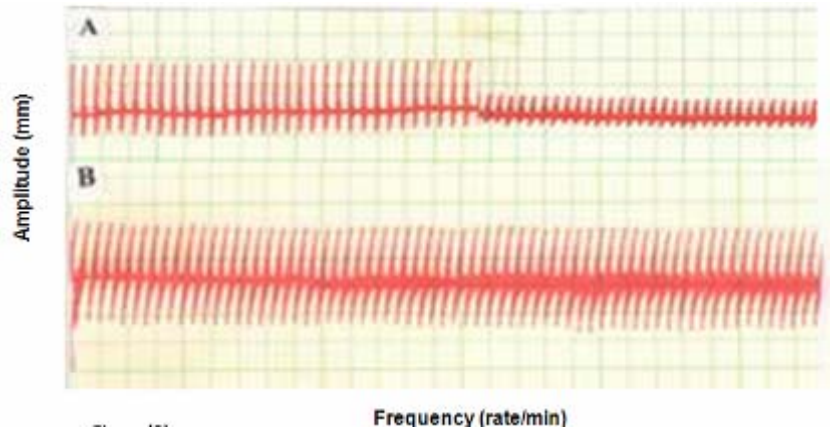

Figure (3): Recording of sympathetic nerve activity response to intravenous dopamine infusion at a rate of 1 µg/kg/min (A) and 12 µg/kg/min (B) in adult male rabbits.

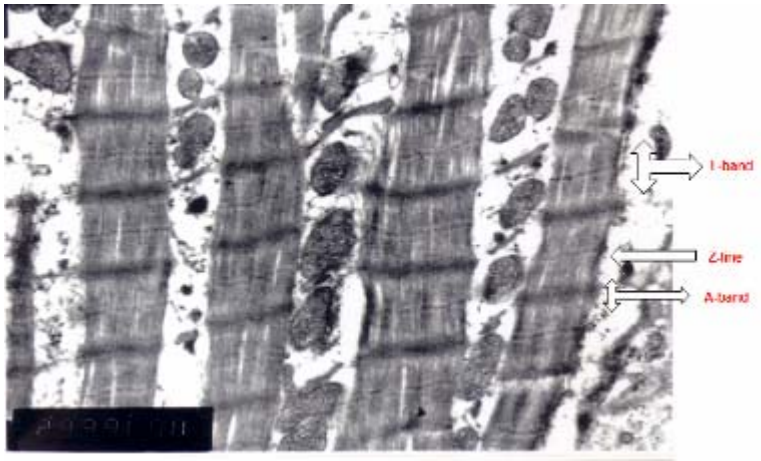

Fig (4): Electron micrograph of longitudinal section of cardiac muscle of control rabbits shows the Z disc, I, A and H bands and M line are readily defined. (X 8,000)

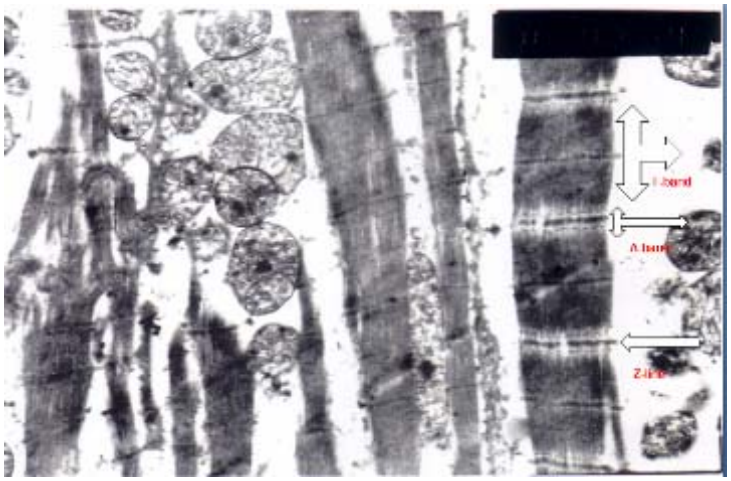

Fig (5): Electron micrograph of longitudinal section of rabbit's cardiac muscle after intravenous dopamine infusion at a rate of 1µg/kg/min, shows the relaxation of myofibrils (as evident by A: I ratio) (X 8,000)

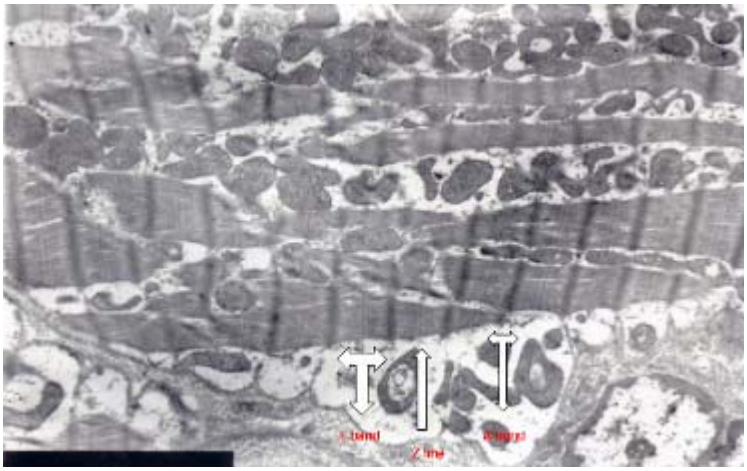

Fig (6): Electron micrograph of longitudinal section of rabbit's cardiac muscle after intravenous dopamine infusion at a rate of 12 µg/kg/min, shows the contraction of myofibrils (as evident by A: I ratio) (X 8,000)

DISCUSSION

The pharmacological effects of dopamine are unique sequence of receptor activation and dose dependent. The observations of the present study demonstrated that dopamine elicits biphasic effect on ABP and CC. At low infusion rates of dopamine (1 μg/kg/min), MBP and CC were decreased, whereas at high infusion rates (12 μg/kg/min), MBP, HR and CC were increased. The effect of dopamine infusion was apparent immediately and gradually (by 1 min), maximal change was seen during the first 15 min of infusion and tended to return to the baseline levels by the end of infusion. Thus the effects of dopamine occur only during the infusion periods. With dose of 1μg/kg/min of dopamine infusion, the depressor effect resulted mainly from decrease in the diastolic blood pressure, whereas the pressor effect seen with a dose of 12 μg/kg/min caused by elevations of both diastolic and systolic blood pressure.

A decrease in MBP in the absence of changes in HR as observed after dopamine at low infusion rate (1μg/kg/min) in the present study suggests a vasodilatation. The cardiovascular effects of exogenously administered dopamine in different animals and human were investigated sparsely. Dobrowolski et al.[18] reported that infusion of dopamine caused vasodilatation in rabbits. Olsen[19] found that with 1 and 2 μg/kg/min of dopamine the MBP was decreased in human. Low dose dopamine (2-5μg/kg/min) has been used to augment renal perfusion in critically ill surgical patients[20]. Schenarts et al.[21] reported that low dose dopamine increase renal blood flow.

Vascular actions of dopamine are mediated primarily through its interaction with specific receptors located in the vascular system. However, only limited information is available concerning the molecular nature and subtype(s) of cardiovascular dopamine receptors in rabbits, so their functions are not established yet. In rabbits, dopamine receptors are located in the renal, mesenteric, pulmonary, coronary and splenic arteries[22,23,24,25]. In this study, D_1-like receptor activation with SKF-38393 (5μg/kg/min) and D_2-like receptor activation with bromocriptine (1μg/kg/min) decreased MBP compared with baseline levels. This observation is similar to the hypotensive effect of other D_1-like agonists such as fenoldopam and apomorphine (26) and D_2-like receptors agonists, such as pengolide and quipinole[26]. For confirmation of the suggestion that dopamine acts via dopaminergic receptors at low infusion rates, dopamine (1μg/kg/min) was iv infused after pre-treatment with selective D_1-like antagonist SCH-23390 (50 μg/kg, ip) and D_2-like antagonist metoclopramide (15 mg/kg, ip). D_1- and D_2-like receptor blockade attenuated but didn't abolish the hypotensive response to dopamine. Dopamine interaction with adrenergic receptors was, also, investigated in this work. Dopamine infusion (1μg/kg/min) into animals pre-treated with reserpine (α-adrenergic receptor blocker) and

propranolol (β-adrenergic receptor blocker) caused decrease in MBP. Chemical sympathectomy didn't modify the extent of inhibition of MBP by dopamine.

In this study, activation of D_2-like receptors diminished not only MBP but also, RSNA. These results suggest that dopamine, via D_1-and D_2-like receptors, has a hypotensive effect at low infusion rates. Stimulation of D_1-like receptors was suggested to cause direct hypotensive effects whereas, stimulation of D_2-like receptors was suggested to inhibit norepinephrine release to indirectly induce hypotension. Biochemical and pharmacological evidence has suggested a postjunctional localization of D_1-like receptors and their stimulation causes direct vasorelaxation and reduction of vascular resistance. Although, investigation of the mechanism of D_1-like receptors activation was not an objective of this study, there are several potential explanations. The vasodilator effect of dopamine via D_1-like receptors is mediated mainly by cAMP/ protein kinase A (PKA)[27]. Protein kinase A stimulates a phosphatase enzyme which, in turn, dephosphorylates calcium channels leading to their inactivation and inhibition of inward calcium currents[28]. There are experimental reports that dopamine depresses the cardiac functions through the inhibition of catecholamine release via stimulation of D2-receptors in addition to postsynaptic D_1-receptor mediated vasodilatation. Yoon et al.[29] hypothesized that the increased norepinepherine concentration in the synaptic cleft might be required for elicitation of cardiovascular depression through dopaminergic receptors. D_2-like receptors were considered mainly prejunctional and their stimulation induces indirect vasorelaxation by modulating norepinephrine release[6,19,30,31,32]. Accordingly, stimulation of postjunctional (D_1-like) or prejunctional (D_2-like) dopamine receptors may represent a therapeutic principle in hypertension treatment.

Dopamine at low dose (1μg/kg/min), apart from its action on ABP, has been observed to cause decreased CC. In the same time, sarcomere length and A:I ratio were increased after 1μg/kg/min dopamine treatment which will contribute to a decrease in developed force[33]. In addition, CC decreased not only after D_2-like receptor activation but also after D_1-like receptor blockade. Cardiac contractility, also, decreased after β-adrenergic receptor blockade. According to these data, dopamine-induced cardiac relaxation at low doses suggests to be mediated by dopamine receptors and is D_2-like dependant by modulating norepinephrine release. Activation of presynaptic D_2 receptors inhibits neuronal norepinepherine release from renal sympathetic nerve endings[34]. However, only limited information is available concerning the profile and the subtypes in the heart. The presence of D_1 and D_2 receptors has been reported in rat and human cardiac tissue[35,36]. D_2-like receptors in the heart were mainly postjunctional and located primarily in atrial tissue[37]. Gomez et al.[38] and Ricci et al.[39] by autoradiographic studies of guinea pig hearts support

the presence of D_3 and D_4 receptors in the right and left ventricle. Yoon et al. (29) hypothesized that the increased norepinepherine concentration in the synaptic cleft might be required for elicitation of cardiovascular depression through dopaminergic receptors. Ozono et al.[35] demonstrated postjunctional D_1-receptors on myocardial sarcolemma of rats, the stimulation of which caused a small but significant increase in cAMP concentration. Several previous experimental studies also indicated no significant role of D_1 receptors in the inotropic effects of dopamine on isolated guinea-pig atria[40].

In contrast to a decrease of MBP and CC after low infused doses of dopamine (1 μg/kg/min), an increase in MBP, HR and CC was observed after high infusion doses of dopamine (12 μg/kg/min). To clarify whether these hypertensive effects of dopamine as well as the chronotropic and inotropic ones are direct actions on the cardiac muscles or indirect ones by releasing noradrenaline from the sympathetic nerve terminals in the cardiac muscles, first the dopamine receptor subtype(s) involved in the cardiovascular effect of dopamine at high doses was investigated. This study demonstrated that iv infusion of dopamine at a rate of 12 μg/kg/min after pre-treatment with D_1-like antagonist (SCH-23390) and D_2-like antagonist (metoclopramide) increased MBP, HR and CC. Thus, D_1 and D_2-like receptors are not important in the vascular and cardiac effects of the higher doses of dopamine. In an attempt to investigate the interaction between dopamine and sympathetic nervous system, 12 μg/kg/min dopamine infusion resulted in an increase in RSNA. In addition, a chemical denervation of the sympathetic nerve terminals was made by a pre-treatment of the animals with reserpine and propranolol. This experiment revealed that dopamine infusion at high rate (12 μg/kg/min) into animals after reserpine caused increase in HR and CC and after propranolol caused increase in MBP when compared with pre-injected dopamine level (control level). These results collectively suggest that vascular and cardiac actions of higher dose of dopamine are mediated by the activation of α and β-adrenoceptors. The arterial blood pressure effect is α-adrenergic dependant, whereas HR and CC was β-adrenergic dependant. These results are in agreement with Olsen (19) who reported that with increasing doses of dopamine (at and above 7.5 μg/kg/min), the renal blood flow was decreasing. Furukawa et al.[41] found that in dogs, improvement in hemodynamics indicated by marked increase in cardiac blood flow, cardiac output and mean arterial blood pressure was observed at higher doses of dopamine (10 and 20 μg/kg/min). Meneton[42] stated that at higher concentrations of dopamine, α- and β-adrenergic receptors are occupied. Jasiñska et al.[43] found that dopamine infusion at 10 μg/min/kg improved myocardial contractility in rabbits. Recently, Wakita[44] observed that administration of dopamine into the perfusate of the isolated rabbit heart at doses of 100 to 1000 μg was found to produce dose-related increases in contractile activities and heart rates in

the normal preparation, and this effect was greatly suppressed in the denervated preparations, suggesting that the primary chronotropic and inotropic effect of dopamine is an indirect one via norepinephrine release of from sympathetic nerve terminals.

It is evident from the forgoing discussion on multiple dopamine receptors that activation and /or blockade of these receptors can lead to pronounced changes in cardiovascular functions. Therefore, an obvious question that can be asked is whether sufficient quantities of endogenous dopamine are available to act on these receptors and thereby play a physiological role in control of cardiovascular function. In the present study, D_1-like receptor antagonist SCH-23390 and D_2-like receptor antagonist metoclopramide were used to investigate the interaction between endogenous dopamine and ABP, HR and CC in normal rabbits. Blockade of either D_1-like receptor by SCH-23390 or D_2-like receptors by metoclopramide alone has no effect on baseline levels of MBP, HR and CC. Furthermore, iv dopamine infusion alone at low rate (1 µg/kg/min) decreased significantly MBP and CC, whereas change in HR wasn't significantly altered. These data suggest that under basal conditions endogenous, dopamine may not alter the basal cardiac and vascular functions. There is no physiological activation of cardiovascular dopaminergic receptors in rabbits. Oliva et al.[45] claimed that microinjection of dopamine into the caudal nucleus tractus solitarii does not affect either the autonomic activity to the cardiovascular system or the autonomic and respiratory responses of chemoreflex activation in awaken rats.

There are two possible sources of endogenous dopamine which can activate these receptors. Circulating dopamine and dopamine containing neurons in close proximity to these receptors. Levels of circulating dopamine have been measured accurately in various animals and humans. The levels of free dopamine in plasma are too low to exert any significant effect. The affinity of dopamine to its receptors is in the nanomolar range. Circulating concentrations of dopamine (picomolar range) are not sufficiently high to activate dopamine receptors, while in dopamine producing tissues concentrations in the high nanomolar to micromolar range can be attained[4]. Circulating dopamine reportedly synthesized in neural and non neural tissues[4].

In conclusion. The results of these experiments indicate that dopamine elicit a biphasic effect on cardiovascular system in normal anesthetized adult male Balady rabbits. At low infusion rate of dopamine (1 µg/kg/min) a hypotensive and negative inotropic effects were observed, whereas at high infusion rates (4 & 12 µg/kg/min) dopamine has hypertensive, positive chronotropic and inotropic effects. The effect of dopamine infusion was apparent immediately (1 min) and gradually with maximal changes seen at 15 min. At low infusion rate (1 µg/kg/min), cardiovascular effect of dopamine

predominantly due to stimulation of dopaminergic receptors (D_1-and D_2-like receptors), but at high infusion rate (12 μg/kg/min), action occurs via stimulation of α- and β-adrenergic receptors. The arterial blood pressure effect is α-adrenergic dependent, whereas HR and CC were β-adrenergic dependent. These results demonstrated also, that D_1- and D_2 like activation decreased MBP and CC. In the present study, at low rate of infusion, MBP, HR and CC were not significantly changed after D_1- and D_2-like receptor blockade, whereas a significant decrease was observed after D_1- and D_2 like activation. These data demonstrate that normal rabbit's endogenous dopamine may not alter the basal cardiovascular functions.

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وظائف الجهاز الدورى والدوبامين: الية العمل فى ذكور الأرانب البلدى المخدرة

ايناس أحمد حامد؛ امتثال محمود مصطفى؛ نشوى على عبد المطلب
قسم الفسيولوجيا، كلية الطب، جامعة أسيوط

تهدف هذه الدراسة الى توضيح الاليات التى يعمل بواسطتهم الدوبامين لتنظيم وظائف الجهاز الدورى. اشتملت هذه الدراسة على ثمانية وأربعون ذكرا بالغا من الأرانب البلدى المخدرة (٤ تجارب، ٨ مجموعات، ٦ ارانب فى المجموعة). التجربة الأولى قيمت تأثير الحقن الوريدى التسريبى للدوبامين (١.٠، ١، ٤، ١٢ ميكروجرام/ كجم/ دقيقة) على ضغط الدم الانبساطى، ضغط الدم الانقباضى، متوسط ضغط الدم، سرعة نبضات القلب، انقباض القلب، ونشاط العصب الكلوى السمبثاوى. التجربة الثانية قيمت تأثير الحقن الوريدى التسريبى للدوبامين على طول عضلة البطين. التجربة الثالثة تؤكد مساهمة مستقبلات الدوبامين الفرعية فى عمل الدوبامين. التجربة الرابعة تقييم اكتناف مستقبلات الادرينين فى عمل الدوبامين. متوسط ضغط الدم، انقباض القلب، سرعة نبضات القلب، نشاط العصب الكلوى السمبثاوى تم تسجيلهم بالفسيوجراف. عند الحقن التسريبى للدوبامين بجرعة منخفضة ، وجد أن ضغط الدم الانبساطى، متوسط ضغط الدم، انقباض القلب، ونشاط العصب الكلوى السمبثاوى قلوا بينما طول عضلة البطين، نسبة (أ: أي) زادوا. عند الحقن التسريبى للدوبامين بجرعة عالية ، وجد أن ضغط الدم الانبساطى، ضغط الدم الانقباضى، متوسط ضغط الدم، سرعة نبضات القلب، انقباض القلب زادوا بينما طول عضلة البطين، ونسبة (أ: أي) قلوا. اثارة مثل المستقبل (د١) قللت متوسط ضغط الدم؛ بينما اثارة مثل المستقبل (د٢) قللت متوسط ضغط الدم؛ انقباض القلب، ونشاط العصب الكلوى السمبثاوى.اقفال مثل مستقبلات (د١،د٢) يقلل هبوط ضغط الدم، بينما يتم الغاء انقباض القلب باقفال مثل المستقبل (د٢). متوسط ضغط الدم؛ سرعة ضربات القلب، وانقباض القلب لم يتغيروا بعد اقفال مثل مستقبلات (د١،د٢) ولكنهم قلوا بعد تنشيط مثل المستقبلات (د١،د٢). الحقن التسريبى للدوبامين بجرعة منخفضة الى الارانب السابق معالجتها باقفال مستقبل الادرينالين الفا (باستخدام الريزربين) أو باقفال مستقبل الادرينالين بيتا (باستخدام البروبرانولول) قلل متوسط ضغط الدم، وانقباض القلب. بينما حقن الدوبامين بجرعة عالية فى الارانب السابق معالجتها باقفال مستقبل الادرينالين الفا أدى الى زيادة ضربات القلب، انقباض عضلة القلب بينما اقفال مستقبل الادرينالين بيتا أدى الى زيادة متوسط ضغط الدم. متوسط ضغط الدم، ضربات القلب، وانقباض القلب لم يتأثروا بعد اقفال مثل المستقبلات (د١، د٢) ولكنهم قلوا بعد اثارة مثل المستقبلات (د١،د٢). من هذه الدرسة نستخلص أن الدوبامين له تأثيرين على الجهاز الدورى. جرعة الدوبامين المنخفضة تعمل بواسطة اثارة مثل مستقبلات (د١، د٢). مع زيادة جرعة الحقن يعمل الدوبامين بواسطة مستقبلات الادرينالين الألفا والبيتا. الدوبامين الذاتى الطبيعى قد لايؤثر على وظائف الجهاز الدورى الاساسية.