

Dopamine and Hypertension

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ABSTRACT

Dopamine, a neurotransmitter precursor of norepinephrine, produces cardiovascular and renal effects including increase of myocardial contractility and cardiac output, without changing the heart rate, active and passive vasodilatation, diuresis and natriuresis. These cardiovascular and renal effects are mediated by the interaction of dopaminergic receptors named D1, D2, D3, D4, D5, D6 y D7; the letters of recent description. Actions are attributed to Dopamine that controls blood pressure through central and peripheral nervous systems and target organs such as kidney and adrenal glands in some types of hypertension. Renal dopaminergic deficiency has been related with the capacity to excrete salt in some forms of hypertension. Although it has been proven that dopamine and its derivatives have antihypertensive actions, research continues and for this reason it is important to clarify some physiological and pharmacological aspects of dopamine, its receptors and the clinical uses that could be important in the management of hypertension.

Key Words: Dopamine, Dopaminergic receptor, Hypertension and Dopaminergic agonist.

INTRODUCTION

With the discovery of new dopamine (DA) receptors and the description of depressor actions of DA on the vascular system, the research on receptors, their interaction and the possible effects on different organs have been intensified. Once demonstrated that the pressor action of high doses of dopamine could be abolished by α -adrenergic blockers (Goldberg LI, Sjoerdsma A. 1959)¹ the presence of specific receptors for dopamine was suspected and thought they could participate in reducing blood pressure and considered that these should be taken into account when treating hypertension. Dopamine and its derivatives have been studied during the last four (4)

decades⁽²⁾, and described its pharmacological and therapeutic aspects that could be of use for clinical application. Furthermore, there are increasing evidences for the use of these compounds in the treatment of hypertension^(3,4). Despite having proved that dopamine and its derivatives have antihypertensive effects, the group as such, still under investigation. The mechanism by which the dopaminergic compounds exert their antihypertensive action could be attributed to the activation of dopaminergic receptors, DA1 postsynaptic or DA2 presynaptic⁽⁴⁾. Up-to-date, the dopaminergic agonist bromocriptine and its derivatives and also fenoldopam and 7-OH-DPAT, represent the typical agonists of DA2, DA1 and DA3 receptors, which are respectively used in the treatment of high blood pressure⁽⁵⁾.

DOPAMINE AND DOPAMINERGIC RECEPTORS

Dopamine (DA) is a catecholamine produced at the terminal end of neurons from its precursor the amino acid tyrosine, by two sequential steps carried out by the enzymes tyrosine hydroxylase and carboxylase for L-aromatic amino acids. At the nerve ending DA travels towards the storage vesicles by action of a transport protein (T) related to the vesicle's membrane⁽⁶⁾, Calcium entry and cellular depolarization take place allowing dopamine entering in contact with dopamine's postsynaptic receptors⁽⁶⁾. There are several different receptor types named D1, D2, D3, D4 y D5⁽⁷⁾; more recent studies report the presence of receptors D6 and D7 which physiological and pharmacological actions similar to those of D1 and D2⁽⁸⁾. These have several common structural features, which are among them are the presence of seven α -helicoidal segments capable of going through the cell membrane. According to their structural and pharmacological properties, the five DA receptors can be classified in two groups⁽⁷⁾, class D1 including receptors D1 and D5 and class D2 integrated by receptors D2, D3 and D4.

DA1 RECEPTOR

The activation of this receptor produces stimulation of the activity of adenylate cyclase with formation of cyclic AMP⁽⁹⁾ and hydrolysis of phosphatidyl-inositol with release of arachidonic acid. These postsynaptic receptors are distributed among the central nervous system (striatum and neocortex) and in the periphery including renal arterioles, mesenteric, hepatic, pulmonary, splenic, coronary, cerebral, etc. and juxtaglomerular system⁽¹⁰⁾. Dopaminergic stimulation to arterioles induces vasodilatation due to the

relaxation of smooth muscle fibers. In the kidney there is increase in blood flow, natriuresis and increased sodium excretion ⁽¹⁰⁾.

DA2 RECEPTOR

Activation of this receptor produces adenylate cyclase inhibition and reduction of cyclic AMP production rising potassium conductance and lowering calcium conductance. This receptor is distributed at the presynaptic end (in the sympathetic nerve endings) ganglia and central nervous system (striatum, dopaminergic neurons of the compact area of the substantia nigra and pituitary gland); it is also found in resistance mesenteric, renal and coronary vessels ⁽¹⁰⁾. Stimulation of dopaminergic DA2 receptor induces reduction of release of norepinephrine at the nerve endings.

Dopaminergic receptors DA3, DA4 and DA5 ⁽¹¹⁾, Ricci et al. 1990^(12,13), are located predominantly in the central nervous system, olfactory bulbs, accumbens nucleus, hypothalamus and brain cortex; however, genetic expression (RNAm) for DA4 was found in a concentration 20 times higher in the cardiovascular system than in the central nervous system, (Tab. 1). Recent studies report location of D3 and D5 in mononuclear circulating cells of human blood ⁽¹⁴⁾.

The actions of DA disappear by the sequential action of the enzymes catechol-O-methyl-transferase (COMT) and mono-amino-oxidase (MAO), by the recovery of this hormone at the nerve ending or by the use of drugs with antagonist effect such SCH23390 capable of blocking D1 receptor and sulpiride and domperidone that block receptor D2 ⁽⁶⁾.

DOPAMINERGIC DRUGS

Selective DA1 agonists:

Fenoldopam, piribedil

Selective DA2 agonists:

Bromocriptine, pergolide, lergotril, lisuride, carmoxirol

Selective DA1 antagonists:

Clozapine, SCH-23390

Selective DA2 antagonists:

Metoclopramide, domperidone, haloperidol, sulpiride

CARDIOVASCULAR EFFECTS

Dopamine acts through the β_1 -adrenergic and dopaminergic DA1 and DA2 receptors. With an intravenous dose of 0.5-3 $\mu\text{g}/\text{Kg}\cdot\text{min}$ blood pressure rises by the activation of dopaminergic receptors⁽¹⁵⁾, and the heart rate rises slightly. At doses somewhat higher, DA exerts positive inotropic effect on myocardium by activation of β_1 adrenergic receptor. Intravenous doses higher than de 3 $\mu\text{g}/\text{Kg}\cdot\text{min}$ activate also the α_1 adrenergic vascular receptors inducing the rise in blood pressure by vasoconstriction. DA usually rises systolic and differential blood pressures without producing important changes in diastolic blood pressure. In patients pretreated with labetalol, when dopamine is given intravenously at a dose of 0.5-3 $\mu\text{g}/\text{Kg}\cdot\text{min}$ it produces reduction in blood pressure without any changes in heart rate (Martin et al. 1993)⁽³⁾. Goldberg et al⁽¹⁵⁾, reported also hypotensive effects in patients with Parkinson's disease and in experiments with animal pretreated with fenoxibenzamine⁽¹⁵⁾.

RENAL EFFECTS

Dopamine induces increase in renal blood flow, natriuresis and rises renal sodium excretion. Induces also vasodilatation of renal arterioles and at the same time inhibits the Na^+/K^+ ATP ase, tubular interchange of Na^+/H^+ and blocks the effects of vasopressin in the collecting tubules^(15,16,17). The presence of DA receptors classes DA1 and DA2 could regulate blood pressure influencing the intermediate range mechanisms of blood pressure control⁽¹⁰⁾, which include modifications in the interaction relaxation stress of vascular structures in the renal arginine-vasopressin system⁽¹⁰⁾.

Dopamine can have an important part in the long-term mechanisms of blood pressure control, promoting the release of water and salts by the kidney and increasing renal blood flow. The capacity for of interaction between DA receptor D1 to inhibit hypertrophy of renal smooth muscle, suggests the importance of this catecholamine in the long-term regulation of blood pressure⁽¹⁰⁾.

Alterations of the kidney's dopaminergic system in three aspects could produce arterial hypertension: 1) Changes in the renal production of dopamine. 2) Changes in the transduction effect of dopamine in the renal

vascular system. 3) Alterations in the transduction effect of dopamine in the renal tubular system. Any alteration of the dopaminergic receptor in the renal tubular system could be compensated with a rise in DA production ⁽¹⁸⁾.

HORMONAL EFFECTS

Dopamine rises the concentration of insulin in the blood by stimulating dopaminergic receptors while metoclopramide blocks this effect ⁽³⁾. Dopaminergic activation by the use of bromocriptine lowers plasmatic concentration of prolactine in patients with hyperprolactinemia ⁽¹⁵⁾. The same occurs in the yuxtaglomerular system when stimulated by a dopaminergic DA1 agonist [Antonipillani et al. 1989] ⁽¹⁹⁾. Dopamine rises plasma renin activity. Dopaminergic receptors are also involved in the release of aldosterone and in the regulation of circulating potassium ⁽²⁰⁾.

RESPIRATORY EFFECTS

Preliminary results show that inhaled dopamine induces bronchial relaxation in patients with asthma. This bronchio-relaxation is dose dependent but was not elicited by intravenous dopamine. The acting mechanism is unknown (Cabezas GA et al. 1999) ⁽²¹⁾.

COLD PRESSOR TEST

Gomez et al. (1.995) ⁽²²⁾ showed that during the cold pressor test (CPT) performance dopaminergic receptors are stimulated. Metoclopramide given intravenously at a dose of (7.5 µg/Kg.min) induces a rise in blood pressure during the CPT; this blood rise is blocked by bromocriptine. This effect is related to gender [Blanco et al. 1996] ⁽²³⁾.

TREADMILL EXERCISE TEST

Recent results from our laboratory show that dopamine is also released during the exercise test in a treadmill ⁽²⁾. Fourteen (14) subjects (normotense and hypertense) were studied with placebo, domperidone and metoclopramide and requested to exercise in a treadmill ⁽²⁴⁾. Our results suggest the presence of an excitatory influence modulating the dopaminergic receptor acting on the sympathetic activity during exercise [Velasco et al. 1995] ⁽²⁾.

CLINICAL APPLICATIONS OF DOPAMINERGIC DRUGS

1. Hypertension
2. Shock
3. Hypertension associated to renal failure
4. Hypertension associated to cardiac failure
5. Cerebrovascular insufficiency
6. Cerebral subarachnoid hemorrhage
7. Asthma
8. Parkinson's disease
9. Hyperprolactinemia
10. Psicosis
11. Reflux esophagitis
12. Irritable colon syndrome
13. Hepatic cirrhosis

CLINICAL USE OF DOPAMINE IN HYPERTENSION

The therapeutic effect of dopamine and its derivatives is secondary to the activation of dopaminergic receptors: 1. Postsynaptic DA1 induces relaxation of smooth muscle and vasodilatation of arterioles in kidney, liver, spleen, mesentery and heart. Secondary to the activation of the baro-receptors appears a slight rise in the heart rate. 2. Presynaptic DA2 induces reduction in the norepinephrine release at the sympathetic endings and reduces sympathetic activity (reduction of the heart rate and activity of the renin-angiotensin system). Kollock et al. (1980)⁽²⁵⁾, studied the effect produced by bromocriptine in patients with essential hypertension and concluded that bromocriptine can reduce blood pressure reducing at the same time plasmatic noradrenaline and renin-angiotensin. Luchsinger et al. (1992)⁽²⁶⁾, compared bromocriptine, a DA2 agonist, and piribedil, a DA1 agonist, in patients with

low degree hypertension and concluded that both drugs can lower blood pressure to the same extent, but through different hemodynamics mechanisms. Recently, Luchsinger et al. (1995)⁽⁴⁾, demonstrated that the hypotensive effect induced by bromocriptine could be blocked by metoclopramide and domperidone, both dopaminergic compounds. Pergolide and lisuride, DA2 agonists, produced antihypertensive effects in rats with normal blood pressure and with hypertension^(27, 28).

Carmoxirol is a new dopaminergic DA2 agonist. At a dose by mouth of 0.5, 1 and 2 mg a day this drug produced reduction of blood pressure in patients with essential hypertension; also, "in vitro" and "in vivo" inhibits platelet aggregation⁽²⁹⁾. They conclude that carmoxirol has antihypertensive effect with potential antithrombotic properties.

Intravenous dopamine at a dose of 0.5-3 µg/Kg.min produces reduction in blood pressure in patients with pretreatment with labetalol α₁ and β adrenergic blocker without producing changes in heart rate⁽³⁾. Also, it was demonstrated a rise in blood insulin. Other dopaminergic compounds are being investigated (propildopamine, butilpropildopamine). Fenoldopam, dopaminergic DA1 agonist, has been used for the treatment of hypertension and during acute hypertensive emergencies. White and Halley (1989)⁽³⁰⁾, concluded that fenoldopam is an antihypertensive compound that concomitantly induces diuresis and natriuresis. This pharmacological effect is secondary to the activation of DA1 receptor and blocked by SCH-23390, a dopaminergic blocker.

Table 1: Characteristics and Distribution of Receptors for Dopamine

Receptor name	Class D1		Class D2				
	D1	D5	D2	D3	D4	D6	D7
Number of Aminoacids	446	477	443	400	387	446-443	?
More important Sites of action	Striatum Neocortex Kidneys And mesenteric arterioles	Limbic structures, Hypothalamus and Lymphocytes	Striatum, Resistance vessels in Kidneys and mesentery Coronary vessels	CNS Monocuclear cells	CNS Cardiovascular system	Similar to D1 and D2	Similar to D1 and D2

REFERENCES

1. Goldberg LI, Sjoerdsma A. Effects of several monoamine oxidase inhibitors on the cardiovascular actions of naturally occurring amines in the dog. *J Pharmacol Exp Ther* 1959; 127:212-218.
2. Velasco M, Corujo M, Valery J, Luchsinger A, Morales E. Dopaminergic influence on the cardiovascular response to exercise in normotensive and hypertensive subjects. *Int. J. Clin Pharmacol Ther.* 1995; 33:504-508
3. Martin G, Forte P, Luchsinger A, Mendoza F, Urbina A, Hernandez PO, Romero E, Velasco M. Effect of intravenous dopamine on blood pressure and plasma insulin in hypertensive patients. *Europ. J. Clin. Pharmacol* 1993; 45: 503-505
4. Luchsinger A, Grilli M, Forte P, Morales E, Velasco M. Metoclopramide blocks bromocriptine induced antihypertensive effect in hypertensive patients. *Int. J. Clin. Pharmacol. Therap* 1995; 33: 509-512
5. Romero E, Velasco M, Luchsinger A. Dopamina e hipertensión arterial: Implicaciones terapéuticas del uso de agonistas y antagonistas. *Arch. Venez. Farmacol. Terap* 1993; 12: 158-163
6. Standaert DG, Young AB. Tratamiento de los trastornos degenerativos del sistema nervioso central En Goodman y Gilman editores, las Bases Farmacológicas de la Terapéutica 1996; Vol. I, 9na ed. México: McGraw-Hill-Interamericana; p. 539-556.
7. Jarvie, KR and Caron MG. Heterogeneity of dopamine receptors. *Adv in neurolo*; 1993,60:325-333.
8. Murphy MB: Role of dopamine in the pathogenesis and treatment of hypertension. *J.Hum Hypertens* 2000; 14(51): 47-50.
9. Kebabian JW, Kalne DB. Multiple receptors of dopamine. *Nature* 1979; 277: 93-96.
10. Jose PA; Eisner GM; Felder RA. Role of dopamine in the pathogenesis of hypertension. *Clin Exp Pharmacol Physiol* 1999; Supl 26: S13.

11. Misalle C, Costelli L, Memo M, Caruba O, Spano PF. Identification and characterization of postsynaptic D1 and D2 dopamine receptors in cardiovascular system. *J. Cardiovasc. Pharmacol* 1988; 11: 643-650
12. Ricci A, Amenta F. Auto radiographic localization of dopamine DA2 receptor sites in rat mesenteric vascular tree. *J. Pharmacol. Exp. Therap* 1990; 254: 750-755
13. Ricci A, Amenta F. Dopamine D5 receptors in human peripheral blood lymphocytes: a radioligand binding study. *J. Neuroimmunol* 1994; 53: 1-7.
14. Ricci A, Bronzetti E, Mulatero P, Schema M, Veglio F, Amenta F. Dopamine D3 receptor in peripheral mononuclear cells of essential hypertensives. *Hypertension* 1.997; 30: 1.566-71.
15. Goldberg LI. Cardiovascular and renal actions of dopamine. Potential clinical applications. *Pharmacol Rev.* 1972 ; 24: 1-29.
- 16 Andrejak M, Hary L. Enhanced dopamine renal responsiveness in patients with hypertension. *Clin. Pharmacol. Therap* 1986; 40:610-614
- 17 Ohbu K, Kaskel FJ, Kinoshita S, Felder RA. Dopamine 1 receptors in the proximal convoluted tubule of Dahl rats defective coupling to adenylate cyclase. *Amer J.Physiol* 1995; 268: R231-R235.
- 18 Kuchel O. Peripheral dopamine in hypertension and associated conditions. *J.Hum Hypertens* 1999; 13: 605-615
- 19 Antonipillani I, Broes MI, Larg D. Evidence that specific dopamine-1 receptor activation is involved in dopamine-induced renin release. *Hypertension* 1989; 13: 463-468
20. Barret J, Wright F, Taylor R, Proakis G. Involvement of dopamine receptor subtypes in dopaminergic modulation aldosterone secretion in rats. *Life Sic.* 1987; 40: 1499-1506
21. Cabezas GA, Lezama Y, Vidal A. and Velasco M. Inhaled dopamine induces bronchodilatation in patients with bronchial asthma. *Int.J.Clin.Pharmac and Therap.*1.999; 37:510-513.

22. Gómez J, Forte P, Luchsinger A, Romero E, Arreaza R, Hernández O, and Velasco M. Dopaminergic influence on the cardiovascular and hormonal responses to cold stress in hypertensive patients. *Amer. J. Therap.* 1995; 2: 175-179
23. Blanco M, Alemán A, Jelambi I, Hurtado N, Franco T, Bello N, Velasco M. Gender-related cardiovascular responses to cold pressor test in normotensive subjects. *Amer. J. Therap.* 1996; 3:419-422
24. Blanco M, Hurtado N, Jelambi I, Pérez G, Carrillo M, Gómez J, Bravo C, Gómez H, Velasco M. Dopaminergic influence on cardiovascular responses to exercise stress in hypertensive patients. *Amer. J. Therap* 1997; 4:34-38.
25. Kollock R, Kobayashi K, Dequattro V. Dopaminergic control of sympathetic tone and blood pressure: evidence in primary hypertension. *Hypertension* 1980; 2: 390-394
26. Luchsinger A, Velasco M, Urbina A, Morillo J, Romero E, Álvarez R, Hernández PO. Comparative effects of dopamine agonist on cardiovascular, renal and renin-angiotensin systems in hypertensive patients. *J. Clin. Pharmacol.* 1992; 2: 390-394
27. Sued AF. Reduction in blood pressure in normal and spontaneously hypertensive rats by lergotriple mesylate. *J. Pharm. Pharmacol.* 1979; 31:814-817
28. Yen T, Stamm NB, Clemens JM. Pergolide, a potent dopaminergic antihypertensive. *Life Sci.* 1979; 25: 814-817.
29. Kirsten R, Breidert M, Sparwasser K, Ochs JC, Hesse K, Nelson K. Carmoxirole inhibits platelet aggregation in vitro and ex in vivo. *Int. J. Clin. Pharmacol. Therap.* 1995; 2:76-80
30. White WB, Halley S. Comparative renal effects of intravenous administration of fenoldopam mesylate with severe hypertension. *Circulation* 1989; 149: 870-874