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Cardiovascular Actions of the Dopamine Receptor Agonist Z1046 in Swine

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Summary. **Dopamine receptor agonists can be useful in the treatment of hypertension or heart failure. Consequently, the present study investigated the hemodynamic profile of the novel dopamine D_1/D_2 receptor agonist Z1046 in open-chest, pentobarbital-anesthetized swine. Z1046 was administered in a dose of 10 μg/kg (n = 9) or 100 μg/kg (n = 8), which was injected over 1 minute; hemodynamic responses were studied for 90 minutes after administration. Both doses of Z1046 produced sustained decreases in mean aortic blood pressure (15–20%). The hypotension produced by the lower dose was principally due to a decrease in cardiac output, as the trend toward a lower systemic vascular resistance failed to reach levels of statistical significance. Conversely, the decrease in mean arterial blood pressure produced by the higher dose of Z1046 was mainly due to a decrease in systemic vascular resistance (up to 17%), as the trend toward a decrease in cardiac output at 60 and 90 minutes after administration was not different from the changes in the saline-treated group. Heart rate decreased slightly with both doses of Z1046. Z1046 decreased left ventricular myocardial blood flow (up to 28 ± 9%, $p < 0.05$) in parallel with the decrease in myocardial oxygen consumption (up to 24 ± 7%, $p < 0.05$), with no change in the transmural distribution of myocardial blood. Z1046 in a dose of 10 μg/kg did not produce significant vasodilation of regional vascular beds, but in a dose of 100 μg/kg produced vasodilator responses in the small intestine (34 ± 2% decrease in vascular resistance), spleen (43 ± 7%), and kidneys (22 ± 3% all $p < 0.05$ vs. baseline). In conclusion, Z1046 produced systemic hypotension with negligible reflex activation of sympathetic tone.**

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Key Words. **blood pressure, coronary blood flow, dopamine receptors, hemodynamics, myocardial oxygen consumption, regional blood flows, radioactive microspheres, swine, Z1046**

In the early 1970s it became clear that dopamine produced vasodilation by a mechanism different from beta-adrenoceptor activation [1]. Since that time, two functionally separate dopamine (D) receptor subtypes have become recognized. D_1-like receptors are located on the smooth muscle of arterial blood vessels that supply the kidney, intestine, coronary, and cerebral vessels, although the presence of D_1-like receptors on the latter two vessel types may be species dependent [2–5]. Stimulation of these D_1-like receptors produces vasodilation. D_1-like receptors are also located on renal tubular cells (producing inhibition of Na^+ reabsorption) and juxtaglomerular cells (producing increased renin release), where they promote natriuresis and diuresis. D_2-like receptors are situated on sympathetic nerve endings (producing inhibition of norepinephrine release), in the zona glomerulosa cells of the adrenal cortex (producing inhibition of aldosterone release), and in sympathetic ganglia (producing inhibition of ganglionic transmission). Thus, while D_1-like receptors produce direct vasodilation and diuresis, D_2-like receptors modulate sympathetic nerve activity. Experimental and clinical evidence is accumulating that dopamine receptor agonists are useful in the treatment of hypertension or congestive heart failure [1,5–9]. In the present study we investigated the cardiovascular actions of the novel mixed D_1-like/D_2-like agonist Z1046 (Figure 1) [10–12]. Experiments were performed in the same open-chest, anesthetized swine model in which we performed earlier studies on dopamine and the selective D_1-like receptor agonist, fenoldopam [5].

Materials and Methods

Studies were performed in accordance with the Guiding Principles in the Care and Use of Laboratory Animals, as approved by the Council of the American Physiological Society, and with prior approval of the Animal Care Committee of Erasmus University, Rotterdam.

Surgical instrumentation

Cross-bred Landrace × Yorkshire swines (HVC, Hedel, The Netherlands) of either sex (n = 21, 27 ± 2

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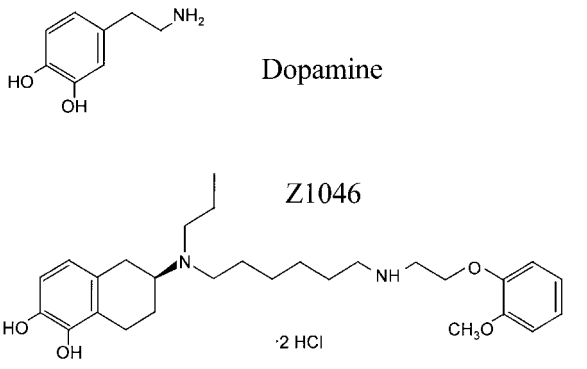

Fig. 1. *Chemical structure of dopamine and Z1046 ((S)-6-[[6[(2-(2-methoxyphenoxy)ethyl)amino] hexyl]propylamino]-5,6,7,8-tetrahydro-1,2-naphtalenediol dihydrochloride).*

kg) were sedated with an intramuscular injection of ketamine (20 mg/kg) and were anesthetized with sodium pentobarbitone (20 mg/kg; Apharma, Arnhem, The Netherlands) administered via a dorsal ear vein. Animals were intubated and connected to a ventilator for intermittent positive-pressure ventilation with a mixture of oxygen and nitrogen (1:2). Respiratory rate and tidal volume were adjusted to keep arterial blood gases (ABL505, Radiometer, Copenhagen, Denmark) within the physiological range. In the superior caval vein a 7 French (r) catheter was placed for infusion of 5–10 mg/kg/h sodium pentobarbitone to maintain a constant depth of anaesthesia. Catherers were also placed in the superior vena cava for administration of saline or Z1046. A 7 r Sensodyn micromanometer-tipped catheter (B. Braun Medical B.V., Oss, The Netherlands), inserted via the left carotid artery, was used to measure left ventricular pressure and its first derivative (LVdP/dt). The femoral arteries were cannulated with 8 r catheters, which were advanced into the descending thoracic aorta for measurement of central aortic blood pressure, for withdrawal of blood samples for blood gas analysis, and for withdrawal of reference samples to calibrate regional blood flows measured with the radioactive microsphere technique. Rectal temperature was monitored throughout the experiment and was maintained between 37°C and 38°C with external heating pads and coverage of the animal with blankets.

After intravenous administration of 4 mg pancuronium bromide (Organon Teknika, Boxtel, The Netherlands), a midline thoracotomy was performed, and the heart was suspended in a pericardial cradle. The left mammary vessels were ligated and the second left rib removed for ease of further instrumentation. The adventitia surrounding the aorta was dissected free, and an electromagnetic flow probe (Skalar, Delft, The Netherlands) was positioned around the artery for measurement of ascending aortic blood flow (AoF). In 17 animals, the cardiac vein accompanying the left anterior descending (LAD) coronary artery was cannulated for withdrawal of blood samples for determination of oxygen content. Myocardial oxygen consumption (MVO_2) was calculated as the product of myocardial blood flow measured with radioactive microspheres (see later) and the difference in the oxygen content of the arterial and coronary venous blood.

Regional myocardial contractile function

Regional myocardial segment shortening was measured by sonomicrometry (Triton Technology, San Diego, CA, USA) in 15 animals using one pair of ultrasonic crystals implanted approximately 10 mm apart in the midmyocardial layer of the left ventricle. From the tracings, segment shortening (SS) was computed as

$$SS\ (\%) = 100 \times (EDL - ESL)/EDL,$$

where EDL and ESL are the segment length at end diastole (onset of positive dP/dt) and end systole (20 ms before the peak negative dP/dt), respectively.

Regional blood flow

To determine regional blood flows, the left atrial appendage of 17 animals was cannulated for injection of a batch of 1–2 $\times$ 10^6 carbonized plastic microspheres (15 $\pm$ 1 Mm [SD] in diameter) labeled with either ^{95}Nb, ^{103}Ru, ^{113}Sn, or ^{141}Ce. Starting 15 s before the injection of microspheres, blood was withdrawn from the abdominal aorta at a rate of 10 ml/min until 60 s after completion of the injection of microspheres. After the animals were killed with an overdose of sodium pentobarbitone, various organs (lungs, adrenals, liver, spleen, small intestine, brain, and kidneys) and tissues (abdominal skin, various skeletal muscle groups) were excised, weighed, and put into vials. The heart was divided into the atria and right and left ventricle, and fixed with formaldehyde (3.7% v/v). Two days later, approximately 10 g of myocardium of the left ventricular free wall was divided into three layers of equal thickness: the subepicardium, mesocardium, and subendocardium. The radioactivity of the tissues and blood samples was counted for 5 minutes in a gamma-scintillation counter (Packard, Minaxi gamma) equipped with a multichannel pulse height analyzer (Conrac) using suitable energy windows for discriminating the different isotopes. The amount of blood flow to the various tissues (Q_{tis}) was calculated as:

$$Q_{tis}(ml/min) = (i_{tis}/I_{art}) \times Q_{art},$$

where I_{tis} and I_{art} are the radioactivity (cpm) for each isotope in a particular tissue and in the arterial blood sample, respectively, and Q_{art} is the rate of withdrawal of the blood sample. The resistance of a particular tissue was calculated as the ratio between the mean aortic blood pressure and Q_{tis}. The full details of the procedures and calculation of the flow data using this technique were reported earlier [13,14].

Experimental protocols

Following a 30-minute stabilization period, measurements of systemic and coronary hemodynamic variables and regional myocardial segment length were made. Blood samples were withdrawn from the aorta and coronary vein, and microspheres were injected for determination of regional blood flows. Then, animals received either 10 ml saline (n = 4) or Z1046 at a dose of 10 μg/kg (n = 9), or 100 μg/kg (n = 8), dissolved in 10 ml of saline and injected intravenously over 2 minutes. All hemodynamic and contractile function measurements were repeated 5, 15, 30, 60, and 90 minutes after the injection of saline or Z1046. Microsphere injections were repeated at 5, 30, and 90 minutes following saline or drug administration.

Data analysis

Intragroup comparison was performed using one-way analysis of variance for repeated measures. When a significant effect was observed, posthoc testing was done using the paired t-test. Changes from baseline produced by Z1046 were compared with the changes from baseline in the saline-treated control group using two-way analysis of variance for repeated measures. A p value of a ≤ 0.05 was considered statistically significant (two tailed). All data are presented as the mean ± SEM.

Drugs

Z1046 ((S)-6-[[6[[2-(2-methoxyphenoxy)ethyl]amino] hexyl]propylamino]-5,6,7,8-tetrahydro-1,2-naphtalenedi ol dihydrochloride; courtesy of Dr. F. Marchini, Zambon Group, Italy) was dissolved in warm saline. Fresh drug solutions were prepared on the day of each experiment.

Results

Systemic hemodynamics

Table 1 shows that there were no changes in any of the systemic hemodynamics variables of the saline-treated control animals during the 90-minute post–saline injection observation period, confirming earlier studies in which we have also shown good stability of the open-chest swine preparation over comparable time periods [5,16]. Intravenous administration of Z1046 in a dose of either 10 or 100 μg/kg produced significant decreases (15–20%) in the mean arterial blood pressure within 15 minutes following injection that were sustained during the remainder of the 90-minute observation period. The hypotension produced by the lower dose was similar to the decrease in cardiac output, implying that systemic vascular resistance (mean aortic pressure/cardiac output) was not altered (p = NS vs. baseline; p = NS vs. change in saline group). With the higher dose, cardiac output remained essentially unchanged, although there was a trend toward a decrease at 60 and 90 minutes after administration (up to 10%; $p < 0.05$ vs. baseline; p = NS vs. changes in saline group). Consequently, the decrease in mean arterial blood pressure produced by the higher dose of Z1046 was principally due to a decrease in systemic vascular resistance (up to 17%). Heart rate decreased with both doses of Z1046, although only with the lower dose was significance reached. Stroke volume was not affected by the low dose, but increased slightly and transiently after administration of the high dose. $LVdP/dt_{max}$ decreased with both doses, but this was likely due to the decrease in diastolic arterial blood pressure (DAP) because $LVdP/dt_{max}$/DAP was not altered by either dose of Z1046.

There were no changes in regional myocardial segment length at end-diastole or end-systole, nor in fractional segment shortening in the saline-treated control group during the 90-minute observation period. End-diastolic and end-systolic segment lengths and, consequently, systolic segment shortening, were not affected by Z1046 in either dose.

Myocardial blood flow and oxygen consumption

Table 2 shows that in the saline-treated control group there were no changes in myocardial blood flow and myocardial oxygen consumption during the 90-minute observation period. Both doses of Z1046 produced a small decrease in myocardial blood flow, parallel to the decrease in the rate-pressure product (heart rate times left ventricular systolic pressure). Myocardial oxygen extraction (i.e., the difference between the arterial and coronary venous oxygen contents expressed as a percent of the arterial oxygen content) increased only slightly following administration of Z1046, so that myocardial oxygen consumption decreased with both doses of Z1046.

Table 2 also shows that there were no changes in the transmural distribution of myocardial blood in the saline-treated control group. The Z1046-induced decrease in myocardial perfusion was similar in the inner and outer layer of the left ventricular free wall, so that the endocardial/epicardial blood flow ratio remained unchanged. Myocardial blood flow decreased parallel to the decrease in blood pressure, from which it follows that computed myocardial vascular resistance remained unchanged.

Regional tissue and organ blood flows and vascular resistances

Saline had no effect on any of the organ blood flows (Table 3) or regional vascular resistances (Table 4), which agrees with earlier findings from our laboratory [16]. Z1046 produced a dose-dependent decrease in liver blood flow (50 ± 4%, $p < 0.05$, after the high dose), which exceeded the decrease in blood pressure so that vascular resistance increased. The low dose of Z1046 did not produce significant vasodilation of the regional vascular beds. In contrast, the high dose of Z1046 produced vasodilator responses in the small intestine (34

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Table 2. *Myocardial blood flow and myocardial oxygen consumption responses to intravenous bolus injections of the dopamine receptor agonist Z1046 in open-chest anesthetized swine*

				Minutes after administration		
	Group	n	Baseline	5	30	90
Myocardial blood flow	Saline	4	135 ± 17	128 ± 15	129 ± 19	129 ± 25
(ml/min/100g)	Z1046 10 μg/kg	6	152 ± 8	120 ± 16	109 ± 12[a,b]	111 ± 10[a]
	Z1046 100 μg/kg	7	119 ± 10	99 ± 10[a,b]	97 ± 9[a]	93 ± 6[a]
Endo/epi	Saline	4	1.05 ± 0.22	1.05 ± 0.22	1.08 ± 0.22	1.05 ± 0.22
	Z1046 10 μg/kg	6	1.04 ± 0.05	1.07 ± 0.08	1.10 ± 0.08	1.16 ± 0.07
	Z1046 100 μg/kg	7	1.20 ± 0.08	1.16 ± 0.15	1.31 ± 0.12	1.24 ± 0.07
Myocardial vascular	Saline	4	0.64 ± 0.09	0.64 ± 0.07	0.67 ± 0.13	0.69 ± 0.13
Resistance	Z1046 10 μg/kg	6	0.55 ± 0.04	0.66 ± 0.06	0.68 ± 0.05	0.66 ± 0.02
[mmHg/(ml/min/100 g)]	Z1046 100 μg/kg	7	0.71 ± 0.05	0.77 ± 0.05	0.72 ± 0.02	0.78 ± 0.02
Arterial O_2 sat (%)	Saline	4	93.8 ± 1.3	94.4 ± 1.0	93.8 ± 1.5	92.5 ± 1.6
	Z1046 10 μg/kg	6	92.8 ± 0.9	94.7 ± 0.9	93.6 ± 0.6	93.4 ± 0.7
	Z1046 100 μg/kg	7	97.7 ± 0.6	97.9 ± 0.6	97.7 ± 0.6	97.4 ± 0.6
Coronary venous O_2 sat (%)	Saline	4	20.9 ± 3.2	23.5 ± 3.9	21.9 ± 2.7	20.7 ± 2.7
	Z1046 10 μg/kg	6	26.3 ± 1.3	24.0 ± 1.6	22.9 ± 2.3	21.4 ± 2.6[a,b]
	Z1046 100 μg/kg	7	30.6 ± 1.9	23.6 ± 1.2[a,b]	26.5 ± 2.3[a,b]	26.1 ± 1.9[a,b]
O_2 extraction (%)	Saline	4	77 ± 4	75 ± 4	76 ± 3	77 ± 3
	Z1046 10 μg/kg	6	69 ± 1	71 ± 1	73 ± 3	74 ± 4
	Z1046 100 μg/kg	7	69 ± 2	73 ± 2[a,b]	73 ± 2[a]	73 ± 2[a]
Myocardial O_2 consumption	Saline	4	537 ± 71	492 ± 51	498 ± 70	500 ± 104
(Mmol/min/100 g)	Z1046 10 μg/kg	6	496 ± 37	408 ± 61	374 ± 37[a]	382 ± 33[a]
	Z1046 100 μg/kg	7	432 ± 22	373 ± 19[a,b]	371 ± 35[a]	365 ± 37[a]

Data are mean ± SEM;
[a]$p < 0.05$ vs. corresponding baseline.
[b]$p < 0.05$ vs. saline-induced change from baseline.
endo/epi = subendocardial to subepicardial blood flow ratio; O_2-sat = oxygen saturation.

± 2% decrease in vascular resistance), spleen (43 ± 7%), and kidneys (22 ± 3%; all $p < 0.05$). The vasodilation in the spleen was large enough to overcome the decrease in blood pressure and to result in an increase in blood flow ($p < 0.05$ vs. saline-induced change); blood flow to the small intestine and kidneys was maintained. Neither dose of Z1046 produced a significant change in vascular resistance in the brain, adrenals, skin, or skeletal muscle.

Discussion

Systemic hemodynamics

The open-chest pentobarbital anesthetized swine preparation that was used in the present study confirmed previous observations of good hemodynamic and myocardial functional stability [5,16], so that the responses obtained in the two Z1046 treatment groups (low-dose and high-dose) can be ascribed to the compound. At the low dose (10 μg/kg) Z1046 produced a 15–20% decrease in cardiac output, which resulted in a similar decrease in the mean aortic pressure, because the trend toward a lower systemic vascular resistance failed to reach levels of statistical significance. The decrease in cardiac output was due to a decrease in heart rate, because stroke volume did not change. An unchanged stroke volume (and segment shortening) in the face of a decrease in afterload could indicate a negative inotropic effect of Z1046. This appears to be supported by the decrease in $LVdP/dt_{max}$.

However, interpretation of changes in $LVdP/dt_{max}$ as changes in contractility in the face of changes in aortic blood pressure is complicated by the dependence of $LVdP/dt_{max}$ on diastolic aortic pressure (DAP). Thus, no significant changes in $LVdP/dt_{max}$/DAP were observed, suggesting that the Z1046-induced decrease in $LVdP/dt_{max}$ was primarily due to the decrease in DAP. The bradycardia produced by Z1046 is in agreement with inhibition of norepinephrine release from the sympathetic nerve endings produced by presynaptic D_2-like receptor stimulation, while the absence of vasodilation (particularly in the renal and mesenteric bed) suggests negligible D_1-like receptor stimulation with this dose [1]. In contrast, Z1046 at a dose of 100 μg/kg produced a similar decrease in mean aortic pressure, but this was principally due to a decrease in systemic vascular resistance as the trend toward a decrease in cardiac output at 60 and 90 minutes after administration was not different from the time-related changes in the saline-treated group.

Myocardial oxygen consumption decreased by 15% with this dose. The minimal effect of the high dose of

Table 3. *Regional blood flow responses to intravenous bolus injections of the dopamine receptor agonist Z1046 in open-chest anesthetized swine.*

				Minutes after administration		
	Group	n	Baseline	5	30	90
Brain	Saline	4	28 ± 3	26 ± 2	27 ± 3	27 ± 2
	Z1046,10 μg/kg	6	32 ± 2	31 ± 3	31 ± 3	31 ± 2
	Z1046,100 μg/kg	7	36 ± 4	32 ± 3	31 ± 2	31 ± 2
Kidneys	Saline	4	241 ± 36	232 ± 37	239 ± 44	255 ± 47
	Z1046,10 μg/kg	6	258 ± 23	271 ± 22	253 ± 22	257 ± 22
	Z1046,100 μg/kg	7	268 ± 19	303 ± 18	280 ± 17	288 ± 17
Small intestine	Saline	4	39 ± 8	43 ± 10	40 ± 8	43 ± 5
	Z1046,10 μg/kg	6	41 ± 4	41 ± 4	40 ± 4	38 ± 3
	Z1046,100 μg/kg	7	40 ± 4	53 ± 4[c]	39 ± 3	41 ± 4
Adrenals	Saline	4	102 ± 19	101 ± 22	109 ± 21	135 ± 26
	Z1046,10 μg/kg	6	98 ± 15	94 ± 14	93 ± 15	106 ± 8
	Z1046,100 μg/kg	7	143 ± 36	127 ± 16	116 ± 13	116 ± 11
Liver	Saline	4	46 ± 8	40 ± 7	49 ± 1	55 ± 8
	Z1046,10 μg/kg	6	54 ± 13	41 ± 9	39 ± 9	45 ± 12
	Z1046,100 μg/kg	7	70 ± 8	35 ± 5[a,b]	58 ± 8[a]	50 ± 6[a]
Spleen	Saline	4	153 ± 11	148 ± 9	145 ± 12	155 ± 8
	Z1046,10 μg/kg	6	170 ± 25	168 ± 30	153 ± 25	164 ± 26
	Z1046,100 μg/kg	7	131 ± 20	206 ± 21[c,b]	141 ± 15	120 ± 15
Skeletal muscle	Saline	4	4.9 ± 0.7	4.7 ± 0.7	4.4 ± 0.7	4.3 ± 0.8
	Z1046,10 μg/kg	6	8.3 ± 1.7	5.6 ± 0.8	5.0 ± 0.6	4.8 ± 0.5
	Z1046,100 μg/kg	7	7.0 ± 1.3	5.8 ± 1.1	5.1 ± 0.5	4.0 ± 0.2
Skin	Saline	4	1.70 ± 0.33	1.23 ± 0.23	1.19 ± 0.10	1.09 ± 0.07
	Z1046,10 μg/kg	6	2.09 ± 0.46	2.81 ± 1.06	2.09 ± 0.55	1.91 ± 0.21
	Z1046,100 μg/kg	7	2.86 ± 1.20	1.64 ± 0.18	1.84 ± 0.61	1.65 ± 0.28

Date are presented as mean ± SEM.
[a]$p < 0.05$ vs. corresponding baseline.
[b]$p < 0.05$ vs. saline-induced change from baseline.
Blood flows are presented in ml/min/100 g.

Z1046 on cardiac output was somewhat surprising. If the low dose produced a decrease in cardiac output via D_2-like receptor–mediated inhibition of sympathetic activity to the heart (which is suggested by the decrease in heart rate and $LVdP/dt_{max}$), it would be expected that a higher dose would produce an even greater D_2-like mediated decrease in heart rate and cardiac output. It is possible that the high dose produced a direct stimulation of beta-adrenoceptors, which antagonized the D_2-like receptor–mediated effects on the heart. However, in view of observations that Z1046 is devoid of significant beta-adrenoceptor agonistic properties in guinea-pig atrium and trachea [11], this would seem an unlikely explanation.

Alternatively, it is possible that the peripheral vasodilation produced by the high dose resulted in reflex-mediated activation of the sympathetic nervous system and withdrawal of vagal activity, thereby partially counteracting the direct effects of D_2-like receptor stimulation on sympathetic activity. This is supported by the observation that the higher dose resulted in smaller decreases in heart rate compared with the low dose and that a small increase in stroke volume occurred 5 minutes after its administration. Nonetheless, even with this dose we failed to observe reflex-mediated *increases* in heart rate and $LVdP/dt_{max}$, which contrasts with previous observations with other vasodilators, such as the dihydropyridine calcium antagonist nisoldipine and the K^+_{ATP} channel opener bimakalim, in the same experimental model [15,16].

Regional vascular resistances

The systemic vasodilation produced by 1046 was located primarily in the kidneys, small intestine, and spleen. Vasodilation in the kidneys and small intestine was likely to be the result of stimulation of D_1-like receptors, which are abundant in these vascular beds. In support of this hypothesis, we have previously observed in the same swine model that dopamine (in the absence or presence of nonselective alpha- and beta-adrenergic receptor blockade; Figure 2) or the selective D_1-like receptor agonist fenoldopam produced vasodilation in these beds [5]. On the other hand, the absence of significant cerebral vasodilation, which we *did* observe previously when we infused fenoldopam or dopamine in the presence of adrenergic receptor blockade, suggests that the vasodilation produced by the

Table 4. *Regional vascular resistance responses to intravenous bolus injections of the dopamine receptor agonist Z1046 in open-chest anesthetized swine*

				Minutes after administration		
	Group	n	Baseline	5	30	90
Brain	Saline	4	3.02 ± 0.28	3.04 ± 0.16	2.99 ± 0.30	2.98 ± 0.16
	Z1046,10 μg/kg	6	2.70 ± 0.29	2.51 ± 0.31	2.38 ± 0.21	2.36 ± 0.22
	Z1046,100 μg/kg	7	2.62 ± 0.34	2.55 ± 0.25	2.35 ± 0.21	2.31 ± 0.16
Kidneys	Saline	4	0.36 ± 0.05	0.37 ± 0.05	0.37 ± 0.07	0.35 ± 0.06
	Z1046,10 μg/kg	6	0.35 ± 0.05	0.30 ± 0.05	0.30 ± 0.04	0.30 ± 0.05
	Z1046,100 μg/kg	7	0.34 ± 0.03	0.26 ± 0.02[a,b]	0.26 ± 0.02[a,b]	0.25 ± 0.02[a,b]
Small intestine	Saline	4	2.26 ± 0.34	2.04 ± 0.30	2.22 ± 0.40	1.93 ± 0.25
	Z1046,10 μg/kg	6	2.15 ± 0.29	1.92 ± 0.26	1.87 ± 0.20	1.95 ± 0.17
	Z1046,100 μg/kg	7	2.29 ± 0.24	1.49 ± 0.12[a,b]	1.90 ± 0.17[a]	1.79 ± 0.17[a]
Adrenals	Saline	4	0.89 ± 0.16	0.86 ± 0.13	0.81 ± 0.15	0.64 ± 0.08
	Z1046,10 μg/kg	6	0.92 ± 0.12	0.86 ± 0.11	0.85 ± 0.11	0.70 ± 0.06
	Z1046,100 μg/kg	7	0.82 ± 0.16	0.67 ± 0.08	0.66 ± 0.08	0.64 ± 0.06
Liver	Saline	4	2.03 ± 0.54	2.24 ± 0.52	1.60 ± 0.05	1.51 ± 0.14
	Z1046,10 μg/kg	6	2.53 ± 0.83	4.31 ± 2.55	3.00 ± 1.08	2.39 ± 0.68
	Z1046,100 μg/kg	7	1.35 ± 0.17	2.49 ± 0.40[a,b]	1.41 ± 0.68	1.56 ± 0.24
Spleen	Saline	4	0.54 ± 0.04	0.54 ± 0.05	0.55 ± 0.04	0.52 ± 0.05
	Z1046,10 μg/kg	6	0.54 ± 0.08	0.47 ± 0.04	0.50 ± 0.05	0.48 ± 0.05
	Z1046,100 μg/kg	7	0.75 ± 0.1	0.40 ± 0.05[a,b]	0.54 ± 0.06	0.64 ± 0.08
Skeletal muscle	Saline	4	17.4 ± 2.2	17.8 ± 2.5	19.0 ± 2.3	20.3 ± 3.1
	Z1046,10 μg/kg	6	13.2 ± 2.9	14.3 ± 1.9	15.7 ± 2.5	16.0 ± 2.2
	Z1046,100 μg/kg	7	14.5 ± 2.1	15.5 ± 2.4	14.6 ± 1.2	18 ± 0.7
Skin	Saline	4	53 ± 9	69 ± 9	67 ± 6	74 ± 2
	Z1046,10 μg/kg	6	47 ± 18	43 ± 18	41 ± 15	34 ± 7
	Z1046,100 μg/kg	7	52 ± 10	50 ± 6	35 ± 6	49 ± 7

Data presented as mean ± SEM.

[a]$p < 0.05$ vs. corresponding baseline.

[b]$p < 0.05$ vs. saline-induced change from baseline.

Vascular resistances are presented in mmHg/(ml/min/100 g).

high dose of Z1046 occurred, at least in part, via another mechanism. Recent investigations revealed that there is more than one D_1-like receptor subtype (D_{1a} and D_{1b} receptors) [17]. It is possible that Z1046 has little affinity for the cerebral D_1-like receptor subtype but does stimulate the mesenteric and renal D_1-like receptor subtype. Involvement of D_1-like receptors in the renal vasodilation produced by Z1046 is supported by data obtained in anesthetized dogs [10]. Thus pretreatment with the selective D_1-like receptor antagonist SCH23390 abolished the renal vasodilation produced by Z1046 administered at a dose of 30 μg/kg, intravenously [10]. The vasodilation in the porcine spleen may be due to stimulation of presynaptic D_2-like receptors. Thus, we previously observed that nonselective alpha- and beta-adrenergic receptor blockade abolished the vasodilator response to dopamine in the spleen, whereas the vasodilation in the kidneys and small intestine persisted, suggesting that the vasodilator response to Z1046 in the spleen could be due to D_2-like mediated withdrawal of alpha-adrenergic tone. It is possible that the splenic D_2-like vasodilation is species specific for swine because vasodilation produced by Z1046 in the isolated rabbit splenic artery is antagonized by the D_1-like receptor antagonist SCH23390.

In anesthetized dogs, Z1046 (30 μg/kg, intravenous) was reported to produce a 47% decrease (which was D_2-receptor mediated) in the resistance of the femoral bed, which represents mainly skeletal muscle [10]. In contrast, we failed to observe vasodilation in skeletal muscle tissue in the present study. Similarly, we previously reported that dopamine, either in the absence or presence of alpha- and beta-adrenergic receptor blockade, failed to elicit a vasodilation response in porcine skeletal muscle [6]. It is possible that in pentobarbital anesthetized dogs sympathetic activity is higher than in swine, due to the pentobarbital-induced vagal withdrawal that occurs in dogs [18]. This would allow D_2-like receptor stimulation to produce vasodilation via inhibition of alpha-adrenergic constriction in dogs.

In the present study, Z1046 had no effect on coronary vascular resistance, because decrease in myocardial blood flow (which was the result of decreased myocardial oxygen requirements) paralleled the decrease in aortic blood pressure. It has been suggested that D_1-like receptor stimulation produces coronary vasodilation in anesthetized dogs [2,19,20], although one re-

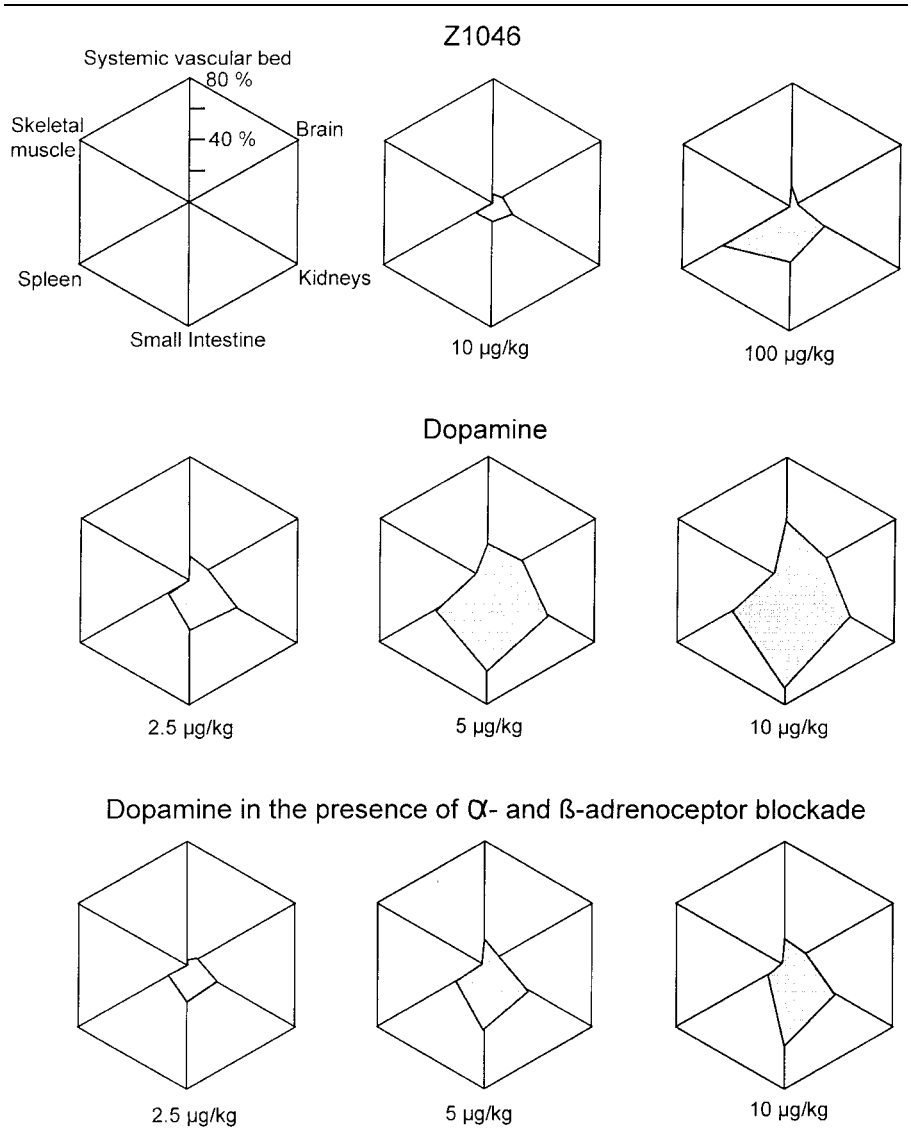

Fig. 2. *Hexagonals showing the percent change in systemic and regional vascular resistance in response to the mixed D_1-like/D_2-like receptor agonist Z1046 in the present study (upper panels), and to dopamine in the absence (middle panels) and presence of alpha- and beta-adrenergic receptor blockade (lower panels) [5]. Note that while Z1046 dilates the splenic, renal, and mesenteric bed, it lacks significant cerebral vasodilation at the doses studied. Dopamine dilated the splenic, renal, mesenteric, and cerebral vascular beds, and splenic artery dilation was abolished by pretreatment with adrenergic receptor blockade.*

port in dogs was negative [21]. In swine, we also failed to observe D_1-like mediated coronary vasodilation after intracoronary infusions of fenoldopam or intravenous infusions of dopamine in the presence of adrenergic blockade [5]. These findings suggest that the presence of D_1-like receptors in the coronary circulation is species dependent. In human isolated coronary arteries precontracted with norepinephrine, fenoldopam failed to elicit a vasodilator response in 6 out of 7 patients [22], implying that human conduit coronary arteries may also be devoid of D_1-like receptors.

Conclusions

In open-chest swine, the novel mixed dopamine receptor agonist Z1046 is a hypotensive agent that produces minimal reflex activation. Future research is war-

ranted to determine the efficacy of this class of drugs in animal models of cardiovascular disease, such as hypertension and heart failure.

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