Finally, it is apparent that the stereochemistry of the substituent on the 9-position of the purine nucleus can vary considerably from that of ribose without appreciably affecting binding to the enzyme. For example, in the present case, the hydroxy group at $C_{5'}$ is absent, and the hydroxy group at $C_{3'}$ is in the opposite configuration than found in the normal substrate, adenosine. These results support the previously stated view that the active site of adenosine deaminase has a large bulk tolerance in the area where the 9-substituent of adenosine analogs bind (6). Furthermore, an inspection of molecular models shows that the hydrogen of the $C_{3'}$-hydroxy group of the 5-deoxyxylofuranosylpurines can occupy an almost identical position as the hydrogen of the $C_{5'}$-hydroxy group in one of the conformations of adenosine. It, therefore, is possible that in compounds like IX, X, and XIII the hydrogen of the $C_{3'}$-hydroxy group is bound to the enzyme at that position where the hydrogen of the $C_{6'}$-hydroxy group of adenosine would be bound normally.

REFERENCES

(1) Schroeder, W., and Hoeksema, H., *J. Am. Chem. Soc.*, **81**, 1767(1959).
(2) Kaczka, E. A., *et al.*, *Biochem. Biophys. Res. Commun.*, **14**, 456(1964).
(3) Suzuki, S., and Marumo, S., *J. Antibiotics Tokyo Ser. A*, **14**, 34(1961).
(4) Waller, C. W., *et al.*, *J. Am. Chem. Soc.*, **75**, 2025 (1953).
(5) Baker, B. R., *et al.*, *ibid.*, **77**, 12(1955).
(6) Schaeffer, H. J., Marathe, S., and Alks, V., THIS JOURNAL, **53**, 1368 (1964).
(7) Schaeffer, H. J., Kaistha, K. K., and Chakraborti, S. K., *ibid.*, **53**, 1371 (1964).
(8) Schaeffer, H. J., Godse, D. D., and Liu, G., *ibid.*, **53**, 1510(1964).
(9) Levene, P. A., and Raymond, A. L., *J. Biol. Chem.*, **102**, 317(1933).
(10) *Ibid.*, **102**, 331(1933).
(11) Gulland, J. M., and Holiday, E. R., *J. Chem. Soc.*, **1936**, 765.
(12) Baker, B. R., Schaub, R. E., and Joseph, J. P., *J. Org. Chem.*, **19**, 638(1954).
(13) Baker, B. R., "The Chemistry and Biology of Purines," Ciba Foundation Symposium, Summit, N. J., 1957, p. 120.
(14) Gorin, P. A. J., Hongh, L., and Jones, J. K. N., *J. Chem. Soc.*, **1953**, 2140.
(15) Kaplan, N. O., in "Methods in Enzymology," Vol. II, Colowick, S. P., and Kaplan, N. O., eds., Academic Press Inc., New York, N. Y., 1955, p. 473.
(16) Baker, B. R., and Sachdev, H. S., THIS JOURNAL, **52**, 933(1963).

Hypotensive Activity of Two Benzothiadiazine Derivatives

By ALBERT I. EDLIN*, WILLIAM J. KINNARD, EUGENE E. VOGIN, and JOSEPH P. BUCKLEY

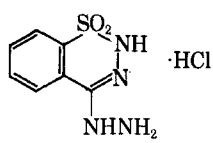
4-Hydrazino-1,2,3-benzothiadiazine-1,1 dioxide hydrochloride (EX 4211A) and 6-chloro-3,4-dihydro-3-(β-oxo-*n*-propyl)-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide phthalazone azine (EX 5004) were studied in the rat and dog to elucidate the mechanism(s) by which these compounds produced hypotensive effects. EX 4211A and EX 5004 were potent hypotensive agents in the anesthetized rat, mildly hypotensive in the anesthetized normotensive dog, and produced a moderate degree of hypotension in unanesthetized renal hypertensive dogs. EX 5004 and EX 4211A appeared to produce their hypotensive effect by the lowering of peripheral resistance through a direct action on vascular smooth muscle.

CHLOROTHIAZIDE and other benzothiadiazine derivatives have been utilized to lower the blood pressure of hypertensive patients and to enhance the hypotensive activity of other antihypertensive compounds (1, 2). This present report describes the hypotensive activity and possible mechanisms of action of two benzothiadiazine derivatives[1]: EX 4211A, 4-hydrazino-1,2,3-benzothiadiazine-1,1 dioxide hydrochloride, and EX 5004, 6-chloro-3,4-dihydro-3-(β-oxo-*n*-propyl)-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide phthalazone azine.

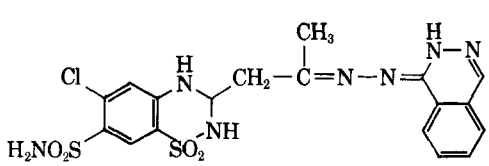
Received May 7, 1964, from the Department of Pharmacology, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pa.
Accepted for publication September 10, 1964.
This investigation was supported in part by research grant HE-03475 from National Heart Institute, National Institutes of Health, U. S. Public Health Service, Bethesda, Md., and a grant from Lakeside Laboratories, Inc., Milwaukee, Wis.
The authors acknowledge the very capable technical assistance of John Gloss and Beatrice Stampahar during this study. The authors also thank Dr. John Wagner, Ciba Pharmaceutical Products, Inc., for the generous supplies of Hypertensin (angiotensin II) and Pyribenzamine hydrochloride (tripelennamine hydrochloride).
* Present address: Department of Pharmacology, College of Pharmacy, Idaho State University, Pocatello.
[1] Kindly supplied by Lakeside Laboratories, Milwaukee Wis.

EXPERIMENTAL

Hypotensive Activity in Rats.—The compounds were evaluated for their hypotensive activity in anesthetized normotensive rats using a modification



EX 4211A



EX 5004

of the method described by Bickerton *et al.* (3). Wistar rats, anesthetized with urethan, 1.25 Gm./Kg. i.p. and prepared for direct blood pressure recording *via* a cannulated carotid artery, were administered EX 4211A in aqueous solution or EX 5004 in 50% dimethylacetamide *via* a femoral vein in doses ranging from 1–40 mg./Kg. Each animal received a single dose of one of the compounds. The dose producing a drop in blood pressure of approximately 50% was estimated for each compound for these initial studies. The dose was administered to a minimum of six rats, utilizing equal numbers of each sex. The mean per cent drop in arterial pressure and the duration of activity were determined for each compound. In another series of anesthetized rats, EX 4211A, 3 mg./Kg. i.v., was tested against the vasoactive responses to intravenous injections of 5 mcg. of epinephrine, 5 and 8 mcg. of norepinephrine, and 1 mcg./Kg. of angiotensin II.

Hypotensive Activity in Dogs.—Mongrel dogs were anesthetized with pentobarbital sodium, 35 mg./Kg. i.v., and the trachea cannulated to insure adequate respiration. Femoral arterial blood pressure was recorded *via* a mercury manometer onto a smoked kymograph. Following a 30-minute stabilization period, initial responses were obtained to intravenous injections of 10 mcg. of epinephrine, 10 mcg. of norepinephrine, 1 mcg./Kg. of angiotensin II, and 15-second bilaterial carotid occlusion. The experimental compounds were administered intravenously in the following doses: 10 mg./Kg. of EX 4211A and 20 mg./Kg. of EX 5004. The above challengers were tested at various time intervals following drug administration.

Cat Nictitating Membrane Preparation.—Cats of either sex were anesthetized with pentobarbital sodium, 35 mg./Kg. i.p., and the trachea cannulated. Femoral arterial blood pressure was measured *via* a Statham pressure transducer (P23AC), and contractions of the nictitating membrane were measured *via* a Grass force displacement transducer (FT03) onto a Grass polygraph. Pre- and postganglionic fibers of the superior cervical sympathetic nerve were stimulated with a Grass stimulator, and the voltage necessary to induce a submaximal membrane contraction was determined for each. The effects of EX 4211A, 10 mg./Kg. i.v., on the response of the nictitating membrane to pre- and postganglionic stimulation and to epinephrine, 10 mcg. i.v., were investigated.

Vagotomized Pithed Cats.—Cats were anesthetized as described above and placed on artificial respiration using a Harvard respirator. Following a midline dorsal incision and exposure of the atlanto-occipital articulation, a rod (65 × 5 cm.) was passed down the spinal canal. The animals then were vagotomized bilaterally, and femoral arterial blood pressure was recorded as described above.

Dog Cross-Circulation Preparation.—Recipient dogs were anesthetized with pentobarbital sodium, 35 mg./Kg. i.v. The neck musculature was removed utilizing electrocautery to expose the vertebral column from C-2 to C-5. A dorsal laminectomy was performed between C-3 and C-4; the vertebral venous sinuses and vertebral arteries were occluded utilizing 21-gauge stainless steel wire, as described by Bickerton and Buckley (4) and Buckley *et al.* (5). Circulation was established between the left common carotid artery of the pentobarbital anesthetized donor and the head of the recipient *via* the recipient's two common carotid arteries and from the two jugular veins of the recipient's head to the left jugular vein of the donor animal. This resulted in a neurally intact, vascularly isolated, recipient head preparation. Circulatory leakage between the recipient's head and trunk was determined utilizing I^{131} (radio-iodinated serum albumin) administered into the recipient's carotid inflow. Femoral arterial blood pressures of both dogs were recorded as previously described. The experimental compounds were administered into the carotid inflow to the recipient's head (IA-R) *via* a femoral vein in the recipient's trunk (IV-R) or *via* a femoral vein of the donor (IV-D).

Cardiac Output.—Cardiac output was determined with an electromagnetic flowmeter (Medicon FM6) by a modification of the method described by Olmsted (6). Mongrel dogs were anesthetized with pentobarbital sodium, 35 mg./Kg. i.v., and femoral arterial blood pressure was recorded as described above. The animals were placed on intermittent positive pressure respiration with 95% O_2 and 5% CO_2 using a Mine Safety Appliance respirator *via* a tracheal cannula. A thoracotomy was made using electrocautery at the fourth intercostal space, the lungs retracted, and the pericardium incised and attached to the chest wall. The ascending aorta was isolated and a 12- or 14-mm. flo-probe placed around the vessel. The lungs were overinflated during final suturing of the chest, and voluntary respiration was allowed to resume. Cardiac output and heart rate were recorded on the Grass polygraph. Total peripheral resistance was calculated from

$$\frac{\text{mean blood pressure (mm. Hg)}}{\text{cardiac output (ml./minute)}} = \text{total peripheral resistance}$$

Hypotensive Activity in Unanesthetized Renal Hypertensive Dogs.—The hypertensive dogs used in this study were prepared according to the method of Grollman (7). The indirect blood pressure determinations on unanesthetized dogs were made utilizing the method of Prioli and Winbury (8). The microphone of an Infraton unit (Beckman Instruments) was secured to the tail beneath the coccygeal artery. Typical arterial pressure pulse waves could be observed on the screen of an oscilloscope (Visoscope, Sanborn Instruments). A digital pressure cuff was applied proximal to the microphone. Pressure was increased within the cuff until pulse waves on the oscilloscope were no longer visible. The pressure was then slowly reduced until pulse waves again appeared. At this point, the pressure in mm. Hg was recorded as systolic blood pressure. Several readings were taken, and the average was reported to the nearest 5 mm. Hg.

Prior to the drug studies, control systolic blood pressure and heart rate measurements were obtained hourly for an 8-hour period daily until these measurements were reproducible. Each animal was used in a crossover study, thereby receiving both compounds under study. Each animal was placed on a drug-free period for a minimum of 48 to 72 hours to allow for excretion of the previous

drug before completing the crossover study. EX 4211A, 25 or 40 mg./Kg., *per os*, or EX 5004, 40 mg./Kg., *per os*, in capsule form was administered after control blood pressure and heart rate values and hourly readings were obtained 10 hours per day for a 2- to 5-day period.

RESULTS

Hypotensive Activity in Rats.—EX 4211A, in doses of 1.0 to 7.5 mg./Kg. i.v., produced a decrease in blood pressure ranging from 24 to 78% for periods greater than 165 minutes. EX 5004, in doses of 2.5 to 40 mg./Kg. i.v., produced a decrease in blood pressure ranging from 25 to 55% for periods greater than 90 minutes. The effects of 2.5 mg./Kg. EX 4211A and 20 mg./Kg. EX 5004 are summarized in Table I. EX 4211A was the more potent of the two compounds. EX 4211A, 3.0 mg./Kg. i.v., potentiated the pressor responses to intravenously administered epinephrine, 32–40%, angiotensin II, 60%, and norepinephrine, 100–120%.

Hypotensive Activity in Dogs.—EX 4211A, 10 mg./Kg., and EX 5004, 20 mg./Kg. i.v., produced mild hypotensive effects in anesthetized dogs, ranging from 13 to 32% and 15 to 35%, respectively (Table II). Both compounds demonstrated minor adrenolytic activity and slightly depressed the angiotensin pressor responses. Neither compound appreciably altered the bilateral carotid occlusion pressor response. When EX 4211A was administered intravenously in a dose of 20 mg./Kg. in another series of tests, the response to epinephrine was reversed. However, this reversal was not seen when the epinephrine challenges were given until approximately 50 minutes after the administration of EX 4211A. The response to norepinephrine was depressed only moderately.

Cat Nictitating Membrane.—EX 4211A, 10 mg./Kg. i.v., did not alter the contraction of the nictitating membrane elicited by epinephrine, 10 mcg. i.v., or submaximal stimulation of the pre- or postganglionic fibers of the superior cervical sympathetic nerve in three cats.

Vagotomized Pithed Cats.—EX 4211A at dosages of 5 and 7.5 mg./Kg. i.v., decreased both systolic and diastolic blood pressure by 43 and 58% and 29 to 37%, respectively. Pressor responses to 10 mcg. of epinephrine, 5 mcg. of norepinephrine, and 1.0 mcg./Kg. of angiotensin II, were also diminished. These data suggest that EX 4211A may decrease blood pressure *via* a direct action on vascular smooth muscle.

Dog Cross-Circulation Preparation.—EX 4211A, in a dosage range of 10 to 30 mg./Kg., IA-R, did not demonstrate centrally mediated effects on blood pressure in three cross-circulation experiments. In this same dosage range, however, EX 4211A (IV-D) produced a vasodepressor response in the donor animal of approximately 20 to 35 minutes duration (Table III). A vasodepressor response of the same duration was produced when EX 4211A was administered (IV-R) into the trunk of the recipient animal. In one cross-circulation experiment, EX 5004, 25 mg./Kg., IV-D, did not produce a hypotensive effect in the recipient; however, this dose did produce a moderate vasodepressor response of some duration in the donor animal (Table III). EX 4211A, 10 to 30 mg./Kg., IA-R, and EX 5004, 25 mg./Kg., IV-D, did not demonstrate centrally mediated effects on blood pressure, and it appears that these compounds produced a peripheral vasodepressor response in the donor animal. The data obtained in the dog cross-circulation studies suggested that these compounds have only a peripheral site of action.

Cardiac Output and Total Peripheral Resistance.—EX 5004, 20 mg./Kg. i.v., lowered mean blood pressure, increased cardiac output, and reduced total peripheral resistance (Table IV, Fig. 1). EX 4211A, 20 mg./Kg. i.v., demonstrated similar effects and also increased heart rate (Table V, Fig. 2).

Unanesthetized Renal Hypertensive Dogs.—EX 4211A, 40 mg./Kg. *per os*, produced a 42% decrease in systolic blood pressure within a 2- to 3-hour period and marked tachycardia (43% above control)

Table I.—Evaluation of Hypotensive Activity of EX 4211A and EX 5004 on Blood Pressure of Normotensive Anesthetized Rats

Compd.	Dose, mg./Kg. i.v.	Rats, No.	Mean Predrug Blood Pressure, mm. Hg	Mean Drop in Blood Pressure, % ± S.D.	Duration of Expt., Min.
EX 4211A	2.5	6	115	50.7 ± 14.0	432+–938+
EX 5004	20.0	6	108	57.0 ± 11.4	324+–721+

Table II.—Effects of EX 4211A and EX 5004 on Blood Pressure and Vascular Responses in Normotensive Anesthetized Dogs

Expt. No.	Wt., Kg.	Sex	Compd.	Dose, mg./Kg. i.v.	Control Mean Blood Pressure, mm. Hg.	Drop, %	Control Responses, % BCO	Epi	Norepi	Ang
1	6.8	F	EX 4211A	10	144	13	62	83	84	72
2	9.7	M	EX 4211A	10	116	13	83	142	88	80
								−20 mm. Hg		
3	9.5	F	EX 4211A	10	134	32	110	76	50	91
								−25 mm. Hg		
4	11.8	F	EX 5004	20	166	15	90	100	76	90
5	8.0	M	EX 5004	20	100	...	104	62	71	79
6	12.8	M	EX 5004	20	130	15	105	62	72	63
7	7.6	F	EX 5004	20	140	35	100	40	62	70

TABLE III.—EFFECTS OF EX 4211A[a] AND EX 5004 ON DONOR AND RECIPIENT BLOOD PRESSURES IN DOG CROSS-CIRCULATION PREPARATION

Expt. No.	Compd.	Dose	Route	Donor: Mean Blood Pressure, mm. Hg	Donor: Change in Mean Blood Pressure, mm. Hg	Donor: Duration, Min.	Recipient: Mean Blood Pressure, mm. Hg	Recipient: Change in Mean Blood Pressure, mm. Hg	Recipient: Duration, Min.
1	Angiotensin II	1 mcg./Kg.	IA-R	125	+35	..	140	+20	..
	EX 4211A	30 mg./Kg.	IV-D	85	+15	20	135	−10[b]	..
	EX 4211A	20 mg./Kg.	IA-R	85	0	..	120	0	..
	Angiotensin II	1 mcg./Kg.	IA-R	70	+35	..	120	−20	..
2	Angiotensin II	1 mcg./Kg.	IA-R	160	+35	..	85	+30	..
	EX 4211A	10 mg./Kg.	IA-R	160	−35[c]	..	95	0	..
	Angiotensin II	1 mcg./Kg.	IA-R	125	+55	..	100	+30	..
	Angiotensin II	1 mcg./Kg.	IV-R	100	...	..	100	+110	..
	EX 4211A	10 mg./Kg.	IV-R	...	...	..	105	−30	20
	Angiotensin II	1 mcg./Kg.	IV-R	...	...	..	75	+135	..
3	Angiotensin II	1 mcg./Kg.	IA-R	160	+55	..	80	+30	..
	EX 4211A	10 mg. /Kg.	IA-R	165	−50	35	80	+15	..
	Angiotensin II	1 mcg./Kg.	IA-R	115	+85	..	90	+35	..
	Angiotensin II	1 mcg./Kg.	IV-R	...	...	..	105	+115	..
	EX 4211A	10 mg./Kg.	IV-R	115	...	..	85	−25	35
	Angiotensin II	1 mcg./Kg.	IV-R	...	...	..	60	+100	..
	EX 4211A	10 mg./Kg.	IV-D	115	...	..	...	...	..
4	EX 5004	25 mg./Kg.	IV-D	135	0[d]	..	140	0	..

[a] pH of aqueous solution was 2.5; 3 ml. of control acid solution, pH 2.5, was administered IA-R and did not produce effects on blood pressure. [b] Donor's pressure rising at this time; the fall in blood pressure was probably due to carotid sinus reflex. [c] Donor's blood pressure slowly falling before IA-R administration of EX 4211A. [d] Blood pressure gradually dropped in a 45-minute period to 100 mm. Hg and remained at this level for approximately 2 hours.

TABLE IV.—EFFECTS OF EX 5004 (20 mg./Kg., i.v.) ON BLOOD PRESSURE, CARDIAC OUTPUT, AND TOTAL PERIPHERAL RESISTANCE IN THE ANESTHETIZED DOG

Expt. No.	Sex	Wt., Kg.	Time, Min.	Mean Blood Pressure, mm. Hg	Cardiac Output, ml./Min.	Control Cardiac Output, %	Total Peripheral Resistance[a]
1	F	15.3	0	100	624	100	.16
			0.5	70	884	140	.08
			14.0	95	624	100	.15
2	M	12.7	0	75	520	100	.14
			17.0	65	780	150	.08
			42.0	60	1300	250	.05

[a] Total peripheral resistance = $\frac{\text{mean blood pressure (mm. Hg)}}{\text{cardiac output (ml./minute)}}$.

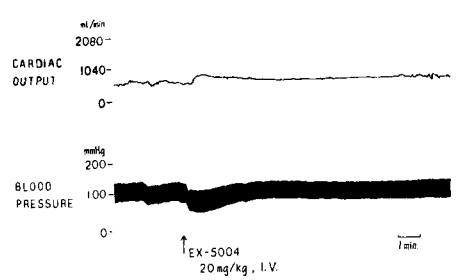


Fig. 1.—The effects of EX 5004 on blood pressure and cardiac output in the dog.

1 hour after drug administration in the first crossover study. On the following day, the systolic pressure was still 27% below predrug levels. Blood pressure and heart rate returned to normal in approximately 35 hours. EX 5004, 40 mg./Kg. *per os*, administered to the above dog produced a 30% reduction in systolic pressure 7 hours after administration and a 50% increase in heart rate within 3 hours after treatment. These effects persisted for 5 days. In the second and third crossover studies, the same dosage of EX 4211A produced effects similar to those described above. On the second day, the drug was again administered and the above results duplicated. EX 5004, at the same dosage, produced effects in the second study similar to those noted in the first; but in the third experiment, its hypotensive effect was not so prominent (only 15% reduction in blood pressure), and subsequent administration on days 2 and 3 failed to produce hypotensive activity.

DISCUSSION

EX 4211A, 4-hydrazino-1,2,3-benzothiadiazine-1,1 dioxide hydrochloride, and EX 5004, 6-chloro-3,4-dihydro-3-(β-oxo-*n*-propyl)-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide phthalazone azine, produced marked hypotensive effects for relatively long periods of time in anesthetized rats but produced relatively mild hypotensive effects in anesthetized dogs. There was a species variation between the rat and the dog, not only in the hypotensive effect produced by the two compounds but also in the effects on responses produced by vasoactive compounds. Whereas EX 4211A and EX 5004 depressed the norepinephrine, epinephrine, and angiotensin II pressor effects in anesthetized dogs, both compounds potentiated these pressor responses in anesthetized rats. EX 4211A was an adrenolytic agent more effective than EX 5004. EX 4211A, in a dose of 10 mg./Kg. i.v. administered to anesthetized dogs, produced a secondary reversal

TABLE V.—EFFECTS OF EX 4211A (20 mg./Kg., i.v.) ON BLOOD PRESSURE, HEART RATE, CARDIAC OUTPUT, AND TOTAL PERIPHERAL RESISTANCE IN THE ANESTHETIZED DOG

Expt. No.	Sex	Wt., Kg.	Time, Min.	Mean Blood Pressure, mm. Hg	Cardiac Output, ml./Min.	Control Cardiac Output, %	Total Peripheral Resistance[a]	Heart Rate, Min.	Control Heart Rate, %
1	M	13.1	0	120	988	100	0.12	156	100
			1.5	105	1196	120	0.09	168	110
			2.5	100	1300	130	0.08	180	115
			6.5	75	1404	140	0.05	192	125
			20.5	90	1196	120	0.08	216	138
			60.5	70	1092	110	0.06	192	125
2	M	12.4	0	95	988	100	0.10	94	100
			0.5	85	1170	120	0.07	84	90
			1.0	90	1300	130	0.07	84	90
			7.5	100	1300	130	0.08	108	115
			10.0	100	1404	140	0.07	156	165
			23.0	85	1430	145	0.06	144	155
3	M	18.8	0	120	1238	100	0.10		
			5.0	95	1575	125	0.06		
			40.0	85	1463	120	0.06		
4	M	12.4	0	130	720	100	0.18		
			1.0	130	810	115	0.16		
			2.5	130	855	120	0.15		
			9.0	135	900	125	0.15		
			10.0	120	955	135	0.13		
			21.0	95	675	95	0.14		
			31.0	110	765	105	0.14		

[a] Total peripheral resistance = $\frac{\text{mean blood pressure (mm. Hg)}}{\text{cardiac output (ml./minute)}}$.

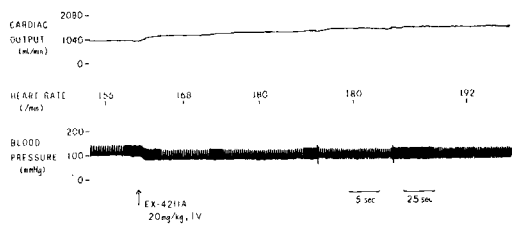


Fig. 2.—The effects of EX 4211A on cardiac output, heart rate, and blood pressure in the dog.

of the epinephrine pressor response in two of three dogs, whereas 20 mg./Kg. of EX 5004 only partially depressed the epinephrine pressor response in three dogs.

All of the data obtained in the current study suggest that the compounds produce their immediate hypotensive effects *via* peripheral mechanisms. The following data support this hypothesis for EX 4211A. (*a*) The compound did not produce a centrally mediated vasodepressor effect in dog cross-circulation studies, while it did produce a potent peripheral hypotensive response in the donor animals. (*b*) The compound produced its hypotensive response entirely through a reduction of peripheral resistance, and the main mechanism of this reduction appeared to be a depression of vascular smooth muscle. (*c*) The compound produced hypotensive effects in the pithed vagotomized cat and markedly reduced the pressor responses to intravenously administered epinephrine, *l*-norepinephrine, and angiotensin II in these preparations. (*d*) The compound produced a secondary reversal of the pressor effect to exogenous epinephrine and depressed the pressor activity of norepinephrine and angiotensin II in the anesthetized dog.

Data obtained in anesthetized dogs and in the pithed vagotomized cats indicate that EX 4211A lowers arterial blood pressure through a direct relaxation of vascular smooth muscle. Although EX 4211A possessed mild adrenolytic properties, 10 mg./Kg. i.v. in the cat failed to depress the contraction of the nictitating membrane induced by exogenous epinephrine. EX 5004 also appears to act peripherally and generally produced similar qualitative effects to EX 4211A. Both compounds produced marked hypotensive effects in unanesthetized renal hypertensive dogs; however, EX 4211A appeared to be the more potent hypotensive agent with a quicker onset of action.

SUMMARY

Two benzothiadiazine derivatives, EX 4211A, 4-hydrazino-1,2,3-benzothiadiazine-1,1 dioxide hydrochloride, and EX 5004, 6-chloro-3,4-dihydro-3-(β - oxo - *n* - propyl) - 7 - sulfamyl - 2H - 1,2,4 - benzothiadiazine 1,1-dioxide phthalazone azine, produced marked hypotensive effects in anesthetized rats and mild hypotensive effects in anesthetized dogs.

These compounds produced their hypotensive response entirely through a reduction of peripheral resistance by a depression of vascular smooth muscle.

The oral administration of EX 4211A and EX 5004 lowered the blood pressure of renal hypertensive dogs.

REFERENCES

(1) Wilkins, R. W., *New Engl. J. Med.*, **257**, 1026 (1957).
(2) Freis, E. D., and Wilson, I. M., *Med. Ann. District Columbia*, **26**, 468(1957).
(3) Bickerton, R. K., *et al.*, THIS JOURNAL, **49**, 183(1960).
(4) Bickerton, R. K., and Buckley, J. P., *Proc. Soc. Exptl. Biol. Med.*, **106**, 834(1961).
(5) Buckley, J. P., *et al.*, *Ann. N. Y. Acad. Sci.*, **104**, 299 (1963).
(6) Olmsted, F., *IRE Trans. Bio-Med. Electron.*, **ME-6**, 210(1959).
(7) Grollman, A., *Proc. Soc. Exptl. Biol. Med.*, **57**, 102 (1944).
(8) Prioli, N. A., and Winbury, M. M., *J. Appl. Physiol.* **15**, 232(1960).