Brit. J. Pharmacol. (1949), **4**, 162.

THE ACTION OF SODIUM THIOCYANATE ON CARDIAC OUTPUT

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(Received February 2, 1949)

Sodium thiocyanate has been introduced with variable success into the treatment of human hypertension. Its mode of action is little understood. Two series of observations indicated a possible hypothesis which might be tested experimentally: (1) the SCN anion markedly and rapidly sensitizes striped and cardiac muscle to the action of K ions (Bacq, 1942, 1947; Derouaux, 1942); (2) injection of veratrine, another substance which sensitizes mammalian tissues to K ions (Szent-Györgyi, Bacq, and Goffart, 1939; Bacq and Goffart, 1939; Bacq, 1939), induces a rapid fall of blood pressure if the vagi are active (Amann and Jarisch, 1943; Amann, Jarisch, and Richter, 1941; Jarisch and Richter, 1939). This fall of blood pressure (also called the Bezold effect) is a reflex originating in the heart itself, mainly in the left ventricle (Dawes, 1947); the afferent fibres travel in the vagi, and the fall of blood pressure is due to inhibition of the vasoconstrictor centre; the simultaneous slowing of the heart has less importance because atropine does not restore the original level of the arterial pressure (Amann *et al.*, 1941, 1943; Jarisch and Richter, 1939).

Sodium thiocyanate does not alter the blood pressure if given in reasonable amounts (Amann and Jarisch, 1943), but one might expect to observe, after injection of NaSCN, a fall in cardiac output, compensated by vasomotor action in the normal animal.

Methods

Dogs anaesthetized with chloralose were used. The blood pressure in the femoral artery was registered and the heart rate could be obtained accurately at any moment. Calculations of the cardiac output were based on the well-known Fick's principle that the cardiac output (in ml. per minute) equals the oxygen consumption (in ml. per minute) divided by the difference (in ml. per litre) between the oxygen content of arterial blood and the oxygen content of mixed venous blood. Samples of blood were collected with the usual care to avoid air contamination. Mixed venous blood was obtained directly from the right ventricle by right heart catheterization according to Cournand's technique (Cournand and Ranges, 1941), the catheter being passed along the right jugular vein. Arterial blood taken from the femoral artery was invariably found to be 95–97 per cent saturated with oxygen. Blood gas analyses were carried out in Haldane's classical apparatus. Oxygen consumption was determined by analysis of expired air collected in a Douglas bag and measured in a spirometer; the gas analysis apparatus of Haldane was used for the measurements of oxygen and carbon dioxide. Thiocyanate concentration in plasma was easily determined thanks to the colour reaction of this ion with ferric ions (Bacq and Fischer, 1947). Potassium concentration of plasma was obtained by the classical cobaltinitrite method of Leulier, Velluz, and Griffon. Sodium thiocyanate and all other substances were injected intravenously in aqueous solution, injections being made slowly (in 7 to 20 minutes).

Results

Tables I and II show that thiocyanate decreases the cardiac output down to 50 per cent if the vagi are normally active (Exps. 1, 2, 3, 11, 12). The fall of cardiac output is bigger when in the same animal the level of thiocyanate in blood is higher, but there is no strict proportionality. An effect on cardiac output is visible when thiocyanate reaches concentrations considered to be therapeutically useful and safe in human hypertensive patients (Barker *et al.*, 1941; del Solar *et al.*, 1945). The single curious exception is that of dog 8 (Table II); its cardiac output increased after injection of thiocyanate; this dog had no vagal tone since 4 mg. atropine sulphate failed to change the heart rate.

The femoral blood pressure generally remains unaltered; if it falls, it is only at the end of the experiment, when cardiac output has been considerably reduced for a long period (Exp. 1).

The oxygen consumption does not decrease and quite naturally the oxygen desaturation of the mixed venous blood increases as the cardiac output falls. Typical instances may be seen in Exps. 1 and 12.

In several animals (Nos. 2, 4, and 9) muscular tremor and spontaneous or reflex convulsions

TABLE I

Exp. number and dog's weight	Time	Experimental conditions	Oxygen consumption (ml./min.)	Oxygen arterio-venous difference in blood (ml./l.)	Cardiac output		Heart rate		Systolic output in % normal	Arterial blood pressure in mm. of Hg	SCN^- in plasma mg./100 ml.	Observations
					ml./min.	in % normal	minute rate	in % normal				
1 (13 kg.)	9.53	Normal	75	28.5	2,630	100	142	100	100	140	—	
	10.01	NaSCN, 5 mg./kg. ..										
	10.08		72	39.5	1,830	70	124	87	80	130	—	
	10.19	NaSCN, 10 mg./kg.										
	10.26		75	59	1,280	49	90	63	77	120	—	
	10.47		70	49.5	1,410	54	100	70	71	100	—	
	11.18		67	59	1,140	43	132	93	47	80	—	
2 (12.5 kg.)	9.51	Normal	74	32	2,306	100	164	100	100	145	0.6	
	9.57	NaSCN, 10 mg./kg.										
	10.01	NaSCN, 10 mg./kg.										
	10.06		71	34.5	2,070	90	164	100	90	150	12.1	
	10.33	NaSCN, 20 mg./kg.										
	10.52	NaSCN, 20 mg./kg.										
	10.59		97	57	1,696	74	180	110	67	160	13.1	Convulsions
	11.30	NaSCN, 50 mg./kg.										
	11.38		138	106	1,305	57	160	99	58	160	20.8	
3 (19.5 kg.)	9.29	Normal	85	54.5	1,560	100	90	100	100	100	0.4	
	9.45	NaSCN, 20 mg./kg.										
	9.53		85	70	1,217	78	78	87	90	100	5.2	
	10.02	NaSCN, 40 mg./kg.										
	10.11		95	88	1,075	69	87	97	72	100	9.6	
	10.19	NaSCN, 80 mg./kg.										
	10.27		100	109	917	59	93	103	57	100	25.0	
	10.34	Both vagi cut ..										
	10.39		81	61	1,332	85	183	203	42	70	25.4	
	11.19		91	76	1,193	76	164	182	42	45	18.3	
4 (14.5 kg.)	9.15	Both vagi cut ..										
	9.45		89	30	2,980	100	168	100	100	125	0.4	
	9.54	NaSCN, 30 mg./kg.										
	10.01		81	28	2,900	97	135	80	121	135	6.7	
	10.10	NaSCN, 50 mg./kg.										
	10.18		81	28	2,900	97	128	76	128	140	13.2	
	10.28	NaSCN, 60 mg./kg.										
	10.35		81	28	2,900	97	130	77	126	140	19.8	
	11.15		90	55	1,640	55	140	83	66	120	22.3	Hyperreflectivity
5 (11.5 kg.)	9.19	Both vagi cut ..										
	9.48		102	39	2,620	100	186	100	100	155	0.4	
	9.59	NaSCN, 30 mg./kg.										
	10.06		103	31	3,330	127	186	100	127	165	8.1	
	10.17	NaSCN, 100 mg./kg.										
	10.24		104	33	3,160	120	186	100	120	180	23.1	
	11.22		110	46	2,390	91	182	98	93	200	18.3	
6 (13 kg.)	9.16	Atropine, 2 mg. ..										
	9.46		64	88	730	100	146	100	100	135	0.3	
	9.54	NaSCN, 30 mg./kg.										
	10.01		61	85	720	98	140	96	102	145	9.4	Hyperreflectivity
	10.09	NaSCN, 100 mg./kg.										
	10.16		61	79	775	106	136	93	114	155	25.5	
	11.14		60	110	550	75	130	89	84	140	23.6	
7 (17.5 kg.)	9.18	Atropine, 2 mg. ..										
	9.47		82	39	2,100	100	180	100	100	135	0.4	
	9.56	NaSCN, 30 mg./kg.										
	10.03		83	41.5	1,990	95	164	92	103	145	7.0	
	10.09	NaSCN, 50 mg./kg.										
	10.16		78	40	1,950	92	158	88	105	145	14.3	
	10.27	NaSCN, 60 mg./kg.										
	10.34		73	40	1,820	87	160	89	98	145	24.7	
	11.32		65	57	1,140	54	148	82	66	130	20.6	

TABLE II

Exp. number and dog's weight	Time	Experimental conditions	Oxygen consumption (ml./min.)	Oxygen arterio-venous difference in blood (ml./l.)	Cardiac output		Heart rate		Systolic output in % normal	Arterial blood pressure in mm. of Hg	SCN^- in plasma mg./100 ml.	Observations
					(ml./min.)	in % normal	minute rate	in % normal				
8 (11.5 kg.)	9.32	Normal	51	56	920	100	96	100	100	120	0.2	
	9.38	NaSCN, 30 mg./kg.										No vagal tone
	9.45		49	41.5	1,190	129	86	90	144	135	—	
	9.50	NaSCN, 30 mg./kg.										
	9.57		56	38.5	1,450	158	87	91	174	145	13.8	
	10.04	Calcergyl,* 50 mg./kg.										
	10.15		49	34.5	1,430	156	91	95	164	135	12.4	
	10.25	Calcergyl, 50 mg./kg.										
	10.33		50	43.5	1,140	124	88	92	134	125	12.1	
	10.38	NaSCN, 80 mg./kg.										
	10.45		48	53.5	900	98	88	92	106	120	22.5	
9 (9.5 kg.)	9.37	Normal	59	39.5	1,500	100	111	100	100	150	0.3	
	9.43	NaSCN, 30 mg./kg.										
	9.50		69	49	1,400	93	103	93	100	170	9.5	Convulsions
	10.00	NaSCN, 50 mg./kg.										
	10.07		72	57	1,270	84	105	95	88	185	14.6	Convulsions
	10.13	Calcergyl, 50 mg./kg.										
	10.24		84	53.5	1,570	104	113	102	102	180	12.1	
	10.32	Calcergyl, 50 mg./kg.										
	10.40		84	53	1,585	105	106	96	110	190	13.0	
	10.52	NaSCN, 80 mg./kg.										Convulsions
	10.59		82	52	1,570	104	124	112	93	190	24.1	
10 (25 kg.)	9.30	Normal	120	57	2,110	100	125	100	100	175	0.3	
	9.39	Calcergyl, 100 mg./kg.										
	9.47		122	52.5	2,315	110	102	82	135	180	—	
	9.54	NaSCN, 30 mg./kg.										
	10.00		111	47.5	2,340	111	96	78	145	180	7	
	10.08	NaSCN, 50 mg./kg.										
	10.15		114	42	2,715	129	96	78	168	185	12.7	
	10.33	NaSCN, 80 mg./kg.										
	10.40		110	46	2,390	113	92	74	155	185	19.8	
	11.40		99	57	1,730	82	84	67	123	185	21.3	
11 (16 kg.)	9.36	Normal	85	34	2,500	100	141	100	100	130	0.3	
	9.41	NaSCN, 30 mg./kg.										
	9.48		84	39	2,160	86	107	76	114	140	6.4	
	9.54	NaSCN, 30 mg./kg.										
	10.01		90	42	2,145	86	98	70	124	140	9.7	
	10.08	NaSCN, 50 mg./kg.										
	10.15		92	47	1,955	78	101	72	109	160	16.1	
	10.21	Calcergyl, 100 mg./kg.										
	10.32		97	37	2,615	104	86	61	172	170	15.1	
12 (16.5 kg.)	9.34	Normal	87	35.5	2,465	100	188	100	100	140	0.3	14 mg. K/100 ml. serum
	9.41	NaSCN, 80 mg./kg.										
	9.48		86	48	1,785	72	128	68	106	155	12.8	Convulsions
	9.57	NaSCN, 80 mg./kg.										
	10.05		89	47	1,900	77	128	68	114	155	19.1	12.7 mg. K/100 ml. serum
	10.22	KCl, 12 mg./kg. ..										Continuous muscular
	10.56	KCl, 12 mg./kg. ..										tremor; 16.6 mg. K/
	11.03		165	70.5	2,340	95	228	121	79	145	17.7	100 ml. serum
	11.16		226	100	2,260	92	232	123	74	145	14.8	15.5 mg. K /100 ml. serum
13 (19.5 kg.)	9.28	Normal	124	23	5,380	100	176	100	100	160	0.5	11.8 mg. K/100 ml. serum
	9.36	NaSCN, 150 mg./kg.										Hyperreflectivity
	9.49		121	32.5	3,715	69	116	66	105	185	15.8	12.4 mg. K/100 ml. serum
	10.02	KCl, 5 mg./kg. ..										
	10.16		124	37	3,365	63	110	63	100	170	15.4	13.2 mg. K/100 ml. serum
	10.32	KCl, 5 mg./kg. ..										
	10.43		111	43	2,585	48	90	51	94	170	15	12.8 mg. K/100 ml. serum
	11.06		116	52	2,235	42	77	44	95	170	14.8	11.9 mg. K/100 ml. serum
	11.12	KCl, 10 mg./kg. ..										
	11.23		101	52	1,950	36	72	41	89	175	14.4	12.9 mg. K/100 ml. serum

* Calcergyl = calcium thiosulphate Labaz.

occurred, which introduced the complicating element of an increased oxygen consumption; nevertheless, the fall in cardiac output persisted; it simply failed to deepen when thiocyanate concentration increased in the blood (see beginning of Exp. 12) or was smaller than usual (beginning Exp. 9).

That the vagi (and not their afferent but their inhibitory cholinergic efferent fibres) are involved in this process is proved by the following observations: (1) if both vagi are cut in the neck before injection of thiocyanate, no significant decrease of cardiac output takes place although the concentration of thiocyanate in blood reaches high levels (Exps. 4 and 5); the final fall in Exp. 4 is of little value at the end of the experiment and was preagonic; (2) bilateral vagotomy, performed during the experiment, when the cardiac output was reduced to 59 per cent, increased this output at once, although the SCN^- concentration in blood did not decrease (Exp. 3); (3) two dogs with vagi intact but given a moderate dose (2 mg.) of atropine sulphate reacted to thiocyanate very much like the vagotomized animals (Nos. 6 and 7).*

That potassium ions are involved in the response to thiocyanate is more difficult to prove. A first attempt (Exp. 12, Table II) to increase K^+ concentration in plasma by slow intravenous injection of

* Cardiac output decreases two hours after injection of atropine because the effect of atropine wears off (Exps. 6 and 7).

TABLE III

Exp. number and dog's weight	Time	Experimental conditions	Oxygen consumption (ml./min.)	Oxygen arterio-venous difference in blood (ml./l.)	Cardiac output		Heart rate		Systolic output in % normal	Arterial blood pressure in mm. of Hg
					ml./min.	in % normal	minute rate	in % normal		
14 (19.5 kg.)	9.46	Normal	100	44	2,275	100	105	100	100	125
	10.02	Veratrine, 20 μg./kg.								
	10.04					—	—	—	—	65
	10.15	Veratrine, 20 μg./kg.								120
	10.21		98	48	2,040	90	121	115	77	95
	10.39	Veratrine, 20 μg./kg.								
	10.48		77	66.5	1,160	51	78	74	68	70
	11.36		83	54	1,540	70	108	103	66	90
15 (15 kg.)	9.36	Normal	109	38	2,860	100	88	100	100	145
	9.46	Veratrine, 26 μg./kg.								
	10.01		100	58.5	1,715	60	78	89	68	120
	10.19	Veratrine, 13 μg./kg.								145
	10.34	Veratrine, 130 μg./kg.								140
	10.46		97	85.5	1,140	40	54	61	65	70
	10.50	Atropine, 4 mg. ..								
	11.15		96	69	1,400	49	200	227	22	70
	11.21	Both vagi cut ..								
	11.39		137	60	2,280	80	236	268	29	135
16 (25.5 kg.)	9.40	Normal	108	35	3,090	100	76	100	100	150
	9.53	Veratrine, 40 μg./kg.								
	10.08		91	53.5	1,700	55	100	132	42	120
	10.24	Veratrine, 80 μg./kg.								
	10.37		99	54.5	1,810	59	87	115	51	95
	10.43	Calcergyl, 100 mg./kg.								
	10.51		97	42.5	2,280	74	178	234	31	110
17 (23.5 kg.)	9.33	Normal	162	58	2,800	100	140	100	100	150
	9.47	Veratrine, 83 μg./kg.								
	10.00		143	57.5	2,490	89	123	88	102	120
	10.17	Veratrine, 144 μg./kg.								
	10.22		113	99.5	1,130	40	96	69	59	95
	10.37		105	85.5	1,235	44	68	49	91	70
	10.42	Calcergyl, 100 mg./kg.								
	10.56		137	53.5	2,570	92	134	96	96	115
	11.04	Both vagi cut ..								
	11.15		175	56	3,120	112	196	140	80	150

KCl in a dog under the influence of SCN^- was followed by vigorous and continuous muscular twitchings which increased oxygen consumption and cardiac output. A second observation (No. 13, Table II) is at first sight more successful; after a single injection of NaSCN, which decreased cardiac output to 69 per cent of normal, several injections of KCl did not cause convulsions and brought the output progressively down to 36 per cent, although the thiocyanate concentration in the blood decreased slightly; a more careful analysis shows: (1) that the potassium level in serum was just slightly higher, (2) that the heart rate was exceptionally low, and (3) that a progressive heart failure due to SCN^- alone is a quite possible interpretation of the data.

Better evidence is given by the relief brought about by Ca ions which are known to antagonize K ions and the sensitizers to K ions (Bacq, 1939, 1947); we used supersaturated stabilized solutions of calcium thiosulphate* which are highly ionized and perfectly tolerated. A suitable dose of Ca ions injected before large amounts of thiocyanate prevents the fall of output (Exp. 10, Table II); when given after NaSCN, it restores cardiac efficiency (Exps. 9 and 11, Table II) and protects against a further administration of thiocyanate (Exp. 9, Table II); given alone, calcergyl is inactive.

In order to have the necessary data for a clear discussion, we made four observations with veratrine under similar experimental conditions (Table III). Small doses of veratrine decrease cardiac output, systolic output, and heart rate if the vagi are present. After veratrine, atropine has little effect on reduced cardiac output, although the heart rate is more than trebled in Exp. 15; calcium ions are quite effective in antagonizing veratrine action (Exps. 16 and 17), but the relief is not complete since bilateral vagotomy results in a further increase (Exp. 17).

The last important fact is a considerable increase in cardiac output following vagotomy in the dog after treatment with veratrine and atropine (Exp. 15). These observations are in close agreement with the data of Jarisch and his colleagues, showing that the efferent fibres in the vagi have, in veratrine reflex action, a much smaller importance than the afferent fibres.

Discussion

The fall of cardiac output after sodium thiocyanate does not happen in absence of the vagi and is inhibited by Ca ions just as the similar action of veratrine. Potassium ions are involved in the process as expected; but the mechanism is not yet clear. Does SCN^- increase the reaction to K ions of the sensitive elements in the ventricle? Does it act on the vagal centres? Or does it simply increase at the periphery the response of the heart to the inhibitory impulses of the efferent fibres?

The last possibility is probably correct for the following reasons: (1) atropine is nearly as effective as vagotomy in thiocyanate, but not in veratrine, poisoning; (2) thiocyanate increases remarkably the inhibitory effects of peripheral vagus nerve stimulation (Bregante, 1945, 1947; Goutier, 1948); (3) thiocyanate increases the direct effect of acetylcholine on the muscle, by a mechanism which is certainly not the inhibition of tissue cholinesterase, but most probably the potentiation of the K ions released by the action of acetylcholine (Vanremoortere, 1949); (4) thiocyanate differs from veratrine in the absence of decurarizing properties, in its lack of action on the end plate (Coppée, 1943); (5) there is no true Bezold effect with NaSCN (Amann and Jarisch, 1943); (6) our dog 8, which was insensitive to NaSCN, had practically no vagal tonus; (7) in previous experiments, two of us (Charlier and Philippot, 1947, 1948a) have observed that bilateral vagotomy in the dogs under chloralose results in irregular, generally small, changes in cardiac output. Eleven animals were used: in six, there was an increase (mean value + 10 per cent); in five, a decrease was noted (mean value −19 per cent); the highest changes recorded were +22 per cent and −27 per cent. In dogs given thiocyanate, bilateral vagotomy increases cardiac output and this increase is bigger than in normal dogs (44 per cent).

The main action of thiocyanate should be to increase the inotropic effect of the vagal tone and thus decrease the contractile power of the heart. This inotropic effect cannot exist without some chronotropic action; as a rule NaSCN decreases the dog's heart rate when the vagi are present (Exps. 1, 3, 8, 9, 11, 12, 13); Exp. 2 is an exception, and so is Exp. 4, in which no slowing of the heart should have happened in absence of the vagi. In the normal dog under chloralose, thiocyanate does not induce a fall of blood pressure. Since the cardiac output is diminished, it means that the total peripheral resistance of the blood vessels increases at the same time. A similar phenomenon—namely, decrease of cardiac output and simultaneous increase in total peripheral resistance, resulting in no change of arterial blood pressure—occurs under light anaesthesia with chloroform (Charlier and Philippot, 1948b).

The therapeutic implications of this work are serious. Thiocyanate just weakens the heart; it

* We wish to thank the "Laboratoires de recherches pharmaceutiques de l'Azote (Liége)" for a generous supply of this preparation (Calcergyl Labaz).

does not act on the kidneys or the vessels; it does not seem to change anything in the basic mechanism of hypertension; its use, which is not devoid of danger, should thus be confined to those cases where the pressure has become dangerous to the heart and is unnecessarily high for a suitable glomerular filtration; in other words, where the reaction of the organism to renal ischaemia or general sclerosis is out of proportion. The fall in cardiac output in the hypertensive patient should not be so easily compensated as in the normal dog, or the hypertrophied heart might be more sensitive. This would explain why hypotension is observed in hypertensive patients and not in normal animals.

When symptoms of thiocyanate intoxication occur, quick relief may be obtained by intravenous injection of ionized calcium salts. It is interesting to note that the human organism reacts to chronic intoxication with KSCN by liberation of Ca ions from the bones; Hinchey, Hines, and Ghormley (1947) have reported osteoporosis occurring in 2 per cent of the hypertensive patients treated with potassium thiocyanate three to six months after the start of the treatment. Cessation of treatment was always followed by relief.

One wonders if the therapeutic effects of SCN^- in hypertension might not be obtained with eserine, which increases the peripheral effects of vagal tone by a completely different mechanism.

Summary

1. NaSCN decreases the cardiac output of dogs under chloralose; this action is antagonized or prevented by bilateral vagotomy, by atropine, or by injection of Ca ions.

2. Arterial blood pressure remains normal even when the cardiac output is decreased 50 per cent by NaSCN.

3. Veratrine also decreases the cardiac output, and its action is inhibited by vagotomy and Ca ions but not by atropine.

4. Discussion shows that the action of SCN ions in normal dogs and hypertensive patients is probably due to an increase of the heart response to vagal tone; the sensitization of the heart muscle to K ions is quite sufficient to account for the action of thiocyanate.

5. The use of calcium in thiocyanate intoxication is logical and advisable.

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