STUDIES ON VERATRUM ALKALOIDS. XXI. THE ACTION OF VERATRAMINE UPON IMPULSE GENERATION IN THE DOG HEART[1, 2]

OTTO KRAYER, R. B. ARORA[3] AND EDWARD MEILMAN[4]

Department of Pharmacology, Harvard Medical School, Boston

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The inhibitory action of veratramine upon the cardioaccelerator effect of sympathomimetic amines has been extensively studied (Krayer, 1952; Krayer and Ourisson, 1954). Moreover, in the first publication on this subject it was shown that veratramine is capable of decreasing the heart rate of the mammalian heart in the presence of normal sino-auricular (S-A) rhythm (Krayer, 1949, figures 6 to 9). In the past, the assumption was made that the site of action of veratramine in causing its antiaccelerator effect is the S-A node. However, the possibility has been kept in mind that veratramine may act upon subsidiary pacemakers, and that this action may be demonstrated after the exclusion of the S-A node. The experiments reported here supply further information on the action of veratramine upon the normal pacemaker of the heart not under the influence of extraneously supplied sympathomimetic amines. They demonstrate the effect of veratramine upon heart rate in the presence of atrio-ventricular (A-V) rhythm. In addition, reference is made to the lack of action of veratramine upon other foci of automaticity in the heart. This study is based on observations made on twenty eight heart-lung preparations of the dog and on the heart *in situ* in nine animals.

METHODS AND MATERIALS. The 28 heart-lung preparations of the dog discussed in this paper were prepared as described in earlier studies. The general conditions from experiment to experiment as to systemic output, total blood volume, and mean arterial pressure were fairly uniform. The ranges were as follows: systemic output 400 to 700 ml. per minute, total blood volume 800 to 1200 ml., mean arterial pressure 100 to 116 mm. Hg. The temperature of the blood entering the heart varied from experiment to experiment over a range of 37.0°C. to 39.0°C. Within a single experiment the maximal range of change, during the period of observation under discussion, was not greater than 0.5°C. With the exception of the experiments with spontaneous auricular fibrillation, heart rate was read from electrocardiographic recordings taken by means of a Grass inkwriting oscillograph. In order to be certain that uniform conditions of temperature and heart rate were reached (especially in the experiments of section I), a period of 30 minutes was usually allowed between the beginning of recording and the administration of veratramine. The term "initial rate" refers to the rate established at the end of this control period.

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[2] Some of the results of this investigation were reported at the Federation Meetings, New York, 1952 (Arora, Meilman and Krayer, 1952).

[3] Rockefeller Travelling Fellow. Present address: Department of Pharmacology, S. M. S. Medical College, Jaipur, India.

[4] Present address: Long Island Jewish Hospital, New Hyde Park, New York.

In order to study the effect of veratramine upon subsidiary pacemakers, experiments were carried out in 9 open-chest dogs (see table 2). In all experiments, except experiment 7, general anesthesia was produced by intraperitoneal injection of 0.8 ml. Dial-urethane[5] per kgm. body weight. In experiment 8, this dose was supplemented by an additional 2 ml. before the start of the operation. In experiment 3, after clamping off the S-A node, the anesthesia depth was increased by intravenous injection of 1.5 ml. of a 3.5 per cent solution of sodium pentobarbital. In experiment 7, chloralose, 0.09 gm./kgm. body weight, was administered intravenously. In addition, two doses of 1 ml. each of 3.5 per cent sodium pentobarbital solution were required to establish a satisfactory level of general anesthesia. Artificial respiration was maintained by a Starling respiration pump. A mixture of 95 per cent oxygen and 5 per cent carbon dioxide was employed for ventilation, except in experiment 9 (of table 2) in which room air was used.

With the heart beating *in situ* a curved clamp was applied to the right atrium beyond the S-A nodal tissue in the *sulcus terminalis* and reaching up to the neighborhood of the coronary sinus. In two of the earlier experiments of this kind (experiments 1 and 3 of table 2) the clamp was removed after the tissue around the S-A node had been crushed. The exclusion of the S-A nodal tissue was more reliably achieved in later experiments by leaving the clamp in place. As in the heart-lung preparations, heart rates were counted and changes of rhythm followed by recording the electrocardiogram with a Grass inkwriting oscillograph; conventional bipolar lead II and unipolar pericardial leads were used.

The sympathomimetic amines *l*-epinephrine[6], *l*-norepinephrine[6], tuaminoheptane[7], and isopropylarterenol[6] were administered by continuous intravenous infusion, or by intravenous injection of single doses. The stated doses, or infusion rates, refer to the bases.

Two pharmacologically equivalent samples of veratramine were used in these experiments, *i.e.*, veratramine "Jacobs" for all experiments of table 1 carried out prior to 1951, and 'veratramine "Lederle" purified' for all other experiments. A detailed account of the preparation of 'veratramine "Lederle" purified' and of the physical properties of the two samples of veratramine was published by Krayer and George (1951). All doses of veratramine refer to the base.

In some of the experiments atropine sulfate was administered in order to prevent cardiodecelerator effects caused by vagal stimulation from interfering with the action of veratramine. Unless otherwise stated, the dose was 10 mgm. in the heart-lung preparation and 1 mgm./kgm. in the open-chest dog. All doses refer to atropine sulfate.

In order to produce ventricular tachycardia with a cardiac glycoside, ouabain[7] was employed in doses ranging between 0.3 and 0.5 mgm. for the individual heart-lung preparation.

In the intact circulation, all substances given as single doses were administered into one of the femoral veins; continuous infusion of sympathomimetic amines was made into the right external jugular vein. In the heart-lung preparation, all substances were administered into the tubing carrying the blood supply, in close proximity to the cannula inserted into the vena cava superior.

RESULTS. *I. Effect of veratramine upon the rate of the isolated heart in the presence of S-A rhythm.* Of the conditions determining the activity of veratramine upon the initial rate in the presence of S-A rhythm, the level of the initial rate and the dose of veratramine can be shown to play a role (figure 1). In figure 1 are plotted the results of 17 experiments on the heart-lung preparation of the

[5] Dial-urethane solution was generously supplied by Ciba Pharmaceutical Products, Inc., it contained in 1 ml.: diallylbarbituric acid 0.1 gm., urethane 0.4 gm., monoethylurea 0.4 gm.

[6] Generously donated by Winthrop-Stearns, Inc.

[7] Generously donated by Eli Lilly & Co.

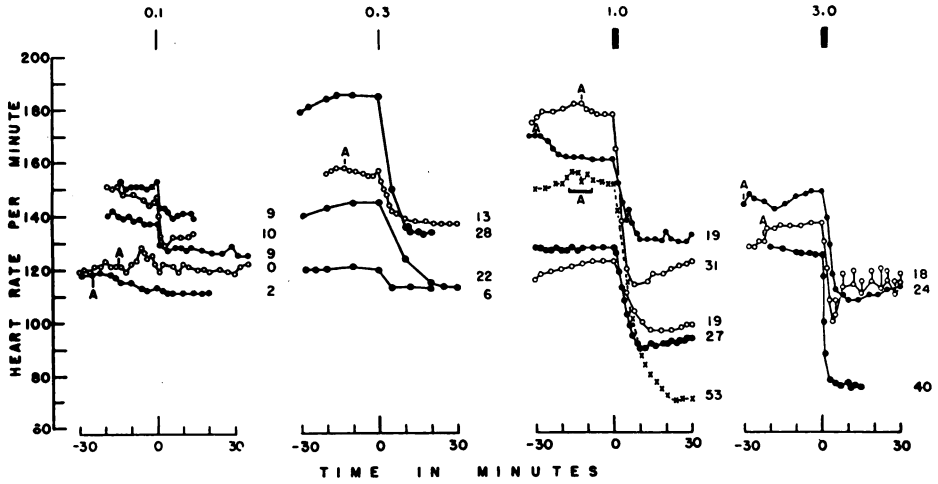

FIG. 1. The effect of veratramine upon initial rate in the isolated dog heart. Seventeen heart-lung preparations (for details see table 1). The figures at the top are the doses of veratramine in mgm. given in the individual experiments of the four groups. The injection started at zero time. The figure to the right of the end of every curve gives the relative decrease in heart rate in per cent of the initial rate. At A, atropine sulfate was injected in the particular experiment (for further details and explanations see table 1 and text).

dog. Pertinent data on the individual experiments are given in table 1. As can be seen in figure 1, the dose of 0.1 mgm. veratramine had no apparent action at initial rates of 120, while a distinct effect could be obtained at initial rates between 135 and 150. The dose of 0.3 mgm. veratramine was effective in all experiments, but again the heart rate decreased by only a few beats in the experiment with the relatively low initial rate of 120. Marked effects were invariably seen with the dose of 1 mgm. Apparently no further maximal increase in slowing, above that caused by 1 mgm., could be obtained by increasing the dose to 3 mgm. veratramine. The average relative decrease in heart rate in per cent of the initial rate for all the experiments (of figure 1), in the individual dosage groups of 0.1, 0.3, 1.0 and 3.0 mgm. veratramine, was 5, 18, 27 and 28 per cent respectively.

In one of the experiments of figure 1 the dose of 1 mgm. led to slight irregularities of S-A rhythm consisting in the periodical appearance of slightly faster runs of sinus rate lasting for a few beats. In the one experiment with 3.0 mgm. exhibiting irregularities of rhythm of the same type, these were more intense than in the experiment with 1.0 mgm., *i.e.*, the faster runs of sinus rate were more pronounced so that the difference between slow and fast was of the order of 10 beats/min. or more, and the fast runs were more numerous so that several periods were noticeable during a single minute.

The lowest heart rates reached in these experiments were 71 beats/min. and 75 beats/min., respectively, in two experiments. There was a slight irregularity of rhythm in one of these experiments but none in the other, indicating that

TABLE 1

Effect of veratramine upon initial rate in the heart-lung preparation of the dog

Experiment Date	Dog		Total Blood Vol.	Systemic Output	Initial Rate	Temp.	Veratramine
	Body weight	Sex					
	kgm.		*ml.*	*ml./min.*	*beats/min.*	*°C.*	*mgm.*
3/11/49	11.3	Female	1110	500	153	38.0	0.1
3/15/49	11.4	Male	1120	580	147	37.7	0.1
3/16/49	11.6	Male	1080	480	137	38.6	0.1
6/24/52	11.8	Male	1190	670	120 A	37.8	0.1
6/9/52	11.0	Female	1170	600	113 A	38.1	0.1
12/5/50	8.0B	Female	1020	580	185	38.8	0.3
6/18/52	12.5	Female	800	600	157 A	39.0	0.3
1/3/51	9.5	Male	1050	670	145	38.9	0.3
12/12/50	10.1	Male	1060	700	120	38.4	0.3
6/6/52	11.0	Male	1150	700	178 A	38.0	1.0
6/5/52	12.9	Male	1140	530	161 A	38.1	1.0
6/13/52	11.3	Male	1190	590	153 A	38.0	1.0*
3/3/52	10.6	Male	1110	520	128	38.0	1.0
4/3/52	10.3	Male	1150	600	123	38.0	1.0
6/11/52	10.4B	Male	1150	600	149 A	38.0	3.0
6/3/52	13.0	Male	1150	700	137 A	38.7	3.0*
12/22/48	12.0	Male	1060	400	120	38.3	3.0
Average.....	11.1		1100	600		38.2	

A—Atropine sulfate 10 mgm. was given except in exp. 6/24/1952 in which the dose was 5 mgm.

B—Beagle hound.

* Slow and fast runs of sinus rhythm.

heart rates as low as 70 to 80 beats/min. were reached while the S-A rhythm remained regular as shown by the electrocardiographic record.

Atropine did not prevent the decrease in heart rate and was incapable of abolishing it; it also was unable to prevent the sinus arrhythmia caused in the two experiments, by 1.0 and 3.0 mgm. veratramine, respectively.

When large doses of veratramine (1 to 3 mgm.) were given, the effect developed rapidly and maximal slowing was usually reached 2 to 3 minutes after the end of the injection. In some cases, this was followed by a slight rise in rate over a period of 15 to 20 minutes. With small doses (0.1 to 0.3 mgm.), even if they were given within one minute, the rate decrease in some experiments developed rather slowly.

By the successive administration of increasing doses of veratramine a graded response could be obtained, as was reported earlier (Krayer, 1949, figure 8). In an unpublished experiment of the same series (1/12/1949; dog 12 kgm.),

TABLE 2

Change in blood pressure and heart rate due to exclusion of the S-A node, and effect of sympathomimetic amines upon heart rate in the presence of A-V rhythm in the dog

Experiment		Dog		Blood Pressure, mm. Hg		Heart Rate, beats/min.			Sympathomimetic Amine Given by Continuous Infusion	
No.	Date	Kgm.	Sex	S-A rhythm	A-V rhythm	S-A rhythm		A-V rhythm	Substance	Range of dosage, microgm./kgm./min.§
1	11/20/51	11.0	Male	Not recorded	80	135		102	Epinephrine	(0.7), 1.3, 2, 3.2, 4.9, 8.9*
2	11/23/51	10.5	Male	70‡	60	155A 38°C.		54–58 38°C.	Epinephrine	2, 5.3*, 9.4*
3	11/27/51	9.3	Male	106–108	70	140A 36.7°C.	129V 35.7°C.	53–64 35.6°C.	Epinephrine	2.4*
4	11/29/51	12.1	Male	112	96	140A 37.3°C.	138V 37.2°C.	78–82 37.2°C.	Epinephrine Tuaminoheptane	0.9*, 0.9†, 1.7* 3 mgm. single dose
5	12/ 4/51	14.1	Male	128–135	106–114	178 38.9°C.		90–105 38.5°C.	Tuaminoheptane Isopropylarterenol	(1.4), (5), 12.5, 14.5, 25* 0.05* mgm., 0.1* mgm. single doses
6	12/ 6/51	10.1	Female	100–105	98	132 38°C.		60–62 38°C.	Norepinephrine	1.1, 2, 4.1*
7	12/11/51	9.9	Female	120	108–112	157–162 37.8°C.		128–131 38°C.	Norepinephrine	1.1*, 2*
8	12/21/51	10.4	Female	105	98	130 38.4°C.		75–89 38.3°C.	Norepinephrine	0.4*, 1*, 2*, 4*
9	1/29/52	11.5	Male	110	80	150 38°C.		54–60 38°C.	Norepinephrine	(0.13), 0.24, 0.4*

A—Atropine sulfate was given at the beginning of the experiment.
V—Veratramine had been given (48 min. in experiment 3 and 40 min. in experiment 4) prior to the time of this rate.
* Infusion at this rate caused the appearance of A-V nodal rhythm with preceding atrial activation.
† When this dose was infused later it did not cause the appearance of a P wave.
‡ In this experiment the blood pressure was 110 mm. Hg at the start; epinephrine was then given at the rate of 2, 5.3 and 9.4 microgm./kgm./min. After discontinuation of epinephrine infusion the arterial pressure fell to the low level.
§ The figures in parentheses denote infusion rates of doubtful effectiveness.

successive doses of 0.1, 0.3, 1.0 and 3.0 mgm. were given to a heart-lung preparation with an initial rate of 154 beats/min. The steady-state heart rate levels corresponding to the successive fractional total doses of 0.1, 0.4, 1.4 and 4.4 mgm., respectively, were 146, 134, 123 and 118 beats/min. The maximal decrease in rate in this experiment was 36 beats (from 154 to 118) and was brought about by the total dose of 4.4 mgm. veratramine. No atropine had been administered. In a similar experiment under 5 mgm. atropine sulfate (6/26/1952; dog 10.8 kgm.), successive doses of 0.3, 0.7 and 2.0 mgm. of veratramine were administered to the heart-lung preparation. The fractional total doses of 0.3, 1.0 and 3.0 mgm. veratramine decreased the heart rate from the initial value of 135 to 114, 95 and 83 beats/min., respectively. In this case the total dose of 3 mgm. caused a maximal decrease in rate of 53 beats.

II. Effect of veratramine upon the rate of the heart in situ. 1. S-A rhythm. In the intact circulation of the anesthetized dog, as well as in the isolated heart, veratramine was capable of reducing the normal sinus rate. In the present series of the nine experiments of table 2, this was demonstrated in experiments 3 and 4. The phenomenon is illustrated in figure 2A. With an increase in the dose, the intensity of the effect increased, *e.g.*, in the experiment of figure 2A the dose of 0.03 mgm./kgm. caused a maximal decrease from 144 to 133 beats/min., while the dose of 0.1 mgm./kgm. reduced the rate from 140 to 107 beats/min.

As was pointed out earlier (Krayer, 1949), the effect of a single dose of veratramine does not persist in the intact animal, and the heart rate, even after doses causing marked effects, gradually returns towards the original level. In the experiment of figure 2A (experiment 3 of table 2), the duration of action of the dose of 0.1 mgm./kgm. was more than 50 minutes. In experiment 4 of table 2, the dose of 0.06 mgm./kgm. reduced the normal sinus rate from 140 to 122 beats per minute; the rate gradually returned to the initial value within 30 minutes. Dose-response effects of veratramine are difficult to study over a wider range in the intact animal, because doses above 0.2 mgm./kgm. cause convulsions even in the anesthetized dog (Krayer, 1949). For this reason the dosage range used in the present experiments was kept between 0.01 and 0.1 mgm./kgm. body weight.

2. A-V rhythm. After clamping off the S-A node the heart rate consistently fell to lower values (see table 2). This is a well known phenomenon, as is the observation that the level of heart rate after establishing A-V rhythm was neither uniform nor did it bear an obvious relation to the level of the rate during S-A rhythm (for earlier literature see Eyster and Meek, 1921).

In the same dosage range in which it slowed the heart rate in the presence of S-A rhythm in experiments 3 and 4, veratramine proved capable of slowing the rate after A-V rhythm was established. This occurred consistently in all experiments in which veratramine was given without the simultaneous presence of an extraneously supplied sympathomimetic amine, *i.e.*, in experiments 3, 4, 5, 7 and 8 of table 2. An illustrative example is presented in figure 2A. Figure 2B shows the disappearance of the P wave in the electrocardiographic record (lead II) and the characteristic slowing of the rate during the shift from S-A rhythm to A-V rhythm, as well as the further slowing under the influence of veratramine.

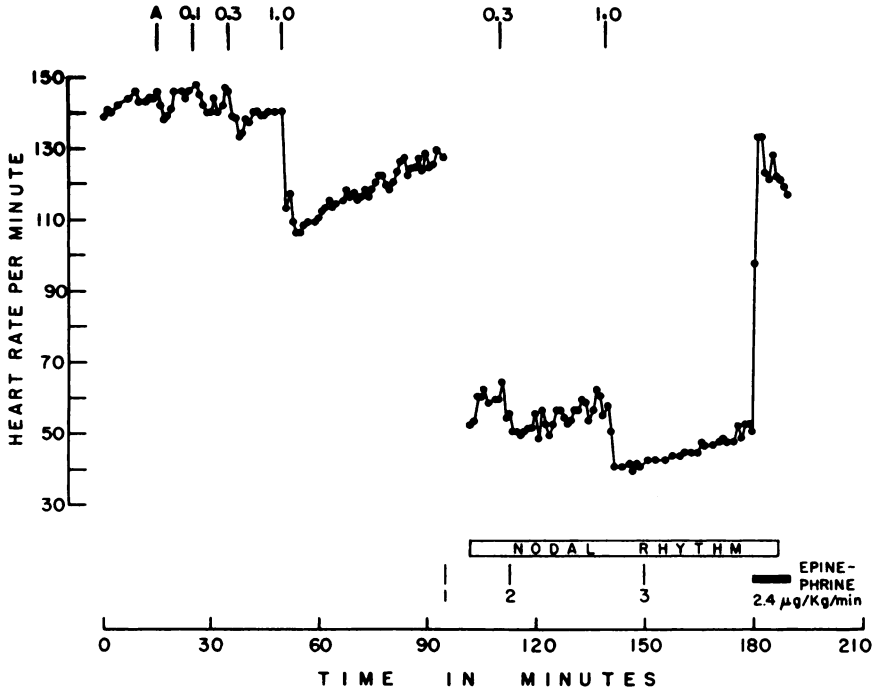

FIG. 2A. The effect of veratramine upon heart rate in the presence of S-A rhythm or A-V rhythm. Dog, male, 9.3 kgm. Between time 96 and 102 the S-A node was clamped off, and A-V rhythm was established. At A, atropine sulfate 1 mgm./kgm. was injected intravenously. The figures at the top are the total doses of veratramine injected intravenously at the respective signal marks. The open horizontal bar (nodal rhythm) indicates the period during which A-V rhythm with simultaneous atrial and ventricular activation was present. Its end marks the change to A-V rhythm with preceding atrial activation. The horizontal black bar at the bottom right indicates the continuous infusion of 2.4 microgm. epinephrine/kgm./min. The signals 1, 2 and 3 above the time line give the times at which the electrocardiograms of figure 2B were recorded. (This is experiment 3 of table 2; for further explanation see text.)

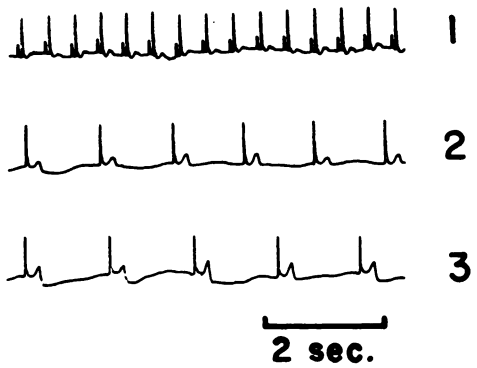

FIG. 2B. The effect of veratramine upon heart rate in the presence of S-A rhythm or A-V rhythm. Same experiment as figure 2A. 1 (S-A rhythm), 2 and 3 (A-V rhythm). The records were taken during the experiment of figure 2A at the times indicated. (Further explanations in text.)

The relative decrease in rate, caused, for example, by 0.06 mgm. veratramine per kgm. and its duration of action were of the same order in the presence of A-V rhythm as during S-A rhythm. Furthermore, the negative chronotropic action of veratramine, when A-V rhythm was established, was not prevented by atropine. In experiments 3 and 4, atropine sulfate had been administered at the start; in experiment 8, it was given after the S-A node had been excluded.

In all experiments of table 2, clamping off the S-A node led to A-V rhythm with simultaneous atrial and ventricular activation characterized by the absence of a P wave in the electrocardiographic record, as illustrated in figure 2B.

3. A-V rhythm with cardioacceleration caused by sympathomimetic amines. Increased heart rate with A-V rhythm and simultaneous atrial and ventricular activation was obtained in experiments 1 and 2 (of table 2) by the administration of epinephrine, in experiments 6 and 7 by norepinephrine, and in experiments 4 and 5 by tuaminoheptane. The three substances had qualitatively the same effect. As a representative example, the action of norepinephrine is illustrated in figure 3A and figure 3B. With suitable rates of continuous infusion, steady-state conditions of increasd heart rate could be maintained. The rates of infusion used are the figures without asterisk in the last column of table 2; infusion rates of doubtful effectiveness upon heart rate are in parentheses. Several of the experiments clearly indicated that an increased rate of infusion led to an increased level of heart rate; however, no attempt was made to gather quantitative data on the relationship between dose and response, inasmuch as the following observations presented considerable difficulties.

In these experiments with administration of a sympathomimetic amine in the presence of A-V rhythm with simultaneous atrial and ventricular activation, it happened occasionally that after a considerable period of infusion at a certain rate, atrial activation suddenly preceded ventricular activation. This manifested itself by the appearance in the electrocardiogram of a P wave preceding the ventricular complex. As a rule, the electrocardiographic change coincided with an abrupt shift of the heart rate to a higher level. This whole phenomenon invariably occurred immediately, or with a delay of not more than a few minutes, when the rate of infusion of the sympathomimetic amine was sufficiently increased. In the last column of table 2 the rates of infusion leading promptly to the appearance of a P wave preceding the ventricular complex are indicated by an asterisk. As can be seen, infusion rates causing this change in experiment 4 with epinephrine, and in experiments 7 and 8 with norepinephrine, did not produce it in other experiments. The infusion rate of 0.9 microgm./kgm./min. provoked the effect at the beginning of experiment 4, but no longer at a later stage.

The figures of infusion rates in table 2 give the impression that the change from A-V rhythm with simultaneous atrial and ventricular activation to A-V rhythm with preceding atrial activation occurred most readily, *i.e.*, at the lowest rates of infusion, with norepinephrine, less readily with epinephrine, and still less so with tuaminoheptane.

It is of interest in this connection that at the height of the heart rate increase

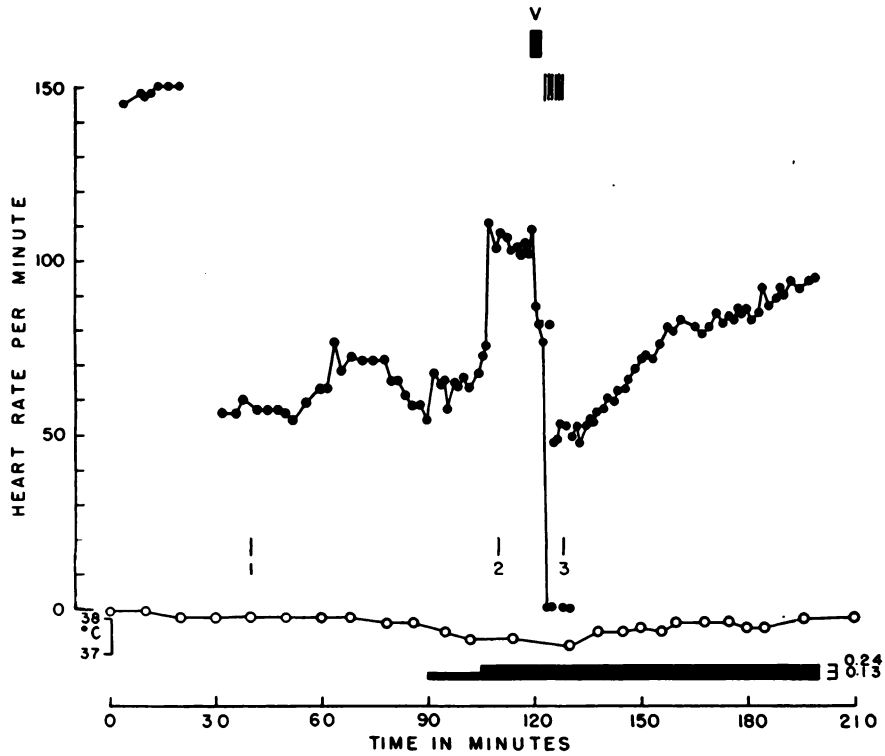

FIG. 3A. The effect of veratramine upon heart rate accelerated by norepinephrine in the presence of A-V rhythm. Dog, male, 11.5 kgm. Between time 25 and 30 the S-A node was clamped off and the clamp left in place. Full circles, heart rate/min. Open circles, temp. in °C. The horizontal black bar indicates the continuous infusion of norepinephrine first at the rate of 0.13 and then at the rate of 0.24 microgm./kgm./min. At V, 0.06 mgm. veratramine/kgm. was injected intravenously. The closely spaced vertical lines indicate that during this time the heart was repeatedly stimulated mechanically by touching the ventricles with a blunt instrument. The signals 1, 2 and 3 give the times at which the electrocardiograms of fig. 3B were recorded. (This is experiment 9 of table 2; for further explanation see text.)

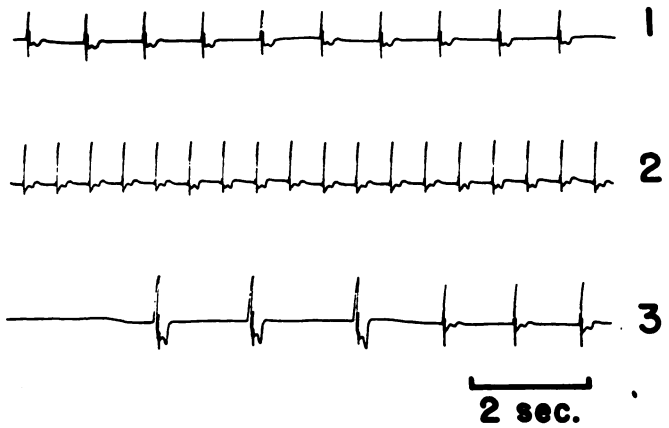

FIG. 3B. The effect of veratramine upon heart rate accelerated by norepinephrine in the presence of A-V rhythm. Same experiment as fig. 3A. The records 1, 2 and 3 were taken at the times indicated in fig. 3A by the corresponding figures. (Further explanations in text.)

(from 83 to 142), caused by a single total dose of 3 mgm. tuaminoheptane given intravenously in experiment 4, there was still simultaneous atrial and ventricular activation; while the injection of 0.05 mgm. isopropylarterenol in experiment 5 caused A-V rhythm with preceding atrial activation. However, in the latter experiment the heart rate prior to the injection was 108 beats/min. and the maximal rate 210 beats/min.

As was mentioned above, in the experiments with continuous infusion of sympathomimetic amines an abrupt rise in heart rate usually occurred coincident with the shift from A-V rhythm with simultaneous atrial and ventricular activation to A-V rhythm with preceding atrial activation. Conversely, after the discontinuation of the continuous infusion there was, as a rule, a gradual decrease in rate until the P wave disappeared; while the latter event coincided with an abrupt fall of the heart rate to a lower level.

After A-V rhythm with preceding atrial activation had been established by continuous infusion of a certain dose of epinephrine, norepinephrine or tuaminoheptane, the corresponding steady-state heart rate level could be maintained as long as the infusion continued. With successive increases in the rate of infusion, new steady-state levels of cardioacceleration could be achieved and maintained.

Veratramine was capable of exerting its antagonistic action to the cardioaccelerator effect of epinephrine and norepinephrine in the presence of A-V rhythm with preceding atrial activation as well as when there was simultaneous atrial and ventricular activation. Even if the heart rate was decreased to very low levels by veratramine, A-V rhythm, with preceding atrial activation, remained as long as the continuous infusion of the sympathomimetic amine continued. The experiment presented in table 3 illustrates this fact for epinephrine. It demonstrates, furthermore, the prompt reappearance of A-V rhythm with simultaneous atrial and ventricular activation after the discontinuation of the epinephrine infusion.

4. Asystole caused by veratramine in the presence of A-V rhythm. It was shown in these experiments that doses of veratramine in the range of 0.01 to 0.1 mgm./kgm. body weight were capable of reducing the heart rate in the presence of A-V rhythm, irrespective of whether the rate was normal or was elevated by the administration of sympathomimetic amines. The largest doses of veratramine, *i.e.*, 0.06 to 0.1 mgm./kgm., occasionally caused an effect not encountered so far in this dosage range when the S-A node was the pacemaker of the heart. When, in the course of the slowing, a critical rate level was reached, the heart stopped, to resume beating again after a few seconds. Thereafter, periods of asystole occurred once, or several times, before a regular beat was again established. During the asystole, the heart remained excitable and the ventricles could easily be made to contract, for example, by application of mechanical stimuli to the surface. The phenomenon is illustrated in figure 3A and figure 3B,3. The vertical line from rate 76 to 0 (in figure 3A, at time 123) indicates the first occurrence of asystole. During the next minute, the rate jumped once to 80 and, during the subsequent 9 minutes, it oscillated between 0 and 50 beats/min.

TABLE 3

*The effect of epinephrine and veratramine upon the sequence of atrial and ventricular activation during A-V rhythm**

Time	Heart Rate	P†	A-V Interval	Remarks
	beats/min.		%	
11:27	128	P	100‡	S-A rhythm
12:40	138A	P	96	S-A rhythm
12:40 to 12:46				S-A node clamped off; A-V rhythm
12:51	80	None		
2:54	63	None		
2:55				Begin of epin. inf. 0.9 microgm./kgm./min.
4:00	76	None		
4:00				Epin. inf. increased to 1.7 microgm./kgm./min.
4:01	83	P	73	
4:32	87	P		
4:35	90	P		
4:35				Veratramine 0.06 mgm./kgm.
15″	84	P		
30″	47	P		Rhythm irregular
45″	30	P		Rhythm irregular
4:36		P	69	2 periods of asystole of 4″ and 12″ duration
4:38	57	P		Rhythm regular
4:40	65	P		
4:42	70	P	68	
4:45	76	P		
4:45				End of epinephrine infusion
4:46	50	P		
4:47	67	None		
4:51	75	None		
4:55	70	None		
5:00	70	None		

* Data taken from experiment 4 of table 2.

† P indicates that atrial activation precedes ventricular activation, its absence means that atrial and ventricular activation occur simultaneously.

‡ The absolute value of the A-V interval was 0.11 seconds.

A—Atropine sulfate had been administered at 11:50.

Ten minutes after the injection of veratramine the rate became steady again and gradually returned near the level of 100 beats/min. Figure 3B,3 shows a period of asystole, the electrical changes accompanying three heart beats elicited by mechanical stimulation of the ventricles, and the electrical complexes of the subsequent spontaneous contractions.

This phenomenon of asystole occurred in experiments 3, 4, 5, 8 and 9 of table 2. It was seen in the presence of A-V rhythm without the administration of a sympathomimetic amine, as well as when the A-V node was under the influence of epinephrine, norepinephrine or tuaminoheptane. As table 3 indicates, it did occur also when there was A-V rhythm with preceding atrial activation. "Periodic activity" of the S-A node caused by veratramine has been observed and studied in the spinal cat, a preparation which permits the use of larger doses of veratramine (Kosterlitz, Krayer and Matallana, 1954, 1955).

III. Inactivity of veratramine against cardioacceleration due to impulse generation outside the S-A and A-V nodes. 1 Spontaneous auricular fibrillation in the isolated heart. In the course of setting up the heart-lung preparation of the dog, disturbances of rhythm of the character of auricular fibrillation occasionally occur for unknown reasons. In three such experiments with "spontaneous" auricular fibrillation in which the ventricular rate was high and irregular, veratramine was given in single doses of 0.8 to 1.0 mgm. No distinct effect was noted. For example, in one of these experiments (10/1/1952; dog 10.4 kgm.) 0.8 mgm. veratramine was administered within two minutes. Prior to veratramine the ventricular rate had oscillated between 210 and 218 beats/min. (temp. 37.5°C.). At the end of the veratramine injection it was not changed and during the following 13 minutes it varied between 196 and 212 beats/min. (temp. 37.8°C.). Auricular fibrillation continued. Fifteen minutes after the beginning of the veratramine injection, 10 mgm. of quinidine (as quinidine sulfate) was given within two minutes. At the end of the injection the ventricular rate varied between 156 and 165 beats/min. (temp. 38.0°C.). Three minutes later the fibrillation suddenly ended and the rate decreased to 139 beats/min. (temp. 38°C.). S-A rhythm had been established. This well known effect of quinidine was typical of that which occurred in two earlier experiments when, under similar conditions of spontaneous auricular fibrillation and without previous administration of veratramine, quinidine was given to the heart-lung preparation.

2. Ventricular tachycardia in the isolated heart caused by ouabain. It is well known that ventricular tachycardia very frequently precedes the fatal ventricular fibrillation of the mammalian heart when cardiac glycosides are administered in lethal doses. In the heart-lung preparation of the dog the ventricular tachycardia often lasts for a considerable time (15 to 30 minutes) and the rate may be quite regular. In four such experiments with ouabain, veratramine was given in single doses of 0.8 to 1.0 mgm. after heart block was complete, and after levels of ventricular rate of 200 per minute or above were reached. Apart from a slight slowing by a few beats in one experiment, no change in ventricular rate was noticed.

DISCUSSION. The decrease of the heart rate in the mammalian heart with

normal S-A rhythm caused by veratramine differs from the effect of vagal stimulation and from the action of parasympathomimetic substances in that atropine does not prevent or abolish it. Whether or not an antiaccelerator action participates in this negative chronotropic effect cannot be decided at present since no adequate data are available in support of the assumption (Krayer, 1950a) that the initial heart rate of the isolated mammalian heart is determined in part by sympathomimetic amines present at, or released in close proximity to, their site of chronotropic action.

The assumption that the S-A node is the exclusive site of the negative chronotropic action of veratramine is not supported by the evidence presented above. The A-V node responds to veratramine in qualitatively the same way as does the S-A node in that normal activity, as well as increased activity due to the influence of sympathomimetic amines, is reduced by veratramine. Consequently, the entire expanse of the cardiac tissue capable of serving, actually or potentially, as a physiological pacemaker must be regarded as the site of action of veratramine.

It has been pointed out in the past that a change from A-V rhythm with simultaneous atrial and ventricular activation to A-V rhythm with preceding atrial (or preceding ventricular) activation, might be due to a shift of the focus of automaticity within the A-V node. Moreover, it was emphasized that the phenomenon might be explained by changes in conductivity of the tissues which must be traversed by the impulses from the A-V node before atrial and ventricular activation can be effected (for a discussion of the problem see Holzmann, 1945; Scherf and Schott, 1953). The experiments with epinephrine and norepinephrine, presented above, stress the importance of effects upon conductivity. It is of interest in this connection that veratramine was shown not to influence the functional refractory period of auriculoventricular transmission in the dog heart and was unable to counteract the effect of epinephrine upon it (Krayer, Mandoki and Mendez, 1951). Hence, if, *e.g.*, in the experiment of table 3, the shift to A-V rhythm with preceding atrial activation is presumed to be due to an epinephrine effect upon conductivity, veratramine would not be expected to antagonize this effect in spite of its marked heart rate decreasing action.

The occurrence of asystole in the presence of A-V rhythm, in a dosage range of veratramine not leading to this effect in the presence of S-A rhythm, clearly indicates a greater vulnerability of the heart when the A-V node is the pacemaker. It remains doubtful, however, whether this constitutes a qualitative pharmacological difference between the S-A node and the A-V node. The decision must be left to further studies on the mechanism of asystole caused by veratramine.

The heart rate decreasing action of veratramine does not appear to extend to ventricular tachycardia caused by ouabain, and does not manifest iself when the heart rate is increased in spontaneous auricular fibrillation. This emphasizes further the well recognized pharmacological difference between ectopic impulse generation and impulse generation in the actual or potential physiological pacemaker.

The difference between the effects of veratramine and quinidine in spontane-

ous auricular fibrillation points to the difference between antiaccelerator action and antiarrhythmic action. While quinidine possesses antiaccelerator activity, its potency in this regard is certainly less than $\frac{1}{300}$ of that of veratramine (Krayer, 1950b). That is, in terms of antiaccelerator activity 0.8 to 1.0 mgm. veratramine is equivalent to 240 to 300 mgm. quinidine. Because this dose of veratramine was incapable of interfering with auricular fibrillation, while 10 mgm. of quinidine promptly abolished this arrhythmia, one must assume that veratramine—in a dose in which it exerts strong antiaccelerator action—has very little, if any, quinidine-like antiarrhythmic effect.

SUMMARY

The heart rate in the presence of S-A rhythm in the heart-lung preparation of the dog, as well as in the heart *in situ*, is reduced by veratramine. This negative chronotropic action of veratramine is not abolished or prevented by atropine.

The heart rate in the presence of A-V rhythm in the anesthetized dog is influenced by veratramine in qualitatively the same way as in the presence of S-A rhythm in the intact circulation and in the heart-lung preparation. After A-V rhythm has been established in the anesthetized dog by clamping off the S-A node, the heart rate is increased by the sympathomimetic amines *l*-epinephrine, *l*-norepinephrine, isopropylarterenol and tuaminoheptane. Veratramine antagonizes the positive chronotropic action of the sympathomimetic amines in the presence of A-V rhythm.

In the anesthetized dog in the presence of A-V rhythm, veratramine in a dose of 0.06 to 0.1 mgm./kgm. body weight is capable of producing asystole lasting for short periods, while, when the S-A node is the dominant pacemaker, asystole has not been observed under the same conditions and in this dosage range.

In the heart-lung preparation veratramine does not influence the increased heart rate resulting from spontaneous auricular fibrillation, or from the increased spontaneity of the ventricles in ventricular tachycardia caused by ouabain.

Veratramine, in doses which exert strong antiaccelerator action, or which cause a marked negative chronotropic effect in the presence of S-A rhythm, appears to possess little, if any, quinidine-like antiarrhythmic properties.

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