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# Action of Rubidium & Caesium on Frog's Heart

by

S. Ringer.

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# AN INVESTIGATION REGARDING THE ACTION OF RUBIDIUM AND CÆSIUM SALTS COMPARED WITH THE ACTION OF POTASSIUM SALTS ON THE VENTRICLE OF THE FROG'S HEART.

By SYDNEY RINGER, M.D., *Professor of Medicine at University College, London.* Plate XXII.

It is generally held that chemical similarity indicates similarity in physiological and therapeutic action, but whilst this inference is to some extent true, yet some substances closely allied chemically differ from each other widely in physiological and therapeutic effect. For instance, the physiological action of potash salts differs greatly from the action of sodium salts; and it is well known that, therapeutically, chlorides cannot replace iodides nor either of these take the place of bromides. To further test the correspondence between chemical and physiological action I made some experiments with chloride of calcium, chloride of strontium and chloride of barium[1]. I have shown[2] that a lime salt in the circulation is necessary to maintain the heart's contractility, but that when lime only is added to the circulating saline solution (sodium chloride ·75 p.c.), the diastolic dilatation is greatly prolonged. The addition of a physiological quantity of a potassium salt will obviate this effect, and if to saline solution we add a suitable quantity of a lime and a potash salt and render the solution slightly alkaline with bicarbonate of soda we get a circulating fluid fit to maintain rhythmic contractions in the detached ventricle for many hours. Now I find that in all these respects strontium acts very similarly to lime, that it can indeed to a large extent replace lime. On the other hand barium differs almost entirely from either calcium or strontium in its physiological action. Now these three elements form a group of which strontium is chemically more allied to lime than is barium. The physiological action therefore of these three substances corresponds to a great extent to what we should anticipate; except that we should expect barium to possess

[1] *Practitioner*, Aug. 1883.

[2] *Journal of Physiology*, Vol. IV. Nos. 1 & 2.

more of the characteristic effects of calcium and barium than is actually the case.

The close chemical relationship between potassium, rubidium and cæsium, led me next to investigate the degree of physiological correspondence between rubidium and cæsium on the one hand and potassium on the other.

I employed the chloride of each of these elements, using a solution prepared and calculated on their molecular weights. The potassium chloride solution was ·745 per cent., the rubidium chloride 1·205 per cent. and the cæsium chloride 1·68 per cent.

The experiments were made with the ventricle of the frog's heart attached to a perfusion cannula by a ligature placed as nearly as possible in the auriculo-ventricular groove. An artificial circulation was maintained through the ventricle by a syphon action. I employed Roy's tonometer to record as usual on a revolving cylinder the movements of the lever produced by the contraction of the ventricle. The experiments were made in June and July.

It is necessary to preface these experiments with rubidium and cæsium, with a brief statement of the physiological action of potassium on the frog's heart.

When the circulating fluid supplied to the detached ventricle consists of simple saline solution, the contractility at first grows weak or ceases and then gradually recovers itself more or less completely. Now a physiological dose of potassium chloride prevents the occurrence of this recovery.

When the ventricle is fed with saline solution containing a physiological quantity of a lime salt, diastolic dilatation is much retarded, so that if the contractions remain of normal frequency much fusion ensues. A physiological dose of a potassium salt accelerates this dilatation and makes the contraction similar to that which occurs when the circulating fluid consists of blood.

Sodium carbonate and sodium bicarbonate added to saline solution broaden the beat, cause much fusion of the beats and induce tonic contraction. A physiological dose of potassium chloride obviates all these effects.

When the circulating fluid consists of blood mixture[1] potassium salts

(1) greatly prolong the latent period,

[1] Blood mixture is made by dissolving dried bullocks' blood so as to imitate fresh blood and diluting this with two parts of saline made with tap water.

(2) greatly prolong the period of diminished excitability and consequently greatly diminish the frequency of the spontaneous contractions and greatly diminish the frequency with which contractions can be excited by electric stimulation.

With blood mixture[1], faradization induces tetanus by fusion of the beats, but when a potassium salt is added to the blood mixture then faradization completely arrests the contractions, which recommence on discontinuing faradization.

Potassium salts arrest the ventricle in diastole.

The following experiments with Rubidium Chloride show that in all the foregoing particulars the action of rubidium corresponds to the action of potassium.

Like potassium chloride, rubidium chloride prevents that recovery of the ventricle which occurs when it is supplied with simple saline solution. With simple saline at first there is considerable weakening of the beats and even arrest of the contractility but considerable or complete recovery soon sets in. On replacing blood mixture with saline solution containing rubidium chloride in the proportion of 1 c.c. of 1·205 per cent. solution of rubidium chloride in 100 c.c. of saline solution the ventricular contractility grows less and less till it disappears. On the addition however of either calcium chloride or strontium chloride good contractions speedily return.

Like potassium, rubidium obviates the effect of a calcium salt on the ventricular dilatation. As I have formerly shown a lime salt added to saline broadens the beat, rounds its top and later greatly retards dilatation. 1 c.c. of 1·2 per cent. solution of rubidium chloride to the 100 c.c. of circulating fluid completely removes these lime effects and restores to the beat the same character it possessed when fed with blood mixture.

Like potassium, rubidium obviates the effect of sodium bicarbonate. I replaced blood mixture by 200 c.c. of saline solution containing 5 c.c. of 1 per cent. solution of sodium bicarbonate; the sodium bicarbonate as usual broadened the beat and caused much fusion of the beats and induced a little tonic contraction. 1 c.c. of 1·205 per cent. solution of rubidium chloride obviated all these effects.

I have elsewhere[2] shown, that a circulating fluid, to sustain the contractility of the heart must be alkaline in reaction and must in

[1] Blood mixture is made by dissolving dried bullocks' blood so as to imitate fresh blood and diluting this with two parts of saline made with tap water.

[2] This Journal, *loc. cit.*

addition to sodium chloride contain both lime and potassium salts. The following experiment shows that rubidium chloride will replace potassium chloride in this solution and will sustain the heart's contractility. I replaced blood mixture by 200 c.c. saline solution containing 2 c.c. of 1 per cent. solution of calcium chloride, 1·5 c.c. of 1·205 solution of rubidium chloride and 5 c.c. of 1 per cent. solution of sodium bicarbonate; fifty-five minutes after the substitution the contractions continued in all respects the same as with blood mixture.

On another occasion after replacing blood mixture by a similar solution, at the expiration of an hour after the substitution, the beats continued as good as the beats with blood mixture.

We find then that rubidium can largely replace potassium and I have shown in a previous paper[1] that strontium can replace lime. I therefore experimented to ascertain whether I could devise a fluid capable of sustaining the heart's contractility containing rubidium and strontium in place of potassium and calcium. Among other combinations I employed the following: 200 c.c. of saline solution containing 2·5 c.c. of 1·58 per cent. solution of strontium chloride, 1·5 c.c. of 1·2 per cent. solution of rubidium chloride and 4 c.c. of 1 per cent. solution of sodium bicarbonate. The character of the contractions remained unchanged but the beat grew slowly weaker so that in thirty-five minutes there occurred a reduction of one third the height of the trace of each contraction. Strontium and rubidium therefore, though decidedly inferior to calcium and potassium, will sustain the contractility for a considerable time.

Dr Sainsbury kindly tested the effect of rubidium on tetanus induced by continuous faradization. Potassium salts, it will be remembered, not merely prevent tetanus by continuous faradization, but so influence the cardiac muscular tissue, that on the application of faradization all spontaneous contractions cease and the ventricle remains in diastole, but on suspending the application of the faradic current spontaneous contractions return. Rubidium in this respect is similar to potassium. At the commencement of the experiment, when blood mixture was alone used he obtained well-marked fusion with the secondary coil at 8. After the addition of 6 c.c. of 1·205 per cent. solution of rubidium chloride to the 100 c.c. of circulating fluid, the fusion became notably less, there was indeed no fusion at all, simply acceleration during the time of faradization; after 10 c.c.,

[1] *Practitioner, loc. cit.*

the already existing rhythm remained undisturbed, the faradization producing no effect. After 12 c.c. the same obtained; but although the faradization with the coil at 8 had lost all power to cause fusion, there was no actual inhibition of the beats during faradization. On putting the secondary coil at 6, the characteristic potash effect at once came out, viz. the beats ceased completely during faradization, commencing starting again almost at once on its cessation; the same obtained with the coil at 4. Hence increasing the strength of the faradic current, instead of tending towards the production of tetanus, gave an opposite effect.

Again rubidium like potassium increases "the period of diminished excitability." In these experiments break shocks alone were employed and by means of a metronome placed in the primary circuit, which latter included the time marker, he was able to increase or diminish the interval between successive stimuli and also to record the moment of stimulation. The result showed no very decided effect on the latent period, but if anything the effect was in the way of prolongation: on the period of diminished excitability however the effect was decided. Here the experiment started with the stimuli so distanced as to yield considerable fusion of the two beats; i.e. the pair of stimuli produced a pair of beats which overlapped each other. This occurred with the metronome standing at 22 on the scale, and the secondary coil at 7. After the addition of rubidium chloride, at the end of the experiment the secondary coil at 7 was unable to excite a contraction at all, and with the coil pushed up to 3, it was no longer possible to produce double excitation, except by increasing considerably the interval between the stimuli, viz. with the metronome advanced from 22 on the scale to 5.

Like potassium chloride, rubidium chloride arrests the ventricle in diastole.

Whilst rubidium is so closely similar to potassium, the case is far different with cæsium, the physiological action of this metal being much more akin to barium and strontium.

On replacing blood mixture by 200 c.c. of saline solution containing 1·2 to 2 c.c. of 1·68 per cent. solution of cæsium chloride, the frequency of the spontaneous contractions is much increased, the trace of each beat becomes much broadened with much fusion of the contractions. Much tonic contraction also occurs. The primary fall with simple saline only is prevented or becomes very slight, but cæsium cannot sustain the heart's contractility and so the trace falls nearer and nearer to the

base line, and in about twenty minutes all contractility ceases. When the ventricle beats less frequently the trace of each beat then becomes still broader.

The following experiment well illustrates many of the properties of cæsium.

I first took a trace with blood mixture (see Fig. 1. A.). I then substituted for the blood mixture, 200 c.c. of saline solution, containing 2 c.c. of 1·685 per cent. solution of cæsium chloride. The trace of each beat soon grew broader, and tonic contraction ensued. Ten minutes after the change of fluid the trace beat had become very greatly broadened (see B.). The ventricle then grew weaker and weaker till at last contraction almost ceased, when I added 3 c.c. of 1 per cent. solution of sodium bicarbonate to 150 c.c. of circulating fluid. The contractions grew stronger but retained the same character and never became so complete as with blood mixture (see C, ten minutes after adding the sodium bicarbonate).

I then added 1 c.c. of 1 per cent. solution of potassium chloride to 150 c.c. of circulating fluid. This weakened the contractions almost to the point of extinction. On adding 1·5 c.c. of 1·586 per cent. solution of strontium chloride, an equivalent quantity to the cæsium chloride contained in the fluid, the contractions immediately improved and became as complete as with blood mixture, but retained the cæsium quality, indeed they became broader than under cæsium and saline alone (see D. after a long diastolic pause). The length of the contraction was proportionate to the interval of rest between each beat.

I then added 1·5 c.c. of 1·11 per cent. solution of calcium chloride or an equivalent quantity molecule for molecule to the cæsium chloride contained in the fluid and immediately the lime prevailed over the cæsium, the beats grew shorter and shorter till they became almost identical with the beats under blood mixture (see E.). Here whilst an equal molecular quantity of strontium failed to remove the cæsium effects an equal molecular quantity of calcium chloride almost entirely replaced the cæsium effects.

It appears then, that cæsium differs considerably from potassium and rubidium and is closely allied in its physiological action on the ventricle to barium.

Whilst strontium is powerless to antagonize an equal molecular quantity of cæsium, yet by increasing the quantity of strontium the cæsium effect may be overcome.

In the preceding experiment lime antagonizes cæsium but at the

same time cæsium antagonizes some of the calcium effects, if the salts are employed in equal molecular quantities.

I replaced blood mixture by 200 c.c. saline solution containing 4 c.c. of 1 per cent. solution of sodium bicarbonate and 2 c.c. of 1·11 per cent. solution of calcium chloride and 2 c.c. of 1·685 per cent. of cæsium chloride. The trace of each beat grew somewhat broader and its top rounded, but no other change occurred. The diastole did not become delayed, nor did any contraction or fusion of the beats occur. The ventricle continued to beat spontaneously and three hours after the substitution, the trace of each contraction measured about one-eighth less and was a little broader and rounder at its top than at the beginning of the experiment with blood mixture.

Here, then, whilst calcium antagonized the cæsium, the cæsium antagonized the calcium preventing its effect on dilatation and in this respect acting like potassium.

Here we have an instance of mutual antagonism. The lime prevented the cæsium effects whilst the cæsium obviated one of the calcium effects and as the result of this mutual antagonism we obtained a good circulating fluid capable of sustaining good contractions for upwards of three hours, the character of the contractions differing little from the contractions with blood mixture.

This mutual antagonism is shown in another interesting way.

I replaced blood mixture by 200 c.c. of saline solution containing 4 c.c of 1 per cent. solution of sodium bicarbonate and 2 c.c. of 1·11 per cent. solution of calcium chloride. The usual calcium effects ensued, see Fig. 2. B. Then to the 200 c.c. of circulating fluid I added 2 c.c. of 1·685 per cent. solution of cæsium chloride. At first the fusion increased much. Five minutes after the addition of cæsium I obtained the trace shown at C.

The contractions then grew gradually more regular and about twelve minutes after adding the cæsium the beats became just like those with blood mixture. An hour after the replacement the ventricle beat spontaneously and its beats were equally good and of the same character as with blood mixture: see D. Here the cæsium before it had time to expend its full antagonistic effect, caused much irregularity in the character of the beat, but when the antagonism became complete, the contractions assumed a natural character just like those with blood mixture.

Cæsium, then, in spite of its close chemical affinity to potassium, differs considerably from potassium. Cæsium, indeed, produces for the

most part the opposite effects to potassium, broadening the trace, rounding its top, inducing fusion; yet in spite of this great difference in its action still cæsium, like potassium, possesses the property of obviating the effect of calcium on the dilatation.

Next I endeavoured to ascertain whether with strontium and cæsium together we could constitute a fluid able to sustain the heart's contractility.

I replaced blood mixture by 100 c.c. saline solution containing 4 c.c. of 1 per cent. solution of sodium bicarbonate, 1 c.c. of 1·685 per cent. solution of cæsium chloride and 1 c.c. of 1·586 per cent. solution of strontium chloride. The contractions grew much broader and in about ten minutes, the dilatation became much prolonged and the contractions grew feeble. I then added 1 c.c. of 1·11 per cent. solution of calcium chloride and the contractions at once improved and the trace soon quite recovered its original height, and the delay in dilatation disappeared, the trace remaining only a little broader than with blood mixture.

We find then that strontium and cæsium cannot sustain the heart's contractility, and that on the addition of equivalent molecular quantity of lime the strontium effects are removed, the contractions recover and become normal again.

As cæsium is so similar to barium in its action on the ventricle, I resolved to ascertain if barium could take the place of cæsium and when associated with a lime salt could sustain the contractility of the ventricle. I replaced blood mixture by 100 c.c. of saline solution containing 2 c.c. of 1 per cent. solution of sodium bicarbonate, 1 c.c. of 2·08 per cent. solution of barium chloride and 1 c.c. of 1·11 per cent. solution of calcium chloride. The beats became broader and fused and grew much weaker. I then added 1 c.c. of 1·685 per cent. solution of cæsium chloride. The fusion ceased, and at first lime effects persisted, for the dilatation continued much delayed, but this condition soon disappeared and the trace became almost the same as with blood mixture.

Here, then, as might be expected, in spite of the close similarity in their action on the ventricle, barium cannot replace cæsium, see Fig. 3.

Cæsium differs in part from both potassium and rubidium in respect to its influence on the effect from continuous faradization. Under the influence of cæsium chloride, faradization does not inhibit the cardiac contractility. I made experiments exactly similar to those with rubidium, using a 1·685 per cent. solution of cæsium chloride. Additions from

time to time of this solution produce gradual loss of excitability of the cardiac tissue for the faradic stimulus. Starting with a good tetanus, this gradually lessened and at last the faradization is without effect, the existing rhythm being unmodified. This occurred after the addition of 3 c.c. of the cæsium chloride solution, but the inhibitory effect was not seen even after 4 c.c. though the ventricle was practically arrested in full diastole; it was possible to see for each period of faradization, a faint corresponding waviness of the trace, indicating faint contractions.

Dr Sainsbury tested the effect of cæsium on the period of diminished excitability by experiments performed exactly like those with rubidium.

The period of latency was somewhat increased but the effect was not very marked. The period of diminished excitability was very decidedly increased, the metronome being advanced from 15, which position was effective up to the top of the scale (0) and yet the second stimulus remained without effect. This occurred after the addition of 2 c.c. of the cæsium solution. In this experiment the ligature was placed well below the auriculo-ventricular groove, through the substance of the ventricle, yet in spite of this spontaneous contractions set in after the drug was commenced and this increase in the period of diminished excitability occurred in spite of the increased frequency of the spontaneous contractions.

Cæsium chloride, then, in its physiological action on the ventricle, only corresponds to potassium chloride in these respects, both obviate the delay in dilatation caused by calcium salts and both increase the period of diminished excitability and so prevent tetanus from continuous faradization.

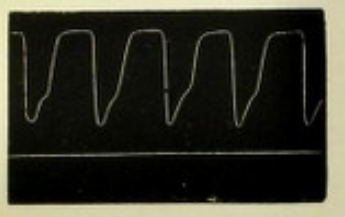
It is interesting to compare the effect of chemical similarity on physiological similarity in the group calcium, strontium and barium and in the group including potassium, rubidium and cæsium.

Strontium is chemically more allied to calcium than barium is to calcium and whilst strontium is in its physiological action very similar to calcium, barium is far less similar to calcium. So it is with the group potassium, rubidium and cæsium. Rubidium is chemically more allied than cæsium to potassium and yet rubidium is almost identical in its physiological action with potassium, whilst cæsium differs in most of its physiological effects from potassium.

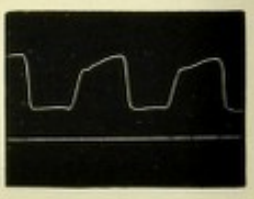
Fig. 1.

A.

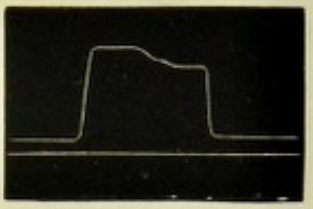
B.



C.



D.



E.

Fig. 2.

A.

B.

C.

D.

Fig. 3.

A.

B.

C.

## EXPLANATION OF FIGURES. PLATE XXII.

### Fig. 1.

A. Trace with blood mixture.

B. Trace taken ten minutes after the substitution of blood mixture by 200 c.c. of saline solution containing 2 c.c. of 1·685 per cent. of cæsium chloride.

C. Ten minutes after the addition of 3 c.c. of a 1 per cent. solution of sodium bicarbonate to 150 of the above.

D. After the addition of 1 c.c. of a 1 per cent. solution of potassium chloride to 150 of circulating fluid and subsequently of 1·5 c.c. of a 1·586 per cent. solution of strontium chloride.

E. After the addition of 1·5 c.c. of a 1·11 per cent. solution of calcium chloride.

### Fig. 2.

A. Trace with blood mixture.

B. Trace about fifteen minutes after replacing blood mixture with 200 c.c. saline solution containing 4 c.c. 1 per cent. solution of sodium bicarbonate and 2 c.c. 1·11 per cent. solution of calcium chloride.

C. Trace five minutes after adding 2 c.c. of 1·685 per cent. solution of cæsium chloride to 200 of circulating fluid.

D. Forty-five minutes after the addition of cæsium chloride and an hour after the replacement of blood mixture by saline solution containing sodium bicarbonate and calcium chloride.

### Fig. 3.

A. Trace with blood mixture.

B. Effect of replacing blood mixture by saline containing chloride of calcium, chloride of barium and sodium bicarbonate.
It shews also the effect of adding cæsium to the circulating fluid; the cæsium chloride was added at the point indicated by an arrow.

C. Trace twenty minutes after adding cæsium chloride and forty minutes after replacing blood mixture by saline containing barium chloride and calcium chloride.