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Chemical Character and Physiological Action of the Potassium Ion

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CHEMICAL CHARACTER AND PHYSIOLOGICAL ACTION OF THE POTASSIUM ION.

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I. INTRODUCTION.

Zwaardemaker[1] has recently made the interesting suggestion that the rôle of potassium in physiologically balanced salt solutions—*e.g.* the blood or the sea water—is due to the very slight radioactivity of this element and not to its chemical character as determined by its position in the series of elements. It has been pointed out by R. F. Loeb[2] in another paper in this *Journal* that K cannot be replaced by Th and U as far as the development of the sea urchin egg is concerned, that the non-radioactive element Cs is capable of replacing potassium to some extent in this case, and that Zwaardemaker's observations on the influence of radioactive substances on the heart beat might be explained without the assumption that the physiological action of K is due to its radioactivity.

This then suggests that the physiological action of potassium is due to its chemical character. We know through the work of Sir Ernest Rutherford that radioactivity is caused by an explosive charge in the nucleus of the atom while the chemical and most of the physical properties of the atom depend upon its external ring or shell of electrons. These latter properties are repeated periodically in the series of elements arranged by their atomic numbers and if we can show that the physiological action of an element corresponds to its position in the periodic table we know that we are dealing with purely chemical effects and not with radioactive effects. We intend to show in an indirect way that the action of K in physiologically balanced salt

[1] Zwaardemaker, H., *J. Physiol.*, 1919–20, liii, 273

[2] Loeb, R. F., *J. Gen. Physiol.*, 1920–21, iii, 229.

solutions corresponds to its purely chemical character; *i.e.*, its position in the periodic table (or rather to its atomic number and arrangement of external electrons).

II. The Resemblance in the Antagonistic Effects of the NH_4 and K Ions.

According to their physiological action the ions of the alkaline metals can be arranged in two distinct groups, the one including Li and Na, the other K, Rb, and Cs. The difference in the two groups is noticeable in various phenomena. Isotonic solutions of LiCl and NaCl will give rise to muscular twitchings while KCl, RbCl, and probably CsCl will not. Experiments on the egg of *Fundulus* show that toxic solutions of salts with bivalent metals, such as $MgCl_2$ or $CaCl_2$, can be rendered less toxic by the addition of KCl, RbCl, or CsCl, but not or practically not by the addition of NaCl or LiCl.[3] It is known that the NH_4 ion resembles in its chemical behavior the K ion more closely than it does the sodium ion, and Langmuir[4] has utilized this fact in support of his theory of the cubical atom. If it be true that the physiological action of K depends upon its chemical character, the close resemblance between the chemical character of NH_4 and K should express itself in phenomena of antagonism. NH_4Cl is generally very toxic for cells but it can be used with good effect in experiments on the egg of *Fundulus* which is surrounded by a rather impermeable membrane. In experiments on *Fundulus* it can be shown that the antagonistic action of the NH_4 ion is like that of the members of the K group and not like that of the members of the Na group.

When newly fertilized eggs of *Fundulus* are put into a 5 M/32 solution of $CaCl_2$ practically no egg (*i.e.* less than 2 per cent of the eggs) can form an embryo. When the 5 M/32 $CaCl_2$ solution is made up in solutions of different chlorides instead of in H_2O it is found that in LiCl and NaCl the toxicity of the $CaCl_2$ solution is not diminished. When, however, the 5 M/32 $CaCl_2$ solution is made up in KCl, RbCl, CsCl, or NH_4Cl a considerable percentage of the eggs can develop into embryos as is shown in Table I.

[3] Loeb, J., *J. Biol. Chem.*, 1914, xix, 431.

[4] Langmuir, I., *J. Am. Chem. Soc.*, 1920, xlii, 274.

The same fact can be demonstrated equally well with other toxic solutions; *e.g.*, Na_3 citrate. If newly fertilized eggs of *Fundulus* are put into M/100 Na_3 citrate practically no egg can form an embryo, and the result remains the same if the M/100 solution of Na_3 citrate is made up in different concentrations of LiCl or NaCl. When, however, the M/100 solution of Na_3 citrate is made up in KCl, RbCl, CsCl, or NH_4Cl a considerable number of eggs develop into embryos as indicated in Table II.

TABLE I.

	Percentage of newly fertilized *Fundulus* eggs which can form embryos in 5 M/32 $CaCl_2$ when this solution is made up in						
	0	M/80	M/40	M/20	M/10	M/5	3 M/10
LiC	1.5	0	0	0	0	0	0
NaCl		1	2	1	0	0	0
KCl		5	21	21	44	60	64
RbCl		19	23	26	40	54	43
CsCl		3	4	14	9	17	30
NH_4Cl		1	0	3	4	17	16

TABLE II.

	Percentage of eggs of *Fundulus* which can develop in M/100 sodium citrate solution if this solution is made up in					
	0	M/40	M/20	M/10	M/5	3 M/10
LiCl	0	3	2	0	0	0
NaCl	0	6	0	2	1	0
KCl	0	26	19	57	52	53
RbCl	8	46	55	60	55	42
CsCl	8	40	60	56	32	
NH_4Cl	8	2	1	2	45	36

The table shows that when the M/100 Na_3 citrate solution is made up in M/5 KCl, RbCl, CsCl, or NH_4Cl practically half the eggs form embryos. In this experiment the addition of the Cl ion may diminish the toxicity of the citrate solution but if this be true the fact remains that the Cl ion can have this effect only when it is added with K or NH_4 ions and not when added with Na or Li ions.

The NH_4 ion, therefore, resembles in its physiological behavior the K ion more than it does the Na or Li ion.

III. The Antagonism between Li and K.

In any series of ions based on their chemical or physical behavior Na occupies a position between Li and K. Li has a smaller and K has a larger ionic radius than Na. If we replace some of the Na ions of sea water by Li ions we alter the properties of the solution in one sense, and if we replace part of the Na ions by K ions we alter the properties in the opposite sense. We should, therefore, expect that if we replace a certain percentage of Na ions in sea water by Li ions the toxic character of the solution should be diminished if we replace at the same time also a certain percentage of the Na ions by K ions; since with the combined increase of the K ions and of Li ions the effect of Na ions might be more nearly approximated.

The newly fertilized egg of the sea urchin (*Arbacia*) can develop into gastrulæ in an "artificial sea water" of the following composition.

100.0	cc. of M/2 NaCl
1.75	cc. of M/2 $CaCl_2$
2.2	cc. of M/2 KCl
7.8	cc. of M/2 $MgCl_2$
3.8	cc. of M/2 $MgSO_4$

To this was added 0.8 cc. of M/10 $NaHCO_3$ to bring the artificial sea water to a pH of about 7.4.

We prepared the following solution in which M/2 NaCl of the artificial sea water was replaced by M/2 LiCl and which was free from K. Its composition was:

100.0	cc. of M/2 LiCl
1.75	cc. of M/2 $CaCl_2$
7.8	cc. of M/2 $MgCl_2$
3.8	cc. of M/2 $MgSO_4$
0.8	cc. of M/10 $NaHCO_3$

This solution, which we will call the Li mixture, permitted us to replace the Na in natural or artificial sea water by Li without altering the constitution of the sea water in any other direction except in regard to K, the concentration of which it was our intention to vary in the experiments.

Our first experiments consisted in mixing various quantities of natural sea water and Li mixture to find out the maximal amount of Li in natural sea water which still permitted the formation of normal blastulæ in about 16 or 20 hours; the eggs were put into the solution immediately after fertilization. It was found that only 8 per cent of the Li mixture could replace the natural sea water without preventing the development of the eggs into swimming blastulæ. When, however, the proportion of KCl contained in the sea water was increased thirteen times its normal amount the eggs were able to develop into larvæ when as much as 52 per cent of Na was replaced by Li. It is therefore possible to increase the tolerance of the sea urchin egg

TABLE III.

Maximal Amount of Li in which Swimming Blastulæ of Arbacia Can Be Obtained.

K mixture.	Natural sea water.	Li mixture.
cc.	*cc.*	*cc.*
0.0	23.0	2.0
0.5	19.5	5.0
1.0	18.0	6.0
2.0	16.0	7.0
4.0	12.0	9.0
6.0	6.0	13.0

against Li 600 per cent by increasing simultaneously the amount of K normally present in the sea water by 1,300 per cent. Since it was necessary to keep all the other constituents of the sea water constant the KCl was not added in the form of a pure M/2 solution of this salt but in the form of a mixture of the following composition which we will call the KCl mixture.

100.0 cc. of M/2 KCl
1.75 cc. of M/2 $CaCl_2$
7.8 cc. of M/2 $MgCl_2$
3.8 cc. of M/2 $MgSO_4$
0.8 cc. of M/10 $KHCO_3$

Systematic experiments showed that the maximum dose of Li in which the eggs could develop into larvæ increased with the concentration of K added to the sea water. This is indicated in Table III.

The table shows that if we wish to replace in normal sea water more Na by Li we must at the same time also replace an increasing proportion of Na by K.

In order to obtain a more regular curve than expressed in Table III we replaced the natural sea water by a NaCl mixture free from KCl and made up as follows:

100.0 cc. of M/2 NaCl
1.75 cc. of M/2 $CaCl_2$
7.8 cc. of M/2 $MgCl_2$
3.8 cc. of M/2 $MgSO_4$
0.8 cc. of M/10 $NaHCO_3$

Experiments were then made to ascertain the maximal amount of Li mixture which permitted the formation of swimming blastulæ for each given amount of KCl. The results are contained in Table IV.

TABLE IV.

Maximal Amount of Li Mixture Permitting Formation of Swimming Blastulæ.

K mixture.	Na mixture.	Li mixture.
cc.	*cc.*	*cc.*
0.1	24.0	1.0
0.2	23.0	2.0
0.5	22.0	3.0
1.0	20.0	4.0
2.0	17.0	6.0
4.0	13.0	8.0
6.0	10.0	9.0
7.0	8.0	10.0

When 8 cc. of K mixture were used no more larvæ were obtained on account of the fact that this concentration of K itself was too toxic.

Table IV shows more clearly than Table III that by replacing more Na ions by K ions we increase at the same time the proportion of Na ions which can be replaced by Li ions, without preventing the development of the sea urchin egg into a swimming larva.

It was then shown that Rb has a similar but not quite so great an effect as K (Table V). RbCl was also added in the form of a mixture containing all the other constituents of sea water except K and Na.

Cs acts also somewhat like K but still less weakly than Rb. Only one series of experiments was made in an attempt to replace K by Cs, and this series proved that in 2 cc. of M/2 CsCl mixture + 19 cc. of natural sea water + 4 cc. of M/2 Li mixture swimming larvæ could be obtained. When no sea water was replaced by CsCl, 2 cc. of the Li mixture in 25 cc. was the maximum which still permitted the development of larvæ.

These results show that the toxic effects of Li, which occupies in the periodic table a position on one side of NaCl, are mitigated by the addition of ions like K, Rb, and Cs, occupying a position on the other side of Na. A mixture of Li and K ions in proper proportions acts more like a solution of Na ions than do the Li ions alone.

TABLE V.

Maximal Amount of Li Mixture Permitting Formation of Swimming Larvæ.

Rb mixture.	Sea water.	Li mixture.
cc.	*cc.*	*cc.*
1.0	20.0	4.0
2.0	18.0	5.0
4.0	14.0	7.0

It should be taken into consideration that in these experiments the balance between monovalent and bivalent cations was not disturbed.

If we replace a smaller or larger percentage of the Na ions contained in sea water by Mg or by Ca ions the toxicity of LiCl is not diminished. This is probably due to the fact that the quantity of Ca or Mg required for balancing the monovalent cations is naturally present in the sea water.

The antagonism between LiCl and KCl can also be demonstrated in the eggs of *Fundulus*. When newly fertilized eggs of *Fundulus* are put into M/5 LiCl all the eggs are dead before an embryo is formed. If, however, the M/5 solution of LiCl also contains a small quantity of RbCl or of KCl, as many as 20 per cent of the eggs live long enough to form embryos. When, however, the M/5 LiCl solution contains NaCl not a single embryo is formed. CsCl also gives a positive effect. The M/5 LiCl solution was made up in distilled water and in different concentrations of the salts mentioned. Table VI gives the results of an experiment. The first horizontal row gives the molecular concentration of NaCl, KCl, RbCl, and CsCl in which the M/5 solution of LiCl was made up. The figures in the next horizontal rows give the percentage of eggs which formed embryos.

The table shows that the addition of NaCl did not protect the *Fundulus* eggs against the toxic effects of LiCl, while the KCl, RbCl, and CsCl had a protective or antagonistic effect. The protective effect of these salts is considerably less than that produced by a salt with a bivalent cation since in the latter case 80 per cent or more of the eggs form embryos in a M/5 solution of LiCl.

TABLE VI.

	Percentage of eggs which formed embryos in M/5 LiCl made up in					
	0	M/40	M/20	M/10	M/5	3 M/10
NaCl	0	0	0	0	0	0
KCl	0	18	10	14	11	6
RbCl	0	7	13	18	20	2
CsCl	0	2	0	5	9	2

These examples may suffice to show that the action of the potassium ion in the phenomena of antagonism (which underlie the physiological balance of ions in salt solutions) is in agreement with the purely chemical character of this ion, *i.e.* its position in the periodic table; and that hence there is no reason to attribute its physiological action in these cases to some other factor; *e.g.*, its extremely minute radioactivity.

SUMMARY.

1. It is shown that the NH_4 ion acts in cases of antagonism on the egg of *Fundulus* more like the K ion than the Na ion; this corresponds to the fact that in its general chemical behavior the NH_4 ion resembles the K ion more closely than the Na ion.

2. It is shown that the tolerance of sea urchin eggs towards the Li ion can be increased 500 per cent or more if at the same time a certain amount of Na ion is replaced by K, Rb, or Cs ions. Since in the

periodic table Na occupies a position between K and Li it is inferred that the Li and K ions deviate in their physiological action in the opposite direction from the Na ion.

3. These data indicate that the behavior of the K ion in antagonistic salt action (which forms the basis of the physiologically balanced action of ions) is due to its purely chemical character, *i.e.* its position in the periodic table or rather to its atomic number, and not to those explosions in its nucleus which give rise to a trace of radioactivity.