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THE INFLUENCE OF POTASSIUM AND CALCIUM IONS ON THE ACTION OF PROCAINE

BY

H. J. BEIN

From the Department of Pharmacology, Oxford

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It has long been established that the optimum functioning of cells is dependent on optimum amounts of different electrolytes in the fluid surrounding them. In particular it is known that function is still maintained if an excess of one electrolyte is compensated by a corresponding increase of another, the best-known pair being the potassium and calcium ions, chiefly studied in the heart by Ringer.

It is important, however, to realize that pharmacological investigations which consider the action of drugs in relation to this variable content of electrolytes are very different from observations of body functions only. Electrolytes may prevent or assist the action of a drug on a tissue, and it is not only the affinity of an electrolyte to a cell which is important, but also its affinity to the drug. In the complicated system composed of the cell, a variable content of electrolytes and the drug, with all their mutual relations, the response of the tissue will not necessarily follow the same laws as it would in the absence of the drug.

Two recent papers show that the absolute concentration of potassium is of great importance for some drug actions, more so than its relative concentration to calcium, i.e., the K/Ca ratio. Baker (1947) tested the interrelation between Ca, K and ouabain on the isolated heart and in the whole animal; Goffart and Brown (1947) investigated the correlation of K and adrenaline on the isolated striated muscle. In order to see whether the effects described are peculiar to these two drugs or have a more general significance I have tested the effect of changing the K and Ca concentrations on another drug action, namely that of procaine on the refractory period of the isolated rabbit auricles.

METHOD

The method of measuring the activity of pharmacological agents on the refractory period has been described in detail by Dawes (1946a). The auricles, carefully dissected from the heart of a rabbit, are suspended in a bath containing 100 c.c. of oxygenated Ringer-Locke at 29° C. The composition of the Ringer-Locke is as follows: NaCl 9.0 g.; KCl 0.42 g.; $CaCl_2$ 0.24 g.; $NaHCO_3$ 0.5 g.; dextrose 2.0 g.; distilled water 1,000 c.c.

The contractions of the auricles are recorded on a smoked drum. The auricles contract rhythmically by themselves and they can also be driven by break-shocks from an induction coil at any desired speed. The maximal rate is observed at which the auricles will follow electrical stimulation. The reduction or the increase in maximum rate caused by a drug is calculated and expressed as a percentage of the maximum rate before the drug was applied. This percentage is, within wide limits, independent of the initial maximum rate, as Dawes observed.

RESULTS

Procaine

Procaine reduces the maximum rate, i.e., it prolongs the refractory period of the isolated rabbit auricles (for references see Dawes, 1946a and b).

The activity of procaine was tested on 9 preparations. The effect was measured after the procaine had been allowed to act for a fixed time. The average results of all observations are shown in Table I.

TABLE I

Concentration of procaine acting for 10 minutes	3×10^{-6}	10^{-5}	2×10^{-5}
Percentage reduction of the maximal rate	13·8 ± 0·4	23·9 ± 0.98	34·4 ± 0.88

The effects of procaine were clear, easy to estimate, and the muscle recovered in 25–30 minutes. This relatively rapid recovery was one of the reasons why procaine was chosen rather than any of the other substances with "quinidine-like properties" tested by Dawes (1946a and b).

The spontaneous rhythm was slightly increased, or remained unaltered, by a low concentration of procaine (3×10^{-6}), while it was decreased by a higher concentration (2×10^{-5}); this effect was more pronounced if the original pulse-rate was high.

Potassium and calcium ions

Potassium is reported to be without effect on the refractory period of the frog ventricle (Kanda, 1939), although many authors have found that it lengthens the refractory phase (Boehm, 1914; Cicardo and Marenzi, 1938; Lueken and Schuetz, 1939). Calcium has been found to be without any clear effect (Cicardo and Marenzi, 1938).

In my experiments an increase in potassium lengthened the refractory period; for example, the maximum rate was reduced by 23 per cent and the spontaneous rate by 25 per cent, if the potassium concentration of the Locke solution was raised by 50 per cent.

If the auricle was left beating in potassium-free Ringer solution for about 2 hours this had no effect on the refractory period; there was, however, an effect on the pacemaker, since the spontaneous rhythm increased by 40 per cent.

When the amount of $CaCl_2$ was doubled or tripled, the maximal rate increased by no more than 3–7 per cent, and even very high concentrations (8 times normal) either did not affect the refractory period or lengthened it by about 5 per cent only, at a time when the spontaneous rate was increased by 47 per cent.

Reduction of the calcium concentration by 50 per cent prolonged the refractory period; the maximum rate at which the auricle responded to electrical stimuli was reduced by 15 per cent. This decrease resembled the effect on the refractory period produced by increasing the potassium content, but while the pacemaker was depressed by excess K, it was not affected by lowering the calcium concentration to 50 per cent.

Effect of K and Ca on the action of procaine

When the influence of changes in K or Ca content on the action of procaine was tested, the change of electrolyte concentration was first allowed to establish its own intrinsic effect for a period of 1 to 3 hours before the procaine was added; this was done in order to ensure that the result observed was not due to summation of the effects of the electrolyte and of procaine. Increasing the amount of potassium (Fig. 1A) or decreasing the amount of calcium (Fig. 1B) both potentiated the action of procaine. About the same proportional change was obtained by raising the K by 50 per cent or by lowering the Ca by 50 per cent.

A reduction of the potassium or an increase of the calcium content produced the same effect qualitatively but not quantitatively; in these conditions the action of procaine was depressed. However, in order to obtain the same degree of depression as that produced by reducing the K concentration by 50 per cent, it was necessary to increase the Ca concentration by 600 per cent (see Fig. 1C and D); for example, the effect of 2×10^{-5} procaine in Locke solution containing half the normal amount of K was depressed by 66 per cent, but a depression of 64 per cent was only produced by raising the Ca concentration to 7 times the normal amount. In another experiment even 8 times more Ca was required.

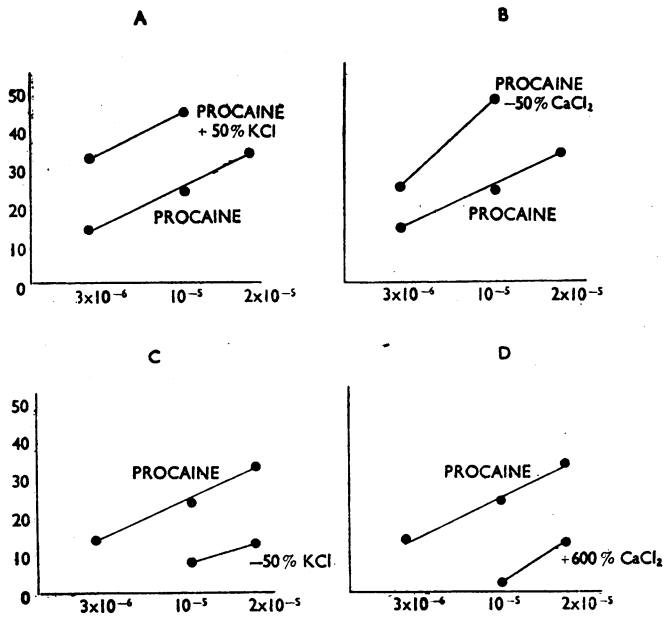

FIG. 1.—Effect of procaine on isolated rabbit auricles with different K and Ca concentrations. Ordinates: percentage reduction in the maximal rate at which the auricles follow electrical stimulation. Abscissae: concentration of procaine.

DISCUSSION

The experiments described show that the influence of potassium and calcium on the refractory period

of the isolated rabbit auricles is antagonistic. Although an excess of calcium or a reduction of potassium is without intrinsic effect over a period of 2–3 hours, this change of electrolytes nevertheless influences the action of procaine, demonstrating that an optimal amount of all electrolytes is necessary for the usual response of the cell to drugs, even though an intrinsic effect of variation in the contents of electrolytes itself is not immediately visible. The quantitative aspect, however, shows the importance of the absolute concentration of potassium for drug action. Baker (1947) has shown it for the action of ouabain, and in this paper it has been demonstrated for procaine. Under the experimental conditions of this investigation the alteration of procaine activity by a reduction of potassium cannot be reproduced by a correspondingly increased amount of calcium; on the other hand the effect of an increased amount of potassium can be imitated by a corresponding loss of calcium, which shows that at least the normal amount of Ca should be present.

Summary

(1) The action of procaine on the refractory period of the isolated rabbit auricle was determined in the presence of variable amounts of potassium and calcium.

(2) Qualitatively, an excess of potassium and a reduction of calcium potentiate the activity of procaine; a reduction of potassium and an excess of calcium diminish the effect of procaine on the refractory period.

(3) Quantitatively, the determining factor is not the ratio K/Ca but the absolute amount of potassium present, although a certain amount of Ca is necessary.

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References

Baker, J. B. E. (1947). *Brit. J. Pharmacol.*, **2**, 259.
Boehm, R. (1914). *Arch. exp. Path. Pharmak.*, **75**, 230.
Cicardo, v. H., and Marenzi, A. D. (1938). *Rev. Soc. Argentine Biol.*, **14**, 59.
Dawes, G. S. (1946a). *Brit. J. Pharmacol.*, **1**, 90.
Dawes, G. S. (1946b). *Brit. med. J.*, **1**, 43.
Goffart, M., and Brown, G. L. (1947). *C.R. Soc. Biol., Paris*, **141**, 958.
Kanda, Z. (1939). *Arch. exp. Path. Pharmak.*, **190**, 417.
Lueken, B., and Schuetz, E. (1939). *Z. Biol.*, **99**, 186, 339.