PROPRANOLOL BLOCK OF ADRENALINE-INDUCED
HYPOPHOSPHATAEMIA IN MAN

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SUMMARY

1. The effect of propranolol on adrenaline- and insulin-induced hypophosphatohaemia was studied in man.

2. β-Adrenergic blockade with propranolol almost completely abolished and significantly inhibited adrenaline- and insulin-induced hypophosphataemia respectively; in addition, the drug clearly prevented the normally observed rise in plasma lactate, while causing only a slight change in blood glucose levels.

3. It is suggested that the fall in blood phosphate values induced by adrenaline and, in part, that caused by insulin, is mediated by β-adrenergic receptors.

The availability of drugs with specific β-adrenergic blocking properties has recently been exploited as a means of defining the role of β-adrenergic receptors in the metabolic changes caused by catecholamines, e.g. increased blood glucose, lactate and free fatty acids (FFA) (Harris et al., 1964; Pilkington et al., 1966; Antonis et al., 1967; Abramson & Arky, 1968). It would, however, appear that no similar work has yet been done on adrenaline-induced hypophosphataemia, a finding that has been fully documented both in the experimental animal and in man (Perlzweig, Latham & Keefer, 1923; Vollmer, 1923; MacVicar & Heller, 1941; Natelson, Pincus & Ranazzisi, 1963), though its meaning is not entirely clear.

The present study was therefore designed to compare adrenaline-induced blood inorganic phosphate decrease under basal conditions and after β-receptor blockade. We also examined the effect of such blockade on insulin-induced hypophosphataemia, since this state involves the endogenous release of catecholamines.

MATERIAL AND METHODS

The twelve subjects were hospital inpatients with small non-toxic goitres or with slight obesity. Each was randomly subjected to the adrenaline (six patients), or the insulin test (six patients).

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in basal conditions and after propranolol, with an interval of at least 4 days between the two tests. A cannula used for blood sampling was inserted into the antecubital vein in the recumbent, overnight-fasting patient and, after 15–30 min rest, 100 ml of isotonic NaCl solution, with or without the addition of 15 mg propranolol (Inderal, Imperial Chemical Industries Pharmaceutical Division, Macclesfield, England) were perfused over a period of 10 min into the contralateral vein. At the completion of perfusion (time 0 min), adrenaline or insulin was intravenously administered as follows: adrenaline, 10 μg/min for 30 min by means of a constant-rate pump, with blood sampling at −10, 0 and then every 10 min until 70 min; glucagon-free insulin (from pig glands, 10 times recrystallized, Novo, Copenhagen, Denmark) 0.15 units/kg body wt within a few seconds, with blood sampling at time 0 and at 15, 30, 45, 60, 90 and 120 min.

In two patients the adrenaline test was also carried out after blockade of α-receptors by means of phentolamine (Rogitine, Ciba, Basel, Switzerland) perfusion (2 mg/min from −10 to 0 min and 0.5 mg/min from 0 to 30 min).

Glucose (Nelson, 1944), plasma inorganic phosphate (Fiske & SubbaRow, 1925) and plasma lactic acid were estimated upon blood samples withdrawn, without stasis, into a heparinized syringe. The aliquot for lactic acid determination was placed immediately in a test tube held in a freezer on its own support and centrifuged for 2 min. The plasma was then deproteinized with an equal volume of 3.5% (w/v) perchloric acid, and lactic acid values were determined by means of the enzymatic method (lactic acid test; Boehringer & Soehne, Mannheim, Germany).

RESULTS

The adrenaline test results are shown in summary form in Figs. 1 and 2. (Full details are available in a table (Clinical Science, Table 38/1) deposited with the Librarian, The Royal Society of Medicine, from whom copies may be obtained.)

![Fig. 1. Effect of propranolol on the adrenaline-induced decrease in plasma inorganic phosphate. Adrenaline test (——); adrenaline + propranolol test (---).]
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Fig. 2. Effect of propranolol on the adrenaline-induced increase in plasma lactate (a) and blood glucose (b). Adrenaline test (——); adrenaline + propranolol test (-----). P = paired t-test. The vertical bars indicate the mean ± SEM of observations on six patients.

Fig. 3. Effect of propranolol on the insulin-induced decrease in plasma inorganic phosphate. Insulin test (——); insulin + propranolol test (-----). P = paired t-test. The vertical bars indicate the mean ± SEM of observations on six patients.
Propranolol almost completely abolished adrenaline-induced falls in blood phosphate values. In six controls, the level at 20 min decreased from that at 0 min by from 0.4 to 1.3 mg/100 ml (mean 0.88 SD 0.31); after β-blockade, the decrease was significantly less (−0.3 to +0.5 mg/100 ml; mean −0.13 SD 0.28; \( P < 0.01 \)). The drug also abolished the increase in plasma lactate but had only a slight effect on the increased blood glucose values (Fig. 2).

Treatment with phentolamine, however, did not effect the adrenaline-induced decrease in blood phosphate values (the decrease at 20 min was 0.6 mg/100 ml in case 1 and 0.9 mg/100 ml in case 4).

The insulin test results are summarized in Fig. 3. (Full details are available in a table (Clinical Science Table 38/2) deposited with the Librarian, The Royal Society of Medicine.) As in the case of adrenaline, propranolol prevented significantly the fall in phosphate values. In the controls, the level decreased by 0.9−1.9 mg/100 ml at 30 min (mean 1.43 SD 0.37); after β-blockade, the difference was significantly less (0.5−1.0 mg/100 ml; mean 0.76 SD 0.22; \( P < 0.01 \)). Once again, there was a very clear flattening of the plasma lactate curve, whereas the blood sugar curve showed only a slight and non-significant delay in the rebound stage.

**DISCUSSION**

The observation of almost 100% blockade of adrenaline-induced hypophosphataemia suggests that this metabolic change is mediated by the β-receptors; the α-receptors would appear to be without influence here, since phentolamine was not followed by abolition.

The meaning of the fall in blood phosphate observed after adrenaline is not clear. Experiments with \(^{32}\)P have shown that it is due to a more rapid removal of phosphate from the plasma (Hevesy & Dal Santo, 1954; Dury, 1955); since a renal mechanism seems out of the question (Perlzweig et al., 1923; Allan, Dickson & Markowitz, 1924), this would seem to be a tissue-wards movement, as suggested by Cori & Cori (1931) and Hevesy & Dal Santo (1954).

The administration of glucose is known to cause a fall in blood phosphate, this being in part due to the passage of phosphate into tissues in relation to the utilization of glucose. It is widely held, though without the support of experimental evidence, that adrenaline-induced hypophosphataemia is secondary to the utilization of hormone-mobilized glucose. Our results, however, run counter to this view. Values fall rapidly in the first part of the test, when glucose utilization is decreased by adrenaline either directly or via blockade of insulin release, whereas they increase at the end of adrenaline perfusion, i.e. when glucose utilization is presumably maximal due to increased insulin secretion (Porte, 1967).

Work in the rat has shown that muscle glycogenolysis is mediated by the β-receptors (Kennedy & Ellis, 1963; Ali, Antonio & Haugaard, 1964). This finding would also seem to hold for man. As shown by Antonis et al. (1967) and Abramson & Arky (1968), and by our results, β-receptor blockade inhibits the rise of plasma lactate with adrenaline, this rise being considered as an expression of muscle glycogenolysis. The fact that this blockade abolishes the adrenaline-induced decrease in blood phosphate indicates that this fall may also be an expression of the same process. This interpretation is favoured by the observation of McArdle (1951) that, in muscle disease attributable to defective glycogenolysis, adrenaline produced only a slight increase in blood lactate and a very slight fall in blood phosphate values, in addition to the normal finding of hyperglycaemia. Further support is to be found in the experimental demonstration by Cori & Cori (1931) that adrenaline-induced glycogenolysis, by depressing muscle
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inorganic phosphate levels, leads to the passage of phosphate into muscle tissue from the plasma. Lastly, we may point to the significant relationship ($P < 0.02$) between decreased plasma inorganic phosphate and increased lactate values in the adrenaline test (Fig. 4).

The significant abolition of decreased phosphate values following the combined administration of propranolol and insulin shows that at least one component of insulin-induced hypophosphataemia is mediated by stimulation of $\beta$-receptors and is thus dependent on an adrenergic mechanism. This fact must be kept in mind in interpreting the significance of the insulin-induced decrease in blood phosphate values, since this has hitherto been seen as solely due to the utilization of glucose (Cheetham, 1963; Massara, Camanni & Molinatti, 1966).

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REFERENCES


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