

## INHIBITION BY PARATHYROID HORMONE OF GLYCOGEN SYNTHESIS IN THE PERFUSED RAT LIVER

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### 1. Introduction

Parathyroid hormone can exert effects on metabolic processes; thus it may stimulate renal gluconeogenesis [1–3] or adipose tissue lipolysis [4–6]. The renal content of cyclic adenosine 3'5' monophosphate (cyclic AMP) is increased in response to parathyroid hormone, [1,7]. Hormones which act in the above fashion on kidney or fat, might be expected, by analogy with e.g. adrenalin and glucagon, to stimulate hepatic glycogen breakdown. Therefore this possibility was tested in the perfused rat liver. Rather than following glucose output, glycogen metabolism was tested directly, to exclude effects on gluconeogenesis; thus net glycogen synthesis was measured, as previously described [9,10]. This process exhibits greater sensitivity to another 'catabolic' hormone, viz. vasopressin, than does glycogen breakdown in livers from fed rats [10], which was another reason for selecting glycogen synthesis for study.

The results presented here demonstrate that parathyroid hormone can inhibit hepatic net glycogen synthesis. During the progress of these experiments, reports appeared of stimulation by parathyroid hormone of glucose output in hepatocytes [11] and of cyclic AMP formation by the liver [11,12]. The present work complements these studies, in documenting the hormone concentration-dependence of the action on hepatic glycogen metabolism, in the perfused liver, i.e. in a preparation where hormone responses may be reasonably presumed to correspond closely to events *in vivo*.

### 2. Materials and methods

Male Sprague-Dawley rats (200 g) were starved for 48 h from 10.00 h. Net glycogen synthesis was measured by a sequential-biopsy procedure in livers perfused with 50 ml saline containing albumin, red cells, glucose and gluconeogenic precursors, as described previously [9,10].

Parathyroid hormone (Lot 74/286) was very kindly provided by Dr J. A. Parsons (National Institute of Medical Research, Mill Hill, London, NW7, UK), and Dr J. R. L. O'Riordan (Middlesex Hospital, London W.1., UK). This material contained, per ampoule, 170 µg highly purified hormone, and 259 mg mannitol. For use, it was dissolved in about 1 ml 1% (w/v) bovine serum albumin ('Crystalline', Sigma Ltd) which had been heated at 56°C (pH 7.0) for 2 h. When the entire ampoule of hormone was not used during a day's perfusions, the solution (pH 4.0) was rapidly frozen (using liquid nitrogen) in small aliquots, being used subsequently after only one thaw.

### 3. Results

Parathyroid hormone caused a gradually increasing inhibition of net glycogen synthesis, over the concentration range 0.6–2.0 µg/ml (about  $6 \times 10^{-8}$  M– $2 \times 10^{-7}$  M) as shown in fig.1. In control perfusions with an appropriate amount of mannitol and albumin diluent (corresponding to maximum hormone additions), no change in glycogen synthesis occurred

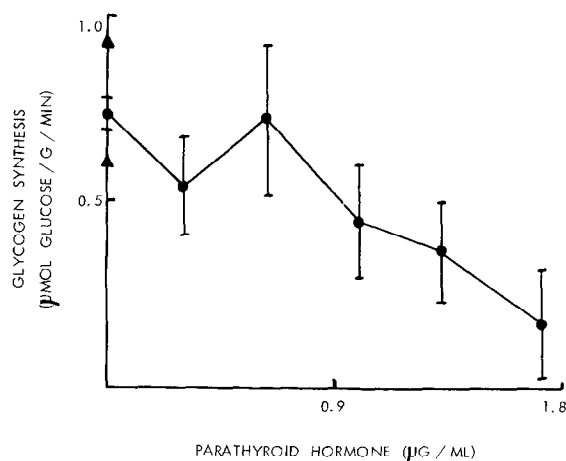


Fig.1. Livers from 48-h starved rats were perfused as described in the text, and elsewhere, [9,10]. Parathyroid hormone was added as a single dose after 15 min, and glycogen synthesis (expressed per g of wet liver) was measured by a serial biopsy technique, involving liver samples removed after 20 and 50 min. The perfusate volume was 50 ml, except in two of the three perfusions at 630 ng/ml, when parathyroid hormone was added in a single dose to 150 ml perfusate. In two control perfusions (without parathyroid hormone:  $\blacktriangle$ ) mannitol was added, since this carrier was present in the hormone preparation (see text). Results are means  $\pm$  S.E.M. (bars) of three perfusions, except for those without hormone (12 perfusions).

(fig.1). The inhibitory effect of parathyroid hormone (fig.1) was confirmed in two further perfusions in which two doses of hormone were added, after 15 and 25 min perfusion, producing concentrations (each time) of 0.8 and 1.3  $\mu\text{g/ml}$ , respectively; the rates of glycogen deposition were 0.08  $\mu\text{mol}$  and 0.00  $\mu\text{mol}$  of glycogen—glucose/min/g, respectively.

An inhibition of net glycogen synthesis should also be manifest as a stimulation of glycogen breakdown in livers from fed rats. We sought such an effect in many experiments, but no consistent action was discerned, (results not shown), presumably because any effects were too slow and slight to be detectable over basal glucose output, despite the slow rate of glucose release before hormone addition (as in comparable experiments with vasopressin: ref. [10]). This could also reflect a relative insensitivity to hormone in fed rat livers, as in the case of vasopressin [10].

#### 4. Discussion

The concentration—response curve for the action of parathyroid hormone on hepatic glycogen metabolism corresponds to those reported for its actions on hepatic cyclic AMP, [11,12], on renal gluconeogenesis [1,3], and on adipose tissue triglyceride [4,6]. Also, stimulation of glucose output in hepatocytes [11] exhibits the same concentration-dependence; thus in the particular case of parathyroid hormone, there appears to be no alteration in receptors during hepatocyte preparation, and no involvement of the intact cyto-architecture in hormone action (these being possible explanations of the decrease in sensitivity to glucagon or adrenalin, in hepatocytes compared to perfusions: ref. [13]).

The glycogenolytic action of parathyroid hormone, reported here for the intact liver, raises questions about the metabolic status of patients with parathyroid disorders. Mild alterations in glucose tolerance [14] or insulin status [14,15] can occur in hyperparathyroidism, as can increased plasma parathyroid hormone levels in diabetes [16]; however, these changes do not appear to be very great. Also the concentration-dependence of the hepatic action, and indeed of all the metabolic actions of parathyroid hormone yet reported, suggest that these effects may not have great significance in the intact animal, where circulating hormone levels apparently do not exceed about 10 ng/ml [17] and could be much less [18,19]. Yet it remains possible that these effects have counterparts with functional importance, e.g. on different processes (in the same organ), and perhaps exerted by a hormone fragment [20] or requiring unknown cofactors.

It is possible that the present experiments have produced an under-estimate of the sensitivity of the liver to the hormone, as only one dose was added during perfusion. This is however, unlikely on general grounds, since glycogen synthesis was measured during only 30 min of perfusion, and also for the following reasons: (i) results agree with those in other preparations, (ii) two experiments with larger perfusion volumes (which would minimise hormone destruction) did not reveal inhibition of synthesis at a concentration of about 0.6  $\mu\text{g/ml}$ . (iii) the destruction of parathyroid hormone in the perfused liver does not appear to be rapid [20]. However, it is

possible that rat parathyroid hormone might have more potent effects on rat liver, than bovine hormone, or that sensitivity to hormone might be increased in different perfusion conditions.

There are clues about where the significance of a hepatic action of parathyroid hormone may lie. Thus actions on liver mitochondria [21] and blood flow [22] have been observed. Any such putative effect does not appear to involve rapid fluxes of calcium or phosphate in response to native parathyroid hormone, as no changes in these parameters, in effluent perfusate, were observed in the present experiments (results not shown). However, liver may have a role in calcium movements [23-25] e.g. in the longer-term. Broader aspects of a hepatic effect of parathyroid hormone could involve inter-relations with calcitonin [26], liver regeneration [27,28], haemorrhagic shock [29], or acidosis [30]. It seems reasonable to speculate [12] that parathyroid hormone might influence hepatic vitamin D metabolism.

Clearly, there are further aspects of the role of the parathyroid gland in metabolic events, including possible hepatic effects, which require clarification.

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