Reversible resistance to the renal action of parathyroid hormone in man

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Summary

1. Normal subjects showed a highly reproducible, rapid increase in plasma adenosine 3':5'-cyclic monophosphate (cyclic AMP) after an intravenous injection of 200 MRC units of highly purified bovine parathyroid hormone.

2. No significant increase in plasma cyclic AMP was observed after administration of bovine parathyroid hormone to patients with severe chronic renal failure.

3. Even when renal function was not impaired, some patients with primary hyperparathyroidism, who had high concentrations of endogenous parathyroid hormone, showed resistance to bovine parathyroid hormone and when this was injected intravenously it caused only a small increase in plasma cyclic AMP. This resistance was reversible since there was marked improvement in the response after parathyroidectomy, when endogenous parathyroid hormone concentration had fallen.

4. It was possible to reproduce this resistance to the hormone by intravenous infusion of bovine parathyroid hormone into normal subjects. When the hormone (1000 MRC units) was infused over 2 h, after an initial increase there was a progressive decline in plasma cyclic AMP concentration and a fall in urinary cyclic AMP excretion. The response to a standard test stimulus (200 MRC units of bovine parathyroid hormone given as a rapid intravenous injection) was examined at intervals after 1000 units of bovine parathyroid hormone had been infused.

5. The mechanism of this reversible resistance to parathyroid hormone remains to be elucidated; it seems unlikely that circulating hormone fragments could account for the prolonged impairment in the responsiveness to the intact hormone. It is possible that alteration in the formation, intracellular degradation or, perhaps, release of cyclic AMP from the cells, is the cause. Changes in the characteristics of the hormone receptor sites might also explain the phenomenon.

Key words: cyclic AMP, hyperparathyroidism, kidney, parathyroid hormone, receptor.

Introduction

In both animals and man, administration of exogenous parathyroid hormone causes an increase in the excretion of adenosine 3':5'-cyclic monophosphate (cyclic AMP) in urine, which precedes the phosphaturic response (Chase & Aurbach, 1967). We have shown that bovine parathyroid hormone also causes rapid changes in plasma cyclic AMP, largely due to the effects of the hormone on the kidney (Tomlinson, Barling, Albano, Brown & O'Riordan, 1974). By measuring cyclic AMP in...
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Corrected plasma calcium (mmol/l)</th>
<th>Alkaline phosphatase (King-Armstrong units/l)</th>
<th>Urea clearance (ml/min)</th>
<th>Creatinine clearance (ml/min)</th>
<th>PTH (ng/ml)</th>
<th>PTH (rmol/l)</th>
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</thead>
<tbody>
<tr>
<td>J.L.</td>
<td>M</td>
<td>53</td>
<td>Primary hyperparathyroidism</td>
<td>2.73 (10.9)</td>
<td>7</td>
<td>7.2 (31)</td>
<td>87</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
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<td>F</td>
<td>62</td>
<td>Primary hyperparathyroidism</td>
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<td>13</td>
<td>3.8 (23)</td>
<td>75</td>
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<td>64</td>
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<td>19</td>
<td>5.3 (32)</td>
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<td>0.7</td>
<td></td>
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<tr>
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<td>F</td>
<td>56</td>
<td>Primary hyperparathyroidism</td>
<td>3.28 (13.3)</td>
<td>15</td>
<td>8.3 (38)</td>
<td>55</td>
<td>3.3</td>
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<td>60</td>
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<td>2.38 (12.8)</td>
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<td>6.5 (39)</td>
<td>60</td>
<td>0.86</td>
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<tr>
<td>F.B.</td>
<td>M</td>
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<td>Primary hyperparathyroidism</td>
<td>2.43 (13.3)</td>
<td>26</td>
<td>4.5 (37)</td>
<td>71</td>
<td>5.1</td>
<td></td>
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<tr>
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<td>55</td>
<td>Chronic renal failure</td>
<td>2.25 (8.9)</td>
<td>10</td>
<td>2.7 (136)</td>
<td>6</td>
<td>1-6</td>
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<tr>
<td>M.B.</td>
<td>F</td>
<td>58</td>
<td>Chronic renal failure</td>
<td>1.5 (6.0)</td>
<td>2</td>
<td>1.55 (9)</td>
<td>60</td>
<td>&lt;0.15</td>
<td></td>
</tr>
<tr>
<td>L.R.</td>
<td>F</td>
<td>64</td>
<td>Surgic hyperparathyroidism, vitamin D intoxication</td>
<td>2.9 (11.6)</td>
<td>15</td>
<td>1.9 (54)</td>
<td>60</td>
<td>&lt;0.15</td>
<td></td>
</tr>
<tr>
<td>H.E.</td>
<td>M</td>
<td>50</td>
<td>Carcinomatosis</td>
<td>3.02 (12.3)</td>
<td>14</td>
<td>6.5 (39)</td>
<td>57</td>
<td>&lt;0.15</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 1.** Details of patients studied. 

PTH = parathyroid hormone.
plasma and in urine, it has been possible to investigate further the renal response to parathyroid hormone in man. Measurement of plasma cyclic AMP, in particular, allows rapid changes to be followed. It has been shown previously (Gershberg & Harrison, 1959; Becker, Purnell & Jones, 1964; Evanson, 1966) that there can be impairment in the phosphaturic response to parathyroid extract in primary and in secondary hyperparathyroidism. We have now shown that, in addition, in these conditions the cyclic AMP response can be impaired. We regard this refractory state as representing a form of 'resistance' to the action of the hormone. In primary hyperparathyroidism this impairment in response to bovine parathyroid hormone is reversible and furthermore it has been possible to reproduce this 'reversible resistance' to the hormone in normal subjects.

Materials and methods

Subjects

Normal subjects, male or female, were between the ages of 25 and 30 years. Details of the patients involved in these studies are shown in Table 1.

Parathyroid hormone

Intact, native bovine parathyroid hormone was prepared as described previously (Tomlinson et al., 1974). The synthetic amino-terminal fragment 1–34 was obtained from Beckman (Palo Alto, California, U.S.A.); it had a stated potency of 3100 units/mg in the rat renal cortical adenylate cyclase assay in vitro of Marcus & Aurbach (1969). The hormone was prepared for intravenous administration as a solution in glucose (278 mmol/l) containing human albumin (0.25 g/l) to prevent its adsorption to glass. In some studies, 200 MRC units of bovine parathyroid hormone were administered intravenously as a single bolus injection in 10 ml of vehicle over 5–10 s. In other studies, by means of a Harvard infusion pump, 500 MRC units in 50 ml of vehicle were infused over 1 h, or 1000 MRC units in 50 ml of vehicle were infused over 2 h. In a further study, 300 μg (1000 units) of the synthetic amino-terminal fragment 1–34 was infused over 2 h in a normal subject. After some infusions, an additional 200 MRC units of intact bovine hormone were injected in 10 ml of vehicle. Blood samples were obtained at frequent intervals from a catheter in the opposite antecubital vein. Each subject was encouraged to drink as much fluid as possible before each experiment, to allow frequent urine collections. The informed consent of the patients and normal subjects was obtained for these studies.

Assays

Cyclic AMP. Cyclic AMP was measured by means of a competitive protein-binding assay (Brown, Albano, Ekins, Sgherzi & Tampion, 1971), modified to measure the nucleotide in plasma (Barling, Albano, Tomlinson, Brown & O'Riordan, 1974).

Parathyroid hormone. An immunoradiometric assay (Addison, Hales, Woodhead & O'Riordan, 1971) was used to measure endogenous human parathyroid hormone. A partially purified extract of human parathyroid adenomas was used as a standard. The upper limit of normal in peripheral serum is 1.0 ng/ml and the detection limit of the assay is 0.15 ng/ml (O'Riordan, Watson & Woodhead, 1972).

Exogenous bovine parathyroid hormone was measured by using immunoradiometric assays specific for either the amino-terminal or carboxy-terminal regions of the molecule. A guinea-pig antiserum (As 215) raised against bovine parathyroid hormone was used. Labelled antibodies specific for antigenic determinants within the amino-terminal (fragment 1–34) or carboxy-terminal (fragment 53–84) regions were adsorbed from the antiserum as previously described (Barling, Hendy, Evans & O'Riordan, 1975). Human parathyroid hormone reacted poorly in these systems so that in subjects with normal amounts of endogenous hormone, only bovine hormone was detected.

Urinary creatinine and phosphate, and plasma calcium and phosphate. Automated techniques were used for these assays. Urinary and plasma phosphate was measured by a modification of the method of Fiske & Subbarow (1925), with 1-amino-2-naphthol-4-sulphuric acid as reducing agent. Creatinine was measured by the Jaffe reaction. Plasma calcium was measured by the method of Gitelman (1967).

Results

Effects of injection of bovine parathyroid hormone in normal subjects

The changes in plasma cyclic AMP after administration of bovine hormone are highly reproducible
in an individual subject. For example, when a normal subject (M.C.E., Fig. 1) was given 200 units of hormone intravenously at intervals of 1 week, on each occasion plasma cyclic AMP rose from basal values between 18 and 27 nmol/l up to a maximum value between 230 and 300 nmol/l.

Response to prolonged infusion of bovine parathyroid hormone

In the first two studies of this type, 500 units were infused in normal subjects over 1 h. The pattern of response was very similar in both cases. As shown in Fig. 2, the concentration of cyclic AMP in plasma increased threefold in about 40 min and then remained steady until the end of the infusion. Urinary excretion of cyclic AMP increased fivefold by the end of infusion, and then both the plasma concentration and urinary excretion of cyclic AMP declined rapidly.

Fig. 1. Effects on plasma cyclic AMP of injection of 200 units of bovine parathyroid hormone at intervals of 1 week, in a normal subject (M.C.E.). Times of injection are indicated by arrows.

Fig. 2. Effects on plasma cyclic AMP concentration and urinary cyclic AMP excretion of an infusion of 500 units of bovine parathyroid hormone in a normal subject (A.S.) over 1 h. The horizontal bar indicates the period of the infusion.

Fig. 3. Effect of an infusion of 1000 units of bovine parathyroid hormone in a normal subject (J.P.) over 2 h, on plasma cyclic AMP concentration. The horizontal bar indicates the period of the infusion.
In a further five subjects such an infusion was continued at the same dose rate for a further hour (giving a total of 1000 units in 2 h). Again, there was an initial rise in plasma cyclic AMP concentration. However, during the latter part of these longer infusions, plasma concentrations of cyclic AMP fell, almost returning to basal values (Fig. 3). Similarly, urinary cyclic AMP excretion, having risen, fell during the second half of the infusion; in contrast, the phosphaturic response increased and continued to rise throughout the infusion when urinary cyclic AMP excretion was falling. The phosphaturic response was maintained after the termination of the infusion, when urinary cyclic AMP had fallen to the basal excretion rate (Fig. 4).

This decline in plasma and urinary cyclic AMP during the infusion occurred despite maintenance of high concentrations of amino-terminal immunoreactive bovine parathyroid hormone in the circulation (Fig. 5). At the end of the infusion this amino-terminal material was rapidly cleared from the plasma, with a half-life of 5 min. In contrast, carboxy-terminal immunoreactive material persisted in the circulation for several hours after the disappearance of the amino-terminal bovine parathyroid hormone.

Plasma calcium and phosphate were little affected by infusion of 1000 units of bovine hormone over 2 h. For example, in one subject (from whom blood samples were obtained up to 24 h after the start of the infusion) plasma calcium was initially 2.3 mmol/l (9.2 mg/100 ml) and reached a peak of 2.43 mmol/l (9.7 mg/100 ml) 35 min after the end of the infusion. In this subject plasma phosphate was 0.9 mmol/l before the infusion and fell to a minimum of 0.7 mmol/l at 75 min. Forty-five minutes after the termination of the hormone infusion, the plasma phosphate concentration had returned to 0.9 mmol/l.
Response to an injection of hormone after an infusion

In order to investigate this refractory state further, at the end of a 2 h infusion of 1000 units of bovine parathyroid hormone in a normal subject (D.P.), 200 units of the hormone were injected intravenously (Fig. 6). The response obtained was compared with that observed after an injection of hormone after a control infusion of vehicle alone.

The normal response to the injection in this subject (D.P.) was an increase in plasma cyclic AMP from a basal value of 15 nmol/l to a peak of 140 nmol/l, with urinary cyclic AMP rising from 5 nmol/min up to 300 nmol/min. When the injection of 200 units of bovine parathyroid hormone had been preceded in the previous 2 h by infusion of 1000 units of the hormone, plasma cyclic AMP concentration increased from a pre-injection level of 20 nmol/l to a maximum of only 30 nmol/l, with an associated small rise in the excretion of urinary cyclic AMP. Plasma calcium did not change significantly during the experimental period.

The recovery of the response to an injection of 200 units of bovine parathyroid hormone was investigated in the same normal subject (D.P.), by giving, on separate occasions, the test stimulus at 0-5, 4 or 24 h after the end of the prolonged infusion of the hormone (Fig. 7). When the injection was given 0-5 h after the end of the infusion there was still no response in concentration of plasma cyclic AMP. When the interval was extended to 4 h, the concentration of circulating cyclic AMP increased from 15 nmol/l to only 46 nmol/l. However, when the injection was given 24 h after the end of a prolonged infusion the plasma cyclic AMP concentration rose normally from 20 nmol/l to 170 nmol/l.

![Fig. 7. Effect on plasma cyclic AMP concentration of an injection of 200 units of bovine parathyroid hormone given at 0, 0-5, 4 and 24 h after the termination of infusion of 1000 units of the hormone to the same normal subject (D.P.). The arrows indicate the time of the injections.](image)

![Fig. 8. Effects on plasma and urinary cyclic AMP of 1000 units of fragment 1-34 infused in a normal subject (D.P.) over 2 h. At the end of the infusion, an injection of 200 units of intact bovine parathyroid hormone was given. The horizontal bar indicates the period of infusion and the arrow shows the time of the injection.](image)
Reversible resistance to parathyroid hormone

Response to an injection of intact hormone at the end of a prolonged infusion of amino-terminal fragment 1–34

Fig. 8 shows that when 300 μg of fragment 1–34 (1000 units) was infused over 2 h in a normal subject, plasma cyclic AMP increased from 15 nmol/l to 60 nmol/l within 30 min. This was followed by a progressive decline in plasma concentration of the nucleotide, until, at the termination of the infusion, it was only 10 nmol/l above the basal value. Urinary cyclic AMP excretion initially rose and then fell during the second half of the infusion. When at the end of this infusion, an injection of 200 units of intact bovine parathyroid hormone was given the increase in plasma cyclic AMP concentration was only 15% of that observed after a control infusion of vehicle alone. Similarly, there was little change in urinary cyclic AMP excretion.

Effects of an injection of exogenous hormone in patients with primary hyperparathyroidism

Some patients with primary hyperparathyroidism showed a normal response to an injection of bovine parathyroid hormone, but others had an impaired response. Lack of response seemed to be associated with high concentrations of endogenous parathyroid hormone (see Table 2 and Fig. 9). In Fig. 10 is shown, as an example, the effect of parathyroidec- tomy in one of the patients (A.L.), who, before operation, had an impaired response to the bovine hormone. When the adenoma had been removed and the concentration of endogenous parathyroid hormone had fallen, there was a marked improvement in the response to an injection of exogenous hormone.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plasma cyclic AMP (nmol/l)</th>
<th>10^{-2} \times \text{Increase in cyclic AMP} (% of basal value)</th>
<th>PTH (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>J.L.</td>
<td>17.5 102</td>
<td>6.0 0.32</td>
</tr>
<tr>
<td>2</td>
<td>E.O.</td>
<td>12.8 240</td>
<td>19.0 0.70</td>
</tr>
<tr>
<td>3</td>
<td>I.A.</td>
<td>26.5 210</td>
<td>8.0 1.30</td>
</tr>
<tr>
<td>4</td>
<td>M.T.</td>
<td>28.5 39</td>
<td>1.4 5.36</td>
</tr>
<tr>
<td>5</td>
<td>A.L.</td>
<td>33.0 54</td>
<td>1.6 3.80</td>
</tr>
<tr>
<td>6</td>
<td>F.B.</td>
<td>23.7 50</td>
<td>2.1 5.10</td>
</tr>
</tbody>
</table>

TABLE 2. Response of plasma cyclic AMP concentration to injected bovine parathyroid hormone in patients with primary hyperparathyroidism

Patients 1–3 are those with primary hyperparathyroidism who responded normally to an injection of 200 units of bovine parathyroid hormone. Patients 4–6 are those with primary hyperparathyroidism who showed an impaired response to the hormone. PTH = parathyroid hormone.

Where previously in patient A.L. (Fig. 10) there had been only a 50% increase in plasma cyclic AMP concentration and a threefold rise in urinary cyclic AMP excretion, after operation, when an injection of hormone was given, the plasma cyclic AMP concentration increased 300% and urinary excretion of the nucleotide increased over fortyfold. Similarly, in patient M.T., who showed a pre-operative increase in plasma cyclic AMP of 30% with a twofold increase in urinary cyclic AMP, after parathyroidec- tomy the injection of hormone caused almost a 300% rise in plasma cyclic AMP concentration and a twentyfold increase in urinary excretion of the nucleotide.

![Fig. 9. Effects on plasma cyclic AMP of an injection of 200 units of bovine parathyroid hormone in two of the patients (J.L. and M.T.) with primary hyperparathyroidism, before parathyroidec- tomy. The concentration of endogenous human parathyroid hormone in patient J.L. was 0.32 ng/ml and in patient M.T. it was 5.36 ng/ml. The arrows indicate the time of injection.](image-url)
Fig. 10. Changes in plasma cyclic AMP concentration and urinary cyclic AMP excretion after an injection of 200 units of bovine parathyroid hormone in patient A.L. with primary hyperparathyroidism: (a) before parathyroidectomy; (b) after parathyroidectomy. Parathyroidectomy resulted in the concentration of endogenous human parathyroid hormone falling from 3.8 ng/ml to 0.86 ng/ml. The arrows indicate the time of injection.

Effect of hypercalcaemia on the response to bovine parathyroid hormone

The effect of hypercalcaemia per se on the response to exogenous hormone was studied in two patients.

Patient H.E. had surgical hypoparathyroidism with no detectable endogenous parathyroid hormone in his peripheral circulation. He had inadvertently become hypercalcaemic as a result of vitamin D intoxication. The response to an injection of bovine hormone in this patient (Fig. 11) was normal. Similarly, in a patient (M.C.) with hypercalcaemia attributable to malignancy, endogenous parathyroid hormone in the peripheral circulation was again undetectable and an injection of bovine hormone gave a 300% increase in plasma cyclic AMP and a tenfold rise in urinary cyclic AMP excretion.

Administration of bovine parathyroid hormone to patients with chronic renal failure

The effect of chronic renal failure on the response to exogenous parathyroid hormone is shown in Fig 12. No significant increase in plasma cyclic AMP concentration and little change in urinary cyclic AMP excretion occurred after an injection of 200 units of hormone in three patients (J.C., M.B. and L.R.) with severe impairment of renal function (creatinine clearance less than 10 ml/min). These patients had higher basal concentrations of plasma cyclic AMP (>25 nmol/l) and lower urinary excretion of the nucleotide (<1.8 nmol/min) than normal.
Reversible resistance to parathyroid hormone

Discussion

Although parathyroid hormone activates adenylate cyclase in bone, the changes in plasma cyclic AMP concentration after administration of bovine parathyroid hormone appear to be due to the effects of the hormone on the kidney adenylate cyclase system (Tomlinson et al., 1974). Under basal conditions, patients with chronic renal failure have higher concentrations of plasma cyclic AMP and excrete less of the nucleotide in urine than normal. Presumably this partly reflects diminished glomerular filtration, although only 15% of endogenous cyclic AMP is cleared in this way (Broadus, Kaminsky, Hardman, Sutherland & Liddle, 1970), and we cannot exclude reduced metabolism or increased production of the nucleotide from non-renal sources as a cause of the elevated plasma cyclic AMP. Here, we have shown that severe impairment of renal function inhibits the response to parathyroid hormone. Clearly, therefore, in assessing responsiveness to parathyroid hormone by changes in extracellular cyclic AMP it is necessary to take account of renal function (Lilienfeld-Toal, Hesch & McIntosh, 1974).

Some patients with primary hyperparathyroidism had a normal cyclic AMP response to bovine parathyroid hormone, but others showed an impaired response. Those with reduced sensitivity had higher concentrations of endogenous parathyroid hormone, and it might be suggested that the apparent resistance to the action of exogenous hormone was the result of the renal adenylate cyclase being already maximally stimulated. When studied again several weeks after parathyroidectomy (when they were normocalcaemic on no treatment and had normal concentrations of endogenous parathyroid hormone) the response in these patients had markedly improved. The resistance therefore is reversible.

Because parathyroid hormone in normal subjects increases cyclic AMP excretion, several groups have attempted to use the urinary excretion of the nucleotide as an aid in the diagnosis of hyperparathyroidism. Unfortunately, discrimination between normal subjects and patients with primary hyperparathyroidism is not good (Dohan, Yamoshita, Larsen, Davis, Deftos & Field, 1972; Neelon, Birch, Drezner & Lebovitz, 1973). This may be partly due to the relatively minor parathyroid hormone-dependent contribution that the kidney makes to urinary cyclic AMP excretion under basal conditions (Kaminsky, Broadus, Hardman, Jones, Ball, Sutherland & Liddle, 1970). Our studies have also clearly shown that impairment of renal function will reduce urinary cyclic AMP excretion. Furthermore, the fact that some patients with primary hyperparathyroidism are resistant to exogenous hormone may indicate that there is impairment in the response to endogenous parathyroid hormone as well. As a result, the amount of cyclic AMP excreted in the urine may not be a simple function of parathyroid overactivity.

It has been possible to reproduce this reversible resistance to the action of parathyroid hormone in normal subjects. Infusion of bovine parathyroid hormone for 2 h caused an initial increase in plasma cyclic AMP concentration and urinary cyclic AMP excretion, followed by a decline despite maintenance of high concentrations of immunoreactive aino-
terminal parathyroid hormone. In addition, when an injection of hormone was given at the termination of a prolonged infusion, when the immunoreactive parathyroid hormone in the circulation was high, the response was impaired in an analogous way to that observed in patients with primary hyperparathyroidism, and had recovered 24 h later when exogenous hormone in the circulation was undetectable.

The refractory state induced by an infusion of bovine parathyroid hormone in normal subjects was not due to changes in plasma calcium, and, in patients with hypercalcaemia due to causes other than hyperparathyroidism, a normal cyclic AMP response was observed after an injection of hormone. Changes in extracellular calcium cannot therefore account for resistance to the hormone and other explanations must be sought.

The heterogeneity of circulating immuno-assayable parathyroid hormone provides the basis for one possible explanation. In the circulation fragments of the hormone exist, the majority of which are derived from the biologically inert carboxy-terminal end of the molecule (Segre, Habener, Powell, Tregear & Potts, 1972). It might be that biologically inactive fragments, derived from either the amino- or carboxy-terminal regions, are binding to the hormone receptor and inhibiting activation of adenylate cyclase by biologically active material.

Our studies have shown that the refractory state is present when most of the amino-terminal immuno-reactive material has disappeared from the circulation, and that the response has only partially recovered when most of the carboxy-terminal material has disappeared as well. Furthermore, we observed a declining plasma cyclic AMP response during an infusion of the biologically active amino-terminal fragment 1–34 and subsequent impairment of the response to an injection of the intact hormone. Therefore, although we cannot exclude the possibility that biologically inactive material from within the amino-terminal region is binding to the hormone receptor, our studies clearly show that neither circulating fragments nor receptor-bound material derived from the carboxy-terminal (fragment 35–84) region of the molecule can be responsible for the refractory state. In addition, our previous studies with porcine parathyroid hormone have shown that, in the rat renal adenylate cyclase assay, material oxidized at the methionine residue in position 8 (therefore biologically inactive) did not alter the potency of biologically active hormone when added in equal concentration (O'Riordan, Woodhead, Hendy, Parsons, Robinson, Keutmann, Dawson & Potts, 1974). However, other studies have shown that an amino-terminal fragment of bovine parathyroid hormone (fragment 2–34), which is completely without activity in the chick kidney adenylate cyclase assay, is capable of partially inhibiting the response to fragment 1–34 (Martin, Vakakis, Eisman, Livesey & Tregear, 1974).

The declining cyclic AMP response despite continued stimulation has been observed with other polypeptide hormones. For example, Liljenquist, Bomboy, Lewis, Sinclair-Smith, Felts, Lacy, Crofford & Liddle (1974) reported a declining response in plasma cyclic AMP derived from hepatic adenylate cyclase during infusions of glucagon in normal man. Also a declining response in cyclic AMP production has been observed in autotransplanted sheep adrenal glands during infusions of adrenocorticotropic hormone (Espiner, Livesey, Ross & Donald, 1974). For insulin it has been suggested that changes in receptor number or affinity could be the explanation of a decrease in response despite apparent continued stimulation (Gavin, Roth, Neville, De Meys & Buell, 1974) and likewise with thyrotropin-releasing hormone (Hinkle & Tashjian, 1975). Equally, in the studies described here, alteration in the responsiveness of the adenylate cyclase system itself could be the cause.

We have not found any increase in plasma phosphodiesterase activity after the infusions of parathyroid hormone, nor did addition of the phosphodiesterase inhibitor aminophylline affect the development of the refractory state in the studies of Espiner et al. (1974) with adrenocorticotropic hormone. This, of course, does not exclude the possibility of an increase in intracellular phosphodiesterase activity that is not reflected by changes in the extracellular fluid. Finally, it may be that an inhibitor is formed during the initial period of stimulation by bovine parathyroid hormone which blocks cyclic AMP formation. Synthesis and release of such an inhibitor in rat adipocytes has been reported (Ho & Sutherland, 1971).

Although the precise mechanism of the phenomenon described here remains to be elucidated, the declining response to continued biological stimulus may represent a control system for the regulation of hormone action on target tissue. Furthermore, the nature of the relationship between the changes in
cyclic AMP and the final biological response to the hormone, for example, the phosphaturic action of parathyroid hormone, clearly merits further investigation.

Acknowledgments

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References


