Parathyroid Hormone Receptors in Circulating Human Mononuclear Leukocytes*

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In this article we demonstrate receptors for parathyroid hormone in circulating mononuclear leukocytes using the radioiodinated analogue (8,18 norleucine, 34 tyrosine) bPTH 1-34 (bovine parathyroid hormone 1-34). Specific binding, which is reversible and saturable, equilibrates within 5 min at 0–4 °C with a calculated $K_D$ of 8.9 $\times$ 10$^{-11}$ M. This binding has a pH maximum of 7.0, is magnesium-dependent, and is inversely related to medium calcium concentration. Such binding is completely inhibited by simultaneous addition of 4 ng/ml of bovine parathyroid hormone 1-34, 5 ng/ml of bovine parathyroid hormone 1-84, or 5 ng/ml (8,18 norleucine, 34 Tyr) of 3-34 bPTH, but is unaffected by a biologically inactive parathyroid hormone fragment or other unrelated peptide hormones. Cyclic AMP accumulation increases 3-fold after 5 min exposure of mononuclear leukocytes to bPTH 1-34 in concentrations as low as 1 $\times$ 10$^{-9}$ M. Lymphocytes appear to be the circulating cells which interact with PTH as indicated by the observations that: 1) lymphocyte-enriched preparations bind three times as much radioligand/cell as do mixed mononuclear leukocytes, 2) monocytes, platelets, granulocytes, and erythrocytes do not bind PTH, and 3) monocytes, but not lymphocytes, degrade the hormone."

PTH$^+$ is a major stimulator of bone resorption, exerting its effect via recruitment and activation of osteoclasts (1). The mechanism of this effect is, however, unclear, since much evidence suggests that osteoclasts may not respond directly to this peptide (2). For example, autoradiographic studies have failed to demonstrate PTH binding by osteoclasts (3), but do show binding of the hormone by osteocytes and osteoblasts. These findings suggest that osteoclastic stimulation by PTH is modulated through progenitor or other intermediate cells. While the identity of such putative modulators of bone resorption is unknown, mononuclear leukocytes (monocytes and lymphocytes) are likely candidates for a variety of reasons. As an example, osteoclasts are probably derived from a monocyte-like precursor (4, 5), and it is possible that PTH stimulates proliferation of osteoclasts by directly promoting maturation of these progenitors. Furthermore, T and B lymphocyte deficiencies are associated with failure of osteoclastic activity in human (6) and rodent (7, 8) osteopetrosis despite the presence of hyperparathyroidism (9). Moreover, activated lymphocytes, in the presence of monocytes, produce the potent bone resorptive agent, osteoclast activating factor (10, 11). Finally, mononuclear leukocytes contain a variety of receptors for other "bone-seeking" peptides, such as calcitonin (12) and growth hormone (13). In light of these observations, we have determined if mononuclear leukocytes possess PTH receptors. In this article, we demonstrate specific, saturable, and reversible binding of a PTH analogue by circulating mononuclear cells with induction of a biological event following this interaction.

MATERIALS AND METHODS

All chemicals were acquired from Sigma unless otherwise stated. Hormones—Bovine parathyroid hormone 1-34 (lot 1220) was purchased from Beckman Instruments, Inc. and synthetic (8,18 norleucine, 34 tyrosine) 3-34 bovine PTH (lot 002410) and 53-84 PTH (lot 001447) from Peninsula Laboratories, Inc., San Carlos, CA. Ovine follicle-stimulating hormone (lot AF-0511B) and bovine luteinizing hormone (lot AF-0011B) were gifts of the National Pituitary Agency, and salmon calcitonin was purchased from Armour (Phoenix, AZ). Bovine PTH 1-84 was the gift of Dr. Jeremiah Morrissey, Renal Division, Washington University School of Medicine.

Preparation of Mononuclear Cell Fractions—All procedures were carried out at room temperature. Sixty cc of normal human venous blood were diluted 1:1 with 0.9% NaCl and layered over a Ficoll-Hypaque gradient (specific gradient 1.028) (Winthrop, New York, NY) as previously described (14). The band of leukocytes at the serum-Ficoll interface was aspirated and diluted 1:1 with 0.3% NaCl and centrifuged for 10 min at 2000 g. The supernatant was decanted, the pellet resuspended in 1 cc of Lebowitz’s 15 media (L-15) (Grand Island Biological Co., Grand Island, NY) with 0.1% D-Nase and centrifuged for 10 min at 1000 $\times$ g. The pellet was washed twice in L-15 and the number of cells adjusted to its final concentration. At this point, more than 95% of cells were viable as assessed by toluidine blue exclusion.

Red Cell Free Mononuclear Leukocytes—Contaminating red cells were lysed as previously described (15). Specifically, the mononuclear cell mixture was incubated in Tris-NH$_4$Cl for 5 min at 37 °C and centrifuged for 1000 $\times$ g at room temperature. The pellet was then resuspended in 1 cc of L-15, placed over a second Ficoll-Hypaque gradient and the mononuclear leukocytes isolated as above. Wright stained preparations showed no red cell contamination.

Platelet Free Mononuclear Leukocytes—Noncoagulated blood was mixed with 6% dextran ($M_\text{r}$ = 150,000) in normal saline and 4-mm glass beads on a rocking platform (Yandee Rotator Clay-Adams, Inc., New York, NY) for 15 min at 37 °C as previously described (16). The cellular fraction was decanted and allowed to settle. The opalescent,
cellular fraction was then placed over a Ficoll-Hypaque gradient.

Separation of Lymphocytes and Monocytes—Lymphocytes were separated from monocytes on the basis of plastic adherence (17). Briefly, the mononuclear cell fraction in L-15 obtained from the Ficoll-Hypaque gradient was pipetted in L-15 into 35-mm plastic Petri dishes at a density of 2 x 10^6 cells/dish. After 30 min at 37 °C, the nonadherent cells were removed by vigorous rinsing with L-15, collected by centrifugation at 1000 x g for 10 min, resuspended in L-15 and again plated into plastic Petri dishes. When necessary, monocytes were rinsed from the plastic plates using either cold (0-4 °C) phosphate-buffered saline or following an incubation at 37 °C in L-15 with 0.1% lidocaine (15). These cells were again rinsed twice and resuspended in L-15 and counted in a hemocytometer. Monocytes may be differentiated from lymphocytes on the basis of nonspecific esterase activity in the former (17). By these criteria, purified populations of lymphocytes (nonadherent cells) were 97-99% pure. Approximately 20% of the initial mononuclear cells were recovered in fractions of lymphocytes (nonadherent cells) were 97-99% pure. By these criteria, purified populations of lymphocytes (nonadherent cells) were 97-99% pure. Approximately 20% of the initial mononuclear cells were recovered in the final lymphocytic fraction. Purified populations of monocytes were also separated from lymphocytes on the basis of carboxyl ingestion and migration in a magnetic field (18). In all three preparations of monocytes, approximately 20% of the original mononuclear leukocytes were present in the final mononuclear fraction; as assessed by nonspecific esterase staining, 70-80% of these cells were monocytes.

Preparation of Radioligands—Na[125I] was purchased from American Corp. The PTH analogues [8,18-norleucine, 34-tyrosine]-1-34 bPTH, was a generous gift of Drs. Michael Rosenblatt and John T. Potts, Jr. (Harvard University Medical School, Boston, MA). Using a modified lactoperoxidase method (19), radioiodinated analogue was prepared with a specific activity ranging from 300 to 400 mCi/μg.

Binding Assays—All assays were carried out at 0-4 °C unless otherwise stated. 2.5 x 10^6 mononuclear cells in 0.3 ml of L-15 were pipetted into a borosilicate glass test tube (12 x 75 mm) (Fisher) containing 0.5 ml of assay buffer (25 mm Tris-HCl, pH 7.0, 4 mM MgCl2, and 0.5% bovine serum albumin (Pentex, Miles Laboratories, lot 349, Fort Wayne, IN) with or without bovine PTH 1-34 (Beckman Instruments) and 80-110 X 10^3 cpm of radioiodinated PTH analogue (final Me concentration = 3.5 μM). The tubes were vortexed for 3-5 s, incubated approximately, vortexed again, and 0.225 ml of the reaction mixture pipetted into plastic 0.4-ml Eppendorf tubes (Beckman Instruments) which were centrifuged at 10,000 X g for 5 min, after which it remains unchanged for at least an additional 15 min (Fig. 1). Nonreversible (nonspecific) binding also plateaux by 5 min. Binding at temperatures greater than 10 °C was difficult to reproduce. All further studies were conducted at 0-4 °C with 15-min incubation.

Under these circumstances nonspecific and total binding are greatest at low pH but maximum specific binding occurs at pH 7.0. At lower hydrogen ion concentrations, both nonspecific and specific binding diminish (data not shown). Mean specific binding is slightly inhibited by the addition of calcium to the medium and is maximal at 2 mM magnesium (p < 0.05). Neither cation influences nonspecific binding (data not shown). Subsequent experiments were therefore performed without added calcium, in the presence of 2 mM magnesium at a pH of 7.0.

We next examined the dissociation of [125I]([8,18-Nle, 34-Tyr]-1-34 bPTH from mononuclear leukocytes (Fig. 2). Binding equilibrium is reached by incubating mononuclear leukocytes and radioligand in the presence or absence of 1 μg/ml of bPTH 1-34 for 5 min. Both cell-ligand mixtures (presence or absence of 1 μg/ml of bPTH) were then diluted with a 10-fold excess of buffer and sampled at various intervals. Under these conditions, approximately 59% of reversibly bound counts are eluted within 5 min and virtually all by 30 min. Nonspecific binding at equilibrium approximates that found at 30 min.

We next examined mononuclear leukocytes for possible

RESULTS

Characterization of Ligand Binding to Mononuclear Cells—Total binding ranges from 6 to 10% of added radioligand. Specific binding (total binding of radioligand in the absence of unlabeled bPTH 1-34) minus the radioligand bound in the presence of 1 μg/ml of unlabeled bPTH 1-34 (3.4 x 10^7) is approximately 3 fmol of [125I]([8,18-Nle, 34-Tyr]-1-34 bPTH/10^6 mononuclear leukocytes. At 0-4 °C, specific binding is half-maximal by 2.5 min and equilibrates at 5 min, after which it remains unchanged for at least an additional 15 min (Fig. 1).

![Fig. 1. Time course of radioligand binding.](http://www.jbc.org/) 

![Fig. 2. Disassociation of radioligand and mononuclear leukocytes.](http://www.jbc.org/)
receptor alterations associated with radioligand binding. Cells were incubated with radioligand for 5 min to achieve equilibrium. The assay mixture was then diluted 10-fold with assay buffer and the mixture incubated an additional 30 min to elute radioligand from the cells. These cells were collected and then incubated with fresh iodinated ligand and specific binding determined. We noted no alteration of specific binding to these as compared to fresh cells (i.e., mononuclear leukocytes from the same preparation but not previously exposed to $^{125}$I$[8,18$-Nle, 34-TyrIbPTH (1-34) (data not shown). Similarly, a second series of experiments indicates that specific binding of radioligand to mononuclear leukocytes does not decrease for at least 4 h after cell isolation (data not shown). We concluded that mononuclear leukocytes are not altered by exposure to radioligand. Alternatively, our previous experiments had shown that association of radioligand and mononuclear cells is difficult to reproducibly demonstrate at temperatures above 10 °C. We were therefore concerned that the radioligand might be altered by exposure to mononuclear leukocytes. Hence, we next examined rebinding of eluted radioligand to freshly isolated mononuclear leukocytes (Table I). These experiments demonstrate that radioligand, bound to and then eluted from mononuclear leukocytes, is rebound by fresh cells.

Since the receptor and radioligand appear unaltered after incubation at 0–4 °C, we postulated that radioligand might be degraded at higher temperatures, accounting for the inability to demonstrate binding at higher temperatures. To examine this possibility we chromatographed radioligand prior to and following exposure to mononuclear leukocytes for 5 min at 22 °C. In the latter experiment, we doubled the concentrations of $^{125}$I$[8,18$-Nle, 34-TyrIbPTH (1-34) and increased the number of mononuclear leukocytes 10-fold. The chromatogram of fresh radioligand is presented as Fig. 3A. Radioligand from the major peak (fractions 25–30) binds specifically to mononuclear leukocytes (data not shown). A proportion of radioactivity recovered from the cell–ligand mixture appears in fractions 38–40 indicating modest tracer degradation (Fig. 3B). The radioligand from this peak fails to bind specifically to mononuclear leukocytes (data not shown). We have concluded that enough radioligand degradation occurs at 22 °C to prevent reproducible binding.

Radioligand Binding to Lymphocytes—Fig. 4 shows saturation studies performed using constant receptor (cell) number and variable amounts of radioligand. Under these conditions, specific binding passes through the origin and is linear when plotted against added radioactivity until saturation. Satura-

**Fig. 3.** Gel chromatography of radioligand. Fresh radioligand (A) was chromatographed over a Sephadex G-50 column (0.8 x 40 cm). Fractions were collected and radioactivity determined as described in the text. Cyanocobalamin (Mr = 1,800) and blue dextran peaks (determined by absorbance at 240 nm) are indicated by arrows. In B, 2.4 × 10$^6$ mononuclear leukocytes were incubated 10$^5$ cpm of radioligand for 5 min and the assay mixture centrifuged at 10,000 × g for 30 s. 250 μl of supernatant was chromatographed on the same column. A portion of the radioactivity elutes later in B, consistent with a radioligand of lower molecular weight. More than 95% of added radioactivity was recovered from the column.

**Fig. 4.** Binding of radioligand to mononuclear leukocytes. 2.4 × 10$^6$ mononuclear leukocytes (Ο) or enriched lymphocytes (Ο) were incubated with varying concentrations of radioligand for 15 min at 0–4 °C and the total and nonspecific binding determined in triplicate. Each point represents the mean of two separate assays. 10$^6$ mononuclear leukocytes bind 3.4 fmol of radioligand with approximately 23,000 sites/cell. In contrast, 10$^6$ lymphocytes bind 10.2 fmol of radioligand with approximately 61,000 sites/cell.

**TABLE I**

Rebinding of eluted radioligand

Radioligand was incubated with 2.4 × 10$^6$ mononuclear leukocytes for 5 min to equilibrium (final volume 1 cc). The mixture was centrifuged, the supernatant aspirated, the pellet reassembled in 1 cc of assay buffer, and incubated 30 min at 0–4 °C. The mixture was then centrifuged and the supernatant pipetted off and added to fresh mononuclear leukocytes, in the presence and absence of 1 μg/ml of bPTH, incubated for 15 min, and specific binding determined in triplicate as described previously.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Ligand added</th>
<th>Ligand bound specifically mean ± S.D.</th>
<th>Eluted ligand added</th>
<th>Ligand rebound specifically mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>94,800</td>
<td>3,770 ± 190</td>
<td>3,410</td>
<td>96 ± 27</td>
</tr>
<tr>
<td>2</td>
<td>136,100</td>
<td>4,350 ± 320</td>
<td>4,080</td>
<td>110 ± 22</td>
</tr>
<tr>
<td>3</td>
<td>184,700</td>
<td>5,600 ± 690</td>
<td>4,950</td>
<td>110 ± 45</td>
</tr>
</tbody>
</table>

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FIG. 5. Gel chromatography of radioligand testing. Supernatant radioligand after 30 min exposure to lymphocytes at 22 °C. Radioligand was incubated with 2.4 x 10^6 enriched lymphocytes for 30 min at 22 °C and the assay mixture centrifuged at 10,000 x g for 30 s. The supernatant radioligand was chromatographed as described in text and radioactivity in each fraction determined. More than 95% of added radioactivity was recovered from the column.

FIG. 6. Displacement of radioligand from mononuclear leukocytes. 80,000-110,000 cpm of ^125I[8,18-Nle, 34-Tyr]bPTH 1-34 were incubated with 2.4 x 10^6 mononuclear leukocytes and various concentrations of bPTH 1-34 for 15 min and the bound radioligand was determined in triplicate (final volume 1.0 cc). Each point represents the mean and S.E. of six assays. In each assay only cells from a single individual were used. In other experiments, the bPTH 1-34 was replaced by 10^-6 M bovine insulin (O), bovine adrenocorticotropin (A), or salmon calcitonin (C).

FIG. 7. Displacement of radioligand from mononuclear leukocytes II. 80-110 x 10^3 cpm of ^125I[8,18-Nle, 34-Tyr]bPTH 1-34 were incubated with 2.4 x 10^6 cells for 15 min in the presence of varying amounts of 1-34 bPTH (O). [8,18-Nle, 34-Tyr]3-34 bPTH (C), bPTH 1-84 ( ), or bPTH 53-84 ( △). Final volume 1 cc. Bound radioligand was determined in triplicate. Each point represents the mean of two such assays.

FIG. 8. Scatchard analysis of radioligand binding. Displacement of specifically bound radioligand is complete by the addition of 4 ng/ml of bPTH and binding at higher concentrations is therefore considered nonspecific. The binding at 4 ng/ml was subtracted from each point in Fig. 4, and the data analyzed as described (21). A line generated by linear regression analysis of these points demonstrated the x intercept is 38.4 fmol/10^6 cells, equivalent to approximately 20,000 sites/cell. The Kd calculated from the slope of this line is 8.9 x 10^-11 M (p < 0.01).

FIG. 9. cAMP accumulation following exposure to bPTH. After 30 min preincubation at 37 °C in Earle's buffered salt solution with 2 mM isobutylmethylxanthine and 0.5% bovine serum albumin, varying amounts of bPTH 1-34 or 5 prostaglandin E2 were added to 10^6 mononuclear leukocytes in triplicate. Final volume 1 cc. After 5 min incubation at 37 °C, the reaction was stopped by the addition of 5% (final concentration) trichloroacetic acid. The cAMP in each tube was determined in duplicate as described in the text.

Specificity and Sensitivity of Radioligand Binding—Almost all specific binding of radioligand and cells is blocked by the simultaneous addition of 4 ng/ml of 1-34 bPTH (Fig. 6). Similarly, biologically active PTH 1-84 or [8,18-Nle, 34-Tyr]3-34 bPTH compete with ^125I[8,18-Nle, 34-Tyr]bPTH 1-34 (Fig. 7). As in the case of 1-34 bPTH, all radioiodinated PTH analogue is displaced by 5 ng/ml of 1-84 bPTH or (8,18-Nle, 34-Tyr)3-34 bPTH. In contrast, concentrations as high as 10^-6 M of other hormones including bovine insulin, adrenocorticotropic, lutetinizing hormone, salmon calcitonin, ovine
follie-stimulating hormone (Fig. 6), or 10^-6 M of a nonbiologi-
cally active PTH fragment, PTH 53-84 (Fig. 7), do not
compete with 125I-[8,18-Nle, 34-Tyr]bPTH 1-34. Scatchard
analysis (21) of this displacement data using bPTH 1-34 is
presented in Fig. 8. The apparent Kd of this binding is 8.9 ×
10^-11 M and there are approximately 20,000 binding sites/cell.

Biologic Effect of bPTH Binding to Mononuclear Cells— Five
min exposure to bPTH leads to increased cAMP accumulation
in mononuclear leukocytes (data not shown). In the experi-
ment illustrated in Fig. 9, maximal cAMP accumulation at 5
min in these cells follows exposure to as little as 1 × 10^-9 M
bPTH 1-34.

DISCUSSION

In this study, we observed that circulating mononuclear
leukocytes are targets of PTH, and therefore potential mod-
ulators of bone resorption. Other investigators have demon-
strated such receptors in lymphoproliferative cell lines (25)
and in human lymphocytes (25). Similar to PTH receptors in
other cells, this demonstration was made possible by the
availability of an analogue which may be radiiodinated to
high specific activity with retention of biological potency (19,
24). Binding of the analogue to mononuclear leukocytes re-
sembles authentic hormone-receptor interaction in that: 1) it
is saturable and reversible, and 2) PTH fragments which
activate adenylate cyclase also competitively displace the
radioigand. In contrast, biologically inactive PTH fragments
and unrelated hormones, including ACTH, do not inhibit
radioiodinated binding; 3) the time course of association and
dissociation, respectively, of 125I-[8,18-Nle, 34-Tyr]1-34
bPTH to and from mononuclear leukocytes is similar to that
observed in the chick kidney, a tissue with established PTH
receptors (25); 4) like canine renal membranes (19), Mg2+
fluences hormone interaction with mononuclear leukocytes;
5) the Kd (8.9 × 10^-11 M) of the reaction, as determined by
Scatchard analysis (21), is similar to the dissociation con-
stant of PTH receptors in other tissues (19, 24, 25). In these
studies, the maximal induction of cAMP accumulation oc-
curs at the lowest concentration of bPTH which displaces all
specifically bound radioigand, confirming the biological sig-
nificance of binding of the hormone to mononuclear leuko-
cytes. These observations are confirmatory of other studies
since several investigators have published studies demonstrat-
ing biologically significant effects following exposure of mono-
nuclear leukocytes to PTH (26-28).

Our data suggest that lymphocytes are the circulating target
cells of PTH. Reversible binding is unaltered by the presence
of granulocytes, erythrocytes, and platelets, and isolated mon-
ocyes, like osteoclasts (9), apparently do not recognize the
hormone. This conclusion is supported by the 3-fold increase
in the binding capacity of enriched population of lymphocytes
as compared to mixed mononuclear leukocytes.

We also noted that mononuclear leukocytes degrade the
radioigand at 22°C whereas the hormone is essentially un-
altered by enriched populations of lymphocytes at that tem-
perature even when incubated six times longer. The apprecia-
table degradation of radioigand by mononuclear leukocytes is
probably responsible for the lack of reproducibility of the
assay at temperatures greater than 10°C. In contrast, signif-
ificant ligand alteration does not appear to occur at 0-4°C as
evidenced by the observations that eluted ligand rebinds to
mononuclear leukocytes (Table I) and equilibrium binding
remains constant for at least 40 min (Fig. 1), which is well
within the time frame of our assays.

This report, taken in the context of previous reports of the
ability of activated lymphocytes to produce the lymphokine
osteoclast-activating factor (10, 11) and reports of induction
of DNA synthesis in lymphocytes (26) exposed to PTH (pos-
sible activator), suggest a possible physiologic role for a PTH
lymphocyte interaction in the control of osteoclastic activity.

In conclusion, the specific, reversible, and saturable binding
of a PTH analogue to mononuclear leukocytes, probably
lymphocytes, and the associated accumulation of cAMP in-
dicate the presence of a PTH receptor in these cells. These
findings, taken with prior demonstration of lymphocyte par-
ticipation in bone resorption (10, 11), add to the evidence
suggesting mononuclear leukocytes participate in skeletal ho-
meostasis.

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