Secondary hyperparathyroidism – an Update on Pathophysiology and Treatment

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HPT IN CRF

- Renal mass ↓
- Ca$^{2+}$ ↓
- CaR ↓
- $1,25(OH)_2D_3$ ↓
- VDR ↓
- Hyperparathyroidism
- P ↑
- PTHrP
- Paracrine autocrine factors
- Skeletal Resistance ↑
- Altered PTG function
Impaired calcium sensing in sec. HPT

N=12

Lewin E et al, KI 1997
Regulation of PTH secretion from parathyroid cells by extracellular Ca$^{2+}$

Basal levels of PTH mRNA are determined by a balance between protective and degrading factors in the cytoplasm.

In hypocalcemia, there is an increase in PTH mRNA associated with an increase in the binding of protective factors, which leads to a more stable transcript.

In hypophosphatemia, there is a decrease in protective factors, which leads to a less stable transcript and a decrease in PTH mRNA levels.
Extracellular Ca$^{2+}$
Effect on the parathyroids

1. Regulation of PTH synthesis- posttranscriptional
   Effect of low Ca$^{2+}$ on PTH mRNA stability

2. Regulation of intracellular PTH degradation
   Low Ca$^{2+}$: secretion of intact PTH
   High Ca$^{2+}$: secretion of COOH-terminal PTH fragments

3. Regulation of PTH secretion
   CaR activation

4. Regulation of cell proliferation
   Low Ca$^{2+}$: role of CaR ?, via ET-1?
* — Activating
  Glu127Ala
  Gln245Arg

X — Inactivating
  Pro39Ala
  Ser53Pro
  Pro55Leu
  Arg62Met
  Arg66Cys
  Thr138Met
  Gly143Glu
  Arg185Gln
  Asp215Glu
  Tyr218Ser
  Arg227Leu (Gln
  Glu297Lys
  Cys582Tyr
  Ser607Stop
  Ser657Tyr
  Gly670Arg
  Pro747F-shift
  Pro748Arg
  Arg795Trp
  Val817Ile
  S — Stop

R. Butters 1995 (Modified from M. Pollak et al., Cell 1993; 75: 1297-1303)
Nagano N,
Pharmacology Therapeutics 2006

The calcium receptor in the parathyroid gland by immunohistochemical measurements.
Mutations in CaR gene

- Inactivating mutations of one allele: Familiar Hypocalciuric Hypercalcemia
- Inactivating mutations of both allele: Neonatal Hyperparathyroidism
- Activating mutations: Familiar Hypocalcemia

- In uremia no mutations related to HPT have been reported
Effect of pharmacological doses of vit. D on CaR but no effect of dietary calcium

Fig. 5. Effect of dietary calcium and 1,25-dihydroxyvitamin D$_3$ [1,25-(OH)$_2$D$_3$] administration on parathyroid gland CaR mRNA.

Brown A.J.
AJP 1996
Canaff L & Hendy GN
JBC 2002:

Induction of parathyroid CaR by 1,25(OH)₂D₃.

A functional vit. D responsive element was demonstrated in the human CaR gene.
CaR mRNA in the parathyroids in uremia and after kidney transplantation

Lewin E, KI 2006
<table>
<thead>
<tr>
<th>Regulation</th>
<th>Effects</th>
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<tbody>
<tr>
<td>• By vit. D nutritional status</td>
<td>• On PTH synthesis</td>
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<tr>
<td></td>
<td>CaR regulates PTH gene expression</td>
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<tr>
<td>• By pharmacological doses of vit. D</td>
<td>• On PTH secretion</td>
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<tr>
<td></td>
<td>CaR activation suppresses secretion</td>
</tr>
<tr>
<td>• By proliferative activity</td>
<td>• On cell proliferation</td>
</tr>
<tr>
<td></td>
<td>Are changes in CaR expression secondary to proliferation ? or</td>
</tr>
<tr>
<td></td>
<td>is proliferation secondary to downregulation of CaR ?</td>
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<tr>
<td>• By phosphorus ?</td>
<td></td>
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<tr>
<td>• By calcium ?</td>
<td></td>
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<tr>
<td>Is upregulated by calcimimetics</td>
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</table>
Chemical structure of the phenylalkylamine calcimimetic compounds.
Figure 7  NPS R-568 inhibits PTH secretion from human pathological parathyroid cells. Dissociated parathyroid cells from a patient with primary (adenoma) or secondary (hyperplasia) hyperparathyroidism were studied.
Inverse sigmoid curve showing the relationship between plasma Ca²⁺ and serum PTH in normal control and NPS R-568-infused (5 mg/day intraperitoneally for 4 days) rats.
A correlation with posttranslational modification of the trans acting factor AUF1 was demonstrated.

Increased PTH gene expression in SHPT of experimental uremia is reversed by R-568, a posttranscriptional effect.
Calcimimetics upregulate decreased CaR expression in parathyroid glands of rats with chronic renal insufficiency

Effect of daily oral administration (100 µmol/kg body wt) of R-568 for 1 wk on CaR mRNA expression and on parathyroid cell proliferation in rats with severe SHPT at 8 wk after 5/6 nephrectomy.
Parathyroid glandular weight in CKD rats with SHPT: effect of cinacalcet

Colloton M et al, KI 2005
Wada M et al, KI 1998

Long-term effect of R-568 on uremic rats
Three years control of SHPT with cinacalcet

Moe SM et al. NDT 2005
Mean percentage change in intact PTH and Ca x P at each study visit, according to dialysis modality.

Lindberg JS et al, JASN 2005
Mean percent change in iPTH, serum Ca and P in CKD patients with a mean GFR of 23 ml/min.
Serum PTH, calcium and phosphate before and during treatment with cinacalcet 30 mg/day in renal transplanted patients.

Serum creatinine: 139±16 before and 148±16 µmol/l after cinacalcet.

N=14
Effect of cinacalcet on PTH levels in uremic SHPT

Quarles LD et al. JASN 2003; 14: 463A
PTH levels during treatment with cinacalcet ± vitamin D or ± P-binders

Cinacalcet + standard therapy (N = 665)
Standard therapy (N = 471)

Proportion of patients with ≥30% reduction in PTH (%)

Vitamin D use at baseline

Yes
No

15
78
72
9

Phosphate binder
Ca-based
Sevelamer

15
79
73
9

Goodman W et al. JASN 2003; 14: 460A
Calcimimetics in secondary hyperparathyroidism

- Calcimimetics offer a potent approach for treatment of even severe sec. HPT

- Calcimimetics upregulate the expression of CaR in uremic parathyroids and suppress directly or indirectly parathyroid cell proliferation and hyperplasia

- Long-term control of PTH levels can be obtained without risk of hypercalcemia and hyperphosphatemia

- Calcimimetics can be used in combination with vitamin D analogs and different P-binders
1,25(OH)$_2$D$_3$
**Effect on the parathyroids**

1. **PTH synthesis**
   - Inhibition of PTH gene transcription
   - Pharmacological effect
   - Physiological effect ?
   - Largely via calcemic activity

2. **PTH secretion**
   - Increases the sensitivity to Ca$^{2+}$ ?
   - Upregulation of CaR ?

3. **Cell proliferation**
   - Inhibition
Naveh-Many T. et al, JCI 1990

VDR in the parathyroids

Regulation of Parathyroid VDR Expression by Extracellular Calcium

![Bar chart showing VDR/Actin-mRNA in parathyroid and kidney (% vs. Ca 0.6 mM) with Ca 0.6 mM and Ca 1.5 mM conditions for parathyroid glands, renal cortex, and renal medulla.]
Serum PTH, 1,25(OH)₂D, Ca++ & P in relation to decline in GFR

Rix M et al, KI 1999

N=113
VDR mRNA in Uremia

Lewin E et al, JASN 2002
Effect of calcitriol ($10^{-8}$ mol/L) on parathyroid cell proliferation
# VDR in the parathyroids

## Regulation
- By calcium
- By pharmacological doses of vit. D
- By phosphate?

## Effects
- **On PTH synthesis**
  - Regulates PTH gene expression
- **On PTH secretion**
  - CaR activation suppresses secretion
- **On cell proliferation**
  - Directly and indirectly due to changes in CaR expression
25(OH) D₃ 1α-Hydroxylase expression in normal and pathological parathyroid glands

Segersten U et al, JCEM 2002
25(OH)D₃ suppresses PTH synthesis and secretion in bovine parathyroid cells, but is several hundred times less potent than 1,25(OH)₂D₃, correlating with its lower VDR affinity.

Reverse transcription-PCR of 1α–OHase mRNA from cultured bPTC.

Suppression of PTH secretion by 25(OH)D₃ and 1,25(OH)₂D₃.

Ritter CS et al, KI 2006
Brown AJ et al, NDT 2006

The vitamin D prodrugs $1\alpha$(OH)$D_2$, $1\alpha$(OH)$D_3$ and BCI-210 suppress PTH secretion by bovine parathyroid cells

All three prodrugs suppressed PTH secretion with approximately 10% of the activity of $1,25$(OH)$_2$D$_3$; much higher activity than expected based on the VDR affinities of these prodrugs (0.25% of $1,25$(OH)$_2$D$_3$).
Effect of intermittent intravenous and oral doses of $1\alpha$(OH)D$_3$ on plasma intact PTH, N-terminal PTH, C-terminal PTH and plasma Ca$^{2+}$
Paricalcitol Effects in CKD Stages 3 and 4

Serum calcium, phosphorus, and iPTH levels during treatment with paricalcitol. N=107

Paricalcitol versus calcitriol during 32 weeks of treatment of sHPT

A. Paricalcitol patients experienced a more rapid reduction over time in mean PTH levels,

B. Patients in the paricalcitol group achieved a 50% reduction from baseline PTH in a median of 87 days compared to 108 days for calcitriol patients.

C. Hypercalcemia and/or CaXP > 75 in 68% of calcitriol (N=133) and 64% of paricalcitol (N=130) patients

Sprague SM et al, KI 2003
Effects of direct maxacalcitol injection into parathyroid glands of uremic rats on VDR, CaR, induction of apoptosis, and weight
Vitamin D in secondary hyperparathyroidism

- Plasma levels of $1,25(\text{OH})_2 \text{D}_3$ are significantly diminished and $25(\text{OH})\text{D}_3$ deficiency is common in CKD patients.

- Sufficient levels of the substrate - $25(\text{OH})\text{D}_3$ – are of importance for the non-renal $1\alpha$-hydroxylase activity.

- $1,25(\text{OH})_2 \text{D}_3$ has positive effects on the cardiovascular system and substitution may reduce cardiovascular mortality.

- The therapeutic window of $1,25(\text{OH})_2 \text{D}_3$ is narrow and $1,25(\text{OH})_2 \text{D}_3$ is associated with an increased risk of cardiovascular calcifications, partly due to high Ca and P.

- The toxic effect of pharmacological doses of $1,25(\text{OH})_2 \text{D}_3$ is potentially reversible and might be ameliorated by calcimimetics.
Calcimimetics decrease calcifications in uremic rats treated with calcitriol

Ca (A) and P (B) content of the aorta in sham-operated rats or in 5/6 Nx rats treated with vehicle, calcitriol (80 ng/kg on alternate days), R-568 1.5 mg/kg per d, or calcitriol + R-568 1.5 mg/kg as above, for 56 d.
### Calcimimetics and vitamin D analogs

#### Mechanisms of action

<table>
<thead>
<tr>
<th>Calcimimetics</th>
<th>Vitamin D analogs</th>
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<tbody>
<tr>
<td>• Reduce PTH release by decreasing exocytosis of PTH via CaR activation</td>
<td>• Reduce PTH release via CaR upregulation and via calcemic effect</td>
</tr>
<tr>
<td>• Reduce PTH gene expression</td>
<td>• Reduce PTH gene transcription - directly via VDR</td>
</tr>
<tr>
<td>• Rapid onset of action</td>
<td>• Slow onset of action</td>
</tr>
<tr>
<td>• Fluctuating PTH levels</td>
<td>• Stable PTH levels</td>
</tr>
<tr>
<td>• Reduce plasma Ca++</td>
<td>• Increase plasma Ca++</td>
</tr>
<tr>
<td>• Reduce plasma P</td>
<td>• Increase plasma P</td>
</tr>
<tr>
<td>• May arrest parathyroid hyperplasia</td>
<td>• May arrest parathyroid hyperplasia</td>
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</tbody>
</table>

WG. Goodman
Therapeutic strategies using calcimimetics and vitamin D analogs in secondary hyperparathyroidism

- Calcimimetics effectively lower PTH with a favorable effect on plasma P and Ca x P product
- Calcimimetic treatment can be combined with any P-binder and vitamin D analogs, where the effect is complementary on the suppression of PTH
- Vitamin D supplementation is necessary in CKD patients due to its many non-renal and non-skeletal effects
- Both vitamin D analogs and calcimimetics may arrest parathyroid hyperplasia
- Both vitamin D analogs and calcimimetics may directly or indirectly reduce PTH release
- Calcimimetics reduce plasma Ca and P, while vitamin D analogs increase plasma Ca and P
- Optimal therapy might combine calcimimetics with vitamin D analogs
Paracrine/autocrine factors in the regulation of parathyroids

- Chromogranin A
- Chromogranin A related peptides (Parastatin)
- Endothelin-1
- Chemokines/cytokines (IL-1, IL-6, IL-8, TGF-α)
- PTH/PTHrP receptor ligands
Distribution of PTH and PTHrP in parathyroid hyperplasia secondary to CRF.

**PTH**: green fluorescence.
**PTHrP**: red fluorescence

Matsushita et al, KI 1999
Effect of PTHrP on PTH secretion

Lewin E et al KI 2000 & 2003
Effect of hPTH 7-84 on p-Ca\(^{2+}\) and PTH 1-84 levels in normal rats and on low-Ca\(^{2+}\)-stimulated PTH 1-84 secretion

Huan J et al, JASN 2007
Autoregulation of PTH secretion -
A model integrating the parathyroids and bone

Parathyroids

Bone

C-PTH fragments

PTH 1-84

↑ p-Ca²⁺

stimulate

inhibit
Mean systolic blood pressure (left) and diastolic blood pressure (right) in subtotally nephrectomized (SNX) rats that were treated with R-568 (solid line) or solvent (dashed line).