



**PRAXIS**  
PEPTIDE INSTITUTE

# PYY

## ADVANCED MECHANISM AND EVIDENCE GUIDE

DISTAL-GUT SATIETY SIGNAL, Y-RECEPTOR LIGAND, AND ILEAL-BRAKE COORDINATOR  
36 amino acids • L cells • PYY1-36 • DPP-4 • PYY3-36 • Y2R • satiety • ileal brake • gut-brain signaling

MEMORY KEY: PYY IS THE POST-MEAL DISTAL-GUT BRAKE: DPP-4 CONVERTS PYY1-36 TO PYY3-36, SHIFTING RECEPTOR PREFERENCE TOWARD Y2 AND SATIETY SIGNALING.

Educational monograph • Strong human physiology and acute feeding evidence • Validated ileal-brake biology • Difficult long-term obesity-drug translation

# HOW TO USE THIS GUIDE

This guide converts a long-form research narrative into a repeatable learning system. Every future PPI molecule guide can use the same architecture, visual language, evidence labels, and memory devices.

|    |                                                                  |
|----|------------------------------------------------------------------|
| 01 | IDENTITY<br>What it is - and what it is not                      |
| 02 | PHYSIOLOGY<br>The normal system before the compound              |
| 03 | MECHANISM<br>Target, pathway, and downstream logic               |
| 04 | EVIDENCE<br>Cell, animal, and human evidence separated           |
| 05 | RISK<br>Known concerns, unknowns, and translation limits         |
| 06 | MONITORING<br>What a legitimate research framework would measure |
| 07 | PATIENT CONTEXT<br>Which phenotype might fit the biology         |
| 08 | RECALL<br>Memory hooks, seven questions, and bottom line         |

|                  |                                                                                           |                                                                                                                         |
|------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| EVIDENCE<br>CODE | CELL = mechanistic<br>ANIMAL = organism-level preclinical<br>HUMAN = clinical translation | CORE DISCIPLINE<br>Mechanism does not equal outcome. Unknown does not equal failed - and unknown does not equal proven. |
|------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|

# RAPID RECALL

Read this page first. These anchors provide the complete high-level story of Pyy; the remaining pages add mechanism, evidence, context, and nuance.

|    |                                                                                                                                                              |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 01 | <b>IDENTITY</b><br>A 36-amino-acid gut hormone released mainly from distal-intestinal and colonic L cells after nutrient exposure.                           |
| 02 | <b>PROCESSING</b><br>DPP-4 removes two N-terminal residues: PYY1-36 becomes PYY3-36, changing receptor preference and functional emphasis.                   |
| 03 | <b>TARGET</b><br>PYY3-36 preferentially engages Y2 receptors and can reduce orexigenic NPY/AgRP signaling through central and gut-brain pathways.            |
| 04 | <b>BRAKE</b><br>PYY helps slow gastric emptying, intestinal transit, and selected secretions when nutrients reach the distal gut.                            |
| 05 | <b>CONTEXT</b><br>Meal composition, gut anatomy, metabolic state, receptor location, and baseline motility determine whether the signal helps or harms.      |
| 06 | <b>HUMAN EFFECT</b><br>Controlled infusion can reduce acute caloric intake, but short-term satiation is not proof of durable weight loss.                    |
| 07 | <b>LIMIT</b><br>Nausea, vomiting, aversion, delivery, exposure, and modest trial outcomes constrain obesity-drug translation.                                |
| 08 | <b>PRAXIS QUESTION</b><br>Is distal-gut feedback inadequate or excessive, which PYY form and receptor matter, and did function improve without over-braking? |

## ONE-SENTENCE MEMORY

**PYY IS THE POST-MEAL DISTAL-GUT BRAKE: DPP-4 CONVERTS PYY1-36 TO PYY3-36, SHIFTING RECEPTOR PREFERENCE TOWARD Y2 AND SATIETY SIGNALING.**

## UNDERSTAND THE PEPTIDE

Peptide YY - PYY - is a 36-amino-acid gastrointestinal peptide hormone released primarily from enteroendocrine L cells of the distal small intestine and colon after nutrient exposure.

PYY belongs to the same structural peptide family as:

- Neuropeptide Y - NPY
- Pancreatic polypeptide - PP

But its dominant physiological identity is very different from the powerful orexigenic - appetite-promoting - effects commonly associated with:

**NPY.**

PYY helps communicate:

**“NUTRIENTS HAVE ARRIVED DOWNSTREAM.”**

The body then responds by changing:

- |                       |                        |
|-----------------------|------------------------|
| • appetite            | • meal size            |
| • gastric emptying    | • intestinal transit   |
| • GI secretion        | • pancreatic secretion |
| • gut-brain signaling |                        |

Two forms are especially important:

**PYY1-36**

and:

**PYY3-36.**

And that distinction changes:

**RECEPTOR SELECTIVITY**

and therefore:

**BIOLOGICAL EFFECT.**

PYY3-36 has particular affinity for the:

**Y2 RECEPTOR**

and has become the form most closely associated with:

**POSTPRANDIAL APPETITE SUPPRESSION.**

The best way to understand PYY is not:

**“AN APPETITE-SUPPRESSING PEPTIDE.”**

That is only one piece.

A better description is:

A DISTAL-GUT FEEDBACK HORMONE THAT TELLS THE STOMACH, INTESTINE, PANCREAS, AND BRAIN THAT NUTRIENTS HAVE PROGRESSED FAR ENOUGH THROUGH THE GI TRACT THAT DIGESTIVE DELIVERY SHOULD SLOW AND FURTHER FOOD INTAKE MAY NO LONGER BE NECESSARY.

That is the deeper biology.

## WHAT IS PYY?

PYY is:

**36 AMINO ACIDS LONG.**

It is secreted mainly from:

**ENTEROENDOCRINE L CELLS**

located predominantly in:

- distal ileum
- colon
- rectum

PYY concentrations are relatively low during:

**FASTING.**

They rise after:

**FOOD INTAKE.**

Plasma PYY can begin increasing within approximately:

**15 MINUTES**

after a meal and remain elevated for several hours.

That is interesting because distal L cells may not yet have been directly contacted by the meal during the earliest part of that response.

This tells us PYY release is coordinated by more than:

**SIMPLE LOCAL NUTRIENT CONTACT.**

Potential contributors include:

- |                          |                                         |
|--------------------------|-----------------------------------------|
| • proximal gut signaling | • neural pathways                       |
| • endocrine signals      | • later direct distal nutrient exposure |

**Again:**

**THE GUT FUNCTIONS AS A NETWORK.**

## THE IDENTITY MODEL

MEAL

Nutrients move  
through GI tractDistal intestinal L  
cells

PYY



Conversion of:

### PYY1-36

to:

PYY3-36

- Y-receptor signaling

Especially:

Y2R

Potential:

APPETITE ↓

## GASTRIC EMPTYING ↓

INTESTINAL TRANSIT ↓

GI SECRETIONS ↓



Potential:

LONGER PROCESSING TIME + LOWER SUBSEQUENT INTAKE

The central concept is:

**PYY IS A FEEDBACK SIGNAL FROM THE DISTAL GUT TO THE REST OF THE DIGESTIVE SYSTEM - AND TO THE BRAIN.**

## PYY1-36 VS PYY3-36

This distinction is essential.

Native PYY is secreted initially as:

**PYY1-36.**

Then the enzyme:

**DPP-4 - DIPEPTIDYL PEPTIDASE-4**

**removes the first two amino acids.**



**PYY3-36**

That small structural change alters:

**RECEPTOR PREFERENCE.**

### PYY1-36

PYY1-36 can interact with several Y-family receptors, including:

**Y1**

**Y2**

**Y4**

**Y5**

Its biological profile is therefore:

**BROADER.**

### PYY3-36

After DPP-4 cleavage:

PYY3-36 becomes much more selective for:

**Y2R.**

And Y2 receptor signaling is central to its:

**APPETITE-SUPPRESSIVE BIOLOGY.**

This is another powerful peptide lesson:

**REMOVING TWO AMINO ACIDS CAN CHANGE THE FUNCTIONAL IDENTITY OF THE HORMONE.**

## THE PROCESSING MODEL

PYY1-36



DPP-4

Removes residues  
1-2

PYY3-36



Greater:

Y2 RECEPTOR SELECTIVITY



Different physiological emphasis

Again:

PEPTIDE PROCESSING IS PART OF THE SIGNAL.

## THE Y-RECEPTOR FAMILY

PYY belongs to the broader:

NPY RECEPTOR SYSTEM.

Major receptors include:

Y1

Y2

Y4

Y5

These are:

G-PROTEIN-COUPLED RECEPTORS.

They generally couple predominantly through:

Gi/o



Adenylyl cyclase activity ↓



cAMP ↓

But the biological outcome depends on:

WHICH RECEPTOR

and:

WHERE IT IS LOCATED.

That is critical.

## THE Y2 RECEPTOR

The:

Y2 RECEPTOR - Y2R

is especially important for:

### PYY3-36.

Y2 receptors occur in:

- hypothalamic pathways
- enteric circuits
- vagal pathways
- peripheral tissues

In feeding regulation, PYY3-36 has been proposed to act partly through Y2 receptors associated with hypothalamic: NPY / AgRP NEURONS.

**Y2 signaling can reduce NPY release. → Orexigenic drive falls. → Appetite decreases.**

## THE CENTRAL SATIETY MODEL

PYY3-36



Y2R



NPY / AgRP signaling  
↓



Relative  
melanocortin / POMC  
influence ↑



Potential:

APPETITE ↓



Potential:

**FOOD INTAKE ↓**

This is a useful model.

But modern appetite physiology is more complex than:

### ONE HYPOTHALAMIC SWITCH.

Vagal and brainstem signaling also matter.

## THE VAGUS

PYY can participate in:

### GUT-BRAIN COMMUNICATION.

Peripheral PYY signals can engage:

- vagal afferents
- brainstem circuits
- hypothalamic pathways

This means the intestine can tell the brain:

**“ENOUGH NUTRIENTS HAVE ARRIVED.”**

**Again:**

appetite is not generated exclusively by:

### THE BRAIN IN ISOLATION.

The gut continuously informs the brain about:

### WHAT IS HAPPENING BELOW.

## PYY AND SATIETY

PYY concentrations increase after eating.

The magnitude of the response often depends on:

- caloric content
- nutrient composition
- intestinal exposure
- surgical anatomy

PYY3-36 can reduce:

### SUBSEQUENT FOOD INTAKE.

In a classic double-blind crossover study, PYY3-36 infusion reduced buffet-meal calorie intake by approximately:

- 30%

in both obese and lean participants.

That was important because it demonstrated:

### DIRECT HUMAN PHARMACOLOGICAL APPETITE EFFECT.

## OBESITY AND PYY RESPONSIVENESS

The same study found obese participants retained a substantial:

### APPETITE RESPONSE TO EXOGENOUS PYY3-36.

That suggested obesity did not necessarily produce the same severe hormonal resistance seen with:

### LEPTIN.

However, the broader story became more complicated.

Later studies have found substantial variability in:

- fasting PYY
- postprandial PYY
- obesity associations
- PYY3-36 concentrations

and some research failed to confirm a simple:

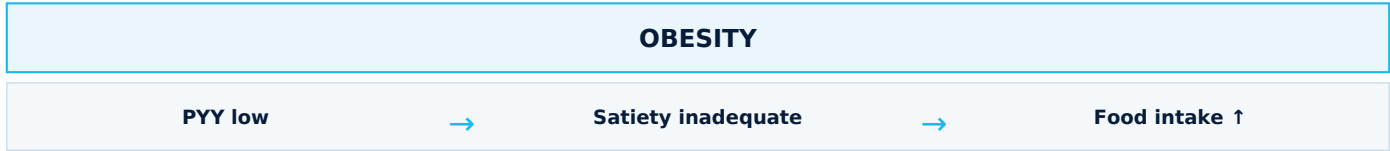
### “OBESITY = PYY DEFICIENCY”

model.

That is an important evidence correction.

# THE OBESITY LESSON

Early model:



But the real biology appears more complex.

A patient may have:

- |                                                                                                                                                                               |                                                                                                                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>• normal fasting PYY</li><li>• altered receptor responsiveness</li><li>• reward-driven intake</li><li>• different gut anatomy</li></ul> | <ul style="list-style-type: none"><li>• altered meal response</li><li>• competing appetite pathways</li><li>• different gastric emptying</li></ul> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|

So:

OBESITY ≠ PYY DEFICIENCY.

That distinction matters.

## PYY AND THE ILEAL BRAKE

One of PYY's most important gastrointestinal roles is participation in:

### THE ILEAL BRAKE.

The ileal brake is a feedback system activated when nutrients - especially:

### FAT

- reach the distal small intestine.

The intestine essentially says:

**“NUTRIENTS ARE STILL ARRIVING DOWNSTREAM. SLOW EVERYTHING ABOVE ME.”**

Responses can include:

- slower gastric emptying
- slower small-bowel transit
- altered secretion
- reduced food intake

PYY is one of the important peptide mediators of this response.

## THE ILEAL-BRAKE MODEL

Fat reaches distal intestine → L-cell PYY ↑ → Enteric + neural signaling → GASTRIC EMPTYING ↓ → INTESTINAL TRANSIT ↓ → Potential:

**MORE TIME FOR DIGESTION + ABSORPTION**

and:

**APPETITE ↓**

This is an elegant:

**DOWNSTREAM FEEDBACK LOOP.**

## WHY THE ILEAL BRAKE EXISTS

Imagine nutrients are reaching the end of the small intestine:

**FASTER THAN THEY CAN BE ABSORBED.**

A sensible physiological response is:

**SLOW THE INPUT.**

That means:

- slow the stomach
- slow proximal transit
- reduce secretion
- reduce further eating

This allows the remaining intestine:

**MORE TIME TO FINISH THE JOB.**

**Again:**

PYY is not simply:

**AN APPETITE HORMONE.**

It is:

**A DIGESTIVE LOAD-MANAGEMENT HORMONE.**

## PYY AND GLP-1 - NATURAL PARTNERS

PYY and GLP-1 are both secreted from:

**INTESTINAL L CELLS.**

They often rise together after:

**MEALS.**

Both can:

- reduce appetite
- slow GI transit
- participate in gut-brain signaling

But their pharmacology differs.

### GLP-1

Major additional effects:

- glucose-dependent insulin secretion
- glucagon suppression
- major therapeutic diabetes role

### PYY3-36

Major emphasis:

**Y2R**

- appetite / satiation
- ileal brake
- GI transit regulation

**So:**

**GLP-1 = METABOLIC + APPETITE SIGNAL**

while:

**PYY = DISTAL-GUT SATIETY + BRAKE SIGNAL.**

The overlap is precisely why combining the systems is:

**THERAPEUTICALLY INTERESTING.**

**PYY AND CCK**

Another useful comparison:

**CCK**

Released primarily from:

**PROXIMAL SMALL INTESTINE**

especially after:

**FAT + PROTEIN.**

Strong effects on:

- gallbladder
- pancreatic enzymes
- early meal termination

**PYY**

Released predominantly from:

**DISTAL INTESTINE**

Strong effects on:

- |                                |                    |
|--------------------------------|--------------------|
| • ileal brake                  | • gastric emptying |
| • later postprandial satiation | • appetite         |

So the meal generates a sequence:

**CCK EARLIER**

**GLP-1 / PYY DISTALLY**



**Increasing feedback as nutrients progress through:**

**THE INTESTINE.**

That is digestive systems biology.

## PYY VS MOTILIN

This may be the clearest temporal contrast.

### MOTILIN

Fasting



MMC



Move contents forward.

### PYY

Fed state



Distal nutrients detected



Slow delivery.

So:

**MOTILIN = MOVE BETWEEN MEALS**

while:

**PYY = BRAKE DURING / AFTER NUTRIENT DELIVERY.**

Normal GI physiology requires:

**BOTH.**

The gut must know:

**WHEN TO MOVE**

and:

**WHEN TO SLOW DOWN.**

## PYY AND GASTRIC EMPTYING

PYY inhibits:

**GASTRIC EMPTYING.**

This is part of the ileal-brake response.

**Why?**

Because when distal nutrient exposure remains high:

continuing to dump food rapidly from the stomach would:

**OVERLOAD THE SYSTEM.**

PYY therefore helps couple:

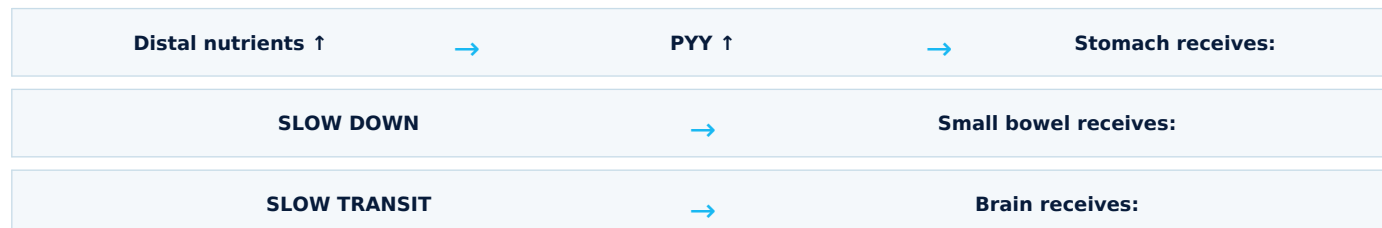
**DOWNSTREAM NUTRIENT LOAD**

to:

### UPSTREAM DELIVERY RATE.

Reviews of PYY physiology describe inhibition of gastric emptying and multiple gastrointestinal secretory functions as major actions of the peptide.

## THE FEEDBACK MODEL



### REDUCE FURTHER INTAKE

That is:

### ONE SIGNAL ACTING AT THREE LEVELS.

## PYY AND INTESTINAL TRANSIT

PYY can reduce:

### PROPULSIVE INTESTINAL TRANSIT.

**Again:**

slower transit is not automatically:

### PATHOLOGICAL.

During nutrient absorption:

it can increase:

### CONTACT TIME.

More contact time may mean:

### GREATER ABSORPTION.

But excessive slowing could produce:

- constipation
- fullness
- bloating
- nausea

**So:**

### MORE PYY EFFECT ≠ BETTER GI FUNCTION.

The correct physiology depends on:

**THE RATE MATCHING THE ABSORPTIVE CAPACITY.**

## PYY AND GI SECRETIONS

PYY has inhibitory effects on several digestive secretions.

Reported effects include reductions in:

- gastric acid secretion
- pancreatic exocrine secretion
- intestinal electrolyte / chloride secretion

depending on form, dose, and experimental context.

This is again consistent with:

**THE DISTAL BRAKE.**

If nutrients are already downstream:

the system reduces:

**ADDITIONAL SECRETORY LOAD.**

## THE SECRETORY-BRAKE MODEL

Distal nutrients → PYY → Secretions ↓ → Less luminal fluid / digestive output → Potential:

**SLOWER DELIVERY + BETTER ABSORPTIVE MATCHING**

This becomes particularly interesting in conditions involving:

**HIGH OUTPUT OR RAPID TRANSIT.**

## SHORT BOWEL BIOLOGY

PYY physiology has particular relevance when the:

**COLON OR DISTAL ILEUM REMAINS IN CONTINUITY.**

**Why?**

Because distal L cells can produce:

**PYY + GLP-1 + GLP-2.**

After bowel resection:

these distal gut hormones may participate in the:

**ADAPTIVE BRAKING RESPONSE.**

PYY can slow:

**GASTRIC EMPTYING + TRANSIT,**

while GLP-2 increases:

**ABSORPTIVE CAPACITY.**

This creates a very logical adaptation system:

**SLOW WHAT ENTERS**

and:

**IMPROVE WHAT REMAINS.**

## PYY VS GLP-2

**PYY**

**SLOW THE FLOW.**

**GLP-2**

**INCREASE THE ABSORPTIVE CAPACITY.**

Together:

Potential:

**MORE ABSORPTION FROM LESS BOWEL.**

**Again:**

different peptides can solve:

**DIFFERENT PARTS OF THE SAME PROBLEM.**

## BARIATRIC SURGERY - ONE OF THE MOST IMPORTANT PYY STORIES

One of the most important discoveries in modern metabolic surgery is that procedures such as:

**ROUX-EN-Y GASTRIC BYPASS**

and:

**SLEEVE GASTRECTOMY**

do more than:

**MAKE THE STOMACH SMALLER.**

They profoundly alter:

**GUT-HORMONE PHYSIOLOGY.**

After Roux-en-Y gastric bypass,  
nutrients reach more distal intestinal  
regions rapidly. →

L-cell stimulation increases. →

Postprandial:

**GLP-1 ↑**

and:

**PYY ↑**

This may contribute to:

- reduced hunger
- improved glucose regulation
- earlier satiety
- reduced food intake

PYY is therefore considered one component of the neuroendocrine changes that help explain why bariatric surgery is:

**METABOLIC SURGERY**

rather than simply:

**MECHANICAL RESTRICTION.**

## THE BARIATRIC MODEL

Altered GI anatomy → Nutrients reach distal gut earlier / more rapidly → L-cell stimulation ↑ → PYY + GLP-1 ↑ → Potential:

**SATIATION ↑**

**APPETITE ↓**

**GASTRIC / INTESTINAL FEEDBACK CHANGES** →

Potential contribution to:

## WEIGHT LOSS + METABOLIC IMPROVEMENT

Again:

PYY is:

**ONE PART OF THE EFFECT.**

Not:

**THE ENTIRE EXPLANATION.**

## WHY THIS MATTERS

Bariatric surgery challenged the old idea:

**WEIGHT LOSS = SMALLER STOMACH + LESS FOOD.**

Instead:

changing anatomy changes:

**SIGNALING.**

That signal changes:

**BEHAVIOR + METABOLISM.**

This is extremely important for peptide medicine because it means:

**ALTER THE GI ENVIRONMENT**

**ALTER PEPTIDE OUTPUT**



**ALTER WHOLE-BODY PHYSIOLOGY.**

## PYY AS AN OBESITY DRUG TARGET

Given the human appetite effects of PYY3-36:

the therapeutic logic seemed compelling.

Could we create:

### A PYY-BASED OBESITY DRUG?

Early human infusion studies were promising.

But translation became difficult.

#### Why?

Because increasing PYY sufficiently to suppress appetite can also produce:

- nausea
- abdominal discomfort
- vomiting
- aversion

The problem becomes:

### THERAPEUTIC WINDOW.

## THE INTRANASAL PYY TRIAL

A randomized 12-week trial tested intranasal:

### PYY3-36

in adults with obesity.

The high-dose arm was limited by substantial:

### NAUSEA AND VOMITING.

At the better-tolerated lower dose, weight loss was not significantly greater than placebo.

The authors concluded that the tested intranasal regimen was not effective for inducing clinically meaningful weight loss.

This is a crucial translational lesson.

## MECHANISM VALIDATED ≠ DRUG SUCCESS

We know PYY3-36 can:

### REDUCE FOOD INTAKE.

That is not the same as proving:

### A PARTICULAR PYY DRUG WILL PRODUCE DURABLE, TOLERABLE WEIGHT LOSS.

The therapeutic molecule must solve:

- half-life
- exposure
- nausea
- route
- peak concentration
- adherence

- receptor selectivity

**Again:**

**BIOLOGY IS ONLY THE BEGINNING OF PHARMACOLOGY.**

## THE NAUSEA PROBLEM

PYY demonstrates the same issue we saw with:

**GDF15**

in a different receptor system.

There are multiple ways to:

**EAT LESS.**

One is:

**PHYSIOLOGICAL SATIATION.**

Another is:

**FEEL TOO SICK TO EAT.**

If PYY exposure becomes high enough to produce:

**NAUSEA + VOMITING,**

then weight loss may become:

**PHARMACOLOGIC AVERSION**

rather than optimized satiety.

**Again:**

**LOWER INTAKE  $\neq$  AUTOMATICALLY BETTER THERAPY.**

**PYY + GLP-1 COMBINATION THERAPY**

A newer strategy is not to rely on PYY alone.

Instead:

combine a:

**PYY3-36 ANALOG**

with:

**GLP-1 RECEPTOR AGONISM.**

The logic is:

**MULTIPLE PHYSIOLOGICAL SATIETY SIGNALS**

may allow stronger appetite control without requiring extreme activation of:

**ONE PATHWAY.**

This is conceptually similar to:

- tirzepatide
- retatrutide
- multi-agonist endocrine strategies

**Again:**

**COMBINATION BIOLOGY MAY OUTPERFORM SINGLE-SIGNAL ESCALATION.**

## PYY1875

A recent long-acting:

**PYY3-36 ANALOG - PYY1875**

was studied both alone and as an add-on to:

**SEMAGLUTIDE.**

The program progressed from preclinical work into phase 1 and phase 2 human studies.

However, in phase 2, adding PYY1875 to semaglutide produced only a:

**MODEST, NOT CLINICALLY MEANINGFUL ADDITIONAL WEIGHT-LOSS EFFECT**

at the dose studied.

This is highly important.

**Why?**

Because it tells us the pathway remains:

**BIOLOGICALLY INTERESTING**

but turning that biology into substantial added clinical benefit is:

**NOT AUTOMATIC.**

## THE MODERN PYY LESSON

PYY has:

**HUMAN APPETITE EFFECT.**

That is real.

**But:**

**PYY MONOTHERAPY HAS BEEN DIFFICULT TO TRANSLATE.**

And even long-acting combination approaches have not yet produced the dramatic therapeutic success seen with:

**GLP-1-BASED PHARMACOLOGY.**

That is evidence calibration.

Not dismissal.

## PYY AND BLOOD GLUCOSE

PYY is not primarily an:

**INCRETIN.**

It does not have the same direct glucose-dependent insulinitropic identity as:

**GLP-1**

**or:**

**GIP.**

But by changing:

- |                    |                        |
|--------------------|------------------------|
| • gastric emptying | • nutrient delivery    |
| • food intake      | • pancreatic secretion |

it can indirectly influence:

**POSTPRANDIAL METABOLISM.**

**Again:**

**INDIRECT METABOLIC EFFECT  $\neq$  INCRETIN IDENTITY.**

## PYY AND THE COLON

Because PYY is strongly expressed in:

**DISTAL L CELLS,**

the colon is an important endocrine organ in this system.

This is important conceptually.

The colon is often taught merely as:

**THE ORGAN THAT ABSORBS WATER.**

But it contains a dense network of enteroendocrine cells producing:

**PYY**

## GLP-1

## GLP-2

So the distal gut is:

**A MAJOR ENDOCRINE SENSOR.**

That changes how we think about:

**MICROBIOME + FIBER + SHORT-CHAIN FATTY ACIDS + PEPTIDE SIGNALING.**

# MICROBIOME / SHORT-CHAIN FATTY ACIDS

Fermentation of dietary fiber by colonic bacteria produces:

- acetate
- propionate
- butyrate

These short-chain fatty acids can interact with enteroendocrine cells and influence secretion of:

**PYY**

and:

**GLP-1.**

This creates an important pathway:

**DIET**

**Microbiome fermentation** → **Microbial metabolites** → **L-cell signaling** → **PYY / GLP-1** → **Gut-brain / metabolic response**

This is one mechanism through which:

**THE MICROBIOME MAY INFLUENCE APPETITE AND GI FUNCTION.**

But again:

**MICROBIOME EFFECT ≠ SINGLE-PEPTIDE EXPLANATION.**

## THE FOOD-FIBER MODEL

**Dietary fiber** → **Colonic fermentation** → **Short-chain fatty acids** → **L-cell stimulation** → **Potential:**

PYY ↑



Potential:

**SATIETY + TRANSIT SIGNALING**

This helps explain why dietary structure can alter:

**ENDOCRINE PHYSIOLOGY.**

Not merely:

**CALORIES.**

## PYY AND PROTEIN

Higher-protein meals can generate substantial:

**PYY RESPONSES.**

This may contribute to the strong:

**SATIATING EFFECT OF PROTEIN.**

**Again:**

protein satiety is not solely:

**A STOMACH-FILLING EFFECT.**

It includes:

**ENDOCRINE SIGNALING.**

This may be one reason protein-rich meals often produce:

**LONGER POSTPRANDIAL SATISFACTION.**

## PYY AND FAT

Fat is also a strong stimulus of:

**DISTAL BRAKE PHYSIOLOGY.**

When fat reaches the ileum:

**PYY release increases.****Gastric and intestinal transit slow.**

This helps maximize:

**FAT ABSORPTION.**

**Again:**

what may appear to be:

**“SLOW DIGESTION”**

can actually be:

**NORMAL NUTRIENT-MATCHING PHYSIOLOGY.**

## PYY AND RAPID TRANSIT

This leads to an interesting theoretical therapeutic area.

If a patient has:

**RAPID GI TRANSIT**

or:

**INSUFFICIENT DISTAL-BRAKE SIGNALING,**

then enhancing PYY-like pathways could potentially increase:

**CONTACT TIME.**

But the correct question remains:

**WHY IS TRANSIT RAPID?**

Potential causes include:

- bowel resection
- inflammatory disease
- endocrine disease
- autonomic dysfunction
- bile-acid diarrhea
- post-surgical anatomy

Again:

**RAPID TRANSIT  $\neq$  PYY DEFICIENCY.**

## PYY AND CONSTIPATION

Now consider the opposite.

If PYY slows:

**GASTRIC + INTESTINAL TRANSIT,**

excessive signaling could theoretically contribute to:

**SLOWER MOTILITY.**

Therefore:

a molecule attractive for one patient may be:

COUNTERPRODUCTIVE

in another.

Again:

SAME MECHANISM. DIFFERENT PATIENT.

THE CORE MECHANISM MAP



STOMACH

GASTRIC EMPTYING ↓

SMALL INTESTINE

TRANSIT ↓

DIGESTIVE SYSTEM



The core concept is:

PYY TELLS THE REST OF THE DIGESTIVE SYSTEM THAT NUTRIENTS HAVE REACHED THE DISTAL GUT AND THAT DELIVERY AND FURTHER INTAKE SHOULD SLOW.

WHAT THIS MECHANISM MAY SUGGEST

Mechanistically, PYY deserves research interest in:

- appetite regulation
- combination obesity pharmacology
- rapid intestinal transit
- short-bowel adaptation
- nutrient sensing
- microbiome-endocrine interactions
- obesity
- bariatric-surgery physiology
- ileal-brake dysfunction
- gut-brain signaling
- postprandial satiety

Its strongest identities remain:

### POSTPRANDIAL FEEDBACK

### DISTAL-GUT BRAKING

### APPETITE REGULATION.

## WHAT THIS MECHANISM DOES NOT PROVE

PYY biology does not prove that:

- every patient with obesity has low PYY
- more PYY means better satiety
- PYY alone explains bariatric-surgery weight loss
- every patient with constipation has excessive PYY
- PYY3-36 and PYY1-36 are interchangeable
- increasing PYY always causes useful weight loss
- nausea-induced eating suppression is desirable
- every patient with rapid transit has inadequate PYY
- high-protein diets work only through PYY
- all Y receptors produce the same physiological effect

**Again:**

**PEPTIDE FORM + RECEPTOR + TISSUE + DOSE MATTER.**

# THE EVIDENCE, POTENTIAL APPLICATIONS, AND LIMITATIONS

## ENDOGENOUS PHYSIOLOGY

### STRONG

PYY is a well-established gut hormone released primarily from:

#### DISTAL L CELLS

after nutrient ingestion.

Its roles in:

- appetite
- intestinal transit
- gastric emptying
- digestive secretion

are well characterized.

## RECEPTOR BIOLOGY

### STRONG

PYY1-36 can act at multiple Y receptors.

PYY3-36 has much greater functional selectivity for:

#### Y2R.

This receptor distinction is central to understanding:

#### APPETITE BIOLOGY.

#### HUMAN APPETITE EVIDENCE

### STRONG ACUTELY

PYY3-36 infusion has significantly reduced food intake in controlled human experiments.

In one landmark study:

#### CALORIC INTAKE FELL ~30%

in both lean and obese participants.

That establishes:

#### REAL HUMAN PHARMACOLOGICAL EFFECT.

#### LONG-TERM OBESITY THERAPEUTIC EVIDENCE

### MUCH LESS IMPRESSIVE

Attempts to translate PYY3-36 into durable obesity pharmacotherapy have encountered:

- nausea
- tolerability problems
- vomiting
- limited weight-loss efficacy

An intranasal 12-week trial did not demonstrate clinically meaningful efficacy at the tolerable dose, while the high dose caused substantial discontinuation because of nausea and vomiting.

### MODERN COMBINATION EVIDENCE

## STILL DEVELOPING

A long-acting PYY3-36 analog added to semaglutide produced only modest additional weight loss in a recent phase 2 program.

### Again:

the pathway is valid.

The optimal drug:

### HAS NOT YET BEEN SOLVED.

- Research

### APPETITE AND FOOD INTAKE

This is PYY's most recognizable research domain.

PYY3-36 can clearly:

### REDUCE ACUTE ENERGY INTAKE.

But long-term weight regulation is far more complex.

It includes:

- |                        |                      |
|------------------------|----------------------|
| • hunger               | • satiety            |
| • reward               | • food environment   |
| • metabolic adaptation | • energy expenditure |
| • defended body weight |                      |

### So:

### EAT LESS AT ONE MEAL

does not necessarily equal:

### LOSE SUBSTANTIAL WEIGHT FOR YEARS.

## OBESITY

PYY remains an attractive obesity pathway because:

- it is endogenous
- humans remain responsive to pharmacologic PYY3-36
- it complements GLP-1 biology

But simple replacement therapy assumes:

### OBESITY IS A PYY DEFICIENCY STATE.

The evidence does not support such a universal model.

A better framework is:

**PYY IS ONE NODE IN A MULTYPEPTIDE APPETITE NETWORK.**

## BARIATRIC SURGERY

Postoperative PYY elevation provides an excellent physiological demonstration that:

**ALTERING GI ANATOMY CHANGES HORMONE SIGNALING.**

The result may contribute to:

- smaller meals
- reduced appetite
- improved weight control

alongside:

### GLP-1

- bile acids
- altered nutrient delivery
- vagal changes
- central adaptation

**Again:**

**SURGERY CHANGES BIOLOGY, NOT JUST SIZE.**

## THE ILEAL BRAKE

This remains one of PYY's strongest GI functions.

Distal fat exposure:



PYY release



Upper GI transit slows



Nutrient exposure is matched to:

## ABSORPTIVE CAPACITY.

This could eventually be therapeutically useful in selected:

**RAPID-TRANSIT OR MALABSORPTIVE CONDITIONS.**

## SHORT BOWEL SYNDROME

PYY has a particularly elegant conceptual fit alongside:

### GLP-2.

After bowel loss:

### GLP-2

may help:

**BUILD MORE ABSORPTIVE CAPACITY.**

## PYY

may help:

**SLOW TRANSIT.**

Thus:

**MORE TIME**

**MORE SURFACE**



**Potential:**

## BETTER ABSORPTION.

This is systems-based intestinal rehabilitation.

**RAPID TRANSIT / DIARRHEA**

PYY can slow:

**GI PROPULSION**

and reduce selected:

**SECRETORY PROCESSES.**

This creates mechanistic interest in some:

**HIGH-OUTPUT STATES.**

But diarrhea is extraordinarily heterogeneous.

Potential causes include:

- infection
- inflammation
- osmotic load
- short bowel
- bile acids
- pancreatic insufficiency
- endocrine disease

**Again:**

**DIARRHEA ≠ LOW PYY.**

**BARIATRIC POSTPRANDIAL SYMPTOMS**

An exaggerated distal-gut hormone response after surgery can also create:

**TRADEOFFS.**

Rapid nutrient delivery can produce large increases in:

**GLP-1**

## PYY

- other gut hormones

This can contribute to:

- profound satiety
- nausea
- altered motility

## Again:

the same physiology helping:

**WEIGHT LOSS**

may contribute to:

**POSTPRANDIAL INTOLERANCE**

in another context.

## MICROBIOME / DIETARY FIBER

PYY provides an important bridge between:

**MICROBIOME SCIENCE**

and:

**ENDOCRINOLOGY.**

Microbial metabolites can signal:

**ENTEROENDOCRINE L CELLS.**

That means:

dietary fiber → microbial fermentation → short-chain fatty acids → PYY / GLP-1 signaling → potential:

**APPETITE + TRANSIT EFFECTS.**

## Again:

microbial metabolism becomes:

**HOST ENDOCRINOLOGY.**

## HIGH-PROTEIN DIETS

Protein is among the strongest macronutrient signals for:

**POSTPRANDIAL SATIETY.**

PYY likely contributes.

So when someone reports that:

**HIGHER PROTEIN MAKES THEM FULLER LONGER,**

part of that experience may reflect:

**GUT-PEPTIDE PHYSIOLOGY.**

Not simply:

**FOOD VOLUME.**

## PYY AND THE FUTURE OF MULTI-AGONIST THERAPY

PYY may ultimately become more useful as:

**ONE COMPONENT OF A MULTI-SIGNAL STRATEGY**

than as:

**A SINGLE-HORMONE OBESITY DRUG.**

For example:

**GLP-1**

- satiety + glucose control

**PYY**



**distal-gut Y2 braking**

Potential combined effect:

**MORE COMPLETE POSTPRANDIAL SIGNALING.**

But current human trials remind us:

**THEORETICAL SYNERGY MUST STILL PRODUCE CLINICALLY MEANINGFUL RESULTS.**

## WHAT WE KNOW

PYY is a 36-amino-acid gastrointestinal peptide hormone.

It is secreted predominantly by enteroendocrine L cells of the distal ileum and colon.

Its circulating concentration rises after meals and can remain elevated for several hours.

PYY is initially released as PYY1-36.

DPP-4 can convert PYY1-36 into PYY3-36.

PYY1-36 interacts with multiple neuropeptide-Y-family receptors, while PYY3-36 has much stronger selectivity for Y2R.

PYY3-36 is the form most strongly associated with appetite suppression.

Y2R-mediated signaling can suppress orexigenic NPY-related circuitry.

PYY also participates in vagal and brainstem gut-brain signaling.

PYY reduces gastric emptying and intestinal transit.

It is an important mediator of the ileal brake.

The ileal brake allows distal nutrient exposure to slow upstream GI delivery.

This helps match nutrient flow to intestinal absorptive capacity.

PYY can also inhibit selected gastric, pancreatic, and intestinal secretory processes.

Human PYY3-36 infusion can substantially reduce acute caloric intake.

One controlled study reported approximately 30% lower buffet-meal caloric intake in both obese and lean subjects.

Obesity does not appear to cause universal resistance to exogenous PYY3-36.

But the idea that obesity is simply a PYY-deficiency state is not supported consistently across the literature.

PYY rises substantially after some bariatric procedures and likely contributes to postoperative appetite and meal-size changes.

This reinforces that bariatric surgery alters endocrine physiology rather than functioning purely through restriction.

Turning PYY biology into a successful obesity drug has been difficult.

Intranasal PYY3-36 did not produce clinically meaningful weight loss at the better-tolerated dose in a randomized 12-week study, while higher exposure caused substantial nausea and vomiting.

More recent long-acting PYY3-36 analog development has also reached human phase 2 testing.

A long-acting PYY analog added to semaglutide produced only modest, not clinically meaningful, additional weight loss at the studied dose.

This is a powerful reminder that validating a pathway is not the same as developing a successful drug.

## WHAT WE THINK MAY BE HAPPENING

PYY may function as:

### THE DISTAL GUT'S "WE HAVE ENOUGH COMING THROUGH" SIGNAL.

A meal begins. → The stomach sends food forward. → The proximal intestine digests. → Nutrients continue moving. → Eventually nutrients reach:

### THE DISTAL SMALL INTESTINE.

At that point the system learns:

### THE UPSTREAM DELIVERY RATE MAY BE OUTPACING WHAT HAS ALREADY BEEN PROCESSED.

L cells release:

**PYY.**

The stomach receives:

**SLOW DOWN.**

The intestine receives:

**SLOW TRANSIT.**

Secretory systems receive:

**REDUCE ADDITIONAL LOAD.**

The brain receives:

**YOU MAY NOT NEED MORE FOOD.**

That is:

**FEEDBACK CONTROL.**

PYY is not simply trying to:

**STOP EATING.**

It is helping synchronize:

**INTAKE**

with:

**DIGESTIVE CAPACITY.**

That may be its deeper physiological identity.

## WHAT REMAINS CONTEXT-DEPENDENT

Important questions include:

What determines PYY1-36 versus PYY3-36 exposure in different patients?

How strongly does DPP-4 activity modify PYY physiology?

Which Y2R populations are most important for human appetite suppression?

How much of PYY's appetite effect is vagal versus directly central?

What determines individual nausea sensitivity to PYY analogs?

Can Y2 agonism be separated from aversive signaling?

Can slower release avoid high peak concentrations and improve tolerability?

Is PYY more effective as part of multi-agonist therapy?

Which GLP-1 / PYY combinations produce genuine synergy?

Why did recent combination trials produce only modest added weight loss?

Does obesity alter postprandial PYY secretion differently across phenotypes?

Is there a clinically meaningful subgroup with low post-meal PYY?

How does insulin resistance modify PYY response?

How does bariatric anatomy alter long-term PYY physiology?  
How much PYY contributes independently to bariatric weight loss?  
How does dietary protein alter PYY secretion over time?  
How do fiber and microbial metabolites influence L-cell PYY output?  
Can targeted nutrient delivery to the ileum activate the ileal brake therapeutically?  
Could PYY analogs help selected rapid-transit disorders?  
Could excessive PYY contribute to post-surgical nausea or slowed transit?  
How does PYY interact with GLP-2 after intestinal resection?  
Can Y-receptor-selective analogs preserve GI benefit without excessive nausea?  
What objective biomarkers best identify meaningful PYY responsiveness?

**Again:**

these are the questions needed to move from:

**DISTAL-GUT FEEDBACK HORMONE**

to:

**PRECISION APPETITE AND MOTILITY THERAPEUTICS.**

# THE PRAXIS LENS

**DO NOT BEGIN WITH PYY**

Begin with:

**WHAT PART OF POSTPRANDIAL FEEDBACK IS ACTUALLY FAILING?**

Then:

## PHYSIOLOGY

**PATTERN** → **MECHANISM** → **EVIDENCE** → **RISK** → **MONITORING** → **DECISION**

## PHYSIOLOGY

Healthy meal regulation requires coordination among:

- stomach
- distal intestine
- brainstem
- absorptive surface
- proximal intestine
- vagus
- hypothalamus

PYY appears especially relevant to:

**DISTAL-GUT FEEDBACK + APPETITE + TRANSIT BRAKING.**

## PATTERN

What is actually present?

excessive hunger?

unusually large meals?

rapid intestinal transit?

post-bariatric physiology?

short bowel?

inadequate satiation?

nausea?

constipation?

obesity?

**Again:**

**"I'M HUNGRY" IS NOT A PYY DIAGNOSIS.**

## MECHANISM

Does PYY biology match:

**THE DOMINANT BOTTLENECK?**

If excessive intake is driven by:

**SLEEP DEPRIVATION + REWARD EATING,**

PYY may not be:

**THE PRIMARY PROBLEM.**

If intestinal transit is rapid because:

**MOST OF THE BOWEL HAS BEEN REMOVED,**

PYY-like braking becomes:

**MUCH MORE MECHANISTICALLY INTERESTING.**

If the patient already has:

**SEVERE CONSTIPATION OR GASTROPARESIS,**

additional slowing may be:

**COUNTERPRODUCTIVE.**

**Again:**

**DIRECTION MATTERS.**

## EVIDENCE

Ask:

**WHAT CLAIM ARE WE MAKING?**

PYY rises after meals?

**STRONG HUMAN PHYSIOLOGY.**

PYY3-36 reduces acute food intake?

**STRONG HUMAN EXPERIMENTAL EVIDENCE.**

PYY is important in the ileal brake?

**STRONG PHYSIOLOGICAL RATIONALE.**

PYY monotherapy causes major durable weight loss?

**NOT ESTABLISHED.**

PYY adds major weight loss to semaglutide?

**NOT DEMONSTRATED IN THE RECENT PHASE 2 PROGRAM AT THE STUDIED DOSE.**

**Again:**

**EVIDENCE CLASS MATTERS.**

## RISK

Potential consequences of excessive pharmacological PYY signaling include:

- nausea
- abdominal discomfort
- slowed intestinal transit
- vomiting
- slowed gastric emptying
- reduced food intake beyond what is nutritionally appropriate

The intranasal obesity trial demonstrated this therapeutic-window problem clearly, with substantial nausea and vomiting at higher exposure.

**Again:**

**MAXIMUM APPETITE SUPPRESSION IS NOT THE SAME AS OPTIMAL PHYSIOLOGY.**

## MONITORING

Monitoring should follow:

**THE TARGET HYPOTHESIS.**

### APPETITE / WEIGHT

- hunger
- caloric intake
- body composition
- meal size
- body weight

### GI TOLERANCE

- nausea
- fullness
- vomiting
- abdominal discomfort

### MOTILITY

- gastric-emptying pattern where appropriate
- intestinal transit
- stool frequency
- constipation / diarrhea

**SHORT BOWEL / RAPID TRANSIT**

- stool or ostomy output
- nutrient absorption
- hydration
- parenteral-support requirements

**METABOLIC**

where relevant:

- glucose
- lipids

- insulin
- weight trajectory

**Again:**

monitor:

**WHAT Y2 / DISTAL-BRAKE SIGNALING IS SUPPOSED TO CHANGE.**

## THE PRAXIS 5

### MECHANISM

PYY's dominant postprandial pathway is:

**DISTAL NUTRIENTS → L-CELL PYY → PYY3-36 → Y2R → APPETITE + GI BRAKING.**

Its strongest systems identity is:

**DISTAL-GUT FEEDBACK.**

## EVIDENCE

Endogenous physiology:

**STRONG.**

Y2 receptor biology:

**STRONG.**

Acute human appetite effect:

**STRONG.**

Ileal-brake physiology:

**STRONG.**

Long-term obesity monotherapy:

**DISAPPOINTING SO FAR.**

Combination obesity therapy:

**STILL DEVELOPING.**

## RISK

The major conceptual mistake is:

**ASSUMING THAT BECAUSE PYY REDUCES EATING, MORE PYY MUST PRODUCE BETTER OBESITY THERAPY.**

At high exposure:

**NAUSEA + VOMITING**

can become the dominant phenotype.

**Again:**

**APPETITE CONTROL MUST REMAIN PHYSIOLOGICALLY TOLERABLE.**

## MONITORING

Monitor:

**APPETITE + TRANSIT + GI TOLERANCE + FUNCTIONAL OUTCOME.**

If the hypothesis is:

**BETTER DISTAL-GUT FEEDBACK,**

**then:**

**MEALS OR TRANSIT SHOULD BECOME BETTER REGULATED WITHOUT CREATING PATHOLOGICAL SLOWING OR AVERSION.**

# PATIENT CONTEXT

A patient with:

**OBESITY + INADEQUATE SATIATION**

is not identical to:

someone with:

**SEVERE GASTROPARESIS.**

A patient with:

**RAPID POST-RESECTION TRANSIT**

is not identical to:

someone with:

**CHRONIC CONSTIPATION.**

A patient after:

**ROUX-EN-Y GASTRIC BYPASS**

may already have:

**STRONG POSTPRANDIAL PYY SIGNALING.**

Same peptide.

Different:

**POSTPRANDIAL CONTEXT.**

## SEVEN QUESTIONS TO ASK BEFORE PYY

### 1. WHAT ARE WE TRYING TO CHANGE?

appetite?  
meal size?  
rapid transit?  
ileal-brake function?  
bariatric physiology?

### 2. WHICH MOLECULAR FORM ARE WE DISCUSSING?

**PYY1-36**

or:

**PYY3-36?**

That matters.

### 3. WHICH RECEPTOR IS RELEVANT?

For appetite pharmacology:  
Y2R is central.

### 4. IS THE PROBLEM INADEQUATE PYY SIGNALING - OR SOMETHING COMPLETELY DIFFERENT?

Obesity is not automatically:

**PYY DEFICIENCY.**

### 5. WHAT EVIDENCE SUPPORTS THE APPLICATION?

endogenous physiology?  
acute human feeding study?  
bariatric association?  
long-term clinical trial?

## 6. WHAT WILL WE MONITOR?

appetite?  
meal size?  
weight?  
nausea?  
gastric emptying?  
intestinal transit?

## 7. WHAT WOULD DEFINE SUCCESS?

Not:

**"PYY WENT UP."**

**But:**

POSTPRANDIAL FEEDBACK IMPROVED - FOOD INTAKE, DELIVERY RATE, OR INTESTINAL TRANSIT BECAME BETTER MATCHED TO THE PATIENT'S ACTUAL PHYSIOLOGICAL NEED WITHOUT CREATING EXCESSIVE NAUSEA OR MOTILITY SUPPRESSION.

## KEY TAKEAWAYS

PYY is a 36-amino-acid gastrointestinal peptide hormone.

It is secreted predominantly from enteroendocrine L cells in the distal ileum and colon.

PYY rises after food intake and can remain elevated for several hours.

PYY is initially secreted as PYY1-36.

DPP-4 converts PYY1-36 into PYY3-36.

This structural processing changes receptor selectivity.

PYY1-36 can interact with several Y receptors.

PYY3-36 has much greater selectivity for Y2R.

PYY3-36 is therefore the molecular form most closely associated with postprandial appetite suppression.

Y2 signaling can suppress orexigenic NPY-related circuitry.

PYY also participates in vagal and brainstem gut-brain communication.

This allows the distal intestine to influence feeding behavior.

PYY is an important component of the ileal brake.

When nutrients - especially fat - reach the distal intestine, PYY helps slow upstream gastric and intestinal delivery.

That gives the gut more time to process and absorb what has already arrived.

PYY can slow gastric emptying and intestinal transit.

It can also suppress selected digestive secretions.

PYY therefore should not be reduced to an appetite peptide.

Its broader identity is distal-gut feedback and digestive load management.

Human pharmacology confirms that PYY3-36 can substantially reduce acute food intake.

A landmark controlled study found roughly 30% lower caloric intake after PYY3-36 infusion in both obese and lean participants.

However, obesity should not be reduced to PYY deficiency.

Human studies have produced conflicting findings regarding fasting and postprandial PYY differences in obesity.

Bariatric surgery often increases postprandial PYY signaling.

This likely contributes to the profound endocrine changes that follow altered GI anatomy.

Bariatric surgery is therefore not merely mechanical restriction.

Changing anatomy changes peptide signaling.

PYY has been difficult to translate into a stand-alone obesity drug.

High pharmacological exposure can produce nausea and vomiting.

A 12-week intranasal PYY3-36 trial failed to demonstrate clinically meaningful efficacy at the more tolerable dose, while the higher dose was poorly tolerated.

This demonstrates that a peptide can have a very real biological mechanism and still be difficult to develop into an effective drug.

A newer long-acting PYY3-36 analog has also been tested as an add-on to semaglutide.

The studied regimen produced only modest, not clinically meaningful, additional weight loss in phase 2.

That does not invalidate PYY biology.

It defines the current translational limit.

PYY and GLP-2 provide an especially useful intestinal comparison.

PYY can slow transit.

GLP-2 can increase absorptive capacity.

One increases time.

The other increases surface and function.

Together they illustrate how multiple peptides can coordinate intestinal adaptation.

PYY also shows how the microbiome can become endocrine physiology.

Dietary substrates can be fermented into metabolites that influence enteroendocrine L-cell signaling.

That gives us a pathway from diet → microbes → metabolites → gut peptide → brain and motility.

- The best question is not “does PYY suppress appetite?”

The better question is “has the distal gut detected enough nutrient to justify slowing upstream delivery and further intake, is that feedback response inadequate or excessive in this patient, and would modifying PYY/Y2 signaling improve the actual physiological mismatch without simply producing nausea or pathologic slowing?”

## THE BOTTOM LINE

PYY may be one of the best peptides for understanding:

**FEEDBACK.**

The stomach sends food forward.

The proximal intestine digests it.

But eventually the distal intestine needs a way to say:

**“WAIT.”**

**“WE STILL HAVE NUTRIENTS DOWN HERE.”**

**“STOP SENDING SO MUCH SO FAST.”**

That message is carried, in part, by:

**PYY.**

**So:**

**DISTAL NUTRIENTS**

**L CELLS**



**PYY**



**The stomach receives:**

### **SLOW DOWN.**

The intestine receives:

**SLOW TRANSIT.**

The digestive glands receive:

**REDUCE SOME OF THE ADDITIONAL SECRETORY LOAD.**

And the brain receives:

**YOU PROBABLY DO NOT NEED ANOTHER SERVING YET.**

That is not simply:

**APPETITE SUPPRESSION.**

It is:

**SYSTEM COORDINATION.**

And it creates a beautiful comparison with the peptides we just covered.

### **MOTILIN**

says:

**MOVE DURING FASTING.**

## CCK

says:

**FAT AND PROTEIN ARRIVED - RELEASE BILE AND ENZYMES.**

## SECRETIN

says:

**ACID ARRIVED - SEND BICARBONATE.**

## GLP-2

says:

**BUILD MORE INTESTINAL CAPACITY.**

And:

**PYY**

says:

**ENOUGH IS REACHING THE DISTAL GUT - SLOW THE SYSTEM DOWN.**

That is why memorizing:

**"PYY = SATIETY"**

misses almost the entire story.

PYY also gives us a crucial pharmacology lesson.

We can give PYY3-36 to humans and:

**FOOD INTAKE FALLS.**

So the mechanism is:

**REAL.**

But when researchers tried to convert that biology into:

**A PRACTICAL WEIGHT-LOSS DRUG,**

nausea, vomiting, exposure, and limited long-term efficacy became:

**THE REAL-WORLD BOTTLENECKS.**

That is what translational medicine is supposed to reveal.

A mechanism may be:

**CORRECT.**

A drug strategy may still be:

**INCOMPLETE.**

So the Praxis question becomes:

“WHAT is the distal gut trying to communicate, is nutrient delivery exceeding absorptive capacity, is satiation signaling inadequate, is transit too fast or already too slow, which form of PYY and which receptor actually matter, and can modifying that signal restore the correct postprandial feedback without turning physiological satiety into nausea, aversion, or pathological motility suppression?”

That is the difference between:

**CALLING PYY A SATIETY HORMONE**

and:

**UNDERSTANDING DISTAL-GUT FEEDBACK CONTROL.**

**FINAL RECALL**

| PROCESS                                          | BRAKE                                                       | VERIFY                                                       |
|--------------------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------|
| Two-residue cleavage changes receptor preference | Match nutrient delivery to appetite and absorptive capacity | Measure intake, motility, tolerance, and meaningful function |

**STOP MEMORIZING PEPTIDES. START UNDERSTANDING THE SYSTEM.**

Praxis Peptide Institute provides educational information and is not a substitute for individualized medical diagnosis or treatment. Peptide YY is an endogenous 36-amino-acid gastrointestinal hormone involved in postprandial appetite regulation, Y-receptor signaling, the ileal brake, gastric emptying, intestinal transit, digestive secretion, and gut-brain communication. Its biological effects depend importantly on whether PYY1-36 or PYY3-36 is being considered, receptor selectivity, nutrient and surgical context, gastric and intestinal motility, underlying disease, and the balance between desirable satiation and excessive GI slowing or nausea. Human studies validate acute appetite suppression by PYY3-36, but development of PYY-based obesity pharmacotherapy has been limited by tolerability and modest durable efficacy, emphasizing the distinction between pathway validation and successful therapeutic translation.