

Chapter 5: Chemical Messengers and the Serotonin Myth

Summary

"Ninety percent of your serotonin is in your gut" is one of the most shared gut-brain facts online, and it's true. The conclusion people draw from it, that your gut controls your happiness, is not. This chapter explains how nerve cells pass chemical messages, follows serotonin from the amino acid tryptophan to the cells that make it, and shows why serotonin made in the gut stays out of the brain. It covers how SSRI medicines work and why they often upset the stomach at first, what the "low serotonin causes depression" debate is really about, and what we know (and don't) about chemicals like GABA and dopamine made by gut microbes.

Concepts Covered

1. Synapse
2. Neurotransmitter
3. Serotonin
4. Tryptophan
5. Tryptophan Hydroxylase
6. Enterochromaffin Cell
7. Serotonin Transporter
8. SSRI
9. Blood-Brain Barrier
10. Gut Serotonin Mood Myth
11. Dopamine
12. GABA
13. Acetylcholine
14. Microbe-Made Neurotransmitter
15. Kynurenine Pathway
16. Spore-Forming Bacteria

Prerequisites

- [Chapter 1: The Brain in Your Belly \(and Why That Phrase Is Misleading\)](#) for enteric neurons and the Hype Meter
- [Chapter 2: The Vagus Highway](#) for enteroendocrine cells and upward vagus signals
- [Chapter 3: Meet the Microbiome](#) for germ-free mice and correlation vs causation
- [Chapter 4: The Immune System as a Sense Organ](#) for inflammation and the inflammation-depression debate

The most famous gut-brain number



If you've seen one gut-brain fact on social media, it's probably "90% of your serotonin is made in your gut." That true number is often used to sell a false conclusion. Learning exactly where serotonin goes will help you spot a whole family of wellness myths. It also explains something many teens on antidepressants notice: why a brain medicine can upset your stomach.

5.1 Sam's Cousin Has a Theory

Sam's older cousin posted a video that got thousands of likes. Over a shot of a smoothie, the caption read: "90% of your serotonin is made in your GUT. Serotonin = happiness. So heal your gut and you'll be happy. Link in bio for my gut-healing powder." Sam, who has IBS and gets stomach trouble before big races, sent it to Riya with one word: "Real?" (Sam and Riya are fictional students who appear throughout this book.)

Riya thought about it. The first sentence sounded familiar, and she had heard Dr. Alvarez mention gut serotonin once. But the jump from "made in your gut" to "you'll be happy" felt too easy. This chapter explains why: the first sentence is solid science, the second is an oversimplification, and the third does not follow from the first two at all. To see why, we need to know what serotonin is, where it's made, and where it can and can't go.

5.2 Two Bakeries, One Recipe

Start with a comparison. Picture two towns separated by a high wall with a few guarded gates. Each town has its own bakery, and by coincidence both bake the same kind of bread from the same flour. The bakery in the big valley town makes far more bread, and that bread feeds the valley. The bakery in the hilltop town is smaller, but it makes all of the bread the hilltop eats. The guards won't let finished bread through the gates, but they will let sacks of flour through.

Now suppose someone says, "90% of all the bread in this region is baked in the valley, so if you want the hilltop to eat better, improve the valley bakery." You can see the problem. The valley's bread never reaches the hilltop. The only thing that crosses the wall is flour.

In your body, the valley is your gut, the hilltop is your brain, the wall is the blood-brain barrier, the bread is serotonin, and the flour is an amino acid called tryptophan. Keep this picture in mind. The rest of the chapter fills in the details.

5.3 How Nerve Cells Pass Chemical Messages

Here's a quick refresher from biology. A neuron sends an electrical signal down its long fiber (axon) to its tip. But neurons don't usually touch the next cell. There's a tiny gap, and the signal has to cross it as chemistry.

A **synapse** is the junction where a neuron passes a signal to another cell (another neuron, a muscle cell, or a gland cell), usually across a tiny gap called the synaptic cleft. A **neurotransmitter** is a chemical messenger that a neuron releases at a synapse; it crosses the gap and binds to receptor proteins on the receiving cell, making that cell more or less likely to fire or changing how it works. After the message is delivered, the neurotransmitter is cleared away, often by being pumped back into the cell that released it, so the next message can be sent cleanly. For a deeper review, see [From Neuron to Bedside, Chapter 3](#).

One more idea matters here. The same chemical can act as a neurotransmitter when a neuron releases it into a synapse and as a hormone when a cell releases it into the blood to act far away. Serotonin does both, and that is exactly why it causes so much confusion.

Four neurotransmitters show up again and again in gut-brain research:

Serotonin (also called 5-hydroxytryptamine, or 5-HT) is a chemical messenger made from the amino acid tryptophan. In the brain it acts as a neurotransmitter involved in mood, sleep, appetite, and many other functions; in the gut it controls movement, secretion, and sensations like nausea; and in the blood it is carried by platelets.

Dopamine is a neurotransmitter that the brain uses in movement, motivation, and learning from rewards; it also acts in other parts of the body, including the gut.

GABA (gamma-aminobutyric acid) is the brain's main inhibitory neurotransmitter, meaning it mostly makes receiving neurons less likely to fire, like a brake pedal.

Acetylcholine is a neurotransmitter that activates muscles and many glands; in the gut it is a main "go" signal used by enteric motor neurons to make smooth muscle contract, and it is the main chemical the vagus nerve's outgoing (motor) fibers release onto their targets. (You met it in Chapter 1 as the messenger of excitatory enteric motor neurons.)

Messenger	A main brain role	A main gut role	Made by gut microbes?
Serotonin	Mood, sleep, appetite	Movement, secretion, nausea signals	Microbes influence how much the gut makes (mouse studies)

Messenger	A main brain role	A main gut role	Made by gut microbes?
Dopamine	Movement, motivation, reward	Local control of gut function	Microbes take part in dopamine chemistry (mostly lab and animal studies)
GABA	Main "brake" signal	Local signaling in the gut wall	Some common gut bacteria make large amounts in the lab
Acetylcholine	Attention, memory	Main "go" signal for gut muscle	Not a focus of this chapter

5.4 Meet Serotonin: More Than a "Happy Chemical"

Serotonin's story starts in the gut. Vittorio Erspamer studied a substance made by special hormone cells in the gut lining and called it "enteramine." In 1952, [Erspamer and Asero](#) reported in the journal *Nature* that enteramine was the same molecule as 5-hydroxytryptamine, the chemical we now call serotonin.

So serotonin has been a gut chemical from the start. Reviews by [Michael Gershon \(2013\)](#) and by [Gary Mawe and Jill Hoffman \(2013\)](#) describe its jobs outside the brain:

- **In the gut wall**, serotonin released from the lining activates sensory nerve endings that start local reflexes for movement and secretion, and that send information to the brain through the vagus and spinal nerves.
- **In sensations**, activation of those vagus and spinal fibers can lead to nausea, vomiting, fullness, and discomfort.
- **In the blood**, platelets (cell fragments that help blood clot) soak up serotonin and store it, which helps with clotting.
- **In bone**, gut-made serotonin acting as a hormone slows the growth of bone-building cells, at least in animal studies.

Inside the brain, serotonin is made mainly by neurons in the brainstem, whose fibers reach many other brain areas. Brain serotonin is involved in mood, but also in sleep, appetite, pain, and much more. Calling it "the happy chemical" is a bit like calling a smartphone "a calculator": not wrong, but it misses most of what it does.

Two names, one molecule



When you read research, watch for "5-HT." It's just the chemical name for serotonin (5-hydroxytryptamine), and it's the same molecule whether it's in your gut, your blood, or your brainstem. What differs is where it's made and where it can travel.

5.5 How Serotonin Is Made: Tryptophan and Its Enzymes

Every bit of serotonin in your body starts as tryptophan.

Tryptophan is an essential amino acid, meaning your body can't make it and must get it from protein in food, such as meat, dairy, seeds, and many other foods. A 2016 review by [Jenkins and colleagues](#) describes it as found in many protein-based foods. Besides being a building block for proteins, tryptophan is the raw material for serotonin.

To turn tryptophan into serotonin, cells need an enzyme (a protein that speeds up a chemical reaction).

Tryptophan hydroxylase (TPH) is the enzyme that performs the first and key step in making serotonin from tryptophan. There are two versions.

- **TPH1** works in the gut's serotonin-making lining cells and other cells outside the brain.
- **TPH2** works in neurons, including the brain's serotonin neurons and serotonin-making neurons in the gut wall.

The second version was discovered in 2003 by [Diego Walther and colleagues](#), who reported it in *Science*. Two separate enzymes in two separate places means two separate supplies of serotonin, like the two bakeries using different ovens. Drug designers have used this: a 2013 review by Mawe and Hoffman describes TPH inhibitors designed to lower gut serotonin without reaching the brain, by limiting their ability to cross the blood-brain barrier.

The recipe has two steps. Tryptophan hydroxylase turns tryptophan into an in-between molecule called 5-HTP (5-hydroxytryptophan), and a second enzyme then turns 5-HTP into serotonin (Jenkins 2016). Unlike serotonin, 5-HTP can be carried across the blood-brain barrier (Section 5.7), and it is sold in some dietary supplements.

A 2020 review by [Maffei](#) notes that too much 5-HTP can cause serotonin syndrome, a dangerous overload of serotonin activity, and MedlinePlus lists tryptophan among the products that can interact with fluoxetine, an SSRI you'll meet in Section 5.9. Dietary supplements are not approved as drugs to treat any condition, so questions about them belong with a doctor.

Most tryptophan takes a different road

Serotonin gets the headlines, but it uses only a small share of the tryptophan you eat. The **kynurenine pathway** is the main chemical route for breaking down tryptophan, mostly in the liver, producing a molecule called kynurenine and a series of other products, some of which can act on brain cells. [Dantzer's 2008 review](#) (the same one from Chapter 4) states that more than 95% of dietary tryptophan is broken down through the kynurenine pathway, and only a small portion becomes serotonin.

This pathway links back to Chapter 4. Dantzer's review describes how some pro-inflammatory cytokines boost an enzyme (called IDO) that pushes tryptophan toward kynurenine. In mice given a bacterial trigger for inflammation, this shift happened alongside depression-like behavior, and some kynurenine products can act on receptors in the brain. Whether this matters for human depression is still being studied, so treat it as a mouse-based idea, not a settled explanation. A 2018 review by [Agus, Planchais, and Sokol](#) adds that gut

microbes directly or indirectly influence how tryptophan is split among serotonin, kynurenine, and a third route that makes molecules called indoles.

5.6 The Gut's Serotonin Factories: Enterochromaffin Cells

In Chapter 2 you met enteroendocrine cells, the hormone-releasing sensor cells scattered through the gut lining. One type does most of the body's serotonin work.

An **enterochromaffin cell** (EC cell) is a type of enteroendocrine cell in the gut lining that senses conditions inside the gut and releases serotonin, making most of the body's serotonin using the enzyme TPH1. Here is the fact this book uses throughout:

More than 90% of the body's serotonin is made in the gut, mostly by enterochromaffin cells (some estimates say about 95%).

A 2015 study by [Yano and colleagues](#) and a 2017 study by [Bellono and colleagues](#) both put it at more than 90%; Gershon's 2013 review puts about 95% of the body's serotonin in the gut. Surprisingly few cells do this work. Bellono's team reported that EC cells make up less than 1% of the cells lining the intestine. Working with lab-grown mouse gut tissue (organoids) and mice, they also showed that EC cells carry specific chemical-sensing receptors, are electrically excitable, and form synapse-like connections with sensory nerve fibers. That makes them tiny chemical sensors wired to the nervous system, a good example of the "gut as sense organ" idea from Chapter 4.

What happens to gut serotonin after an EC cell releases it? Mawe and Hoffman's review traces three paths, and they are the same three you'll see in the MicroSim:

1. **It acts on nearby nerves.** Serotonin binds receptors on the endings of enteric, vagal, and spinal sensory nerves, starting local reflexes and sending signals toward the brain. Note the key difference: the *nerve signal* travels to the brain; the serotonin molecule does not.
2. **It is cleared back into lining cells.** The message has to be switched off, and here a pump does the work.
3. **It enters the blood and is stored in platelets.** Serotonin not taken up by the lining enters tiny blood vessels, where platelets take it in and store it.

The pump in path 2 is worth its own definition. The **serotonin transporter** (SERT) is a protein pump in cell membranes that moves serotonin from outside a cell back inside, ending its signal. In the brain, SERT sits on serotonin neurons and recycles serotonin from synapses. In the gut, Mawe and Hoffman report that SERT is found on essentially all of the lining's epithelial cells, which clear away serotonin after EC cells release it. Platelets use SERT too, which is how they load up on serotonin from the blood.

If you're going through this

If you have IBS like Sam, you may hear that serotonin is involved in gut sensitivity and bowel habits. That's an active research area, and some IBS medicines do act on gut serotonin receptors, which your care team can explain. What it doesn't mean is that your symptoms are "all chemical" or that a supplement can rebalance them. If a product promises to "fix your serotonin," bring it to your doctor before you try it.

5.7 The Wall Between: The Blood-Brain Barrier

Now for the wall in our two-towns picture.

The **blood-brain barrier** (BBB) is the specialized lining of the brain's blood vessels, made of tightly sealed endothelial cells supported by other cells, that tightly controls which ions, molecules, and cells can pass from the blood into the brain. A 2015 review by [Daneman and Prat](#) describes how these vessel cells regulate traffic between blood and brain far more strictly than vessels elsewhere in the body. Think of it as the wall with a few guarded gates: specific transporter proteins act as gates that let in nutrients the brain needs, such as certain amino acids.

Here is the fact at the heart of this chapter:

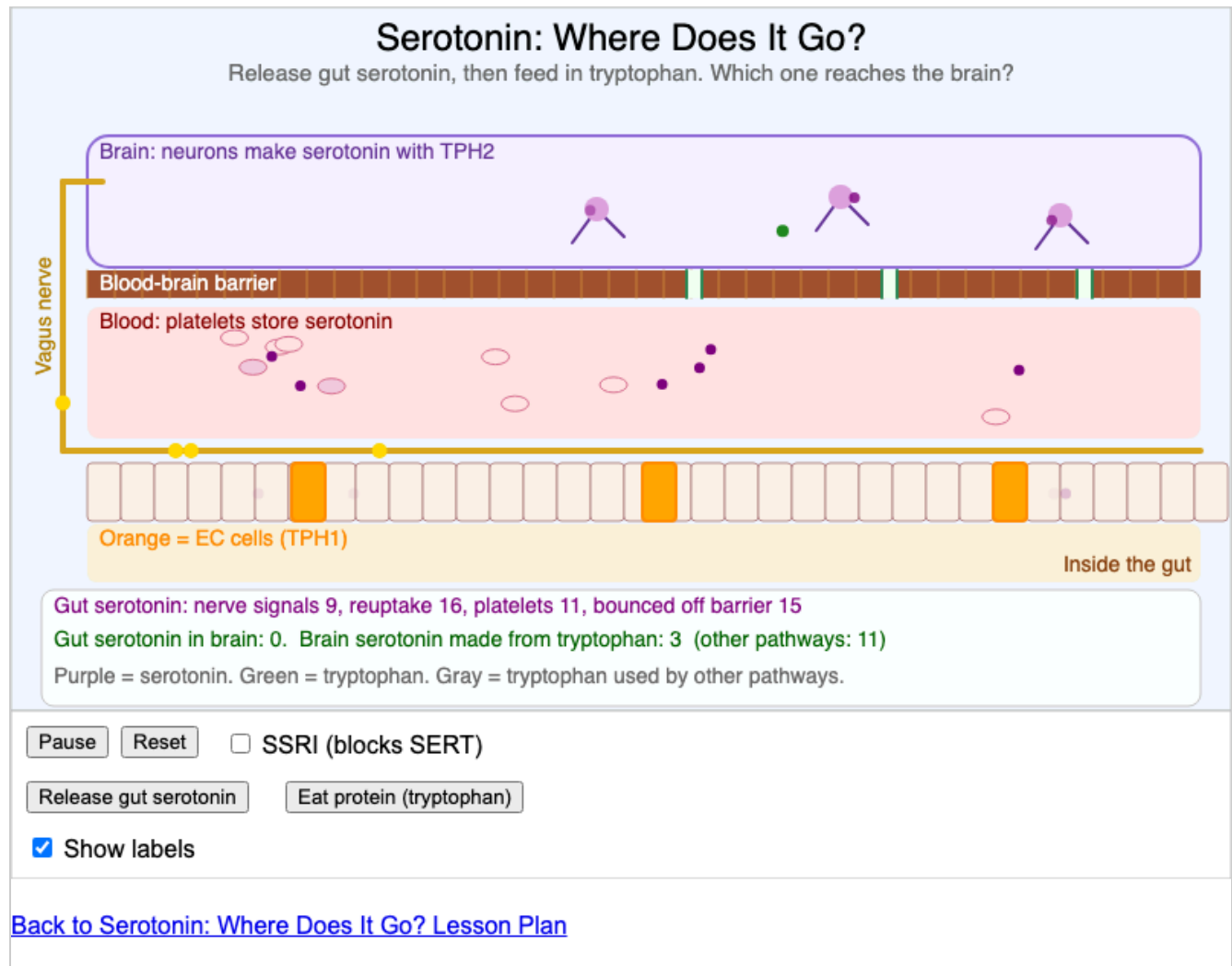
Serotonin made in the gut does not cross the blood-brain barrier. The brain makes its own serotonin from tryptophan, an amino acid that can cross.

A 2020 editorial by [Bektaş and colleagues](#), titled "Does serotonin in the intestines make you happy?", states this directly: serotonin made in the intestines cannot reach the brain because it can't cross the blood-brain barrier, so the gut's serotonin acts as a peripheral hormone and isn't what sets emotional state. A 2022 review by [Cai and colleagues](#) likewise describes the body's serotonin and the brain's serotonin as functionally separate systems for this reason. A 2025 review of nutrition and the serotonin system in *Advances in Nutrition* ([Tang and colleagues](#)) says the same: serotonin made in the body stays out of the brain, acts locally (for example, on gut movement), and can still affect the brain indirectly through the vagus nerve. Bektaş's editorial adds a related myth: eating bananas, which contain serotonin, doesn't raise brain serotonin either, for the same reason.

So how does the brain get its supply? Tryptophan crosses. The 2016 Jenkins review explains that tryptophan rides into the brain on a transporter that carries a group of "large neutral amino acids," and that it competes with those other amino acids for a seat. Once inside, brain neurons use TPH2 to turn it into serotonin. That's the flour going through the gate, with the hilltop bakery doing the baking.

One caution about barriers: in **germ-free mice**, a 2014 study by [Braniste and colleagues](#) found that the blood-brain barrier was leakier than normal and tightened after the mice received gut microbes. That's an interesting mouse result (Chapter 6 covers it), but even a somewhat leaky barrier in mice is a long way from "gut serotonin floods the human brain," and no study in this chapter shows that.

Diagram: Serotonin: Where Does It Go?



Interactive simulation: <https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch05-serotonin-where/main.html>

Open Serotonin: Where Does It Go? fullscreen



MicroSim specification: Serotonin: Where Does It Go?



Type: microsim **sim-id:** ch05-serotonin-where

Library: p5.js

Status: Implemented

Bloom Level: Understand

Bloom Verb: distinguish

Learning Objective: The learner will distinguish gut (peripheral) serotonin from brain (central) serotonin by tracing where serotonin released by enterochromaffin cells goes (nerves, reuptake, platelets, blocked at the blood-brain barrier) and how the brain makes its own serotonin from tryptophan.

Canvas: 460 px drawing area plus 110 px controls (iframe 572 px); responsive to about 380 px wide.

Controls: Start/Pause, Reset, "SSRI (blocks SERT)" checkbox; "Release gut serotonin" and "Eat protein (tryptophan)" buttons (each starts the animation); Show labels checkbox.

Rules: Each release sends 7 purple serotonin dots from each of 3 EC cells. Without an SSRI, about 35% act on the nerve (a gold pulse travels up the vagus nerve to the brainstem), 35% are taken back into lining cells by SERT, and 30% enter the blood, where platelets that touch them take them up. With the SSRI box checked, reuptake and platelet uptake are blocked, so about 55% act on the nerve and the rest stay in the blood longer. Serotonin dots that reach the blood-brain barrier always bounce off. Each meal adds 15 green tryptophan dots; about 75% turn gray (used by other pathways, mainly kynurenine) and about 25% pass through transporter gates into the brain, where neurons turn them into serotonin. Brain serotonin lingers longer with the SSRI box checked.

Feedback: A counter panel tallies nerve signals, reuptake, platelet uptake, bounces off the barrier, gut serotonin in the brain (always 0), and brain serotonin made from tryptophan.

Provenance: Mawe and Hoffman 2013 (three fates of gut serotonin; SERT on epithelial cells and platelets); Bektaş 2020 and Cai 2022 (no BBB crossing); Jenkins 2016 (tryptophan transport); Dantzer 2008 (most tryptophan to kynurenine). Percentages and speeds are illustrative.

Press **Release gut serotonin** and follow the purple dots. Some hit the gold nerve line under the lining, and a pulse travels up the vagus nerve: that's information reaching the brain, not serotonin. Some disappear into the lining cells (reuptake by SERT), and some drift into the blood, where platelets turn purple as they store them. Watch the dots that reach the blood-brain barrier: the counter for "gut serotonin in brain" never moves off zero, however many times you press the button.

Now press **Eat protein (tryptophan)**. Most green dots turn gray and fade (used by the kynurenine pathway and other routes), but a few find the gates in the barrier, cross, and turn purple inside the brain's neurons. Finally, check **SSRI (blocks SERT)** and release more gut serotonin. With reuptake blocked, more serotonin reaches the gut nerves, which is one reason SSRIs can cause nausea or loose stools. Ask yourself: did the SSRI change how much gut serotonin reaches the brain?

What this model leaves out

- Real serotonin release is constant and tiny, measured in molecules, not a few dozen dots on a button press; the percentages are made-up teaching values. In real life, far more of the tryptophan you eat goes to other pathways than the sim shows (more than 95%).
- The model shows only one type of serotonin receptor on one nerve. The gut has many serotonin receptor types with different effects, including on gut muscle and the lining.
- The brain's serotonin neurons are in the brainstem and send fibers across the whole brain; the sim shows three cartoon neurons.
- The sim leaves out how the body breaks down serotonin in the blood over time, and serotonin's roles in bone and clotting.
- SSRIs take weeks to change mood and work through changes in brain circuits over time, which the sim does not show.

5.8 The Gut Serotonin Mood Myth

Now we can grade Sam's cousin's post. The **gut serotonin mood myth** is the popular but unsupported claim that because most of the body's serotonin is made in the gut, the gut directly controls mood or happiness, and so "healing your gut" will raise your brain's serotonin and make you happier.

It's a chain of three links, and only the first one holds:

Link in the claim	Verdict	Why
"More than 90% of serotonin is made in the gut"	True	Yano 2015; Bellono 2017; Gershon 2013
"Serotonin = happiness"	Oversimplified	Brain serotonin does many jobs; depression is not simply "low serotonin" (Section 5.10)
"So healing your gut makes your brain happier"	Does not follow	Gut serotonin can't cross the blood-brain barrier; the brain makes its own

Grade the chain, not the first link



I see this trick everywhere: start with a true number, then attach a conclusion that sounds like it follows. When a claim has several steps, I check each link separately, because a chain is only as strong as its weakest one.

Hype Meter: "90% of your serotonin is in your gut, so your gut controls your happiness"

Strong

Moderate

Preliminary

Hype

Verdict: Hype. The number is Strong: more than 90% of the body's serotonin is made in the gut, mostly by enterochromaffin cells. But that serotonin does not cross the blood-brain barrier, and the brain makes its own from tryptophan using a different enzyme (TPH2). Gut serotonin mainly runs gut movement, secretion, sensations like nausea, and platelet storage. The gut does send signals to the brain through nerves and other routes, but "gut serotonin controls your mood" is not what the evidence shows. **What would change the grade:** Human studies showing that changing gut serotonin production, by itself, reliably changes brain serotonin and mood. Drugs designed to lower gut serotonin without entering the brain would be a natural way to test this.

That doesn't mean the gut has nothing to do with the brain; this whole book is about the ways it does. Gut serotonin can affect the brain *indirectly*, by activating vagus and spinal nerves that carry signals upward (Chapter 2), and the gut influences the brain through immune signals (Chapter 4) and microbial chemicals (Section 5.11 and Chapter 6). The myth isn't "the gut and brain are connected." The myth is that gut-made serotonin is the brain's happiness supply.

5.9 SSRIs: Why a Brain Medicine Can Upset Your Stomach

Some of the most widely prescribed medicines for depression and anxiety work on the serotonin transporter.

An **SSRI** (selective serotonin reuptake inhibitor) is a type of medicine that blocks the serotonin transporter, so serotonin stays outside cells longer after it is released; SSRIs such as fluoxetine are prescribed for depression, anxiety disorders, and other conditions. MedlinePlus, the US National Library of Medicine's drug information site, explains that fluoxetine is in this class and works by increasing the amount of serotonin available, and that it may take 4 to 5 weeks or longer to feel the full benefit.

An SSRI taken as a pill doesn't only reach the brain; it reaches the whole body, including the gut, where SERT is on essentially every lining cell and on platelets. Block those pumps, and gut serotonin lingers longer near the nerve endings that control gut movement and send nausea signals. Mawe and Hoffman's review notes that SSRIs can change gut movement in people, sometimes speeding it up and sometimes slowing it down.

MedlinePlus lists nausea, heartburn, and diarrhea among fluoxetine's possible side effects. That's the same two-towns story in reverse: the medicine is aimed at the hilltop, but it also changes the valley.

For teens, one more fact matters. MedlinePlus carries a warning for fluoxetine and similar medicines: they may increase the risk of suicidal thoughts and actions in children, teenagers, and young adults under 24, especially in the first few months or when the dose is increased. That's why doctors watch closely at the start and ask families to call right away about new or worse depression or thoughts of self-harm. If you ever have thoughts of suicide, you can call or text 988 in the US. MedlinePlus is also clear that people shouldn't stop taking fluoxetine without talking to their doctor, because stopping suddenly can cause withdrawal symptoms.

Sam asked his own doctor about the post. She explained that several IBS treatments act on gut serotonin receptors, which is good evidence that serotonin matters for gut symptoms. "But notice," she said, "those medicines are aimed at your gut's serotonin system, and SSRIs are aimed at your brain's, and when one affects the other's territory, we call it a side effect."

For families

If your teen starts an SSRI and gets an upset stomach in the first weeks, that's a common and usually understood side effect, not a sign the medicine is "poisoning" them or that they are weak. Help them write down what they notice and when, and bring it to the prescriber rather than stopping or changing the dose at home. Also know the warning signs the prescriber will mention, such as new or worse depression or thoughts of self-harm, and call right away if you see them.

5.10 Is Depression Just "Low Serotonin"?

For decades, ads and textbooks explained depression as a "chemical imbalance" caused by too little serotonin. Scientists have been questioning that simple story for a long time.

In July 2022, [Joanna Moncrieff and colleagues](#) at University College London published a widely discussed umbrella review (a review of reviews) in *Molecular Psychiatry*. They gathered 17 studies, including systematic reviews, meta-analyses, and large genetic studies, covering measures such as serotonin levels in body fluids, serotonin receptor and transporter imaging, tryptophan depletion experiments, and serotonin transporter genes. They concluded that there was no consistent evidence that depression is caused by lowered serotonin activity.

The review sparked strong reactions, and many comments and replies were published. In 2023, a group of 35 psychiatrists and brain scientists led by Sameer Jauhar answered in the same journal ([Jauhar and colleagues, 2023](#)). They argued that the review's conclusion was overstated. They criticized how it chose and reported studies, and they said that tryptophan depletion experiments and brain imaging do point to a role for serotonin in people who are vulnerable to or living with depression. Moncrieff's team published a reply the same year and stood by its conclusion.

New data keep arriving, too. In a 2023 brain-imaging (PET) study, Erritzoe and colleagues gave a single dose of amphetamine, a drug that makes neurons release serotonin (along with other messengers), to 17 adults in a depressive episode who were not taking antidepressants and to 20 adults without depression (Erritzoe and colleagues, 2023). The scans showed less serotonin release in the depressed group. That is one small study. It measured release during an episode, not whether low serotonin comes first, so it can't settle the cause question. The debate is still going on. Two points help you read it fairly:

- **What the review is about:** whether low serotonin is the *cause* of depression. Rejecting a simple "low serotonin" story is not the same as saying serotonin plays no role in mood.
- **What the review is not about:** whether antidepressants help. The review didn't test that, and it isn't evidence that people should stop their medicine. SSRIs could help through effects that develop over weeks, even if depression doesn't start with low serotonin.

As Bektaş and colleagues put it in their 2020 editorial, psychiatric conditions don't develop from a single cause. Depression is linked to many factors, including stress, life events, and inflammation in some people (Chapter 4). The slogan "depression is low serotonin" is too simple for the evidence.

Hype Meter: "Depression is caused by low serotonin"

Strong

Moderate

Preliminary

Hype

Verdict: Hype. A 2022 umbrella review of 17 studies found no consistent evidence that depression is caused by lowered serotonin, and depression is widely understood to have more than one cause. Critics of that review argue that the serotonin system is disturbed in some people with depression (Jauhar 2023; Erritzoe 2023), and serotonin may be involved in how some treatments work. But even those critics describe a role for serotonin, not a single cause, so the simple cause-and-effect slogan is not supported. This grade is about the slogan only; it is not a judgment on whether antidepressants help, which is a separate question. **What would change the grade:** Consistent, repeated human evidence that serotonin activity is reduced before depression begins, and that restoring it reliably prevents or ends depression.

Don't flip the myth



A common mistake is to swing from "depression is low serotonin" to "antidepressants are fake." The 2022 review tested the first claim, not the second, so never treat it as a reason to change a medicine; that's a conversation for you and your doctor.

5.11 Do Gut Microbes Make Your Mood?

The other big claim in gut-brain posts is that your gut bacteria make "happy chemicals." Let's check the evidence, one chemical at a time.

Microbes that turn up the gut's serotonin

Spore-forming bacteria are bacteria that can survive harsh conditions by forming tough, dormant spores; in the gut, a mix of them (dominated by a group called Clostridia) has been shown in mice to boost serotonin production by the gut lining. In 2015, Jessica Yano, Elaine Hsiao, and colleagues at Caltech reported in *Cell* that germ-free mice had lower serotonin in the colon and blood than normal mice. When the researchers gave germ-free mice spore-forming bacteria taken from mouse or human gut microbes, the mice's EC cells made more serotonin, partly by raising TPH1 levels. The change also affected gut movement and how platelets worked.

This is careful work, but notice what it is and isn't. The bacteria raised *gut and blood* serotonin, the serotonin that can't enter the brain. And it was done in mice. So it supports "in mice, certain gut bacteria increase the gut's serotonin production," not "your bacteria control your brain's serotonin."

How to read a gut-brain claim: spore-forming bacteria and gut serotonin (Yano et al., 2015)

Question	This study
Mouse or human?	Mouse. Germ-free and normal mice; the bacteria came from mouse and human gut samples, but all effects were measured in mice (plus some cell cultures).
Correlation or cause?	Cause, in mice: adding spore-forming bacteria to germ-free mice raised gut and blood serotonin, an experiment rather than an observation.
How many?	Small groups, often 3 to 8 mice per group in a given experiment, which is typical for mouse work.
How long?	Short: many measurements were taken about two weeks after the bacteria were given.
Who paid for it?	Public and university funding: an NIH Director's Early Independence Award, a Caltech center award, the National Science Foundation, and grants from three NIH institutes (NHGRI, NIDDK, NIMH).
Is something being sold?	No product in the paper. But it is often cited in ads for probiotics and "serotonin-boosting" supplements, which the study never tested.

The conclusion: strong evidence, in mice, that microbes influence the gut's own serotonin system. It says nothing directly about mood, and it can't, because the serotonin it measured was outside the brain.

Microbes that make neurotransmitters themselves

A **microbe-made neurotransmitter** is a chemical produced by bacteria or other microbes that is the same molecule the human body uses as a neurotransmitter, such as GABA, dopamine, or serotonin. A 2018 review by [Philip Strandwitz](#) describes gut bacteria that produce or consume dopamine, norepinephrine, serotonin, and GABA.

The best-studied example is GABA. In 2019, [Strandwitz and colleagues](#) reported in *Nature Microbiology* that some very common human gut bacteria, especially *Bacteroides* species, made large amounts of GABA in lab cultures, and that GABA-making genes were actively used by bacteria in stool samples from healthy people. For dopamine, a 2022 review by [Hamamah and colleagues](#) describes gut microbes taking part in dopamine chemistry, but mostly from lab and animal studies.

Two cautions keep this honest. First, "bacteria can make GABA" is not the same as "bacterial GABA reaches your brain." Most such molecules act locally in the gut or on gut nerves, and the sources in this chapter don't show microbial GABA or dopamine crossing into the human brain. Second, the human mood evidence is correlational. In 2019, [Mireia Valles-Colomer, Jeroen Raes, and colleagues](#) studied the gut microbes of 1,054 people in Belgium's Flemish Gut Flora Project and checked the results in other data sets of about 1,000 more people. Certain butyrate-making bacteria were linked to better quality of life, and two groups of bacteria (*Coprococcus* and *Dialister*) were lower in people with depression, even after the researchers accounted for antidepressant use. The authors stressed how much confounding factors matter, and a study like this shows a link, not a cause.

A 2021 review by [Kara Margolis, John Cryan, and Emeran Mayer](#) sums up the field: animal studies of the microbiota-gut-brain axis have shown much promise, but they haven't yet been turned into proven diagnoses or treatments for patients.

Hype Meter: "Gut bacteria make neurotransmitters that reach your brain"

Strong

Moderate

Preliminary

Hype

Verdict: Hype, as stated. The first half is real: it's well shown in lab cultures that common gut bacteria make GABA and other neurotransmitter molecules, and in mice that bacteria raise the gut's own serotonin production. But the "reach your brain" part is not shown in people: most of these molecules act in the gut, and human links between microbes and depression (about 1,000 people in one major study) are correlations. **What would change the grade:** Human studies tracing a microbe-made molecule from the gut into the brain, followed by controlled trials showing that changing those microbes changes brain chemistry and mood.

At the Bedside: Stomach Trouble on a New Medicine



Meet the patient (fictional)

Jordan is 15 and has been seeing a psychiatrist for depression for two months, alongside weekly therapy. Jordan recently started an SSRI. In the first two weeks, Jordan has felt queasy most mornings, had loose stools a few times, and hasn't noticed any change in mood yet. Jordan's mom wonders if the medicine is "messing up Jordan's stomach" and whether to stop it.

What the doctor checks: The psychiatrist asks when the stomach symptoms started compared with the first dose, how bad they are, whether Jordan can eat and drink normally, and whether there is fever, blood in the stool, or severe pain that might point to something else, like an infection. The doctor also checks in carefully about mood, sleep, and any thoughts of self-harm, because the first months of treatment need close watching in teens.

Connecting the signals: The timing fits a known effect. The SSRI blocks the serotonin transporter in the brain, which is the goal, but also on the gut's lining cells. Gut serotonin from enterochromaffin cells lingers longer near nerve endings, which can trigger nausea signals through the vagus nerve and speed up gut movement.

Diagnosis: Common early gastrointestinal side effects of an SSRI.

Why it happens: Gut and brain use the same molecule and the same kind of pump, even though their serotonin supplies are separate (Sections 5.6 and 5.9). A medicine in the bloodstream reaches both.

The mind-body side: Feeling sick to your stomach while also waiting weeks for a mood medicine to work is discouraging, and it can make teens want to quit. The psychiatrist explains that early stomach effects are common and worth reporting, that the full benefit can take several weeks, and that stopping suddenly can cause its own symptoms. Jordan's therapist helps Jordan track symptoms without catastrophizing, and the family agrees on a plan for who to call if mood worsens. The doctor also reminds them that 988 is available any time in a crisis.

Treatment today: Depression in teens is commonly treated with therapy, medicine, or both. Any change to an SSRI, such as timing, dose, or switching medicines, is decided with the prescriber, not at home. The care team may suggest practical steps for nausea and will watch whether side effects fade over the first weeks.

What's new in research: Scientists have developed drugs that block tryptophan hydroxylase to lower serotonin production outside the brain; Mawe and Hoffman's 2013 review describes versions designed not to cross the blood-brain barrier. In February 2017, the FDA [approved telotristat ethyl \(Xermelo\)](#), a tryptophan hydroxylase blocker that lowers serotonin production, for adults with carcinoid syndrome diarrhea, taken together with somatostatin analog therapy when that therapy alone doesn't control it. (Carcinoid syndrome is caused by tumors that release too much serotonin.) A 4-week placebo-controlled trial of a related compound, LX-1031, in 155 people with non-constipating IBS found some symptom relief, but the improvement on its main measure was statistically clear only in the first week ([Brown and colleagues, 2011](#)). The drug's maker ran that trial, and LX-1031 has not been approved for any use. **Evidence grade: Preliminary** for IBS (one small, short, company-run trial).

? Your turn: reason through a variation



A few weeks later, Jordan's stomach symptoms have faded and mood is starting to improve. Jordan's aunt says, "See, the medicine fixed the serotonin in Jordan's gut, and that's what made Jordan happier." What's wrong with that explanation?

Answer: The stomach side effects came from the SSRI acting on the gut's serotonin system, but mood improvement doesn't come from gut serotonin, which can't cross the blood-brain barrier. The SSRI acts separately in the brain, where neurons make their own serotonin from tryptophan, and its benefits likely build up through changes in brain circuits over weeks. Therapy, time, and support may also have helped. The gut effects and the mood effects happen in two different "towns."

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Serotonin made in the gut travels to the brain and boosts mood.

Reality: Gut serotonin does not cross the blood-brain barrier. The brain makes its own serotonin from tryptophan, which can cross. Gut serotonin mainly works in the gut and is stored in platelets.

Myth: Serotonin is just the "happy chemical."

Reality: Serotonin does many jobs: gut movement, nausea signals, blood clotting, and in the brain, sleep, appetite, pain, and more. Mood is only one of its roles.

Myth: Low serotonin is proven to cause depression.

Reality: A 2022 umbrella review found no consistent evidence for that simple cause. Other scientists argue that serotonin still plays a part in some people, and that debate continues. Depression has many causes, and the debate is separate from whether antidepressants help.

Myth: Gut microbes "make your mood."

Reality: Some gut bacteria make GABA and other neurotransmitter molecules in the lab, and in mice some raise gut serotonin. Whether these chemicals reach the human brain and change mood has not been shown; human links are correlations.

Myth: Eating foods with serotonin, like bananas, raises brain serotonin.

Reality: Serotonin in food can't cross the blood-brain barrier any better than gut serotonin can.

Your Gut Check

Test yourself. Try each one before you open the answer.

? **1. Claim Check: "Your gut makes 95% of your serotonin! This probiotic boosts gut serotonin so you'll feel calmer and happier in two weeks."** ✓

Grade: Hype. The "95%" figure is within the range scientists report (more than 90%, some estimates about 95%). But gut serotonin can't cross the blood-brain barrier, so raising it wouldn't raise brain serotonin. The best evidence that bacteria boost gut serotonin comes from mice (Yano 2015), and it measured gut and blood serotonin, not mood. A careful version: "Most of your serotonin is made in your gut, where it controls digestion; in mice, some gut bacteria increase that production."

? **2. Predict: Riya's grandmother hears that tryptophan is the building block of serotonin and wonders if a big turkey dinner will flood Riya's brain with serotonin. Predict what actually happens to the tryptophan, using this chapter.** ✓

Most of the tryptophan will be used for building proteins or broken down by the kynurenine pathway; more than 95% of dietary tryptophan goes that way. The part that reaches the blood-brain barrier has to compete with other large neutral amino acids for the same transporter. Only a small amount enters the brain and becomes serotonin, so one meal won't "flood" the brain. The body regulates this closely.

? **3. Explain: Why can an SSRI cause nausea even though it's prescribed for the brain?** ✓

An SSRI blocks the serotonin transporter everywhere the drug reaches, not just in the brain. The gut lining's cells and platelets also use SERT to clear serotonin. With SERT blocked, serotonin released by enterochromaffin cells lingers near sensory nerve endings, which can send nausea signals through the vagus nerve and change gut movement.

? **4. Apply: A drug company designs a TPH1 blocker that can't cross the blood-brain barrier. Predict its effect on gut serotonin, blood serotonin, and brain serotonin.** ✓

Gut serotonin should fall, because EC cells use TPH1. Blood serotonin should fall too, since platelets get their serotonin from the gut. Brain serotonin should stay about the same, because brain neurons use TPH2 and the drug can't get into the brain anyway. That's the idea behind the TPH inhibitors described in Mawe and Hoffman's review, and it's a good test of the two-supplies model.

5. Read the data. The "90%" figure appears in many sources. Here are the estimates from three sources cited in this chapter, along with the kind of paper each one is:

Source	Type	Share of the body's serotonin in or made by the gut
Gershon, 2013	Review	About 95% located in the gut

Source	Type	Share of the body's serotonin in or made by the gut
Yano et al., 2015	Mouse study (cites earlier work)	More than 90% made in the gut
Bellono et al., 2017	Mouse and cell study (cites earlier work)	EC cells make more than 90%

? 5. What does this data show, and what can't it show? ✓

It shows that independent sources agree the gut makes or holds the large majority of the body's serotonin, somewhere between more than 90% and about 95%, so the "90%" number is solid. It can't show anything about mood, because none of these numbers measures brain serotonin or happiness; they describe where serotonin is made. It also doesn't tell us how much varies between people. A useful follow-up would be a human study measuring gut serotonin production, blood serotonin, and brain serotonin activity in the same people to confirm how separate the two supplies are.

Exercises

Remember

1. Name the enzyme that starts serotonin production, and say which version works in the gut's EC cells and which works in brain neurons.

Answer ✓

Tryptophan hydroxylase (TPH). TPH1 works in enterochromaffin cells; TPH2 works in neurons, including the brain's serotonin neurons.

1. List the three fates of serotonin released by an enterochromaffin cell.

Answer ✓

It acts on nearby nerve endings, it is taken back into lining cells by the serotonin transporter (SERT), or it enters the blood, where platelets store it.

Understand

1. Explain the two-towns comparison in your own words, naming what the valley, hilltop, wall, bread, and flour each stand for.



Answer



The valley is the gut, which makes most of the body's serotonin; the hilltop is the brain, which makes its own. The wall is the blood-brain barrier. The bread is serotonin, which can't get through the wall. The flour is tryptophan, which passes through transporter "gates" so the brain can make its own serotonin.

1. Explain why a signal from gut serotonin can reach the brain even though the serotonin molecule itself cannot.



Answer



Gut serotonin activates vagus and spinal sensory nerve endings in the gut wall. Those nerves carry electrical signals up to the brainstem. The information travels; the molecule stays in the gut.

Apply

1. Use the MicroSim to compare the counter values after five presses of "Release gut serotonin" with and without the SSRI box checked. Describe what changed and connect it to a real SSRI side effect.
2. A supplement label says "Contains 5-HTP and tryptophan to boost serotonin naturally!" Using this chapter, identify which parts of the claim are plausible chemistry and which parts are unsupported, and give it a Hype Meter grade. (Don't evaluate whether anyone should take it; that's a question for a doctor.)

Analyze

1. Compare the evidence in the Yano 2015 mouse study and the Valles-Colomer 2019 human study. For each, answer at least three of the six questions. Which is better at showing cause, and which tells you more about people?
2. Sam's cousin's post has three links (Section 5.8). Analyze a different gut-brain claim you've seen online (or make a realistic one up) by breaking it into links and grading each link separately.

Evaluate

1. Some people argue the Moncrieff 2022 review shows antidepressants don't work. Evaluate this argument using what the review did and didn't test.
2. Should the phrase "your gut makes 90% of your serotonin" be used in health class at all? Write a paragraph weighing the value of the fact against how often it's misused, and propose the exact sentence you would

teach.

Create

1. Design a study in humans that could test whether a probiotic changes brain serotonin, not just gut serotonin. Describe the groups, how you would measure brain serotonin activity (in general terms), how long it would last, and what result would support the claim.
2. Create a 30-second video script that corrects the gut serotonin mood myth for a teen audience without making people feel foolish for having believed it.

Key Takeaways

- Neurons pass messages at synapses using neurotransmitters such as serotonin, dopamine, GABA, and acetylcholine; the same chemical can act as a neurotransmitter or a hormone.
- More than 90% of the body's serotonin is made in the gut, mostly by enterochromaffin cells using TPH1. Gut serotonin runs gut movement, secretion, and nausea signals, is cleared by the serotonin transporter, and is stored in platelets.
- Serotonin made in the gut does not cross the blood-brain barrier. The brain makes its own serotonin from tryptophan, an amino acid that can cross, using TPH2. Most dietary tryptophan goes down the kynurenine pathway instead.
- "90% of your serotonin is in your gut, so your gut controls your happiness" is Hype: the number is Strong, the conclusion is not.
- SSRIs block the serotonin transporter in both brain and gut, which is why early nausea or loose stools are common. Changes to any medicine are decided with the prescriber.
- "Depression is caused by low serotonin" is too simple for the evidence; that debate is separate from whether antidepressants help.
- Gut bacteria can make neurotransmitter molecules and, in mice, boost gut serotonin, but evidence that microbe-made chemicals reach the human brain and change mood is Preliminary.

You followed serotonin all the way!



You can now trace serotonin from tryptophan to the gut, the blood, and the wall it can't cross, and you can grade the internet's favorite gut-brain fact link by link. Next, in Chapter 6, we'll follow what your microbes make from fiber, and look closely at the blood-brain barrier and the "leaky gut" claim.

Quiz: Chemical Messengers and the Serotonin Myth

Test your understanding of Chapter 5. Choose the best answer, then click **Show Answer** to check.

Question 1

Which cells make most of the body's serotonin?

- A. Serotonin neurons in the brainstem
- B. Platelets in the blood
- C. Enterochromaffin cells in the gut lining
- D. Gut bacteria in the colon

 **Show Answer**



The correct answer is **C**. More than 90% of the body's serotonin is made in the gut, mostly by enterochromaffin (EC) cells, even though they are less than 1% of the gut's lining cells. Platelets (option B) store serotonin from the gut but don't make it.

Concept Tested: Enterochromaffin Cell **Bloom's Level:** Remember

Question 2

What is tryptophan?

- A. An essential amino acid from food that the body uses to make serotonin
- B. An enzyme that breaks serotonin down in the brain
- C. A type of gut bacterium that produces serotonin
- D. A medicine that blocks the serotonin transporter

 **Show Answer**



The correct answer is **A**. Tryptophan is an essential amino acid, so it must come from protein in food, and it is the raw material for serotonin. Option B mixes it up with enzymes; the enzyme that turns tryptophan into serotonin is tryptophan hydroxylase.

Concept Tested: Tryptophan **Bloom's Level:** Remember

Question 3

Which neurotransmitter is the brain's main inhibitory ("brake") signal?

- A. Acetylcholine
- B. Dopamine
- C. Serotonin
- D. GABA

 **Show Answer**



The correct answer is **D**. GABA mostly makes receiving neurons less likely to fire. Acetylcholine (option A) is a main "go" signal for gut muscle and is released by enteric motor neurons and the vagus nerve's motor fibers.

Concept Tested: GABA **Bloom's Level:** Remember

Question 4

Why can't serotonin made in the gut raise serotonin levels in the brain?

- A. The liver turns all gut serotonin into tryptophan.
- B. Serotonin cannot cross the blood-brain barrier, so the brain makes its own from tryptophan.
- C. Gut serotonin is a different molecule from brain serotonin.
- D. The vagus nerve blocks serotonin from traveling upward.

 **Show Answer**



The correct answer is **B**. The blood-brain barrier keeps gut serotonin out, and brain neurons make their own serotonin from tryptophan, which can cross. Option C is a common mix-up: it's the same molecule (5-HT) in both places; what differs is where it's made and where it can travel.

Concept Tested: Blood-Brain Barrier **Bloom's Level:** Understand

Question 5

Why do scientists say the body has two separate serotonin supplies?

- A. Gut EC cells use TPH1, brain neurons use TPH2, and the blood-brain barrier keeps the two pools apart.
- B. Men and women make different kinds of serotonin.
- C. Serotonin made in the morning and at night comes from different organs.
- D. Platelets make one supply and gut bacteria make the other.

 Show Answer



The correct answer is **A**. Two versions of tryptophan hydroxylase work in two places, TPH1 in EC cells and TPH2 in neurons, and the blood-brain barrier separates the gut and blood pool from the brain pool. Option D is wrong because platelets store gut serotonin rather than make it.

Concept Tested: Tryptophan Hydroxylase **Bloom's Level:** Understand

Question 6

What does the serotonin transporter (SERT) do in the gut lining?

- A. It carries serotonin across the blood-brain barrier into the brain.
- B. It makes serotonin from tryptophan inside EC cells.
- C. It pumps serotonin back into cells, ending its signal.
- D. It releases serotonin into the gut to trigger peristalsis.

 Show Answer



The correct answer is **C**. SERT is a pump that clears serotonin by moving it back into cells; in the gut it is found on essentially all lining cells, and platelets use it too. Option B describes the job of tryptophan hydroxylase, not SERT.

Concept Tested: Serotonin Transporter **Bloom's Level:** Understand

Question 7

A 16-year-old starts an SSRI for anxiety and has nausea and loose stools in the first two weeks. Which explanation best fits this chapter?

- A. The medicine sends brain serotonin down into the gut.

- B. The medicine kills helpful gut bacteria that make serotonin.
- C. Nausea means the medicine isn't reaching the brain at all.
- D. The medicine also blocks SERT in the gut, so gut serotonin lingers near nerves that control movement and nausea.

 Show Answer



The correct answer is **D**. SSRIs reach the whole body, and the gut lining and platelets use SERT too. Blocking it leaves gut serotonin active longer near sensory nerves. Option A is backwards: brain serotonin doesn't travel to the gut, just as gut serotonin doesn't travel to the brain. Any change to the medicine should be decided with the prescriber.

Concept Tested: SSRI **Bloom's Level:** Apply

Question 8

A friend says, "I'm going to eat a lot of turkey so all that tryptophan turns into serotonin in my brain." Using this chapter, what is the best response?

- A. Right, nearly all tryptophan becomes brain serotonin within an hour.
- B. Most tryptophan goes to the kynurenine pathway and protein building, and what reaches the brain competes with other amino acids to cross.
- C. Tryptophan can't cross the blood-brain barrier, so none of it reaches the brain.
- D. Tryptophan only becomes serotonin in the gut, never in the brain.

 Show Answer



The correct answer is **B**. More than 95% of dietary tryptophan is broken down through the kynurenine pathway, and tryptophan competes with other large neutral amino acids for the transporter into the brain. Option C goes too far the other way: tryptophan can cross, which is how the brain makes its own serotonin.

Concept Tested: Kynurenine Pathway **Bloom's Level:** Apply

Question 9

In the Yano et al. (2015) study, spore-forming bacteria given to germ-free mice raised serotonin in the colon and blood. Which conclusion does this study best support?

- A. Spore-forming bacteria cure depression in people.
- B. Gut bacteria control the amount of serotonin in the human brain.

- C. In mice, certain gut bacteria increase the gut's own serotonin production.
- D. The gut serotonin mood myth has been proven true.

 **Show Answer**



The correct answer is **C**. The study was done in mice and measured gut and blood serotonin, which can't enter the brain, so it says nothing directly about brain serotonin or mood. Option B is the overstatement often made in ads: it jumps from mice to people and from gut serotonin to brain serotonin.

Concept Tested: Spore-Forming Bacteria **Bloom's Level:** Analyze

Question 10

A post says: "Gut bacteria make GABA, the brain's calming chemical, so the right bacteria will calm your anxiety." Which analysis is most accurate?

- A. Some gut bacteria make GABA in lab cultures, but it hasn't been shown that microbial GABA reaches the human brain or calms anxiety.
- B. The post is fully proven, because GABA from any source enters the brain easily.
- C. The post is impossible, because no bacteria can make GABA.
- D. The post is proven by the human study that found *Coprococcus* lower in depression.

 **Show Answer**



The correct answer is **A**. Strandwitz and colleagues showed that common gut bacteria such as *Bacteroides* make large amounts of GABA in culture, but most such molecules act locally in the gut, and the human evidence linking microbes to mood is correlational. Option D treats a correlation in a human study as proof of cause, which it isn't.

Concept Tested: Microbe-Made Neurotransmitter **Bloom's Level:** Analyze
