The Love Bug

How does a gut bacterium influence oxytocin release in an animal's brain?

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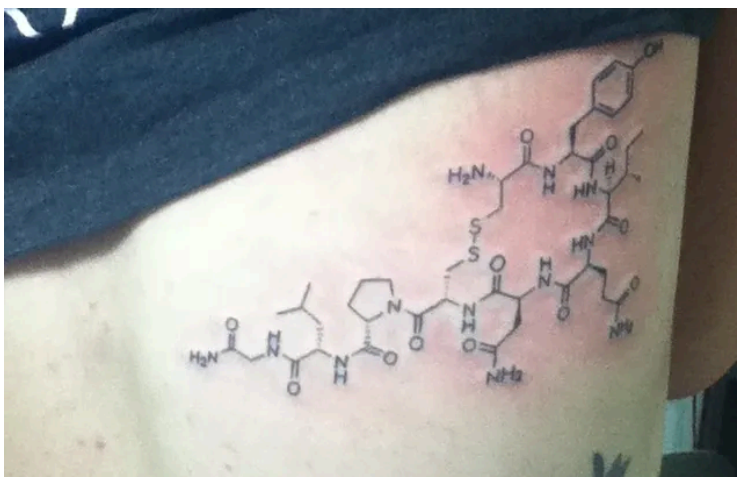
You've probably heard of oxytocin. In fact, it's probably the only neuropeptide hormone that your average person *has* heard of. It gets popular press as the "love drug", or the "cuddle chemical".



Flowchart for identifying molecule tattoos: Is it more complicated than LSD?
Yes → Probably oxytocin. Image source

And it's true, its release in the brain is triggered by friendly social interactions, physical touch, and—of course—sex. A surge of oxytocin is what triggers the birthing process in a pregnant woman, kickstarting the mother-child bond. This is actually where the name comes from; the Greek *oxus*- meaning sharp or sudden, and *tokos,* for childbirth. After birth, the continued release every time a woman breastfeeds helps forge that bond into the strongest love a human can experience.

But things in the human body are rarely as simple as "one molecule = one feeling", and oxytocin is no exception. For starters, it moonlights as an immune-stimulating hormone.

There's a bacterium, *Lactobacillus reuteri*, which—when fed to mice—increases the amount of oxytocin in their bloodstream, with the upshot that mice fed *L. reuteri* were found to have a lower risk of cancer, and healed wounds *twice as fast* as control counterparts.

The fact that there's a bacterium with its finger on the "love" button is wild enough in and of itself. The paper reporting that link was one of the first gut/brain axis papers I ever read, and it's part of what drew me to the field—but we'll come back to the bug in a minute.

A while after I first read that article, I was explaining it to a friend, and telling him about the role of oxytocin in the immune system, when he thought for a moment and said:

"Huh. Is that why people can die of a broken heart?"

My mouth fell open a little. At the back of my mind, a metaphorical librarian removed a sheaf of paper from the file labeled “folk wisdom, and other things mom says”, photocopied it, and gingerly placed the copy in another folder labeled “fairly rational beliefs with solid mechanistic support”.

Widow’s Wailing

There’s a concept in evolutionary biology called the “gay uncle hypothesis”, which addresses the apparent paradox of genes that predispose a person to homosexuality: how does a gene variant which makes someone LESS likely to have kids not get selected out of existence? The answer emerges when you look at a societal level: in a world with finite resources, having a few people in every generation who don’t have kids can make the whole family fitter in the long run.

There’s a corollary to this, which I suppose we’d call the “sweet, wise grandma hypothesis”: people who are well past their reproductive years, and even beyond the stage in their life where they can do the physical labor necessary to feed themselves, still improve their community’s fitness by doing things like caring for young children, mediating disputes, and telling you whether or not the mushroom you just found is poisonous. In many ways, oxytocin is the biological currency mediating this entanglement of societal and physical health.

Imagine you and your partner have lived together for fifty years, falling asleep holding each other every night, giving each other your daily doses of this feel-good, immune-stimulating hormone. Then one day, your partner is gone—and the nights are suddenly very cold and lonely.

If you’re part of a village, and you have a thriving family with kids and grandkids, you will grieve—but you will hold your loved ones and cry together. The physical touch, the social interaction will still be there, and the oxytocin will still flow. Those bonds will grow stronger through the grief and the pain, and they will carry you through.

But imagine a hermit couple, living together on an isolated hilltop—two people who are the whole world to each other. The wailing of a widow is a call to her people, a plea for consolation and commiseration; it’s a question, sometimes voiced literally: “Can’t I just die, too?”.

And a loved one’s embrace is the answer: *No. There are still people here who love you, who count on you.*

But if that call goes unheard or unanswered, your immune system begins to close up the shop. There’s a beautiful kind of mercy in this, and a strong reminder of the physical reality of our thoughts and feelings.

If you truly have nothing left to live for and you know it, mother nature will sort of say: *You may go*.

Love and war

There’s another time when the brain’s oxytocin system lights up. It’s one which doesn’t quite fit in with “sex, cuddles, and socialization”, but it’s equally key to understanding its role in our evolution: war.

People often talk about altruism, a willingness to sacrifice yourself for others, as if it's incompatible with the concept of the "selfish gene". But, like the gay uncle, that's only true if you just look at genes at the level of the individual.

Imagine it's prehistoric times, and you're out hunting in the jungle. You come to a clearing, and meet someone you've never seen before. He's got a spear, and looks menacing. Then you hear a sound, off to one side. You both turn and see, at the edge of the clearing, a tiger lurking in the brush—paws as big as your face, ready to pounce.

When you look back at that stranger, it's the surges of oxytocin and the closely related *vasopressin* in your brain that lead you to the conclusion "Okay, I may not like the look of this guy very much, but I like him a hell of a lot better than *that* guy, so I guess we're on a team here."

In an instant, you've created an *in-group* and an *out-group*. And that whole internal conversation has a genomic parallel: from a "selfish gene" perspective, it makes sense that the natural inclination is to form an in-group with someone whose genome more closely resembles your own.

The point here is that **oxytocin doesn't let us be "selfless"—it lets us expand the definition of "self" to include other individuals.**

Oxytocin and vasopressin are part of the "band of brothers" phenomenon, part of why veterans often feel like they'll never be closer to anybody than they were to their platoon down in the trenches. But when we start talking about war—people fighting people, rather than tigers—we start to see the dark side of the "love drug": it necessarily *polarizes*.

Think about the love a mother has for her child. She'll kill another person to protect that child, if she needs to. She'll steal from another person to feed them, even if she knows it means that somebody else's kid is going to starve to death.

And, because being up all night wracked with guilt about that decision is not a very fit trait, she needs to be able to condemn another person's child to death *without feeling too bad about it*.

Sorry kid, baby's got to eat, and mama's gotta sleep.

This is the dark side of oxytocin: we don't usually have an in-group without an out-group, an *us* without a *them*. In bringing the in-group closer in, we're necessarily pushing an out-group further away.

Experiments with synthetic oxytocin have borne this out. While it's well established that giving someone a dose of the peptide enhances cooperation, it's also been found to promote ethnocentric attitudes: in a Dutch study from 2010, men receiving intranasal oxytocin were reliably more ethnocentric than people receiving a placebo. (Oxytocin is a big molecule, meaning intranasal delivery is one of the only ways to get a substantial amount into the brain. This will be important later.)

This ethnocentrism manifested in a number of ways over a series of experiments. In one, participants were presented with a "trolley problem" which required them to sacrifice a named individual to save an anonymous group of 5 people. By toying with

the names (e.g. “Maarten” vs. “Mohammed”), the researchers found that participants given oxytocin were more likely to sacrifice an “out-group” target compared to participants given placebo. Interestingly, the effect was mediated primarily by in-group favoritism, rather than “out-group derogation”—meaning oxytocin makes your average Dutch man more likely to choose Maarten’s life over those five anonymous strangers, but doesn’t make him more likely to throw Mohammed under the bus.

But real life rarely presents us with anonymous trolley problems. We make choices that favor one person or another all the time. And the split-second decisions a person makes in real life—say, if they’re a cop with a gun drawn in a tense situation—are often very different from the ones you get out of people answering questions in a university lab, very conscious of the fact that they’re under close observation.

The Love Bug

So: back to the bacterium, *Lactobacillus reuteri*. The “Love Bug”, if we want to be cute. I mentioned that the paper linking it to oxytocin release was part of what drew me to the field, and in fact I ended up doing some work in the lab of Dr. Erdman, one of the lead researchers on that paper.

One weird effect of the *L. reuteri* was that it made the mice…*shiny*. This was initially a chance observation by a lab tech, but it turned into a fun series of experiments, one of which involved holding up a mouse for a panel of unbiased raters and going “scale of 1 to 6, how shiny?” and eventually led to a pretty solid paper on the bacterium’s effects on skin health.

They did a lot of followup work and, although I don’t remember whether they showed the oxytocin impact translating to humans, the wound-healing did. The strain Erdman’s lab used, ATCC 6475, is available as a probiotic called Biogaia Osfortis; I use it when I have an injury and, although I don’t have a control Stephen to compare to, I *do* tend to heal up remarkably quickly. It’s marketed as being for bone health in menopausal women, but don’t let that fool you, the same strain apparently helped mice maintain testosterone levels into old age. (In case this sounds a bit too much like I’m shilling for BioGaia, I’ll remind everyone: the nice thing about live microbes is that you only have to buy ‘em once. A capsule of the stuff apparently makes an excellent starter culture for yogurt.)

There are a couple of remarkable things about this dynamic of a bacterium mediating oxytocin levels, though.

One: this is *not a microbe that produces oxytocin*; this is a microbe that *causes its host to produce and release more of their own oxytocin*. That's an important distinction: oxytocin itself isn't very useful as a drug, outside the OB/GYN ward where it can be injected to initiate a birth. Its size and composition make it susceptible to degradation in the GI tract—so eating it doesn't do much good for your immune system. When it's injected, it doesn't cross the blood-brain barrier, and its half-life in the bloodstream is something like 5 minutes. Even when you can get it into the brain with tricks like intranasal administration, most of the receptors are distributed far from the olfactory bulb, so the results we get from the nasal spray likely reflect only the crudest of its functions. Finding a simple way to bypass all of these problems at once is too incredible to be a stroke of luck.

How *L. reuteri* causes the host to produce more oxytocin isn't fully understood, but it seems to act via the vagus nerve. This is one of the twelve sets of cranial nerves, the major wires which carry information from your body to your brain and back again. Think of the optic nerve, which carries the signals from the machinery in your eye to the brain for processing. The vagus is like that, but carrying chemical sensory information from your gut, like a giant tongue with a thousand different taste buds. They found that cutting it prevents *L. reuteri* from producing the oxytocin increase in its host.

To me, this suggests that *L. reuteri* isn't a one-off fluke. If it were doing something like producing oxytocin, it might be seen as a microbe "hijacking" the signaling hormone. But the fact that our bodies have some kind of receptor down in the gut, a button which a bug can push to release oxytocin in your brain? That implies that gut bacteria are a natural part of the systems and mechanisms regulating the levels of these hormones. If there was a "hijacking", it happened eons ago, and by now we've decided we like the direction these guys are taking the bus anyway. It implies that dysfunctions in oxytocin signaling—like the kind we see in certain personality disorders—might be caused by the absence of certain gut microbes to begin with.

It also implies that we're all supposed to have this internal immune-cheerleading squad. Earlier, we talked about the wailing widow finding comfort and a reason to carry on in the community that needs her—but even if there's nobody around, she's still got a trillion organisms that depend on her for their continued survival and propagation. And it looks like they get a vote in whether or not she calls it a day.

Remarkable thing #2: the strain of *L. reuteri* used in that study was isolated from human breast milk. And since its destination is the child's gut, it seems clear that this is an "heirloom" gut microbe, one that's meant to be passed down across generations, as much a part of the human organism as the mitochondria.

Third: this heritable trait, this "bonus gene", is only loosely under our control. Typically, epigenetic processes govern gene expression, letting your body crank up the amount of one gene, silence another as needed—but with the microbiome, we're more like gardeners or goatherds. Diet plays a huge role in determining which kinds of bugs flourish or languish. If you allow that gut bacteria can influence our behavior through subtle mechanisms like oxytocin, unnerving questions begin to arise.

Could you overdo it on oxytocin with the help of certain bacteria? I'm sure we can all think of someone who has pathological levels of esteem for their in-group. More, what would it look like to have loads of oxytocin but no friends?

How much of a food craving is something "you" want, versus a gut bacterium pulling a lever to get the kind of calories it'll thrive on? Do you really *love* cheese, or is that the *Lactobacillus* talking, via a lifetime of classical conditioning? And in the end, what's the difference? Unless you believe in the "ghost in the machine", there's no real *you* driving the bus—you *are* the bus, passengers and all.

This, more than anything, is the lesson that I've taken from studying the microbiome: that we need to expand our definitions of the self. Inward, to encompass all our little passengers, each trying to balance their own needs against the needs of the collective—and outward, to include all the other people in our worlds, all the living things in the ecosystem that we're a part of.

There's a reason that pathogens are comparatively rare among bacteria: if an organism pursues endless growth at the expense of the ecosystem around it, it's only fit in the very short-term. Eventually, the host will die and be buried. Symbiosis is the long game: rather than reproducing as much as possible, trying to cause enough diarrhea to make their way to a new host, most gut microbes improve their own fitness by improving ours, knowing that—if we're successful—they'll have a new generation of hosts to feed them, house them, and shit them out into the soil for another fifty years.

The degree to which we favor our in-group over the out-group may be determined partly by our biochemistry, but who we think of as belonging to each…that's learned, that's up to us. It's not always possible, especially when times are hard, but seeing all people, and even all life as part of an in-group—that's a goal worth striving toward.

To let go of the notion of self, except as a sum of parts, and as part of a whole…it sounds suspiciously like enlightenment, doesn't it?

—✋🏽💩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