The Placebo Effect

So what is this placebo stuff? Well, it's really—well, there's two aspects of placebo. One and the most—probably the one you see that's most important—is the expectation, that you have this expectation that you're going to have pain relief. The doctor hands you a pill, so this is going to make your pain go away, and you think it's going to make it go away, and that's a big part of it. But there's also conditioning, where if you get your same pill every day, every day, and then one day you get a bad batch, even if you know that it's a bad batch—and Benedetti in Italy has done very nice experiments where every day, they'd bring a subject in and give them an analgesic under a certain situation. And then one day after they'd been coming in every day for a week, they come in, he said this is a control day, I'm just going to give you an antibiotic today. But he did the same injection, the same procedure, and they had an analgesic effect even though he told them this was just an antibiotic, but just being in the whole situation. So that's conditioning. And generally in the real life, you have both expectation and conditioning together. Expectations have been studied a lot more than conditioning.

So here is an example, again, in healthy people, experimental situation, heat pain on the arm, I think, and of just creating a placebo expectation of pain relief. And the red globs here now show regions where there's significantly less activation when the person has received the placebo suggestion of pain relief, and in fact feels less pain than when he hasn't. And again, these areas, the cingulate cortex, insular cortex, the thalamus, again a lot of particular areas involved in the affective aspects of pain perception are, in fact, reduced. The pain of activation is reduced based on the placebo suggestion. And if you look what happens during the actual suggestion itself, we get activation in this dorsolateral prefrontal cortex, midbrain, PAG descending circuitry that I talked about earlier, suggesting that this circuitry—that this descending system is activated by the placebo expectation. That expectation is naturally activating a descending control system.

And we also know now that there's at least two neurotransmitters in the brain that are important that are released during this placebo expectation, and that is the opiate system and dopamine. And again, Benedetti did some classic studies where he brought people in and they did a pain tolerance either having ischemia or putting hands in cold water and they brought them in on four separate days and gave—just looked at their tolerance levels and they gave day one nothing, day two, they did a hidden infusion of naloxone. Naloxone is an opiate antagonist that's used clinically if somebody has overdosed on opiate to reverse it. It binds to the opiate receptors and blocks from the opiate binding to them. And so but if you just give naloxone by itself, it has no effect on this pain tolerance. Did that twice—no naloxone and naloxone—just to show that naloxone itself, a hidden infusion of it, doesn't have any effect. Then he brought the people in—or a different group of people—and brought in, day one, did the tolerance, day two, walks in with a big needle and said this is a powerful analgesic, it's going to make your pain go away, gives them the injection, and lo and behold they could tolerate more pain now than they could when they didn't have this injection. This is just a saline injection which is a placebo injection. Another group of people did the same thing, but now instead of this being saline in the syringe, it's naloxone. And so they get their tolerance, they come in, this is a powerful analgesic, he injects it, and now there is no change in the tolerance when you have naloxone on board, suggesting that opiates must be being released here to increase that tolerance because when you block their release, then you don't get that change in tolerance.

And using positron emission tomography and doing competitive binding studies using a competitive antagonist called fentanyl, you can show that, in fact, there are opiate receptors throughout the brain that are activated in response to placebo and showing directly that, in fact, placebo is releasing opiates in the brain. And the same types of studies, where the PET studies have been done with the dopamine receptor agonist D2/D3, receptor agonist raclopride. This only shows binding in the basal ganglia, but again you see this release of dopamine when the person gets this placebo analgesic suggestion. So these are—it's a real physiological effect, so people are not crazy by being a placebo responder. In fact, it's just a natural way of activating real systems in the brain. And again, this just shows that the bigger the analgesic response, the more of either—of opiates or dopamine that are released in the brain.