Reefer Sanity
The brain's cannabinoid receptor is the target of a rush (ha!) to develop new drugs.
FORTUNE
Tuesday, November 11, 2003
By Meredith Wadman

If you're among those of us who did inhale, you'll recall one of the weed's enjoyable side effects: intense attacks of the munchies that sent you scurrying for baked beans and Moon Pies faster than Pooh after honey. So you may appreciate this tasty irony: Drug companies are racing to develop pills that plug into the same brain-signaling system that once had boomers flying high—this time to help them lose weight.

Experimental drugs that block the brain receptor activated by marijuana—called the cannabinoid receptor—are showing clear promise in fighting obesity. And that's not the only vice that may soon be treatable with this new breed of mind medicine. Predilections for Marlboros and martinis are also targets of a new drug now in human trials and nearing the clinic, with imitators hot on its tail.

Farther from the pharmacist's counter but still firing up a lot of interest are experimental compounds that work not by blocking cannabinoid receptors but by activating them. These are squelching strokes, allaying anxiety, and easing pain in lab animals. There's even a suggestion that drugs that stimulate cannabinoid receptors in sperm may one day yield a contraceptive for men. If only they'd remember to take it! (All is not lost on this score—the cannabinoid system is important in the function of memory as well.)

"The cannabinoid area is getting ready for prime time," says Daniele Piomelli, a leading researcher at the University of California at Irvine. "What makes it particularly promising is that there are a lot of companies working on these classes of compounds."

It's hard to overstate just how important—and rare—it is to identify an entirely new class of brain receptors, the neurotransmitters that act on them, and the molecules that ferry those neurotransmitters or break them down. Consider the pharmaceutical and cultural revolution launched with the discovery of the transporter for serotonin, which led to the development of Prozac, Zoloft, and other antidepressants. The body's home-grown cannabinoid neurotransmitters and their receptors—discovered only in the past 13 years—could give rise to a whole new generation of blockbusters. "It's one of the hottest areas in
neuroscience," says George Kunos, scientific director at the National Institute on Alcohol Abuse and Alcoholism.

The big players now in the lab with cannabinoid-related experimental drugs include Merck, Pfizer, and Bristol-Myers Squibb. But the undisputed leader is the French company Sanofi-Synthelabo, which is in late-stage human trials for its drug Rimonabant. Sanofi’s pill is helping fat people slim down and quit smoking at the same time.

Rimonabant works by blocking CB1, the brain receptor that marijuana’s active ingredient plugs into. It turns out that nerve cells in the brain make their own neurotransmitters that plug in here too, called endogenous cannabinoids. When we enjoy steaks, stogies, or Scotch, these chemical messengers are pumped out and bind to CB1 receptors in a key "reward" area of the brain. This sets free a different neurotransmitter: dopamine, the pleasure queen. So by blocking endogenous cannabinoids from docking at CB1, Rimonabant snuffs that dopamine buzz and takes the fun out of our worst habits.

In an early round of the Sanofi trials, which wrap up late next year, obese people on the highest trial dose of Rimonabant lost an average of ten pounds in just under four months. Twenty percent of smokers taking the drug didn’t light up during a ten-week trial and lost 2.6 pounds in the bargain. Trials of Rimonabant in alcoholics are in earlier stages, but in lab mice with drinking problems its effectiveness is clear.

Sanofi scientists in the late 1980s applied a logic that now seems obvious: If marijuana brings on the munchies, why not make a molecule that blocks its action, on the theory that it will fight obesity? Scientists had long been operating on the faulty theory that the brain didn’t have specific receptors for marijuana’s active ingredient. They didn’t figure out until 1988 that those receptors existed. CB1 was identified in 1990. All of a sudden, the cannabinoid system was the hot new kid on the brain-transmitter block. And Big Pharma, normally shy about reefer-related research, snaps to attention when the subject is diet pills.

Ultimately, the cannabinoid system could yield therapies that go well beyond helping people shrink their beer bellies and pitch the Pall Malls. Compounds that activate cannabinoid receptors are also presenting exciting possibilities. For instance, it’s well established in animals that drugs that stimulate cannabinoid receptors can limit brain damage in trauma and stroke. Other promising applications seem to emerge by the month.

Of course, man-made drugs that turn on cannabinoid receptors are bound to freak out the drug police. So scientists are trying to develop
compounds that fight disease without giving users the giggles. Scientists at the University of Arizona and the University of Connecticut have used an experimental drug to increase pain tolerance in rats and mice with nerve-injured paws. The drug binds to a class of cannabinoid receptors that occur only outside the brain, meaning that the furry guys get pain relief without getting high. The applications aren't trivial: Neuropathic pain from nerve injury affects millions of Americans and doesn't respond well to existing painkillers. AlexiPharma, a Connecticut startup, is hoping to move the drug into human trials within a year.

Pain sufferers have been toking up for as long as hemp has been used for rope. Similarly, the calming effects of low-dose ganja are now being harnessed—without the high—in experimental drugs that boost levels of one of the brain's key cannabinoid neurotransmitters, damping down anxiety in lab rats. That's what Daniele Piomelli is working on at UC-Irvine. "Rimonabant is the beginning of a chapter, not the end of it," he says. And he's not just blowing smoke.