Most neurotransmitters were discovered long before their receptors, but new techniques have tended to reverse this tradition. This is a story of receptors in search of transmitters.

*Cannabis sativa* is the botanical name for hemp, a fibrous plant used through the ages for making rope and cloth. These days, cannabis is much more popular as dope than rope; it is widely, and usually illegally, sold as marijuana or hashish. The Chinese first recognized the potent psychoactive properties of cannabis 4000 years ago, but Western society learned of its intoxicating properties only in the nineteenth century, when Napoleon III’s troops returned to France with Egyptian hashish. As a member of Napoleon’s Commission of Sciences and Arts reported in 1810: “For the Egyptians, hemp is the plant par excellence, not for the uses they make of it in Europe and many other countries, but for its peculiar effects. The hemp cultivated in Egypt is indeed intoxicating and narcotic” (cited in Piomelli, 2003, p. 873).

At low doses, the effects of cannabis can be euphoria, feelings of calm and relaxation, altered sensations, reduced pain, increased laughter, talkativeness, hunger, and lightheadedness, as well as decreased problem-solving ability, short-term memory, and psychomotor performance (i.e., the skills necessary for driving). High doses of cannabis can cause profound personality changes, and even hallucinations. In recent years, forms of cannabis have been approved for limited medicinal use in the United States, primarily to treat nausea and vomiting in cancer patients undergoing chemotherapy, and to stimulate appetite in some AIDS patients.

The active ingredient in cannabis is an oily chemical called Δ⁹-tetrahydrocannabinol, or THC. During the late 1980s, it became apparent that THC can bind to specific G-protein-coupled “cannabinoid” receptors in the brain, particularly in motor control areas, the cerebral cortex, and pain pathways. At about the same time, a group at the National Institute of Mental Health cloned the gene for an unknown (or “orphan”) G-protein-coupled receptor. Further work showed that the mystery receptor was a cannabinoid (CB) receptor. Two types of cannabinoid receptors are now known: CB₁ receptors are in the brain, and CB₂ receptors are mainly in immune tissues elsewhere in the body.

Remarkably, the brain has more CB₁ receptors than any other G-protein-coupled receptor. What are they doing there? We are quite certain they did not evolve to bind the THC from hemp. The natural ligand for a receptor is never the synthetic drug, plant toxin, or snake venom that might have helped us identify that receptor in the first place. It is much more likely that the cannabinoid receptors exist to bind some signaling molecule made naturally by the brain: THC-like neurotransmitters called endocannabinoids. Recent research has identified several molecules that are possible endocannabinoids. Among the most promising are anandamide (from *ananda* the Sanskrit word for “internal bliss”) and arachidonylglycerol (2-AG). Anandamide and 2-AG are both small lipid molecules (Figure A), quite different from any other known neurotransmitter.

As the search for new transmitters continues, the hunt is also on for further subtypes of CB receptors, and for more selective compounds that bind to them. Cannabinoids are potentially useful for relieving nausea, suppressing pain, relaxing muscles, treating seizures, and decreasing the intraocular pressure of glaucoma. As we write this, a cannabinoid receptor antagonist is being tested as an appetite suppressant in human clinical trials. Cannabinoid therapies might be more practical if new drugs can be developed that retain the therapeutic benefits without causing psychoactive side effects.