leagues at NIMH took that same high-potency cannibinoid and used it to map the distribution of the marijuana receptor in rat, guinea pig, dog, and monkey brains, as well as in human brains obtained from people who had died of neurological diseases. The localization of the receptor proved to fit nicely, Herkenham says, with what's known about cannabinoid action.

Marijuana has little effect on respiratory and cardiac function, for example, and the brainstem, which contains the main control centers for those activities, has few of the receptors. But movement control centers, such as the cerebellum, are rich in the receptors, a finding consistent with the drug's ability to cause uncoordinated movements. The receptors are also plentiful in the cerebral cortex and hippocampus, areas important for cognition and memory.

In fact, the receptor is generally so abundant, Herkenham says, that "I realized that the gene was going to come out of some screen someday." He was right.

By the beginning of last year, Matsuda was beginning to get suspicious that her group's mystery receptor might bind cannabinoids. She had found, for example, that the receptor gene was active in the same cell line that Howlett's group had used in much

Substance P Causes Pain—But Also Heals

The National Institute of Mental Health researchers who cloned the gene for the marijuana receptor didn't start out looking for that gene. In fact, they began by looking for genes that encode receptors for peptides known to transmit pain signals in the nervous system, among them the peptide known as substance P.

Found in many organ systems, including the central nervous system, the skin, the lungs, and the intestines, substance P is one of three mammalian neuropeptides known as tachykinins. Its functions are remarkably diverse: in addition to a role in pain, substance P is involved in causing arthritis, psoriasis, and asthma. And some scientists have begun to think that substance P may be a key player in one of the hottest research areas around: links between the immune system and the nervous system.

Paying homage to the varied aspects of substance P, 200 researchers showed up at a recent conference devoted solely to it and its relatives. The conference was put together by Susan Leeman, a University of Massachusetts Medical Center physiologist, who set the field in motion in 1970 by purifying and sequencing the 11–amino acid neuropeptide when she was at Brandeis University.

The best known of substance P's many faces is pain transmission. Noxious stimuli such as heat, pressure, and caustic chemicals, so the theory goes, cause thinly myelinated or nonmyelinated neurons to fire, releasing substance P. Physiologist James L. Henry of McGill University says that substance P then shuts down potassium channels, exciting the nerve cells and making them more responsive.

Experimentally increasing substance P levels in a rat, for example, makes the animal flick its tail sooner in reponse to heat. But, in a surprise twist, substance P also increases cell sensitivity to the body's natural pain killers, such as the enkephalins and the adenosine-mediated neurotransmitters. "What substance P is doing is making the cell more responsive to *any* stimulus that comes along, whether it's a pain input or an analgesic one," says Henry. "That way it's ready for anything."

Substance P also has counterbalancing roles in inflammation: promoting inflammatory processes and perhaps also recruiting cells that heal the damaged area. Neurophysiologist Patrick Mantyh of Veterans Hospital in Minneapolis showed conference attendees that inflamed bowel tissue from patients with Crohn's disease or ulcerative colitis have very large numbers of substance P receptors around blood and lymph vessels; normal tissue has almost none. Similar increases are observed in inflamed joint tissues of rheumatoid arthritis patients and lung tissues of those suffering from asthma.

Likewise, in astrocytes (nervous system cells that are packed in among neurons but don't transmit signals) responding to injury, the population of substance P receptors increases greatly. Ordinarily, astrocytes have few receptors for the neuropeptide. But if a nerve is crushed or damaged, the reactive astrocytes that are nearby "light up like crazy with substance P receptors," Mantyh explained.

This response prevents axons from regenerating—and if a way could be found to block substance P binding, then perhaps central nervous system injuries could be healed by regeneration. In May a group at the Yale University Medical School led by epidemiologist Michael B. Bracken showed that injections of the steroid methylprednisolone within 8 hours of spinal cord injury increase the chance of recovery; the steroid may play some role in blocking substance P binding to its receptor.

Substance P affects inflammation by dilating blood vessels and increasing their permeability and also by stimulating the proliferation of T lymphocytes. It can also recruit leukocytes into inflamed tissue by stimulating them to produce endothelial-leukocyte adhesion molecules, as shown in recent work by dermatologist George Murphy and his colleagues at the University of Pennsylvania School of Medicine.

That ability to "converse with" immune cells suggests a role for substance P well outside the nervous system. "We're increasingly recognizing that the nervous system and the immune system talk to each other," says biologist G. Miller Jonakait of Rutgers University. "And one of the communications links has got to be substance P." She found that a factor produced by white blood cells called interleukin-1 increases transcription of the substance P messenger RNA by injured sympathetic nervous system ganglia—thereby completing an "inflammatory loop" between leukocytes and the neurons that make substance P.

Understanding this loop may have commercial consequences. Many pharmaceutical companies are looking for ways to cut the loop and prevent substance P from transmitting its signals—actions that could promote healing or dampen pain. That task has been made easier by the cloning of the substance P receptor, a task carried out recently by James E. Krause and Andrew Hershey of the Washington University School of Medicine as well as by Shigetada Nakanishi of Kyoto University. Knowing the shape of the receptor will make it possible to focus the search for blocks.

The vast potential for applying the tools of molecular biology to uncover intricate interactions between the nervous system and the immune system—in this case, as mediated by neuropeptides—had conference attendees buzzing, but it also left them with a sense of enormous anticipation. "This meeting has left people dangling," says McGill's Henry, "waiting to see what will happen next." ■ **P. J. SKERRETT**

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