Meeting on the Mind

Last month, the American College of Neuropsychopharmacology (ANCP) held its 26th annual meeting. Sessions included the biological and genetic aspects of brain diseases; mechanisms that regulate biologic and behavioral development; origins and treatments of stress, panic, anxiety, and obsessive-compulsive disorders; receptor-neurotransmitter mismatches; mechanisms of action of therapeutic and abused drugs; and the neuropsychiatry of AIDS. The following are highlights of three reports from the conference.*

Need for Mother's Touch Is Brain-Based

To a rat pup or a human infant, a mother's touch has real biological effects—it means growing and thriving. Depriving infants of maternal contact produces the opposite effect; neither rats nor human babies will gain weight or develop according to a normal schedule. These effects of maternal deprivation can be traced to the brain peptide β-endorphin, according to new data from Saul Schanberg of Duke University Medical Center in Durham, North Carolina.

Schanberg, Jorge Bartolome, and Cynthia Kuhn, also of Duke, find that a very specific pattern and strength of maternal touching somehow promotes protein synthesis and weight gain in infant rats. Without the maternal contact or an artificial substitute, rat pups fail to synthesize growth proteins but they continue to synthesize other proteins. The deprived pups are not suffering from a lack of nutrition, however. Instead, the key to their response appears to be β-endorphin. By injecting this peptide directly into the brains of rats pups up to 3 weeks of age, before they are naturally weaned, the researchers can mimic the growth-stunting effects of maternal deprivation.

"This is brain control beyond whatever I thought existed," said Schanberg. "Just think, a substance secreted by the brain affects the way the entire body responds to two early regulators of growth—insulin and growth hormone." The effects of experimentally administered β-endorphin apparently occur without the involvement of the pituitary gland, the master hormone gland at the base of the brain. Schanberg and his coworkers have not yet demonstrated which parts of the brain actually release β-endorphin during maternal deprivation.

The new results are a culmination of more than 10 years of studies, which Schanberg stresses could not have been done without the use of laboratory animals. "This is one case in which animal work has led directly to the clinic," he says. He and Tiffany Field of the University of Miami studied the effects of touching premature human infants and found that they, too, thrive better with extensive skin-to-skin contact.

"We used a combination of back massage, neck rubbing, and kinesthetic movement (moving the arms and legs)," says Schanberg. "The touched babies showed a 50% increase in body weight and enhanced neurological development over a 12-day period." Eight months later, after the infants had lived at home, the touched babies still fared better.

To measure the biochemical effects of maternal deprivation in rats, the Duke researchers monitor the activity of the enzyme ornithine decarboxylase (ODC). ODC is important for the synthesis of putrescine, spermidine, and spermine. These substances help to regulate the synthesis of nucleic acids and proteins in organs such as the heart, lungs, brain, and spleen. "Within a half-hour from the time the pups are deprived of contact with their mothers we see a shutdown in ODC activity in major organs throughout the body," says Schanberg.

Two things restore protein synthesis and weight gain in the pups to normal levels. One is reuniting them with their mothers. The other is licking the pups, as the mother rat naturally would. "I couldn't get the lab technicians to actually lick the pups," says Schanberg. But Gary Evoniuk, also of Duke, observed that stroking them heavily with a wet paintbrush had the same effect. Apparently a combination of the mother's wet, rough tongue and the pressure and massaging action it has on the pups is biologically important. The licking stimulates the pups to urinate, which they are unable to do alone at early ages, and it also appears to keep brain β-endorphin levels in check.

In general, β-endorphin exerts its effects by binding to opiate receptors on nerve cells—the same receptors that are stimulated by morphine and heroin. But the β-endorphin effects seen during maternal deprivation are different. They cannot be inhibited by drugs that block the pain-reducing and addictive effects of opiate drugs. "This is a nonclassical opiate effect," says Schanberg. He thinks that it may depend on the so-called epsilon class of opiate receptors, which are as yet poorly understood.

The Receptor Mismatch Controversy

A central dogma about nerve cell communication in the brain is being challenged. During the past few years, Miles Herkenham of the National Institute of Mental Health has shown that the distribution of receptors for neurotransmitters often does not follow the same pattern as the distribution of the neurotransmitters themselves. Herkenham terms this discrepancy a mismatch and suggests many neurotransmitters and drugs in the brain may act outside brain synapses, rather than at them.

At the same time that he offers this provocative interpretation about what his data might mean, Herkenham is cautious. "I only arrive at the idea of communication outside synapses after ruling out all the alternatives," he says. "It is not a direct demonstration." Until recently, many in the field dismissed Herkenham's data, but he now has so much anatomical evidence supporting the mis-

Maternal contact is essential

A mother rat's touch promotes normal growth and development in her pups and keeps their brain β-endorphin levels in check.

David Barron

* The ACNP meeting was held from 6 to 12 December 1987 in San Juan, Puerto Rico.

match phenomenon that it is impossible to ignore. Still, some neuroscientists question the extent of Herkenham's findings and view his notion of transmitter action at a distance from synapses as premature.

Herkenham infers the existence of nonsynaptic receptors in experimental animals by examining brain sections that have been selectively stained for either receptors or neurotransmitters. "Perhaps the most glaring example of a mismatch is in the substance P family of peptides in the substantia nigra," says Herkenham. Housed at the base of the brainstem, the substantia nigra helps to control movement. "You would expect to see a high density of substance P receptors in the substantia nigra where the nerve terminals are, but receptors there are virtually undetectable." In contrast, the neocortex and the hippocampus have very high concentrations of receptors for substance P, but these regions contain very low levels of the peptide.

Receptor-transmitter mismatching also occurs in the opiate peptide system of the globus pallidus, another deep brain structure important for voluntary movement. "The globus pallidus has nerve terminals that contain high concentrations of opiate peptides but the receptors for these peptides are very sparse," says Herkenham. Still another mismatch occurs in the same brain region. "The major transmitter between the striatum and the globus pallidus is the inhibitory amino acid, gamma-aminobutyric acid (GABA). It is a poor match because the globus pallidus has low levels of receptors for GABA."

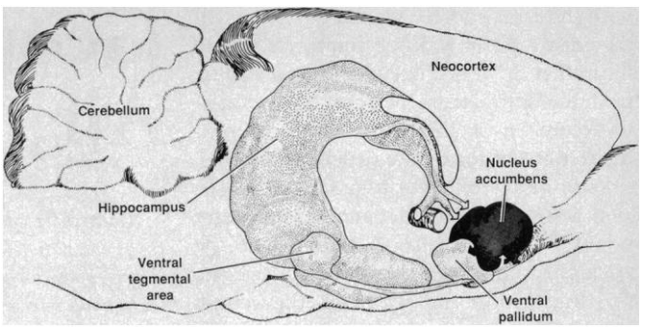
Herkenham proposes a way, as yet unsupported by data, in which nonsynaptic receptors might be activated by naturally occurring neurotransmitters. He notes that the fluid bathing the brain and spinal cord contains many transmitter substances and suggests that they may diffuse from this pool through the spaces between neurons, much as hormones diffuse through the blood. These diffusing transmitters might then engage in a form of nonsynaptic communication. But not everyone is as enthusiastic about these ideas as Herkenham.

"This whole mismatch business started in the late 70s," says Michael Kuhar of the Addiction Research Center in Baltimore. Kuhar and his colleagues have also mapped the locations of brain transmitters and receptors, but they stress matches rather than mismatches.

"We had always been a little reluctant to push the mismatch concept because there is certainly a match between the brain locations of many receptors and neurotransmitters," says Kuhar. He also notes that many drugs act in areas of the brain and spinal cord that contain high densities of neurotransmitter receptors, sites that he believes are synaptic.

Brain pathway in drug dependence

Side view of a rat brain shows three structures (at bottom) important in dependence on opiate drugs. [Adapted from R. L. Hakan and S. J. Henriksen, Soc. for Neurosci. Abstr. 13, 1282 (1987)]



Kuhar emphasizes that current techniques do not enable researchers to detect nerve terminals that contain very low levels of transmitter. He also stresses that today's methods cannot identify all receptors and subtypes of receptors. "I believe that mismatches exist, but I worry that Herkenham's conclusions about their significance might be premature and based on incomplete data," he says.

But Herkenham is persistent. He points out that many receptors are located on the presynaptic terminals of nerve cells. These receptors often do not match the kind of neurotransmitter released at that particular synapse, and they must therefore be responding to neurotransmitters released elsewhere. This characteristic makes them nonsynaptic. For instance, the nerve terminals in the spinal cord that contain the opiate peptide enkephalin are an example of a presynaptic mismatch, according to Herkenham. These terminals do not make synaptic contacts with the sensory neurons entering the spinal cord that contain receptors for enkephalin.

"In retrospect it is easy to explain the mismatch between receptor locations in the brain and sites of neurotransmitter release," says Herkenham. Why should a high density of receptors be found at a synapse where neurotransmitter concentration is the highest? Instead, why not put the receptors in places where transmitter concentration is low? This design would allow transmitters to exhibit the two modes of communication advocated by Herkenham—synaptic and nonsynaptic. But until someone demonstrates that nonsynaptic receptors affect brain function, the notion of widespread nerve cell communication outside synapses will continue to be greeted with skepticism.

Drug-Brain Interaction Sparks Debate

"The neural system that makes you feel good from opiates is the same one that makes you feel bad when you withdraw from them," says George Koob of the Research Institute of the Scripps Clinic in La Jolla, California. Koob's new data, which he reported at the recent meeting, support a 1950s concept that people take drugs primarily to avoid the discomfort of drug withdrawal rather than to experience pleasure. His ideas not only trigger a debate about the biological mechanisms that underlie drug dependence, they also highlight a controversy about the terminology used to describe drug dependence.

In contrast to Koob, Roy Wise of Concordia University in Montreal, Quebec, thinks that two distinct brain systems are responsible for drug-induced pleasure and the alleviation of pain. In an interview with *Science*, he also objected to linking the term "psychological" with "dependence." The notion of dependence should be confined to the relief of pain, he contends, which is clearly different from the psychological mechanism of pleasure. And unlike Koob, he advocates the idea that people take drugs primarily to feel pleasure rather than to avoid pain.

Koob and Wise generally agree on the identity of a brain circuit that is responsible for the pleasurable aspects of drug-taking. But they disagree on which part of the circuit is most important.

Koob, Floyd Bloom, also of Scripps, and their colleagues focus on the role of the nucleus accumbens in drug dependence. They view this structure in the lower part of the forebrain as part of a circuit that allows the brain to reward itself during normal pleasurable experiences and also during drug-taking. Apparently, abused drugs act on this neural pathway to potentiate drug-taking behavior.

Koob tests the role of the nucleus accumbens in drug dependence by chemically disrupting the neural pathway that leads to it. This pathway, from the ventral tegmental nucleus to the nucelus accumbens, contains the neurotransmitter dopamine. "If I remove this dopamine system, rats that are not physically dependent on drug will continue to self-administer opiates," says Koob. But

with the same surgery, the rats cease to self-administer cocaine. Koob interprets this to mean that the dopamine connection leading from the ventral tegmental area to the nucleus accumbens is critical for cocaine dependence but not for opiate dependence.

Wise disagrees. "Koob and I both envision a brain circuit that has several entry points," he says. "Koob thinks that the nucleus accumbens is the most sensitive site for drug action and we think the ventral tegmental area is the most sensitive. It is like a chain of nerve cells. Drugs can activate neurons at link 1 or link 2. We study link 1 where dopamine is the transmitter, and Koob studies link 2."

Koob and Wise also clash on whether the same brain pathway is responsible for both the pleasurable and painful aspects of drug use. For Koob, it is the same. His idea is a modernized version of the viewpoint held 30 or more years ago that physical dependence on drugs was the key to addiction. "The nucleus accumbens seems to be important for both psychological and physical dependence. I think that it somehow becomes sensitized in animals that are physically dependent."

Koob's reversion to the 1950s concept of drug dependence is an anathema to Wise, who sees a clear separation between the psychological mechanisms of pleasure and physical dependence on drugs. "We tend to look at the ventral tegmental area and its link to the nucleus accumbens as a pleasure mechanism, and the periaqueductal gray area (PAG) as a pain mechanism," says Wise. The PAG is composed of nerve cell bodies that surround the central canal connecting two of the major fluid-filled cavities in the brain called ventricles. According to Wise, opiate drugs act in the PAG to alleviate three kinds of pain—physical pain, the pain of loneliness and social withdrawal, and the drug-induced pain of opiate withdrawal.

Wise also challenges Koob's use of the term psychological to describe drug dependence. "The notion of physical dependence is clear," he says. "Extending it to include psychological dependence is messy because we have no way to measure that aspect objectively. I think there should be a big distinction between physical dependence—which is what people were talking about in the 1950s—and psychological dependence."

"Obviously, more work is needed to assess the behavioral changes associated with physical dependence and the underlying changes in the brain," says Koob. "I think physical dependence has manifestations all over the brain. The question is what responses go with what systems, and what drives drug-seeking behavior?" ■

DEBORAH M. BARNES

Geophysics: Ancient Air, Ozone, and Faults

Researchers who gathered in San Francisco in December at the annual fall meeting of the American Geophysical Union heard the usual variety of talks treating everything from Earth's core to the tenuous wisps of solar particles far beyond Pluto. Earthquakes, the local California variety in particular, figured prominently, as did the currently popular subjects of ancient air trapped in amber and the deepening Antarctic ozone hole.

No Ancient Air to Be Found in Amber?

The latest analyses of the air trapped for tens of millions of years in fossilized tree resin are in. They totally contradict earlier, independent analyses that indicated complete preservation of samples of an oxygen-enriched atmosphere of 80 million years ago.

In October Robert Berner of Yale University and Gary Landis of the U.S. Geological Survey (USGS) in Denver reported that cracking open 80-million-year-old amber released gases that, after an adjustment for the conversion of oxygen to carbon dioxide, resembled modern air but with about 30% rather than 21% oxygen (*Science*, 13 November, p. 890). The gases released from Baltic amber, which formed about 40 million years ago, contained about 21% oxygen.

But Yoshio Horibe and Harmon Craig of Scripps Institution of Oceanography reported at the AGU meeting that when they ground up their samples of Baltic amber in a ball mill, the gas released bore no resemblance to air, modern or ancient. Instead, it appeared to be a well-preserved sample of the gases that would have been dissolved in the sap of the tree that produced the amber. The ratio of nitrogen to argon was 39, as it is in oceans and lakes, not 84, as it is in air. The ratio of oxygen to argon was 0.4, not 22, as it is in air.

There is enough carbon dioxide to account for the missing oxygen, Craig noted, but he doubts that it is that simple. Oxygen exposed to amber in the laboratory at 107°C disappears within a few days, he and his colleague found. At room temperature, the half-life of oxygen was about a month, not millions of years. And they found that oxygen consumed by reactions with the amber did not reappear in carbon dioxide. They conclude that any carbon dioxide present in amber now was there when the resin formed or somehow reappeared.

The Scripps group would thus be surprised to find the gases trapped in amber enriched in oxygen, as reported by Berner and Landis. If oxygen were found in higher amounts than in air, they would conclude that it was enriched over the concentration in air because its greater solubility enriches it in any water solution.

The only significant differences between the two studies seem to be the analysis of different samples and the gas extraction by grinding or cracking. A sample exchange is under way.

A Hidden Earthquake Hazard in Los Angeles

The moderate Whittier Narrows earthquake that struck Los Angeles last October did not occur on the Whittier Fault, according to seismologists at a hastily organized session of the AGU meeting. Instead it ruptured a previously unknown, hidden fault more than 11 kilometers beneath the surface. That is bad news for residents of the Los Angeles basin, who already face the threat from 95 known faults that break the surface (*Science,* 16 October, p. 269).

Egill Hauksson of the University of Southern California reported that a patch of fault slipped that is aligned in an east-west direction and dips at a gentle 30-degree angle to the north. It lies in the basement rock beneath an upward arching fold of sediment called an anticline. Jian Lin of Brown University and Ross Stein of the USGS in Menlo Park reported leveling measurements that showed that the fold had grown about 45 millimeters during the earthquake, which could be accounted for by about 1 meter's slip on the fault buried within the heart of the fold. The Coalinga earthquake of 1983, which also took seismologists by surprise, led to anticline growth in just the same way.

Hauksson pointed out that the Whittier Narrows earthquake and its associated fold are not unique. The fold is part of a trend extending from east of Whittier Narrows westward around the northern edge of the basin all the way to the Channel Islands. The moderate-size Point Mugu and Malibu