

Do-it-yourself Valium in the brain

From thousands of litres of urine Danish researchers have isolated two milligrams of a compound that may outclass Valium as an anti-anxiety drug. At the meeting in Atlanta this week of the Society of Neuroscience Claus Braestrup of A/S Ferrosan Co. in Soeborg described the identification of the compound, which he and Mogens Nielsen of Sankt Hans Hospital in Roskilde also have found in the human brain. Braestrup, however, did not reveal the structure of the potent chemical, reportedly to avoid jeopardizing patent rights.

Gamma-compound, as Braestrup calls the agent, binds to receptors involved in the action of Valium, Librium and other benzodiazepine drugs. But this natural brain substance binds even more tightly than do the anti-anxiety drugs. Other chemicals that have been isolated from the brain as possible anti-anxiety agents are far weaker candidates. Those compounds — the purines, hypoxanthine and inosine — bind 100,000 times more weakly than does Valium (SN: 12/16/78, p. 424). In fact, scientists examining purines admit that the amounts they use to demonstrate binding to benzodiazepine receptors is probably 10 to 100 times the amount present in an entire brain.

The strategy that led to isolation of a natural Valium-like agent is reminiscent of the identification of enkephalins and endorphins as "the brain's own morphine" (SN: 6/26/76, p. 406). In each case, scientists identified brain sites that bind a widely used pharmacological agent. But they reasoned that it would be unlikely that specific receptors evolved solely to detect a plant product or a synthetic chemical. Thus, the brain probably contains an endogenous substance that binds at the site. All they had to do was find it.

The evidence that gamma-compound is a natural Valium-like compound "sounds pretty good," says Solomon Snyder of Johns Hopkins University, a leader in the identification of morphine-like brain peptides. "Braestrup is a very smart scientist," he adds. "I believe him."

Snyder explained to reporters that although Braestrup did not detail the gamma-compound structure, he did report that it is a small molecule, soluble in lipids rather than in water and it has a 6-carbon, aromatic ring. The compound is in the same general chemical family as the nerve cell transmitters norepinephrine and serotonin, Snyder says. Therefore, it is chemically more similar to Valium-like drugs than morphine is to enkephalins.

Although tests of the biological effects of gamma-compound are not now complete, Braestrup expects the chemical to lead to improved drugs. In addition to binding more strongly to receptors, gamma-compound appears to favor

groups of benzodiazepine receptors in some parts of the brain over receptors in other parts. Valium and the other benzodiazepines have had a frustrating constellation of actions. They are sedatives, hypnotics and anti-convulsives, as well as anti-anxiety agents. Because gamma-compound seems to differentiate benzodiazepine receptors, Braestrup argues that it may have a more selective pharmacological effect. "That is, the compound might interfere specifically with anxiety without having sedative properties, or the compound might be a selective

anti-convulsant," Braestrup says. Such a selective action would greatly add to the potential value of a drug.

Braestrup suggests that as an analogy to enkephalins, the newly discovered gamma-compound could serve as the chemical transmitter that links nerve cells in a brain pathway. There might be a natural anxiety-relieving, or for that matter an anxiety-generating, pathway in the nervous system. A rapidly increasing number of chemicals are being suspected as signals that carry specific types of messages in the complex business of the brain. □

Dopamine and age: Turning back the clock

Even in the healthiest of people, advanced age usually brings a slowing of bodily movements and reflexes and a decline in stamina. This "normal" aging process contrasts with the occurrence of Parkinson's disease, in which motor problems result from a loss of brain cells containing the chemical transmitter dopamine. Now, research results indicate that dopamine depletion may be responsible for both normal and disease-related motor problems among the elderly; and dopamine-stimulating drugs similar to those used to treat Parkinson's disease could conceivably help the mobility of senior citizens who do not have Parkinson's.

The experiments compared aged rats (24 to 27 months old) with young adult rats (3 to 4 months old). Animals from each group were tested for their ability to swim, "which requires the coordinated movement of the limbs and trunk [and] is a common measure of the motor ability of rodents," researchers John F. Marshall and Norberto Berrios explain in the Oct. 26 SCIENCE. The young rats swam vigorously, keeping their bodies nearly horizontal and their heads above the water. The aged rats swam well initially but soon lapsed into a vertical posture and struggled to keep their heads above water as they repeatedly sank.

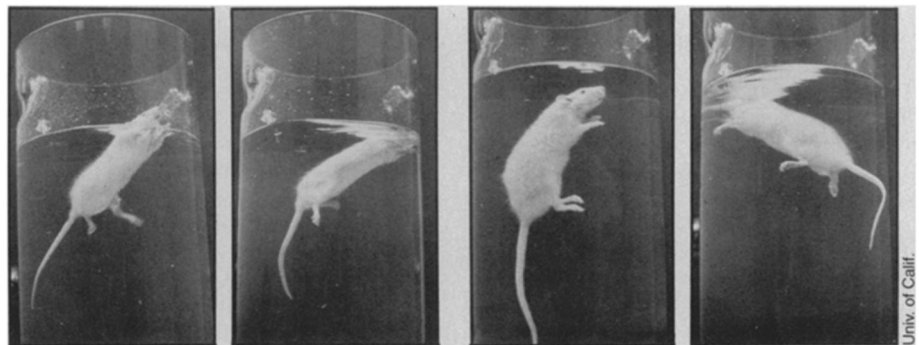
The researchers noted that the poor performance of the elderly rats closely resembled the impaired swimming of young adult rats whose dopamine-containing neurons had been damaged in previous

experiments. Marshall and Berrios then administered the drug apomorphine, a dopamine receptor stimulant, to the older rats. The results bore out their suspicions.

"The performance of aged rats given apomorphine was dramatically restored," they report. "Even the lowest dose induced senescent rats to swim more vigorously and successfully than ... young adults." The researchers then obtained similar results using L-dopa, another dopamine stimulant used in treating Parkinson's patients.

"These experiments demonstrate for what we believe to be the first time that aged rats suffer from severe disturbances of movement," say the scientists. "The dramatic rejuvenation of performance by compounds that enhance the activity of brain dopamine receptors holds potential significance for understanding the movement disturbances of aging ... the results suggest a central nervous system origin of this deficit. In particular, the poor performance of the aged animal seems linked to the age-related changes in neurotransmission at the brain dopaminergic synapses [connective gaps between cells]."

The finding that the post-drug swimming of the aged rats was "remarkably similar" to that of much younger rats "indicates that the central programs for these movements are intact in aged rats," the researchers say. "The findings offer the opportunity to illuminate the neurological basis for some movement disorders of elderly humans." □



Aged rat (second from right) struggles to swim; after apomorphine treatment (far right), the same rat swims vigorously and horizontally like younger rats (two at left).