alone (*16*). The fish were killed 48 or 72 hours later, and the brains were removed and fixed in 2.5 percent glutaraldehyde in Karlsson and Schultz's phosphate buffer (*17*) (36 hours at 4°C). The injected tectum was bisected sagittally, with one-half processed for light microscopy and one-half for electron microscopy. For light microscopy, serial sagittal sections (10 μm) were stained by a modification (*7*) of the silver impregnation method of Holmes (*18*). Neurofibrillary rings, approximately 1 μm in diameter, that appeared to be identical to those occurring in fish kept at 5°C for prolonged periods were observed in the fish receiving leupeptin but not in the controls (Fig. 1). Moreover, electron microscopy revealed neurofilaments in the synaptic terminals of the leupeptin-treated fish but not of the control fish (Fig. 2). Thus, the injection of leupeptin into the optic tectum does result in the accumulation of neurofilaments. These observations not only support the hypothesis that the rings appearing in fish after long periods at 5°C are the result of the inhibition of a protease, but provide evidence in vivo in support of the Lasek-Hoffman hypothesis. Neurotubules were also observed in the terminals of leupeptin-treated fish. They occur also in some terminals of fish exposed to 5°C for long periods. There is evidence from studies in vitro that under some conditions the calcium-activated protease found in the peripheral nerve of rats may degrade microtubule as well as neurofilament protein (*14*). Hence the disaggregation of microtubules in axon terminals may be brought about by both a higher calcium ion concentration, as postulated by Lasek and Hoffman (*2*), and the action of a calcium-activated protease as indicated by the present experiments.

The regulation of neurofilament degradation has many implications for neuropathology (*19*). Studies in which leupeptin is used in vivo may help to answer questions about how accumulations of neurofilaments affect axoplasmic transport and synaptic transmission. The loss of plasticity in the nervous system during development and aging has been related to changes in cytoskeletal elements (*20*); the use of leupeptin in vivo and in tissue culture should facilitate the elucidation of the regulatory mechanisms involved. Regeneration, another expression of neural plasticity, could be studied by observing the effects of leupeptin on the reestablishment of optic axon connections in the optic tectum during regeneration of the optic nerve of goldfish. Thus, the demonstration that leupeptin inhibits endogeneous calcium-activated proteases in vivo provides a pharmacological tool that may be used to answer questions on the control of the growth of axons in normal and pathological conditions and on the plasticity of the nervous system (*21*).

BETTY I. ROOTS
Department of Zoology and *Erindale College, University of Toronto, Mississauga, Ontario, Canada L5L 1C6*

References and Notes

1. P. A. Weiss and H. B. Hiscoe, *J. Exp. Zool.* **107**, 315 (1948); B. Droz and C. P. Leblond, *J. Comp. Neurol.* **121**, 325 (1963); R. J. Lasek, *Int. Rev. Neurobiol.* **13**, 289 (1970); P. N. Hoffman and R. J. Lasek, *J. Cell Biol.* **66**, 351 (1975).
2. R. J. Lasek and P. N. Hoffman, in *Cell Motility*, R. Goldman, T. Pollard, J. Rosenbaum, Eds. (Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1976), p. 1021.
3. E. J. Gray and R. W. Guillery, *J. Physiol. (London)* **157**, 581 (1961).
4. Evidence for the equivalence of neurofibrillary (argyrophilic) rings and annuli of neurofilaments was presented by E. G. Gray and R. W. Guillery (*3*) and in the papers listed in (*5*). The observation that Bodian's silver method is specific for neurofilament proteins [P. Gambetti, L. Autilio-Gambetti, S. Ch. Papasozomenos, *Science* **213**, 1521 (1981)] and the electron microscopic examination of identified silver stained rings (R. L. Bondar and B. I. Roots, in preparation) establishes the equivalence beyond doubt.
5. M. Colonnier and R. W. Guillery, *Z. Zellforsch. Mikrosk. Anat.* **62**, 333 (1964).
6. B. B. Boycott, E. G. Gray, R. W. Guillery, *Proc. R. Soc. London Ser. B* **154**, 151 (1961); H. D. Potter, *J. Neurocytol.* **2**, 29 (1973); ——— and G. S. Hafner, *J. Comp. Neurol.* **155**, 409 (1975).
7. R. L. Bondar and B. I. Roots, *Exp. Brain Res.* **30**, 577 (1977).
8. B. I. Roots and R. L. Bondar, *J. Neuropathol. Exp. Neurol.* **36**, 453 (1977).
9. D. S. Gilbert, B. J. Newby, B. H. Anderton, *Nature (London)* **256**, 586 (1975).
10. B. Katz and R. Miledi, *J. Physiol. (London)* **207**, 789 (1970); R. Llinás, J. R. Blinks, C. Nicholson, *Science* **176**, 1127 (1972).
11. P. R. Baker, A. L. Hodgkin, E. B. Ridgway, *J. Physiol. (London)* **218**, 709 (1971); A. L. Hodgkin and R. D. Keynes, *ibid.* **138**, 253 (1957).
12. R. J. Lasek and M. M. Black [in *Mechanisms, Regulation, and Special Functions of Protein Synthesis in the Brain*, S. Roberts, A. Lajtha, W. H. Gispen, Eds. (Elsevier, Amsterdam, 1977), p. 161] showed that cytoskeletal proteins are not degraded in transit as suggested by Weiss and Hiscoe (*1*) and must therefore be disassembled when they reach the terminals.
13. W. W. Schlaepfer and M. B. Hasler, *Brain Res.* **168**, 299 (1979); M. N. Malik *et al.*, *Life Sci.* **29**, 795 (1981).
14. K. Kamakura, S. Ishiura, H. Sugita, Y. Toyokura, *J. Neurochem.* **40**, 908 (1983).
15. J. Z. Young, *Pubbl. Stn. Zool. Napoli* **12**, 425 (1933).
16. Forty-two experimental and six control fish were used. Two of the experimental fish died.
17. U. Karlsson and R. L. Schultz, *J. Ultrastruct. Res.* **12**, 160 (1965).
18. W. Holmes, *Anat. Rec.* **86**, 157 (1943).
19. W. S. Schlaepfer, *Progress in Neuropathology*, H. M. Zimmerman Ed. (Raven, New York, 1979), vol. 4, p. 101.
20. R. J. Lasek and J. R. Morris, in *Biological Functions of Microtubules and Related Structures*, H. Sakai and H. Mohri, Eds. (Academic Press, New York, 1982), p. 329.
21. This work was reported at the meeting of the American Society for Neurochemistry in March 1983 [B. I. Roots, *Trans. Am. Soc. Neurochem.* **14**, 216 (1983)].
22. I thank K. Gaebel and R. C. Cameron for technical assistance, and the United States–Japan Cooperative Cancer Research Program for providing the leupeptin used in the preliminary experiments. Supported by grant A-6052 from the National Science and Engineering Research Council of Canada.

3 May 1983

Regional Brain Concentrations of Neuropeptides in Huntington's Chorea and Schizophrenia

Abstract. *To ascertain whether Huntington's chorea and schizophrenia are associated with specific regional alterations in neurotensin, somatostatin, and thyrotropin-releasing hormone, the concentrations of these putative neurotransmitters were measured by radioimmunoassay in postmortem brain samples from patients with Huntington's chorea or schizophrenia. Compared to 50 patients without psychiatric or neurological disease, the patients with Huntington's chorea showed significantly elevated concentrations of all three neuropeptides in the nucleus caudatus. In the nucleus accumbens somatostatin levels were increased threefold, while in the amygdala thyrotropin-releasing hormone levels were elevated. In contrast, the schizophrenics exhibited reduced levels of thyrotropin-releasing hormone in two frontal cortical regions, reduced somatostatin levels in one frontal cortical area, and increased neurotensin levels in one frontal cortical area. None of the differences between the diseased brains and the controls could be accounted for by differences in age, sex, or time between death and autopsy.*

Anticipating that the etiology of Huntington's chorea and schizophrenia might be elucidated, as was Parkinson's disease (*1*), by detailed biochemical analysis of postmortem brain samples, researchers have sought for biochemical abnormalities in the brains of patients with these disorders. Abnormal concentrations of some neurotransmitters have been observed, but the pathophysiological significance of this is not known. Huntington's chorea is inherited as an autosomal dominant trait (*2*) and is characterized by major motor abnormalities (hypertonicity and chorea) and by mental disturbances (dementia and affective disorder). Neuropathological and radiological observations indicate significant neuronal loss in the caudate nucleus (*2*). Schizophrenia, a major behavioral disorder that affects approximately 0.6 percent of the population (*3*), may be associated with neuropathological alterations of the limbic forebrain. Its active phase

is characterized by hallucinations, delusions, and disturbances in thought.

Recent anatomical studies (*4, 5*) have revealed the presence of large quantities of neurotensin (NT), somatostatin (SS), and thyrotropin-releasing hormone (TRH) in the striatum and limbic forebrain, and physiological studies suggest a neurotransmitter or neuromodulatory role for these three central nervous system peptides in the control of movement and behavior (*6*). Interaction of these peptides with brain monoamine systems has been reported (*6*). We therefore attempted to determine whether there are specific regional excesses or deficiencies of any of these peptides in the brains of patients with Huntington's chorea or schizophrenia.

Human postmortem brain samples that had been dissected, rapidly frozen, and stored at the Medical Research Council Brain Bank in Cambridge, England (*7*), were provided to us by M. N. Rossor and L. L. Iversen. Psychiatric and neurological diagnoses were determined after chart review by two independent attending physicians. Samples were obtained from 50 control subjects without neurological or psychiatric disease, 46 schizophrenics, and 24 Huntington's chorea patients. The mean age and age range of the three populations did not differ significantly from each other: controls, 71 years and 27 to 103 years; schizophrenics, 58 years and 20 to 86 years; and Huntington's chorea patients, 54 years and 26 to 78 years. The sex distributions of the groups were also not significantly different from each other: controls, 66 percent male and 34 percent female; schizophrenics, 59 percent male and 41 percent female; and Huntington's chorea patients, 54 percent male and 46 percent female. Data were obtained on the time between death and freezing of brain samples, duration of illness, and cause of death.

Samples of amygdala, nucleus accumbens, and caudate nucleus were available from patients in all three groups. Cerebral cortical regions [Brodmann's areas (BA) 12, 24, and 32] and hypothalamus were available only in normal subjects and schizophrenics. The frozen brain samples were weighed, thawed, and homogenized in 20 volumes (weight to volume) of 1*N* HCl, and a portion of the homogenate was taken for protein determination with the Folin reagent (*8*). The samples were centrifuged at 12,000*g* for 30 minutes and the supernatant was lyophilized. The lyophilized samples were reconstituted in radioimmunoassay buffer and assayed for NT by the method of Manberg *et al.* (*5*), TRH by our modification (*9*) of the method of Bassiri and Utiger (*10*), and SS by our modification (*9*) of the method of Arimura *et al.* (*11*). The sensitivity of the assays was 10 pg per tube for NT, 1 pg per tube for SS, and 5 pg per tube for TRH. All samples were coded and analyzed by members of the research team without knowledge of the diagnostic identity of the tissue samples. Peptide concentrations for the groups were compared by analysis of variance, and covariate analysis was

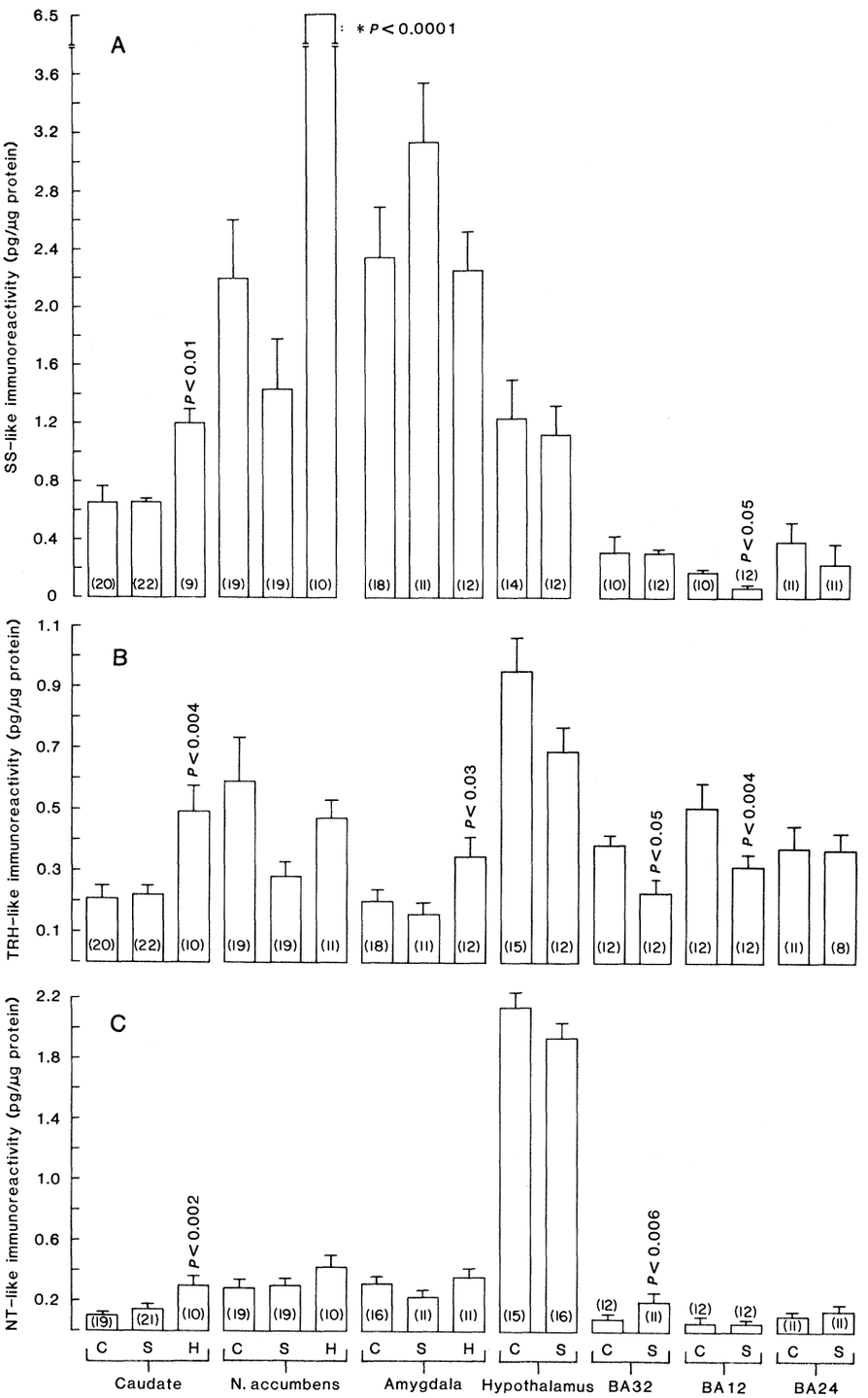

Fig. 1. Regional brain concentrations of (A) SS-like, (B) TRH-like, and (C) NT-like immunoreactivity in normal controls (*C*), schizophrenics (*S*), and Huntington's chorea patients (*H*). Values are means ± standard errors; numbers in parentheses refer to the number of samples per group. Huntington's chorea patients had significantly higher concentrations of SS, TRH, and NT in the caudate nucleus, SS in nucleus accumbens, and TRH in the amygdala. The schizophrenics had significantly lower concentrations of SS and TRH in one frontal cortical region (BA12) and reduced levels of TRH in another frontal cortical region (BA32) as well. In the latter region the concentration of NT was elevated. *P* values were derived from analysis of variance.

used to evaluate the possible effects of age, sex, and time from death to freezing of tissue on peptide concentrations.

In control subjects the distribution of the three neuropeptides was similar to that reported previously (Fig. 1) (*4, 5, 12*). In the Huntington's chorea group the concentrations of all three peptides were significantly increased in the caudate nucleus, confirming previous findings (*13*). The concentration of SS but not TRH or NT was markedly increased in the nucleus accumbens of the Huntington's chorea patients (Fig. 1A), who also showed increased TRH in the amygdala (Fig. 1B).

In schizophrenics no alterations in the three peptides were observed in any of the subcortical brain regions studied. However, the concentration of SS was significantly reduced in BA12 (Fig. 1A). Similarly, the concentration of TRH was reduced in BA12 and BA32 (Fig. 1B). Finally, the concentration of NT was significantly elevated in BA32 (Fig. 1C).

Covariate analysis did not show any significant between-group differences with respect to age, sex, or time from death to autopsy.

Postmortem studies of brains from Huntington's chorea patients have shown a variety of neurochemical changes (*2*). These include decreased activity of glutamic acid decarboxylase, choline acetyltransferase, cysteic acid decarboxylase, and cysteinsulfinic acid decarboxylase and decreases in the concentration of γ-aminobutyric acid (GABA). Furthermore, in Huntington's chorea there appear to be reduced numbers of brain membrane receptors for cholecystokinin (CCK), quinuclidinyl benzilate, benzodiazepine, haloperidol, dopamine, GABA, and kainic acid.

Our results confirm the findings of two previous studies (*13*) in which increased concentrations of TRH and SS were observed in the caudate nucleus of patients with Huntington's chorea. The concentrations of NT and of other neurotransmitters and related enzymes, including dopamine, norepinephrine, γ-hydroxybutyric acid, and monoamine oxidase are also increased in the caudate nucleus of these patients (*14*). Histological and radiological studies, however, have repeatedly demonstrated loss of volume in the caudate nucleus in Huntington's disease patients (*2*), suggesting that the increased neuropeptide and neurotransmitter concentrations in this region result from sparing of the neuropil containing these substances. It is also possible, however, that an increase in the density of the nerve terminals containing these substances occurs in the caudate nucleus. The concentration of SS in the nucleus accumbens, an area reported to exhibit neuropathological changes in this disease (*15*), was three times higher than in controls, but there was no difference in the concentration of TRH or NT. These findings and those of studies (*16*) in which no alteration was observed in the levels of CCK octapeptide, Met-enkephalin, substance P, vasoactive intestinal peptide, or serotonin in this brain region imply a disease-specific process leading to an elevation of SS in the nucleus accumbens. Similarly, the concentration of TRH in the amygdala was significantly elevated while the concentrations of the other two neuropeptides were unchanged.

In the postmorten brain samples from schizophrenics an entirely different pattern of neuropeptide alteration was observed. There were no changes in the concentrations of SS, NT, or TRH in any of the subcortical brain regions. However, in BA12 the levels of SS and TRH but not NT were significantly reduced. Furthermore, in BA32 the concentration of TRH was reduced and that of NT increased. The concentrations of the three peptides were unaltered in an area of cingulate cortex (BA24). The relevance of these findings to those of other studies is uncertain. Gillin *et al.* (*17*) found no difference in the levels of immunoreactive NT between schizophrenics and normal controls, although they did not assay cortical areas as we did; Adrian *et al.* (*18*) reported increased NT in the lateral thalamus of schizophrenics relative to a normal patient population.

Previously documented neurochemical alterations in schizophrenia include increases in brain dopamine and reductions in the activity of glutamic acid decarboxylase and choline acetyltransferase (*19*). Increases in dopamine receptor binding have also been observed in the brain tissue of schizophrenics (*20*).

Although we do not know the pathophysiological significance of these alterations in SS, NT, and TRH in Huntington's chorea and schizophrenia, they do appear to be disease-associated. The patterns of alteration in the two disease states were dissimilar, and no between-group differences with respect to age, sex, or time from death to autopsy could be discerned by covariate analysis. Finally, the patient populations were sufficiently large to render the possibility of our observations being random occurrences extremely low.

Peptides are rapidly degraded by brain peptidases, and the delay in obtaining the tissue and freezing it might have resulted in peptide degradation. However, many peptides are remarkably stable in brain tissue for as long as 3 days after death when kept at a room temperature of 22°C (*21*). As to the effect of age on neuropeptide concentrations in brain tissue, Buck *et al.* (*22*) reported that substance P, NT, and SS are stable with aging, although they noted a significant age-related reduction in NT concentration in the substantia nigra but not in the frontal cortex, caudate, putamen, or globus palladus. There was no correlation between peptide concentration and patient age in our study.

CHARLES B. NEMEROFF*
Biological Sciences Research Center, Department of Psychiatry and *Neurobiology Program, University of North Carolina School of Medicine, Chapel Hill 27514*
WILLIAM W. YOUNGBLOOD
Biological Sciences Research Center, Department of Biochemistry and Nutrition and *Neurobiology Program, University of North Carolina*
PAUL J. MANBERG
Biological Sciences Research Center, University of North Carolina, and *Burroughs Wellcome Company, Research Triangle Park 27709*
ARTHUR J. PRANGE, JR.
Biological Sciences Research Center, Department of Psychiatry and *Neurobiology Program, University of North Carolina*
JOHN S. KIZER
Biological Sciences Research Center, Departments of Medicine and *Pharmacology* and *Neurobiology Program, University of North Carolina*

References and Notes

1. W. Birkmayer and P. Riederer, in *Transmitter Biochemistry of Human Brain Tissue*, P. Riederer and E. Usdin, Eds. (Macmillan, London, 1981), p. 271.
2. M. R. Hayden, *Huntington's Chorea* (Springer-Verlag, Berlin, 1981).
3. T. C. Manchreck, *N. Engl. J. Med.* **305**, 1628 (1981).
4. R. M. Kobayashi, M. R. Brown, W. Vale, *Brain Res.* **126**, 584 (1977); K. Kataoka, N. Mizuno, L. A. Frohman, *Brain Res. Bull.* **4**, 57 (1979); I. M. D. Jackson, *Front. Horm. Res.* **6**, 35 (1980).
5. P. J. Manberg, W. W. Youngblood, C. B. Nemeroff, M. N. Rossor, L. L. Iversen, A. J. Prange, Jr., *J. Neurochem.* **38**, 1777 (1982).
6. D. T. Kreiger and J. B. Martin, *N. Engl. J. Med.* **304**, 876 (1981); A. J. Prange, Jr., and C. B. Nemeroff, *Annu. Rep. Med. Chem.* **17**, 31 (1982); S. H. Snyder, *Science* **209**, 976 (1980).
7. E. G. S. Spokes, *Brain* **102**, 333 (1979).
8. O. H. Lowry, N. J. Rosebrough, A. L. Farr, P. J. Randall, *J. Biol. Chem.* **193**, 265 (1951).
9. J. S. Kizer, M. Palkovits, M. J. Brownstein, *Endocrinology* **98**, 311 (1976).
10. R. Bassiri and R. D. Utiger, *ibid.* **90**, 722 (1971).
11. A. Arimura, H. Sato, D. H. Coy, A. V. Schally, *Proc. Soc. Exp. Biol. Med.* **148**, 784 (1975).
12. P. E. Cooper, M. H. Fernstrom, O. P. Rorstad, S. E. Leeman, J. B. Martin, *Brain Res.* **218**, 219 (1981).
13. E. R. Spindel, D. J. Pettibone, R. J. Wurtman, *N. Engl. J. Med.* **303**, 1235 (1980); P. E. Cooper, N. Aronin, E. L. Bird, S. E. Leeman, J. B. Martin, *Neurology* **31**, 64 (1981).
14. E. G. S. Spokes, *Brain* **103**, 179 (1980); R. H. Roth, N. Ando, J. R. Simon, E. D. Bird, B. I.

Gold, *Adv. Neurol.* **23**, 557 (1979); J. J. Mann, M. Stanley, S. Gershon, M. Rossor, *Science* **210**, 1369 (1980).
15. G. T. A. M. Bots and G. W. Bruyn, *Acta Neuropathol.* **55**, 2122 (1981).
16. E. D. Bird and L. J. Kraus, in *Transmitter Biochemistry of Human Brain Tissue*, P. Riederer and E. Usdin, Eds. (Macmillan, London, 1981), p. 201; P. C. Emson *et al.*, *ibid.*, p. 221; H. Bernheimer and O. Hornykiewicz, in *Huntington's Chorea 1872–1972*, A. Barbeau, T. N. Chase, G. W. Paulson, Eds. (Raven, New York, 1973), p. 525; J.-Y. Wu, E. D. Bird, M. S. Chen, W. M. Huang, *Adv. Neurol.* **23**, 527 (1979); E. G. S. Spokes, N. J. Garrett, M. N. Rossor, L. L. Iversen, *J. Neurol. Sci.* **48**, 303 (1980).
17. J. C. Gillin *et al.*, paper presented at the Annual Meeting of the American Psychiatric Association, New Orleans (1981).
18. T. E. Adrian *et al.*, paper presented at the 13th International Congress of Neuropsychopharmacology, Jerusalem (1982).
19. E. D. Bird *et al.*, *Lancet* **1977-II**, 1157 (1977).
20. T. J. Crow *et al.*, in *Transmitter Biochemistry of Human Brain Tissue*, P. Riederer and E. Usdin, Eds. (Macmillan, London, 1981), p. 85.
21. C. M. Lee, P. C. Emson, L. L. Iversen, *Brain Res.* **220**, 159 (1981).
22. S. H. Buck, P. P. Deshmukh, T. F. Burks, H. I. Yamamura, *Neurobiol. Aging* **2**, 257 (1981).
23. We thank D. Quade for aid in statistical analysis and D. Yarbrough for preparing the manuscript. Supported by grants MH-32316, MH-34121, MH-33127, and MH-22536 from the National Institute of Mental Health and by grant HD-03110 from the National Institute of Child Health and Human Development.
* To whom correspondence should be addressed.

23 March 1983

Opiate Antagonists Improve Spatial Memory

Abstract. *Rats trained on an eight-arm radial maze were challenged by placing the maze in new spatial environments. Administration of opiate antagonists, either naloxone or diprenorphine, after exposure to the new environments significantly improved subsequent performance. The effect of naloxone on spatial memory was attenuated when drug administration occurred 2 hours after maze exposure.*

Russell and Nathan's clinical description of retrograde amnesia in humans (*1*) was soon followed by reports that treatment after training could impair later retention of a recently learned response in laboratory animals. The effects of treatments such as electroconvulsive shock and protein synthesis inhibition in laboratory animals depend on time—the sooner the agent is administered after training, the greater the amnesic effect (*2*). In the past few years, many studies have reported that opiates and opioid peptides alter time-dependent memory processes in laboratory animals (*3*). In general, administering opiates and opioid peptides at low doses produces amnesia for events before treatment, and this effect can be blocked by concurrent administration of the opiate antagonist naloxone (*4*). The complementary finding is that administering an opiate antagonist (for example, naloxone) by itself enhances retention (*5*).

Almost all the studies that have examined the effects of opiates on memory have used aversive training procedures. Since opioid peptide systems seem to be activated by noxious stimuli (*6*), it has been proposed that perhaps only those memories involving painful or fear-producing events will be influenced by opioids and their antagonists (*7*). We now report, however, that administering opiate antagonists enhances memory of a nonaversive spatial learning task.

Rats can be readily trained to visit each arm of an elevated eight-arm radial maze only once during a session when a food pellet is placed at the end of each arm (*8*). Accurate performance of this task normally depends on information provided by spatial cues in the environment outside the maze (*9*). We studied possible enhancing effects of posttraining opiate antagonist administration on spatial memory using a procedure in which the performance of normal animals on the eight-arm maze was less than optimal. A 6-hour delay was inserted between the fourth and fifth choices; animals were then challenged by placing the maze in new spatial environments. The effects of experimental treatments on the development of criterion performance were assessed.

Male Sprague-Dawley rats (Charles River Laboratories) (*10*) were originally trained on the eight-arm maze until they reached criterion performance by visiting each arm with no more than two errors (that is, an entry into an already-visited arm) on three consecutive days. Subsequently, increasing delays (1 minute, 30 minutes, 6 hours) were introduced between the fourth and fifth choices, and the animals were trained to criterion at each delay. After completing this training, animals were tested on the same maze placed in two novel environments. The two new rooms were comparable in size to the original room used for training; a number of prominent cues outside the maze (lighting fixtures, objects on the walls and floor) differed from room to room. In one of the novel environments, an opiate antagonist was administered; in the other, the same animals were injected with physiological saline. In order to ensure that the results would reflect neither specific differences in the two rooms nor order effects, treatments were counterbalanced. Animals were trained to criterion under the 6-hour delay in each of the novel environments. All injections were administered intraperitoneally immediately after the first four correct choices at the beginning of the delay period on each day of testing until the criterion was reached. Two separate experiments were done: the opiate antagonist used in experiment 1 was naloxone (2 mg/kg), and that in experiment 2 was diprenorphine (1 mg/kg).

The mean trials to criterion and errors to criterion for each opiate antagonist treatment group, summed over both novel environments, are presented in Table 1 (*11*). In both experiments, administering an opiate antagonist led to acquisition in significantly fewer trials and with fewer errors than were required with saline treatment (*12*). In fact, every animal in experiment 1 required fewer trials to reach criterion with naloxone than with saline.

The spatial nature of the memory in this task was evaluated for both experiments. When the maze was rotated (*13*), accurate performance was based on information provided by spatial cues in the room surrounding the test apparatus. This result indicates that new spatial information was acquired during exposure to each novel environment.

Another experiment was conducted to assess further the reliability of the naloxone effect on spatial memory and to evaluate whether this effect is time-dependent. Ten rats were initially trained

Table 1. Effects of opiate antagonist administration on maze performance (*11*). Values are means ± standard errors.

Treatment	Trials to criterion	Errors to criterion
Experiment 1 (N = *8*)		
Saline	5.38 ± 0.71	12.0 ± 2.89
Naloxone	3.25 ± 0.63*	4.4 ± 2.74*
Experiment 2 (N = *10*)		
Saline	4.90 ± 0.70	12.2 ± 3.03
Diprenorphine	3.60 ± 0.49*	5.8 ± 2.89*

*Significantly different from saline treatment ($P < 0.005$) (*12*).

Table 2. Time-dependent effects of administration on maze performance. Values are means ± standard errors.

Treatment	Trials to criterion	Errors to criterion
Control		
No treatment	4.7 ± 0.64	11.2 ± 3.12
Saline	4.8 ± 0.75	10.6 ± 3.29
Naloxone		
No delay	3.5 ± 0.67*	3.7 ± 1.27*
2-hour delay	4.0 ± 0.89	7.0 ± 2.93

*Significantly different from control treatments ($P < 0.001$) (*14*).