

Recurrent Intraplate Tectonism in the New Madrid Seismic Zone

M. D. Zoback, R. M. Hamilton, A. J. Crone D. P. Russ, F. A. McKeown, S. R. Brockman

In 1811 and 1812, three great earthquakes struck the central Mississippi River valley and virtually destroyed the town of New Madrid, Missouri (1, 2). Major earthquakes are known to have occurred in the New Madrid region earlier (3), and this is currently the most seismically active area of the central and eastern United States (4). Identification of the tectonic processes responsible for this seismicity is crucial for realistically evaluating seismic risk and for estimating ground-motion values for the safe design of critical facilities. Moreover, characterization of the tectonic processes that make this intraplate area unique is important for the evaluation of seismic hazards throughout the central and eastern United States. Understanding the geologic framework of the region and identifying the faults and structures directly related to the seismicity have proved difficult because unconsolidated sediments cover the most seismically active area. In this article, we describe new information on subsurface structure gained through an extensive program of seismic reflection profiling. These data provide the basis for new insight into the tectonic framework of the New Madrid region.

Geologic Setting

The New Madrid region, located in the northern part of the Mississippi embayment, is a broad, southwesterly plunging syncline of unconsolidated Upper Cretaceous and Cenozoic sediments that unconformably overlie deformed Paleozoic rocks (Fig. 1). The major tectonic element of the region is thought to be a northeasterly trending rift of Precambrian age that was reactivated in Mesozoic time (5). Magnetic and gravity data provide strong evidence for the presence of a rift (6). These data also suggest the presence of several plutons along both the flanks and the axis of the rift, an interpretation that is consistent with the identification of cuttings of igneous rocks in well samples (7). These cuttings have been dated by the potas(iii) a relatively short, northeasterly trending zone that passes west of New Madrid. Two of the 1811–1812 earthquakes may have occurred in the latter zone along the rift axis (2).

Researchers previously attributed earthquakes in the New Madrid region to faults associated with the rift (6), to elastic stress concentrations associated with the mafic or ultramafic plutons (12), to faults projected southwesterly beneath the embayment from the "New Madrid fault system" of Kentucky and Illinois (13, 14), and to relief of stress concentrated at the intersection of the downwarped Mississippi embayment and the buried Pascola arch (15).

Seismic Reflection Profiles

About 280 km of multichannel (common-depth-point) seismic reflection profiles were run throughout the active seismic area (Fig. 2). In order to resolve small offsets in the post-Paleozoic section, one type of profile, designated S, was designed to enhance shallower reflections; another type, designated D,

Summary. For the first time, New Madrid seismicity can be linked to specific structural features that have been reactivated through geologic time. Extensive seismic reflection profiling reveals major faults coincident with the main earthquake trends in the area and with structural deformation apparently caused by repeated episodes of igneous activity.

sium-argon method as late Paleozoic (Late Mississippian and Permian) and Late Cretaceous (8). Field mapping suggests that some Tertiary intrusive activity may be associated with the Newport pluton (9) southwest of the seismic zone (Fig. 1). The igneous rocks in the upper Mississippi embayment region are predominantly alkalic (10), indicative of a deep-seated origin (8).

Earthquakes in the region (11) are concentrated along three principal zones: (i) a 100-kilometer linear zone extending from Marked Tree, Arkansas, to Caruthersville, Missouri, approximately along the center of the rift structure; (ii) a zone of relatively more intense activity extending from near Ridgely, Tennessee, northward to west of New Madrid; and was shot to enhance resolution of reflectors below the Paleozoic surface (16). No significant reflectors could be seen below the Late Cretaceous-Paleozoic contact on the S lines. Lines denoted by the prefixes T and R were shot as an initial phase of the embayment reflection program (17).

To establish a correlation between the geologic units and reflectors, a synthetic seismogram was constructed from sonic-velocity and density logs of a research well drilled into Paleozoic rocks near line S-10 (Fig. 2). Correlation between the

M. D. Zoback and R. M. Hamilton are at the U.S. Geological Survey (USGS) National Center, Reston, Virginia 22092. A. J. Crone, D. P. Russ, F. A. McKeown, and S. R. Brockman are at the USGS Federal Center, Denver, Colorado 80225.



Fig. 1. Map of the northern Mississippi embayment region showing earthquake epicenters (open circles) (31); plutons (hachured areas) and rift boundaries (heavy solid lines) (6); and faults (fine solid lines) (14).



Fig. 2. Enlargement of part of Fig. 1 showing earthquake epicenters (dots) (31), the locations of the seismic reflection profiles, and principal faults inferred from the data.

synthetic and real data is excellent (18). Stratigraphic information from other wells in the area was also used for correlation.

From the profiles, three stratigraphic contacts were consistently identified. The contact of Upper Cretaceous and Tertiary sediments is an excellent, continuous reflector. The contact of the Upper Cretaceous sediments and Paleozoic rocks is usually an excellent, continuous reflector, although in some areas it is discontinuous. Within the Tertiary section, the Eocene-Paleocene contact at the top of the Porters Creek Clay is a good but somewhat discontinuous reflector. Within the Eocene section, good reflectors persist locally but cannot be correlated regionally. The three contacts are all unconformities of generally low relief in the study area (19).

The profiles show numerous vertical offsets and abrupt flexures as well as discontinuities and diffractions that are interpreted to be associated with faults (20).

Faults

The resolution of the reflectors is sufficiently precise to identify faults with vertical offsets as small as 5 meters (21). The locations of faults that can be correlated between profiles are shown in Fig. 2; numerous uncorrelatable faults with small vertical offsets are not shown.

The fault with the largest component of vertical Cenozoic offset is seen on profile S-6 (feature C in Fig. 3). The Upper Cretaceous-Paleozoic and Tertiary-Upper Cretaceous reflectors are offset by about 80 m. Since the offset appears to continue essentially undiminished into the middle Eocene section, the faulting is mostly middle Eocene or younger. This feature is apparently a high-angle reverse fault.

An offset with displacement similar to that on line S-6 is seen on line S-4 (feature C in Fig. 3). The similar nature of these two offsets (the amount and sense of displacement) and their uniqueness (no other offsets of similar size were found) strongly suggest that they are the same structure, striking N40°E. This feature has been designated the Cottonwood Grove fault since it lies under the community of that name. Vertical displacement on the fault diminishes to the northeast but is discernible on line S-5 (feature C in Fig. 3). To the southwest, the Cottonwood Grove fault is not seen on lines S-13 and S-8.

Altogether, the Cottonwood Grove fault and other subparallel faults on lines

S-4, S-5, and S-6 define a northeasttrending fault system that is generally coincident with the axis of the larger rift (Fig. 2) (22). As inferred from the profiles, movement on the faults shown in Fig. 3 is predominantly post-middle Eocene in age. Significantly, the Cottonwood Grove and Ridgely faults (Fig. 2) lie beneath a northeast-trending topographic feature known as Ridgely Ridge (23), suggesting recent movement of these faults.

Evidence of a major, deep-seated structural discontinuity interpreted as a fault zone is seen on lines D-1 and D-3. The feature coincides with the northeaststriking, Marked Tree-Caruthersville seismic zone and is defined by an abrupt discontinuity in Paleozoic structure. Reflectors below the Paleozoic surface west of the fault zone on line D-l have a westerly component dip, whereas those east of the zone appear to be nearly horizontal.

Figure 4 shows a part of profile D-1 and an interpretative cross section. Line D-3 shows northerly dipping reflectors that correlate with those west of the fault zone on line D-1. Together, this information defines a N45°E strike and $\sim 12^\circ$ northwest dip for the reflectors northwest of the zone. The strike of the fault zone, as indicated by the termination of these reflectors on lines D-1 and D-3, is

about N45°E. Minor faulting seen in the Paleozoic section on line S-7 may represent the northeastward continuation of this fault zone. The gap in seismicity in the vicinity of line S-7 suggests that the offset along this fault is greatly diminished by this point, but our lack of deepresolution coverage in this area makes this interpretation uncertain.

The rocks underlying the Upper Cretaceous sediments in the region of lines D-l and D-3 are probably of Cambrian-Ordovician age (7, 24). Since the maximum thickness of these rocks is about 4 km (24, 25), reflections from the lower part of D-1 and D-3 may be from Precambrian rocks. If the strongest reflectors on each side of the fault zone (about 2.0 seconds) are from correlative strata, an apparent stratigraphic separation of about 1 km is indicated, with the northwest side up.

It is clear that the major vertical displacement on the fault zone predates Late Cretaceous deposition. Nevertheless, Late Cretaceous and younger strata across the fault zone are disrupted by numerous small faults, with about 50 m of apparent cumulative displacement from west to east. Thus deformation has occurred in Cenozoic time.

Fault-plane solutions for earthquakes in the Marked Tree-Caruthersville zone indicate predominantly right lateral strike-slip movement along a northeaststriking nodal plane, with a component of dip-slip movement (26). The sense of the dip-slip component is consistent with that indicated by the seismic reflection profiles. If the current seismicity is indicative of post-Cretaceous deformation, the predominant strike-slip component in the fault-plane solutions may explain why little vertical separation is observed in the younger strata.

In the area west of New Madrid, the largest apparent offset of reflectors is on line S-2. The vertical displacement is about 35 m on the Tertiary-Upper Cretaceous and Upper Cretaceous-Paleozoic reflectors, with the southeast side down. The Eocene-Paleocene reflector is not discernibly offset. Thus the age of the vertical displacement is Paleocene. The point at which this fault is crossed is essentially coincident with a northeaststriking zone of seismicity (Fig. 2). A similar east-side-down displacement is seen where line S-1 crosses the zone. Farther to the northeast along the same zone of seismicity, another offset with the east side down is seen on line S-11. It appears, therefore, that a fault with a dip-slip component of southeast side down is closely associated with the northeast-trending zone of seismicity. The projection of this zone farther northeast passes near Charleston, Missouri



Fig. 3. Part of profiles S-5, S-4, and S-6, and (bottom) an interpretative, oblique cross section of the fault system. The main features are A, northwest boundary fault; B, Cenozoic intrusion and overlying, arched reflectors; C, Cottonwood Grove fault; and D, possible intrusion. Geologic ages of rocks are indicated as Te, Eocene; Tpal, Paleocene; K, Cretaceous; and Pz, Paleozoic. Note that the depth scale is nonlinear. 29 AUGUST 1980

(Fig. 1), where one of the two largest earthquakes to strike the region since 1812 occurred in 1895 (27).

It is inferred that numerous other faults exist on the northern sections, but they cannot be correlated between lines. It is clear, though, that faulting is more abundant in the area north of Ridgely than to the southwest. Several faults in the Ridgely area show evidence of recurrent movement. Both the Reelfoot and Ridgely faults (Fig. 2) (17) have significantly less offset on the Tertiary-Upper Cretaceous reflector than on the Upper Cretaceous-Paleozoic reflector. Thus motion recurred in Cenozoic time on faults of Late Cretaceous age or older. Holocene surface displacement is reported on faults believed to be part of the Reelfoot fault (3).

Intrusives

The seismic reflection profiles provide evidence that intrusive masses were emplaced in the Ridgely area in pre-Late Cretaceous (possibly Late Cretaceous) and Cenozoic time and in the New Madrid area in pre-Late Cretaceous time. The intrusive activity is indicated on the profiles by arched reflectors that diminish in amplitude upward and by diffractions from below the Upper Cretaceous-Paleozoic contact. In Fig. 3, the features at points B, E, and directly east of C are interpreted to be the result of intrusive igneous activity. The possibility that the features could be an artifact of processing (for example, a statics effect) can be ruled out because the stratigraphic sections thin in the zone of arching.

Three sets of similarly arched reflectors are present at point B in Fig. 3. The character of the arching is the basis for correlating the reflectors as a continuous feature with a northeasterly trend. On line S-4, the Paleozoic reflector is tightly arched; deformation can be traced upward to the shallowest correlated reflectors. Such shallow arching can also be seen on line S-5. On line S-6, the arch is of approximately the same amplitude, but is broader; the Eocene-Paleocene contact is only slightly arched and shallower deformation cannot be seen. A strong reflection below the Paleozoic reflector on S-6 may indicate the top of the intrusive mass.

The features interpreted to be igneous bodies lie near the center of the rift that is inferred from magnetic data, and are approximately collinear with a pluton situated directly to the northeast (Fig. 2). They may have their origin in a deep dike system that fed laccoliths and sills in the upper Paleozoic section. The presence of tabular intrusive masses in the area is documented by well data (10). In addition, a gravity high suggests the presence of a dense body of subsurface rock that corresponds to the location of the inferred intrusive bodies (23). Further evidence for the intrusions is provided by a recent truck-mounted magnetometer survey that reveals magnetic anomalies over the inferred igneous masses (28).

Determination of the timing of the inferred intrusive activity hinges on the amount of thinning of the Upper Cretaceous section, on how high in the Tertiary section arching can be traced, and on possible effects produced by movement on nearby boundary faults. Our preferred interpretation is that in postmiddle Eocene time, magma intruded Paleozoic rocks to form laccoliths and sills. Thinning has reduced the Upper Cretaceous section by about one-third on line S-6 and by about one-half on S-4. Such thinning could be achieved by extension of the strata and compaction. If so, then the arching would be entirely post-Late Cretaceous. Some of the Cretaceous thinning, however, could have resulted from Late Cretaceous deformation or topographic relief on the Paleozoic surface. In any case, arching high in the Tertiary section shows that at least part of the deformation occurred in postmiddle Eocene time. It is clear from thin-



Fig. 4. Part of profile D-1 and a corresponding interpretative line drawing. Ages of units are as indicated in Fig. 3. Note that the depth scale is nonlinear.

ning of the beds immediately east of the Cottonwood Grove fault that the arching preceded the faulting.

Evidence for pre-Late Cretaceous igneous activity lies in the nature of the reflection from the Upper Cretaceous-Paleozoic contact and in the character of the reflections and diffractions from below that contact. Areas unaffected by such activity have an Upper Cretaceous-Paleozoic reflection characterized by a simple wavelet and good lateral continuity. Also, the level of incoherent energy below the Paleozoic surface is quite low. In contrast, reflections in the areas of inferred intrusives lack lateral continuity, have a "scalloped" appearance owing to diffractions, and have a high level of incoherent energy. These characteristics are interpreted as indicating fracturing and alteration caused by nearby intrusive activity (29). Evidence for such intrusive activity is found in the northern part of the study area, and is perhaps related to the intrusion of the plutons defined by gravity and magnetic data (Fig. 2). Profiles S-11 and S-12 show evidence for pre-Late Cretaceous intrusive activity along their whole length, whereas profiles to the south (S-7, S-8, and S-9) do not show it at all. The profiles shown in Fig. 3 (S-4, S-5, and S-6) indicate some areas of pre-Late Cretaceous intrusive activity (for example, under feature A on line S-4).

The timing of the pre-Late Cretaceous intrusive activity is not well constrained. In the areas where the Upper Cretaceous-Paleozoic reflector is extensively disturbed, the shallower reflectors show little evidence of disruption, indicating that the inferred intrusions predate Late Cretaceous sedimentation, thus fixing a minimum age. Since Paleozoic rocks in the area of the reflection profiles are Cambrian and Ordovician in age (7), and since the reflection data show that the intrusions postdate the Paleozoic rocks, a maximum age for this stage of igneous activity is established. A radiometric date on intrusive igneous rocks from a drill hole near Ridgely yielded a Permian age (8). The presence of diatremes, dikes, and other intrusives that would disrupt the Paleozoic rocks is well documented in the region (10, 14).

Tectonic Significance

The data show that the seismicity of the upper Mississippi embayment is spatially related to ancient tectonic structures. The profiles suggest recurrent tectonism in the earthquake zones, and indicate the presence of a major fault zone

of pre-Late Cretaceous age, faulting of post-middle Eocene age, and intrusive activity of Cenozoic, pre-Late Cretaceous, and perhaps Late Cretaceous age. By integrating these new findings with previously known information, a more complete interpretation of the history of tectonic deformation of the northern Mississippi embayment emerges.

Regional geophysical data suggest that the northern Mississippi embayment is underlain by a crustal rift (6). In early Paleozoic time, subsidence resulted in the accumulation of sedimentary rocks several kilometers thick. In the upper Mississippi embayment, post-Early Ordovician uplift began to form the Pascola arch (7); erosion removed much of the Paleozoic section, exposing Cambrian and Ordovician rocks. Well before Late Cretaceous downwarping of the northern embayment (possibly associated with subsidence of the arch in late Paleozoic time), intrusive activity occurred in the Ridgely and New Madrid areas. The deformation of Paleozoic and Precambrian rocks seen on lines D-1 and D-3 could have occurred either in association with formation of the Pascola arch or in late Paleozoic time. The southeasterly axial trend of the Pascola arch implies a southwestward dip for the reflectors on lines D-1 and D-3. However, since these reflectors have a northwestward dip, the deformation does not seem to be related to the formation of the arch. Additional intrusive activity occurred during Late Cretaceous time (8). Minor faulting took place in Late Cretaceous or early Paleocene time before the next marine invasion. After deposition of the middle Eocene sediments, a final stage of intrusive activity and the major post-Paleozoic faulting occurred, including movement on the Cottonwood Grove, Reelfoot, Ridgely, and numerous other faults. Movement on some of these faults occurred in the Holocene.

Characterization of seismogenic faults in intraplate areas such as the central and eastern United States is a formidable problem. This work has shown that the net offsets on such faults can be small relative to those along active continental margins and that little or no vertical offset may be discernible in the sediments overlying bedrock. There are a variety of reasons for this. These faults clearly do not accommodate large strains, and, as reactivated structures, the sense of movement on the faults has not necessarily been the same through geologic time. Moreover, the periodicity of reactivation can apparently be quite long, resulting in small cumulative offsets. Nevertheless, a picture is emerging that suggests that zones of intense seismicity in the central and eastern United States are associated with ancient rift zones (30)that are favorably oriented to the current stress field. In the New Madrid region, the rifting apparently occurred during the late Precambrian (5). In the seismically active areas along the Atlantic Coast, rifting occurred in Triassic and Jurassic time and was related to the opening of the Atlantic Ocean. The present mode of deformation on the old faults is greatly influenced by the orientation of the current stress field. The areas of greatest earthquake potential are likely to be where rift zone faults are favorably oriented for failure. Delineation of such features is critical for seismic risk assessment in intraplate regions.

References and Notes

- 1. M. L. Fuller, U.S. Geol. Surv. Bull. 494 (1912). 2. O. W. Nuttli, Bull. Seismol. Soc. Am. 63, 227
- (1973). (1975).
 D. P. Russ, Bull. Geol. Soc. Am. 90, 1013 (1979).
 J. B. Hadley and J. F. Devine, U.S. Geol. Surv.
- J. D. Hadley and J. T. Devine, C.S. Oct. Surv. Misc. Field Stud. Map MF-620 (1974).
 C. P. Ervin and L. D. McGinnis, Bull. Geol. Soc. Am. 86, 1287 (1975).
- 6. T. G. Hildenbrand et al., U.S. Geol. Surv. Misc. Field Stud. Map MF-914 (1977).
- 7. J. G. Grohskopf, Mo. Div. Geol. Surv. Water Resour. Rep. 37 (1955); H. C. Milhous, Tenn. Div. Geol. Bull. 62 (1959).
- R. E. Zartman, Annu. Rev. Earth Planet. Sci.
 8, 257 (1977); R. E. Zartman et al., Am. J.
 Sci. 265, 848 (1967).
- Sci. 265, 848 (1967).
 E. E. Glick, U.S. Geol. Surv. Adm. Rep. Natl. Earthquake Haz. Reduct. Program Summ. Tech. Rep. 8 (1979), p. 98.
 A. L. Kidwell, Mo. Geol. Surv. Water Resour. Rep. Invest. 4 (1947); Trans. 1st Meet. Gulf Coast Assoc. Geol. Soc. (New Orleans, 1950);
 H. D. Miser and C. S. Ross, Am. J. Sci. 209, 113 (1925); K. E. Clegg and J. C. Bradbury, Ill. Geol. Surv. Rep. Invest. 197 (1956).
 S. I. W. Stauder et al. Bull Seismol Soc. Am.
- Geol. Surv. Rep. Invest. 197 (1956).
 S. J. W. Stauder et al., Bull. Seismol. Soc. Am. 66, 1953 (1976).
 M. F. Kane, U.S. Geol. Surv. Prof. Pap. 1028 (1977), p. 199; D. L. Campbell, Geophys. Res. Lett. 5, 477 (1978); F. A. McKeown, J. Res. U.S. Geol. Surv. 6, 41 (1978).
 A. V. Heyl et al. U. S. Geol. Surv. Prof. Pap. 424-D (1961) p. 3; A. V. Heyl, Econ. Geol. 67, 879 (1972)

- 14. A. V. Heyl and F. A. McKeown, U.S. Geol. Surv. Map MF-1011 (1978).
 15. R. G. Stearns and C. W. Wilson, Jr., Tenn. Val. Auth. Rep. 2.9A-65 (1972).
 16. The S lines were shot in a split-spread configuration.
- tion with a group interval of 100 feet and with vibrator frequencies between 10 and 80 hertz. The D lines were shot off-end with a 200-foot group interval and with vibrator frequencies between 10 and 50 Hz. Further parameter informa-tion and copies of the record sections may be obtained from R. M. Hamilton and M. D. Zo-back, unpublished data.
 M. D. Zoback, Bull. Geol. Soc. Am. 90, 1019
- (1979).
- A. J. Crone and D. P. Russ, U.S. Geol. Surv. 18.
- A. J. Crone and D. P. Russ, U.S. Geol. Surv. Open-File Rep. 79-1216 (1979).
 W. A. Pryor, Bull. Am. Assoc. Pet. Geol. 44, 1473 (1960); W. S. Parks, Tenn. Dep. Conserv. Div. Geol. Bull. 75, B13 (1975). 19.
- K. H. Waters, Reflection Seismology (Wiley, New York, 1979); M. D. Dobrin, Introduction to 20. *Geophysical Prospecting* (McGraw-Hill, New York, 1976).
- Since the average velocity is about 2 km/sec above the Paleozoic rocks, an offset of 1 milli-21. second in two-way time corresponds to a dis-tance offset of about 1 m. Below the Paleozoic surface the interval velocity is about 6 km/sec, so a 1-msec offset corresponds to 3 m. Nearly all the features interpreted to be faults show offset of several horizons and sharp relief, thus distinguishing offsets from possible erosional unconormities
- 22. The Cottonwood Grove and other faults shown

as normal faults in Fig. 3 are actually complex zones with multiple offsets. Some of the faults can be interpreted as high-angle reverse faults

- (line S-6). R. G. Stearns, U.S. Nucl. Regul. Comm. Rep. 23.
- NUREG/CR-0874 (1979). 24.
- NUREG/CR-08/4 (19/9).
 W. M. Caplan, Arkansas Div. Geol. Bull. 20 (1954).
 T. C. Buschbach, U.S. Nucl. Regul. Comm. Rep. NUREG/CR-0450 (1978). 25.
- R. B. Herrmann and J. A. Canas, Bull. Seismol. Soc. Am. 68, 1095 (1978); R. B. Herrmann, J. Geophys. Res. 84, 3543 (1979). R. R. Heinrich, Bull. Seismol. Soc. Am. 31, 187
- (1941)
- T. G. Hildenbrand, personal communication. The research well near line S-10 encountered highly fractured and altered Paleozoic rocks. 29 The mineralogy and geochemistry of the rocks suggests a nearby igneous body.
- See, for example, L. R. Sykes, Rev. Geophys. Space Phys. 16, 621 (1979).
 W. Stauder et al., Cent. Miss. Val. Earthquake
- W. Stauder et al., Cent. Miss. van Zannighan. Bull. 19 (1979).
 We thank R. E. Anderson, W. H. Diment, and O. W. Nuttli, who reviewed the manuscript and-suggested improvements. Appreciation is ex-tended to the U.S. Nuclear Regulatory Commis-tion for meriding the funds for the research. sion for providing the funds for the research well

Brain Peptides as Neurotransmitters

Solomon H. Snyder

It is generally agreed that information processing in the brain largely involves communication among neurons through release of neurotransmitters at synapses. In theory, the brain might make do with one excitatory and one inhibitory transmitter. Until the 1960's the amines acetylcholine, norepinephrine, and serorepresent only 10 percent or less of the total, whose number then may exceed 200.

There has been much debate as to criteria that should be fulfilled before it can be designated a "neurotransmitter." In this article, I regard as transmitters those peptides localized in specific neuronal

Summary. Numerous peptides appear to be neurotransmitter candidates in the brain. Some, such as the opioid peptide enkephalins, neurotensin, and substance P, were first isolated from the brain. Peptides, such as cholecystokinin and vasoactive intestinal polypeptide, were known as intestinal hormones and later recognized as brain constituents. Certain hypothalamic-releasing hormones, pituitary peptides, and blood-derived peptides like angiotensin II and bradykinin, may also be central neurotransmitters. The diversity of localization of these peptides throughout the brain implies a multiplicity of potential roles.

tonin were the only well-recognized transmitters. Then came an appreciation that amino acids such as γ -aminobutyric acid (GABA), glutamic acid, aspartic acid, and glycine, might serve as transmitters. A dramatic explosion in the number of possible neurotransmitters came with increasing recognition in the past decade that various peptides may be neurotransmitters. At present there seem to be about two dozen peptide neurotransmitter candidates, and the number is increasing rapidly (Table 1). Most of the brain peptide transmitters have been discovered serendipitously with no systematic search. It would not be surprising if the known peptide transmitters systems and released on depolarization, which produce changes in neuronal activity, even though for the most recently identified peptides some of these criteria have not yet been examined.

Opiate Receptor and Enkephalins

In most instances, neurotransmitters are identified as endogenous substances and on this basis their receptor effects are characterized. In the case of the enkephalins, the receptors, which were discovered first, provided a means to identify and then isolate these opiate-like peptides. Dramatic properties of the opiate receptor, such as its discriminating agonists and antagonists and the intimate relation between receptor localization and central sites of pain perception (1) suggested that it might interact with a normally occurring opiate-like substance. In

0036-8075/80/0829-0976\$02.00/0 Copyright © 1980 AAAS

addition, analgesia that follows electrical stimulation of the brainstem of rats could be partially reversed by the opiate antagonist naloxone, an indication that a morphine-like substance was being released (2).

To identify the postulated morphinelike factor two approaches were taken. Hughes (3) showed that brain extracts can mimic morphine's effects on electrically induced contractions of smooth muscle in a fashion that is blocked by naloxone. Terenius and Wahlstrom (4) and Pasternak et al. (5) identified in brain extracts a substance that competes for opiate receptor binding. The specificity of this effect was established by showing that the marked regional variations in opiate receptor density are paralleled by similar variations in concentrations of the morphine-like substance (1, 3, 5). Naloxone blockade of the morphine-like actions on smooth muscle and a regional distribution closely mimicking that of the opiate receptor ensured that the substance under study was biologically relevant to opiate receptors. Such guarantees of biological relevance are important, as attempts to isolate a substance solely based on its ability to inhibit the binding of a radioactive drug to membranes run the risk that the substance being isolated may not be physiologically meaningful.

Hughes et al. (6) isolated the morphine-like substance from pig brain and showed that it consists of two pentapeptides, methionine enkephalin (metenkephalin) and leucine enkephalin (leuenkephalin) which differ only in having methionine or leucine at the carboxyl terminal. Using the assay based on competition for receptor binding, Simantov and Snyder (7) isolated the same two peptides from calf brain, confirmed the findings of Hughes et al. (6). Even before the amino acid sequence of enkephalin was established, we showed by radioreceptor assay that enkephalin was localized in nerve endings, which is consistent with a neurotransmitter role, that its detailed regional distribution in monkey brain closely paralleled that of opiate receptors, and that its phylogenetic distribution was the same as that of opiate re-

The author is Director of the Department of Neuroscience and Distinguished Service Professor of Neuroscience, Pharmacology and Experimental Therapeutics, and Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medi-cine, 725 North Wolfe Street, Baltimore, Maryland 21205.