quencies; the rate of this transition appears to increase as the proliferative potential of the clone decreases (Fig. 1a and inset).

The information given in this report should be useful for testing hypotheses that seek to explain the limited doubling potential of human diploid cells. It is clear that neither a precise counting mechanism (*13*) nor the commitment theory of aging (*14*) are compatible in their current form with our findings. However, if one considers the involvement of stochastic mechanisms in stem cell differentiation (*15*), our data may be seen as compatible with a process of genetically controlled terminal differentiation, such as has been proposed by Martin *et al.* (*4*) and Bell *et al.* (*5*). The gradual decrease in proliferative potential would also be compatible with a continuous buildup of damage or errors, a process that has been theorized. However, the wide variability in doubling potentials, especially in mitotic pairs, suggests an unequal partitioning of damage or errors at division. The transition of the proliferative potential subset from large to small suggests the occurrence of a more serious species of damage or the crossing of a threshold level of accumulated damage. In terms of somatic mutation theory, the wide variation at each cell division suggests mutation rates (nonlethal but capable of affecting proliferative potential) approaching one per cell division. Clearly, all current hypotheses should be reexamined in the light of our data.

JAMES R. SMITH
RONALD G. WHITNEY
W. Alton Jones Cell Science Center, Lake Placid, New York 12946

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Entry of Opioid Peptides into the Central Nervous System

Abstract. *Cerebrovascular permeability of four modified opioid peptides—[D-Ala²]methionine enkephalin amide, β-[D-Ala⁶², ¹⁴C-Homoarg⁶⁹]lipotropin 61-69, α-[D-Ala², ¹⁴C-Homoarg⁹]endorphin, and β-[D-Ala², ¹⁴C-Homoarg]endorphin—ranged from 1.4 to 3.9 × 10⁻⁶ centimeters per second in brain regions of the conscious rat. These significant permeabilities should allow the peptides to fill the extracellular brain space with a half time of 3 to 11 minutes, as a result of a step increase in plasma concentration of unbound peptide.*

Some peptides that are derived from the pituitary hormone β-lipotropin are reported to exert central effects when injected systemically, but it is not clear why they do so as they often are reported to be slightly if at all permeable at the blood-brain barrier (*1-4*). An insignificant permeability would appear consistent with the view that the blood-brain barrier, which is composed of cerebrovascular endothelial cells that are connected by tight junctions (zonulae occludentes), is essentially impermeable to water-soluble nonelectrolytes, electrolytes, peptides, and proteins (*5*, *6*). Because of their limited cerebrovascular permeability (*2*), it has been suggested that circulating peptides enter the brain via the choroid plexus and cerebrospinal fluid or, if produced in the pituitary gland, through routes such as the pituitary portal system (*1*).

In contrast, some investigators have reported that peptides are significantly permeable at the blood-brain barrier (*7*). These findings, and the observed positive central effects to some systemically administered peptides (*3*), suggested to us that cerebrovascular permeability of peptides should be reconsidered. Moreover, the method (brain uptake index) most used to show that peptides do not cross the blood-brain barrier, is not sensitive enough to measure uptake of substances whose permeability coefficients are less than 10^{-6} cm sec^{-1} (*2*, *6*, *8*).

We therefore employed a more sensitive method (*9*) to measure cerebrovascular permeability of four radioactive synthetic opioid peptides that are analogs of natural peptides derived from β-lipotropin (*4*, *10*). These synthetic peptides shared a common amino acid terminal sequence, Tyr-D-Ala-Gly-Phe-Met- (*11*), in which the D-alanine residue was placed in position 2 to increase resistance to degradation without significantly reducing biological activity (*4*). They were: [D-Ala²]methionine enkephalin amide; β-[D-Ala⁶², ¹⁴C-Homoarg⁶⁹]lipotropin 61-69; α-[D-Ala², ¹⁴C-Homoarg⁹]-endorphin; and β-[D-Ala², ¹⁴C-Homoarg]-endorphin. They corresponded, respectively, to the following natural peptides: Met enkephalin, β-lipotropin 61-69, α-endorphin, and β-endorphin (*10*).

Conscious and partially restrained rats (adult males) with indwelling femoral artery and vein catheters were injected intravenously with 2 to 10 μCi of a radioactive opioid peptide; samples of arterial blood were removed periodically and centrifuged (*9*). Animals were decapitated 3 minutes after injection of [D-Ala²]methionine enkephalin amide; 3 or 10 minutes after β-[D-Ala⁶², ¹⁴C-Homoarg⁶⁹]lipotropin 61-69; 4, 8, 20, or 30 minutes after α-[D-Ala², ¹⁴C-Homoarg⁹]endorphin; and 5 or 10 minutes after β-[D-Ala², ¹⁴C-Homoarg]endorphin. The brain was removed and dissected into 13 regions, which were weighed. Radioactivity was determined by scintillation counting in samples of brain, arterial plasma, and whole blood. Brain parenchymal tracer concentration (C_{brain}, dpm/g) was calculated by subtracting intravascular radioactivity from net measured regional radioactivity. Intravascular radioactivity was obtained from the product of whole blood concentration (dpm/ml) × regional blood volume (ml/g), where regional volumes ranged from 0.015 to 0.035 ml per gram of brain (*9*).

Tracer purity was confirmed by chromatography of the injected material and of the plasma up to the time that the animal was decapitated. The fraction *r* of tracer not bound to blood proteins was determined by mixing tracer with rat serum and measuring radioactivity in serum and serum ultrafiltrate. The octa-

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Table 1. Cerebrovascular permeability P (10^{-6} cm sec^{-1} ± S.E.) and cerebral distribution volume V of four synthetic peptides. Data were obtained by Eq. 3; V is not given if it was inconsistent among regions. The unbound plasma fraction and partition coefficient were determined experimentally. The numbers in parentheses indicate the number of animals.

Brain region	Met-[D-Ala^2]-enkephalin amide (3)	β-[D-Ala^{62},^{14}C-Homoarg^{69}]-lipotropin 61-69 (6)	α-[D-Ala^2,^{14}C-Homoarg^9]-endorphin (8)		β-[D-Ala^2,^{14}C-Homoarg]-endorphin (6)	
	P	P	P	V	P	V
Olfactory bulb	2.8 ± 0.3	1.6 ± 0.5	1.8 ± 0.99	0.43 ± 0.48	4.6 ± 5.4	0.03 ± 0.02
Caudate nucleus	2.4 ± 0.2	1.3 ± 0.5	2.1 ± 0.82	0.25 ± 0.09	4.4 ± 2.7	0.03 ± 0.01
Hippocampus	1.7 ± 0.4	1.2 ± 0.2	1.8 ± 0.82	0.31 ± 0.19	3.1 ± 2.3	0.02 ± 0.01
Gray matter	2.9 ± 0.1	1.7 ± 0.6	2.7 ± 0.89	0.28 ± 0.06	4.4 ± 2.3	0.03 ± 0.01
White matter	2.3 ± 0.5	1.1 ± 0.5	0.98 ± 0.62	0.20 ± 0.18	4.8 ± 6.7	0.03 ± 0.02
Thalamus plus hypothalamus	2.4 ± 0.2	1.2 ± 0.2	2.1 ± 0.99	0.30 ± 0.14	2.7 ± 1.7	0.02 ± 0.01
Superior colliculus	2.6 ± 0.3	1.5 ± 0.2	2.5 ± 1.2	0.37 ± 0.21	3.3 ± 2.3	0.03 ± 0.01
Inferior colliculus	2.8 ± 0.2	2.0 ± 0.2	3.1 ± 1.3	0.42 ± 0.17	4.8 ± 1.8	0.04 ± 0.01
Cerebellum	2.9 ± 0.2	1.4 ± 0.2	2.5 ± 1.1	0.31 ± 0.14	4.0 ± 2.5	0.03 ± 0.01
Pons	2.3 ± 0.3	1.7 ± 0.2	3.1 ± 1.3	0.36 ± 0.12	4.0 ± 2.7	0.03 ± 0.01
Medulla	2.3 ± 0.2	1.8 ± 0.3	3.1 ± 1.3	0.36 ± 0.12	2.7 ± 2.0	0.02 ± 0.01
Frontal lobe	2.5 ± 0.3	1.5 ± 0.5	2.5 ± 1.1	0.26 ± 0.07	3.5 ± 2.0	0.03 ± 0.01
Occipital lobe	2.5 ± 0.3	1.3 ± 0.2	2.1 ± 1.6	0.27 ± 0.12	3.8 ± 2.3	0.03 ± 0.01
Average	2.5	1.4	2.3	0.32	3.9	0.03
Molecular weight	587	1000	1826		3436	
Partition coefficient*	0.066	0.012	0.0017		0.013	
r, unbound plasma fraction	0.21	0.84	0.34		0.20	

*Between octanol and water.

nol-water partition coefficient was found at room temperature by mixing a portion of tracer with a mixture (1:1, by volume) of *n*-octanol and buffered 0.9 percent (weight to volume) NaCl (*p*H 6.9 to 7.2) and then measuring radioactivity in each of the liquid phases (*8*).

After intravenous injection of tracer, C_{plasma} (dpm/ml) was represented as a sum of declining exponentials

$$C_{plasma} = \sum_{1}^{n} B_i e^{-k_i t} \quad (1)$$

where t = time in seconds, B_i (dpm/ml) and k_i (per second) are constants, and n = 2 to 4 (*9*).

If tracer passively diffuses between brain and plasma, then, in the absence of significant cerebral binding or metabolism over the experimental period (*9, 12*), brain uptake is given as follows

$$dC_{brain}/dt = PA(rC_{plasma} - C_{brain}/V) \quad (2)$$

where A is cerebral capillary area (cm^2/cm^3, or cm^{-1}), V is the ratio of cerebral volume in which the tracer can be distributed to the total volume, and r is the unbound fraction in plasma.

Substitution of Eq. 1 into Eq. 2 and integration gives C_{brain} at time t of decapitation (Eq. 3),

$$C_{brain} = \sum_{1}^{n} \frac{rB_iPA}{PA/V - k_i} (e^{-k_i t} - e^{-PAt/V}) \quad (3)$$

Experiments were limited to periods after intravenous injection when metabolites were not observed in plasma. Equation 3 was fit by a nonlinear least-squares procedure (*13*) to data from three to eight experiments for a given tracer, to give estimates of PA (per second) and of distribution volume V at different brain regions. Table 1 lists resultant values of P [calculated by dividing PA by A = 240 cm^{-1} (*14*)] and of V, as well as the plasma fraction of free tracer and the octanol-water partition coefficient.

Only α-[D-Ala^2,^{14}C-Homoarg^9]endorphin could be studied for a sufficiently long time after intravenous injection (30 minutes) to allow enough tracer into the brain to specify a consistent and meaningful V by the least-squares procedure. Experimental periods longer than 10 minutes could not be used for the other tracers because of the appearance of plasma metabolites or of the very rapid disappearance of tracer from plasma. The mean cerebral V for α-[D-Ala^2,^{14}C-Homoarg^9]endorphin was 0.32, which suggests that it entered the extracellular brain space (15 to 25 percent of the wet weight) (*6*) over the 30-minute experimental period, and perhaps was bound to brain to some extent (*12*). However, the cerebral V values of two other peptides were inconsistent and are not presented in Table 1, and estimated V of β-[D-Ala^2,^{14}C-Homoarg]endorphin was only 0.03. Experiments with these three tracers were limited to 10 minutes or less (see above), probably too short a time to allow sufficient brain uptake of tracer to specify a meaningful and consistent V by the least-squares procedure (*13*).

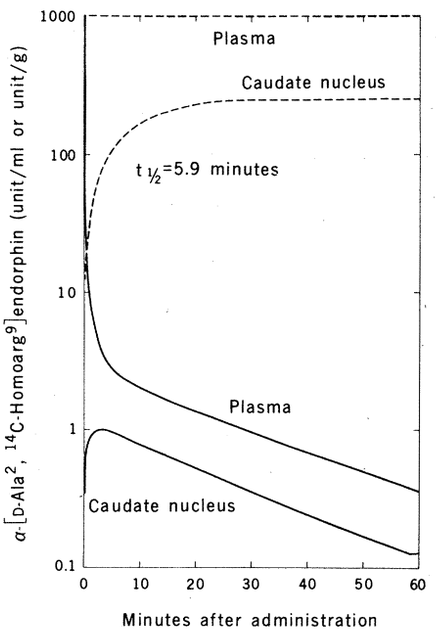

Fig. 1. Concentration of α-[D-Ala^2,^{14}C-Homoarg^9]endorphin in the caudate nucleus, as predicted by Eq. 3, in response to a step increase in plasma concentration of unbound peptide (dashed line) or to a bolus injectin (continuous line, experimentally observed curve). Plasma concentration represents unbound peptide, rC_{plasma}, where r = 0.34. P = 2.2 × 10^{-6} cm sec^{-1}, and V = 0.25 (Table 1).

The cerebrovascular permeability coefficients of the four opioid peptides in Table 1 range from 1.4 × 10^{-6} to 3.9 × 10^{-6} cm sec^{-1}, and approximate permeabilities of the nonelectrolytes glycerol, formamide, and thiourea, which have similar octanol-water partition coefficients (0.003 to 0.1) (*9*). It therefore appears that lipid solubility may play a role in peptide transfer at the blood-brain barrier. Very permeable, lipid-soluble substances like caffeine and antipyrine exhibit coefficients two orders of magnitude higher (10^{-4} cm sec^{-1}) than those of the peptides, whereas poorly permeable, water-soluble compounds

water-soluble compounds like sucrose and erythritol have permeability coefficients equal to 10^{-8} to 10^{-7} cm sec^{-1} (*6, 9*).

Low but significant cerebrovascular permeabilities explain why opioid peptide uptake by brain might not be measurable by the brain uptake index method (in which brain uptake is measured within 15 seconds after injection), or why plasma concentrations must be maintained for minutes if observable central effects are to be produced (*2, 4, 7*). Figure 1 illustrates the prediction by Eq. 3, as based on data in Table 1, that α-[D-Ala^2,^{14}C-Homoarg^9]endorphin will fill half of the extracellular space of the caudate nucleus in 5.9 minutes, after a step rise in plasma concentration of unbound peptide. In contrast, the brain concentration does not rise above 0.1 percent of the initial plasma concentration of unbound peptide if the peptide is injected as a bolus. Whereas the half-time for brain uptake is equal to 0.693 *V/PA* (Eq. 3), the peptides in Table 1 would enter a 30 percent extracellular brain space with half-times of 3 to 11 minutes.

We have shown that four synthetic analogs of natural opioid peptides have a moderate cerebrovascular permeability that is sufficient to produce significant brain uptake within 3 to 11 minutes, after a step rise in plasma concentration. There may be little uptake after a bolus injection if the peptide disappears rapidly from plasma, or if binding to plasma protein is marked. The findings are consistent with observations that some peptides exert central effects in conscious animals when administered systemically (*3, 7*). A significant cerebrovascular permeability suggests, furthermore, that feedback may operate between circulating peptides that have potential central effects, and brain sites that regulate their release into the circulation (*1*).

S. I. RAPOPORT
Laboratory of Neurosciences, National Institute on Aging, Gerontology Research Center, Baltimore City Hospitals, Baltimore, Maryland 21224
W. A. KLEE
Laboratory of General and Comparative Biochemistry, National Institute of Mental Health, Bethesda, Maryland
K. D. PETTIGREW
Theoretical Statistics and Mathematics Branch, National Institute of Mental Health, Bethesda, Maryland 20205
K. OHNO
Laboratory of Neurosciences, National Institute on Aging, Gerontology Research Center

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10. With the exception of methionine[^{3}H-Tyr, D-Ala^2]enkephalin amide (New England Nuclear), each peptide was guanidinated and labeled with ^{14}C as follows: peptide (0.5 to 1.2 mg) was added to 200 μl of 0.2*M* *O*-[^{14}C]methylisourea (58 mCi/mmole), adjusted to *p*H 10.5 with NaOH. After storage for 5 days, the reaction mixtures were neutralized with 10 μl of 4*M* ammonium acetate buffer, *p*H 7. The ^{14}C-labeled guanidinated peptides were purified by passage through Biogel-P-2 columns (1 by 17 cm) in 50 percent acetic acid (α- and β-endorphin analogs), or by adsorption to XAD-2 beads, exhaustive washing with water, and elution with 90 percent aqueous methanol (analog of β-lipotropin 61-69). They were then taken to dryness and dissolved in saline for use. Amino acid analysis of the modified peptides showed that 50 percent of the lysine residues had been converted to ^{14}C-homoarginine by the procedure. *O*-[^{14}C]methylisourea was prepared from ^{14}C-labeled barium cyanamid (DHOM Products Ltd., North Hollywood, Calif.) by treatment with methanolic HCl at room temperature for 3 days, with subsequent filtration and removal of solvent. α-[D-Ala^2]-endorphin was supplied by Dr. Nicholas Ling and β-[D-Ala^2]endorphin by Dr. C. H. Li. β-[D-Ala^2]lipotropin 61-69 was prepared from α-[D-Ala^2]endorphin by treatment with trypsin (1/200) at *p*H 8 for 16 hours at 37°C, followed by XAD-2 chromotography as described.
11. Abbreviations: Ala, alanine; Gly, glycine; Homoarg, homoargenine; Met, methionine; Tyr, tyrosine.
12. Data for α-[D-Ala^2,^{14}C-Homoarg]endorphin were also analyzed by a three-constant model, where k_1 and k_2 (per second) represent inward and outward rate constants at the blood-brain barrier, and k_3 represents the rate constant for binding to brain tissue for free peptide. The mean value of k_3 is equal to 1.03×10^{-3} sec^{-1}; L. Sokoloff *et al.*, *J. Neurochem.* **28**, 897 (1977).
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Gene Affecting Superoxide Dismutase Activity Linked to the Histocompatibility Complex in H-2 Congenic Mice

Abstract. *The activity of cyanide-sensitive, Cu-Zn superoxide dismutase (SOD) was studied in liver cytosols from H-2 congenic strains of mice. Higher SOD activity was found in livers of mice having H-2^b/A.BY, B10, and C_3H.SW/ haplotypes than in those of H-2^a, H-2^k and H-2^d haplotypes. Segregation studies supported these correlations. In H-2 recombinant strains of mice, the genes influencing the liver SOD activity occur, as ascertained by mapping techniques, at or near the H-2D region of the major histocompatibility complex.*

Superoxide dismutase (SOD) (E.C. 1.15.1.1) appears to be detectable in all aerobic cells (*1*). This enzyme catalyzes the dismutation of the superoxide anion, O_2^-, in which one electron is transferred to form molecular oxygen, in the sense of the following equation;

$$2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$

The work of Fridovich (*2*) suggests that the most important function of SOD is to protect aerobic cells from the oxidoreduction effect of the toxic O_2^- formed during aerobic cell metabolism. Atmospheric oxygen is capable of inducing the synthesis of SOD; molecular oxygen may be toxic to cells displaying an anaerobic metabolism and, in high concentration, to aerobic cells also (*3*).

On the basis of studies on the structure of SOD, Richardson *et al.* (*4*) drew attention to the similarity between the three-dimensional protein structures of the immunoglobulin domain and Cu-Zn SOD subunits.

They proposed that the similarity in the tertiary structures of the two molecules of different functions is indicative of their evolutionary relatedness. Furthermore, the structures of immunoglobulins are similar to those of the major histocompatibility antigens (H-2) in mice (*5*) and it has been proposed that both molecules are the products of genes that were differentiated from a common, primor-

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