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Opiate Receptor Gradients in Monkey Cerebral Cortex: Correspondence with Sensory Processing Hierarchies

Abstract. *In order to obtain information on the possible functions of endogenous opiates in the primate cerebral cortex, we assessed the distribution of μ-like opiate receptors (which selectively bind ^{3}H-labeled naloxone) and δ-like opiate receptors (which selectively bind ^{3}H-labeled D-Ala^2, D-Leu^5-enkephalin) throughout the cerebral cortex of the rhesus monkey. Stereospecific [^{3}H]naloxone binding sites increased in a gradient along hierarchically organized cortical systems that sequentially process modality-specific sensory information of a progressively more complex nature. Specific [^{3}H]enkephalin binding sites, in contrast, were relatively evenly distributed throughout the cerebral cortex. These results, in combination with electrophysiological studies of monkeys and humans, suggest that μ-like opiate receptors may play a role in the affective filtering of sensory stimuli at the cortical level, that is, in emotion-induced selective attention.*

Despite evidence that the cerebral cortex contains opiate receptors (*1*, *2*) and opiate peptides (*3*) and responds electrically to opiate compounds (*4*), information regarding the functional significance of cortical opiate systems is scarce. Clues to such functions might be obtained by analyzing the distribution of opiate receptors in structurally or functionally defined systems of the cerebral cortex of the rhesus monkey (*Macaca mulatta*), a species used frequently in neuroanatomical, neurophysiological, and neurobehavioral analyses of cortical function. Although previous studies have provided some information on the regional distribution of opiate receptors in the monkey and the human cortex (*5*), the dissections were not complete, and selective assay conditions for opiate receptor subtypes were not used. We now report that while specific [^{3}H]enkephalin binding hardly varies in different parts of the cortex, opiate receptors labeled by [^{3}H]naloxone (*6*) increased in a gradient along hierarchically organized cortical systems, which sequentially process modality-specific sensory information of a progressively more complex nature.

Rhesus monkeys (young adults, two male and two female, weighing 5 to 7 kg) were rapidly anesthetized with sodium pentothal (125 mg in 1.5 ml saline, intrahepatically) followed by sodium pentobarbital (35 mg per kilogram of body weight, injected intraperitoneally). Cerebral circulation and respiration were maintained while a craniotomy was performed. The brain was removed within 12 minutes after sedation and chilled on crushed ice. The boundaries of the cortical dissection were determined on the basis of the cytoarchitectonic map of von Bonin and Bailey (*7*); the areas obtained are listed according to both anatomical name and cytoarchitectonic designation (Table 1). Tissues were immediately frozen on dry ice and stored at −85°C until assayed.

Tissue was homogenized in 50 volumes of ice-cold 0.05*M* tris HCl buffer (*p*H 7.55 at 4°C) through the use of a Polytron tissue disruptor (setting 6 for 15 seconds) and then centrifuged at 4°C at 10,000*g*. The pellets were resuspended in 2.5 volumes of fresh buffer. To measure stereospecific [^{3}H]naloxone binding, 100 μl of the tissue homogenate was added to tubes containing (in tris) 100 m*M* NaCl, 1 n*M* [^{3}H]naloxone (New England Nuclear; 50 Ci/mmole), and 1 μ*M* dextrallorphan or 1 μ*M* levallorphan in a final volume of 500 μl. After the tubes were incubated at 4°C for 60 minutes, the reactions were stopped by filtration under low vacuum through Whatman GF/B filters. The tubes were washed twice and the filters once with 5-ml portions of ice-cold tris; the filters were placed in vials, 10 ml of Aquassure (New England Nuclear) was added, and the radioactivity was measured by liquid scintillation spectrometry at 38 percent efficiency. Stereospecific [^{3}H]naloxone binding was defined as binding in the presence of 1 μ*M* dextrallorphan minus binding in the presence of 1 μ*M* levallorphan. Triplicate determinations showed a standard error of 2 to 5 percent of the mean, and binding in the presence of levallorphan was usually 10 to 15 percent of binding in the presence of dextrallorphan.

To measure specific enkephalin binding, 100 μl of the homogenate (stored for less than 1 week at −85°C) was added to tubes containing (in 0.05*M* tris HCl, *p*H 7.4 at 25°C) 0.2 percent bovine serum albumin, 0.08 mg of bacitracin per milliliter, 2 μ*M* guanosine triphosphate, 30 m*M* NaCl, 3 m*M* manganese acetate, and 1 n*M* D-Ala^2-[tyrosyl-3,5-^{3}H]enkephalin (5-D-leucine) (Amersham; 52 Ci/mmole) in a final volume of 500 μl. After the tubes were incubated at 25°C for 30 minutes, the reactions were stopped as before. Specific binding of the labeled enkephalin ([^{3}H]D-Ala) was defined as total binding in the above assay minus binding obtained in identical reaction mixtures also containing 1 μ*M* β-endorphin. Triplicate determinations showed a standard error of 2 to 5 percent of the mean, and binding in the presence of 1 μ*M* β-endorphin was usually 5 to 10 percent of the total binding. Specific binding of both ligands was linear with respect to the volume of homogenate added (from 25 to 100 μl).

In the visual system, sensory input seems to be processed sequentially through a series of cortical loci corresponding to the cytoarchitecturally defined areas OC, OB, OA, TEO, TE, and ventral TG (see Table 1 for cytoarchitectonic designations) (*8*, *9*). The density of stereospecific opiate receptors binding [^{3}H]naloxone (Table 1) increased in a gradient (Fig. 1A) along this system from the primary sensory cortex (OC) to the ventral temporal pole (TG), which projects most densely to the amygdala (*9–11*). A similar gradient (Fig. 1A) was detected in the auditory cortical system, from primary sensory cortex (TC/TB)

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through area TA to lateral TG, which then also relays fibers to the amygdala (*9-11*). These gradients peaked at the periamygdaloid cortex (A) on the medial surface of the temporal lobe, an observation consistent with previous findings of an especially high density of opiate receptors in the amygdaloid nuclei of the rhesus monkey (*1, 5*). The gradient declined again through the medial temporal, medial preoccipital, and finally, medial striate cortex (Fig. 1A). In the somatosensory system, although the corticocortical relays are less well understood than for the visual and auditory systems, there is some evidence for functionally significant connections from primary sensory cortex (PB/PC) to the amygdala and adjacent cortex through the secondary sensory area (PF/PCop) and the insula (*9-14*). The density of stereospecific [^{3}H]naloxone binding sites also increased in a gradient along this pathway (Table 1).

Outside the posterior sensory processing areas, the distribution of opiate receptors labeled with [^{3}H]naloxone showed other correlations with functional cortical anatomy. Within the frontal lobe, the agranular cortical areas (*7*), particularly the motor strip (FA/FBA), contained the fewest opiate receptors binding [^{3}H]naloxone. Somewhat more of these receptors were present in the lateral portion of the frontal granular cortex, an area critical for a variety of problem-solving functions (*15*). The highest densities in the frontal lobe, however, were found in the ventromedial frontal granular cortex, a frontal subdivision that has been implicated in autonomic and emotional functions (*16*) and that is characterized by relatively rapid ontogenetic development (*17*) and prominent interconnections with the amygdala and anterior temporal cortex (*11, 14, 18*). Within the ventromedial region of the frontal lobe, the olfactory tubercle (*19*) contained an especially high density of [^{3}H]naloxone binding sites, a finding consistent with the proposed opiate-containing neurocircuitry interconnecting olfactory and limbic structures in the rat (*20*).

In contrast to the pronounced gradients observed through the use of the radiolabeled opiate alkaloid, δ-like [^{3}H]D-Ala opiate receptors showed a relatively even distribution throughout the cortex (Table 1 and Fig. 1C). Significant specific receptor binding of both types was undetectable in the cerebellum. When the ratios of [^{3}H]naloxone to [^{3}H]D-Ala binding in the occipitotemporal areas (Table 1) were plotted according to cytoarchitectonic designation and cortical locus (Fig. 1B), a clear gradient was obtained.

The opiate receptor gradients reported here are remarkably concordant with certain features of primate cerebral anatomy and function. Within the cortical sensory systems, progressively heavier and more widespread corticoamygdaloid projections arise from successively later stages of the sequential processing pathway (*9*), providing a neuroanatomical gradient that exactly parallels that for opiate receptors labeled by [^{3}H]naloxone. The organization of corticoamygdaloid projections has been taken to suggest that a progressively greater influence on amygdaloid activity is exerted by successively more highly processed

Table 1. Binding of [^{3}H]naloxone and [^{3}H]D-Ala^2,D-Leu^5-enkephalin to monkey cortical membranes, in femtomoles bound per milligram of tissue (means ± standard errors). Where only two of the four samples were available, the values for both are given.

Area	Cytoarchitectonic designation	[^{3}H]Naloxone	[^{3}H]D-Ala	Ratio
	Frontal lobe			
Inferior prefrontal	FD/FDγ	1.73 ± 0.21	1.18 ± 0.10	1.47
Midlateral prefrontal	FD	1.56 ± 0.17	1.36 ± 0.11	1.15
Dorsal prefrontal	FD	1.67 ± 0.20	1.29 ± 0.09	1.29
Medial prefrontal	FD	1.99 ± 0.22	1.28 ± 0.14	1.55
Medial orbital	FL	2.33 ± 0.28	1.45 ± 0.15	1.61
Midorbital	FD	2.00 ± 0.26	1.42 ± 0.14	1.41
Posterior orbital	FF	2.25 (1.88, 2.62)	1.36 (1.25, 1.46)	1.65
Olfactory tubercle	FF	3.06 (3.00, 3.12)	0.67 (0.53, 0.80)	4.57
Prearcuate	FDΔ	1.08 ± 0.09	1.02 ± 0.09	1.06
Dorsal premotor	FB/FC	1.33 ± 0.12	1.21 ± 0.10	1.10
Ventral premotor	FCBm	1.50 ± 0.16	1.28 ± 0.07	1.17
Frontal operculum	FCop	1.53 ± 0.16	1.27 ± 0.10	1.20
Anterodorsal motor strip	Ant. FA	0.60 (0.52, 0.67)	1.16 (0.87, 1.44)	0.52
Precentral	Post. FA/FBA	0.95 ± 0.10	1.24 ± 0.07	0.77
	Parietal lobe			
Postcentral	PB/PC	1.04 ± 0.09	1.23 ± 0.10	0.85
Superior parietal	PE/PEm	1.26 ± 0.16	1.30 ± 0.03	0.97
Inferior parietal, anterior	PF	0.99 ± 0.14	1.11 ± 0.11	0.89
Inferior parietal, posterior	PG	1.24 ± 0.19	1.22 ± 0.11	1.02
Parietal operculum	PF/PCop	1.44 ± 0.06	1.16 ± 0.09	1.24
	Cingulate			
Cingulate, anterior	LA	1.71 ± 0.18	1.28 ± 0.11	1.34
Cingulate, posterior	LC	1.70 ± 0.05	1.21 ± 0.07	1.40
	Temporal lobe			
Supratemporal plane	TC/TB	1.07 ± 0.09	1.08 ± 0.11	0.99
Superior temporal, posterior	TA	1.27 ± 0.09	1.19 ± 0.07	1.07
Superior temporal, anterior	TA	2.21 ± 0.17	1.44 ± 0.09	1.52
Temporal pole, dorsal	Dors. TG	2.69 ± 0.27	1.41 ± 0.13	1.91
Inferior temporal, posterior	TEO	1.13 ± 0.08	1.20 ± 0.08	0.94
Inferior temporal, anterior	TE	1.59 ± 0.13	1.23 ± 0.06	1.29
Temporal pole, ventral	Vent. TG	2.74 ± 0. 40	1.41 ± 0.19	1.94
Periamygdaloid	A	4.21 (4.61, 3.81)	1.53 (1.56, 1.50)	2.75
Entorhinal	Ant. TH	2.91 (1.86, 3.95)	1.37 (0.92, 1.82)	2.12
Hippocampal	Post. TH	1.68 (1.21, 2.16)	1.11 (0.93, 1.29)	1.51
Fusiform	TF	1.52 ± 0.10	1.29 ± 0.14	1.18
	Insula			
Insula, anterior	IA	1.91 (1.31, 2.50)	1.19 (0.81, 1.57)	1.61
Insula, posterior	IB	1.57 (2.00, 1.14)	1.19 (1.24, 1.13)	1.32
	Occipital lobe			
Preoccipital, lateral	Lat. OA	1.00 ± 0.11	1.24 ± 0.08	0.81
Preoccipital, medial	Med. OA	1.00 ± 0.10	1.19 ± 0.10	0.84
Peristriate, lateral	Lat. OB	0.93 ± 0.06	1.17 ± 0.10	0.79
Peristriate, medial	Med. OB	0.75 (0.73, 0.78)	0.85 (0.66, 1.04)	0.88
Striate, lateral	Lat. OC	0.55 ± 0.09	1.12 ± 0.17	0.49
Striate, medial	Med. OC	0.71 ± 0.16	0.98 ± 0.08	0.72

sensory information (*9*). The existence of a superimposable μ-like opiate receptor gradient may likewise indicate that endogenous opiates exert a progressively greater influence at successively higher levels of sensory information processing in the cortex. What form could this influence take? By analogy with the proposed gating function of opiates in the spinal somatosensory system (*21*), opiatergic neurons may be involved in the filtering of sensory stimuli (*22*) at the cortical level, and thus play a role in selective attention. Studies in humans have demonstrated effects of opiates and opiate antagonists on electrophysiological indices of attention (*23*).

Further, electrophysiological studies carried out on monkeys have implicated the inferior temporal cortex, particularly the opiate receptor-rich anterior portions, in reward-associated selective attention. In monkeys trained to shift their attention from one stimulus dimension to another, inferior temporal evoked potentials in response to an identical colored pattern differed reliably as a function of which stimulus dimension was made salient by the reward contingency (*24*). Because of the participation of the amygdala in emotional-motivational (*25*) and reward-related (*12, 26*) functions, and because of recent evidence indicating a reciprocal projection from the amygdala back to the cortical sensory processing areas that give rise to the amygdaloid afferents (*27*), we are considering the hypothesis that selective attention may be influenced by a "reverse" gradient of amygdalocortical opiate-containing projections onto cortical neurons containing μ-like opiate receptors. This proposal offers a neural mechanism whereby the limbic-mediated emotional states essential for individual and species survival (*28*) could influence which sensory stimuli are selected for attention.

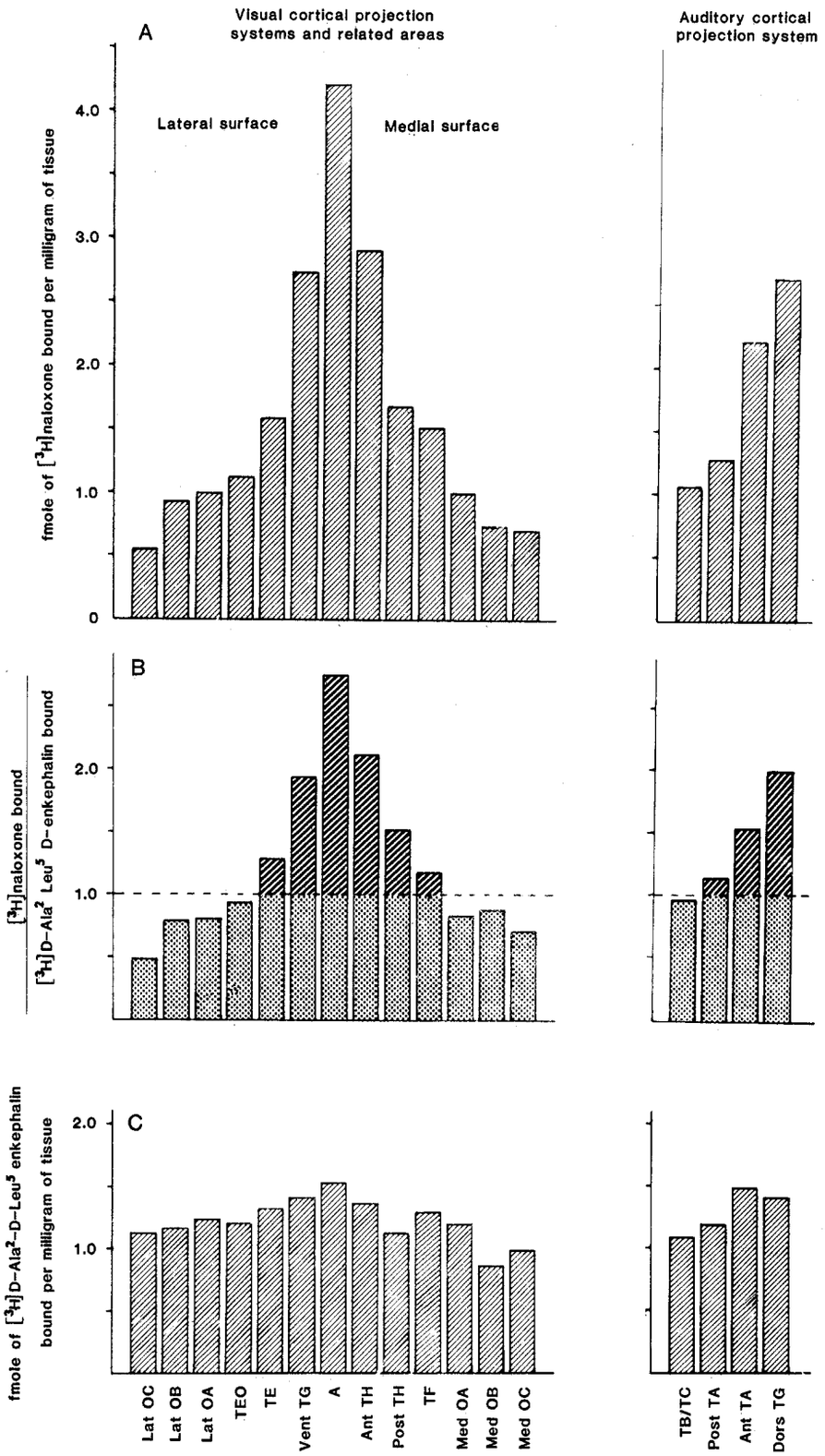

Fig. 1. Gradients of opiate receptor binding in cytoarchitectonically defined, adjacent regions of monkey cerebral cortex (mean values from Table 1).

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Conduction System in a Sponge

Abstract. *The hexactinellid sponge* Rhabdocalyptus dawsoni *is capable of arresting its exhalant water current in response to mechanical and electrical stimuli. The arrest is coordinated by a conduction system with a precise threshold of excitability and a chronaxie of 38 milliseconds. The response is propagated throughout the sponge at a mean velocity of 0.22 centimeter per second, and conduction is unpolarized.*

Sponges show little behavior in the usual sense. Oscular contractions and slow changes in shape have been described in several species, but these usually appear as local responses confined to a few millimeters of tissue (*1*, *2*). Conduction of contractile responses over longer distances occurs in a few cases (*3*, *4*), and an ability to regulate overall water flow has been demonstrated in certain tropical demosponges (*5*). In the latter case, flagellar pumping activity and oscular movements seem to be coordinated, but the conduction system involved has never been demonstrated or characterized physiologically. We present here the first such evidence.

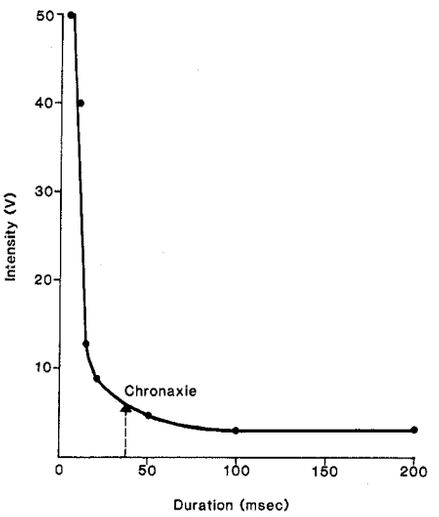

Fig. 1. Intensity plotted as a function of duration showing that the exhalant current of the sponge is arrested by a conduction system with a precise threshold. For most stimulus durations, there is a minimum intensity that will produce a response: the classical "all-or-none" response of excitable tissue. The chronaxie (38 msec) is high compared with that of nerve and muscle, an indication that the conduction system of the sponge may have a low excitability.

Field observations on *Rhabdocalyptus dawsoni* (Lambe, 1892), a large hexactinellid sponge from coastal waters of British Columbia, involved monitoring the exhalant water current with a compensated, thermistor flow-meter (*6*). Arrests occurred in response to local disturbances such as mechanical jarring. Further, as noted in certain demosponges (*5*), periodic arrests were seen in the absence of such stimuli and were assumed to be of endogenous origin. The osculum of *Rhabdocalyptus* cannot change shape, and therefore sudden stoppage of the exhalant current must be due to a coordinated arrest of the individual currents passing through the body wall. This in itself suggests that a diffuse conduction system is present in the sponge.

After being transferred to laboratory tanks, the sponges were maintained in slowly running seawater (11°C) for 2 days before observations were made. Steady pumping activity interrupted by occasional arrests took place as in the natural environment. Mechanical stimulation also induced arrests; a sharp tap

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