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SPATIAL ORGANIZATION OF PATCH AND MATRIX COMPARTMENTS IN THE RAT STRIATUM

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Abstract—The visualization of mu opiate receptors by [^{3}H]naloxone binding was used to determine precisely the spatial organization of the patch compartment in the rat striatum and its reproducibility in different animals. Three-dimensional reconstruction of the patch network was made using maps of autoradiographic data obtained from successive coronal, sagittal or horizontal sections. The extreme rostral pole of the striatum (A 11) was characterized by a large patch territory exhibiting complex and tortuous fields with several extensions. In the intermediate part of the structure (A 9.0–10.0), about 20 serial parallel continuous patch channels running in a mediolateral axis, obliquely oriented and displaying in some cases connecting branches, could be observed. However, no channels could be distinguished in the rostrocaudal direction. More caudally, patches were rare and of small size. In addition, the laterocaudal region of the striatum was almost exclusively represented by a large matrix field. Finally, a fine discontinuous band of [^{3}H]naloxone binding was seen in all sections, bordering and limiting the dorsolateral part of the striatum. The topographical and spatial distribution of the patch compartment was similar in all animals investigated. However, due to the tortuous shape and the labyrinthine organization of the patches, the precise degree of reproducibility from one animal to another could not be established. Nevertheless, the prominent patch compartment observed in the rostral pole of the striatum, the patch channels, oriented in the mediolateral axis as well as the large laterocaudal matrix field were observed in all cases.

These results were compared with previous data obtained in the cat in which patch (striosome) channels oriented along a rostrocaudal axis are also observed.

The two striatal compartments, the striosomes (or patches) and the matrix, are distinguished by several biochemical markers[2,12,20,27,40] and their afferent and efferent connections.[6,7,14,15,23,27–29,36,43,44] Moreover, neurons which will form the patches migrate first in the striatum during ontogenesis.[3,18,21,49] These cells are particularly connected by neurons from deep layers of the cerebral cortex[11] and innervate mainly the substantia nigra pars compacta.[9,10,19] Attempts have already been made to perform a three-dimensional reconstruction of the striosomal network in the adult cat caudate nucleus using either [Met]enkephalin immunoreactivity or acetylcholinesterase poor zones as striosomal markers.[6,24] Briefly, the striosomal field is more extended in the rostral pole and the medial part of the caudate nucleus and distinct tortuous channels exhibiting a rostrocaudal direction were observed in the core of the structure. These striosomal channels are connected by several bridges mainly oriented in the mediolateral direction. The lateral part of the dorsal caudate nucleus is almost exclusively represented by the matrix.[6]

In the rat, [^{3}H]naloxone binding or more specific ligands of mu opiate receptors such as [^{125}I] or [^{3}H][D-Ala^2,*N*-MePhe^4,Gly-ol^5] Enk (DAGO) are generally used for the autoradiographic visualization of striatal patches.[26,45] In fact, Pert *et al.*[42] were the first to describe the patchy organization of mu opiate receptors in the adult rat striatum. They also indicated that fibres originating from thalamic intralaminar nuclei project to the regions outside [^{3}H]naloxone patches i.e. into the matrix.[27] [^{3}H]Naloxone binding has also been used to follow the development of the patch compartment and to investigate some of its topographical characteristics.[39,48,50] The conversion of homogeneous to patchy labelling appears around embryonic day 20 and at this time the dopaminergic islands (only seen in the young animal) are in register with the [^{3}H]naloxone patches.[38,48] However, there is evidence from 6-hydroxydopamine-induced lesions of the nigrostriatal dopaminergic neurons and chronic haloperidol treatment that mu opiate receptors are located on a population of striatal neurons and that their expression depends on the presence of dopaminergic innervation.[4,45,47,50]

The aim of the present study was to determine precisely the spatial organization of the patch compartment in the adult rat striatum using [^{3}H]naloxone binding as a marker. Three-dimensional reconstructions of the patch network were made from autoradiographic data obtained on serial coronal, sagittal or horizontal sections. Results were compared with previous data obtained in the cat.[16,31] They provided the anatomical basis for functional studies in which

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attempts are made to identify the local circuits involved in the presynaptic regulation of dopamine release in discrete patch- and matrix-enriched areas of the rat striatum.[33]

EXPERIMENTAL PROCEDURES

Animals

Adult male Sprague–Dawley rats (Charles River, France) (250 g at the start of the experiment) were used. They were kept for at least eight days in a light-, temperature- and humidity-controlled environment and were killed by decapitation and their brains were frozen rapidly in isopentane at −40°C. A common landmark was performed by tissue perforation with a needle before sectioning the brain. Coronal, sagittal or horizontal sections (30 or 40 μm thick) were cut at −18°C and thaw-mounted on to gelatine-coated slides which were then quickly dried and stored at −30°C until the binding experiments.

[^{3}H]*Naloxone binding*

Sections were incubated for 60 min at 4°C in a solution containing [^{3}H]naloxone (2 nM, 56.1 Ci/mmol, Amersham), Tris-HCl buffer (50 mM, pH 7.4) and NaCl (100 mM).[26] Nonspecific binding was determined on sections incubated with the same medium containing morphine (10 μM). Sections were washed five times for 2 min each time using cold (4°C) Tris-HCl buffer (50 mM) and then dried under a stream of cold air. Finally, they were apposed on to ^{3}H-ultrofilm (LKB) for five to seven weeks in an X-ray cassette. Films were developed with Kodak LX24 developer and fixed with Kodak AL4.

Determination of coordinates

At regularly spaced levels (150 μm), sections were stained with Cresyl Violet which allowed the determination of coronal, sagittal and horizontal coordinates by direct correlation with drawing of the atlas. Coronal, sagittal and horizontal planes and coordinates (in mm) correspond to the atlas of Paxinos and Watson[41] with interaural line (frontal and horizontal sections) and sagittal sinus (sagittal sections) as stereotaxic zeros.

Drawings of autoradiographic data and three-dimensional reconstructions

Drawings of autoradiographic data from individual sections were performed manually using a camera lucida. Three-dimensional reconstructions were made from drawings of individual serial sections. These drawings were regularly spaced and translated in a fixed angle chosen so as to reveal the best visualization of the continuous network of the patches. The spatial reconstruction was then obtained by connecting each individual drawing of patch compartments.

Determination of striosomal surfaces

First, in each section, the surface of the patches was calculated by determining the respective weights of magnified patch and matrix areas cut out from drawings of the sections made on a polyester film.

Second, autoradiograms were also visualized into digitalized maps using an image analyser (IMSTAR Paris, France) giving 256 gray levels per pixel. On each coronal section, the striatum was precisely outlined by hand and the surface of area analysed (in pixels) was obtained from the computer. The lowest patch optical density was then determined and used as a threshold to obtain the surface area (number of pixels) occupied by patches as previously described.[47]

RESULTS

Precise localization of [^{3}H]*naloxone binding sites on coronal and sagittal sections of the rat striatum*

Marked variations in the density and localization of [^{3}H]naloxone binding sites (mu opiate receptors) were seen on coronal sections between anterior and posterior regions of the striatum, as illustrated in Fig. 1. Indeed, intense labelling could be observed in the extreme rostral pole of the structure (A: 11.00), labelled areas (patches) consisting in large zones of complex shapes with several extensions (1 mm or more). More ventrally, high levels of binding sites were also seen in both the core and the shell of the nucleus accumbens. In contrast, at the caudal level (A: 8.5), the section was mainly represented by the matrix (unlabelled areas), labelled [^{3}H]naloxone patches being rare, spaced apart and of small size (100–200 μm). More numerous labelled patches were observed in the intermediate section (A: 9.00), in its more dorsal aspect particularly, some of them appearing regularly spaced along a diagonal axis. Finally, a fine discontinuous rich band of [^{3}H]naloxone binding sites was seen on all sections bordering and limiting the dorsolateral part of the striatum. In some places, this striatal delimitation was represented by serially labelled little barrels with sizes varying approximately between 50 and 100 μm.

On sagittal sections, the topographical organization of the labelled patches confirmed in several ways observations made on coronal sections (Fig. 1). Numerous and irregularly spaced [^{3}H]naloxone patches were observed in the central part of the medial section (L: 1.8) while larger labelled patches occurred in the extreme rostral pole of the striatum. At laterality L: 3.0, a continuous highly labelled area with multiple and large invaginations extending in the matrix was seen in the rostral region, while more caudally, the [^{3}H]naloxone-enriched patches of large diameter (200–400 μm) were more regularly distributed. The lateral part of the striatum (L: 4.5) was mainly represented by a large matrix field (absence of labelling) in its central zone with a densely labelled band in its rostroventral border. Finally, in agreement with results obtained on coronal sections, a rostrodorsal discontinuous thin band of [^{3}H]naloxone binding bordering the striatum was observed on all sections.

Serial horizontal sections were also made at the intermediate level of the striatum (H: 5.2) (Fig. 7). In each section, the rostral region was characterized by a highly labelled band delimiting the striatum and [^{3}H]naloxone patches of different shapes and sizes, some of them forming a continuous mediolateral channel with an oblique orientation. The caudal part of the striatum was devoid of [^{3}H]naloxone binding and thus represented a large matrix territory.

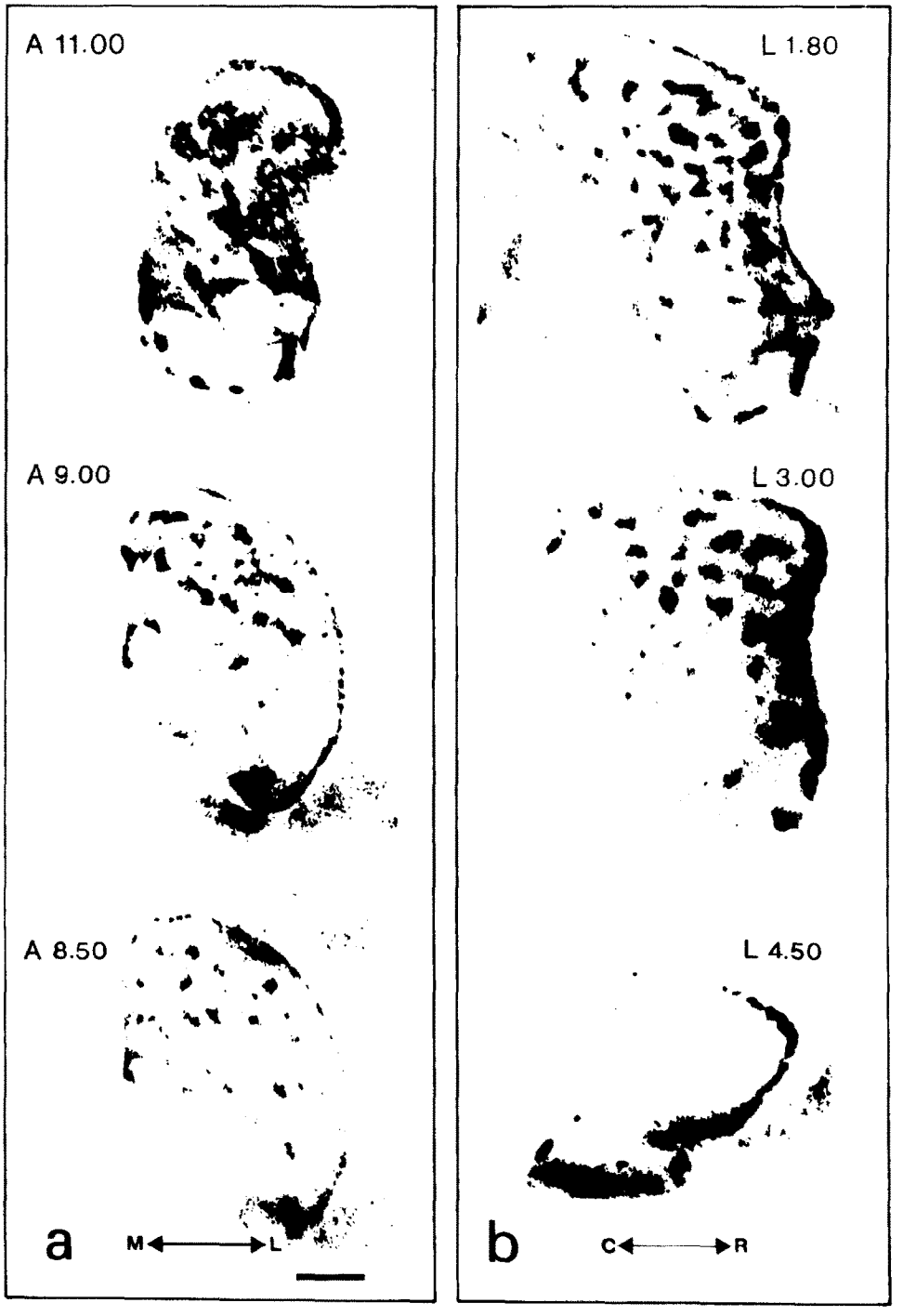

Fig. 1. Localization of mu opiate receptor rich (patches) and poor (matrix) zones on coronal and sagittal sections of the rat striatum. Sections (40 μm thick) taken at various anterior (a) and lateral (b) locations were used for [^{3}H]naloxone binding. Photomicrographs were made from autoradiograms at different levels of the striatum in anterior (A 8.50, A 9.00, A 11.00) and lateral (L 1.80, L 3.00, L 4.50) planes (in mm) (b), according to the atlas of Paxinos and Watson.[41] M: medial, L: lateral, C: caudal, R: rostral. Scale bar = 1 mm.

Reproducibility of the [^{3}H]*naloxone patches organization*

The topographical distribution of [^{3}H]naloxone patches was compared in the striatum of several animals using both coronal (six animals) and sagittal (three animals) sections. A diagrammatic illustration of results obtained at different anterior locations, in three animals, is indicated in Fig. 2. The discontinuous laterodorsal band of the patch compartment was observed in all animals. At each anterior location, the distribution pattern of [^{3}H]naloxone patches was closely similar from one animal to another. In all cases, labelled patches were more numerous and of

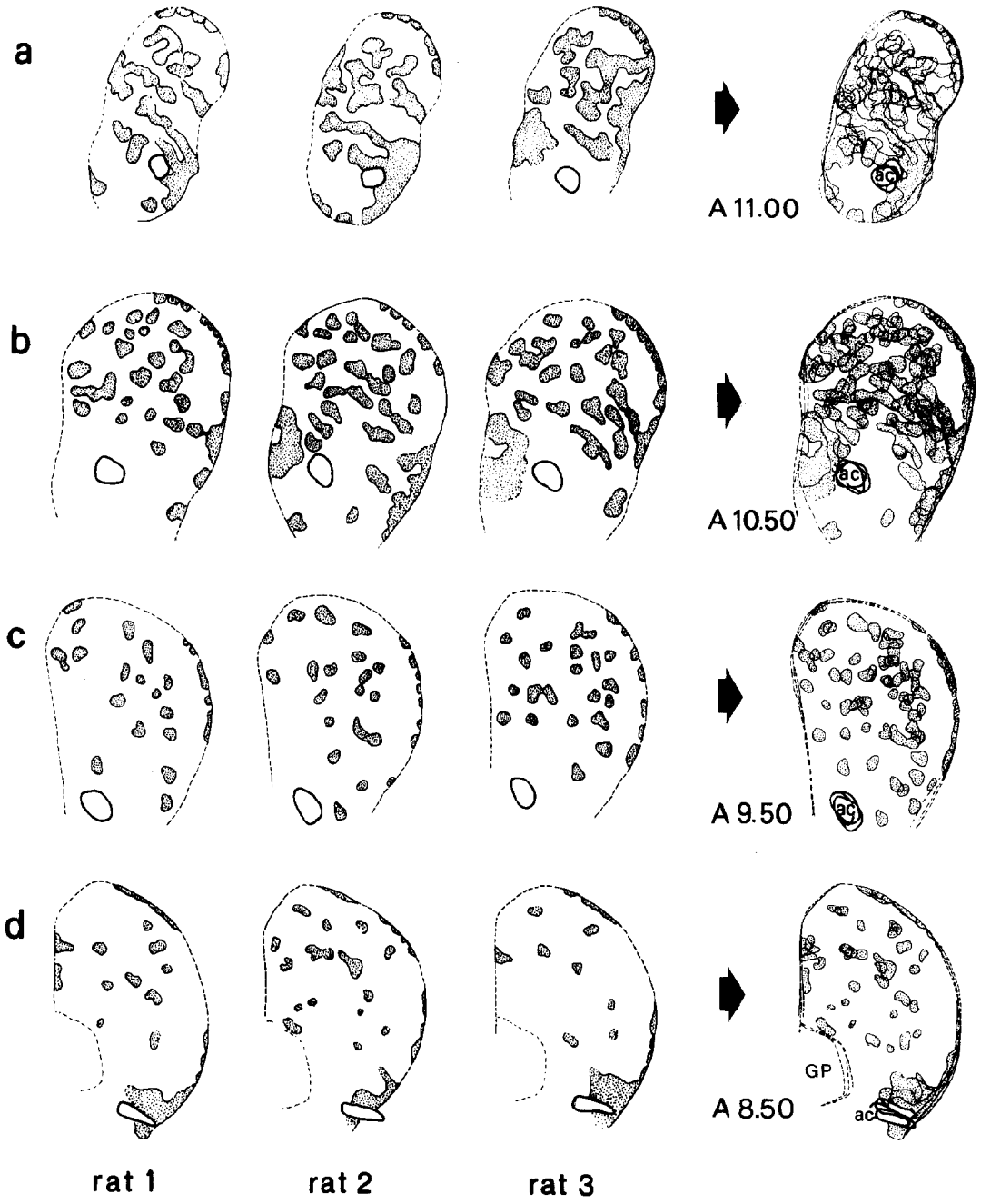

Fig. 2. Reproducibility of the localization of patch and matrix areas on rostral, medial and caudal coronal sections (a–d) of the striatum in three animals. Coronal sections were processed for [^{3}H]naloxone binding and drawings were made from some sections (A 11.00, A 10.50, A 9.50 and 8.50) as described in Experimental Procedures. These drawings schematically illustrate the distribution of the patches (dotted areas) and the matrix (white areas). The superimposition of individual localizations of the patches in the three animals is represented on the right side of the figure. ac, anterior commissura; GP, globus pallidus.

larger size in anterior sections (A: 11.0 and A: 10.50) while their number and size were reduced in posterior sections. In fact, the overall surface of [^{3}H]naloxone patches represented 43.0 ± 1.5 and $13.3 \pm 0.7\%$ of the striatal surface at A: 11 and 8.5, respectively. However, due to the thickness and tortuous shape of the patch compartment in the rostral part of the striatum, the precise degree of reproducibility of the striatal heterogeneity could not be determined from one animal to another. Nevertheless, a large (0.8 mm) matrix zone (no labelling) located in the laterocaudal part of the striatum (A: 8.5) was found in the six animals investigated.

Observations made on sagittal sections (L: 4.5, 3.0, 1.8) confirmed those from coronal sections (Fig. 3). Indeed, in the lateral part of the striatum (L: 4.5) a large matrix field with a thin patch band bordering the rostral, dorsal and ventral parts of the structure was observed in all animals. At the intermediate laterality (L: 3.0), the rostral part of the striatum was characterized by reproducible large [^{3}H]naloxone-labelled fields while a rather random distribution of small [^{3}H]naloxone patches was detected in the core of the structure. Finally, more medially (L: 1.8), irregularly spaced patches of different sizes and shapes were seen in all cases. Altogether, these results demonstrate that the patch compartment is particularly prominent in the rostral pole of the structure while its laterocaudal part is mainly represented by the matrix.

Periodicity of the [^{3}H]naloxone patches in the core of the striatum

The regularity of the distribution of [^{3}H]naloxone patches was first analysed precisely in one sagittal plane (L: 3.0) (Fig. 4). Data obtained from five successive sections (200 μm thick) were superimposed and the centre of the surface delimited by individual superimposed patches was determined. Corresponding dots were connected by lines which, in most cases, were parallel and perpendicular to the rostral pole of the striatum. This analysis indicated that the [^{3}H]naloxone patches were regularly distributed and represented an organized network. Indeed, centre to centre spaces estimated rostrocaudally ranged from 400 to 665 μm (mean $\pm$ S.E.M.: 566 ± 27 μm) while

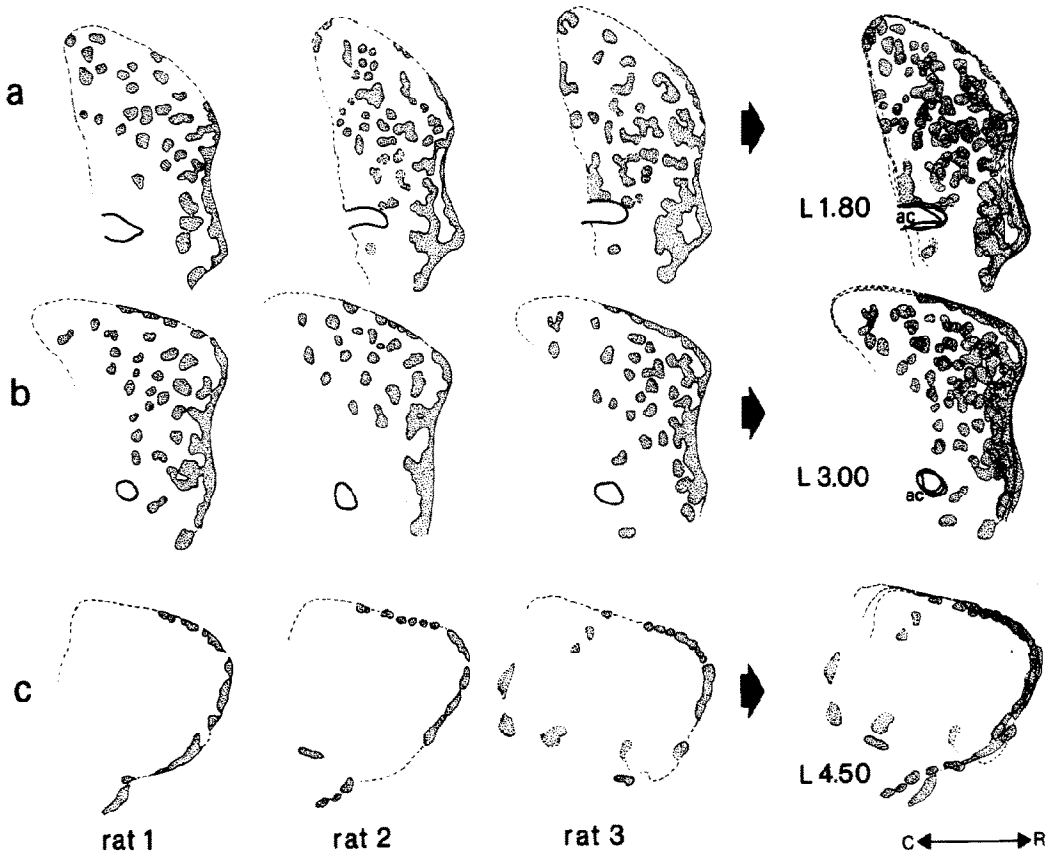

Fig. 3. Comparison of the localization of patch areas on medial (a, L 1.80), central (b, L 3.00) and lateral (c, L 4.50) sagittal sections of the striatum in three animals. Sagittal sections were processed for [^{3}H]naloxone binding and drawings were made for some sections as described in Experimental Procedures. This figure schematically illustrates the localization of the patches (dotted areas) and the matrix (white areas). The superimposition of individual localizations of all patches in a given sagittal plane in the three animals is represented on the right part of the figure. ac, anterior commissura; C, caudal; R, rostral.

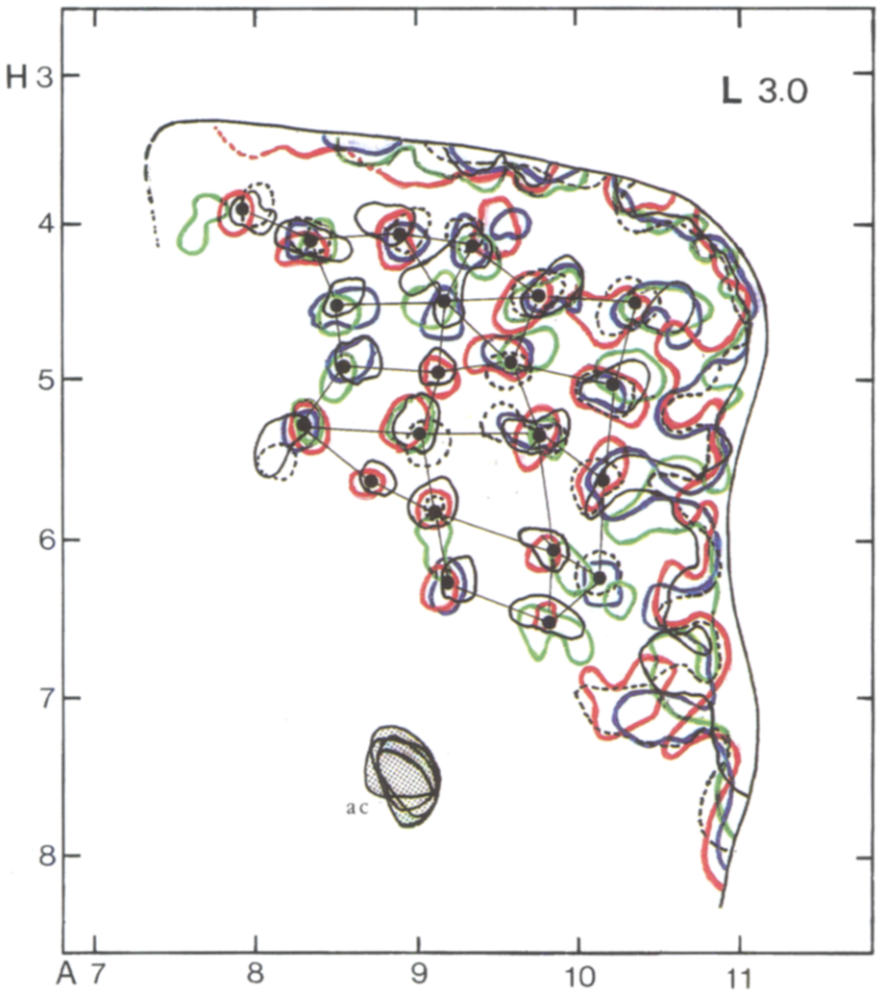

Fig. 4. Spatial distribution of mu opiate patches in the core of the striatum as determined in a sagittal section. Superimposition of data obtained from five successive sections (40 μm thick each) drawn from the autoradiograms (using, separate line or colour coding) (e.g. see Fig. 1b, laterality 3.00). Centre to centre interspaces between superposed patches are indicated by lines exhibiting parallel and perpendicular orientations to the rostral pole of the striatum. ac, anterior commissura.

those determined dorsoventrally ranged from 365 to 665 μm (466 $\pm$ 5 μm), this estimation being made from about 20 patches.

Three-dimensional reconstruction of the patch compartment

The three-dimensional organization of the patch compartment was first reconstructed using successive coronal sections as described in experimental procedures (Fig. 5). In the intermediate part of the striatum, small parallel tortuous channels oriented in an oblique direction could be observed. Occasionally, elongated extensions establishing connecting bridges between mediolateral patch channels were seen. In contrast, no visible organization could be detected at the rostral pole of the structure, the patch field exhibiting a very complex architecture. Finally, as previously indicated, only a few and very spaced apart patches were observed in the caudal part of the striatum.

The patch compartment organization was more precisely revealed by the three-dimensional reconstruction performed with serial sagittal sections (Fig. 6). Two striatal areas were mainly analysed (central: L: 1.8 to L: 3.0 and lateral: L: 3.8 to L: 4.8). In the central region, besides the rostral prominent and tortuous patch field, serial parallel continuous patch channels (approximately 20) running in a mediolateral direction and in some cases presenting connecting branches could be observed. In contrast, the lateral part of the striatum (L: 3.8 to L: 4.8) was characterized by a very large matrix territory delimited in the rostral part by a fine patch border.

Finally, attempts were also made to utilize some horizontal sections (Fig. 7). As expected, the extreme rostral pole of the striatum was characterized by a complex tortuous patch field. Besides this large patch territory, a long channel exhibiting a transverse and oblique orientation could be easily reconstructed from autoradiographic data obtained on four serial

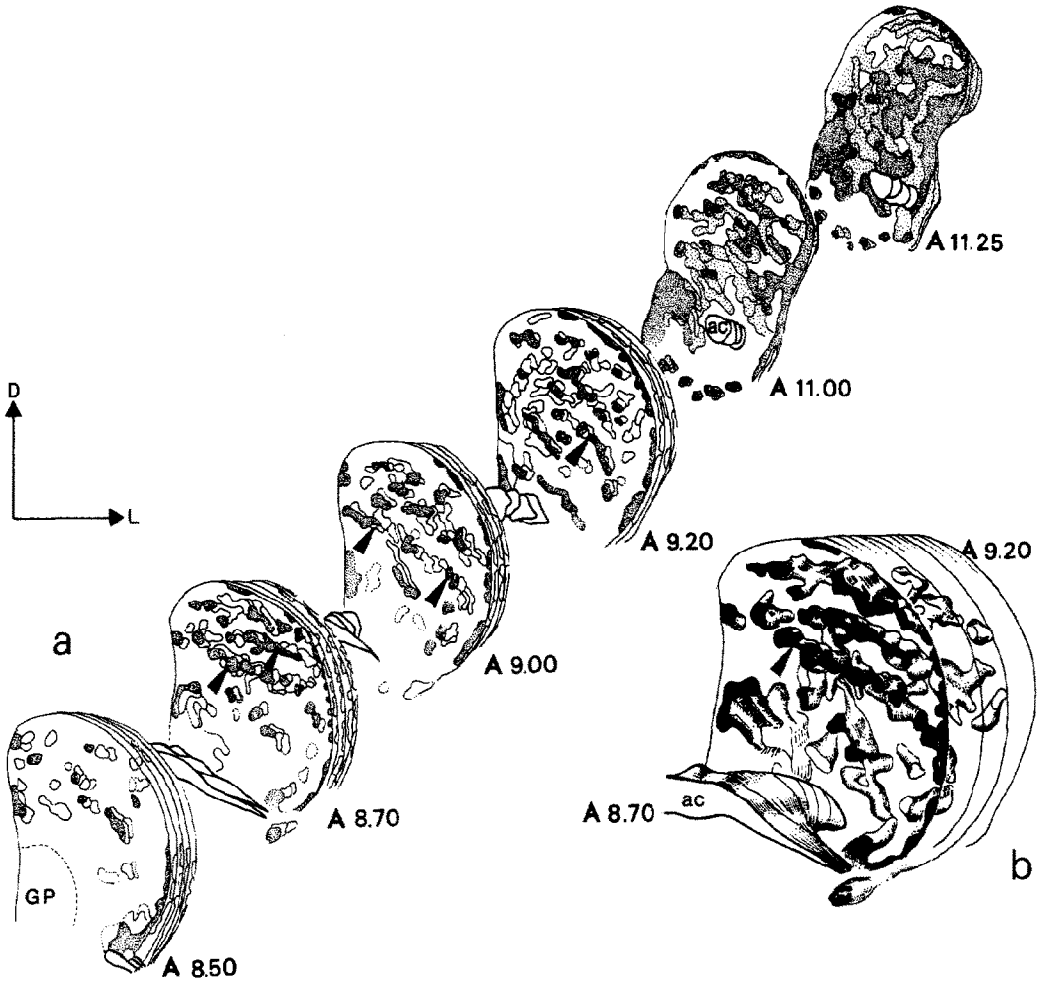

Fig. 5. Three-dimensional organization of the patch and matrix compartments reconstructed from autoradiographic data and corresponding drawings obtained from coronal sections. Sections were taken in the caudal, central and rostral parts of the striatum from A 8.50 to 11.20 (a). A three-dimensional reconstruction (500 μm final thickness) was made from all sections examined between A 8.7 to A 9.2 slightly translated in the lateral direction (b), the limits of the patches being used for this schematic reconstructed drawing of the patch compartment (all successive sections were used in order to avoid any distorsion of the patch topology). ac, anterior commissura; GP, globus pallidus; D, dorsal, L, lateral. Black arrowheads indicate the localization of some oriented mediolateral patch channels.

sections. The caudolateral parts of these sections were exclusively represented by matrix tissue.

DISCUSSION

Using [^{3}H]naloxone binding in most cases as a marker of the patch compartment and coronal brain sections, several authors have described the heterogeneous distribution of the patches within the rat striatum. Indications about their number, shape, size and volume occupancy have been given occasionally and as for other species (the cat, the monkey or the human particularly), it has been mentioned or suggested that the patches (or striosomes) correspond to complex labyrinthine channels.[18,23,25,27,30] However, to our knowledge, no attempt has been made to perform in the rat a systematic analysis of the patch network and to reconstruct its architecture in three dimensions as has been done in the cat by our group[6] and by Groves *et al.*[24]

Anatomical properties of patch compartment

[^{3}H]Naloxone binding is indeed an excellent and constant marker of the patch compartment in the embryonic, young and adult rat. This differs from tyrosine hydroxylase immunoreactivity and acetylcholinesterase activity since the localization of these two markers changes during development. Indeed, in the young animal both tyrosine hydroxylase immunoreactivity and acetylcholinesterase activity are present in the patches[13,18,38,39] while in the adult the whole striatum is innervated by dopaminergic fibres[8,14,28] and acetylcholinesterase activity is particularly dense in the matrix.[6,23,27] Moreover, due to the

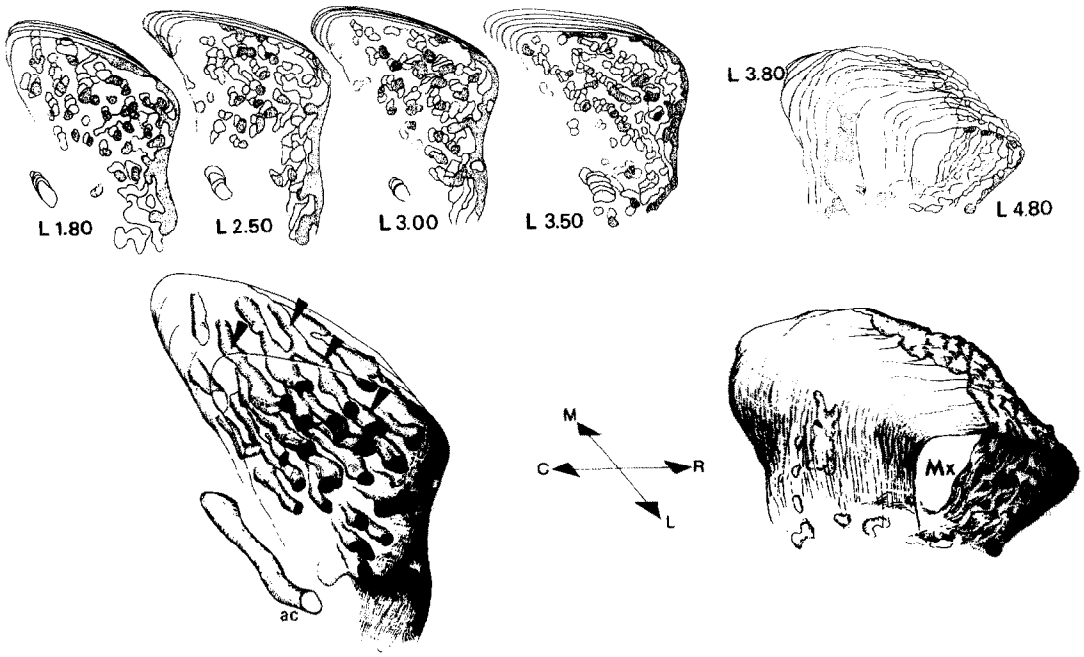

Fig. 6. Three-dimensional organization of the patch and matrix compartments reconstructed from autoradiographic data and corresponding drawings obtained from sagittal sections. Sections were taken in the medial, central and lateral parts of the striatum from L 1.80 to L 4.80. Mediocentral (L 1.80 to L 3.00) (left part of the figure) and lateral (L 3.80 to L 4.80) (right part of the figure) three-dimensional reconstructions were performed by slight translation of each individual two-dimensional drawing along a well-defined axis. Black arrowheads indicate the localization of some mediolateral orientated patch channels. ac, anterior commissura; M, medial; L, lateral; R, rostral; C, caudal; Mx, matrix; P, patches.

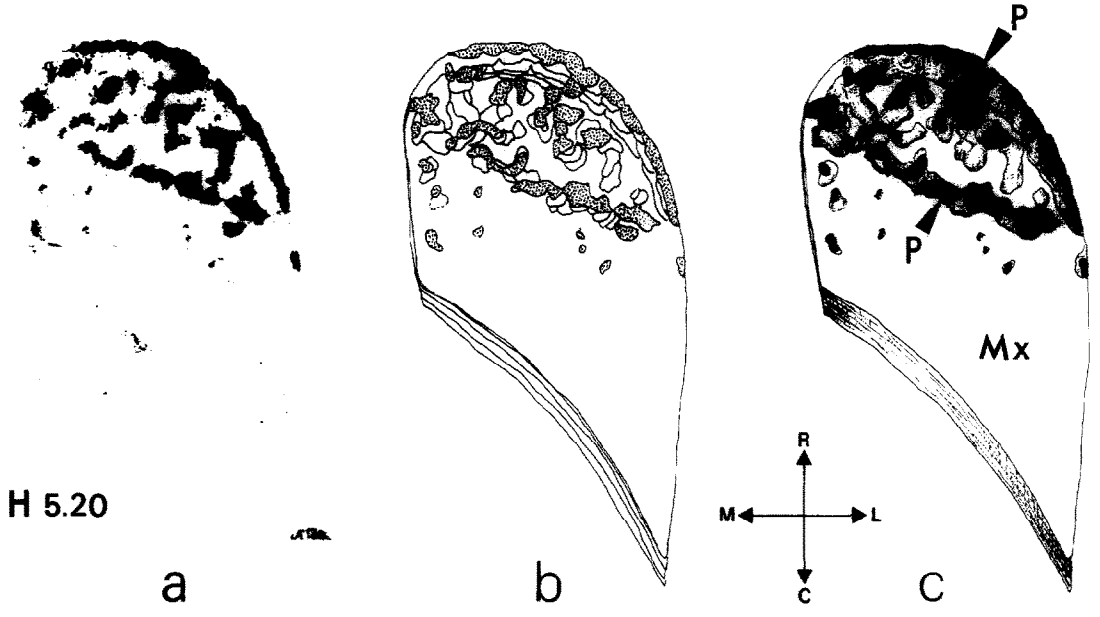

Fig. 7. Partial reconstruction of the three-dimensional organization of the patch compartment obtained from horizontal sections. (a) Distribution of mu opiate rich (patch) and poor (matrix) zones as obtained by superimposition of five successive autoradiograms at level H 5.20. (b) Partial reconstruction from successive individual two-dimensional drawings. (c) Spatial organization of the patch network. Black arrowheads indicate the localization of one oriented lateromedial channel as well as the limiting patch territory of the striatum. M, medial; L, lateral; R, rostral; C, caudal; Mx, matrix; P, patches.

highly contrasted distribution of mu opiate receptors in the rat striatum, the exact correspondence between the patches described in the adult cat and primate (as characterized by their low acetylcholinesterase content) and the [^{3}H]naloxone patches observed in the rat must be firmly established. Herkenham and Pert[27] first reported that acetylcholinesterase-poor zones were in register with [^{3}H]naloxone-labelled patches in the adult rat. In fact, the areas labelled with [^{3}H]naloxone are devoid of somatostatin-immunoreactive fibres and of calcium-binding protein, two markers of the matrix.[12] Interestingly, we have also observed in the adult cat that the areas exhibiting high levels of [^{3}H]naloxone binding sites are in register with acetylcholinesterase-poor zones.[32]

Providing additional proof for the selective localization of [^{3}H]naloxone binding sites in the patches, [^{3}H]thymidine experiments have shown a close correspondence between the localization of the clusters of aggregated early born striatal neurons and of the patchy areas of [^{3}H]naloxone binding in the young rat.[49] Neurons born later which will form the matrix are outside the [^{3}H]naloxone patches[49] and can be visualized by their high content in calcium-binding protein.[12,35] In addition, although differing by their shape and size as well as by their labelling intensity, [^{3}H]naloxone patches can be seen in transplants or grafts made either with embryonic striata or dissociated striatal cells indicating further that mu opiate receptors are mainly located on a population of striatal neurons and not on striatal afferent fibres.[22,34]

Topographical organization and reproducibility of patch compartment

Our results obtained on coronal, sagittal and horizontal sections reveal once more the large heterogeneity of the topographical localization of the patches within the rat striatum. The patch compartment represents 43% and only 13% of the total surface in rostral and caudal coronal sections, respectively, the remaining striatal tissue being represented by the matrix compartment and large bundles of crossing fibres. The decrease in the volume of the patch occupancy observed along a rostrocaudal axis seems to be directly linked to the number, the shape and the diameter of the patches. Indeed, the number of patches decreased progressively from intermediate to more caudal coronal sections and their size ranged from more than 1 mm at the rostral pole to 100 μm or less in caudal sections. This rostrocaudal heterogeneity was also very apparent on sagittal or horizontal sections. In addition, in the latter cases, besides the high density of the patch tissue observed in the rostral and medial parts of the striatum, large territories represented mainly, if not exclusively, by the matrix were seen in the caudolateral part of the structure.

In addition, as expected, a good reproducibility in the respective topographical distributions of the patches and the matrix was found when results obtained with coronal and sagittal sections were compared in different animals. These observations are of interest for functional electrophysiological or biochemical studies in which attempts are made to distinguish the properties of the two striatal compartments in the rat. This also explains why sagittal sections were used in our investigations upon the presynaptic regulation of dopamine release in these compartments.[33] Indeed, in this condition, areas highly enriched in patches or represented exclusively by the matrix can be easily selected ensuring the accurate interpretation of the data.

Spatial organization of patch compartment

A labyrinthine organization of the patch network has been suggested by several workers who have used different biochemical markers and uninterrupted series of serial frontal sections.[6,18,23,27,30] In our three-dimensional reconstruction study made in the cat caudate nucleus using acetylcholinesterase-poor zones for identification of the striosomes, the striosomal compartment was found to be organized in a continuous network of distinct channels oriented in parallel arrays both in the rostrocaudal and mediolateral axis, these crossed channels being particularly distributed in the mediocentral zone of the structure. More precisely, four striosomal labyrinths running parallel to the rostrocaudal axis and seven to eight parallel and equally spaced mediolateral bridges of similar shape and size could be distinguished. In addition, the channels oriented in a rostrocaudal direction converged in the rostral part of the structure where they fuse, forming at this level an homogeneous and extended striosomal field.[6]

In the rat, the first indication for the existence of an organized patch network was obtained from superimposed drawings of autoradiographic data from a few serial sagittal sections taken in the intermediate part of the structure. These superimposed drawings already showed that in the core of the striatum, the patches were equally spaced continuous elongated structures as determined from their distance from one another in the rostrocaudal and mediolateral directions. In addition, reconstructed three-dimensional drawings performed either from coronal, sagittal or horizontal sections allowed us to conclude that the architecture of the patch network was mainly characterized by elongated patches running in parallel along a mediolateral axis and diagonally oriented. Bridges between these elongated channels could be seen in both the rostrocaudal and dorsoventral axes but they seemed to be randomly distributed. This overall organization was particularly striking in the three-dimensional reconstruction performed from sagittal sections which allowed us to distinguish about 20 patch channels parallely distributed. A more partial view of this cytoarchitecture was observed in three-dimensional reconstructions made from coronal or horizontal sections but the oblique orientation of these channels in the mediolateral axis was easily

apparent. Two other aspects of the patch network of the rat striatum should be underlined: first, the large patch bordering its rostral pole characterized by its several extensions in the matrix connected occasionally with other more caudal patches; second, the rather scattered distribution of patches in its caudal region. Curiously, contrasting with results obtained in the cat,[6] channels exhibiting a rostrocaudal direction could not be detected. In addition, the patch channels observed in the mediolateral direction in the core of the striatum were much more numerous in the rat than in the cat.

As just indicated, the architecture of the patch compartment in the rat differs from that of the cat by the absence of rostrocaudal channels and the increased number of mediolateral patch channels. This may be related to some differences in the processes involved in the migration of the patch neurons, their specific recognition through surface adhesion molecules and their final positioning due to the progressive establishment of their afferent and efferent connectivities. It should also be recalled that the segregation of patch neurons in connected channels depends also on the characteristics of the development and final stabilization of the matrix network.[16,18,34,49] The role of the numerous cortical fibres which perforate the striatum in the rat, but not in the cat, or the difference between the two species in the organization of target cells of patch neurons in the pars compacta cannot be neglected. However, one important question for further studies will be to determine whether this difference in the patch cytoarchitecture between these two species has a functional significance. In this context, several studies have indicated that the general principle of organization of corticostriatal fibres is identical in the two species, projections from different functionally related cortical areas being distributed along a rostrocaudal axis.[1,17,19,37] Similarly, striatal neurons innervated by these different cortical areas seem to project to the substantia nigra in curvilinear lamella respecting the rostrocaudal organization.[5,46] The orientation of the main channels of striosome (patch) or matrix cells innervating the substantia nigra respects this organization in the cat (unpublished observations). This is not the case in the rat since the patch channels exhibit mainly a mediolateral orientation. The precise topographical organization of the afferent connections to the patch compartment and of the distribution of the projections from this compartment to their target structures in the rat should perhaps help us to understand this enigma.

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