

## Neuropeptide Y-immunoreactive neurons in corpus striatum of the Korean squirrel (*Sciurus vulgaris coreae*)

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### 청서 뇌 줄무늬체에서 neuropeptide Y 면역반응신경세포의 분포

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**초 록**: 야생 설치류인 청서 뇌의 줄무늬체에서 neuropeptide Y(NPY) 면역반응신경세포의 분포상태를 관찰하기 위하여 뇌를 4% paraformaldehyde로 관류고정한 전뇌를 40 $\mu$ m의 냉동연속관상절편으로 작성한 후 cresyl violet로 염색하여 전뇌의 각 부분을 구분하고 NPY항체에 대한 면역염색을 실시하였다.

줄무늬체는 속섬유막(internal capsule)보다 앞쪽에서는 꼬리핵(caudate nucleus)과 조가비핵(putamen)이 꼬리-조가비핵(caudate-putamen)의 한부분으로 구성되어 있는 반면, 속섬유막이 관통하는 부분에서는 꼬리핵, 조가비핵 및 창백핵(globus pallidus)의 세부분으로 구분되었다.

줄무늬체의 NPY면역반응신경세포는 대부분이 중간크기(12-18 $\mu$ m)의 세포였다. NPY세포체의 분포는 꼬리-조가비핵과 꼬리핵의 경우에 내측 및 배쪽부분에서 다수 존재하였으며, 조가비핵의 경우는 전체적으로 불규칙하였는데 그중 중심부분이 더욱 적은 수로 관찰되었다. NPY면역반응신경섬유의 밀집도는 전체적으로 낮았으나 반응신경세포체가 많은 부분에서 높은 밀집도를 보였다. 꼬리-조가비핵과 꼬리핵의 경우 내측과 배쪽부분에서 높은 밀집도를 나타내었고 조가비핵의 경우는 불규칙한 밀집도를 보였다. 창백핵에서는 매우 적은 수의 반응섬유들만 관찰되었다.

따라서 청서의 줄무늬체는 꼬리핵, 조가비핵 및 창백핵으로 구분되어 비교적 발달된 구조를 가졌으며, NPY함유 신경세포의 분포형태도 이질성을 나타내는 것으로 보아 줄무늬체의 신경환로가 복잡함을 암시하였다.

**Key words**: neuropeptide Y, immunohistochemistry, corpus striatum, Korean squirrel.

#### Introduction

Neuropeptide Y (NPY) was first isolated from por-

cine brain and predominantly expressed in the nervous tissue<sup>1</sup>. NPY consists of 36-amino acid polypeptide which showing structural similarity to pancreatic

polypeptide. Because of its wide distribution<sup>2,3</sup> and a broad spectrum of responses, it has been studied to diverse species in the central nervous system, respectively.

It is now generally accepted that NPY is involved in the direct vasoconstriction action, in the release of neuron modulators, in the postsynaptic effects of noradrenaline, in the changes of epithelial ion transport, and in the glucose-stimulated insulin secretion<sup>4-8</sup>. In the brain, NPY may be involved with the central control of cardiovascular and respiratory functions, feeding behavior, hormone secretion, and the regulation of circadian rhythms<sup>9-13</sup>. There is considerable evidence, therefore, suggesting that NPY may play an important role in the brain like neurotransmitter or neuromodulator.

A large number of NPY-immunoreactive neurons are highly expressed in the striatum of some animals.<sup>2,14-18</sup> The distribution pattern of NPY immunoreactive neurons is diverse between species, whereas size and morphology of these neurons suggesting that they respond to the aspiny type I cells of Golgi classification.<sup>16,19,21</sup> In central nervous system, NPY-immunoreactive perikarya and fibers have been shown to co-exist with catecholamine<sup>22-24</sup>, GABA<sup>25,26</sup> and somatostatin<sup>16,17,27-31</sup>. The functional significance, however, of these various co-expression profiles in the central nervous system mostly remains to be established<sup>32</sup>.

The objective of the present study was to define NPY containing neurons and fibers in the corpus striatum of Korean squirrel, using immunohistochemistry. At the same time, it was thought to be worth while to attempt to identify protein expression for the first time in this species.

## Materials and Methods

**Preparation of tissue**: 5 male and female Korean squirrels weighing 350-430 gm were studied. All subjects were healthy as confirmed by normal behavior. After transportation to laboratory, under pentobarbital anesthesia (40mg/kg, i.p.), the squirrels were perfused through the ascending aorta with following solution: (1) 300-400ml 0.85% saline containing 0.05% heparin; (2) 500ml of 4%-paraformaldehyde solution in 0.1 M phosphate buffer (PB, pH 6.5) for 30 min; (3) 500ml

of 4%-paraformaldehyde solution in 0.1 M borate buffer (pH 11.0) for 30min. The brain and upper cervical spinal cord were removed and then immersed in the last fixative solution for 4-8 hr. And the brain was immersed again in 30% sucrose solution in 0.1 M phosphate buffer (pH 7.4). Cryo coronal serial sections (40  $\mu$ m thickness) were performed with a freezing microtome (Reichert-Jung).

**Immunohistochemical procedure**: The sections were preincubated with 1% normal goat serum, and incubated for 72 hr by neuropeptide Y (NPY) anti-serum raised in rabbit, which were diluted in phosphate buffered saline (PBS, 0.1 M, pH 7.4) containing 0.3% Triton X-100, at 4°C. Another sets of section were stained with cresyl violet for specific neuron localization. Following incubation with the primary antiserum, the sections were washed three times in PBS for 10 min. The sections then were treated in the 1:200 dilution of biotinylated swine anti-rabbit immunoglobulins (Biomakor) containing the 1% bovine serum albumin and 0.3% Triton X-100 at 4°C for 12 hr. Following this step, sections were rinsed in PBS for 10min and were incubated for 12 hr in a 1:200 dilution of peroxidase-conjugated streptavidin (Biomakor) containing the 1% bovine serum albumin. Sections were rinsed twice in PBS for 10min and then were treated for 10-15 min with 3-3'-diaminobenzidine-tetrachloride in PB (pH 7.4) containing 0.003% hydrogen peroxide. The sections were rinsed two times in PB and mounted onto poly-L-lysine (Sigma) coated glass slides. The sections were applied 1% osmium tetroxide, defatted in alcohol, cleared in xylene, and mounted with cover glasses.

**Mapping and photography**: Sections stained with cresyl violet were magnified directly by enlarger (Omega). The prints of the lower magnifications were traced using rotering pen to define neuroanatomical boundary. The immunoreactive-sections were examined using an Axiophot photomicroscope (Zeiss). In order to obtain accurate localization of the neuronal elements present in the corpus striatum, maps were made of all the specimens, with a NPY immunoreactive neurons and fibers elements charted. Counts of identified NPY immunoreactive neurons and fibers were made with attention to their specific location in the corpus striatum. Photographs were made with an Axiophot photomicroscope (Zeiss) with black and white or color

films(Kodak).

## Results

**General observation of corpus striatum :** The corpus striatum of Korean squirrel brain was identified into three nuclei, caudate nucleus, putamen and globus pallidus. Majority of the corpus striatum was divided into the caudate nucleus and lentiform nucleus by the internal capsule, the latter was able to be distinguished into putamen and globus pallidus. Anterior part, however, of the corpus striatum was observed as caudate-putamen, which were combined into one structure(Figs 1-6).

### Distribution of NPY immunoreactivities :

**General observations :** The corpus striatum was recognized throughout by heterogeneously scattering of strongly NPY immunoreactive(NPY-IR) neurons with varicose dendrites and fibers(Figs 1-6,13,14). NPY-IR neurons were small(6-11  $\mu\text{m}$ ) and medium-sized(12-18  $\mu\text{m}$ ). The neurons could be subdivided into three types in shape. The first type, which represented about 70% of all NPY-IR neurons, was of round, oval or fusiform(Figs 13, 14). The second type, which represented about 25%, was triangular(Fig 15). And the third type, about 5%, was multipolar(Fig 17).

The corpus striatum contained a low level of NPY-IR fibers, whose distribution appeared to be related to the immunoreactive perikarya. The fiber density increased in a rostrocaudal direction.

**Caudate-putamen :** The NPY-IR neurons were located in a greater number of the medial and ventral parts of the caudate-putamen; fewer stained neurons were found in the dorsolateral part(Figs 7, 8). The NPY-IR fibers were distributed throughout the caudate-putamen; the density of the NPY-IR fibers was higher in the medial and ventral parts than in the other parts.

**Caudate nucleus :** The number of NPY-IR neurons of the caudate nucleus was more than that in the putamen. Large number of these neurons was located in the medial and ventral parts, especially medial part. The NPY-IR fibers were distributed throughout the caudate nucleus; the density of the NPY-IR fibers was high in the medial half and low in the lateral half. In addition, however, more dense areas of fibers were detected. This finding was on the border of the lateral

ventricle but within the nucleus, where short lengths of varicose fibers appeared orientated perpendicular to the ependymal surface(Figs 11, 12)

No NPY-IR fibers were detected in the myelinated fiber bundles of the internal capsule.

**Putamen :** The density of NPY-IR neurons and fibers of the putamen was lower than that of the caudate nucleus. In the anterior part of the putamen NPY-IR neurons were scattered throughout the nucleus. NPY-IR neurons in posterior part of the putamen were found generally in the lateral and inferior parts; the lowest number of perikarya were found in central area. The NPY-IR fibers of the putamen were low density, but whose distribution appeared to be related to the NPY-IR perikarya(Figs 9, 10).

**Globus pallidus :** The globus pallidus contained no NPY-IR neurons, but contained NPY-IR fibers in the lowest density. The pattern of NPY-IR fibers was scattered throughout the globus pallidus.

## Discussion

A large number of medium-sized multipolar NPY-IR neurons were observed throughout the striatum of the Korean squirrel. A higher density of NPY-IR neurons and fibers was detected medial and ventral parts of the caudate nucleus. In the anterior part of the putamen NPY-IR neurons were scattered throughout the nucleus; in posterior part were detected generally in the lateral and ventral parts. NPY-IR neurons have been reported in higher density in dorsal and lateral striatum of the rat<sup>2,3</sup>. Also the work in the rat and monkey has indicated a higher density of immunoreactive cells in caudal striatum compared to rostral regions<sup>2,3,14,15,16</sup>. The results of present and other studies, therefore, reveal that the striatum is much more heterogeneous in the distribution of the NPY immunoreactivities. The distribution, size and morphology of these immunoreactive cells suggested that they corresponded to the aspiny type I cells of the Golgi classification<sup>30,33,34</sup>.

The mammalian striatum has long been considered as a homogeneous entity. The results of recent various studies, however, reveal that the striatum is much more heterogeneous than previously suspected. Graybiel and Ragsdale<sup>35</sup> demonstrated that the acety-

## Summary

Cholinesterase activity in the cat caudate nucleus is distributed according to a highly heterogeneous and complex mosaic-pattern. Many investigators have demonstrated that the principal striatal afferents, which come from cerebral cortex, substantia nigra, thalamus and amygdala, terminate in distinct patches of various size throughout the striatum<sup>16, 18, 35, 42</sup>. Furthermore, the striatal distributions of tyrosine hydroxylase<sup>19, 43</sup>, certain neuropeptides<sup>16, 17, 19, 44, 46</sup> as well as opiate receptors<sup>38, 47, 48</sup>, also displays marked heterogeneities. Despite the uniform distribution of NPY-positive cells there is evidence that in the cat and human caudate the distribution of cells may be correlated with the so-called 'striosomes'<sup>18, 49</sup>. Clumps of immunoreactive cells in human caudate nucleus avoid zones of low cholinesterase activity<sup>9</sup>. The results of the present study was validated by the evidence observed in the caudate nucleus and putamen of the squirrel as a heterogeneous pattern.

NPY-IR neurons have also been reported to be coexpressed with somatostatin-like immunoreactivities in these cells in rat, monkey and human brain<sup>4, 18, 31</sup>. The neurons also contain a marker of uncertain physiological significance: nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase<sup>9</sup>, and are distinct from the large cholinergic interneurons in the rat<sup>18</sup>.

Many of the immunoreactive fibers in corpus striatum are likely to be of local origin<sup>16</sup>. The striatum contains a non-uniform distribution of fibers, with a low density in the striatum<sup>2, 4, 15</sup> and in addition higher density patches on the lateral ventricle border<sup>14, 16</sup>. In the present study, NPY-IR fibers were distributed throughout the striatum; the density of the NPY-IR fibers was intensely expressed in the medial half and, to a less degree in the lateral half. In addition, however, more dense areas of fibers were detected. This finding was on the border of the lateral ventricle but within the nucleus, where short lengths of varicose fibers appeared orientated perpendicular to the ependymal surface. NPY-IR fibers, therefore, may be abundant on the lateral ventricle border in mammals striatum.

In brief, NPY-immunoreactivities in the corpus striatum are not homogenous but heterogenous in distribution. These findings may reflect innate characteristics of the specific neural circuit in the corpus striatum itself.

The present study was performed to investigate the distribution of neuropeptide Y immunoreactivities in the corpus striatum of the Korean squirrels. The animals were perfused with 4%-paraformaldehyde and the brain was cut serially into 40  $\mu$ m thick coronal sections. Sections either were stained with cresyl violet or were stained immunohistochemically.

The corpus striatum was divided into the caudate nucleus, putamen and globus pallidus. Anterior part, however, of the striatum was observed as the combined caudate-putamen.

NPY immunoreactive (NPY-IR) neurons were medium-sized. The corpus striatum contained a low level of NPY-IR fibers, whose distribution appeared to be related to the immunoreactive perikarya. Large numbers of NPY-IR neurons in the caudate-putamen and caudate nucleus were expressed in medial and ventral parts. In the anterior part of the putamen NPY-IR neurons were scattered throughout the nucleus; in posterior part were found generally in the lateral and ventral parts. The density of NPY-IR fibers of the putamen were low, whose distribution appeared to be related to the perikarya. The globus pallidus contained NPY-IR fibers only in the lowest density.

In brief, NPY-immunoreactivities in the corpus striatum are heterogenous in distribution. These findings may reflect innate characteristics of the specific neural circuit in the corpus striatum itself.

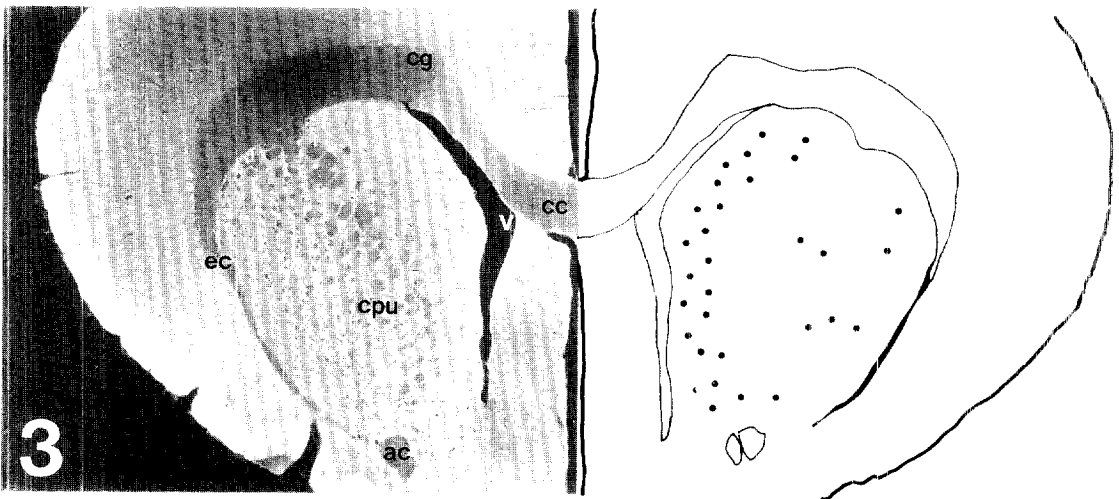
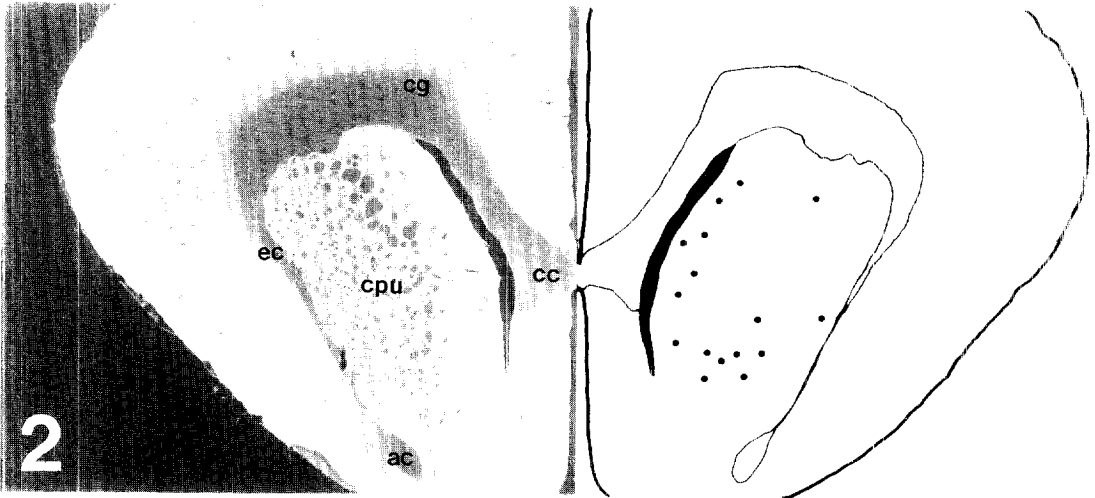
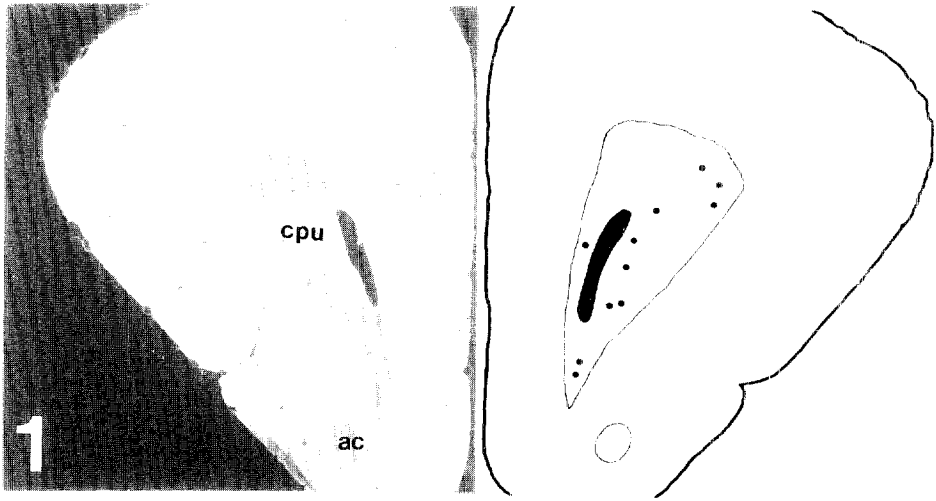
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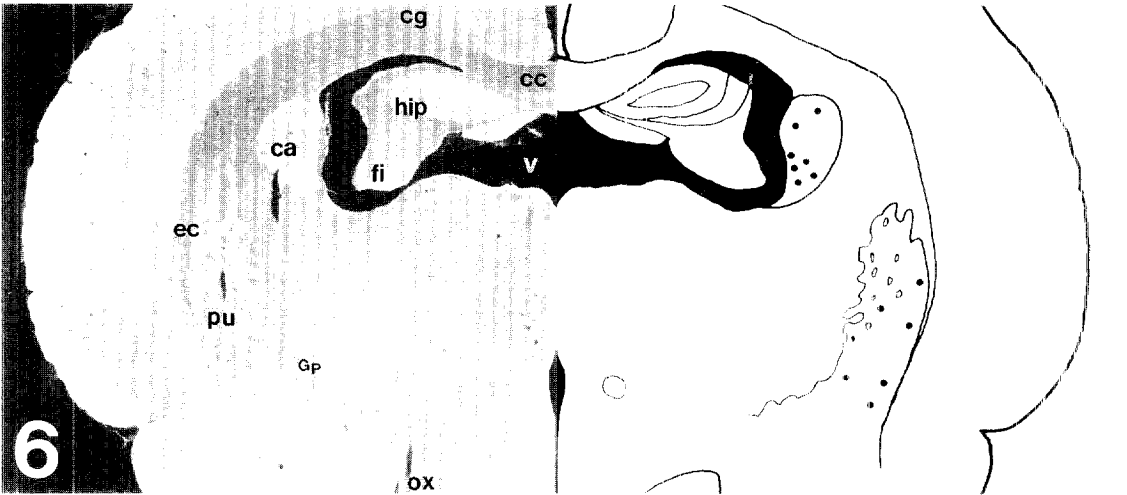
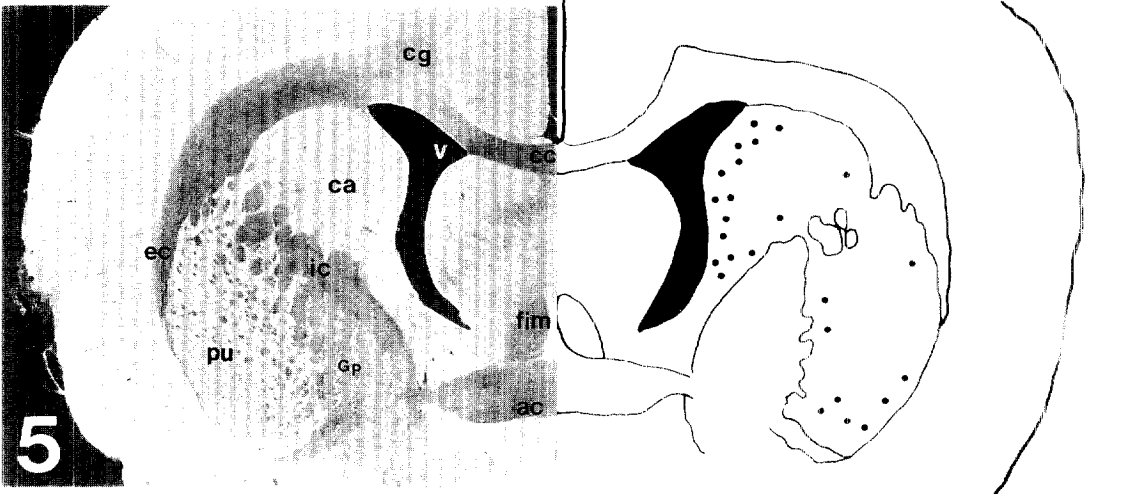
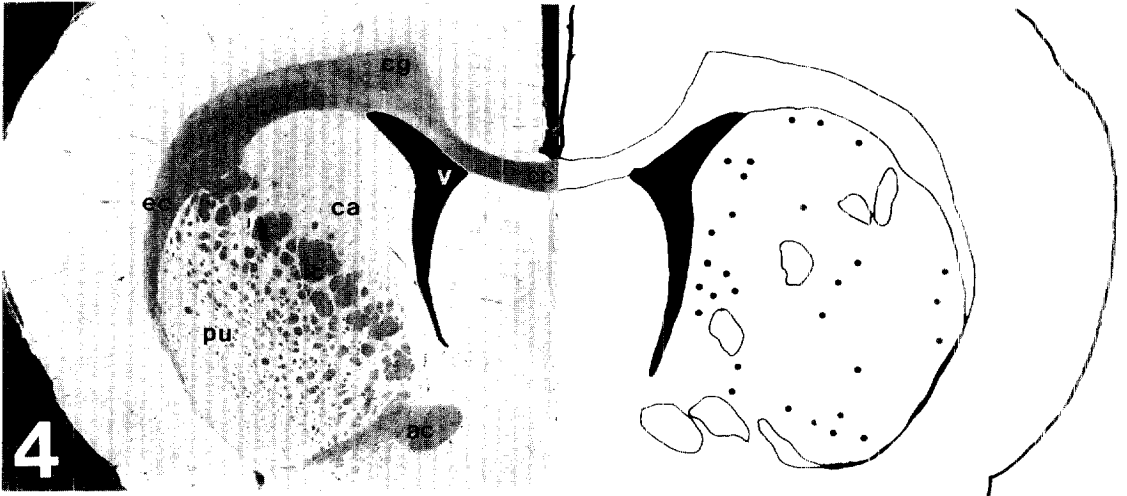
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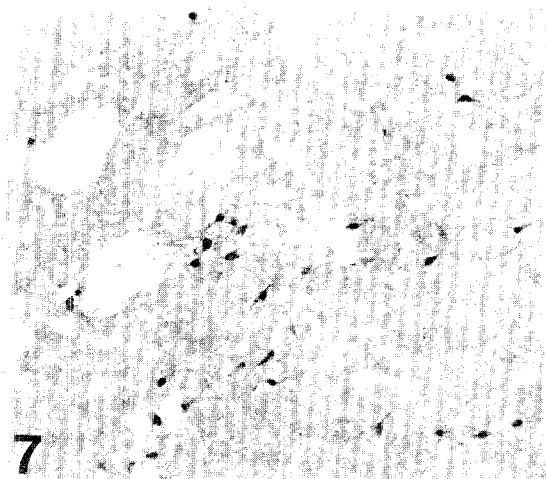
## Legend for figures

- Fig 1-6. Lower magnification photographs from anterior part of corpus striatum(Fig 1, 2 and 3) to posterior part of striatum(Fig 4, 5 and 6) in left part. Overlay drawings of right photographs in right part. The location of NPY-positive neurons is indicated by filled rounds. ac; anterior commissure, ca; caudate nucleus, cc; corpus callosum, cg; cingulum, cpu; caudate putamen, ec; external capsule, fi; fimbria hippocampus, fim; fornix, Gp; globus pallidus, ic; internal capsule, ox; optic chiasm, pu; putamen, v; lateral ventricle.
- Fig 7. Medial portion of caudate-putamen in anterior brain part(X 100)
- Fig 8. Ventral portion of caudate-putamen in anterior brain part(X 100)
- Fig 9. Medial portion of putamen in posterior brain part(X 100)
- Fig 10. Ventral portion of putamen in posterior brain part(X 100)
- Fig 11. Ventral portion of caudate nucleus in posterior brain part(X 100)
- Fig 12. Medial portion of caudate nucleus in posterior brain part. LV; lateral ventricle(X 100)
- Fig 13. Round- or oval-shaped neurons and their processes in the caudate-putamen(X 400)
- Fig 14. Round- or oval-shaped neurons and nerve fibers in the caudate nucleus. LV; lateral ventricle(X 400)
- Fig 15. Triangular-shaped neuron in the putamen(X 400)
- Fig 16. Fusiform-shaped neuron and their processes in the caudate nucleus(X 400)
- Fig 17. Multipolar neuron and their processes in the ventral part of putamen(X 400)
- Fig 18. Multipolar, round or oval shaped neurons and their processes in the caudate nucleus(X 400)

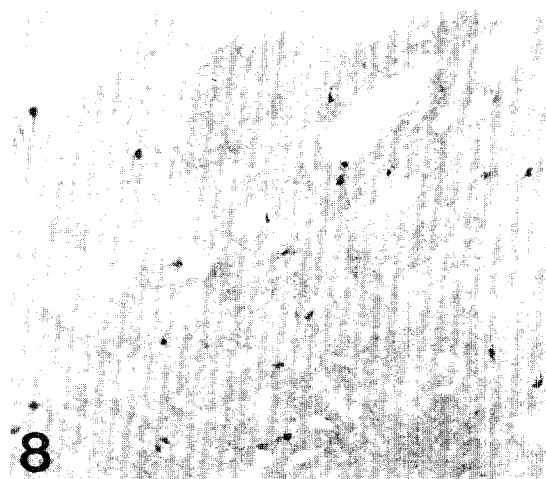
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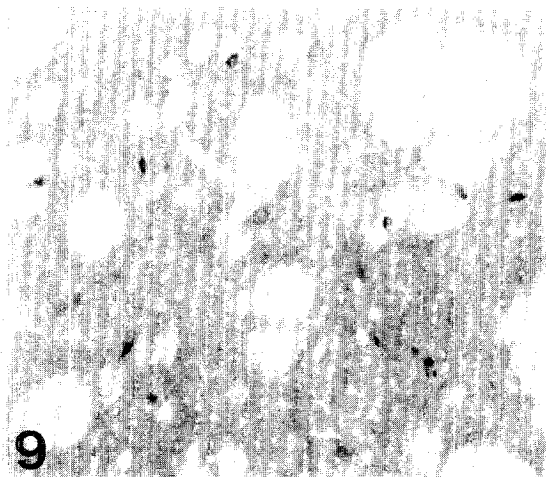




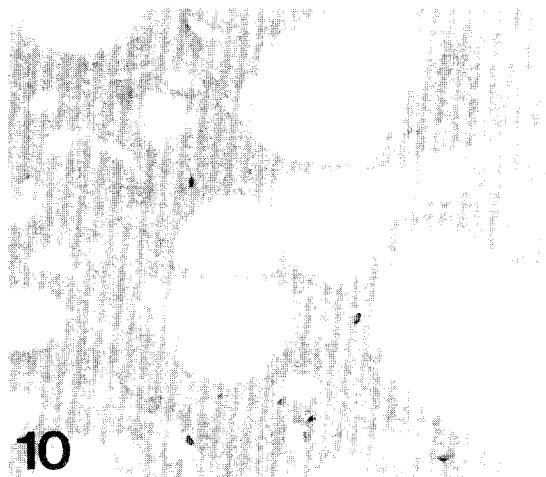
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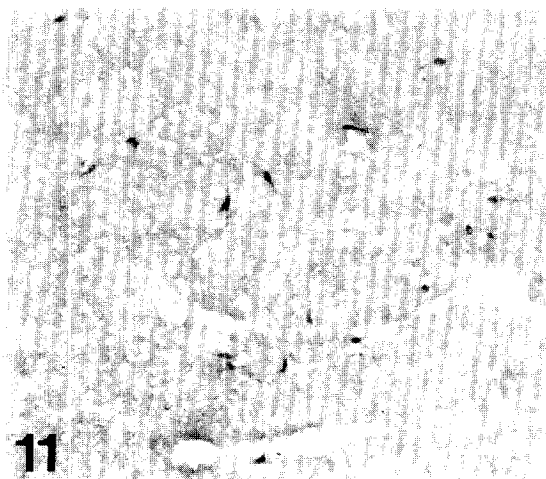
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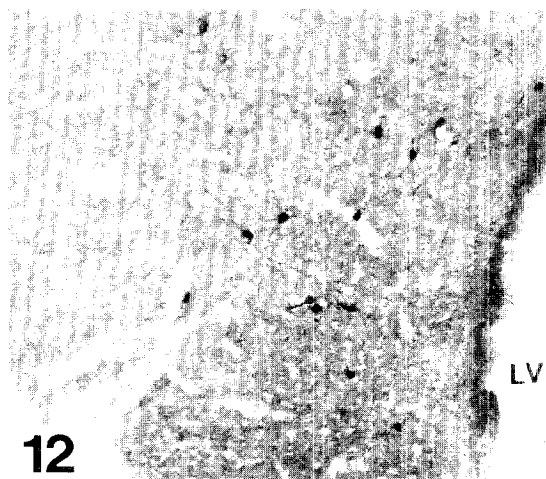
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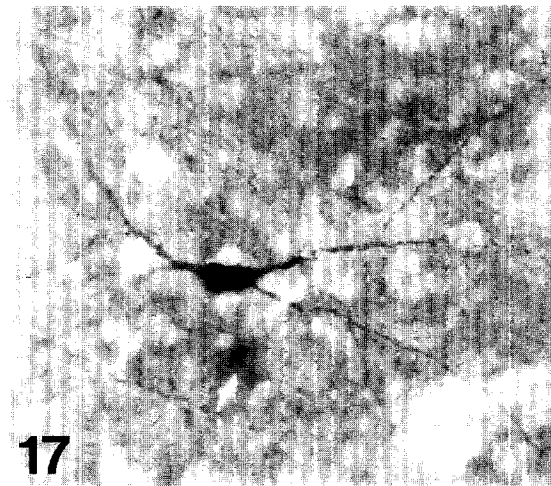
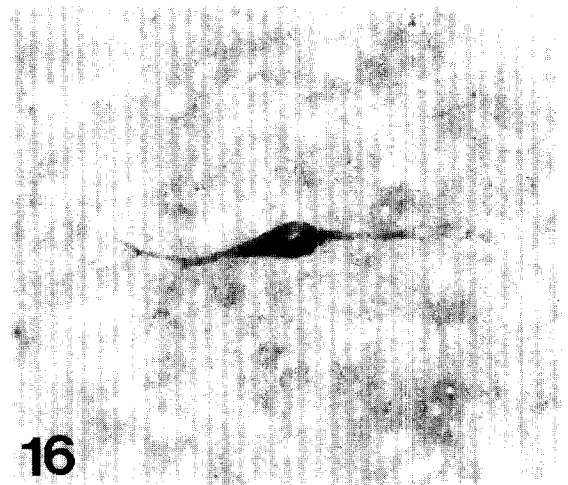
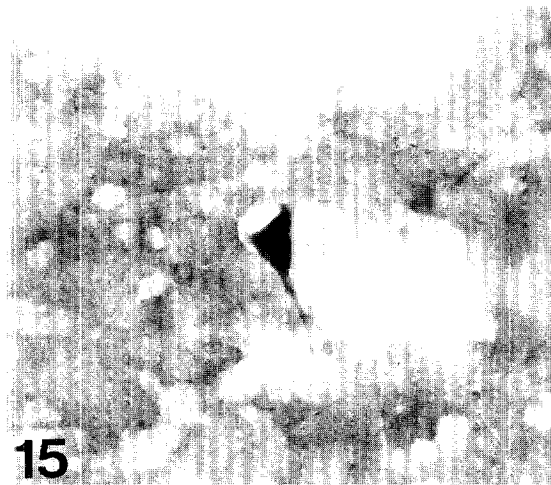
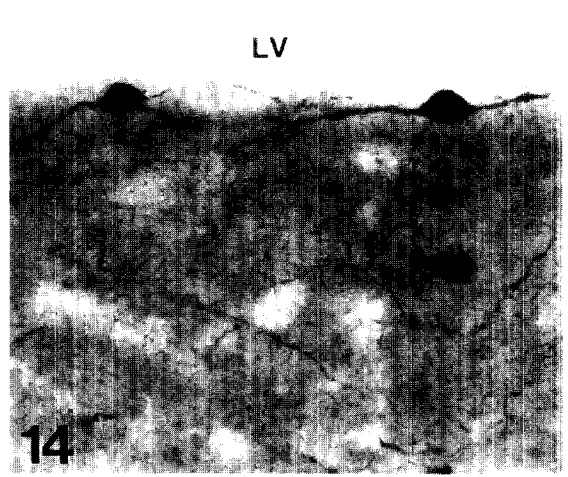
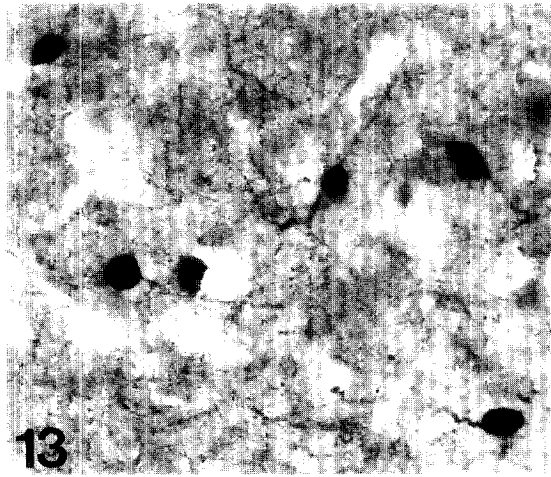
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