

EFFECT OF PARTIAL SENSORY DEPRIVATION ON MONOAMINERGIC NEUROMODULATORS IN STRIATE CORTEX OF ADULT CAT

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Abstract—The role of monoaminergic neuromodulators in the reorganization of cortical topography following limited sensory deprivation in the adult cat was investigated. The total concentrations of dopamine, noradrenaline, serotonin and their major metabolites were measured in the visual cortex of both normal control and experimental animals using microbore high-performance liquid chromatography coupled with electrochemical detection. The experimental animals were subjected to a binocular retinal lesion corresponding to the central 10° of vision and killed two weeks post-lesion. The sensory deprivation was confirmed in area 17 by measuring immediate-early gene *zif-268* messenger RNA expression. Following the retinal lesion, the total concentrations of noradrenaline and dopamine were significantly higher in the non-deprived cortex of retinal lesion cats than in the deprived cortex of retinal lesion cats and the cortex of normal animals. This pattern follows the release of the excitatory neurotransmitter glutamate under the same conditions. Serotonin levels were significantly lower in the deprived cortex, and its metabolite 5-hydroxyindole-3-acetic acid was significantly higher in the non-deprived cortex than in deprived cortex and normal cortex.

From these results, we suggest that the modulation of noradrenaline, dopamine and serotonin is regulated by visual afferent activity. © 2000 IBRO. Published by Elsevier Science Ltd. All rights reserved.

Key words: noradrenaline, dopamine, serotonin, activity-dependent regulation, visual cortex, neuromodulator.

In the visual system of adult cats and monkeys, binocular lesions produce a deprived zone in the corresponding region of the primary visual cortex in which neurons no longer respond to visual stimuli. Within a few months, the cells in the lesion-affected cortical area regain responsiveness to visual stimulation through the acquisition of new receptive fields receiving inputs from retinal locations outside the margin of the lesion. This recovery occurs over a distance of several millimetres of cortex and can result in complete recovery after a few months, depending on the extent of the retinal lesion.^{15,16,20,22} Proposed mechanisms for such a reorganization of cortical topography include alterations in the effectiveness of previously existing connections and the growth of new connections. However, the molecular mechanisms underlying the reorganization of the adult brain are poorly understood.

Our previous work has studied some of the amino acid neurotransmitters of the cat visual cortex, including GABA, glutamate and aspartate.^{1,2,11,39,41} The results suggest that activity-dependent changes in the balance between excitation and inhibition contribute to the plasticity necessary for the retinotopic reorganization.

Noradrenaline (NA), dopamine (DA) and serotonin (5-hydroxytryptamine, 5-HT) are well-known neurotransmitters, and form three different diffuse modulatory systems in the

CNS of mammals.⁴ During development, noradrenergic axons from the locus coeruleus are likely to be the first extrinsic input to the cortical mantle, arriving well before birth. The anatomical¹⁰ and biochemical⁴⁰ evidence suggests that NA can evoke a physiological response at sites distant from the point of release. Several features of the noradrenergic innervation of the visual cortex have focused on its role in developmental plasticity,^{5,23,25,27} attention processes^{13,31} and regulation of visual activity.^{26,29,35,42,44,50} The release of NA either by activation of the locus coeruleus noradrenergic pathway or by microiontophoresis has been shown to facilitate neuronal responses to afferent synaptic input in visual cortices. Furthermore, the effect of NA in the cerebral cortex is thought to be regulated through an *N*-methyl-D-aspartate glutamate receptor-dependent and nitric oxide-mediated process.^{6,12,21,32,48} Therefore, NA may possibly play a role in the cortical reorganization induced by partial sensory deprivation.

However, two other widely distributed neuromodulators may also have a role in the process of cortical reorganization. DA is a biosynthetic intermediate of NA.⁴⁰ In addition, dopaminergic fibres have been shown to project into the cat visual cortex from the DA-containing cells of the ventromedial mesencephalic tegmentum.^{37,45} However, the function of dopaminergic axons in the visual cortex is unclear and there are few reports in the literature suggesting a possible role for these fibres.^{30,43,47} 5-HT, another neuromodulator, is also widely distributed in the cerebral cortex, and has the potential to influence cellular excitability and intracellular messenger systems in a similar way to acetylcholine and NA.^{14,41} Several reports have demonstrated that 5-HT facilitates ocular dominance plasticity in the visual cortex.^{17,18,28} The role of the monoaminergic neuromodulators in response to partial sensory deprivation in adult cats has never been investigated. To obtain further insight into the possible role of monoaminergic

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Abbreviations: DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; 5-HIAA, 5-hydroxyindole-3-acetic acid; HPLC, high-performance liquid chromatography; 5-HT, serotonin (5-hydroxytryptamine); HVA, 4-hydroxy-3-methoxyphenylacetic acid (homovanillic acid); NA, noradrenaline.

Table 1. Size of the retinal lesions in visual degrees (Horizontal × Vertical)

Cat no.	Survival time (weeks)	Lesion size (°)	
		Left eye	Right eye
1	2	10.0 × 9.8	9.7 × 8.6
2	2	9.7 × 9.0	9.8 × 9.5

neuromodulators in the visual cortex and elucidate the underlying mechanism of cortical reorganization, we have investigated the total (intra- and extracellular) concentrations of NA, 5-HT, DA, adrenaline and their metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC), 4-hydroxy-3-methoxyphenylacetic acid (homovanillic acid, HVA) and 5-hydroxyindole-3-acetic acid (5-HIAA), in the visual cortex of adult cats following retinal lesions. The deprived and non-deprived portions of area 17 were identified by different expression of zif-268 mRNA.

EXPERIMENTAL PROCEDURES

Animal preparation

All animal experiments were carried out in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC). All efforts were made to minimize animal suffering, to reduce the number of animals used and utilize alternatives to *in vivo* techniques when available.

Four adult cats (Animal Facilities, Katholieke Universiteit Leuven, Belgium) of both sexes (weight 2.5–5 kg) were used. In two animals, the part of the retinas representing the area centralis of the visual field was photocoagulated. Binocular lesions of the central 10° of the retina were produced under ketamine/xylazine anaesthesia (0.5 ml ketamine, 0.2 ml xylazine, i.m.) using a LOG-2 Xenon light photocoagulator (Clinitex). Fundal photographs were taken of both eyes before and after creating the lesions to aid in estimating lesion size.⁴⁶ The data are shown in Table 1.

Tissue preparation and extraction

The animals were maintained in a normal light environment (10 h light/14 h dark) for two weeks after induction of the lesion. Twenty samples were prepared from each group. These groups were: (1) central vision cortex of normal cat; (2) peripheral cortex of normal cat; (3) deprived cortex of retinal lesion cat; and (4) non-deprived cortex of retinal lesion cat. Two normal cats and two with 10° retinal lesions were killed at the same time of day using an overdose of Nembutal (sodium pentobarbitone; 60 mg/kg, i.v.). The brains were rapidly removed and immediately frozen by immersion in liquid nitrogen-cooled isopentane and stored at -70°C. For normal brains, 200 µm sections were cut on a cryostat. The brains of the lesioned animals were cut in sequences of five 200 µm and one 50 µm sections. The 50-µm sections were used to detect zif-268 by *in situ* hybridization to distinguish the deprived portion of area 17. The 200 µm sections were used to determine total concentration of monoamine neuromodulators. In three of these sections, 2 mm × 4 mm specimens of cortical tissue containing all six cortical layers were dissected out from the peripheral (non-deprived) and central (deprived) portions of area 17 (as shown in Fig. 1) using a surgical blade under a microscope. Tissue from these sections was pooled in a 1.5 ml conical tube as a single sample. Ten samples were prepared from each region for a single brain. The monoamines were extracted from these tissue samples using 80 µl 0.01 M HCl and homogenized by grinding for 30 s at 4°C; the homogenate was centrifuged at 12,000 g for 15 min at 4°C. The supernatant was filtered through a 0.22 µm syringe filter and 10 µl was injected into a high-performance liquid chromatography (HPLC) system. The tissue pellets were used for protein assay to express the results as pg monoamine/µg protein.³⁸

High-performance liquid chromatographic analysis

The HPLC system used was a BAS 200A Chromatograph equipped with an amperometric detector. The monoamines were separated using a SepStik microbore column (150 mm × 1 mm i.d., 3 m ODS; BAS). The flow rate of the mobile phase was 44 µl/min. A BAS Sample-Sentinel autosampler was used and the injection volume was 10 µl. The electrochemical detector was set at 750 mV versus an Ag/AgCl standard, and cell volume was reduced by a 16 µm gasket. The whole system was maintained at 35°C. The chromatographic system was controlled by BAS Control software and the chromatograms were integrated with ChromGraph™ software (BAS).

In situ hybridization

In situ hybridization for zif-268 was performed using a probe complementary to the nucleotides encoding amino acids 2–16 of the rat zif-268 gene.⁴⁹ This oligonucleotide probe against zif-268 has been used previously by this laboratory.⁵¹ Slide-mounted sections were warmed to room temperature, fixed in 0.1 M phosphate buffer containing 4% paraformaldehyde (pH 7.4) for 30 min and rinsed twice for 5 min in 0.15 M phosphate-buffered saline. After dehydration, lipids were removed by transferring the sections through a graded series of ethanol, chloroform, and finally 100% and 95% ethanol. The sections were air-dried, then incubated overnight at 37°C in a humid chamber with approximately 8 × 10⁵ c.p.m. of the appropriate probe in 500 µl hybridization buffer per slide. The hybridization buffer consisted of 50% formamide, 4 × standard saline citrate, 1 × Denhardt's solution, 10% dextran sulphate, 100 µg/ml salmon sperm DNA, 250 µg/ml tRNA, 60 mM dithiothreitol, 1% *N*-lauryl-sarcosine and 20 mM NaHPO₄ (pH 7.4). After the hybridization, the sections were immersed in 1 × standard saline citrate at 42°C for four washes of 15 min each. The slides were dried in a graded series of ethanol and exposed to autoradiographic film (β-max, Amersham, Belgium) for four weeks. The films were developed using the standard procedure: development in D-19 (Kodak, Belgium), rinsing in water and fixing in rapid fixer (Ilford Hypam, Belgium).

Data analysis

The tissue sample was expressed as pg monoamine/µg protein. Data analyses were done with the unpaired Student's *t*-test by using SigmaPlot (version 4.0). In all instances, *P* < 0.05 was considered statistically significant.

RESULTS

Differential expression of zif-268 messenger RNA in the visual cortex of retinal lesion cats

Zif-268 is one of the immediate-early genes, which is thought to have a role in activity-dependent plasticity during development. Zif-268 expression is altered in mammalian visual cortex by complete or partial visual deprivation or stimulation.^{7,33,51} In this work, the creation of homonymous, bilateral lesions in the portion of the retina corresponding to the central 10° of the visual field (Table 1) resulted in a decreased expression of zif-268 in the "lesion-affected" portion, deprived cortex, which is shown in Fig. 1a. Following the indication of this pattern, three pieces of 2 mm × 4 mm tissue sample, as indicated in the stippled area in Fig. 1b, were dissected out of the deprived cortex (Fig. 1bA) and non-deprived cortex (Fig. 1bB) of area 17 in retinal lesion animals and the monoamine levels measured. Thus, the zif-268 changes demonstrate a successful lesion and its effect on area 17.

Noradrenergic neuromodulation

In normal cats, quantification of total NA concentration (intra- and extracellular) revealed no significant differences between the regions of area 17 subserving central (3.31 pg/µg

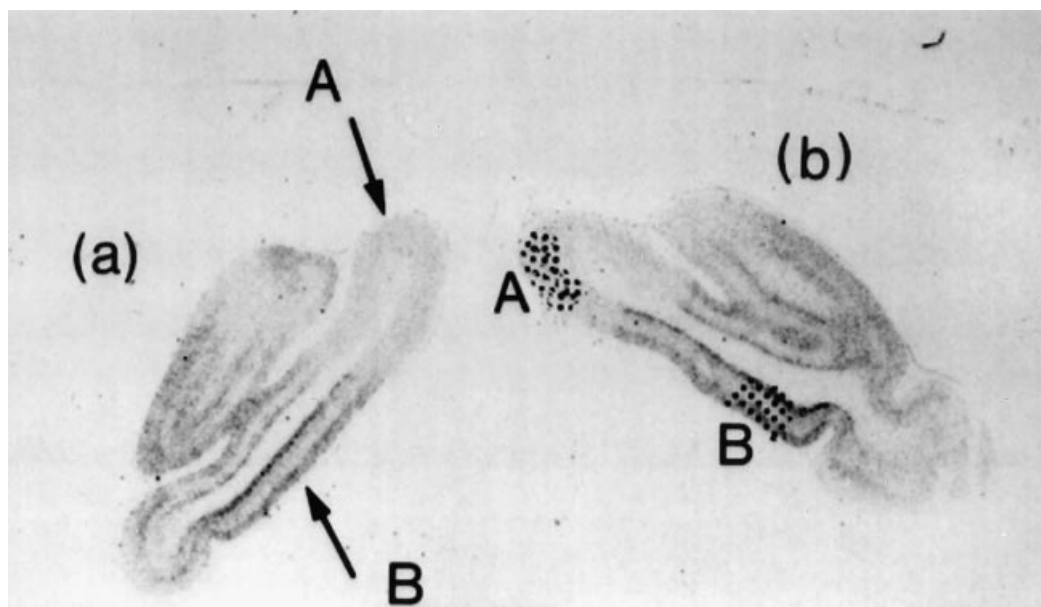


Fig. 1. The expression of zif-268 mRNA in area 17 of a retinal lesion adult cat. (a) Comparison of panels A and B in coronal section, which reveals a decrease in the number of zif-268 mRNA-expressing cells in the central deprived portion of area 17 (A) compared to the peripheral or non-deprived portion of area 17 (B). The solid line indicates the borders between these two cortical regions. (b) The sampling positions in the deprived region of area 17 (A) and non-deprived region of area 17 (B) are indicated by the stippled area in another coronal section.

protein) and peripheral vision (3.38 pg/ μ g protein). The P value is 0.8413. Two weeks after the induction of a 10° lesion, we observed a significantly higher total NA concentration (4.85 pg/ μ g protein) in the non-deprived portion of area 17 in the lesioned cats, whereas the total NA concentration was only 2.51 pg/ μ g protein in the deprived cortex ($P=0.0002$). The data presented in Table 2 illustrate this distinction. Moreover, the total NA concentration in the non-deprived portion of area 17 in the lesioned cats was significantly higher than that in both central and peripheral cortex of normal cat. The comparison data are shown in Table 3.

Dopaminergic neuromodulation

DA levels showed profiles similar to those of NA. In normal cats, the total DA concentrations were 1.15 pg/ μ g protein in the central region of area 17 and 1.11 pg/ μ g protein in the peripheral portion of area 17; thus, no significant differences were observed ($P=0.9033$). In lesioned cats, DA levels in the non-deprived cortex were 1.74 pg/ μ g protein, which is significantly higher than that in the deprived cortex (1.06 pg/ μ g protein, $P=0.00098$; Table 2). As for NA, DA levels in the non-deprived cortex of retinal lesion cats were also significantly higher than in both central and peripheral portion area 17 of control cats (as shown in Table 3).

Neuromodulator inactivation in the CNS can be induced by neuromodulation or by enzymatic breakdown. Two enzymatic breakdown products of DA are DOPAC and HVA. In normal cats, the concentrations of DOPAC and HVA are 1.26 and 2.01 pg/ μ g protein and 1.20 and 2.07 pg/ μ g protein in the central and peripheral regions, respectively. Statistics show no significant differences between the two regions for either DOPAC or HVA (DOPAC: $P=0.86$; HVA: $P=0.88$). In the lesioned cats, DOPAC concentrations in the deprived cortex are 0.444 pg/ μ g protein, which is significantly ($P=0.03$) lower than in non-deprived cortex, where values were 0.919 pg/ μ g protein (Table 2). For HVA, levels were signifi-

cantly ($P=0.0002$) elevated in the non-deprived cortex (1.91 pg/ μ g protein), compared to the deprived cortex (0.883 pg/ μ g protein; Table 2). Comparison of data obtained from normal animals demonstrated that DA was increased in the non-deprived cortex of retinal lesion cats. However, both its metabolites, DOPAC and HVA, were decreased in the deprived cortex following retinal lesions, suggesting a possible impairment in DA metabolism (Table 3).

Serotonergic neuromodulation

In normal cats, no significant differences were found for either 5-HT (6.07 pg/ μ g protein in the central portion and 6.47 pg/ μ g protein in the peripheral portion) or its monoamine oxidase metabolite, 5-HIAA (2.61 pg/ μ g protein in the central portion and 2.97 pg/ μ g protein in the peripheral portion), although there was more variability between the two regions than with other monoamines (5-HT: $P=0.64$; 5-HIAA: $P=0.42$). In the lesioned animals, total 5-HT concentration in the deprived cortex was 3.61 pg/ μ g protein, which was significantly ($P=0.035$) lower than in non-deprived cortex, where levels were 5.79 pg/ μ g protein (Table 2). The greatest difference was found for 5-HIAA. In the non-deprived cortex, the 5-HIAA level was 4.05 pg/ μ g protein, which was threefold greater than that in the deprived cortex, where levels were 1.38 pg/ μ g protein ($P<0.0001$; Table 2). Comparison of data obtained from normal and experimental animals demonstrated that 5-HT decreased in the deprived cortex of retinal lesion cats. However, its metabolite, 5-HIAA, was not only reduced in the deprived cortex by retinal lesions, but actually significantly increased in the non-deprived cortex. The data are shown in Table 3.

DISCUSSION

In the present study, the tissue levels of monoamine neuromodulators were measured by microbore HPLC with

Table 2. Comparison of total concentration of monoaminergic neuromodulators in deprived and non-deprived portions of area 17 of retinal lesion cats

Monoaminergic neuromodulators	Total concentration in deprived cortex of retinal lesion cats	Total concentration in non-deprived cortex of retinal lesion cats	<i>P</i> -value	Significance
NA	2.51 ± 0.23	4.85 ± 0.53	0.0002	***
DA	1.06 ± 0.11	1.74 ± 0.15	0.00098	***
DOPAC	0.449 ± 0.09	0.92 ± 0.19	0.03	*
HVA	0.883 ± 0.12	1.91 ± 0.31	0.0002	***
5-HIAA	1.38 ± 0.17	4.50 ± 0.35	< 0.0001	***
5-HT	3.61 ± 0.71	5.80 ± 2.84	0.035	*

P* < 0.05; **P* < 0.005.

Table 3. Comparison of total concentration of monoaminergic neuromodulators in central/deprived and peripheral/non-deprived portions of area 17 between normal and retinal lesion cats

Monoaminergic neuromodulators	Total concentration in central portion area 17 of normal cats	Total concentration in deprived cortex of retinal lesion cats	<i>P</i> -value	Significance	Total concentration in peripheral portion area 17 of normal cats	Total concentration in non-deprived cortex of retinal lesion cats	<i>P</i> -value	Significance
NA	3.39 ± 0.57	2.51 ± 0.23	0.16		3.22 ± 0.52	4.85 ± 0.53	0.037	*
DA	1.15 ± 0.20	1.06 ± 0.11	0.71		1.11 ± 0.14	1.74 ± 0.15	0.0062	**
DOPAC	1.26 ± 0.30	0.449 ± 0.09	0.014	*	1.19 ± 0.23	0.92 ± 0.19	0.36	
HVA	2.01 ± 0.32	0.883 ± 0.12	0.0023	***	2.07 ± 0.26	1.91 ± 0.31	0.69	
5-HIAA	2.61 ± 0.30	1.38 ± 0.17	0.0013	***	2.97 ± 0.31	4.50 ± 0.35	0.0029	***
5-HT	6.47 ± 1.18	3.61 ± 0.71	0.04	*	5.54 ± 1.60	5.80 ± 2.84	0.88	

P* < 0.05; *P* < 0.01; ****P* < 0.005.

electrochemical detection and expressed as the total concentration of monoamine in the visual cortex of adult cats. Unfortunately, the extracellular concentrations of monoamine in the visual cortex are too low to be detected by *in vivo* microdialysis coupled with our HPLC methods. Although the monoamine pool consists of both extra- and intracellular monoamine pools, we could only measure the combined pool. However, intracellular monoamines form the major part of the total concentration and are stored in the synaptic vesicles. These monoaminergic fibres originate from other parts of the brain: NA in the nucleus locus coeruleus, DA in the tegmental ventral area and 5-HT from raphe nuclei. Monoamines are released into the synaptic cleft by exocytosis. However, the changes in total concentration of monoamine would be expected to parallel the changes in extracellular concentration caused by release of these neuromodulators, since their organization in the visual cortex is rather simple, as there are no cell bodies and only monoaminergic fibres exist in this brain region.⁴⁰

In the normal cats, no significant differences were found in NA, DA and 5-HT levels between the parts of area 17 subserving central and peripheral vision, nor changes in their major metabolites, HVA, DOPAC and 5-HIAA. These results suggest that the monoamine levels in monoaminergic innervation in area 17 are quite homogeneous between these two regions. High amounts of NA, 5-HT and 5-HIAA were found in area 17, as expected. Because of these high levels, NA^{24,40} and 5-HT¹⁷ have been easily and extensively investigated, and are considered as the primary neuromodulators involved in the regulation of visual cortical activity. Only small amounts of DA and its metabolites HVA and DOPAC were found in the visual cortex; because of these low levels, DA function in the visual cortex remains unknown.

Noradrenergic modulation

To pose a role for NA in primary visual cortical functioning several factors must be taken into consideration. First are local mechanisms, which may regulate synaptic transmission of NA in the visual cortex. From our results, NA levels in the non-deprived cortex are 48% higher than in the deprived cortical region by two weeks after a retinal lesion. This observation indicates that the total NA concentration is regulated by visual afferent activity. Under normal circumstances, NA has the potential to improve the cortical neuronal responses to visual afferent activity. These factors have also been demonstrated by other authors.^{26,29,35} In their experiments, NA was applied iontophoretically in the visual cortex and found to enhance the fidelity of encoding sensory input. Furthermore, in the visual cortex, the release of endogenous NA increases during visual stimulation and may well require specific patterns of activity in geniculocortical afferents.³⁶ In our experiment, the loss of visual stimulation and spontaneous retinal cell firing in the deprived cortex of the retinal lesion cats diminishes the need of NA for cortical neuronal responses. In contrast, higher concentrations of NA were obtained in the non-deprived cortex by sensory stimulation through the intact portion of the retina. This is consistent with our observation from extracellular recordings of single units in two-week post-lesion animals. In these electrophysiological experiments, both spontaneous and visually evoked activities were significantly lower in the deprived cortex.

Another issue for consideration is how NA can modulate the function of fast neurotransmitters. It is widely held that the geniculocortical input is predominantly mediated via excitatory amino acids,¹⁹ and there is mounting evidence that excitatory amino acids can regulate NA. From our own

observation, the changed pattern of NA concentration is identical to that of extracellular glutamate. This is described in our previous microdialysis experiments.³⁹ This result suggests that NA may be related to glutamate release in the visual cortex.

Total NA concentration in the non-deprived cortex of retinal lesion cats is not only higher than in the deprived cortex, but also higher than in the normal cortex of control animals, while total NA concentration in the deprived cortex of retinal lesion cats is not significantly lower than in the normal cortex of control animals. This extra increase in NA levels in retinal lesion cats suggests a reorganization requirement which is induced by the partial sensory deprivation.

Dopaminergic modulation

In the dopaminergic system, similar results were obtained as with NA. In cats receiving retinal lesions, the total DA concentration is higher (31%) in the non-deprived cortex, whereas levels in the deprived cortex were comparable to those in normal animals. Hence, the increased levels of DA in retinal lesion cats are suggestive of a reorganization requirement which is induced by the partial sensory deprivation. We found that the levels of DA in normal cats were considerably lower and the levels of their metabolites were higher than that of DA itself. Early research^{36,40} considered DA only as the precursor of NA through the dopamine β -hydroxylase pathway. Because of their common synthetic pathway, these catecholamines could arrive together through noradrenergic fibres, suggesting that changes in DA concentration may be accompanied by similar changes in NA. Our results provide support for this contention.

However, others have described evidence of dopaminergic projection to the visual cortex from the ventral mesencephalic tegmentum.^{37,45} In our experiment, the DA metabolites DOPAC and HVA were decreased by 51% in the deprived cortex of retinal lesion cats compared with normal cats. These results indicate that DA metabolism is regulated only through the neuronal activity induced by sensory input. Part of the dopaminergic projection to the cat visual cortex may be separate from that which is simply a precursor to NA.

Serotonergic modulation

5-HT, another neurotransmitter, is also widely distributed in the cerebral cortex and has the potential to influence cellular excitability and intracellular messenger systems in a manner similar to acetylcholine and NA.^{14,34} In the present study, 5-HT levels were significantly decreased in the deprived cortex of lesioned cats, which suggests that the serotonergic system is also modulated in the visual cortex by an afferent system acting in an activity-dependent manner. However, its metabolite from monoamine oxidase degradation, 5-HIAA, is 69% higher in the non-deprived cortex and decreased in the deprived cortex. This result suggests that the metabolism of 5-HT may not simply be regulated by neuronal activity. For example, in the primary auditory cortex, many serotonergic baskets surround the somata and dendrites of GABAergic neurons.^{8,9} These fibres terminate preferentially on GABA interneurons, but most pyramidal neurons respond to stimulation of the raphe nuclei or local application of 5-HT.³ This stimulation suggests a strong interaction between serotonergic axon terminals and specific GABA neurons. Our previous studies^{39,41} on the response of the GABA circuitry to sensory deafferentation indicated that serotonergic fibres may modulate the GABA inhibitory activity in the visual cortex of the adult cat. However, the influence of extracellular GABA has not yet been fully delineated to give the clear pattern of 5-HT modulation.

Therefore, we may propose that the modulation of NA, DA and 5-HT is regulated by visual afferent activity. These monoamines may play important roles during cortical reorganization in the adult cat.

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