Anat. Embryol. 159, 245–255 (1980)

Anatomy and Embryology

Structural and Biochemical Changes in Rat Cerebral Cortex after Neonatal 6-Hydroxydopamine Administration

B. Onténiente[1], N. König[1], J. Sievers[2], S. Jenner[3]
H.P. Klemm[3], and R. Marty[1]

[1] Laboratoire de Neuromorphologie Fonctionnelle et Neuropathologie expérimentale, Université Montpellier II, France
[2] Abteilung Neuroanatomie, Universität Hamburg, Bundesrepublik Deutschland
[3] Abteilung Funktionelle Anatomie, Universität Hamburg, Bundesrepublik Deutschland

Summary. Newborn rats received an intracisternal injection of 6-hydroxydopamine (100 μg) within 16 h after birth. Treatment effects upon noradrenaline uptake (with or without desmethylimipramine pre-incubation), endogenous noradrenaline, dopamine, and serotonin were biochemically assayed. Noradrenaline uptake and endogenous noradrenaline content were permanently reduced to less than 5% of control values. Reduction of endogenous dopamine content was less marked: at day 60, values were about 40% of controls. Serotonin content remained unaffected.

Cell density countings in postnatal day 15 temporal cortex revealed an about 16% reduction in layers II and III of treated animals. These modifications of cortical geometry were discussed with reference to measurements of cortical thickness and ultrastructural observations on postnatal days 2, 5 and 15. Both supranormal involution *and* growth processes might result from the neurotoxin treatment. Whereas some of the degeneration processes might be due to general cytotoxic effects, this is less likely for the supranormal growth processes.

Key words: Neocortex – Development – 6-Hydroxydopamine – Noradrenaline – Dopamine.

Introduction

It has been suggested that the early appearing monoamine neuron systems could be involved in the control of the development of their target areas (Seiger and Olson 1973; Olson and Seiger 1972; Lauder and Bloom 1974; Lauder and Bloom 1975; Sievers 1979; Sievers et al. 1979; Berry et al. in press a, b). The cerebral neocortex belongs to these areas; it receives monoaminergic

Offprint requests to: N. König, Laboratoire de Neuromorphologie Fonctionelle et Neuropathologie expérimentale, Univ. Montpellier II, 34060 Montpellier Cedex, France

0340-2061/80/0159/0245/$02.20

afferences very early in development (Schlumpf et al. 1977; König and Sievers in preparation).

One method of testing the hypothesis of monoaminergic control of cortical development is the administration of neurotoxins such as 6-hydroxydopamine (6-OHDA), since numerous biochemical studies have shown that neonatal treatment with this drug impairs noradrenergic (NA) and – with relatively high intracisternal or intraventricular doses – part of dopaminergic (DA) systems (for review see: Sachs and Jonsson 1975; Konkol et al. 1978; Schmidt and Bhatnagar 1979a, b).

Effects of 6-OHDA or surgical destruction of catecholaminergic (CA) afferences on cortical development have been studied by several authors; however, information about morphological changes is scanty and often controversial (Maeda et al. 1974; Amaral et al. 1975; Hicks and D'Amato 1975; Wendlandt et al. 1977). The aim of the present study was to detect alterations of morphological development in the temporal cortex of the rat after neonatal intracisternal 6-OHDA administration, the biochemical effects of which were evaluated by uptake measurements and radio-enzymatic assays.

Examination of the cerebella of the same experimental animals as those used in this study has disclosed massive loss of granule cells, defects in foliation and fissurization (Sievers 1979; Sievers et al. 1979, in press; Berry et al. in press a, b). In the cerebral cortex, where neurogenesis is largely a prenatal event, the morphological changes after neonatal 6-OHDA treatment would be expectedly less marked. We therefore chose, as a first step in our investigation, a sensitive method capable of revealing even relatively slight alterations of cortical cyto- and histogenesis: cell density countings. Countings were performed on postnatal day 15 when the development of cortical cells and neuropil is still going on, notably in the uppermost layers of the cortex. Consequently, the countings can be expected to disclose treatment effects not only upon cell proliferation, migration, or cell death, but also upon the time course of differentiation. In order to detect modifications in individual cortical strata, cell density was determined in distinct vertical depth classes.

In addition to the (light microscopic) countings and qualitative electron microscopic observations, cortices of 2 and 5 days old aminals were studied in an attempt to disclose short-term qualitative effects of 6-OHDA treatment upon morphology of cortical cells and afferents.

Material and Methods

Within the first 16 h after birth, Wistar newborn rats (Wiga, Sulzfeld, F.R.G.) received one injection of 10 µl 0.9% saline containing 100 µg 6-hydroxydopamine HCL (6-OHDA; Sigma, Munich, F.R.G.) as free base and 1 mg/ml ascorbic acid into the IV th ventricle. Control animals received the same amounts of diluent and ascorbic acid. To allow for a minimum of biological variation, the pups from at least three litters were mixed, taken randomly for injection and regrouped into litters of ten consisting of 5 treated and 5 control animals. The animals were sacrificed 2, 5, 10, 15, 30 and 60 days post injection (d.p.i.).

A. Biochemical Methods. Contents of noradrenaline (NA), dopamine (DA), and serotonin (5-HT) were measured by a modification of the radioenzymatic assay according to Passon and Peuler

(1973) and Saavedra and co-workers (1973). These data were related to internal standards and expressed as ng/gr fresh weight. The total high affinity uptake capacity for ^{3}H-NA was determined in synaptosomal fractions of cerebral cortex according to Ross and Renyi (1975) and differentiated into a DMI-sensitive (representing pure NA uptake) and a DMI-insensitive (including probably DA uptake) fraction by preincubation with DMI (1×10^{-7} M) according to Cuello and co-workers (1973). Treated and age-matched vehicle injected control groups were incubated in parallel in 0.25×10^{-7} M ^{3}H-NA (specific activity 28.1 Ci/mM) for 6 min at 37° C. After calculating the uptake rates in pmol ^{3}H-NA/gr protein × min, the values for the treated animals were expressed as per cent of age-matched vehicle injected controls.

B. Morphological Methods. The animals were perfused via the left ventricle with a solution containing 6% glutaraldehyde in 0.05 M phosphate buffer at room temperature for 20 min, their skulls removed and left overnight in the fixative. After removal of the brain, pieces including temporal cortex were dissected, post fixed in a 1% osmium tetroxyde solution in a 0.1 M phosphate buffer containing 0.1 M saccharose, dehydrated in increasing concentrations of ethanol and embedded in Epon according to Luft (1961). After polymerization, 1 µm thick sections were made on a Reichert OMU 2 microtome, each separated by 5 µm, and stained with toluidine blue. Thinner sections (0,1 µm) were cut alternatively with the 1 µm, stained with uranyl acetate and lead citrate for electron microscopic examination and viewed under a Jeol 100 B microscope.

C. Morphometric Methods. Estimations of the cellular density were made on frontal sections of temporal cortex on 15 days old animals, by counting nuclei of nervous and glial, but not endothelial cells, with a Reichert visopan (magnification: 25 × 12). Nuclei were counted within a field if the major part of their surface was within the border. In cases where nuclei were exactly halved by the border, half of their number was counted within the field. Countings were done in arbitrary depth classes rather than in real cortical layers since the latter cannot be delimitated with sufficient precision in 1 µm sections of day 15 temporal cortex. The upper limit of the counting surfaces was the border between layers I and II. Starting from that border downward, six depth classes each having 190 µm were analyzed. Class A and B roughly corresponded to layers II to III; class C: layer IV and the upper part of layer V; class D: inferior part of layer V; class E: upper part of layer VI; class F: inferior part of layer VI except for the narrow stratum of polymorphous cells bordering the white matter. The lateral extension of each counted column was 380 µm. Three such columns were analyzed on each section. They were radially disposed, the inferior corner of each column being in contact with that of the neighbouring one. The distance between the most ventral column and the rhinal fissure was about 500 µm. The total surface counted on each section was 1,30 mm^2. For each animal 60 columns were examined. Five control and six treated animals were studied. Preliminary measurements of nuclear section surfaces showed similar size distributions for all groups; therefore, countings of nuclei per surface unit were not corrected for nuclear size. Measurements of the cortical thickness were made from the border between layer I and II to the white matter, on the same sections as those used for the countings.

Results

A. Assessment of Drug Effects on NA and DA Fibres in the Cerebral Cortex

1. NA Uptake Capacity. The differential effects of i.c. injections of 6-OHDA on the NA and DA fibres of the cerebral cortex were monitored by splitting the total ^{3}H-NA uptake into a DMI-sensitive and a DMI-insensitive fraction by parallel measurements of ^{3}H-NA uptake into synaptosomes with and without preincubation with DMI (see Material and Methods). With this procedure, the pure NA uptake is represented by the difference between the DMI-insensitive ^{3}H-NA uptake and the total ^{3}H-NA uptake.

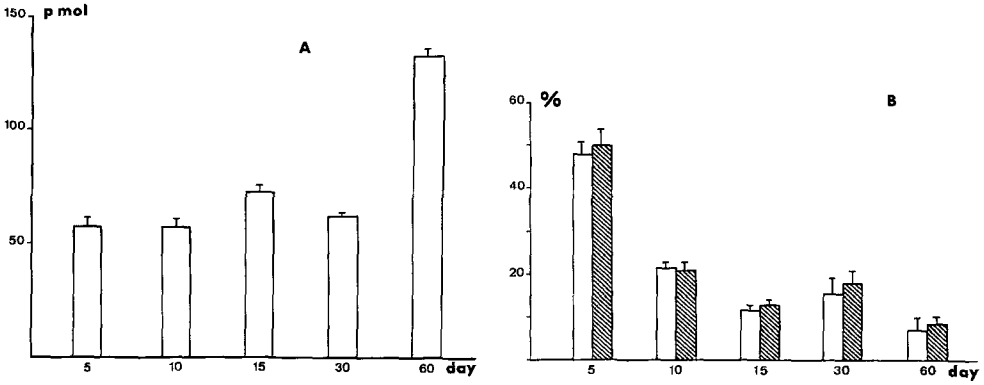

Fig. 1. A Time course of synaptosomal uptake capacity for ^{3}H-NA in rat neocortex. Animals were vehicle injected on the day of birth. Values are expressed as pmol ^{3}H-NA/gr protein × min ± S.E. of five determinations. **B.** □ = Total ^{3}H-NA uptake. ▨ = DMI-insensitive ^{3}H-NA uptake. Time course of synaptosomal uptake capacity for ^{3}H-NA in rat neocortex after i.c. injection of 6-OHDA on the day of birth. Values are expressed as percent of age-matched vehicle-injected controls (± S.E. of five determinations). The uptake into NA synaptosomes is represented by the difference between total and DMI-insensitive ^{3}H-NA uptake

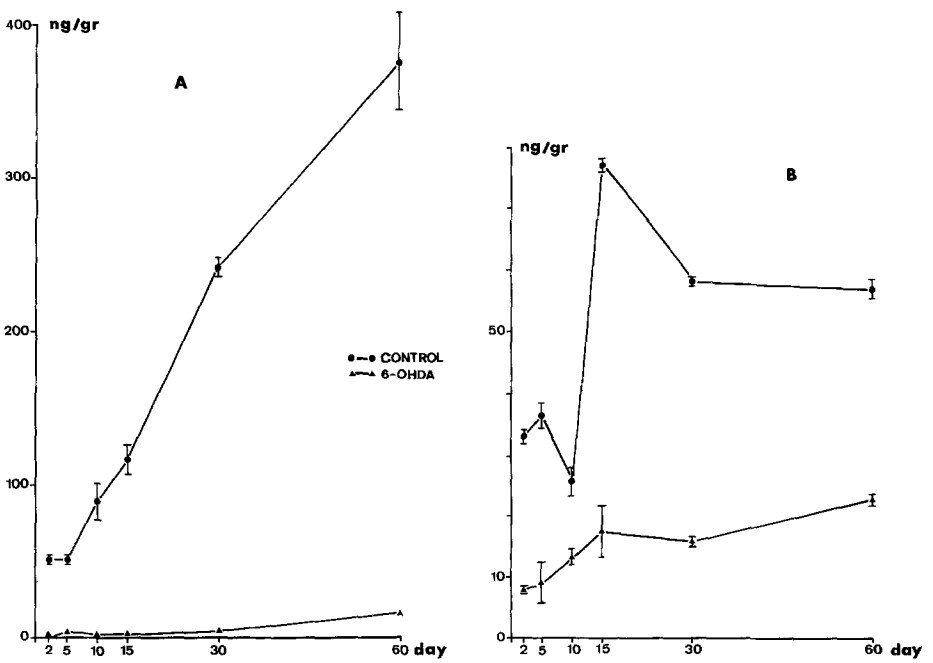

Fig. 2A and B. Time course of endogenous NA (Fig. 2A) and DA (Fig. 2B) content (ng/gr fresh weight) of control and neonatally 6-OHDA treated rats. Values are expressed as mean ± S.E. of five determinations

After treatment with 6-OHDA, the NA fraction of the total ^{3}H-NA uptake was completely absent from the first time point measured up to the adult stage at 60 d.p.i., without any sign of recovery. (Fig. 1). The DMI-insensitive fraction of the ^{3}H-NA uptake declined progressively between 5 and 60 d.p.i. to reach less than 10% of the control total ^{3}H-NA uptake.

2. Content of NA, DA and 5-HT. Determinations of the endogenous content of NA in the cerebral cortices of treated animals showed that, similar to the DMI-sensitive uptake capacity for ^{3}H-NA, this parameter also was very low immediately after the treatment and showed no marked recovery (Fig. 2A).

Measurements of the cortical DA content (Fig. 2B) revealed a reduction of this parameter to about 20% of control values at 5 days after injection of 6-OHDA, and a slow yet steady recovery to about 40% of control at 60 d.p.i.

Measurements of cortical 5-HT content on 5 and 60 d.p.i. did not show any significant modification after 6-OHDA treatment. On day 5, values for treated animals were 130 ± 6.2 ng/gr fresh tissue as against 137 ± 4.2 for controls; on day 60, values for treateds were 196 ± 7.3 versus 188 ± 5.4 for controls.

B. Morphological Effects of Treatment with 6-OHDA

1. Acute Effects. In 6-OHDA treated animals sacrificed on d.p.i. 2 or 5, signs indicating degeneration processes were not infrequent. In particular, the following phenomena were seen:

a) pyknotic cell bodies, debris and processes. Some of the pyknotic and/or phagocytosed cells seem to be extravasated erythrocytes (Fig. 3D).

b) profiles (in some rare cases synapses, Fig. 3C) containing dense or lamellar bodies (Fig. 3A). The subpial feet of radial fibres often contained such inclusions.

c) isolated lamellar bodies

These phenomena seemed to be more frequent in treated than in control animals. However, our qualitative survey cannot give a definite answer to that question. In any case, there were no *massive* degeneration processes at any cortical level. This is particularly true for the interneuronal contacts having the classical features of chemical synapses. As to the isolated membrane specializations which are some times referred to as "free postsynaptic thickenings" (Fig. 3B), these are commonly found in control material also.

2. Long-Term Effects. In 6-OHDA treated animals sacrificed on day 15, degeneration signs were still present. However, they did not seem to be much more frequent than in controls. There was no gross alteration of the cortical tissue or the meninges.

C. Morphometric Observations

Measurements of overall cortical thickness from the upper border of layer II to the white matter border on d.p.i. 15 showed a slight, but not significant,

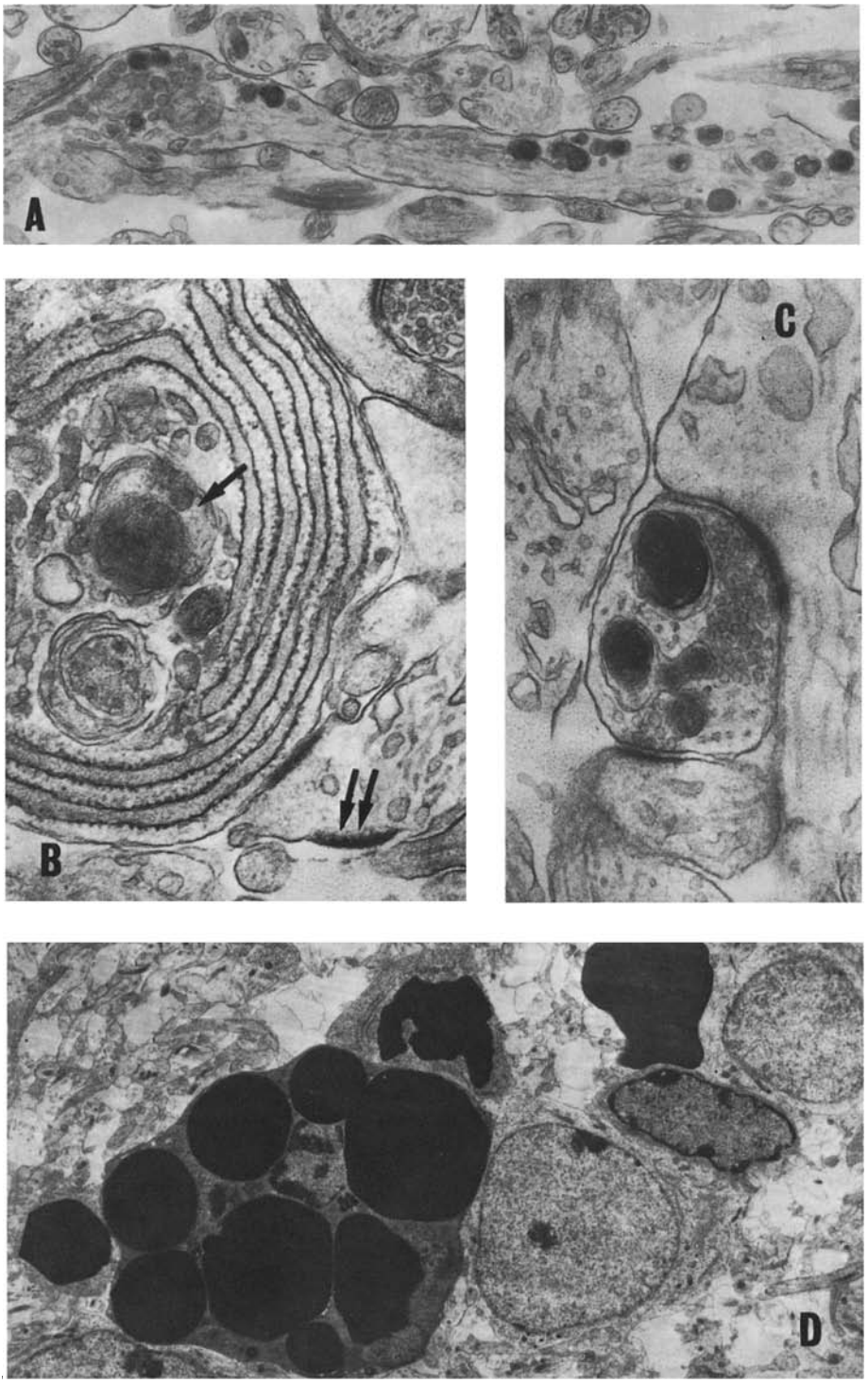

Fig. 3A–D. Ultrastructural features in postnatal day 5 temporal cortex after i.c. 6-OHDA treatment on the day of birth. **A** horizontal process (near to the pial surface) loaded with vesicles and small dense bodies; ×13,800. **B** profile containing dilated cisterns of ergastoplasm and presumably degenerating material (*arrow*). Isolated membrane specializations such as that shown at lower right (*double arrow*) are quite common in control material also. Layer I; ×33,800. **C** Synaptic bouton containing presumably degenerating material. Layer I; ×34,200. **D** Electron dense profiles (probably erythrocytes) some of which are contained within a macrophage. Border between layers IV and V– ×7,400

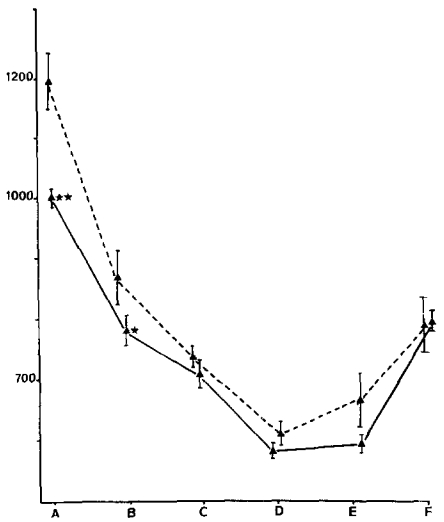

Fig. 4. Evaluation of the cellular densities, on postnatal day 15, at various cortical depths: 6-OHDA injected intracisternally (▲—▲) vehicle-injected intracisternally (▲--▲). Ordinate: number of nuclei per mm^2; abscissa: depth classes. Values represent the mean ± S.E.M. of 5 to 6 animals. * $P<0.1$; ** $P<0.01$, as compared with the control (Student's *t*-test)

increase in treated animals. Cell density countings (Fig. 4) revealed an about 16% decrease in stratum A (which occupies the first 190 μm downward from the layer I/II border). The difference with controls was significant at 0.01. In stratum B (next 190 μm), the reduction was less important, but still significant at 0.1. In stratum E (situated within layer VI) there was also a reduction of cell density in treated animals; however, the difference with controls was not significant.

Discussion

A. Biochemical Effects of Treatment with 6-OHDA on the Developing Cerebral Cortex

Neonatal intracisternal injection of relatively high doses of 6-OHDA reportedly induces drastic and long-lasting NA depletion, and less marked DA depletion, in cerebral cortex (e.g., Tassin et al. 1975; Konkol et al. 1978; Oke et al. 1978). The results of our CA content measurements (near total depletion of NA, and more than 60% depletion of DA) are in line with the previous reports. As to the DA values, they cannot be considered as an unambiguous biochemical correlate of DA innervation in the neocortex since they probably include a certain fraction of precursor DA from NA terminals (Schmidt and Bhatnagar 1979b). On the other hand, we cannot exclude the possibility that neocortical tissue samples might have been "contaminated" by fragments of DA-rich striatum, at least in the youngest animals where dissection is particularly difficult.

Another aspect of 6-OHDA effects upon CA systems in developing cortex is reflected by the results of our ^{3}H-NA uptake measurements. The DMI-sensitive uptake (Coyle and Axelrod 1971) probably represents uptake by NA fibres and terminals, and its weakness or even absence in the treated animals

closely parallels the very low endogenous NA levels measured in these animals. The action of 6-OHDA upon the DMI-insensitive uptake is more difficult to interpret, since this fraction represents not only uptake by DA systems but also by non-catecholaminergic structures. Taken together, our biochemical results suggest that the 6-OHDA treatment resulted in a near total and long-lasting destruction of the uptake and storage capacities of neocortical NA afferences, and in a less important impairment of DA afferences.

B. Morphological Correlates of 6-OHDA Action

Our ultrastructural observations in d.p.i. 2,5 and 15 animals (treated within 16 h after birth) showed signs of degeneration in cells, processes and – rather infrequently – synaptic boutons. However, there was no massive degeneration at any cortical level, including the fourth layer where the majority of neonatal synapses has been said to be monoaminergic (Molliver and Kristt 1975; Coyle and Molliver 1977). The discrepancy between the moderate frequency of morphological degeneration signs on the one hand, and the massive reduction of NA uptake and content on the other hand, possibly results from a very rapid structural elimination of CA fibres. In order to test that hypothesis, animals sacrificed after still shorter post-treatment delays are now under study. The degeneration signs we observed after 6-OHDA treatment might well be interpreted as direct (fibre degeneration) or indirect (degeneration consecutive to CA depletion) effects of the drug. However, it has to be emphasized that there are certain limitations to such conclusions.

Firstly, involutive processes are quite frequently observed even in normal immature rat cortex (König and Marty 1977; König 1978). Therefore, one cannot attribute all the degeneration processes observed after 6-OHDA treatment to the action of the drug.

Secondly, even if there is additional degeneration in cerebral cortex, one has to distinguish between effects of specific destruction of CA nerve terminals, effects on extraneuronal or nonmonoaminergic neuronal structures (Sievers et al. 1979, in press), and even more general effects modifying the physiological state of the animal.

The morphometric evaluation of cell densities in individual strata of d.p.i. 15 temporal cortex showed in treated animals a reduction of cell number per unit area. The reduction was greatest (about 16%) in the uppermost part of the cortical plate. The interpretation of this result has to take into account that, in the course of cortical development, both formative and involutive processes take place, both of which may induce reduction of cell density.

Reduced cell proliferation can hardly account for a substantial part of the cell-density reduction observed on day 15, since layers II/III, although ontogenetically recent, are consituted essentially by neurons "born" before birth (Brückner et al. 1976). On the other hand, impairment of migration processes or enhancement of normally occurring cell death cannot be excluded.

Reduction of cell density in the superficial layers may also result from accelerated and/or enhanced growth of their elements, be they intrinsic to layers II/III or *de passage*. In this connection, it is interesting to note that most of the Golgi studies concerned with morphological effects in cerebral cortex after impairment of CA systems have reported augmentation of some features of dendrite geometry. Maeda and co-workers (1974) described persistence of layer VI neuron dendrites going up to layer I, after electrolytic destruction of the ipsilateral locus coeruleus, whereas these dendrites ended at deeper levels in control cortices. This modification was interpreted as an arrest at a primitive stage of development. However, if layer-VI-neuron dendrites remain in contact with layer I, they still have to *grow* at the moment when normal dendrites loose their contact, since the vertical expansion of the cortical layers is not yet achieved. Although Wendlandt and co-workers (1977) could not confirm Maeda's observations, they still reported significantly enhanced apical dendrite branching in pyramidal neurons located in layer IV and the deep part of layer III. Amaral and co-workers (1975) described abnormally long dendrites of modified pyramidal cells in hippocampal field CA4 reaching into the molecular layer of CA3 in 6-OHDA treated rats.

The fact that the cell density reduction observed in our treated animals was not correlated with any decrease of overall cortical thickness (there was even a slight tendency towards increase) suggests that neonatal 6-OHDA i.c. treatment produces not only destructions but also supranormal *growth* processes in cerebral cortex.

Analyses of 6-OHDA action upon cerebellar development in nomifensin pretreated animals have shown that most of the degenerative changes observed there after 6-OHDA treatment alone (Sievers et al. 1979) are present even if 3H-NA uptake is preserved (Sievers et al. in press). Cerebral cortices of similarly pretreated animals are now under study in order to show if, and to what extent, the morphological changes described in the present report are related with 6-OHDA action upon non-catecholaminergic structures. Some of the degenerative changes might well be due to general cytotoxic effects; on the other hand, induction of the supranormal *growth* processes by such effects seems to be less likely.

Acknowledgements. The present work has been supported by grants from D.F.G. (SI 261-1), C.N.R.S. (ERA 187) and I.N.S.E.R.M. (C.R.L.I. n° 78.1.267.6). The authors would like to thank Mrs. E. Beyer, Mrs. C. Schöbel, Miss C. Saënz de Cabezon and Mr. P. Sibleyras for excellent technical help.

References

Amaral DG, Foss JA, Kellogg C, Woodward DJ (1975) Effects of subcutaneous administration of 6-hydroxydopamine (6-OHDA) in neonatal rats on dendritic morphology in the hippocampus. Neurosci Abstr 1:789

Berry M, Mc Connell P, Sievers J (in press, a) Dendritic growth and the control of neuronal form. In: Hurst RK, Monroy A, Moscona AA (eds) Current topics in Developmental Biology. Academic Press, New York

Berry M, Sievers J, Baumgarten HG (in press, b) The influence of afferent fibres on the development of the cerebellum. In: Di Benedetta C (ed) A multidisciplinary approach to Brain Development. North-Holland Publ, Amsterdam

Brückner G, Mareš V, Biesold D (1976) Neurogenesis in the visual system of the rat. An autoradiographic investigation. J Comp Neurol 1966:245–256

Coyle JT, Axelrod J (1971) Development of the uptake and storage of L-[^{3}H]-norepinephrine in rat brain. J Neurochem 18:2061–2075

Coyle JT, Molliver ME (1977) Major innervation of newborn rat cortex by monoaminergic neurons. Science 196:444–447

Cuello AC, Horn AS, Mackay AVP, Iversen LL (1973) Catecholamines in the median eminence: new evidence for a major noradrenergic imput. Nature 243:465–467

Hicks SP, D'Amato CJ (1975) Six-hydroxydopamine (6-OHDA) alters developing cortex and locomotion in rats. Neurosci Abstr 1:788

König N (1978) Organisation précoce du cortex temporal chez le Rat: aspects neuro-, histo- et synaptogénétiques. Doctoral Thesis, Montpellier, 145 pp

König N, Marty R (1977) Early development and regression processes in normal corticogenesis. Proc IUPS 12:594

König N, Sievers J (In preparation) Neocortical circuitry in foetal rat

Konkol RJ, Bendeich EG, Breese GR (1978) A biochemical and morphological study of the altered growth pattern of central catecholeminergic neurons following 6-hydroxydopamine. Brain Res 140:125–135

Lauder JM, Bloom FE (1974) Ontogeny of monoamine neurons in the locus coeruleus, raphe nuclei and substantia nigra of the rat. I. Cell differentiation. J Comp Neurol 155:469–482

Lauder JM, Bloom FE (1975) Ontogeny of monoamine neurons in the locus coeruleus, raphe nuclei and substantia nigra of the rat. II. Synaptogenesis. J Comp Neurol 163:251–264

Luft JH (1961) Improvements in epoxy resin embedding methods. J Biophys Biochem Cytol 9:409–414

Maeda T, Tohyama M, Shimizu N (1974) Modification of postnatal development of neocortex in rat brain with experimental deprivation of locus coeruleus. Brain Res 70:515–520

Molliver ME, Kristt DA (1975) The fine structural demonstration of monoaminergic synapses in immature rat neocortex. Neurosci Lett 1:305–310

Oke A, Keller R, Adams R (1978) Dopamine and norepinephrine enhancement in discrete rat brain regions following neonatal 6-hydroxydopamine treatment. Brain Res 148:245–250

Olson L, Seiger A (1972) Early prenatal ontogeny of central monoamine neurons in the rat: fluorescence histochemical observations. Z Anat Entwickl Gesch 137:301–316

Passon DG, Peuler D (1973) A simplified radiometric assay for plasma norepinephrine and epinephrine. Analyt Biochem 51:618–631

Ross SB, Renyi AL (1975) Tricyclic antidepressant agents. I. Comparison of the inhibition of the uptake of ^{3}H-Noradrenaline and ^{14}C-5-Hydroxytryptamine in slices and crude synaptosome preparations of the mid-brain hypothalamus region of the rat brain. Acta Pharmacol Toxicol 36:382–394

Saavedra J, Brownstein M, Axelrod J (1973) A specific and sensitive enzymatic – isotopic microassay for serotonin in tissues. J Pharmacol Exp Ther 186:508–515

Sachs C, Jonsson G (1975) Effects of 6-hydroxydopamine on central noradrenaline neurons during ontogeny. Brain Res 99:277–291

Schlumpf M, Shoemaker WJ, Bloom FE (1977) The development of catecholamine fibers in the prenatal cerebral cortex of the rat. Soc Neurosci Abstr 3:361

Schmidt RH, Bhatnagar RK (1979a) Regional development of norepinephrine dopamine-B-hydroxylase and tyrosine hydroxylase in the rat brain subsequent to neonatal treatment with subcutaneous 6-hydroxydopamine. Brain Res 166:293–308

Schmidt RH, Bhatnagar RK (1979b) Assessment of the effects of neonatal subcutaneous 6-hydroxydopamine on noradrenergic and dopaminergic innervation of the cerebral cortex. Brain Res 166:309–319

Seiger A, Olson L (1973) Late prenatal ontogeny of central monoamine neurons in the rat: fluorescence histochemical observations. Z Anat Entwickl Gesch 140:281–318

Sievers J (1979) Experimentelle Studien zur Frage der intracerebralen Induktion: der Nucleus

locus coeruleus und sein terminales Zielgebiet, das Kleinhirn. 73. Versammlung Anat Gesellsch 1978, Verh Anat Ges 73:1159–1160

Sievers J, Baumgarten HG, Berry M, Klemm HP, Jenner S (1979) The locus coeruleus neuroblasts: plasticity and function in development. In: Usdin E, Kopin IJ, Barchas J (eds) Pergamon Press, New York Vol I, pp 848–850

Sievers J, Klemm HP, Jenner S, Baumgarten HG, Berry M (in press) Neuronal and extraneuronal effects of intracisternally administered 6-OHDA on the the developing brain. J Neurochem

Tassin JP, Velley L, Stinus L, Blanc G, Glowinski J, Thierry AM (1975) Development of cortical and nigro-neostriatal dopaminergic systems after destruction of central noradrenergic neurons in foetal or neonatal rats. Brain Res 83:93–106

Wendlandt S, Crow TJ, Stirling RV (1977) The involvement of the noradrenergic system arising from the locus coeruleus in the postnatal development of the cortex in rat brain. Brain Res 125:1–9

Accepted March 12, 1980