Brain Research, 271 (1983) 279–288
Elsevier

Changes in Cortical and Subcortical Levels of Monoamines and Their Metabolites Following Unilateral Ventrolateral Cortical Lesions in the Rat

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(Accepted December 14th, 1982)

Key words: cortical lesions – rat – catecholamines – serotonin – subcortical structures

Suction lesions were made in the anterior, posterior or both halves of the right ventrolateral cortex in rats. Six days later, levels of the monoamine neurotransmitters, norepinephrine (NE), dopamine (DA) and serotonin (5-HT), and their metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA), were measured in cortical and subcortical regions of lesioned rats and compared to values in sham-operated animals. NE and 5-HT were decreased in sections of ipsilateral (right) cortex including, and posterior to lesions, while 5-HIAA was increased throughout the ipsilateral cortex. Decreases in monoamines and increases in metabolites and metabolite:monoamine ratios (especially 5-HIAA:5-HT) were found in ipsilateral subcortical structures, including striatum, nucleus accumbens, hippocampus, hypothalamus, midbrain and brainstem, depending on the type of lesion. Subacutely, focal ventrolateral cortical lesions may profoundly alter the levels and utilization rates of monoamine neurotransmitters in widespread regions of the ipsilateral hemisphere.

INTRODUCTION

A considerable amount of work has centered on acute metabolic and biochemical changes in brain following focal injury in the cerebral hemispheres in an effort to understand and devise rational therapy for the immediate sensorimotor and cognitive deficits that follow stroke or brain trauma. For example, changes in brain levels of the monoamine neurotransmitters norepinephrine (NE), dopamine (DA) and serotonin (5-hydroxytryptamine; 5-HT) have been found within minutes to hours after experimental cerebral infarction[4,9,11,32,34]. In contrast, less work has focussed on the effects of focal cortical injury (such as commonly happens in clinical stroke) on the metabolism and biochemistry of brain regions at a *distance* from injured sites and at *longer times* (days to weeks) after injury. Recently, Robinson and colleagues[21–24] have reported persistent bilateral *depletions* in levels of NE and DA in widespread regions of cerebral cortex and brainstem following small right-sided cortical lesions in rats. Woodruff et al.[33] have reported significant *increases* in concentrations of NE and DA in rat forebrain 90 days after bilateral dorsolateral neocortical ablation.

Persistent changes in the levels and utilization rates of monoamines occurring in anatomically intact (especially in limbic) regions of brain following focal cortical injury may underlie some of the behavioral and neuroendocrine disturbances that follow stroke in humans[3,6,12,14,25] and may point toward possible pharmacological therapies for these disturbances. To test the hypothesis that such changes occur in an animal model of focal cortical injury, we have made suction lesions in the right ventrolateral cortex of rats in the territory supplied by the middle cerebral artery (a common site of cerebral infarction in humans) and have looked for changes in levels of monoamines (NE, DA and 5-HT) and their me-

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tabolites (3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA), major metabolites of DA and 5-HT, respectively) in cortex and subcortical structures at one week after injury. Ratios of metabolite:transmitter (DOPAC:DA and 5-HIAA:5-HT) were also calculated to provide indices of the relative rates of utilization of DA and 5-HT[5]. Cortical lesions were made in the anterior or posterior half of the ventrolateral cortex, or both, in order to assess neurochemical changes in subcortical structures directly adjacent (medial to), vs anterior or posterior to lesions.

MATERIALS AND METHODS

Surgery and dissection

Male Sprague-Dawley rats (Charles River, initially 300–350 g) were housed 4 per cage in a 12 h light–dark (07.00–19.00 h lights on) environment with controlled temperature (23–25 °C) and humidity (40–50%) and with food and water freely available. Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and placed in a stereotaxic apparatus (David Kopf Instruments, Tujunga, CA). The lateral aspect of the right side of the skull was exposed, and a craniectomy was made, extending from the periorbital to the parieto-occipital region and from the zygomatic arch to the ridge between the dorsal and lateral aspects of the skull. The dura was reflected, and the cortex was removed by gentle aspiration through a fine glass pipette held parallel to the cortical surface. Three types of right ventrolateral cortical suction lesions in territory supplied by the middle cerebral artery were made with their inferior borders 0–2 mm above the rhinal fissure (Fig. 1): (1) 'large lateral' lesions, extending from frontal to parieto-occipital cortex (approximately 12 × 4 mm); (2) 'anterolateral' lesions, extending from frontal to fronto-parietal cortex (approximately the anterior half of the 'large lateral' lesions); and (3) 'posterolateral' lesions, extending from fronto-parietal to parieto-occipital cortex (approximately the posterior half of the 'large lateral' lesions). In sham-operated controls, only the craniectomy was done, and the dura was not penetrated. On each day of surgery, 8–10 lesioned rats and an equal number of sham-operated rats were prepared alternately.

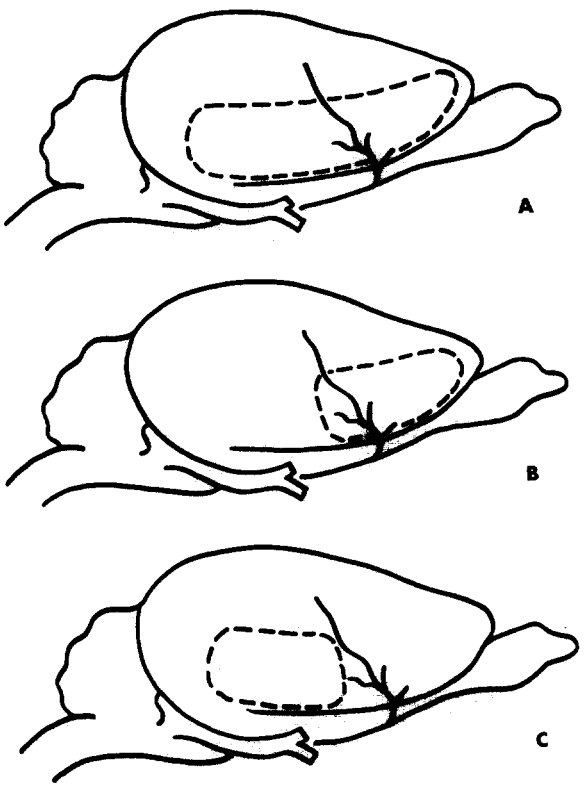

Fig. 1. Locations of right ventrolateral lesions. Cortex within dotted lines was removed by suction. A: 'large lateral' lesion. B: 'anterolateral' lesion. C: 'posterolateral' lesion. The approximate position of the middle cerebral artery is shown.

After surgery, rats were housed in individual cages. The survival rate was approximately 90%. Six days after surgery, rats were sacrificed by decapitation, and their brains were rapidly removed and cooled on a mixture of ice and dry-ice. The extent of superficial cortical damage was measured and photographed. Each brain was placed, ventral side up, on a micrometer-controlled slicing device (L.S. Starrett, Athol, MA), and using the anterior 'notch' of the optic chiasm as an external landmark, 6 coronal cuts were made, separating the brain into 5 'slices' used for subsequent dissection. Slice 1 extended from 3.0 to 0.5 mm rostral to the optic chiasm; Slice 2 from 0.5 rostral to 1.75 mm caudal to the chiasm; and Slices 3–5 from 1.75 to 4.0 mm, 4.0–8.0 mm, and 8.0–12.5 mm caudal to the optic chiasm, respectively. (Approximate König and

Klippel[10] planes of Slices 1–4 were: 10,500–8380, 8380–6280, 6280–3990, and 3990–100 μm, respectively).

Brain slices were examined visually for apparent subcortical damage, and brains in which such damage was detected (approximately 10%) were discarded. Sections of 'anterior' cortex were dissected from Slices 1 and 2, and sections of 'posterior' cortex were taken from Slice 4. These sections included the suprarhinal ventrolateral cortex in which the lesions were made, as well as 3–4 mm of more dorsally placed cortex (Fig. 2). Sections of right 'anterior' cortex always included damaged cortex in rats with 'large lateral' and 'anterolateral' lesions, and were always anterior to the cortical damage in rats with 'posterolateral' lesions. Sections of right 'posterior' cortex always included damaged cortex in rats with 'large lateral' and 'posterolateral' lesions, and were always posterior to the cortical damage in rats with 'anterolateral' lesions. Sections of nucleus accumbens were dissected from Slice 1; striatum from Slice 2; hypothalamus from Slice 3; hippocampus and midbrain from Slice 4; and caudal brainstem from Slice 5. For each of these structures, samples were divided into right and left halves (except for hypothalamus, which was left undivided). Individual samples were weighed in pre-weighed microcentrifuge tubes (VWR Scientific, San Francisco, CA), put immediately on dry-ice, and stored at −70 °C for up to 4 weeks before assay.

Brain slices remained on a mixture of ice and dry-ice throughout the dissection procedure. The total time between sacrifice and freezing of samples was less than 5 min for each rat.

Histology

Rats chosen at random for histological examination of lesions were anesthetized with Chloropent (Fort Dodge Laboratories, Fort Dodge, IA) and perfused transcardially with normal saline followed by 10% (vols.) formalin. The brains were then removed and stored for at least 4 days in 5% (vols.) formalin. Coronal sections of 50 μm were cut on a freezing microtome (American Optical, Buffalo, NY), and every tenth section was stained with cresyl violet. The extent of lesions was examined with a light microscope (Zeiss Universal, F.R.G.).

Assay of monoamines and metabolites

Monoamines and metabolites were assayed by high-performance liquid chromatography with electrochemical detection (HPLC/EC). On the day of assay, individual tissue samples were homogenized by sonication (Biosonik Sonicator, Bronwill Scientific, Rochester, NY) in 0.7 ml of a solution containing 0.5 N perchloric acid, 1.0 mM disodium EDTA and 0.4 mM sodium metabisulfite as antioxidants, and 5 ng/100 μl epinephrine (Sigma Chemicals, St. Louis, MO) as an internal standard. (The amount of added epinephrine [E] far exceeded the trace amounts detectable in tissue samples.) The catecholamines NE, DA and E in 0.4 ml of homogenate supernatant were extracted (by adsorption and desorption on alumina) and chromatographed according to modifications by Sperk et al.[28,29] of the methods of Felice et al.[2]. A 100 μl aliquot of homogenate supernatant was injected directly into a second HPLC/EC system to resolve DOPAC, 5-HT, and 5-HIAA following the method of Sperk[27].

Tissue samples obtained from lesioned and sham-operated rats sacrificed on the same day were also extracted and chromatographed alternately on a single day. Standard solutions, containing 1, 5 or 10 ng/100 μl of authentic NE and DA (Sigma) and 5 ng/100 μl of internal standard (E) were subjected to the extraction process and chromatographed along with each batch of tissue samples. Recovery consistently exceeded 90%. Standard solutions containing 1, 5 or 10 ng/100 μl of DOPAC, 5-HT and 5-HIAA (Sigma), respectively, were also chromatographed. Using these data, standard lines were plotted through the origin[26], with concentration on the abscissa and the ratio of peak height of standard to that of the internal standard (for NE and DA) or peak height alone (for DOPAC, 5-HT and 5-HIAA) on the ordinate. Concentrations of monoamines and metabolites in tissue samples were calculated by mathematical interpolation on these lines with the assistance of a microcomputer and expressed as ng/mg wet weight of tissue.

Data analysis

Levels of NE, DA, 5-HT, DOPAC and 5-HIAA in structures on the right or left side of lesioned rat brains were compared to levels in structures on the same side of sham-operated rats sacrificed on the same day. The metabolite:monoamine ratios, DOPAC:DA and 5-HIAA:5-HT, were also calculated for lesioned and sham-operated animals and compared. These comparisons were tested statistically by Student's *t*-test. To make comparisons among lesioned groups, the 'mean percent changes' of levels in lesioned rats compared to sham-operated rats were also calculated and are displayed on the bar graphs of Figs. 3–5 below. Each bar represents the 'mean percent change' (calculated as [(mean lesion value−mean sham value) × 100]/mean sham value) of tissue monoamine or metabolite levels in animals with a single lesion type, compared to tissue levels on the same side in sham-operated rats sacrificed on the same day. (Most of the bars (91%) represent comparisons between 8 vs 8 rats; 9% represent comparisons between 6 or 7 vs 8 rats.) The standard error of each change was calculated by taking into account variance in both lesioned and sham-operated groups[13]. 'Mean percent change' values among rats with different lesion types were compared using a modified *t*-test[13], which accounted for variance in both lesioned and sham-operated animals.

RESULTS

Lesions

The mean (± S.E.M.) lengths of the 'large lateral' (n = 8), 'anterolateral' (n = 16), and 'posterolateral' (n = 16) lesions were 12.0 ± 0.3, 6.8 ± 0.2, and 7.4 ± 0.3 mm, respectively. The mean widths of the lesions were 4.2 ± 0.5, 4.4 ± 0.2, and 3.8 ± 0.2 mm; and the mean distances of the inferior borders of lesions above the rhinal fissure were 1.2 ± 0.4, 0.7 ± 0.2, and 1.8 ± 0.2 mm for the three lesion types, respectively. The mean area of damaged cortex was 50.0 ± 5.3 for 'large lateral' lesions, 30.3 ± 2.0 for 'anterolateral' lesions, and 28.1 ± 2.6 mm^2 for 'posterolateral' lesions (see Fig. 1).

At the time of sacrifice, visual inspection of the coronal sections revealed no apparent damage to subcortical structures in brains used subsequently for neurochemical assay. Parts of the striatum were directly adjacent (medial) to all of the 'large lateral,' 'anterolateral,' and 'posterolateral' lesions. The hippocampus was directly adjacent to all of the 'large lateral' and 'posterolateral,' but none of the 'anterolateral' lesions. Neither the nucleus accumbens, nor any other subcortical structure assayed was adjacent to lesions.

Detailed histological examinations were made on 4 brains chosen randomly from each of the lesion groups: one with a 'large lateral' lesion, two with 'anterolateral' lesions, and one with a 'posterolateral' lesion. The damage was confined exclusively to the cerebral cortex and underlying white matter, except in two brains, in which there was minimal superficial damage to the striatum observed on two or three 50 μm sections. (The maximal extent of such damage is shown in Fig. 2.) In *no* case was there observable damage or edema involving intact cortex, hippocampus, nucleus accumbens or any of the other subcortical structures assayed neurochemically.

Monoamine and metabolite levels

Levels of monoamines and their metabolites were measured separately in both the right and left halves of each of the cortical and subcortical brain structures (except for the hypothalamus). At 6 days after surgery, the only significant changes in lesioned, compared to sham-operated rats were found on the *right* sides of these structures, in the hemisphere *ipsilateral* to the cortical lesions. (In general, differences between levels of monoamines and metabolites in contralateral (left-sided) structures of lesioned vs sham-operated rats were less than 10%, and none was significant.)

Norepinephrine (NE) content (Fig. 3) was significantly *decreased* by approximately 20–50% in ipsilateral sections of cortex that included the lesions (anterior cortex in animals with 'large lateral' and 'anterolateral' lesions and posterior cortex in animals with 'large lateral' and 'posterolateral' lesions), and in sections of posterior

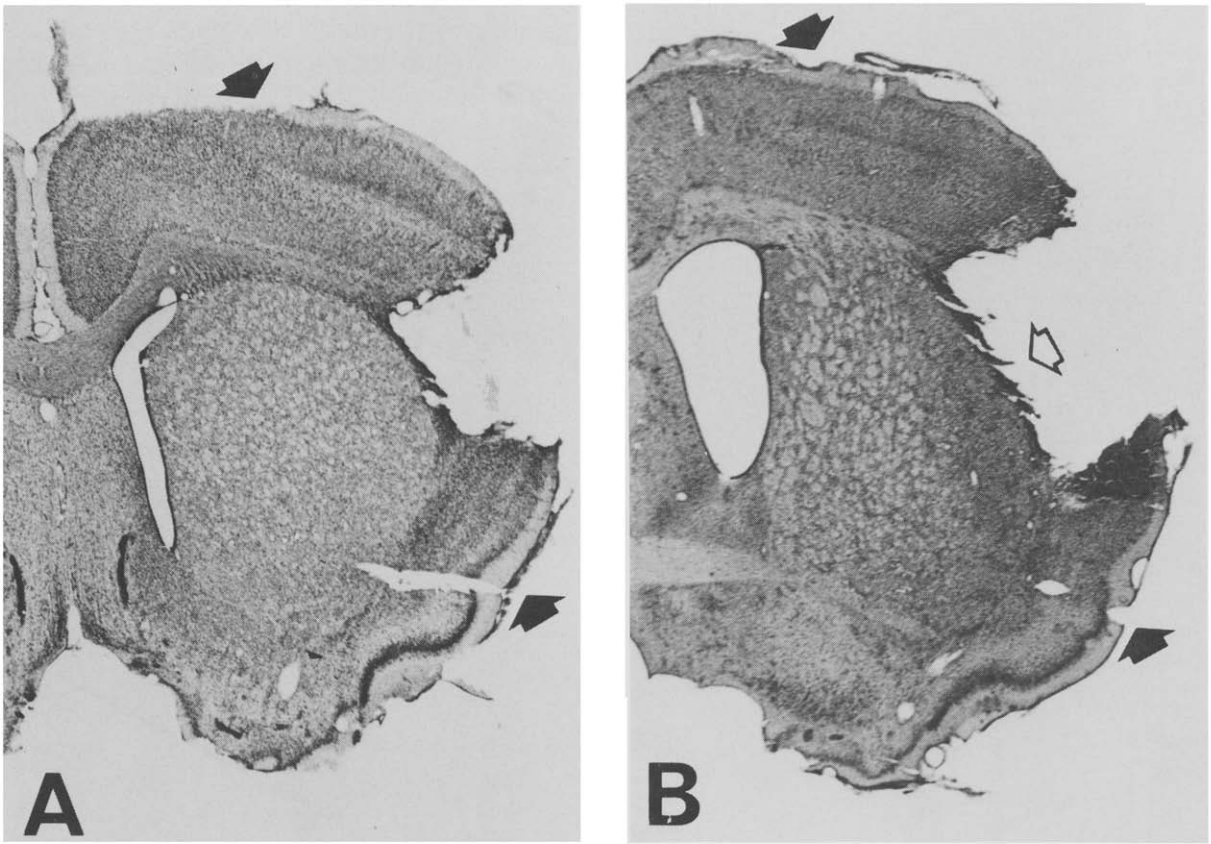

Fig. 2. Two cresyl violet-stained sections of the right side of a brain with an 'anterolateral' lesion. A: removal of ventrolateral cortex with sparing of underlying striatum. B: more posteriorly, removal of ventrolateral cortex with slight superficial damage to underlying striatum (open arrow). The closed arrows mark the approximate ventral and dorsal boundaries of sections of 'anterior' and 'posterior' cortex taken for neurochemical assay.

cortex behind 'anterolateral' lesions. In animals with 'large lateral' lesions, significant decreases (20-30%) in NE content were also found in the ipsilateral nucleus accumbens and hippocampus, and NE was decreased in the ipsilateral hippocampus in rats with 'anterolateral' and 'posterolateral' lesions as well. In contrast, NE tended to be *increased* in ipsilateral striatum in rats with 'large lateral' and 'anterolateral' lesions. No significant changes were found in the NE content of hypothalamus, midbrain or brainstem.

Dopamine (DA) (Fig. 4) was not measured in

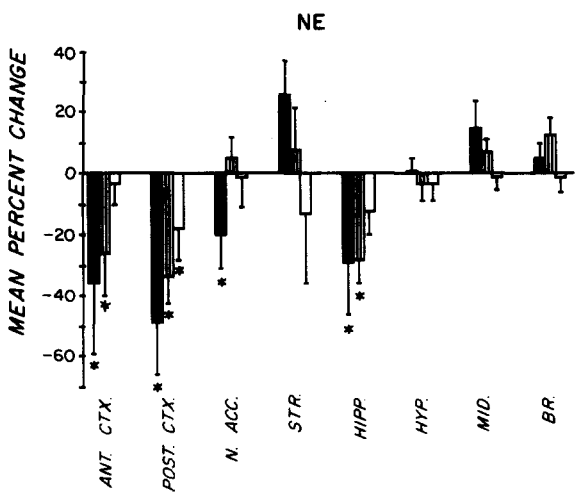

Fig. 3. Mean percent changes (± S.E.M.) of levels of norepinephrine (NE) in ipsilateral (right) structures in lesioned compared to sham-operated animals (see text). Solid, striped, and open bars represent values in animals with 'large lateral', 'anterolateral,' and 'posterolateral' lesions, respectively. Asterisks signify that values in lesioned animals are different from those in sham-operated animals by two-tailed t-test ($P < 0.05$). Abbreviations: ANT. CTX, 'anterior' cortex; POST. CTX, 'posterior' cortex; N. ACC, nucleus accumbens; STR, striatum; HIPP, hippocampus; HYP, hypothalamus; MID, midbrain; BR, brainstem.

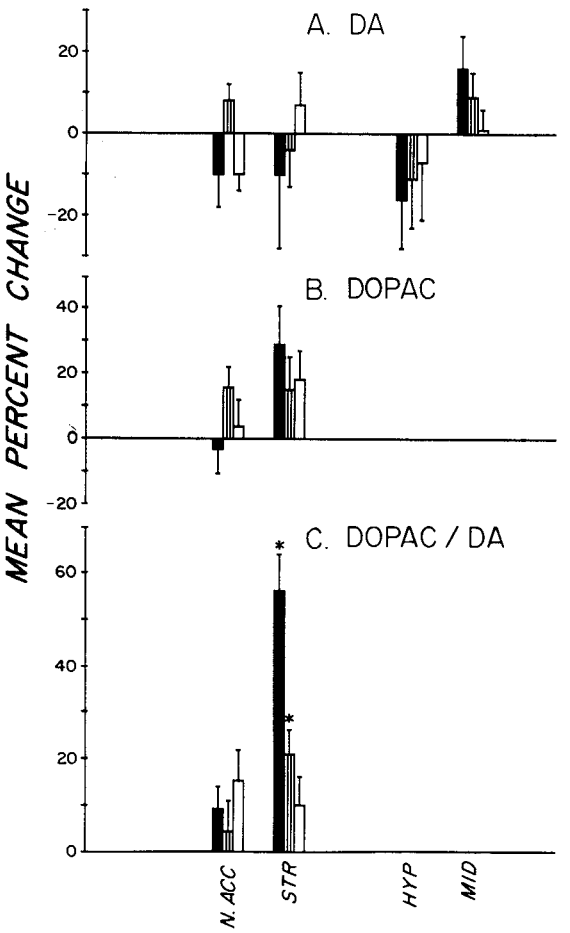

Fig. 4. Mean percent changes (± S.E.M.) of levels of (A) dopamine (DA), (B) 3,4-dihydroxyphenylacetic acid (DOPAC) and (C) DOPAC/DA in ipsilateral (right) structures in lesioned compared to sham-operated animals. (See legend, Fig. 3.)

sections of cortex, hippocampus, or brainstem nor was DOPAC measured in these regions, in hypothalamus, or in midbrain, due to their low levels in these structures. In the other structures examined, no significant changes in the levels of these compounds were found, although DA tended to be decreased in the hypothalamus and DOPAC tended to be increased in the ipsilateral striatum in animals with all 3 lesion types. This latter change, coupled with small decreases in DA content, accounted for significant *increases* in the DOPAC:DA ratio in the ipsilateral striatum, which were greater in rats with 'large lateral,' than in those with 'anterolateral' lesions (56% vs 21%, respectively, $P < 0.01$; Fig. 4).

The neurochemical changes of greatest magnitude and widest extent were found in the ipsilateral serotonin (5-HT) system (Fig. 5). 5-HT levels were significantly *decreased* (by 20–35%) in sections of cortex that included lesions (anterior cortex in animals with 'large lateral' and 'anterolateral' lesions, and posterior cortex in animals with 'large lateral' and 'posterolateral' lesions), and 5-HT levels tended to be decreased in sections of posterior cortex behind the 'ante-

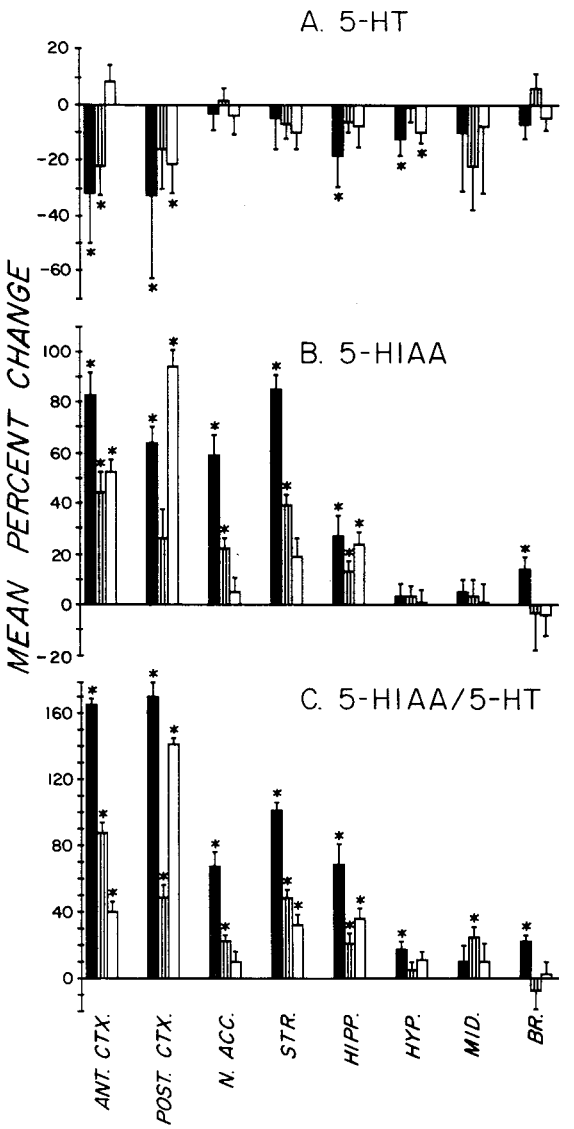

Fig. 5. Mean percent changes (± S.E.M.) of levels of (A) serotonin (5-HT), (B) 5-hydroxyindoleacetic acid (5-HIAA), and (C) 5-HIAA/5-HT in ipsilateral (right) structures in lesioned compared to sham-operated animals. (See legend, Fig. 3.)

rolateral' lesions. 5-HT was also significantly decreased (10–20%) in the ipsilateral hippocampus in rats with 'large lateral' lesions, and in the hypothalamus in rats with 'large lateral' and 'posterolateral' lesions.

On the other hand, 5-HIAA was significantly *increased* by 45–95% (Fig. 5) in cortical sections including lesions and anterior to 'posterolateral' lesions, and tended to be increased in cortex posterior to 'anterolateral' lesions. 5-HIAA was also significantly increased in the ipsilateral striatum and nucleus accumbens in rats with 'large lateral' and 'anterolateral' lesions (20–85%), in the ipsilateral brainstem in rats with 'large lateral' lesions (15%), and in the ipsilateral hippocampus in rats with all three lesion types (15–30%).

The above reciprocal changes in 5-HT and 5-HIAA accounted for moderate-to-striking, and significant *increases* in the 5-HIAA:5-HT ratio in ipsilateral anterior and posterior cortex (40–170%), striatum (30–100%), and hippocampus (20–70%) in rats with all 3 lesion types (Fig. 5). This ratio was also significantly increased in the ipsilateral nucleus accumbens in rats with 'large lateral' and 'anterolateral' lesions (20–70%); in the hypothalamus and ipsilateral brainstem in rats with 'large lateral' lesions (20%); and in the ipsilateral midbrain in rats with 'anterolateral' lesions (25%). The increases in the 5-HIAA:5-HT ratio in sections of cortex including lesions were greater than those in cortex either anterior or posterior to lesions (all $P < 0.05$). In addition, the increases in the 5-HIAA:5-HT ratio in the striatum, nucleus accumbens, and hippocampus in rats with 'large lateral' lesions were greater than those in rats with either 'anterolateral' or 'posterolateral' lesions (all $P < 0.05$).

DISCUSSION

At 6 days after unilateral (right) ventrolateral cortical suction lesions were made in the rat brain, profound and widespread changes in the content of monoamine neurotransmitters and their metabolites were found in cortex and subcortical structures distant from the lesions, including the nucleus accumbens, striatum, hippocampus, and hypothalamus. These changes were significant only in *ipsilateral* structures. The greatest neurochemical changes in subcortical structures were found in rats with the 'large lateral' lesions.

Several lines of evidence suggest that the neurochemical changes observed in subcortical structures were not due merely to direct damage to these structures. First, gross visual inspection of coronal slices of brains used for subsequent neurochemical assay revealed no subcortical damage at 6 days after surgery. Second, detailed histological examination of 4 randomly selected brains (at least one with each type of lesion) also showed no subcortical damage, except for minimal superficial damage to the striatum in two. Third, neurochemical changes were found in subcortical structures and cortex distant from lesions. Thus, changes were found in structures well posterior to the 'anterolateral' lesions (e.g. posterior cortex and hippocampus), anterior to the 'posterolateral' lesions (e.g. anterior cortex), and inferior to all of the lesion types (e.g. nucleus accumbens and hypothalamus).

In a general sense, these results are similar to the findings of Robinson and colleagues[21–24], who reported widespread changes in brain catecholamine content following similar right ventrolateral cortical lesions. However, the pattern of neurochemical changes that we observed was different from that observed by Robinson et al. at approximately the same time (5–8 days) after cortical injury. Whereas they reported *bilateral* decreases of catecholamine content in cortical, midbrain and brainstem structures (including substantia nigra, locus coeruleus and A10 cell groups), we found no such changes in midbrain or brainstem (although our tissue samples were large and may have obscured changes in small nuclei). Further, the changes that we observed in cortical and subcortical catecholamine and 5-HT systems were confined to the hemisphere *ipsilateral* to the lesions.

The changes that we observed in monoamine and metabolite levels were both chemically and anatomically selective. Because metabolites of NE were not measured and DA and DOPAC were not measured in all of the brain structures,

it is difficult to compare the relative magnitudes of change among the monoamine systems. However, it appears that the most widespread changes were in the 5-HT system. For example, although significant decreases in 5-HT (and NE) content and increases in 5-HIAA and in the 5-HIAA:5-HT ratio were found in the nucleus accumbens of rats with 'large lateral' lesions, no changes were found in the DA system of this structure. Also, whereas 5HT was significantly decreased and the 5-HIAA:5-HT ratio was increased in the hypothalamus of such rats, NE and DA content were unchanged.

Two major groups of fibers are reported to project from monoaminergic cell bodies in brainstem to the ventrolateral cortex in the rat, where the lesions were made. The first group, described by Moore and colleagues[7,16] for both NE and 5-HT systems, departs from the medial forebrain bundle and travels *laterally* through the ventral amygdaloid bundle and ansa lenticularis to supply ventrolateral cortex. The second group, described for the NE system (and proposed for the 5-HT system) by Morrison and colleagues[17–19], enters the frontal pole of the hemisphere and courses *longitudinally* backward through both dorso-and ventrolateral cortex. Thus, lesions of the lateral cortex might be expected to denervate partially the monoaminergic input to more posteriorly located cortex. Indeed, Morrison et al.[19] reported decreased levels of NE and 5-HT in cortex posterior to dorsolateral cortical lesions, and we found decreased levels of NE and 5-HT in sections of cortex posterior to our more ventrally placed 'anterolateral' lesions (but not decreased in cortex anterior to the 'posterolateral' lesions). However, whereas Morrison et al.[17] also reported a slight decrease in monoamine metabolites (including 5-HIAA) in cortex posterior to dorsolateral lesions, we found significant increases of 5-HIAA and of the 5-HIAA:5-HT ratio in sections of cortex including, posterior, and anterior to lesions. (These differences might be accounted for by different times of sacrifice after lesioning – generally two weeks in the studies by Morrison and colleagues and six days in our own.) Thus, at 6 days after injury, the decline of NE and 5-HT levels in cortical sections including, and posterior to damaged cortex was accompanied by an apparent increase in the 5-HT utilization rate throughout the ipsilateral cortex.

As in cortex, changes in subcortical monoamine levels in lesioned animals seemed to follow an 'anteroposterior organization.' Thus, significant changes were found in subcortical structures only at the same anteroposterior level, or posterior (but not anterior) to lesions. For example, in animals with 'anterolateral' lesions, NE and 5-HT levels were reduced in the ipsilateral hippocampus, which is well posterior to the lesions. It is thus possible that some afferent monoaminergic fibers to hippocampus arrive in anteriorly-to-posteriorly oriented intracortical pathways as described by Morrison and colleagues[17–19]. The increases in striatal NE content that we observed in animals with 'large lateral' and 'anterolateral' lesions may represent the sprouting of NE fibers in ventral striatum described by Morrison and colleagues[19] in animals with dorsolateral cortical lesions.

Changes in subcortical metabolite levels and in metabolite:monoamine ratios also seemed to have an 'anteroposterior organization.' Thus, significant increases in DOPAC:DA, 5-HIAA or 5-HIAA:5-HT were found in subcortical structures at the same anteroposterior level, and posterior to 'anterolateral' lesions (i.e. in nucleus accumbens, striatum, hippocampus and midbrain). Moreover, similar changes were seen only in subcortical structures at the same anteroposterior level, but not anterior to 'posterolateral' lesions (i.e. in striatum, hippocampus and hypothalamus, but not nucleus accumbens).

The changes in cortical and subcortical metabolite levels and metabolite:monoamine ratios in lesioned rats (especially in 5-HIAA and 5-HIAA:5-HT) were likely due to specific neural mechanisms rather than diffuse circulatory or metabolic causes. Although widespread in the ipsilateral hemisphere, the changes were both chemically and anatomically selective and thus probably not due to general increases in circulating precursor levels (e.g. tryptophan) or to diffuse disruptions of transport systems or the blood–brain barrier. In fact, histological exami-

nation of 4 brains showed no apparent damage to structures other than lesioned cortex and superficial underlying striatum. Specifically, the increases observed in cortical 5-HIAA and 5-HIAA:5-HT might have been due to compensatory overactivity of remaining cortical serotonergic neurons following destruction of others. For example, since the lesions were ventrolateral, and the cortical sections assayed included dorsolateral cortex, the increases in 5-HIAA and 5-HIAA:5-HT in cortical sections including, anterior, and posterior to lesions might reflect hyperactivity of remaining *longitudinally* oriented afferents following loss of afferents of the *laterally* organized system. Mechanistically, loss of fibers in cortex might have caused direct retrograde changes in monoamine cell bodies of origin in the brainstem, resulting in altered activity at terminals of these same neurons at other cortical and subcortical locations. The facts that projections from single locus coeruleus and raphe neurons are extensively arborized and primarily ipsilateral are consistent with this mechanism[7,16,30]. Alternatively, the lesions may have interrupted efferent 'feedback loop' fibers from damaged cortex to brainstem cell bodies; or may have interrupted topographically specific efferent fibers from damaged to undamaged cortex and to subcortical structures that regulate *local* monoamine content and utilization in these structures. Although relatively little is known about efferent pathways from ventrolateral cortex to subcortical structures, fibers from perirhinal cortex to striatum, nucleus accumbens, thalamus, amygdala, presubiculum, hypothalamus and substantia nigra, as well as to the dorsal raphe have been found in rat brain[1,8].

Our findings of widespread increases in the apparent rate of 5-HT utilization following focal cortical lesions are paralleled in studies of unilateral kainic acid-induced lesions of striatum. Sperk et al.[28] and Neff and Neckers[20] reported increases in 5-HIAA and 5-HIAA:5-HT in striatum, substantia nigra, hypothalamus, and frontal cortex that were especially prominent at 2–10 days after such lesions were made.

In summary, our findings support the principle that, at least subacutely, focal damage to the cerebral cortex may profoundly alter the neurochemical functioning of anatomically distinct cortical and subcortical regions of rat brain. The lesions in rat brain were made at a site commonly damaged by human stroke: the ventrolateral cortex in the territory supplied by the middle cerebral artery[15]. If our general findings are also applicable to human brain, it is possible that neurochemical changes in distant (especially limbic) regions may be associated with some of the behavioral (including affective, vegetative, and psychotic[3,12,14,25]) and neuroendocrine[3,6] disturbances that follow damage to the human cerebral cortex by stroke or trauma. Such neurochemical changes in anatomically intact structures may be amenable to pharmacological modification, for example, by drugs that alter monoamine neurotransmission (such as tricyclic antidepressants or lithium[31]).

ACKNOWLEDGEMENTS

The authors wish to thank Günther Sperk, Ph. D. for assistance in establishing the HPLC/EC assay methods; Martin Teicher, M.D., Ph.D. for advice concerning the statistical analysis of the data; and Mila Cason and Christine Triano for preparing the manuscript.

This work was done during the tenure of a Clinician-Scientist Award to S.F. from the American Heart Association and with funds contributed, in part, by its Massachusetts Affiliate. Also partially supported by USPHS (NIMH) Research Grant MH-31154 to McLean Hospital and Career Award MH-47370 to R.J.B. as well as an award from the Bruce Anderson Foundation to R.J.B. and McLean Hospital.

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