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Mechanisms of Lateralized Hyperactivity Following Focal Brain Injury in the Rat

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ROBINSON, R. G. AND A. JUSTICE. *Mechanisms of lateralized hyperactivity following focal brain injury in the rat.* PHARMACOL BIOCHEM BEHAV 25(1) 263–267, 1986.—Recent work in this lab which explores the differential behavioral and neurochemical changes following left versus right cerebral damage is reviewed and neural mechanisms which may account for this asymmetry are proposed. Damage to the right frontoparietal cortex in rats, caused by either ischemia or suction, produces hyperactivity for as long as a month after surgery. These lesions also produce decreases in norepinephrine (NE) levels in both ipsilateral and contralateral cortex and in the locus coeruleus. Similar lesions in the left cortex, however, do not produce these behavioral or biochemical changes. Similar lateralized responses have also been produced by intracortical injections of NE neurotoxins, by cortical island lesions, by destroying cortical efferents, and by producing lesions in the nucleus accumbens, which receives a cortical input. These lateralized responses suggest that the neural mechanisms that mediate this phenomenon include both cortical and subcortical components. It is proposed that the neuroanatomical asymmetry is in either accumbal efferents or their postsynaptic connections.

Middle cerebral artery Catecholamines Neocortex Nucleus accumbens Asymmetry Activity

THE annual incidence of stroke in the United States is approximately 400,000. This represents a major clinical problem for health care in this country not only because it is the third leading cause of death but also because physical, intellectual, and emotional consequences of stroke require large numbers of health care workers for rehabilitation and treatment. In an effort to elucidate some of the mechanisms and potential treatment for post-stroke cognitive or emotional symptoms, our laboratory has developed a rat experimental model of human stroke which involves ligation of the middle cerebral artery (MCA) [9,16]. During the past 10 years, we have investigated the effect of this procedure on spontaneous activity using male Sprague-Dawley rats approximately 7–20 weeks of age.

Anesthetized rats are placed in a stereotaxic apparatus and a craniotomy is made in the lateral skull extending from the coronal suture posteriorly to the periorbital area anteriorly and from the zygomatic arch inferiorly to the ridge separating the dorsal and lateral skull superiorly. Under a dissecting microscope, a semi-circular ophthalmic needle with 6-0 silk suture is passed through the dura behind the MCA, out through the dura, and the suture is tied. A small hole is made in the dura distal to the ligature and the exposed artery is severed to insure completeness of ischemia.

As early as 5 days after operation, histological examination of the area of infarction reveals a focal area of cortical necrosis (Fig. 1). The size and location of the infarction varies slightly from animal to animal, but generally is approximately 1–2 mm in diameter and extends to a variable depth (60–100%) through the cortex, but does not involve the underlying striatum [10]. Neurological examination reveals an immediate postoperative decrease in animals' responsiveness to touching their fur or pinching the limbs contralateral to the lesion [11]. These neurological deficits are evident as soon as the animal has recovered from anesthesia. Although the animals are able to walk, they do not move their contralateral rear limbs as briskly as those ipsilateral to the lesion. This results in a slight limp, but there is no unilateral turning behavior, seizure, or other gross motor abnormality. These motor sensory changes are no longer demonstrable 24 hours after surgery and presumably reflect transient ischemia in the sensory motor cortex medial and dorsal to the site of infarction.

LATERALIZED BEHAVIORAL AND CHEMICAL RESPONSE FOLLOWING EXPERIMENTAL STROKE

Although we have examined numerous aspects of behavior following MCA ligation, such as shock induced aggression [16], intracranial self-stimulation [12], and response to various schedules of reinforcement for water reward [1], the behavior which has received the most attention has been spontaneous activity [9, 11, 13, 16]. Most of the experiments have utilized 24 hour running wheel revolutions as the measure of activity [9,13] although we have also used computerized photocell chambers [16] or visual observations in an open field environment [9] to assess spontaneous activity.

The running wheel cage consists of a stationary wire mesh compartment in which food and water are available ad lib,

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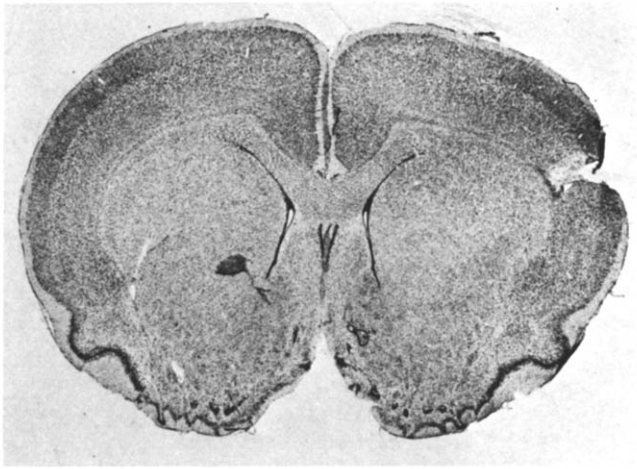

FIG. 1. Nissl-stained coronal section showing a lesion caused by middle cerebral artery ligation. Subcortical tissue is spared.

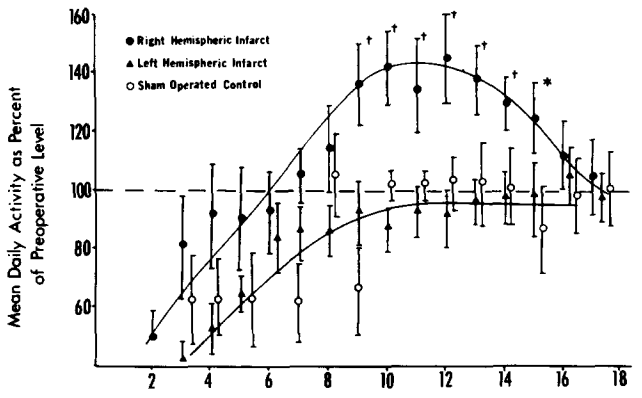

FIG. 2. Daily postoperative running-wheel activity following ischemic lesions as a percent of each animals' preoperative baseline. *$p<0.05$; †$p<0.01$: Right lesion versus left lesion. Figs. 1 and 2: (Reprinted by permission of the AAAS).

connected to a 34 cm diameter running wheel that can rotate freely in either direction. At 24-hour intervals, daily food and water consumption are measured and cyclometer readings from the running wheel cages are taken. Rats are allowed to acclimatize to the cages for 2 weeks preoperatively and baseline preoperative activity is measured in the 3rd week, during which time daily activity measures are relatively stable.

As shown in Fig. 2, rats who were given right MCA ligations became significantly more active than rats receiving left MCA ligations or craniotomies alone beginning approximately 9 days after surgery [9]. Mean daily activity for animals with right hemisphere lesions reached about 150% of preoperative baseline by postoperative day 12 and then slowly declined to preoperative levels by 18–20 days postoperative. In contrast, the activity of animals following control operations or left hemisphere lesions slowly returned to baseline by ten days after surgery and then levelled off without ever exceeding baseline values. We have demonstrated this same differential response to right versus left cortical lesions whether activity was measured in an open field [9], photocell chambers [6], or running wheel cages [9].

Following either right or left hemisphere infarction, food and water intake dropped significantly below preoperative levels for the first four days. By 5–6 days after operation, however, both groups had returned to their preoperative food and water consumption [13,16].

As rapidly as 12 hours after right MCA ligation, significant decreases in norepinephrine (NE) and dopamine (DA) concentrations were measured in several brain regions [15]. The concentration of NE within the cortex surrounding the lesion site was approximately 25% of control levels 12 hours after operation. In addition, there were similar depletions in the nucleus locus coeruleus (LC), where the parent noradrenergic cell bodies are located. Depletions of NE were also found in the cortex contralateral to the lesion and in the LC. NE concentrations slowly recovered over the 40-day postoperative period with some brain regions, such as the contralateral LC, recovering completely, while other regions, such as the ipsilateral LC, showed only partial recovery during this time [13,16].

Similarly, depletions of DA have been found in the substantia nigra where the dopamine cell bodies for the nigrostriatal pathway are located, and in the ventral tegmental area (VTA; A10 cell group), where cell bodies for the mesolimbic pathway are located [13, 15, 16]. DA concentrations in the substantia nigra and VTA did not recover to the same extent as did NE concentrations, but remained at approximately 50% of control levels throughout the 40-day postoperative period. Thus, the effect of right hemisphere infarction in the rat was to produce widespread depletions of NE and DA concentrations in injured and uninjured cortex and subcortical nuclei both ipsilateral and contralateral to the lesion site. We do not yet know, however, how these changes in amine levels relate to changes in turnover or to postsynaptic effects of lesions.

By contrast, following left MCA ligation there were no significant postoperative changes in NE or DA concentrations at 5, 14, or 35 days postoperative in any of the brain regions that demonstrated changes after right side lesions [13]. This lateralized biochemical response to cortical injury did not appear to be the result of an asymmetry in lesion size or location. That is, although the lesion was somewhat variable in size following MCA ligation, independent ratings of lesion size found that mean size for right hemisphere infarcts was not significantly different from mean size for left hemisphere infarcts [9,13]. In addition, lesion location did not appear to be significantly different between right and left hemisphere lesion group in terms of distance of the lesion from the frontal pole. This issue of lesion location is important in the development of hyperactivity, with the most anterior lesions producing the greatest amount of hyperactivity [7].

Because of the technical difficulty inherent in MCA ligation and the variability in the size of the lesions thus produced, we have employed cortical suction lesions as an alternative to ischemic lesions [5–8]. These lesions are made at precise stereotaxic locations and lesion size is determined by the diameter of the suction probe. Effects of suction lesions on hyperactivity and NE depletions including lateralized responses are quite comparable to those of ischemic lesions, with the exception that the effects of suction lesions on spontaneous hyperactivity are still present at 30 days postoperative [8].

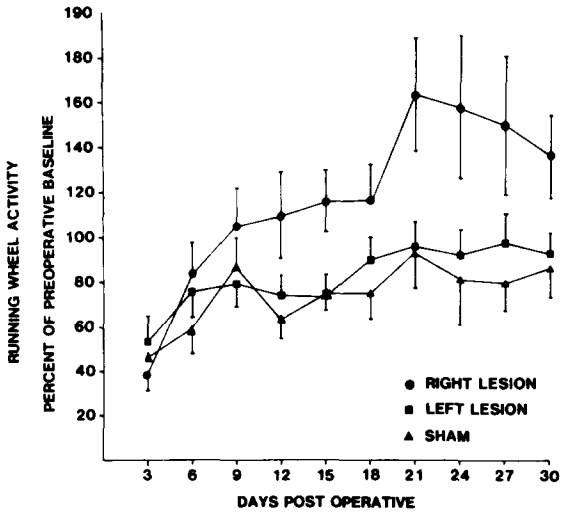

FIG. 3. Running wheel activity following cortical undercut lesions as a percent of preoperative baseline. Right lesion animals were more active than both left lesion and controls from 21 to 30 days postoperative ($p<0.05$). Fig. 3: (Reprinted by permission of Academic Press, Inc.).

ROLE OF CATECHOLAMINERGIC NEURONS IN BEHAVIORAL ASYMMETRY

Although only right MCA ligation [9,13] or focal suction lesions [6–8] of the right frontolateral cortex produced hyperactivity and depletions of NE and DA, it was uncertain whether the biochemical changes were a consequence of the spontaneous hyperactivity, a cause of hyperactivity, or a parallel phenomenon that did not relate directly to the activity changes. In an effort to investigate the relationship between noradrenergic neurons and the lateralized phenomenon of spontaneous hyperactivity, several experiments were conducted in which we (1) directly injured the noradrenergic pathway in either the cortex or dorsal bundle, (2) removed the catecholaminergic innervation of the cortex prior to cortical lesions, or (3) augmented noradrenergic transmission either by intraventricular administration of NE or by blockade of NE reuptake.

Direct injury to the cortical noradrenergic terminals was produced by microinjections of either 6-OHDA [17] or DSP-4 [2] at a specified stereotaxic location in the frontal lateral cortex 1 mm below the brain's surface. Doses between 1 and 4 μg of 6-OHDA or a 10-μg dose of DSP-4 produced hyperactivity when injected into the right hemisphere, but no change in activity when injected into the left hemisphere. Higher doses (6 μg of 6-OHDA or 20 μg of DSP-4), however, did produce hyperactivity when injected into the left hemisphere. Thus, there was a differential sensitivity of the two hemispheres to neurotoxic destruction of cortical noradrenergic terminals as measured by effects on spontaneous activity.

Measurement of NE concentrations following intracortical 6-OHDA or DSP-4 injections demonstrated that either right or left hemisphere injections produced the same degree of depletion of norepinephrine, in both the cortex and LC. Thus, NE depletion in the right hemisphere was sufficient to produce spontaneous hyperactivity while in the left hemisphere it was only the largest dose of neurotoxin and the greatest amount of noradrenergic depletion that produced hyperactivity. The right and left hemispheres were thus differentially sensitive to the behavioral effects of noradrenergic depletion.

These results with cortical injections of neurotoxin were in contrast to our findings when the ascending pathways in the dorsal noradrenergic bundle were injected with 6-OHDA [19]. Using 4-μg doses of 6-OHDA, either left or right bundle lesions produced spontaneous hyperactivity. This treatment produced a 70% to 80% reduction in ipsilateral cortical NE. The same behavioral result was also obtained with small electrolytic lesions of the dorsal bundle, although the cortical depletion of NE was only about 30% to 40% below control. Thus, when the dorsal bundle was destroyed close to its cells of origin, either by electrolytic or 6-OHDA lesions, hyperactivity resulted from either right or left lesions. This result may be analogous to those obtained when high doses of 6-OHDA or DSP-4 were injected into the cortex [2,19]. Alternatively, something within the injured cortex may be responsible for the lateralized response to noradrenergic injury, such as an inhibitory mechanism initiated by left hemisphere injury, or the mechanism of dorsal bundle lesion-elicited hyperactivity may be independent of the mechanisms of cortical lesion-elicited hyperactivity.

In another experiment aimed at investigating the relationship between NE and hyperactivity, whole-brain catecholamine depletions were accomplished by intraventricular injections of 250 μg of 6-OHDA [11]. Three weeks later, ischemic lesions of the right hemisphere were produced by ligation of the right MCA. This resulted in a 65% reduction of cortical NE and prevented the development of post-ischemic lesion hyperactivity (DA changes were less pronounced). That is, although right MCA ligation by itself is sufficient to produce hyperactivity, pre-ligation destruction of the catecholaminergic neurons prevented the development of post-ischemic lesion hyperactivity without affecting activity in non-ligated controls. Thus, at least partial existence of the noradrenergic pathways appears to be necessary for the development of hyperactivity.

Enhancement of noradrenergic transmission has been attempted by administration of desipramine [11], an NE reuptake blocker, or by direct administration of NE into the lateral ventricle. Desipramine (DMI), in a dose of 10 mg/kg, administered intraperitoneally once per day beginning on the day of right MCA ligation, prevented the development of hyperactivity [11]. This appeared to be a specific effect on post-lesion hyperactivity since DMI injections in non-ligated control animals did not cause a significant change in activity compared to saline treated controls.

Using osmotic mini pumps, we have done some preliminary experiments in which NE (0.5 μg/hr) was injected into the right lateral ventricle over a 14-day period. These initial studies have demonstrated a few phenomena. First, continuous intraventricular administration of fluid does not produce a significant degree of non-specific brain damage. Second, NE administered during the first two weeks following focal suction lesions of the right cortex appeared to prevent the development of the expected post-lesion hyperactivity. In contrast, however, administration of NE during the second two weeks post-lesion produced an increase in the degree of spontaneous hyperactivity (Moran, Saad, Kubos, and Robinson, in preparation). These findings suggest the possibility of the development of receptor supersensitivity following suction lesions of the right hemisphere. It remains unclear, however, whether this presumed receptor supersensitivity may play a role in the post-lesion hyperactivity seen

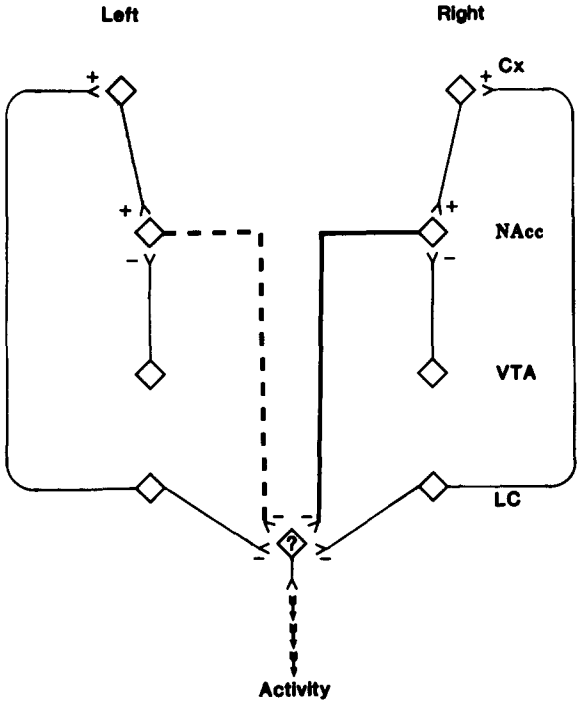

FIG. 4. A schematic model for the hypothesized mechanism of the lateralized hyperactivity response to brain damage. The three serial links in the system that we have investigated have cell bodies in the LC, cortex, and nucleus accumbens, in that order. The first two connections are shown as facilitatory (+) to the next link because damage to either (by cortical ischemia, suction, neurotoxin injection, or undercutting) have similar effects on activity. Each procedure may produce hyperactivity by removing an inhibitory influence, which would normally affect spontaneous activity (−). The fact that right-sided damage is more effective at producing hyperactivity than left-sided damage suggests that an asymmetry exists within the accumbens or its projection, or farther "downstream." The direct inhibitory link from the LC to the activity area is tentatively proposed because dorsal bundle lesions do not have asymmetric effects on activity. The VTA influence is seen as inhibitory in the accumbens because its damage (by accumbal 6-OHDA injections) produces hypoactivity. Abbreviations: Cx, cortex; LC, locus coeruleus; NAcc, nucleus accumbens; VTA, ventral tegmental area.

in animals not given intraventricular NE.

In summary, these experments have strongly suggested that noradrenergic mechanisms are involved in spontaneous hyperactivity seen after suction or ischemic lesions of the right hemisphere. Although noradrenergic injury within the right hemisphere appears to be sufficient to produce spontaneous hyperactivity, this injury does not seem to be necessary to produce the lateralized hyperactivity phenomenon as will be seen in the next section.

ROLE OF NON-CATECHOLAMINERGIC NEURONS IN BEHAVIORAL ASYMMETRY

Since suction or ischemic lesions produce a general destruction of neuronal elements within the area of injury, we tried to determine whether destruction of neurons or their processes post-synaptic to the noradrenergic pathways might be involved in this lateralized response to cortical injury. We have examined non-catecholaminergic neuronal injury produced either by (1) destruction of cell bodies within the right or left cerebral cortex using local injections of kainic acid, (2) severing the afferent and efferent connections of the cortex within the internal capsule underlying the cortex, or (3) electrolytic destruction of the nucleus accumbens.

Injection of 5 nmol of kainic acid into the dorsal lateral cerebral cortex, 1 mm below the brain's surface, produced a significantly greater degree of spontaneous hyperactivity when injected into the right hemisphere as compared to identical injections of the left hemisphere [3]. Although possible diffusion of neurotoxin may have complicated the focal specificity of neuronal destruction, there was a differential sensitivity of the two hemispheres to this neurotoxin without a demonstrable effect on catecholamine concentrations.

Disc shaped lesions were produced within the left or right internal capsule [4] underlying the cortical area that produces post-lesion hyperactivity. The disc shaped lesions were approximately 2 mm in diameter overlying the head of the caudate. As with the kainate lesions, these cortical undercut lesions did not alter catecholamine concentrations, but produced spontaneous hyperactivity when made in the right, but not left hemisphere (Fig. 3). We do not know whether this effect was the result of interruption of efferent or afferent cortical connections. Both kainate lesions and cortical undercut lesions, however, destroyed neuronal processes post-synaptic to the noradrenergic terminals and did not affect norepinephrine levels. These findings are thus consistent with the hypothesis that the anatomical or neurochemical basis for the asymmetric effects of lesions on hyperactivity resides either in the cortico-subcortical projections, or at a point further "downstream" in the neural pathway leading to hyperactivity.

One such sub-cortical projection area from the cortex is the nucleus accumbens, and recent experiments have also demonstrated a lateralized behavioral response of the accumbens to injury. The administration of an electrical current of 10 mA over 2 seconds created a small lesion within the nucleus accumbens. This partial destruction of the nucleus accumbens produced spontaneous hyperactivity following right hemisphere lesion but not left hemisphere lesions (Kubos, Moran, and Robinson, in preparation), and was accompanied by a 35% reduction in DA concentrations within the accumbens, regardless of whether left or right hemisphere lesions were made. These depletions, however, did not appear to be responsible for the spontaneous hyperactivity since 6-OHDA lesions in the nucleus accumbens, while producing 70% to 80% depletions of DA, actually led to *hypo*activity (Kubos, Moran, and Robinson, in preparation). It also appears unlikely that DA depletions are responsible for cortical lesion-induced hyperactivity because some right cortical suction lesion locations that produce hyperactivity produce increases in DA levels [5], and some lesions that decrease DA do not affect activity [7].

HYPOTHESIZED MECHANISM OF LATERALIZED POST-LESION HYPERACTIVITY

We do not know whether the spontaneous hyperactivity produced by right cortical lesions, right cortical undercut lesions, or right nucleus accumbens lesions is mediated by the same mechanism, nor do we know whether the type of hyperactivity following these different lesions is similar. For instance, computerized photocell chamber monitoring of activity indicated that cortical lesions produced a nocturnal increase in velocity and length of individual movements while not affecting either vertical activity, circling behavior, stereotypy, or total number of movements [6]. We are pres-

ently investigating whether hyperactivity produced by other techniques affects these same components of activity.

The studies outlined in this paper have suggested a tentative and partial neural mechanism involved in the asymmetrical response to cortical and subcortical injury (Fig. 4). We propose that noradrenergic pathways, although themselves not anatomically asymmetrical, are, through some cortical inhibitory mechanism, differentially behaviorally sensitive to injury. These noradrenergic pathways constitute the first link in an asymmetrical neural pathway which leads to hyperactivity when certain elements of the system are injured. Neurons post-synaptic to the noradrenergic terminals within the cortex constitute the second link and project subcortically to the nucleus accumbens from which a third neuron projects to another brain region such as a mesencephalic locomotor region or other areas important in the regulation of spontaneous activity. Presumably, the lateralized response to brain injury implies that a neuroanatomical and/or neurochemical asymmetry must exist at some point within the pathway involved in this behavioral production. We do not know whether the neural asymmetry exists in the second neuron (from the cortex), presumably projecting to the nucleus accumbens, or whether it is in the third neuron presumably projecting from the accumbens to another subcortical site or whether it is further "downstream." The effectiveness of the nucleus accumbens lesion in producing a lateralized response to injury, however, suggests that the third neuron or another downstream neuron is the structurally asymmetric component important for this behavioral response.

CLINICAL IMPLICATIONS

Although the exact mechanisms responsible for the production of post-lesion hyperactivity remain to be elucidated, the identification of a lateralized behavioral and biochemical response to brain injury in rats may have important clinical implications. During the past several years, we have also been investigating mood disorders in patients which occur after stroke [14,18]. We have found that left frontal brain injury is associated with symptoms of major depression while injury to the right frontal brain area is associated with inappropriate cheerfulness and apathy [14]. The finding that experimental stroke in rats produces a differential effect on catecholamine concentrations depending upon which hemisphere is injured suggests the possibility that the lateralized emotional response to injury found in stroke patients may be related to a differential biochemical response of the human brain to injury. Depression or inappropriate cheerfulness seen after unilateral injury may be an emotional manifestation of differential response of the human brain to injury depending upon whether the right or left hemisphere is injured. Understanding the biochemical and neuroanatomical basis for post-stroke emotional disorders may have important implications for both treatment of these disorders and understanding the neural mechanisms of mood regulation.

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