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The locus coeruleus and cerebral metabolism: Recovery of function after cortical injury

DENNIS M. FEENEY, RICHARD L. SUTTON, MICHAEL G. BOYESON,
DAVID A. HOVDA, and WILLIAM G. DAIL
University of New Mexico, Albuquerque, New Mexico

Cerebral metabolic effects of locus coeruleus (LC) lesion or drugs affecting LC were investigated after unilateral injury of sensorimotor cortex in rats. Sensoriomotor cortex ablation produced a widespread depression of cerebral ^{14}C-2-deoxyglucose utilization which was reversed by amphetamine (AMP, 2 mg/kg) and worsened by haloperidol (HAL, 0.4 mg/kg). Lesion of LC alone did not affect cerebral oxidative metabolism, measured by a stain for the enzyme alpha-glycerophosphate dehydrogenase (α-GPDH). Lesion of LC prior to undercut laceration of motor cortex shortened time to onset of α-GPDH cortical paling. Treatment with AMP (2 mg/kg) blocked cortical paling of the enzyme stain at 4 days postinjury, an effect prevented by concomitant HAL (0.3 or 0.6 mg/kg). Apomorphine (1 mg/kg) did not block cortical paling. These data parallel effects of these drugs on recovery of function. The results suggest that a metabolic "remote functional depression" (RFD) is alleviated by catecholamine activation after cortical injury, whereas onset of RFD is accelerated by LC lesions and exacerbated by catecholamine blockade.

The locus coeruleus (LC) may have an important role in neuronal development and plasticity (Felton, Hallman, & Jonsson, 1982; Kasamatsu, Pettigrew, & Ary, 1981; Parnavelus & Blue, 1982). With its diffuse noradrenergic arborizations (Descarries, Watkins, & LaPierre, 1977; Foote, Bloom, & Aston-Jones, 1983), the LC may be involved in the development of the receptive fields of cat visual cortex neurons (Kasamatsu, Watabe, Scholler, & Heggelund, 1983), although this is disputed (Daw, Videen, Parkinson, & Rader, 1985). The LC has also been implicated in the environmental enrichment effect (O'Shea, Saari, Pappas, Ings, & Stange, 1968). However, the role of the LC in classical learning is not yet clear (Amaral & Sinnamon, 1977; Ögren, Archer, & Ross, 1980; Wendlandt & File, 1979). Like the neural developmental and enrichment effects, recovery of function after cortical injury, and maintenance of that recovery, may depend on the LC.

Drugs that influence LC activity have marked effects on recovery after cortical injury, but these drugs must be combined with relevant experience (EXP) during drug intoxication or no effect is obtained (cf. Braun, 1966; Braun, P. M. Meyer, & D. R. Meyer, 1966; Ritchie, P. M. Meyer, & D. R. Meyer, 1976). In rats (Feeney, Gonzalez, & Law, 1982) or cats (Hovda & Feeney, 1984) made hemiplegic by unilateral sensorimotor cortex ablations, an enduring acceleration of recovery is obtained with a single dose of amphetamine (AMP), but only if the animal is allowed to move about while intoxicated. This acceleration of recovery can be blocked by haloperidol (HAL), implicating catecholamines (CA) in the recovery process (Feeney et al., 1982). When given early after injury, HAL slows recovery of the hemiplegic rat, but again, only if locomotion is permitted during intoxication (Feeney et al., 1982). HAL affects both norepinephrine (NE) and dopamine (DA) (Bradshaw, Pun, Slater, Stoker, & Szabadi, 1981), but only intraventricular NE, and not DA, reproduces the AMP plus EXP effect (Boyeson & Feeney, 1984). Thus, NE projections of the LC may be important for recovery after cortical lesions.

The AMP/EXP regimen also restores some behaviors lost after cortical injury that would not be recovered otherwise. In cats with bilateral visual cortex ablations there is a complete and permanent loss of depth perception (Cornwell, Overman, Levitsky, & Shipley, 1976), despite significant recovery of visual acuity (Kaye, Mitchell, & Cynader, 1981). However, if such animals are given AMP after surgery there is an immediate restoration of depth perception, enduring for months after discontinuation of the drug treatment (Feeney & Hovda, 1985). However, if the animals are housed in the dark for 24 h after AMP administration, no effect is obtained. The effect is also blocked by HAL (Hovda & Feeney, 1985). In an extension of Feeney and Hovda's (1985) work, we found that the degree of recovery after bilateral visual cortex ablation may be influenced by asymmetry of lesions, and is

M. G. Boyeson is currently with the Department of Rehabilitation, University of Wisconsin Medical School, Madison, WI 53792. D. A. Hovda is currently with the Mental Retardation Center, Neuropsychiatric Institute, UCLA, Los Angeles, CA 90024. W. G. Dail is with the Department of Anatomy, University of New Mexico, and D. M. Feeney and R. L. Sutton are with the Department of Psychology, University of New Mexico. Address correspondence to Richard L. Sutton, Department of Psychology, University of New Mexico, Albuquerque, NM 87131.

less likely to occur in cats that fail to show signs of AMP intoxication (Hovda, Sutton, & Feeney, 1985).

The AMP/EXP treatment does not promote recovery of locomotion after unilateral cerebellar hemisphere ablations (Boyeson & Feeney, 1984), suggesting that the treatment effect may be limited to cerebral cortex or forebrain injury deficits. This may implicate the cerebellum (Cb) in the AMP/EXP promotion of recovery, since the treatment regimen alters NE turnover in the Cb of motor-cortex ablated rats (Boyeson & Feeney, 1984). The LC innervation of the Cb is implicated in motor learning (Watson & McElligott, 1984) and may also be involved in depth perception (Feeney & Hovda, 1985). The contralateral sensorimotor cortex is not necessary for the AMP/EXP effect on recovery from hemiplegia, since the treatment effect is obtained in cats with extensive bilateral frontal ablations (Sutton, Hovda, & Feeney, 1984), suggesting that recovery is mediated by a subcortical structure such as the Cb.

Undoubtedly, many factors could be involved in recovery after cortical injury (for a review, see Finger & Stein, 1982). However, the physiological basis for the AMP/EXP data is most compatible with the concept of a "remote functional depression" (RFD) after cortical injury. The proposal of RFD implies that measurable changes in some spared brain areas would be reflected in reduced neuronal activity and/or metabolism. Depressed metabolism has been reported in the Cb remote from areas of supratentorial tumors (Patronas et al., 1984) and strokes (Kurshner et al., 1984), but these were correlational observations.

One way to test the RFD hypothesis is to determine whether manipulations influencing behavioral recovery after brain injury also influence measures of cerebral metabolism. We have used two measures of cerebral metabolism, ^{14}C-2-deoxyglucose (2-DG) and the histochemical stain for the oxidative enzyme alpha-glycerophosphate dehydrogenase (α-GPDH). Our data indicate that the widespread depression of oxidative metabolism after cortical injury, revealed by the α-GPDH stain (Dail, Feeney, Murray, Linn, & Boyeson, 1981), is influenced by lesions of the LC as well as by drug manipulation known to alter LC single-unit activity and to affect behavioral recovery. Preliminary results were presented as abstracts (Dail, Boyeson, Feeney, & Murray, 1981; Feeney, Rodriguez, Hovda, & Boyeson, 1984).

EXPERIMENT 1

Method

Subjects. Ten male Sprague-Dawley rats (Harlan-Gibco) weighing from 275 to 315 g were used as subjects. Animals were housed in individual cages and maintained on a 12-h/12-h light/dark cycle, with food and water available ad lib.

Procedure. Surgical procedures for inducing suction ablation of the right sensorimotor cortex in 6 rats were performed as previously described (Feeney et al., 1982). Saline (SAL, n=2), HAL (0.4 mg/kg, n=2) or AMP (2 mg/kg, n=2) was administered intraperitoneally (ip) 24 h postinjury and animals were returned to their home cages.

Autoradiography procedures were adapted from those described by Sokoloff et al. (1977). Briefly, the 6 injured animals and 4 normal, uninjured rats were administered ^{14}C-2-DG (50 μCi, ip) 24 h after drug treatment. Animals were sacrificed by decapitation 45 min after 2-DG administation and the brains were quickly removed. Histological sections were cut at 20 μm on a cryostat at -20°C and were mounted onto glass microscope slides. Sections were then autoradiographed with Kodak SB-5 x-ray film for 5 days. The exposed film images were color-enhanced using a VAX 11/780 computer interfaced with a COMTAL image processing unit. Final color images were obtained using a Matrix Instrument Model 3000.

Results

The results from SAL-treated injured animals indicated a widespread depression of glucose utilization (Figure 1A) compared to that of normal controls (Figure 1B). The most affected areas included the contralateral and ipsilateral cortices, the ipsilateral red nucleus, and the LC. AMP dramatically reversed this metabolic depression throughout the cortical areas (Figure 1C) and brain stem of injured animals, whereas HAL worsened glucose utilization, particularly in the cerebellum and brain stem. Most importantly, like the behavioral effects on recovery of function in brain-damaged animals, the effect of AMP was enduring: it alleviated the depressed ^{14}C-2-DG uptake 24 h after administration, at a time when the drug would have been metabolized.

EXPERIMENT 2

Twenty-two male Sprague-Dawley rats were used in this experiment. Housing conditions, light/dark schedule, and access to food and water were the same as for subjects in Experiment 1.

In this experiment, we investigated the effects of undercut laceration of the hindpaw area of the right motor cortex of rats and the effects of unilateral (right) radiofrequency lesions of the LC and various drug manipulations on the α-GPDH staining pattern. Surgical procedures used for the cortical injury and the histochemical methods used are described in Dail, Feeney, Murray, Linn, & Boyeson (1981). The LC lesions were induced at coordinates AP -1.7, LAT 1.3, VERT $+2.4$ relative to the interaural plane, with the incisor bar elevated 1 mm. Current was slowly increased to 14 mA and was maintained for 2 min, using insulated electrodes bared 0.5 mm at the tip. All drugs were administered ip.

To directly determine if the LC is involved in the oxidative enzyme staining pattern of the lesioned cortex, we studied only rats with unilateral LC lesions. In 6 animals, the right LC was lesioned without inducing a cortical injury; this did not affect α-GPDH staining at 1 day (n=2) or 4 days (n=4) postlesion. Additional animals (n=5) received lesions of the right LC followed in 2 weeks by an undercut of the right motor cortex. These 5 rats were sacrificed 12 h after cortical injury. Histochemical analysis revealed that no paling of the α-GPDH stain occurred at 12 h postundercut if the LC was intact (n=3; these le-

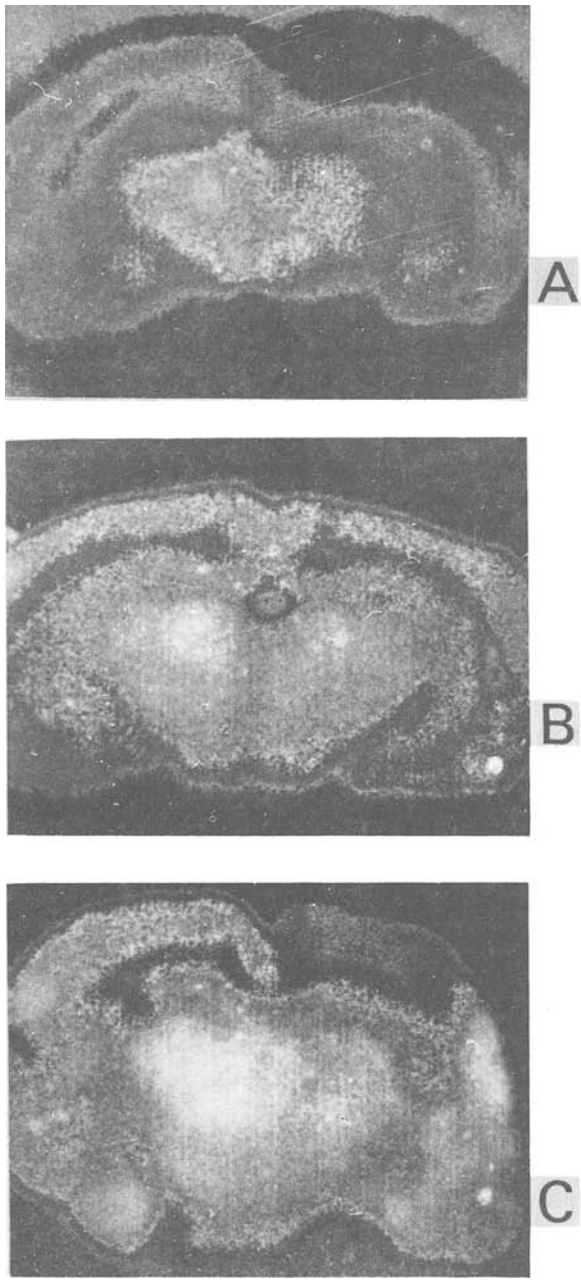

Figure 1. These are black-and-white photographs of computer-enhanced color images of autoradiographs. Darker regions indicate low glucose utilization, whereas lighter regions indicate higher metabolic activity. (A) ^{14}C-2-deoxyglucose (2-DG) utilization 48 h after unilateral sensorimotor cortex ablation in a saline-treated animal. Note darkened cortex ipsilateral (right) and contralateral (left) to injury, indicating widespread reduction of 2-DG uptake and metabolism. This section was taken approximately 0.5 mm posterior to ablation. (B) 2-DG utilization in an uninjured rat. This section was taken at approximately 1.5 mm posterior to bregma. (C) 2-DG utilization 48 h after unilateral sensorimotor cortex ablation in an amphetamine(2 mg/kg)-treated animal. Note the increased 2-DG uptake throughout cortical and subcortical areas as compared with the saline-treated animal, indicating that amphetamine is alleviating a widespread metabolic depression. This section was taken approximately 0.5 mm posterior to injury.

Figure 2.Alpha-glycerophosphate dehydrogenase activity in the cerebrum of a rat with a unilateral lesion of the locus coeruleus, followed in 2 weeks by an undercut laceration of motor cortex. The animal was sacrificed at 12 h postundercut. Note the virtual absence of stain in cortical layers 2 and 3 (between parentheses).

sions were in the inferior colliculus, fourth ventricle, or cerebellum). In the case of a lesion encompassing both the parvocellular and magnocellular portions of the LC, complete paling of the enzyme was evident (n=1; see Figure 2); a lesion of the parvocellular region alone resulted in partial paling of the enzyme stain at 12 h postundercut (n=1). These results indicate that the time to onset of metabolic disturbances following cortical injury is shortened by LC lesions. The earliest we have seen cortical paling following cortical injury alone is 36 h (Dail, Feeney, Murray, Linn, & Boyeson, 1981).

To examine the effects of CA agonists and antagonists on α-GPDH activity in the injured brain, we administered an undercut injury to the right motor cortex of 11 rats, followed in 24 h by drug administration. Brain tissue was removed and stained for α-GPDH activity at 4 days postinjury.

Treatment with AMP (2 mg/kg) prevented depression of enzyme staining in the cortex of the injured hemisphere in 2 out of 3 animals, whereas a lower dose of AMP (1 mg/kg, n=2) did not block paling of the enzyme stain.

Additional animals with laceration injury were given AMP (2 mg/kg) immediately followed by HAL (0.3 mg/kg, n=2; 0.6 mg/kg, n=2). In all cases, the administration of HAL blocked the AMP-induced prevention of cortical paling of the enzyme stain. In animals

given the DA agonist apomorphine (1 mg/kg, n=2), there was no prevention of cortical paling of the enzyme. These data suggest that the CA, most likely NE, affect the RFD that occurs following cortical insult.

DISCUSSION

These results indicate that reduced noradrenergic functioning may exacerbate or accelerate the development of metabolic depression after focal cortical injury. This suggests that the AMP/EXP treatment, which promotes recovery after cortical injury, may affect behavior by alleviating a widespread cerebral metabolic RFD. Our finding that unilateral LC lesions alone did not alter cerebral oxidative metabolism is similar to the finding of Savaki, Graham, Grome, and McCulloch (1984), who reported that unilateral LC lesions had little or no effect on 2-DG utilization in rats. However, LaManna, Harik, Light, and Rosenthal (1981) reported that although depletion of NE does not change "resting" metabolic activity in the cerebral cortex, it does alter the increased oxidative metabolism evoked by electrical stimulation of the cortex. Their finding is similar to that reported here: LC lesions alter the metabolic response to subsequent cortical laceration.

We have previously noted that our AMP/EXP data are compatible with the theory of diaschisis (Feeney et al., 1982; Hovda & Feeney, 1984). Diaschisis can be translated as "shocked throughout." According to this theory, formulated by von Monakow (1914/1969), some of the symptoms of brain damage result from a transient shock to brain regions remote from, but connected to, the area of primary damage. As the hypothesized shock dissipates with time, lost behaviors influenced by these areas recover. As first postulated, diaschisis was circularly defined and provided no mechanism by which the functional shock could be measured. Therefore, we prefer the more specific and descriptive term RFD as a modern revision of part of the concept of diaschisis. Although von Monakow's theory of diaschisis has been supported (Kempinsky, 1958; cf. P. M. Meyer & D. R. Meyer, 1982), refuted (West, Deadwyler, Cotman, & Lynch, 1976), and debated (Markowitsch & Pritzel, 1978; West, 1978), modern techniques are beginning to supply data that will allow us to firmly anchor the concept of diaschisis and escape the circularity of definition. There is now ample evidence that a RFD of CA occurs after cortical injury. Reduced brain CA levels and turnover after stroke or brain trauma have been reported in several species (Boyeson & Feeney, 1984, 1985; Cohen, Waltz, & Jacobson, 1975; Kogure, Scheinberg, Matsumoto, Busto, & Reinmuth, 1975; Robinson, 1979; Robinson & Bloom, 1977; Robinson & Coyle, 1979, 1980; Robinson, Shoemaker, & Schlumpf, 1980; Robinson, Shoemaker, Schlumpf, Valk, & Bloom, 1975; Zervas et al., 1974). These altered CA levels following cortical injury may result from damage to CA axons, producing a shift from transmitter production to protein synthesis for repair (Ross, Joh, & Reis, 1975). Evidence for RFD after injury to the brain is also provided by several histochemical studies (Cooper, Thurlow, & Rooney, 1984; Dail, Feeney, Murray, Linn, & Boyeson, 1981; Frey & Agranoff, 1983; Pappius & Wolfe, 1983; Reinstein, Isaacson, & Dunn, 1979; Schwartz, Sharp, Gunn, & Evarts, 1976) and by studies employing electrophysiological techniques (Glassman, 1970; Glassman & Malamut, 1976; Kempinsky, 1954, 1956, 1958; Pittman, Feeney, & Spiker, 1976).

We propose that after cortical injury pharmacological stimulation of the LC may "enable" (Moore & Bloom, 1979) some functionally depressed neural systems to respond to environmental stimulation (i.e., EXP), alleviating a CA and metabolic RFD and allowing behavioral symptoms to abate. Subsequent to the pioneering work of Maling and Acheson (1946), many studies have suggested the importance of CA activation in recovery after brain injury, with AMP reportedly enhancing recovery following injury to the sensorimotor and/or visual systems (Amassian, Ross, Wertenbaker, & Weiner, 1972; Beattie, Gray, Rosenfeld, P. M. Meyer, & D. R. Meyer, 1978; Boyeson & Feeney, 1984; Braun, 1966; Braun et al., 1966; Cole, Sullins, & Isaac, 1967; Feeney et al., 1982; Feeney & Hovda, 1983, 1985; Glick, 1974; Glick & Zimmerberg, 1978; Hovda & Feeney, 1984, 1985; Jonason, Lauber, Robbins, P. M. Meyer, & D. R. Meyer, 1970; Macht, 1950; P. M. Meyer, Horel, & D. R. Meyer, 1963; Ritchie et al., 1976; Sechzer, Ervin, & Smith, 1973; Sutton et al., 1984) or following lesions of the septal nuclei (Marotta, Logan, Potegal, Glusman, & Gardner, 1977).

The role of CA agonists in recovery must be modulatory, because it would be impossible for the CA somata in the brain stem to take over the functions of such diverse structures as the motor cortex, visual cortex, and septal nuclei, thereby alleviating various behavioral consequences of injury to these areas. Rather, the proposed regulation of cerebral tone or signal-to-noise ratio for NE (Amaral & Sinnamon, 1977; van Dongen, 1981) and sensorimotor integration for DA (Feeney & Weir, 1979) is more compatible with the data. The widespread arborizations of the LC axons throughout the cerebral cortex, cerebellum, and lateral tegmental system to brain stem, spinal cord, and hypothalamus would represent an anatomy expected of the hypothesized enabling system (for a review, see Foote et al., 1983). Studies using a variety of techniques have demonstrated that axons from the LC bifurcate and simultaneously innervate forebrain, cerebellar, and/or spinal areas (Crawley, Maas, & Roth, 1980; Nakamura & Iwama, 1975; Olson & Fuxe, 1971; Room, Postema, & Korf, 1981; Steindler, 1981). Finally, the LC may have an integrative function, since it receives afferents from diverse areas of the brain known to respond to internal and external stimulation (Foote et al., 1983).

Although CA agonists have proven beneficial after brain injury, recovery is vulnerable and may depend on adrenergic compensation. The maintenance of recovery after

unilateral motor cortex injury appears to depend on the integrity of the alpha adrenergic system; a single dose of the alpha-adrenergic antagonist phenoxybenzamine (PBZ) given to cats (Hovda, Feeney, Salo, & Boyeson, 1983) or rats (Boyeson & Feeney, 1984) recovered from sensorimotor cortex lesions dramatically reinstated sensory and motor deficits just as they appeared immediately after injury. The same dose of PBZ had only a mild soporific effect in normal cats and rats. Neither HAL nor propranolol (PROP) reinstated deficits in the recovered animals. Other investigators have found that PBZ increases the incidence of stroke, worsens neurological symptoms, and causes high mortality in an experimental stroke model (McGraw, Pashyan, & Wendell, 1976). Additionally, a clinical study with ischemic or infarcted patients reported that a combined treatment with PBZ and PROP worsened neurological deficits in some patients (J. S. Meyer et al., 1976).

The studies cited above may have important implications for the treatment of stroke and trauma patients (cf. D. R. Meyer & Beattie, 1977; P. M. Meyer & D. R. Meyer, 1982). In one uncontrolled study, AMP enhanced recovery when given to geriatric patients (some with stroke) refractory to rehabilitation, and, significantly, the recovery endured after discontinuation of AMP (Clark & Mankikar, 1979). Two case reports also describe AMP-induced behavioral improvement after trauma (Bugiani & Gatti, 1980; Lipper & Tuchman, 1976). Moreover, a retrospective study of the rate of recovery from aphasia after stroke indicated that thiazides or alpha blockers, especially HAL, slowed recovery compared to recovery of undrugged patients or those given PROP (Porch, Wyckes, & Feeney, 1985). Since PROP can successfully manage aggressive patients (Greendyke, Schuster, & Wooton, 1984), this drug would be preferable to HAL, which is often administered to agitated brain-injured patients (Cowley & Glen, 1979; Smith, Taylor, & Linkous, 1974). Because there is currently no effective treatment to promote recovery from brain injury, and some drugs currently in use may be harmful, this area clearly requires both clinical and basic science investigations.[1]

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NOTE

1. Additional evidence of a role for NE in brain injury was recently reported by Blomqvist, Lindvall, and Wieloch (1985). These authors report that bilateral lesion of the LC increases hippocampal neuronal necrosis induced by cerebral ischemia. (Note added in proof)

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