Alleviation of Brain Injury-Induced Cerebral Metabolic Depression by Amphetamine: A Cytochrome Oxidase Histochemistry Study

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ABSTRACT

Measurements of oxidative metabolic capacity following the ablation of rat sensorimotor cortex and the administration of amphetamine were examined to determine their effects on the metabolic dysfunction that follows brain injury. Twenty-four hours after surgery, rats sustaining either sham operations or unilateral cortical ablation were administered a single injection of D-amphetamine (2 mg/kg; i.p.) or saline and then sacrificed 24 h later. Brain tissue was processed for cytochrome oxidase histochemistry, and 12 bilateral cerebral areas were measured, using optical density as an index of the relative amounts of the enzyme. Compared with that of the control groups, cytochrome oxidase in the injured animals was significantly reduced throughout the cerebral cortex and in 5 of 11 subcortical structures. This injury-induced depression of oxidative capacity was most pronounced in regions of the hemisphere ipsilateral to the ablation. Animals given D-amphetamine had less depression of oxidative capacity, which was most pronounced bilaterally in the cerebral cortex, red nucleus, and superior colliculus; and in the nucleus accumbens, caudate-putamen, and globus pallidus ipsilateral to the ablation. The ability of D-amphetamine to alleviate depressed cerebral oxidative metabolism following cortical injury may be one mechanism by which drugs increasing noradrenaline release accelerate functional recovery in both animals and humans.

KEYWORDS

cerebral oxidative metabolism, diaschisis, stroke, remote functional depression; cytochrome oxidase

INTRODUCTION

Short term treatment(s) with D-amphetamine (AMPH), when administered late after a unilateral sensorimotor cortex ablation, embolic stroke, or traumatic brain injury (TBI) and combined with physical therapy (PT), results in an enduring acceleration of recovery from hemiplegia in rats and cats (Feeney et al., 1982; Hovda & Feeney, 1984; Sutton et al., 1987; Feeney & Westerberg, 1990; Sutton & Feeney, 1992; Feeney 1998a).

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The efficacy of this experimental treatment protocol may require adjustment of the (a) drug dosage, (b) number of treatments, or (c) delay between injury and initiation of therapy, depending on species, injury severity, and type of injury. Significantly, AMPH treatment may be contraindicated after damage to some brain regions producing motor symptoms, such as cerebellar deep nuclei (Boyeson & Feeney, 1991) or the substantia nigra (Mintz & Toner, 1989). In rats with unilateral sensorimotor cortex ablation, a single low dose of AMPH combined with PT, given one day after surgery, significantly enhances functional recovery (Feeney et al., 1982; Goldstein, 1988; Sutton & Feeney, 1992). Rats with embolic or photothrombotic stroke require multiple and/or higher doses of AMPH, beginning 1 day after infarct, to promote functional recovery from hemiplegia (Salo & Feeney, 1987; Hurwitz et al., 1991). Cats with unilateral or bilateral frontal lobe ablation require three high doses of AMPH, beginning 10 days after injury, for drug-induced acceleration of beam-walking recovery to occur (Hovda & Feeney, 1984; Sutton et al., 1989b). In a few clinical trials, this beneficial effect of treatment with AMPH + PT was extended to hemiplegic stroke patients, with preliminary work on aphasic stroke patients (Walker-Batson et al., 1992; 1995; for review, see Goldstein, 1993; Feeney, 1997; 1998a; 1998b). The recovery from hemiplegia of patients receiving short-term treatment with AMPH + PT, begun as long as 1 month after stroke, was significantly enhanced when compared with that of patients given placebo + PT. Significantly, this benficial effect of a 10-week treatment was enduring because it remained significant for months after discontinuing treatment for the 1-year period of study (Walker-Batson et al., 1995). This opportunity to delay treatment for stroke or TBI is very important because it allows the physician time to make a full evaluation and to stabilize the patients before initiating therapy. Significantly, the vast majority of stroke patients do not seek medical attention within the first 3 to 6 hours after an infarct, when alternative treatments for stroke are most effective (Ginsberg & Pulsinelli, 1994), and thus can suffer significant side effects (Bath, 1995). Clearly, further development and evaluation of potential therapies that can be initiated late after brain injury to promote recovery are needed.

The mechanism(s) by which AMPH promotes functional recovery after cortical injury are not well understood. It has been established that essential components of AMPH therapy include the release of cerebral noradrenaline (NA) and the provision of PT during the period of drug action. Using the rat model of unilateral sensorimotor cortex ablation, several studies have shown that any of the family of drugs increasing the release of central NA can promote functional recovery when combined with PT (Feeney & Westerberg, 1990; Goldstein & Davis, 1990; Feeney, 1991; 1998a; Sutton & Feeney, 1992; Boyeson & Harmon, 1993; Goldstein, 1993; Boyeson et al., 1994; Feeney et al., 1994). In addition, intraventricular infusion of NA, but neither dopamine (Boyeson & Feeney, 1990) nor serotonin (Boyeson et al., 1994; Feeney, personal observations), promotes recovery from hemiplegia after cortical injury. The requirement for PT during the period of drug action to optimize functional recovery after AMPH treatment suggests an interaction between two processes during this experimental treatment. As originally proposed (Feeney et al.; 1985; Feeney & Sutton, 1987) and subsequently expanded (Feeney, 1998a; 1998b), the two processes involve drug release of the neuromodulator NA which, by alleviating hypometabolic regions, "enables" PT to act upon intact but nonfunctional "performance" circuits that are normally involved in the behaviors that are lost after injury. These afferent inputs are thought to be both proprioceptive feedback and corollary discharges from the attempted movement. The mechanisms resulting from these processes are unknown, but several have been hypothesized, including (a) NA-induced unmasking or permitting the use of alternative pathways (Dietrich et al., 1990),

(b) enhancing attention by increasing the signal-to-noise ratio of unit activity evoked during PT (Segal & Bloom, 1976a, 1976b; Woodard et al., 1979; Robbins et al., 1985), or (c) enhancing long-term potentiation as a model of plasticity (Gold et al., 1984).

Our own research on the mechanisms of AMPH-induced functional recovery has focused on the ability of this treatment to alleviate an injury-induced metabolic depression in morphologically intact brain tissue, remote from the primary injury. The concept of remote functional depression, or diaschisis, following brain injury has a long history, but only recently have techniques been developed for measuring neuronal function. This evolving concept has been reviewed elsewhere (Feeney & Baron,1986; Feeney, 1991). Studies reporting that injury to the cerebral cortex produces widespread alterations in both glycolytic (Pappius, 1981; Feeney et al., 1985; Hosokawa et al., 1985; Gilman et al., 1987; Sutton et al., 1989a; Yoshino et al., 1991; Hovda et al., 1996; Queen et al., 1997) and oxidative (Feeney et al., 1985; Hovda et al., 1991; Hovda & Villablanca, 1998) metabolism substantially support the concept of an injury-induced remote functional depression. In a number of studies, functional recovery from injury-induced neurobehavioral deficits has been correlated with an alleviation of depressed cerebral metabolism (Colle et al., 1986; Gilman et al., 1987; Hovda et al., 1987; Hovda & Villablanca, 1990; Hovda, 1996).

The concept that producing a functional depression and reduction of neuronal excitability contributes to the symptoms of brain injury is supported by the work of Brailowsky et al. (1986). In his work, Dr. Brailowsky reported that the short-lasting hemiplegia induced by the insertion of saline-filled osmotic minipumps into the sensorimotor cortex of rats was potentiated when the minipumps were filled with GABA. In essence, this worsening of hemiplegia by GABA can be viewed as a drug-induced diaschisis or remote functional depression. Others have reported drug-induced remote functional depression (Khan et al., 1997). During a selective anterior temporal lobe (TL) amobarbital test, aimed at inactivation of the mesiobasal TL structures, the authors measured cerebral glucose utilization using 18F-fluoro-deoxyglucose positron emission tomography (18F-FDG PET) in temporal lobe epilepsy patients. A decreased glucose uptake resulting from amobarbital application was observed, in addition to the intended ipsilateral anterior TL area. All patients showed decreased glucose uptake in contralateral temporolateral regions, and one-half showed "cerebellar diaschisis". This observation indicates that the simple drug inactivation of local regions produces local and remote metabolic deafferentation. Removal of afferent input is sufficient to produce a diaschisis or hypometabolic response. This simple deafferentation must be included with other post-injury events that are hypothesized to produce remote functional depression, such as sublethal excitotoxicity and sensorimotor imbalance, producing a remote functional depression by altering calcium ion homeostasis (Feeney, 1998a). Whereas all these post-injury events may produce diaschisis, none is essential.

Alleviation of remote metabolic depression after brain injury by drugs increasing cerebral NA has been reported in both the rat (Feeney et al., 1985; Feeney & Sutton, 1987; 1988; Feeney, 1991; 1998b; Hovda, 1996) and the cat (Hovda et al., 1987). In rat studies addressing the metabolic depression that is associated with fluid percussion TBI, Hovda (1996) reported that the degree and extent of injury-induced depression of cerebral glucose metabolism is a predictor of functional performance on both sensorimotor and cognitive tasks. More important, a single administration of AMPH (3 hours after the injury) alleviates this trauma-induced metabolic depression, complimented by an enhancement in the rate of functional recovery. In addition, widespread depression of local cerebral glucose utilization (lCMRglc) in cortical regions following a cortical freezing lesion is prevented by pre-treatment with drugs that either inhibit serotonin synthesis or block

alpha$_1$-NA receptors (Pappius et al., 1988; Pappius, 1991). The widespread depression of lCMRglc after cortical infarct or TBI is reversed or attenuated by post-injury administration of AMPH, and this metabolic depression continues to be alleviated long after the drug is metabolized (Dietrich et al., 1990; Queen et al., 1997).

The ability of drug-induced NA release to alleviate hypometabolism after brain injury may be one underlying mechanism for the hypothesized permissive action of NA. What mechanisms are involved when PT is provided during NA increase to produce the enduring enhancement of recovery are not understood. Eliminating PT during the period of AMPH action blocks any beneficial effect of the drug on recovery, as has been reported in hemiplegic rats and cats (Feeney et al., 1982; Hovda & Feeney, 1984; Goldstein & Davis, 1990) and for alleviating some visual deficits in cats following bilateral visual cortex ablation (Feeney & Hovda, 1985). A possibly related drug/experience interaction has been described in a PET study of rCBF in normal human beings who were given a low dose of AMPH before performing different tasks (Mattay et al., 1996). The data from their study indicate that AMPH, rather than having a fixed, global effect on rCBF, induces task-specific activation in selective cortical regions that are involved in the performance of behavioral tasks. This AMPH/experience interaction suggests that the brain area activated by NA depends upon what task the animal or patient is doing during the period of drug action.

Previously, we documented that AMPH can induce an alleviation of a remote functional depression of lCMRglc, measured 48 hours after either unilateral sensorimotor cortex ablation or TBI in the rat (Feeney et al., 1985; Queen et al., 1997). Other authors have reported that short-term treatment with AMPH produces an enduring recovery of responsiveness to vibrissae stimulation in a rat model of focal infarct to the cortical vibrissae barrel fields (Dietrich et al., 1990). During the period of AMPH action, alternative neuronal circuits show activation during vibrissae stimulation that is absent during stimulation in normal rats or in injured rats given saline. Given that glycolysis acts independently from oxidative metabolism, a more complete understanding of the effect of AMPH on cerebral metabolic processes following brain injury requires that both metabolic pathways be studied. Little is known, however, regarding the effects of brain injury and AMPH treatment on oxidative metabolism. Therefore, the current study expands our investigations of brain injury and AMPH treatment to oxidative metabolism, examined using cytochrome oxidase (C.O.) histochemistry (Wong-Riley, 1979) to assess the effect of AMPH on cerebral oxidative capacity after brain injury. In the C.O. histochemistry technique, increases in staining intensity reflect increased activity in the mitochondrial cytochrome chain, which relates to energy production in the cell (Wong-Riley, 1989). Previously, we used this method to show that the accelerated recovery of tactile placing, produced by AMPH treatment in cats with bilateral visual cortex ablation, was associated with an enduring increase in C.O. activity in the superior colliculus weeks after the injury (Hovda et al., 1987). The effect of AMPH on oxidative capacity after sensorimotor cortex ablation has not yet been studied, however. Alteration of oxidative capacity after cortical trauma was studied using C.O. histochemistry (Weisend et al., 1990; Hovda et al., 1991). Cortical contusion injury results in oxidative hypometabolism near the injured cortex, as well as in hypermetabolism in the entorhinal cortex and the adjacent temporal lobe (Weisend et al., 1990). It is not clear whether these mixed metabolic effects are related to the numerous pathological events after cortical contusion, but not after ablation, including (a) selective neuronal death of CA3 hippocampal pyramidal and hilar neurons (Feeney et al., 1989), (b) multiple recurring seizures within 3 hours after trauma (Krobert et al., 1992; Nilsson et al., 1994), and (c) slow development of a panecrosis after trauma. The current study was conducted (a) to determine the effects of a

unilateral sensorimotor cortex ablation on C.O. activity 2 days after injury and (b) to determine the effects of a single AMPH treatment, given one day after cortical injury, on this measure of oxidative capacity.

MATERIALS AND METHODS

Subjects

Sixteen male albino rats (Harlan, Sprague-Dawley, 255 to 290 g), maintained in standard wire cages on a 12:12 light:dark cycle and with ad libitum access to food and water, were used in the experiments. All procedures were approved by the University of New Mexico Institutional Review Board.

Surgery and group assignments

Animals were randomly assigned to sham injury (N=8) or to ablation (N=8) groups before surgery. After overnight fasting, the animals were anesthetized with ketamine hydrochloride (60 mg/kg, i.m.) followed by sodium pentobarbital (21 mg/kg, i.p.) and positioned in a stereotaxic frame. Animals assigned to injury groups had the right sensorimotor cortex ablated, as described previously (Feeney et al., 1982; Sutton & Feeney, 1992). Twenty-four hours after surgery, one-half of the animals in the sham (S) and injury (I) groups were injected with either 0.9% saline (SAL) or AMPH (2 mg/kg in saline, i.p.). The groups were thus designated as S-SAL, S-AMPH, I-SAL; and I-AMPH.

Cytochrome oxidase histochemistry

Twenty-four hours after SAL or AMPH injection, the animals were overdosed with sodium pentobarbital (100 mg/kg, i.p.) and perfused transcardially with room-temperature 0.9% saline (pH 7.4), followed by cold fixative solution (2.5% paraformaldehyde, 1.5% glutaraldehyde, 4% sucrose in 0.1 M phosphate buffer [PB], pH 7.4, 4°C). Brains were post-fixed for 1 h in cold fixative and then cryoprotected by immersion in succeeding concentrations (10%, 20%, 30%) of sucrose/PB solution at 4°C. Brains were frozen (–22°C) and then sectioned in the coronal plane (40-um), and every fifth section throughout the brain was mounted onto gelatin-coated slides. After drying at room temperature, tissue sections were processed for C.O. histochemistry, using the procedure of Wong-Riley (1979). Briefly, sections were reacted for 40 min (in the dark) in an incubation medium (25°C) consisting of 0.6% diaminobenzadine (Sigma), 0.2% cytochrome C, Type III (Sigma), and 4.5% sucrose in 0.1 M PB (pH 7.4). The reaction was stopped using three rinses in PB; the sections were air-dried and then coverslipped using permount. Tissue sections from all groups were simultaneously reacted in each batch of incubation medium to reduce between-group variability.

For quantifying C.O. activity, optical density readings were taken bilaterally from the 12 gray matter structures listed in Table 1, using a manual densitometer (Sargent-Welch Densichron Model PPD, with a 0.20 mm diameter aperture). The regions chosen for study of C.O. activity included the extrapyramidal structures previously reported to show altered lCMRglc metabolism after low-dose AMPH (Porrino et al., 1984) and/or regions showing alterations in lCMRglc or C.O. measures of metabolism after cortical injury and AMPH treatment (Feeney et al. 1985; Hovda et al., 1987; Queen et al., 1997). The readings were taken by an investigator, blinded to the drug treatment conditions of the animals, and were corrected for background (namely, glass, permount, and coverslip). For smaller structures (for example, dorsal tegmental and subthalamic nuclei), a minimum of two to five readings across two to three different sections were taken. For larger structures/regions (for example, cerebral cortex [frontal, parietal, occipital], and the dorsal caudate-putamen), as many as 30 to 38 separate readings from 10 to 15 different sections were

TABLE 1

Mean (±SD) optical density values (× 10) for cytochrome oxidase activity in brain structures of the left (L) and right (R) hemisphere for rats with sham injury (S) or right sensorimotor cortex ablation (I)[1]

Structure	Experimental Group			
	S-SAL	S-AMPH	I-SAL	I-AMPH
Cerebral	L: 262.6 (17.7)	220.3 (5.8)	188.6 (14.3)**	226.6 (16.4)
Cortex	R: 258.5 (19.4	237.0 (8.6)	181.4 (14.9)**,‡	221.9 (18.5)
Nucleus	L: 246.3 (14.6)	241.0 (20.6)	196.4 (9.7)	239.7 (22.1)
Accumbens	R: 248.5 (10.3)	242.0 (20.1	197.3 (9.0)*	241.4 (20.0)
Caudate	L: 230.7 (15.8)	225.1 (14.1)	190.4 (9.4)	220.8 (15.0)
Putamen	R: 230.3 (11.8)	228.7 (13.0)	192.9 (6.5)*	220.7 (14.9)
Globus	L: 189.4 (15.0)	166.9 (21.2)	147.9 (19.9)	176.5 (3.3)
Pallidus	R: 193.6 (14.2)	194.1 (11.4	152.9 (15.6)*, ‡	183.5 (5.5)
Subthalamic	L: 156.6 (14.8)	177.7 (11.0)	127.2 (11.6)	189.8 (29.9)
Nucleus	R: 173.9 (23.7)	186.9 (10.5)	132.6 (12.0)	196.0 (31.2)
Substantia	L: 227.9 (24.3)	222.2 (17.1)	189.2 (4.2)	193.8 (12.7)
Nigra	R: 228.5 (24.1)	220.9 (20.1)	190.2 (5.8)	198.8 (16.2)
Lateral	L: 263.5 (13.8)	234.3 (10.1)	225.0 (17.5)	231.4 (15.9)
Geniculate	R: 260.3 (11.5)	234.3 (4.8)	224.1 (17.9)	232.6 (17.4)
Red	L: 237.3 (19.5)	234.9 (18.3)	184.7 (4.1)*,‡	211.2 (10.5)
Nucleus	R: 240.6 (19.1)	228.8 (13.7)	186.3 (5.7)*,‡	210.9 (12.7)
Superior	L: 251.3 (16.8)	204.7 (15.0)	197.4 (18.3)*	213.7 (20.0)
Colliculus	R: 252.6 (13.1)	207.2 (19.3)	198.7 (16.8)*	222.1 (13.2)
Locus	L: 250.3 (27.3)	228.8 (16.0)	203.2 (23.6)	234.8 (25.9)
Coeruleus	R: 242.9 (19.5)	223.5 (13.8)	202.9 (16.5)	238.1 (24.7)
Dorsal Tegmental	L: 214.6 (25.5)	218.6 (14.5)	218.0 (20.5)	209.4 (11.6)
Nucleus	R: 210.1 (27.6)	211.9 (12.5)	219.8 (23.8)	207.2 (14.9)
Cerebellar	L: 257.1 (18.8)	243.2 (8.7)	224.3 (22.7)	255.9 (12.5)
Cortex	R: 249.6 (17.3)	243.6 (10.1)	218.5 (24.5)	249.1 (11.2)

[1]Animals received either saline (SAL) or AMPH one day after surgery and were sacrificed 24 hours later.

* $p < 0.05$ compared to S-SAL; ** $p < 0.01$ compared to S-SAL; ‡$p < 0.05$ compared to S-AMPH

obtained. The mean optical density readings for each structure was calculated for individual animals and used to calculate the group means for each structure (see Table 1). Thus, we measured the relative (not absolute) values of C.O., as we were interested in the relative differences among the four treatment groups rather than in the absolute amount of C.O. that was present after injury or drug treatment.

Statistical analysis

For statistical analysis, separate repeated measures analysis of variance were conducted for right and left hemisphere structures, with the individual structure serving as the repeated variable. As side was not treated as a within-subject factor, the degrees of freedom were inflated. Given the a priori hypothesis of effects being more prevalent in the hemisphere ipsilateral to the lesion, however, we felt that these independent comparisons were warranted. Following the overall analysis incorporating a least-squares approach, we then made comparisons to determine the significance of the main effect (group), with simple main effects comparisons being made among groups using appropriate contrasts (Hays, 1973; Myers, 1979).

RESULTS

Extent of injury and stain quality

In both SAL- and AMPH-treated groups, the cortical injuries were similar to those described previously (Sutton & Feeney, 1992). In all animals, cortical tissue, designated as the hindlimb and forelimb sensorimotor areas (Hall & Lindholm, 1974), was removed unilaterally (right). Evaluation of histological sections indicated that the lesions extended to the depth of the white matter, from 0.8 to 4.0 mm lateral to midline, and from 3.5 mm anterior to 2.0 mm posterior to bregma in all animals. The underlying hippocampus and caudate were not surgically damaged, and no significant differences were found among the groups with respect to the rostral-caudal, medial-lateral, or dorsal-ventral extent of cortical removal.

Perfusion fixation and the 40-minute reaction in the incubation medium resulted in good differential C.O. staining in various structures and between white- and gray-matter regions. Whereas robust differences in C.O. staining density can be detected by densitometry (see Table 1), the effect of ablation or drug on C.O. depression is difficult to see photographically, so no such illustration is included in this article.

Amphetamine effects in intact animals

The mean (±SD) optical density readings of C.O. activity in the left and right cortex and subcortical structures for the four groups are shown in Table 1. Comparing values for the S-SAL and S-AMPH groups shows that AMPH treatment given to intact animals slightly reduced C.O. activity in several regions, with the greatest reductions occurring within the cerebral cortex, the lateral geniculate, the superior colliculus, and the locus coeruleus. When compared with S-SAL animals, however, this AMPH effect was not significant

Effect of injury on cytochrome oxidase

In several structures, unilateral cortical ablation induced bilateral reductions in cerebral oxidative metabolism 48 hours post injury. Comparisons between S-SAL and I-SAL groups revealed that right cortical injury resulted in significant reductions in C.O. activity, which was evident within the spared ipsilateral cortical tissue ($p<0.01$), as well as in the right nucleus accumbens ($p<0.05$), caudate-putamen ($p<0.05$), globus pallidus ($p<0.05$), superior colliculus ($p<0.05$), and red nucleus ($p<0.05$; see Table 1). Within the contralateral hemisphere, C.O. activity was

significantly decreased in the I-SAL group (vs. S-SAL animals) in the cerebral cortex ($p<0.01$), superior colliculus ($p<0.05$), and red nucleus ($p<0.03$; Table 1). Comparisons were also made between the S-AMPH and I-SAL groups. Because of the slight reduction of oxidative metabolism in the AMPH-treated intact animals, only the left red nucleus and the right cerebral cortex, globus pallidus, and red nucleus of I-SAL rats showed significantly decreased C.O. activity ($p<0.05$ for all) relative to measures in S-AMPH animals (Table 1).

Amphetamine effects in injured animals

In animals with unilateral sensorimotor cortex ablation, AMPH treatment eliminated the ablation-induced loss of C.O. staining density, restoring the C.O. stain intensity to near-normal levels (see Table 1). This effect of AMPH was bilateral and global, as the C.O. activity in both the left and the right structures of I-AMPH rats did not differ significantly from the metabolic activity of corresponding structures of either S-SAL or S-AMPH animals. Interestingly, AMPH-induced attenuation of decreased C.O. staining intensity occurred after cortical injury, despite the trend of AMPH to decrease C.O. activity in intact rats.

DISCUSSION

The results of the current study indicate that restricted, unilateral ablation of the sensorimotor cortex in rat is followed by a widespread reduction in cerebral oxidative metabolism, assessed using C.O. histochemistry. The observed reduction of this mitochondrial enzyme in morphologically intact regions, remote from the site of injury, supports the concept of a remote functional depression or a diaschisis. This concept of distant effects of focal brain injury, mediated by axonal connections to the damaged area and resulting in a suppression of neuronal activity that contributes to symptoms of brain injury, has a long history (see Feeney, 1991 for review). In addition, the current results indicate that a single low dose of AMPH can alleviate the remote metabolic effects that occur following a focal cortical injury.

Effect of brain injury on cerebral metabolism

Consistent with the results of the current study, the results of numerous studies have demonstrated hypometabolism in regions remote from the primary injury (Ginsberg et al., 1977; Dail et al., 1981; Nemoto et al., 1981; Pappius, 1982; Pappius & Wolfe, 1983; Kushner et al., 1984; Dauth et al., 1985; Colle et al., 1986; Hovda et al., 1987; Kiyosawa et al., 1987; Lagreze et al., 1987; Beck et al., 1990; Fiorelli et al., 1991; Yoshino et al., 1991; Yoshino et al.,1992; Bergsneider et al., 1997). Widespread and remote metabolic depression after brain injury has typically been studied using 2-deoxy-D-glucose (2-DG) autoradiography to measure the cerebral metabolic rate for glucose. Whereas glucose is well accepted as a primary fuel for consumption by the brain, measurement of lCMRglc by itself provides only limited information regarding the overall metabolic demands and/or dysfunction in brain tissue. Studies incorporating measures of CBF and oxidative metabolism must also be conducted to assure a more complete understanding of metabolic changes that are produced by brain injury.

To our knowledge, studies specifically addressing CBF following restricted ablation of the cortex have not yet been conducted. CBF has primarily been studied in models of cerebral ischemia (Pulsinelli et al., 1982; Raichle, 1983; Perani et al., 1987; LaManna et al., 1988; Vannucci et al., 1988; Bolander et al., 1989; Dirnagl & Pulsinelli, 1990; Ginsberg, 1990) and of experimental TBI (Lewelt et al., 1980; Dewitt et al., 1986; McIntosh et al., 1987; Unterberg et al., 1988; Yuan et al., 1988; Yamakami & McIntosh,

1989; 1991; Shima & Marmarou, 1991; Muir et al., 1992). In cases where CBF was not directly measured, the investigators measured ATP (MacMillan, 1982; Pulsinelli & Duffy, 1983; Fass et al., 1987; Komatsumoto et al., 1987), protein synthesis (Lipton & Heimbach, 1977; Mies et al. 1991), and extracellular lactate (Pulsinelli & Duffy, 1983; Prasad et al.,1994; Kawamata et al., 1995) to determine whether flow is, in fact, adequate for energy demands. Following brain injury, these types of studies must be conducted using animals at rest and under stimulated conditions to incorporate and understand the metabolic demands during different physiological conditions. Clearly, such studies are currently impossible to do in the same animal using autoradiographic or tissue content analyses. In an effort to understand the enduring metabolic demand of the brain across both at-rest and activated conditions, many studies have incorporated C.O. histochemistry for measuring oxidative capacity (Hovda et al., 1987; Shaw et al., 1988; Jen et al., 1989; Chiaia et al., 1991; Hovda et al., 1991; Hovda & Villablanca, 1998).

As the most efficient method of generating ATP, oxidative metabolism tends to run at a relatively constant optimal level (Ackermann & Lear, 1989; Barinaga, 1997). With its rate of use dictated by the amount of cytochrome c within the mitochondria, oxidative metabolism can only be upregulated above the maximal level via the manufacture of additional protein. Given that the production of protein can take anywhere from hours to days, cells must rely on a more rapid and dynamic process for satisfying the acute increases in energy demands that are associated with ionic pertubation and/or neuronal firing. It would appear that this quickly responsive process is glycolysis, and this has been the basis for the concept of energy compartmentalization described in both cardiac and brain physiology. This is one of many reasons why, when measurements of glucose metabolism are conducted using 2-DG autoradiography, a physiological steady state must be maintained throughout the uptake period (Sokoloff et al., 1977).

As has been described by many investigators who are interested in the recovery of function following brain injury, the very acute period after injury is often quite dynamic in terms of the energy demands being placed on cells, but the most pronounced feature in the chronic state is a widespread or generalized metabolic depression, as studied using several different techniques. A critical question is whether these longer, more chronic measures of metabolism following injury are simply an index for the current state of the animal over a period of minutes (when 2-DG techniques are used), or whether the overall set point of cerebral metabolism has been fundamentally changed (Hovda et al., 1996; Hovda & Villablanca, 1998). In previous work on the pharmacology of recovery from brain injury, we took the position, along with others, that injury to the brain results in a pronounced chronic depression of function, reflected in measures of neurotransmitter levels (Krobert et al., 1994), as well as in metabolism. Evidence that drugs enhancing post-injury behavioral recovery also alleviate injury-induced hypometabolism provides support for such concepts as remote functional depression or diaschisis (Feeney et al., 1985; Feeney and Sutton, 1987; Feeney, 1991). In many cases, the metabolic depression that is induced by brain injury may diminish spontaneously, consistent with von Monakow's construct of diaschisis. Unfortunately, von Monakow gave this concept a circular definition, invoking the term diaschisis to explain the spontaneous remission of symptoms after injury. The measures of metabolic dysfunction provide an independent measure of the concept, eliminating his tautology. As demonstrated in the current paper, as well as in prior studies (Feeney et al., 1985; Hovda et al., 1987; Dietrich et al., 1990; Hovda, 1996; Queen et al., 1997), the alleviation of injury-induced metabolic depression can be markedly enhanced with AMPH administration. If, as hypothesized, metabolic depression contributes to behavioral symptoms after brain injury, then

pharmacological alleviation of the hypometabolism would "enable" dysfunctional neurons so that PT might activate the "performance" circuits that are involved in functional deficits, whose activity may also have been depressed by the injury.

That an indirect catecholaminergic agonist, such as AMPH, would have the ability to alleviate an injury-induced metabolic depression provides some insight into the responsible mechanisms. Over a number of years, we (Feeney et al., 1985; Sutton & Feeney, 1992; Feeney, 1997; 1998a; 1998b) have advocated an NA hypothesis incorporating the locus coeruleus, with others (Pappius et al., 1988; Pappius, 1991) suggesting that serotonin may be involved. Because AMPH has nonspecific effects, it is important to determine if other drugs releasing NA, such as yohimbine and idazoxan, also improve functional outcome and increase cerebral metabolism. Both yohimbine and idazoxan have been shown to be equivalent to AMPH in promoting functional recovery in the rat hemiplegia model (Goldstein, 1988; Sutton & Feeney, 1992). Additionally, these drugs increase cerebral metabolism, as measured by PET-scan studies of rCBF (Schmidt et al., 1995; Bremner et al., 1997). Significantly, similar to the interaction between AMPH and PT to promote recovery, no fixed action of AMPH on cerebral glucose utilization occurs, but rather the activated areas depend upon the task the subject is doing during the period of drug action (Mattay et al., 1996). Whatever the mechanism, clearly an injury-induced metabolic depression is related to the degree and to the extent of recovery of function, given that recovery from deficits is closely correlated with the recovery to normal rates of cerebral metabolism (Hovda, 1996).

Cytochrome oxidase as a marker for oxidative metabolic capacity

In a number of studies, the C.O. technique has been used to characterize the cerebral oxidative capacity in various brain regions. Some of these studies include investigations addressing cerebral maturation (Dehay & Kennedy, 1988; Hovda et al., 1992), cerebral decortication (Hovda & Villablanca, 1998), and the effects of sensory deprivation or stimulation (Kageyama & Wong-Riley, 1986; Wong-Riley & Norton, 1988; Wong-Riley, 1989). As in the current study, previous investigators have used optical densitometry to assess C.O. activity in regions of the cerebrum (Darriet et al., 1986; Hovda et al., 1987, 1991, 1992; Kageyama & Meyer, 1988; Hovda & Villablanca, 1990, 1998; Hyde & Durham, 1990). The intensity of C.O. staining, detected with optical densitometry, correlates highly ($r = .90$) with C.O. activity as measured using more traditional spectrophotometric techniques (Darriet et al., 1986). The analysis of C.O. staining intensity in the current study revealed several interesting alterations of cerebral oxidative metabolism, induced by AMPH administration and/or cortical ablation.

Effect of amphetamine in sham operates

Twenty-four hours after a single administration of AMPH, C.O. histochemistry-assessed cerebral oxidative metabolism was moderately decreased in normal, sham-operated rats. AMPH administration in rats has been reported to induce a widespread activation of lCMRglc within 15 minutes (Porrino et al., 1984). Such an acute increase in lCMRglc after AMPH may be related to the rapid increase in NA that has been reported after drug treatment in rats (Krobert et al., 1994). In the current study, the lack of C.O. increase in normal rats given AMPH most likely reflects the fact that oxidative metabolism in normal animals runs at peak efficiency levels and, therefore, cannot be up-regulated dynamically by a single injection of AMPH. The depression of C.O. observed in our study may be related to a "post-intoxication" effect of AMPH, reflecting the after effects of an initial global neural activation by this drug. In normal human subjects, AMPH was reported to slightly decrease lCMRglc in cortical regions by 3 hours post-drug (Wolkin et al., 1987).

Cerebral metabolic depression after brain injury and the effect of amphetamine

The current results indicate that 48 hours following unilateral sensorimotor cortex ablation, oxidative capacity, assessed by C.O. histochemistry, is decreased in several remote, ipsilateral motor structures, including the nucleus accumbens, caudate-putamen, globus pallidus, red nucleus, and superior colliculus. Prior studies using cortical freezing lesion, ablation, concussion, contusion, or stroke-injury models have also reported a depression of both cerebral oxidative (Dail et al., 1981; Feeney et al., 1985; Hovda et al., 1991; Hovda, 1996;) and glycolytic (Pappius, 1981; Feeney et al., 1985; Colle et al., 1986; Pappius et al., 1988; Sutton et al., 1989a; Dietrich et al., 1990; Yoshino et al., 1991; Queen et al., 1997) metabolism. As with the current findings, such injury-induced metabolic depressions are most evident within the ipsilateral cortical and/or subcortical regions during the first few days post injury. The physiological consequences of these injury-induced metabolic depressions may be functionally related to the neurobehavioral deficits in the contralateral limbs that are exhibited during this same time period post injury (Feeney et al., 1982; Feeney & Sutton, 1987, 1988; Gilman et al., 1987; Sutton et al., 1987; Sutton & Feeney, 1992). AMPH-induced alleviation of metabolic depression may contribute to the ability of the drug to alleviate symptoms (Feeney, 1998b), which has been extended to stroke patients (reviewed in Goldstein, 1993; Feeney, 1997). This effect has also been demonstrated by Hovda and his colleagues (1996), who showed that the AMPH-induced alleviation of metabolic depression following fluid percussion injury was directly related to an increased rate of behavioral recovery.

Prior research on cortical concussion injury (Hovda et al., 1991) revealed that a decrease in C.O. stain intensity appears to be restricted to regions ipsilateral to the injury, and a significant depression is not attained until 5 days post injury. Similarly, the decreased staining of the oxidative enzyme alpha glycerophosphate dehydrogenase that occurs following laceration, ablation, or contusion injury of the sensorimotor cortex, is restricted to regions of the cortex ispilateral to injury and is detectable at 36 hours post injury, and persisting for 9 days (Dail et al., 1981). This enzyme depletion is not lessened by AMPH, but can be prevented by giving the drug during the first 24 hours post injury (Feeney et al, 1985). In the current study, a significant decrease in C.O. activity in the contralateral cerebral cortex, superior colliculus, and red nucleus was evident 2 days following ablation of the right sensorimotor cortex. This finding may indicate that for the detection of depressed oxidative metabolism, the C.O. histochemistry method is more sensitive than staining for alpha glycerophosphate dehydrogenase activity (Feeney et al., 1985). The relatively early, bilateral depression of C.O. activity after suction ablation but not after concussion, produced by fluid percussion (Hovda et al., 1991), suggests that either the severity of injury or the trauma model used influences both the extent and the onset of significant metabolic depression. Unlike ablation, after contusion of the sensorimotor cortex, an increase in C.O. in the ipsilateral auditory and entorhinal cortex has been observed (Weisend et al., 1990). This increase in C.O. after contusion injury may be related to the recurring seizures that have been reported after this type of injury (Krobert et al., 1992; Nilsson et al., 1994).

The current results indicate that acute administration of AMPH (24 hours after injury) is capable of attenuating the bilateral remote functional depression of oxidative metabolism that is produced by unilateral cortical ablation. That AMPH treatment alleviated the depressed oxidative metabolism in all structures examined suggests that the drug exhibits a global effect on neural metabolism. This result is consistent with the hypothesis that AMPH may exert its effects on cerebral metabolism via actions either on the noradrenergic (Feeney et al., 1985; Feeney &

Sutton, 1987; 1988; Feeney 1998b) or on the serotonergic (Pappius, 1991) neurotransmitter systems, which provide diffuse cerebral innervation.

That bilateral reductions in C.O. were found in some structures (for example, cerebral cortex, red nucleus, and superior colliculi) after unilateral sensorimotor cortex ablation, and that AMPH treatment alleviated both ipsilateral and contralateral depression of oxidative capacity in injured rats may not, at first glance, appear to be compatible with the hypothesis that the drug-induced alleviation of hypometabolism is related to functional recovery. Nevertheless, some evidence exists for a role of the contralateral hemisphere in recovery (Dietrich et al., 1990). Most studies on the effect of AMPH on functional recovery after unilateral cortex ablation have employed the beam-walking scale developed by Feeney and colleagues (Feeney et al., 1982; Sutton & Feeney, 1992) for assessing contralateral hindlimb dysfunction. Albeit this rating scale for assessing the recovery from hemiplegia focuses on the ability of the injured animal to use the contralateral hindlimb, in some animals mild and transient deficits in the use of the ipsilateral hindlimb have been observed during beam-walk tests. When using the scale to rate both ipsilateral and contralateral limbs during beam-walk testing, a very mild and transient deficit can be seen in the ipsilateral hindlimb (Feeney, personal observation), which may contribute to the inability of some rats to traverse the beam during the first few days after injury. Mild and transient deficits in the hindlimb ipsilateral to cortical contusion injury (specifically, delayed response times to retract the limb after lateral and posterior displacement (Sutton et al., 1990), has also been observed. At present, we can only speculate that a bilateral decrease in oxidative capacity may contribute to these bilateral deficits, and that an AMPH-induced alleviation of this decreased oxidative metabolism may facilitate recovery in *both* the ipsilateral and the contralateral limbs. Firm conclusions will depend upon further studies employing both behavioral tasks that are sensitive to potential bilateral deficits and analyses of potential bilateral metabolic responses to injury and/or drug treatment.

In conclusion, this study has demonstrated that a single AMPH treatment attenuates the depression of the cerebral oxidative metabolism that occurs after unilateral sensorimotor cortex ablation. We previously reported that AMPH treatment attenuates the decrease in lCMRglc and the paling of alpha glycerophosphate dehydrogenase staining that occurs after sensorimotor cortex injury (Feeney et al., 1985; Queen et al., 1997). Likewise, Dietrich et al. (1990) reported that AMPH treatment increases lCMRglc in cortical regions following photochemically induced cortical infarcts. These effects of AMPH on cerebral metabolism after cortical injury support a general hypothesis (Feeney et al., 1985; Hovda et al., 1987; Feeney & Sutton, 1987, 1988; Feeney, 1991; Feeney, 1998a, 1998b) that AMPH may exert its beneficial effects on behavioral recovery by alleviating a metabolic dysfunction (namely, a remote functional depression) that is induced by cortical injury.

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Note added in proof: A color photo illustrating the effects of brain injury on cytochrome oxidase is available on the internet web site of D. Feeney: http://www.unm.edu/~feeney/index.html