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Metabolic and Neurophysiologic Sequelae of Brain Injury: A Cholinergic Hypothesis

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ABSTRACT

This paper reviews a number of lines of evidence developed in our laboratories indicating that at least some components of neurologic disturbances following concussion may be attributable to increased functional activity of cholinergic systems located within specific brain regions. These lines of evidence include (1) EEG studies indicating that disruption of the reticular activating system is not necessary for production of a reversible, flaccid, comatose state following low levels of concussion, (2) systematic transection studies indicating that regions bounded by collicular and midpontine transections may contribute to at least motor components of the behavioral suppression associated with concussion, (3) local rates of glucose utilization following fluid percussion injury increase in restricted areas bounded by collicular and midpontine transections; microinjection of carbachol (but not tetracaine) into these hypermetabolic regions produced behavioral suppression and electroencephalographic changes resembling those following concussion, (4) systemic administration or microinjections of atropine, but not mecamylamine, antagonized the behavioral effects of carbachol, and (5) data indicating that pharmacologic blockage of muscarinic cholinergic systems can attenuate neurologic deficits. Taken in conjunction with data from earlier clinical and laboratory studies, our research also indicates that anticholinergic therapy may potentially benefit head-injured patients.

Key Words: Concussion-Acetylcholine-Electrophysiology-Brain injury-Metabolism.

INTRODUCTION

CEREBRAL CONCUSSION IS A CLINICAL SYNDROME associated with head injury and characterized by immediate and transient impairment of brain functions, often in the absence of gross structural changes. Although the majority of investigators have related the consequences of cerebral concussion to some form of neuronal injury and reduced brain activity,[1,2] several lines of evidence suggest that at least some consequences may be mediated by neurochemical changes within identifiable endogenous neural systems.[3-6] More specifically, as detailed below, components of neurologic dis-

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turbance following concussion may be attributable to increased functional activity of cholinergic systems located within specific brain regions.

The neurologic description of changes produced by experimental concussion in animals poses unique problems. In general, we have assumed comatose states to be associated with various indices of behavioral suppression and muscle hypotonia, even in the presence of intense stimulation. To this end we have developed an extensive battery of tests to examine the neurologic consequences of concussion or experimentally induced changes in neural activity produced by microinjections or lesions[7-12] These data are important in establishing whether or not animal models of concussion produce neurologic changes similar to those seen in human head injury. Careful neurologic descriptions are also essential to any neurobiologic analyses of neural processes mediating behavioral changes. Thus, we have attempted to measure neurologic signs reflecting changes in postural and nonpostural somatomotor functions as well as visceromotor responses. Some scoring techniques are analogous to motor components of the Glasgow Coma Scale used to assess depth of human coma[13] and, when considered with other neurologic data and supplemented by electrophysiologic measures including EEG, were designed to be indices of altered states of consciousness. A rigorous attempt was made to grade simultaneously the magnitude of the suppression of postural and nonpostural muscle responses. Animals were subjected to a variety of external stimuli. Maximal behavioral effects of manipulations on postural and nonpostural muscle responses were defined as states in which these muscle groups of the animals were totally unresponsive to maximal external stimuli. These stimuli include a variety of manipulations, such as lifting and vigorous shaking, toe-pinching, pin-pricking, or suspending by limbs. Manipulations resulting in tissue damage were not used. In addition, assessments of ongoing behaviors or spontaneous levels of activity were carried out following a minimum of a 1-minute period during which animals were unstimulated. Since suppression of spinally mediated reflex activity is commonly associated with coma, some studies also examined the effects of concussion on electrophysiologic indices of spinal cord sensory and motor integration. Finally, we attempted to distinguish between descriptions of acute neurologic changes (e.g., less than 60 minutes), presumably associated with coma or altered states of consciousness, and chronic deficits (e.g., longer than 24 hours), possibly reflecting simpler motor disturbances.

PRODUCTION OF CONCUSSIVE BRAIN INJURY BY FLUID PERCUSSION

Concussive brain injury was produced by a fluid percussion device developed in our laboratory as a clinically relevant animal model of brain concussion in the cat.[14] The device, patterned after earlier models used in the rabbit, produces graded levels of brain injury associated with brief displacement and deformation of neural tissue produced by injecting small volumes of normal saline into the closed cranial cavity. Fluid percussion injury does not attempt to reproduce precisely the entire spectrum of events following closed head injury in humans, in which injury consists of a rapid and brief acceleration-deceleration of the head with or without impact to the intact skull. However, as others have pointed out,[15] efforts at such clinical simulations have usually resulted in models that do not reliably reproduce pathologies associated with head injury. In contrast, our experience has been that fluid percussion injury can produce graded levels of injury associated with predictable physiologic changes.

In fact, fluid percussion devices reproduce a number of the features of concussive brain injury reported in humans. The technique produces pressure transients ($\cong$20 msec) similar to those recorded in human cadaver skulls during sudden impact[16] as well as neurologic signs of behavioral suppression[7,8] resembling signs of unconsciousness in humans.[13] Diminution or abolition of cerebrovascular responsiveness to changes in $PaCO_2$, similar to that observed in brain-injured humans, has been reported in cats following fluid percussion injury.[17,18] Fluid percussion injury also results in a loss of pressure autoregulation[19,20] similar to that reported in brain-injured patients.[21] In addition, centrally oriented fluid percussion brain injury results in brainstem pathologies[14] reminiscent of those observed in humans.[22] The pathologic changes in multimodality evoked potentials re-

ported in brain-injured humans[23,24] are also observed in cats after fluid percussion injury.[25] These disturbances usually occur without evidence of seizure activity in cortical EEG recordings. Finally, fluid percussion injury results in immediate[14,17,18] and late developing[26] increases in intracranial pressure similar to those reported in humans.[27] More recently, we have also observed that both centrally and temporally oriented fluid percussion injury can be associated with edema, probably of vasogenic origin.[28]

Our fluid percussion device consists of a Plexiglas cylindrical reservoir, 60 cm long and 4.5 cm in diameter, bounded at one end by a Plexiglas, cork-covered piston mounted on O-rings (Fig. 1). The opposite end of the reservoir is fitted with a second hollow Plexiglas cylinder, which is in turn attached to a cylindrical transducer for measuring the pressure generated at the time of injury. The entire device is attached to a right angle hollow metal injury screw, which is rigidly fixed with dental acrylic to an opening in the animal's skull centrally located over the parietal cortex. The dura is left intact at this opening. The central injury screw is tightly connected to the transducer housing, and the entire system is filled with 0.9% sodium chloride solution at 37°C. The injury is induced by a metal pendulum that strikes the piston of the injury device from a predetermined height. The pressure pulse generated at the time of injury is recorded on a storage oscilloscope and photographed with a Polaroid camera. The oscilloscope is triggered photoelectrically by the descent of the pendulum. This device produces a pulse of increased intracranial pressure of fairly constant duration (21–23 msec). This pressure transient is associated with distortion and deformation of brain tissue. The height of the pulse is variable and can be regulated by varying the height from which the pendulum falls. Pulse amplitude is expressed in atmospheres (atm) of pressure.

ELECTROPHYSIOLOGIC STUDIES LOCALIZING CHANGES IN NEURAL FUNCTION FOLLOWING CONCUSSION

While lesions of the reticular activating system (RAS) have been reported to result in a comatose state,[29] some data indicate that RAS disruption may not be necessary to produce a flaccid comatose state following head injury.[30] For example, lesions of the RAS typically result in marked increases in slow wave (5–11 Hz) activity.[31–33] In experiments conducted in our laboratories, cats in which rostral projections of the RAS were interrupted by transections of the rostral midbrain tegmentum (cerveau isole) also showed a predominance of slow wave activity.[30] However, cats subjected to low levels of concussive injury never show abnormal slow waves or a predominance of low-frequency activity associated with the prolonged flexion reflex suppression and postural hypotonia (i.e., coma) produced by the injury. In fact, low levels of concussion resulted in a transient increase in high frequency (11–23 Hz) activity (Fig. 2) following fluid percussion. Thus, at least transient, reversible comatose states are probably not associated with functional changes in the brainstem similar to the effects produced by lesions of the RAS.

Additional data from our laboratories, using systematic transections at varying levels of the neuroaxis, indicate that changes in functional activity within restricted areas of the brainstem differentially contribute to components of sensory and motor suppression following experimental concussion.[34] These experiments used electrophysiologic measures of spinal cord sensory input, assessed by recording primary afferent depolarization (PAD), and motor output, assessed by recording monosynaptic and polysynaptic ventral root potentials (VRPs) (Fig. 3). These electrophysiologic indices of spinal cord sensorimotor integration were used because, as pointed out above, suppression of spinal-mediated reflexes (e.g., flexion to noxious stimuli) is a prominent feature of a flaccid comatose state.

In these studies, a laminectomy of the segments from L-4 to S-1 was performed, and the dorsal roots L-6 and L-7 and the ventral root L-7 were sectioned. The dorsal root L-7 was placed on a bipolar Ag/AgCl wire electrode for single pulse stimulation at supramaximal intensities (frequency 0.2–0.9 Hz, pulse duration 0.01 msec). For recording of dorsal root potentials evoked in adjacent dorsal roots by dorsal root stimulation, the dorsal root L-6 was mounted on a bipolar Ag/AgCl wire electrode, with one pole close to but not touching the cord and with the other on the cut peripheral

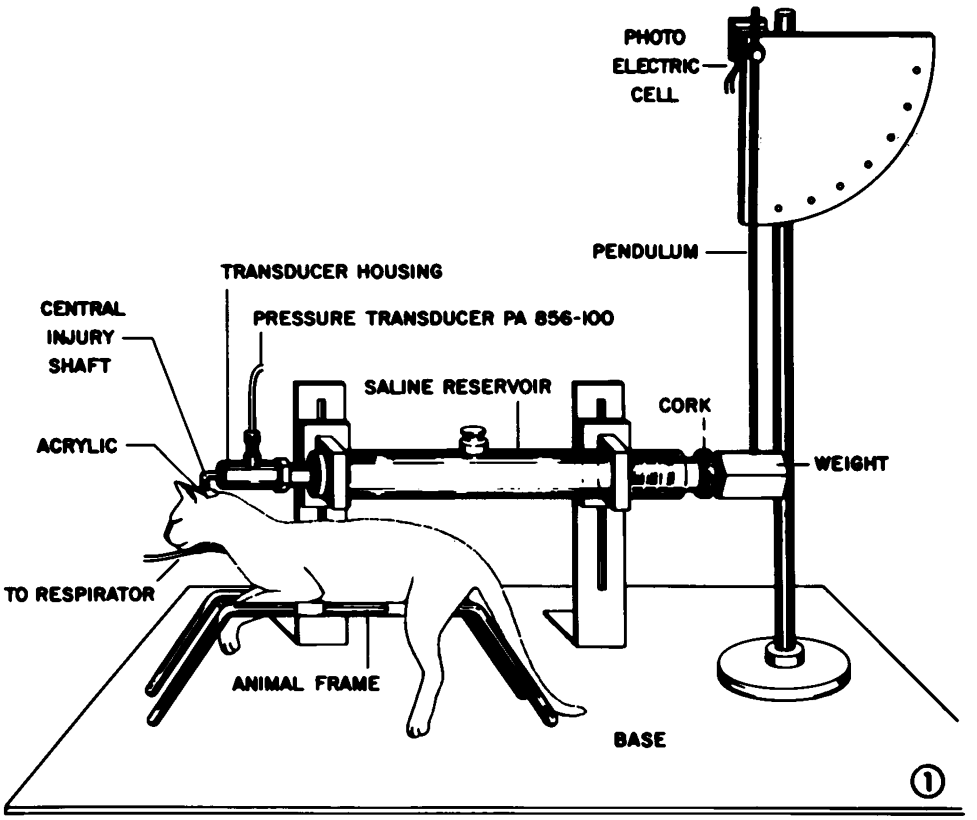

FIG. 1. Schematic of a device for producing mechanical injury to the brain of a cat. A weighted pendulum strikes a cork-tipped piston at the end of a saline-filled reservoir. The device is connected to the cat's skull by a hollow central injury shaft. This is placed above the dura of the brain exposed by a craniotomy and affixed to the skull with acrylic. A fixed volume of fluid is displaced into the cranial cavity, producing deformation of neural tissue. Pressure transients associated with fluid loading of the brain are recorded by a pressure transducer located extracranially. Increased volumes of fluid are associated with larger pressure transients (atm) and increased brain pathology.

end. In some cats in each treatment group, a glass-insulated tungsten microelectrode was inserted into the internuncial cell group of L-6 in the middle of the dorsal horn for stimulation at submaximal intensities (frequency 0.5–1.5 Hz, pulse duration 0.01 msec). Antidromic action potentials in response to stimulation of this site, which reflect the excitability of primary afferent terminals, were recorded from the dorsal root L-6. Another bipolar Ag/AgCl wire electrode was placed for tetanic stimulation of dorsal root L-6 (frequency 100 Hz, pulse duration, 0.01 msec, train pulse for 10 seconds). Stimulation intensities were adjusted to submaximal ranges for posttetanic potentiation of antidromic L-6 dorsal root potentials. To record ventral root potentials evoked by L-7 dorsal root stimulation, the ventral root of L-7 was placed on the bipolar Ag/AgCl wire electrodes. Signals were amplified by an AC amplifier or differential amplifier, displayed and photographed on a storage oscilloscope, averaged by a signal processor, and stored on magnetic tape for subsequent analysis. Averaged potentials were recorded by an ink-writing recorder. In all cases, the amplitude of PAD recorded as the dorsal root potential, the monosynaptic and polysynaptic reflex discharges of the ventral root potential, and each wave of the early near-field cortical potentials were measured as the averaged amplitude (peak to baseline) of each recorded potential taken from potentials averaged by

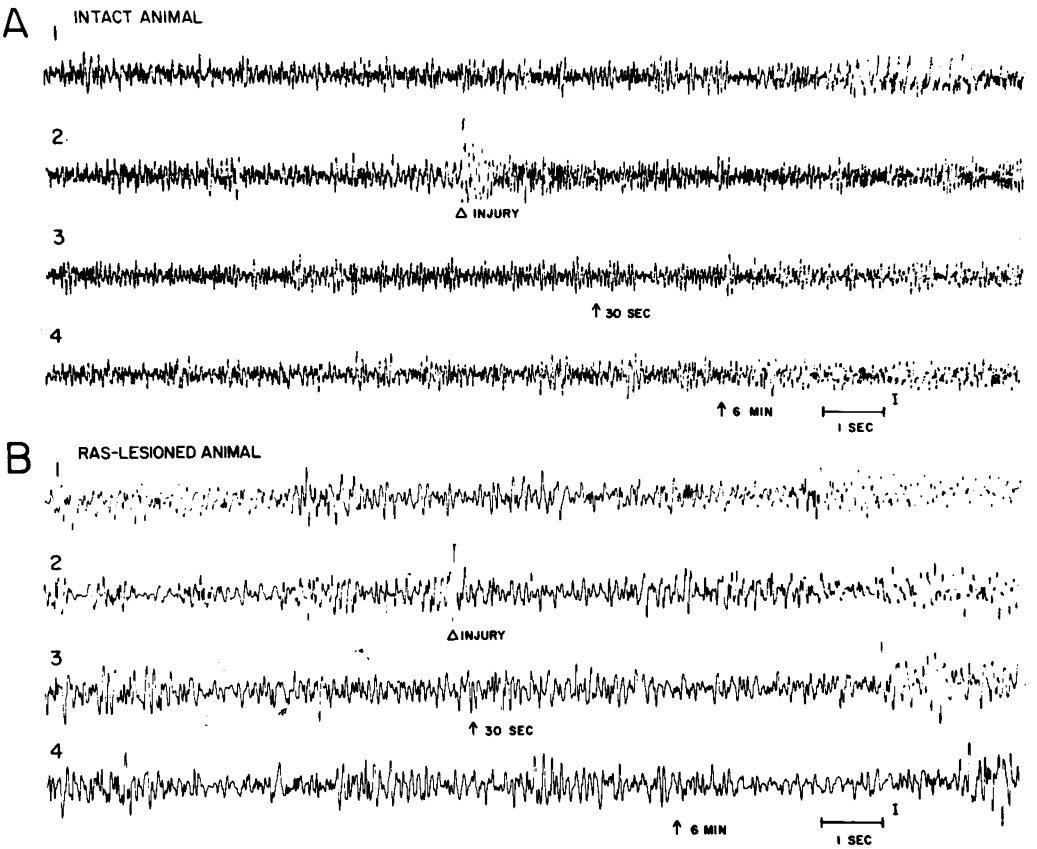

FIG. 2. Representative examples of electroencephalograms prior to and following injury. **A.** Intact animal. **B.** Animal which underwent radiofrequency lesions of the reticular activating system (RAS) at the level of the rostral midbrain tegmentum. In the animal shown in **A**, flexion reflex abolition continued for 620 seconds (approximately 10 minutes). Amplitude calibration, 100 μV for **A** and 50 μV for **B**. Note that injury to the intact brain (**A**) produced transient reduction in amplitude but no increase in slow wave activity similar to that seen when RAS is lesioned (**B**). Injury to an RAS-lesioned animal did not produce changes in EEG activity.

the signal processor (4–8 sweeps were averaged for dorsal and ventral root potentials and 36–90 sweeps for cortical potentials) and displayed by the ink-writing recorder. Data were collected prior to and at various times following brain injury.

Studies in untransected cats showed that low levels of fluid percussion injury suppressed PAD and VRPs over time periods during which flaccid coma had been observed in separate neurologic studies[4,6] (Fig. 3). As shown in Figure 4, concussive injury to cats with prior spinal cord transections failed to produce the suppression of PAD and VRPs typically seen in intact animals subjected to low levels of concussion. These data indicate that disruptions of spinal cord functions following concussion are not attributable to the direct effects of mechanical forces acting on the spinal cord itself. Rather, spinal reflex suppression is attributable to changes in CNS function at supraspinal sites. Injured animals with transections at the midpontine level (Fig. 4), in which neural pathways between the pontomedullary reticular formation and spinal cord were preserved, showed significantly less suppression of monosynaptic and polysynaptic VRPs than observed in intact cats. However, PAD in these injured, midpontine-transected cats was suppressed similar to intact cats following concussion. Thus, whereas areas between the midpontine and spinal transections are critical for

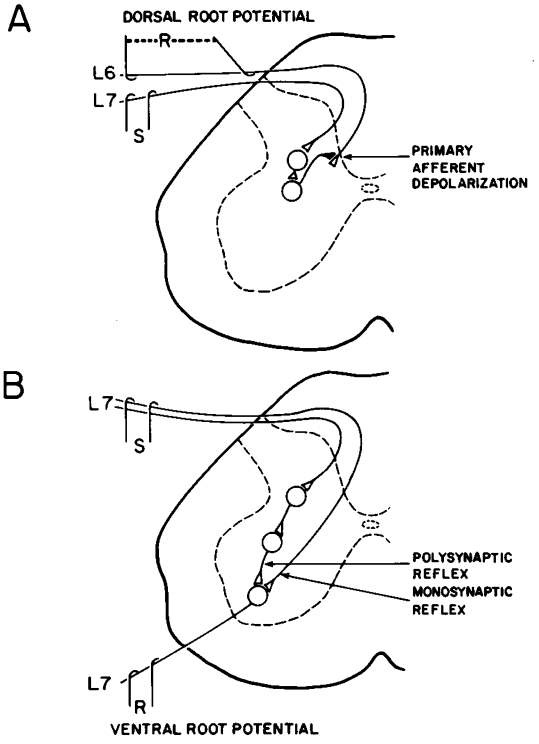

FIG. 3. **A.** Schematic diagram illustrating procedures for monitoring spinal cord functions. Dorsal root potentials evoked by stimulation of adjacent dorsal root. Stimulation (S) of dorsal root excites dorsal horn cells, which in turn produce depolarization of primary afferent terminals. This depolarization can be detected as dorsal root potentials recorded from adjacent dorsal root (R). **B.** Polysynaptic ventral root potentials evoked by dorsal root stimulation. Stimulation of dorsal roots (S) excite dorsal horn cells, which in turn evoke polysynaptic reflex discharges in ventral roots (R).

production of PAD suppression following concussion, areas rostral to the midpontine level appear critical for the motor suppression. In cats with more rostral transections at collicular levels, concussion produced VRP suppression similar to that seen in intact animals.[34] Therefore, the predominance of descending inhibitory influences on spinal cord somatomotor functions following injury appears to originate from areas bounded rostrally by sites of collicular transections and caudally by sites of midpontine transections.

It is important to note that, although transection experiments[34] determined brain regions differentially contributing to sensory and motor suppression following concussion, they provided no direct information as to whether this suppression was attributable to increases or decreases in regional brain activity. However, there is indirect evidence that motor suppression may be attributable to activation of regions bounded by collicular and midpontine transections. Flaccidity associated with VRP suppression does not occur as a result of lesions at any level of the brain unless the pontomedullary reticular formation is included.[34] Therefore, postconcussion descending inhibitory influences on VRPs originating within sites bounded by collicular and midpontine transections are probably not due to mechanical depression of descending facilitatory influences. This possibility is also consistent with the observation that concussion-produced suppression of VRPs in these experiments was not observed in animals in which injury produced hemorrhagic lesions in areas between the collicular and midpontine transections.[34]

NEUROCHEMICAL AND PHARMACOLOGIC STUDIES OF ACTIVATION OF CHOLINERGIC PONTINE SITES: SIMILARITIES TO CONCUSSION

Other studies conducted in our laboratories suggested that increased functional activity of cholinergic systems within areas bounded by the collicular and midpontine transections contributed to

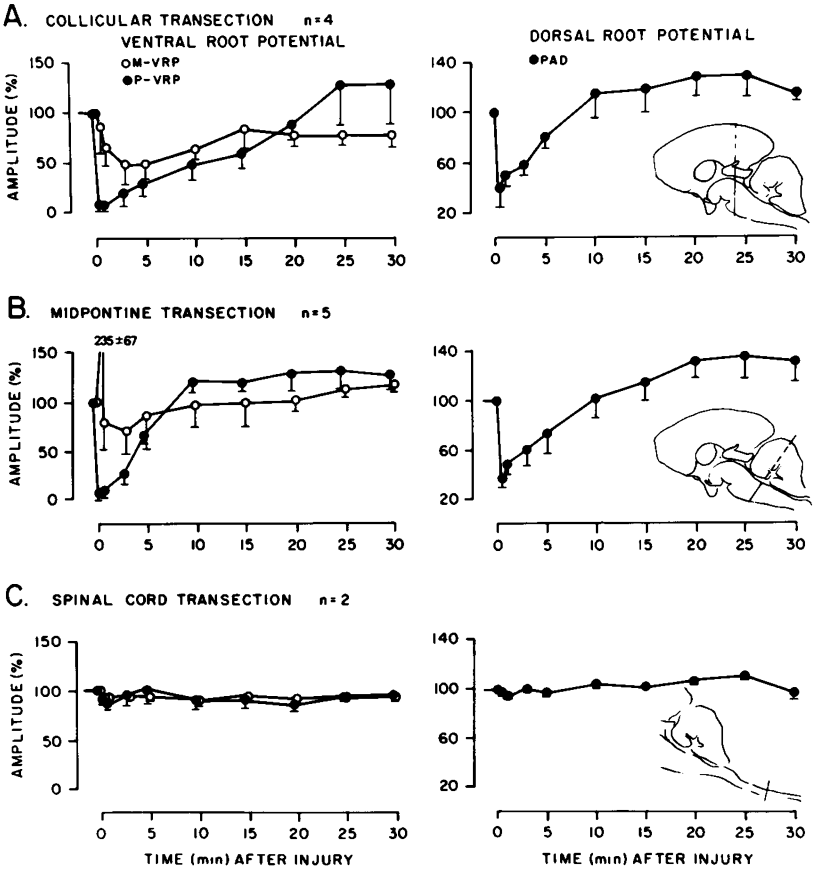

FIG. 4. Differential effects of injury on M-VRP (open circles) and P-VRP (closed circles) of ventral root potential (shown in left column) and PAD of dorsal root potential (shown in right column) in animals that received transection at various levels of CNS. **A.** Collicular-transected animals (n = 4). **B.** Midpontine-transected animals (n = 5). **C.** Chronic spinal cord (T-4) transected animals (n = 2). Note that no significant depression of M-VRP in **B** and of M-VRP, P-VRP, and PAD in **C** were seen following injury.

components of behavioral suppression following concussion.[3,35] For at least 2 hours following low levels of concussion, there were increased rates of glucose utilization in regions within the dorsomedial pontine tegmentum.[3,35] These increased rates of glucose utilization presumably reflected increased functional activity within these regions.[36] Additional studies showed that pharmacologic activation of these hypermetabolic regions by bilateral microinjections of a cholinergic agonist, carbachol, produced behavioral suppression resembling that following low levels of concussion.[3-5] Identical microinjections in surrounding zones showed significantly less behavioral suppression. Tetracaine failed to produce behavioral suppression when microinjected into regions corresponding to the hypermetabolic foci at doses shown to produce reversible inactivation of other neural systems.[37] Other studies showed that systematically administered or microinjected atropine, a muscarinic antagonist, reversed the behavioral effects of carbachol.[3,29] Equimolar doses of mecamylamine, a nicotinic antagonist, failed to reverse the behavioral effects of carbachol.[3,4]

Pharmacologic activation of these same hypermetabolic zones produces electrophysiologic changes similar to those seen following concussion. For example, carbachol microinjection into

these zones in awake cats produces desynchronization of parietal EEG[4] (Fig. 5). This suggests that, similar to data for concussion, the resultant stuporous and comatose states are not induced by generalized depression of forebrain activities, such as that produced by disruption of the RAS. The observation that carbachol microinjection into these zones suppresses M-VRP and P-VRP but not PAD is consistent with brainstem transection studies,[34] indicating that this region on the brain could mediate concussion-produced changes in VRPs but not PAD.

STUDIES OF EFFECTS OF CHOLINERGIC ANTAGONISTS ON NEUROLOGIC RESPONSES TO CONCUSSION

If activation of muscarinic cholinergic systems contribute to coma, pharmacologic blockage of cholinergic systems would be expected to attenuate coma. Data from our laboratories indicate that administration of a muscarinic cholinergic antagonist can attenuate acute and chronic neurologic disturbances following a moderate level of concussion.[38-41] Rats were surgically prepared under sodium pentobarbital anesthesia 24 hours prior to injury by chronically placing a hollow screw epidurally over a hole trephined along the sagittal suture, midway between lambda and bregma. Rats were assigned to one of four groups: scopolamine 0.1 mg/kg, 1.0 mg/kg, 10.0 mg/kg, or saline (equal volume). Drugs were injected IP 15 minutes prior to injury. Experimenters were uninformed of drug and dosage. Animals were anesthetized 5 minutes prior to injury with methoxyflurane. Animals were concussed at 2.86 atm (saline pressure pulse, 18 msec duration) with a fluid percussion injury device.

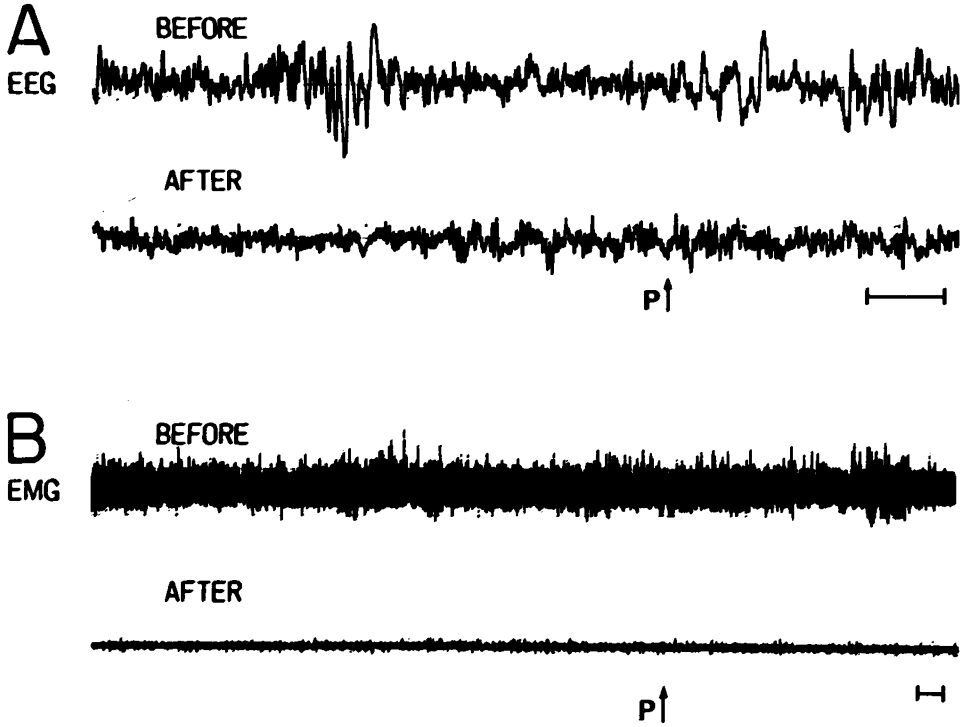

FIG. 5. Examples of parietal EEG (A) and nuchal EMG (B) before (upper traces) and 5 minutes after (lower traces) carbachol microinjections into the sites associated with behavioral suppression. Note that EEG after carbachol microinjection is desynchronous. Noxious pinch (P) produced no changes in EEG or EMG. Calibration, 1 second.

In acute studies, animals were assessed neurologically for 60 minutes immediately following injury. The durations of suppression of righting, pinna, corneal, and auditory startle reflexes were scored. Spontaneous locomotion, ability to support the head, tail and hind paw flexion, proximal tail pinch, and organized escape from tail pinch were also assessed. Scopolamine (1.0 mg/kg dose) produced significantly shorter ($p < .05$) durations of suppression of certain spinally mediated behavioral responses: paw flexion, escape, and proximal tail pinch. Scopolamine had no effect on other response measures. Mortality for the 1.0 mg/kg scopolamine group (23%) was significantly lower ($p < .05$) than for the saline group (72%). Scopolamine administered prior to injury appears to improve behavioral recovery after cerebral concussion and decrease mortality.

Studies of longer-term deficits examined changes in more prolonged motor deficits that persisted after animals had recovered from acute behavioral suppression similar to coma or unconsciousness. In these studies rats were trained on a beam-walking task in which rats traversed a narrow beam to escape white noise and bright light. Baseline intervals to traverse the walking beam were obtained. Additionally, the rats' ability to traverse the beam was assessed by a rating scale (e.g., number of foot slips) made by independent observers. The interval to maintain balance on a separate balance beam task was also assessed prior to injury. Following injury, rats were retested daily for 10 days. Rats were surgically prepared 24 hours prior to injury by chronically placing a hollow injury screw epidurally over a hole trephined along the sagittal suture, midway between lambda and bregma. Scopolamine (0.1, 1.0, or 10.0 mg/kg) or saline was injected IP 15 minutes prior to injury. Under methoxyflurane anesthesia, animals were concussed at 2.86 atm (an injury level associated with transient areflexia and more enduring motor dysfunctions) using a fluid percussion method modified for rats in our laboratories. Results indicated that scopolamine (1.0 mg/kg) facilitated the rate of recovery of locomotor functioning as indicated by a significantly more rapid return to baseline of walking-beam traversal times ($p < 0.5$), rating scale scores ($p < 0.5$), and balance beam times ($p < 0.05$) when compared to saline treatment. These findings indicate that the observed, seemingly beneficial effects of pretreatment with scopolamine associated with acute neurologic recovery may also be associated with an accelerated rate of recovery of more enduring motor deficits.

DISCUSSION

In summary, several lines of evidence support the hypothesis that the behavioral suppression associated with comatose states is, in part, attributable to the activation of cholinergic neural systems in the dorsolateral pontine tegmentum. These observations include (1) EEG studies indicating that disruption of the RAS is not necessary for production of a reversible, flaccid comatose state following low levels of concussion, (2) systematic transection studies indicated that regions bounded by collicular and midpontine transections may contribute to at least motor components (VRPs) of the behavioral suppression associated with concussion, (3) local rates of glucose utilization following fluid percussion injury increase in restricted areas bounded by collicular and midpontine transections; microinjection of carbachol (but not tetracaine) into these hypermetabolic regions produced behavioral suppression and electroencephalographic changes resembling those following concussion, (4) systemic administration or microinjections of atropine, but not mecamylamine, antagonized the behavioral effects of carbachol, and (5) pharmacologic blockade of muscarinic cholinergic systems can attenuate neurologic deficits.

These findings are consistent with earlier experimental and clinical observations. Researchers have noted that experimental brain injury results in high levels of acetylcholine in cerebrospinal fluid.[42,43] Studies have indicated that the levels of acetylcholine in human cerebrospinal fluid are correlated to the clinical state of the patient.[44] The cholinergic antagonist, atropine, has been reported to abolish or reduce coma in humans. Thus, it is possible that the appropriate doses of muscarinic cholinergic antagonists, even when administered after injury, could improve the outcome of head-injured patients. Current animal experiments and clinical trials at our institution will examine this possibility.

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