THE ROLE OF THE RETICULAR FORMATION IN THE COMA OF HEAD INJURY*

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Head injury has been a major problem of man for centuries. The first written account of the treatment of such appeared in the Edwin Smith Papyrus around the 17th century, B.C. Thirty-four centuries later in 1883, Jean Louis Petit was the first to recognize cerebral concussion as a separate entity and distinct from brain compression by hemorrhage. Cerebral concussion was first defined by Benjamin Bell in 1873 when he said, "Every affection of the head attended with stupefaction, when it appears as the immediate consequence of external violence, and when no mark of injury is discovered, is in general supposed to proceed from commotion or concussion of the brain, by which is meant such a derangement of this organ as obstructs its natural and useful functions, without producing such obvious effects on it as to render it capable of having its real nature ascertained by dissection." Little actual refinement in this definition of cerebral concussion has occurred in the subsequent 80 years.12 The physiologic basis for the clinical phenomenon of cerebral concussion is not completely understood even though closed head injury is an increasingly common occurrence.

The mechanics of brain trauma were thoroughly studied by Denny-Brown and Russell14,15 who established the laboratory criteria for concussion and made a distinction between acceleration and compression concussion. Holbourn,12 studying the physical forces involved in head injury, showed that the rotational rather than linear acceleration forces are the main cause of brain damage in head injury, these forces being responsible for "contre-coup" damage, hemorrhage, and "probably" concussion. Gurdjian et al.11 analyzed physical factors in concussion and demonstrated that acceleration, deceleration and compression all result in measurable elevation of the intracranial pressure. They concluded that sudden increase in intracranial pressure caused concussion and that the shorter the time duration of the increased intracranial pressure, the higher the pressure necessary to cause a concussive effect.

Investigations of the physiological basis of head injury have proceeded slowly along two lines—the measurement of biochemical changes and meas-

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urement of cerebral electrical activity alterations. Bornstein\textsuperscript{2} as well as Tower and McCachern\textsuperscript{16} have shown that acetylcholine appears in the cerebrospinal fluid following concussion and that it depresses integrated neuronal activity. Its effects can be counteracted by the use of anticholinergic drugs. Ward\textsuperscript{18} showed that atropine is clinically helpful in severe closed head injuries, and Ruge\textsuperscript{14} substantiated experimentally that atropine prevents the muscarinic effects of the acetylcholine that appears following trauma of the central nervous system.

The changes in electrical activity of the brain following head injury were studied by Walker, Kollros, and Case\textsuperscript{17} who felt that the unconsciousness of concussion was the result of sudden intense neuronal discharge of the brain resembling a seizure discharge. Foltz, Jenkner, and Ward\textsuperscript{6} were unable to support this conclusion since their electroencephalographic studies during experimental concussion showed flattening of the cortical electrogram and changes that were otherwise surprisingly minimal. Their subcortical recordings, likewise, showed the same depression and flattening. The one dramatic exception to this was the activity recorded from the medial reticular formation which always showed far greater and longer electrical depression than other structures studied.

In view of this finding, certain major points concerning the function of this central brain stem area are pertinent: (i) electrical potentials evoked by peripheral stimulation may be corticopetally conducted not only through the classical lemniscal system and thalamic relays, but also are conducted through this central brain stem and medial thalamus;\textsuperscript{9} (ii) electrical stimulation in this area, from which potentials evoked by peripheral stimulation can be recorded, will cause the so-called “arousal” reaction in the dormant animal and is associated with changes in the electroencephalogram from a sleeping to a waking state;\textsuperscript{16} (iii) electrolytic lesions of this area produced in the experimental animal cause prolonged coma and unreactivity to environmental stimuli.\textsuperscript{8}

This central region in the cephalic tegmentum is thus intimately concerned with consciousness. Since this region receives impulses from the classical sensory pathways, it is presumed that this continuous sensory bombardment “drives” the reticular activating system and thus maintains the conscious state. Reduction in this sensory input results in spontaneous sleep from which the subject may be aroused by appropriate increase in the sensory input. Abolition of this sensory driving results in coma.

It was postulated that the unconsciousness produced in cerebral concussion could be based on changes that prevent the normal sensory “driving” of the reticular formation. This could occur by direct neuronal depression of the cells in the reticular core, or by loss of collateral afferent conduction into the central core from the main ascending sensory pathways. Since initial experimental work has shown that the total electrical activity in this area is reduced,\textsuperscript{6} the present effort was intended to determine the effect of concussion on the reactivity of the reticular core to certain of the sensory stimuli which ordinarily “drive” the reticular formation.
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METHODS

Experiments were carried out on 19 monkeys (Macacus rhesus). All weighed 3 kg. (plus or minus 0.2 kg.). Eleven of the animals were used as controls to gain experience and to study the recorded evoked potentials from the reticular formation during peripheral nerve stimulation. Eight identical experiments were then performed immediately after acceleration concussion to demonstrate changes in these potentials recorded from the reticular formation.

Operative procedures, including craniotomy, vein catheterization, peripheral nerve (sciatric or ulnar) exposure, and tracheotomy, were done under light ether anesthesia. Wounds were thoroughly infiltrated with procaine and 1 hour after complete recovery from anesthesia, respiratory paralysis was induced with dihydro-beta-erythroidine HBBr and respirations were maintained with the Palmer respiration pump. Nerve stimulation through silver hook electrodes under mineral oil was accomplished through a Grass stimulator and isolation unit delivering recurrent single square wave pulses of 1 to 0.5 msec. duration at 2–6 V.

Through a small skull trephine, a three-electrode grid was inserted with a stereotactic instrument so as to core down through the reticular formation and medial lemniscus of the brain stem in a plane parallel to its long axis. The electrodes, insulated except at the tip, were stainless steel or tungsten wire, 0.2 mm. in diameter. The medial two electrodes were 1 mm. apart and traversed the reticular formation. Potentials were recorded by bipolar technique between these two electrodes. The single lateral electrode was 2 mm. farther lateral and fixed in the grid to be 5 mm. more advanced in depth than the medial two. Potentials were recorded between this electrode traversing the lemniscus and a deep insulated needle electrode placed well beneath the corresponding ear. Four planes of recording "runs" were made serially in the dorsoventral diameter to assure a complete sampling of the reticular activity in each case and records were taken at millimeter intervals of advance.

Conventional biological amplifiers were used and the brain stem responses were displayed on two dual beam oscilloscopes—one for monitoring, and one for photography.

The contralateral ulnar nerve was stimulated in 2 cases and in 3 cases homolateral, contralateral, and bilateral sciatic nerve stimulation was utilized. Subsequently all animals concussed were stimulated on the contralateral sciatic nerve since this produced the most reliable evoked potentials in the reticular formation.

Production of Concussion. Since there is still controversy as to whether compression and acceleration concussion represent the same phenomenon, we preferred to use acceleration concussion. Fig. 1 demonstrates the gas pressure gun which was designed to produce acceleration concussion. It has been described previously, and consists of a compressed gas chamber from which a piston is driven down the barrel.
at velocities variable from 0 to 50 feet per sec. Acceleration in excess of 2500 feet per sec. is possible. An almost instantaneous blow against the animal's head is achieved by the built-in compression head on the barrel which stops the piston immediately after contact with the skull. The animal is freely suspended with skull held lightly against the baffle plate. A metal plate attached directly to the skull transmits the energy directly to the skull itself.

The end-point in each experiment for production of concussion was loss of consciousness associated with respiratory irregularity, and loss of corneal and pinnal reflexes. Immediately after an adequate concussion was obtained, recording technique as in the control series was followed as rapidly as feasible. The animal was placed in the stereotactic instrument, trephination of the skull was accomplished and the electrode grid was inserted rapidly down into the midbrain and the peripheral nerve stimulation begun. The first adequate recordings were usually obtained at about 20 minutes after concussion. In 6 of the 8 animals it was necessary to use intravenous dihydro-beta-erythroidine to maintain immobility of the animal and allow adequate recording.

At the conclusion of all experiments the animals were perfused, the brains were removed intact, and serial section of the brain stem was done with Nissl and Weil stains to accurately localize the positions of the electrodes. In many cases of adequate concussion skull fracture was produced though in no instance was gross brain damage evidenced. Anatomical verification of electrode position was made in all cases.

RESULTS AND DISCUSSION

The results fall into two categories—observations on the characteristics of the sensory evoked potentials in the reticular formation and the effect of concussive head injury on these sensory evoked potentials. Fig. 2 shows the area of the reticular formation that was investigated, extending from the cephalic tegmental brain stem from the subthalamic region down to the level of the inferior olive. The blocked-in area on this diagram of the parasagittal brain stem of the monkey shows the extent of the area where evoked potentials from peripheral sensory stimulation were actually recorded. This represents a core which is 1 to 3.5 mm. lateral to the midline, and is a longitudinal reconstruction from the histological cross-sections of the brain stems.

Fig. 3 is a photomicrograph of the cross-section of the upper brain stem of the monkey showing the usual location of the grid electrodes. At this level of the superior colliculus, the three-grid electrode tracts are present in four dorsoventral planes. The medial two electrodes traversed the length of the brain stem reticular formation. The recording was bipolar between these two electrodes. The lateral electrode traversed the lateral ascending sensory pathways, the medial lemniscus, where the recording was monopolar with the reference ground lead at the base of the skull laterally. In order to obtain simultaneous evoked potentials from the reticular formation and the medial lemniscus, this electrode was 5 mm. in advance of the other two.

Our results in the control study of the sensory evoked potentials in the reticular formation support the observations of Amassian,1 and French, Magoun et al.7–10 The evoked potentials in the tegmental core contrasted
sharp with those transmitted over classical sensory pathways. Fig. 4A is an oscilloscope record of the potentials in the medial lemniscus (upper trace) and the reticular formation (lower trace) evoked by a single stimulus to the contralateral sciatic nerve. In the classical sensory pathway, the latency was short (5–8 msec.), the wave form was spike-like, and there was little or no attenuation on repetitive stimuli. The evoked response in the reticular core, on the other hand, showed a long latency (14–24 msec.), and a broader gross response indicating temporal dispersion. Interaction and attenuation of successive responses to multiple peripheral stimulation were likewise demonstrated. This record shows the evoked response generally found in 704 recording sites within the reticular formation in the control group.

Fig. 4B shows the typical response recorded from the same area in another animal 25 minutes after concussion. Except for the concussion, the

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Fig. 2. Diagram of parasagittal section of brain stem of monkey. Shaded area is reticular formation where sensory evoked potentials were recorded as determined from histological reconstructions. Scale is in millimeters.
conditions were identical. The upper trace shows the medial lemniscus evoked potential but no evoked response is present in the reticular formation (lower trace). This lack of evoked response in the reticular formation was very striking. In 6 of the 8 animals concussed, practically no sensory evoked response appeared in the reticular formation (396 recording sites). In one

![Image of a cross-section of the midbrain showing recording sites of electrode grid. Weil stain.](image)

**Fig. 3.** Cross-section of midbrain showing recording sites of electrode grid. Weil stain.

![ Oscilloscope record of concomitant evoked potentials in brain stem reticular formation (upper trace) and medial lemniscus (lower trace). (A) Control without concussion. (B) After concussion. Time calibration —10 msec. Voltage calibration —50 μV.](image)

**Fig. 4.** Oscilloscope record of concomitant evoked potentials in brain stem reticular formation (upper trace) and medial lemniscus (lower trace). (A) Control without concussion. (B) After concussion. Time calibration —10 msec. Voltage calibration —50 μV.
animal, only temporary loss of this response appeared, and in the other animal a delayed but progressive loss of this response was obtained. The response in the medial lemniscus, however, was not significantly changed in any instance except immediately ante mortem.

The loss of the reticular response following concussion can be temporary as demonstrated in Fig. 5. In this case, the animal was followed intermittently for 24 hours after concussion had been produced. The oscillograph tracing is the record of the evoked potentials in the reticular formation

![Fig. 5. Spontaneous return of sensory evoked potentials in reticular formation after concussion. Stimulus—contralateral sciatic nerve. (A) 25 minutes after concussion, (B) 1½ hours, (C) 3 hours, (D) 6 hours, (E) 9 hours, and (F) 20 hours after concussion. Time calibration—60 cycle sequence.](image)

under conditions already described. At A, only a suggestion of a response is present 25 minutes post-concussion; at B, 1½ hours post-concussion, a small response has appeared; 3 hours (C), and 6 hours (D) and 9 hours (E) after concussion, progressive improvement has occurred. At (F), 20 hours after concussion, the response is considered normal. This return of the sensory evoked potential in the reticular formation could not be correlated with the return of consciousness under the experimental conditions necessary for these recordings, but such an assumption is at least logical.

The situation demonstrated in Fig. 5 can be correlated with the clinical case of head injury in which the mild to moderate cerebral concussion produces a variable period (1 to 8 hours) of unconsciousness or loss of environmental reactivity or adjustment. This injury is not associated with obvious neurological deficits once the sensorium clears. During recovery, the
clouded sensorium—at times associated with apparent complete unresponsiveness and near coma—can be dramatically reversed by strong, repetitive sensory stimuli. Immediately on cessation of such stimuli, however, the patient lapses back into apparent near coma. Such an "arousal" has many features similar to "arousal" achieved in the narcotized experimental animal during reticular formation stimulation.

Fig. 6 demonstrates the single case of delayed loss in reticular reactivity following concussion. This record occurred in one animal in which a relatively moderate concussion was produced associated with only a momentary apnea and flaccidity. The corneal reflex was gone for 2 minutes following which flailing activity required dihydro-beta-erythroidine for immobilization. At A, 20 minutes following concussion the reticular formation (upper trace) and lemniscus (lower trace) show a near normal response. At B, 1 hour following concussion, the reticular response shows diminution and change whereas the lemniscal response is essentially unchanged. At C, 4 hours after concussion, the reticular response is just barely visible and the lemniscal response is somewhat depressed. The electrodes were held in the same position during this recording. Expiration occurred shortly thereafter. There was no significant gross brain damage. It appears from this that the loss of sensory reactivity of the reticular formation in head injury may be delayed and progressive in certain cases, and unassociated with gross brain lesions.

This record may well simulate the clinical case in which the initial head injury does not appear to be severe and actual initial unconsciousness may be questioned. The patient at first appears superficially to be adaptive and reactive to his environment. Within the next 4 to 12 hours, deterioration ensues and progresses to near coma. The progressive deterioration following a so-called "lucid interval" may necessitate burr-hole exploration to rule out epidural hematoma, but none is found. The phenomenon presented in Fig. 6 adequately explains at least some of the negative explorations for hematoma. It is apparent that depression of the reticular formation can be delayed, progressive and possibly fatal.
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The two types of reticular depression observed following concussion—the prompt, persisting depression, and the delayed, progressive loss—probably do not have identical mechanisms of production. The prompt loss is logically caused by direct traumatic neuronal depression in the reticular substance itself, or traumatic conduction loss in the afferent collaterals feeding in from the lateral sensory tracts. The delayed depression, however, is more suggestive of a pharmacological depression such as might be produced by acetylcholine accumulation. Such a postulate is reasonable since acetylcholine appears rapidly in spinal fluid after concussion and since these clinical cases can respond dramatically to anticholinergic therapy.

SUMMARY AND CONCLUSIONS

1. Sensory evoked potentials in the brain stem reticular formation and medial lemniscus were studied experimentally in the normal monkey and in the monkey immediately after concussion.

2. These responses in the normal animal showed constant characteristics previously described by others. The essential role of these sensory stimuli in maintaining the waking state through constant activation of the reticular formation is re-emphasized.

3. The sensory evoked responses in the reticular formation were selectively, uniformly, and dramatically absent following adequate acceleration concussion, but under proper circumstances spontaneously recovered over a period of time. The responses in the lemniscus recorded at the same time were unchanged.

4. Since unconsciousness is the single major criterion for cerebral concussion, since loss of sensory activation of the reticular formation results in unconsciousness, and since these two conditions were experimentally produced simultaneously, it is postulated that the unconsciousness produced by cerebral concussion is at least in part the result of the sudden loss of sensory activation, or "driving," of the brain stem reticular formation.

5. The delayed, progressive, fatal loss of reactivity of the reticular formation has been recorded following concussion and clinical correlations have been suggested.

REFERENCES


