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CHOLINERGIC ASPECTS OF CONVULSIVE THERAPY

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While the mode of action of convulsive therapies remains enigmatic, one theory holds that the early development and persistence of changes in brain function are requisite to changes in behavior (18, 21, 22). A useful index of neurophysiological change is the appearance of high voltage electroencephalographic slow wave activity (22, 23). While the biochemistry of this activity is poorly understood, demonstrations that it is inhibited by anticholinergic compounds (19, 20, 34, 66) suggest that cholinergic systems may play an active part.

The EEG patterns and the response to anticholinergic drugs in convulsive therapy are similar to experimental and clinical head trauma and, to a lesser extent, spontaneous seizures. Changes in concentration of cholinesterases in brain and spinal fluid also show many similarities in these conditions. This review discusses these observations to provide a hypothesis for the role of cholinergic changes in convulsive therapy.

The activity of acetylcholine in the transmission of nervous impulses has been extensively studied since the early descriptions by Dale (12) and Loewi (38). A constituent of nervous tissue in a bound form, acetylcholine is liberated during the excitation process. It is rapidly hydrolyzed through the mediation of acetylcholinesterase and is rapidly reconstituted by the choline-acetylase system (45). Free acetylcholine has not been measurable in normal cerebrospinal fluid despite the rapid breakdown of bound acetylcholine during periods of activity and excitement (63). But the normal cerebrospinal fluid does have measurable cholinesterase activity (41).

CHOLINERGIC ASPECTS OF CRANIOCEREBRAL TRAUMA

Free acetylcholine was found in the cerebrospinal fluid of cats within a few minutes after experimental head trauma and persisted for varying periods up to 48 hours. The quantity of free acetylcholine varied between 2.7 and 9.0 gamma/100 cc, and the amount was related to the degree of induced trauma (6).

Concurrent electroencephalograms first demonstrated high voltage fast activity, interpreted as evidence of an intense neuronal discharge, which was succeeded by a short period of flattening of all recorded electrical activity. These phases were followed by prolonged periods of high amplitude sharp waves in the delta frequencies.

The behavioral changes related to the degree of induced trauma and to the amount of measured free acetylcholine. With higher levels of acetylcholine, Bornstein (6) reported greater degrees of EEG abnormality and greater changes in consciousness. Spontaneous post-traumatic seizures were also related to the amount of free acetylcholine measured in the cerebrospinal fluid.

Bornstein applied acetylcholine to exposed cat cerebral cortex. When the concentration of acetylcholine was one gamma/100 cc or less, high amplitude sharp waves of low frequency appeared in the electroencephalogram. When the concentration was increased to two gamma/100 cc, the electroencephalogram flattened in

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a fashion parallel to the post-traumatic records.

Investigations in neurological patients by Tower and McEachern (63) demonstrated free acetylcholine in the cerebrospinal fluid only in patients with recent head trauma, recent grand-mal seizures or after electroconvulsive therapy. Free acetylcholine varied from 0.2 to 100 gamma/100 cc. In assaying spinal fluid cholinesterase activity, they noted a sharp rise in the butyrylcholinesterase fraction and a fall in the acetylcholinesterase fraction in patients with head trauma and following convulsive therapy. After spontaneous seizures, however, the cerebrospinal fluid did not exhibit such inversion although it contained free acetylcholine. They concluded that the level of free acetylcholine varied directly with the degree of cerebral damage and that reversal of cholinesterase fractions was a more sensitive indicator of cerebral damage. Electroencephalograms taken at varying intervals following trauma also indicated a relation between the degree of EEG abnormality and the appearance of free acetylcholine in the cerebrospinal fluid.

Increased acetylcholine in rat brain after traumatic shock was also reported by Kovach *et al.* (36). This acetylcholine activity was inhibited by the administration of atropine *in vitro*.

The electrographic, behavioral and neurologic signs of head trauma were blocked by the parenteral administration of 0.5–1.0 mg/kg atropine, as were similar clinical changes occurring after the intracisternal addition of acetylcholine (6). Ward applied these observations to the treatment of closed head injuries. In 20 patients with varying degrees of trauma, he administered atropine subcutaneously in doses of 0.1 mg/kg, noting clinical improvement in some and a reversal of the electrographic effects in others (67). The same changes in the post-traumatic electroencephalogram were reported by Jenkner and Lechner in a study of diethazine, another anticholinergic drug. A single intravenous dose in 40 patients resulted in normalizing the abnormal electroencephalogram in 22 and marked improvement in six others (33).

Similarly, in experiments of post-traumatic shock and cerebral edema in animals, Denisenko (13) reported a blocking of the clinical changes by such anticholinergic compounds as methylbenactyzine and adiphenine (Trasentin).

Thus, the amount of free acetylcholine may increase in the spinal fluid following craniocerebral trauma and the amount of free acetylcholine, the degree and type of electroencephalographic abnormality, and changes in clinical behavior appear as interrelated phenomena, which may be reduced by the administration of anticholinergic drugs.

BRAIN ACETYLCHOLINE AND ANTICHOLINERGIC DRUGS

The effects of the direct application of acetylcholine to the central nervous system may also be blocked by anticholinergic drugs. The administration of the cholinesterase inhibitor di-isopropyl fluorophosphate (DFP) elicited high amplitude rapid frequency EEG patterns similar to status epilepticus and some post-traumatic states (24, 31, 32, 68). These EEG effects were blocked by small doses of parenteral atropine and scopolamine. The great increase in acetylcholine after tetraethyl pyrophosphate (TEPP) was measured and related to the toxic effects and the induced convulsions (29, 59).

Chatfield and Dempsey (9) prepared exposed animal cortex with prostigmine and evoked electroencephalographic spike activity. The prior administration of atropine blocked the appearance of spiking, or if present, this electrical activity could be eliminated by atropine.

In contrast to these findings, Brenner and Merritt (7) applied topical acetylcholine in concentrations of two and one-half to ten per cent to the exposed cortex

of cats and noted no effect on the electroencephalographic changes after intravenous atropine (one mg/kg). The concentrations of acetylcholine in these experiments, however, were higher than the topical applications (one to four gamma/100 cc) and the intracisternal (0.2–10 gamma/100 cc) injections of Bornstein (6). Brenner and Merritt (7) also noted electroencephalographic effects similar to acetylcholine after methacholine (Mecholyl) and carbamylcholine (Doryl) in concentrations much lower than the acetylcholine concentrations. They ascribed the increased effectiveness of these cholinergic drugs to their lack of sensitivity to cerebral cholinesterases.

These data are conflicting and further study is necessary to qualify this issue.

CEREBROSPINAL FLUID ACETYLCHOLINE AND SEIZURES

One view of acetylcholine metabolism finds it in nervous tissues in an inactive and bound form. During periods of activity, acetylcholine is liberated at the cell membrane where it is rapidly deactivated by cholinesterases. The amount of bound acetylcholine is the resultant of the continuous processes of synthesis, liberation and breakdown (15). It has been postulated that the level rises during sleep and falls during waking activity (16, 29, 45, 60).

Tobias *et al.* (60) reported increased free and total acetylcholine after chloroform and pentobarbital anesthesia in rat and frog brain but no changes after strychnine or pictrotoxin convulsions. Richter and Crossland (45) measured the level of acetylcholine (microgamma per mg brain tissue) during anesthesia and sleep in rat brain to be 300 per cent higher than post-seizure levels. The difference in tissue levels is transient, however, as the resynthesis rate for acetylcholine in rat brain is high (seven gamma/gm/minute). These observations were confirmed by Elliott *et al.* (16) and Crossland and Merrick (11). Giarman and Pepeu reported the increase in acetylcholine following various depressants to be roughly proportional to the degree of depression of the central nervous system and the reduction in motor activity (29). Maynert and Buck, however, studying brain acetylcholine levels during sedation concluded that some sedatives were associated with elevated brain acetylcholine but that no rigorous relationships existed (39). In part, this may be related to the earlier observations of McLennan and Elliott (40) that acetylcholine synthesis measured in rat brain slices is accelerated by low dosages of narcotic drugs, but inhibited by high dosages.

Free acetylcholine was reported in the spinal fluid in patients with epilepsy (10, 63). Of 56 epileptic patients, 44 demonstrated free acetylcholine in quantities of 0.02 to 5.0 gamma/100 cc with an average of 1.0 gamma/100 cc. Acetylcholine levels were related to the frequency of seizures, the extent of electoencephalographic abnormality, and to the time since the last seizure, but bore no relation to medication, type of epilepsy or level of cholinesterase activity. Elliott *et al.* (16) also noted free acetylcholine in the spinal fluid in concentrations up to three gamma/100 cc after pentylenetetrazol (Metrazol) convulsions.

Tower and McEachern (63) viewed the increased acetylcholine as a by-product of the seizure and not causal. Studying the hypothesis that seizures were induced by the accumulation of acetylcholine, Torda (61, 62) measured the level of acetylcholine in brain tissue after pentylenetetrazol convulsions. She noted a rise in the acetylcholine content of brain before and a fall during the convulsion. Below certain levels of acetylcholine, convulsions failed to occur. She suggested that the fall in tissue acetylcholine during a convulsion was due to the inhibition of acetylcholine synthesis by increased concentrations of metabolites such as ammonium ions.

Giarman and Pepeu also measured changes in central nervous system acetylcholine following various stimulants (29). Only after methacholine and 3,5-dimethylbutylethyl-barbiturate was there a significant change in the acetylcholine level. They noted a decrease in association with induced convulsions. With other drugs which they classified as stimulants (LSD, iproniazid, iproniazid plus hydroxytryptophan, and iproniazid plus DOPA) there were no changes in the acetylcholine level. They concluded that despite intense excitation produced by these compounds, there were no changes in acetylcholine levels unless these were accompanied by convulsions. (The differences in observations between these observers and Cone *et al.* (10) and Tower and McEachern (63) may be related to the differences in methods of biochemical measurements, for the latter measured changes reflecting free acetylcholine only, while Giarman and Pepeu (29) measured total acetylcholine including bound and free forms of acetylcholine.)

These studies suggest that spontaneous or induced seizures are accompanied by an increase in intercellular free acetylcholine liberated from its bound form which may be reflected in the spinal fluid. Cerebral activity and seizures enhance acetylcholine destruction, lowering tissue levels of acetylcholine, while sleep and anesthesia augment acetylcholine production increasing tissue levels.

CENTRAL NERVOUS SYSTEM CHOLINESTERASES

Tower and McEachern (63, 64, 65) also measured spinal fluid cholinesterase activity. By reporting cholinesterase activity as a ratio of the rate of hydrolysis with two substrates compared to an acetylcholine substrate, acetylcholinesterase/acetylcholine and butyrylcholinesterase/acetylcholine ratios are derived. Normal cerebrospinal fluid contains these esterases in the ratio of 33:17.

In patients with head trauma, Tower and McEachern reported an inversion of the cholinesterases with an increase in the butyrylcholinesterase of the spinal fluid and a decrease in acetylcholinesterase activity. The extent of the cholinesterase reversal was related to the severity of trauma and to the degree of EEG abnormality. A similar reversal was observed in patients undergoing convulsive therapy.

In patients with elevated spinal fluid acetylcholine after spontaneous seizures, however, no change in the ratio of cholinesterases or total cholinesterase activity was found.

Changes in cholinesterase activity may be related to changes in cell membrane permeability. Acetylcholinesterase is found in highest concentration in the central nervous system while butyrylcholinesterase predominates in other tissues, especially blood serum. With increased cerebral acetylcholine, vasodilation and increased cellular permeability may be predicted, with vascular fluid transudation varying with the extent and duration of the vasodilation (35). Spiegel, Spiegel-Adolf and their coworkers (54–58) demonstrated such permeability changes and increased conductivity of the tissues associated with the appearance of various ions (as potassium and phosphate) in the spinal fluid following electrically induced convulsions. Such non-electrolytes as nucleic-acid splitting enzymes also increased. Changes in cellular permeability may be the basis for the high concentrations of acetylcholine and increased concentrations of butyrylcholinesterase after induced seizures or head trauma (65).

That changes in cholinesterases may be large and measurable is suggested by the recent demonstrations that neural stimulation and learning produces changes in brain weight and acetylcholinesterase activity (37, 49). Following these reports,

Pryor and Otis (43) studied the effects of repeated induced seizures in Wistar rats. After as little as four weeks, they observed increases in brain weight and in acetylcholinesterase activity which was related to decrements in behavioral performance.

The persistence of acetylcholine in spinal fluid after head trauma and after seizures despite increased cholinesterase activity may be related to the sensitivity of the acetylcholine-acetylcholinesterase system to concentration relationships (8, 41, 65). At "physiologic" concentrations, hydrolysis of acetylcholine is rapid (three to four microseconds) but at higher and lower concentrations, the activity falls off quickly. In contrast, the butyrylcholinesterase-acetylcholine relationship is non-specific, and the rate of hydrolysis increases with increased concentration.

These relationships relate to theories of the induction of seizures. While the usual concentrations of acetylcholine at cell membranes are destroyed by the specific activity of acetylcholinesterase in a few microseconds, an excessive concentration following excitation may exceed its rate of hydrolysis. The seizure threshold may be reached and a seizure induced, with the seizure itself adding to the amount of free acetylcholine. Increased acetylcholine affects vascular and cellular permeability altering the concentrations of various ions, including butyrylcholinesterase in tissues and in the cerebrospinal fluid. Through the activity of this esterase, though of low efficiency and depending on concentration kinetics, acetylcholine is reduced in tissues to levels for the more direct action of acetylcholinesterase.

Cholinesterases appear in the spinal fluid as a reflection of their increase in intercellular fluids resulting from changes in cell membrane permeability accompanying increased acetylcholine.

EEG HYPERSYNCHRONY AND INDUCED CONVULSIONS

The significance of high voltage EEG slow wave activity for the convulsive therapy process has been repeatedly described (22, 23, 50, 51). In the usual course of convulsive therapy, inter-treatment electroencephalograms record progressive increases in amplitude and in theta activity and a reduction in beta activity. As treatment continues, delta activity appears in bursts and eventually is the dominant activity in all leads. These changes are directly related to the number and rate of induced convulsions and are not specific for a method of induction. While some relationships to type of electrical current have been observed, all seizure inducing methods—electrical, intravenous chemical or inhalant—exhibit the same type of EEG pattern changes (21, 22, 23, 30).

The early appearance of high degree hypersynchrony and its persistence throughout a treatment course has been found to be prerequisite to improvement. Both the electrographic and the behavioral changes of induced convulsions are transiently reversed by the acute administration of experimental anticholinergic compounds (19, 20). The intravenous injection of diethazine, benactyzine, the piperidylbenzilates JB–318, JB–336 and JB–329 (Ditran), and WIN–2299 induced EEG desynchronization in psychiatric subjects. These EEG changes were associated with behavioral alerting, anxiety, tremors, illusions and hallucinations. In patients who had recently received electroconvulsive therapy there was a reduction in slow wave activity and a reversal of euphoria, denial and confusion. Atropine, in low doses, was also associated with EEG desynchronization accompanied by tachycardia, nervousness and tension. At higher dosages, hypersynchronous slow waves followed by lower voltage, poorly organized delta activity with superimposed beta activity was ac-

companied by progressive confusion and disorientation.

The effect of anticholinergic drugs on the slow wave activity of convulsive therapy was also assessed by the chronic administration of atropine (five mgm per day) and scopolamine (one to three mg) during the weeks of treatment. The amount of EEG slowing was significantly less than in a control group (66). The samples were too small for a clinical correlation but the data are consistent with blocking of the clinical effects of electroconvulsive therapy. Marked improvement was reported in two of seven atropine-treated, none of five scopolamine-treated and in four of the six controls receiving unmodified ECT. This study was not replicated by the authors who suggest that dosage factors or population changes may have contributed to the different results in a second study (34).

As in cerebral trauma, the electrographic changes of induced convulsions may be modified by the administration of anticholinergic drugs suggesting that increased amounts of acetylcholine or increased cholinergic receptivity is associated with the high voltage slow wave activity.

ACETYLCHOLINE AND INDUCED CONVULSIONS

Despite a constant application of treatments, however, there is great variability in the time of appearance, the duration, amount, and sensitivity to modification by alerting, hyperventilation and barbiturates of the electrographic slow wave activity in psychiatric populations (30). These differences relate to differences in central cholinergic activity. The failure of certain patients to develop hypersynchrony may be associated with the absence of free acetylcholine and with minimal changes in cerebral function, thus precluding a clinical response to induced convulsions. Tower and McEachern (63), in their study of craniocerebral trauma, included observations of six psychiatric patients undergoing convulsive therapy. Studying the patients after three to seven treatments they reported free spinal fluid acetylcholine in two patients, and an increase in butyrylcholinesterase and a decrease in acetylcholinesterase with a reversal of the ratio of cholinesterases in five of the six patients. Only one patient in the series failed to show either free acetylcholine or a cholinesterase ratio reversal in the spinal fluid and of this patient the authors stated, "It is interesting that this patient was the only one of the six to show no response to treatment." They concluded that the spinal fluid changes in induced convulsions were more like those of craniocerebral trauma than those of spontaneous epilepsy.

Other evidence of alterations in the permeability barrier may be seen in the demonstrations of an increased concentration of cocaine in brain tissues three days after a series of 12 induced convulsions (1). The change in concentration of this large molecule, ordinarily absent in brain tissue, was associated with the appearance of hypersynchrony (delta bursts) in the electroencephalogram.

From these observations we would conclude that induced convulsions, like craniocerebral trauma and spontaneous seizures, are associated with an increase in free acetylcholine in intercellular fluids, altering cerebral permeability and enhancing the appearance of cholinesterases. The level of free acetylcholine is maintained by repeated induced seizures. EEG hypersynchrony is one reflection of altered levels of acetylcholine and the altered permeability of electrolytes and other substances, including cholinesterases. The changes in intercellular electrolytes, including acetylcholine, provide the biochemical substrate for the persistent behavioral changes and EEG hypersynchrony following induced convulsions.

CHOLINESTERASES AND THE CLASSIFICATION OF PSYCHOSES

An application of these conclusions is seen in the studies of the prediction of the convulsive therapy response and the classification of psychoses.

Funkenstein *et al.* (25–27) reported a relationship between the blood pressure response to methacholine and the clinical response to convulsive therapy. Immediately after the injection of methacholine the blood pressure falls, usually returning to the baseline within five to 20 minutes. A return within five minutes places the patients in Groups I, II or III; while a return after 20 minutes place the patients in Groups VI and VII. Group I and Groups II–III have a nine per cent and a 35 per cent recovery rate, respectively, while Group VI and Group VII subjects have 89 per cent and 97 per cent recovery rates to induced convulsions (27). Group I, II and III reactors may be looked upon as patients in whom methacholine is rapidly hydrolyzed; while Groups VI and VII have a slow hydrolysis rate. (The response to injected epinephrine was suggested as a second criteria in the classification, but is of limited discriminating value [48].) While we have no biochemical explanation for the differences in the metabolism of methacholine in these psychiatric groups, it is possible that the blood and tissue cholinesterase activity levels of Groups I–III are high while those of Groups VI–VII are low compared to general psychiatric populations.

The differences in blood cholinesterase levels in normal and mentally ill subjects have been extensively studied. Despite differences in methods (4, 5), elevated cholinesterase levels compared to normal populations have been reported for depressive subjects (44, 46, 47, 52), schizophrenic subjects (14, 28, 53) and a mixed psychiatric population (42). Alpern reported lowered cholinesterase levels in schizophrenic subjects (2). While these studies appear inconclusive, they provide data that the variations in blood cholinesterase levels are generally greater and frequently elevated in the mentally ill. Negative reports include the failure by Ellman and Callaway (17) to confirm Rubin's study; and Altschule's review of the data suggesting no abnormality of cholinesterase levels in the mentally ill (3).

CONCLUSION

This review summarizes some of the available data suggesting that cholinergic mechanisms may be central to the convulsive therapy process. Induced convulsions are associated with cerebral vasodilation and increased cellular permeability, followed by the appearance of increased amounts of enzymes and electrolytes in intercellular and cerebrospinal fluids. The increase in acetylcholine, vasodilation and increased permeability appear as interrelated phenomena associated with trauma, seizures and induced convulsions.

These biochemical changes accompany increased electrical hypersynchrony which is recorded as EEG slow wave activity in scalp electrodes and which can be modified by the acute and chronic administration of anticholinergic drugs as atropine, benactyzine, diethazine, procyclidine and various piperidyl-benzilates.

In these regards, induced convulsions are more similar to cerebral trauma than to spontaneous seizures.

The changes in cerebral biochemistry alter cellular activity sufficiently to affect consciousness and the behavior of subjects. Failure to induce persistent biochemical changes, including the concentration of acetylcholine, results in failure to produce behavioral change.

There is, as yet, no consistent evidence for differences in the sensitivity or dependence of populations on cholinergic mechanisms. Differences in the rate of develop-

ment of cerebral changes to the same number and frequency of induced convulsions and classifications of the mentally ill based on the blood pressure response to methacholine suggest, however, that such differences may be significant in the pathogenesis of different psychoses.

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