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The Effective Agent in Electroconvulsive Therapy: Convulsion or Coma?

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Abstract — The ability of electrically-induced convulsions to alleviate at least some symptoms of mental illness was first reported in the literature 50 years ago; however, the cerebral mechanisms responsible for such therapeutic effects have thus far escaped elucidation. It is thus interesting to note that those seeking explanations for the therapeutic effects of electroconvulsive therapy (ECT) have focused their attention on the convulsion produced by ECT, as opposed to the coma. The present hypothesis emphasizes the coma following the convulsion as a potential explanation of the effectiveness of ECT and other convulsive therapies. It is postulated that the primary effect of the convulsion is to cause the release of adenosine (ARN) from neuronal tissue and that the subsequent depressant effect of ARN on neuronal activity results in the clinical effect observed. Thus hypothesis suggests that chemically-induced coma, particularly coma induced by benzodiazepines, may offer a safe, effective and more acceptable alternative to ECT.

Introduction

The 1930's represent a decade nonpareil in the history of somatic approaches to the treatment of psychiatric disorders. In 1933 Sakel introduced insulin coma as a treatment for functional psychoses, followed by Von Meduna's introduction of pharmacoconvulsive therapy in 1934 and by Moniz's introduction of psychosurgery in 1935. Then, in April of 1938, Cerletti and Bini first used electroconvulsive therapy (ECT) on humans after having experimented with the technique on animals. It was only within a span of two years that the first reports of these diverse approaches to the treatment of psychiatric disorders appeared in the literature (4, 13, 14, 19). Five decades later what is perhaps most noteworthy about these treatments is that we know virtually no more about how they work than did their originators.

Why convulsions, whether chemically of electrically induced, should ameliorate the symptoms of psychiatric disorders is a particularly perplexing puzzle. Nevertheless, one conclusion seems unavoidable: whatever alterations occur in the brain as a result of a convulsion, such alterations are capable of normalizing at least some manifestations of abnormal brain function. The efficacy of convulsive therapies has been demonstrated repeatedly and the role of ECT in the alleviation of life-threatening depression is

widely, if not universally, acknowledged (7, 12). This is not to say that ECT is universally accepted, for many physicians, patients and families have serious reservations about the application of electrical currents to the irreparable substance of the brain. Given our paucity of understanding of what electricity does to the brain, such reservations are well founded regardless of the validity of claims of efficacy and safety. If the therapeutic alterations of the brain produced by ECT could be identified and isolated from non-therapeutic alterations, it might be possible to introduce pharmacological alternatives to ECT which would be precise in their actions, produce less side-effects and would not be encumbered by the social and psychological stigmas attached to ECT.

ECT and the release of adenosine

One well-established neurochemical response to convulsions that may play a therapeutic role in ECT is the release of large amounts of adenine-ribonucleoside (ARN), commonly known as adenosine. While the appropriate measurements have not yet been made in humans, electrically or chemically induced convulsions in animals have been shown to cause a release of ARN from the brain (20, 22). These results are consistent with experiments demonstrating release of ARN from brain tissue preparations that have been electrically or chemically stimulated (3, 6, 9, 18). Furthermore, electrophysiological studies (11, 21) have shown that ARN is a very powerful depressant of neuronal activity. In fact ARN produces an intense quiescence in neurons in virtually all parts of the brain. For these reasons, and others, the elevated levels of ARN in the cerebrum during seizures have been hypothesized to be responsible for the CNS depression and/or coma following seizure activity (15).

This raises further interesting questions: does ECT produce a beneficial effect by virtue of the ARN-induced coma rather than the convulsion? Is the convulsion 'necessary' only insofar as it is a means of releasing ARN and producing a coma? In searching the literature for answers to these questions there appears to have been no serious attempts made to ascertain to what extent the coma produced by ECT contributes to the therapeutic effect. This is most surprising given the reputed efficacy of insulin-induced hypoglycemic shock in treating schizophrenics and depressed patients in the middle part of this century, and given that a coma is obviously a common feature of convulsive therapies and hypoglycemic shock. This is a very salient point, for if the coma is the efficacious "agent", then there may be alternative means of producing such a therapeutic coma without subjecting patients and their families to the emotional trauma associated with "shock-treatments" and the disorientation and memory loss that inevitably follow such treatments.

Is coma therapeutic?

Although there appears to have been no concerted efforts to determine to what extent coma alone (i.e., in the absence of convulsion) can produce therapeutic effects, there are nevertheless strong indications in the literature that this is indeed the case. The best evidence comes from clinical experiments in which the efficacy of ECT has been examined by comparing the therapeutic effects of actual ECT to those of "sham" ECT. In such experiments both the "sham-shocked" controls and the patients receiving ECT are anesthetized, usually with thiopental or other barbiturate. Thus, both the controls and experimental subjects experience a chemically induced coma to some extent. Although the data are not reported, it is likely that the duration of coma in the experimental subjects would be marginally longer as a result of the seizure and this may explain the small but significant effects of ECT over "sham-shocks".

It should be emphasized that the effects of ECT, compared to those of "sham-shocks" are generally pretty minimal and this has led to a hesitant acceptance of ECT by some cautious members of the medical community. In fact, the difficulties in establishing statistically significant effects of ECT arise not from a lack of measurable effects but, rather, from improvement shown by un-shocked controls. What is most surprising about this pattern of results is that no explanation has been sought for the therapeutic effects produced by "sham" ECT, although observant investigators have made mention of such effects (1, 5, 10). Since a period of unconsciousness is the most obvious aspect experienced by both experimental and control patients, one might be compelled to look very closely at the possibility that a prolonged chemically-induced coma might have beneficial effects in treating depression and other forms of mental illness.

The use of benzodiazepines to induce therapeutic coma

It should be explicitly noted that the above proposal to investigate the efficacy of chemically-induced coma as a treatment for depression or other forms of mental illness does not necessarily mean a return to or re-evaluation of hypoglycemic therapies. Given that ECT has been demonstrated to be comparatively safe, and given that the insulin-coma treatments were fraught with dangers and problems, it would clearly be unreasonable to consider a return to hypoglycemic coma, even if it is effective. However, today there are agents which can be relied upon to produce a safe and prolonged coma — the benzodiazepines (BNZ). Thus, arguments that insulin-coma is dangerous may be without merit with respect to the use of BNZ's to produce a therapeutic coma. As an extra added safety feature, BNZ antagonists (e.g., flumazenil) are now available which will quickly terminate a BNZ-induced coma should complications occur (2). Furthermore, the fact that BNZ's are contraindicated in patients about to undergo ECT is, of course, related to the anticonvulsant effect of these drugs and is thus irrelevant were a convulsion is not to be produced. Though there are no direct data available establishing the safety of intentional induction of prolonged, therapeutic coma with BNZ's, there is certainly sufficient clinical experience with BNZ overdoses to have some confidence that a BNZ-induced coma would be as safe, probably safer, than one produced by passing large amounts of electricity through the cerebrum.

As an additional point of interest to the present hypothesis, it should be noted that the BNZ's have been shown to modify the ARN system in the CNS. For instance, BNZ blockade of ARN uptake has been demonstrated (17). It has also been shown that BNZ's potentiate the depressant effect ARN has on central neurons (16). These observations suggest that the coma produced by BNZ's and the coma produced by convulsion may have a common neurochemical basis — ARN. Indeed, in terms of the neurochemical milieu, a BNZ-induced coma may not be too dissimilar from that produced as a result of a chemically-induced or electrically-induced seizure whereas insulin, barbiturates or other agents may produce comas that are neurochemically quite diverse and distinct from coma that follows seizure activity.

Conclusions

The literature is replete with assertions that the convulsion is the necessary and sufficient therapeutic agent of ECT. For instance Fink and Ottoson have stated, "Seizures are necessary for antidepressant activity . . . [of ECT]" (8). The present hypothesis challenges this presumption by emphasizing the coma of the ECT process and suggesting that it is the coma that is responsible for the antidepressant effect. From this point of view the convulsion is merely a rather dramatic way to produce a coma, perhaps by causing the release of endogenous ARN. A corollary to this hypothesis is that comas produced by chemical agents, particularly BNZ's, may produce antidepressant effects comparable to ECT. If BNZ-induced coma proves to be as efficacious as ECT, it would have the potential of replacing ECT in the treatment of depression and, possibly, other psychiatric disorders. This would represent a step forward in the treatment of psychiatric disorders and, possibly, a step forward in understanding the biochemical etiologies of those disorders.

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