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BRIEF COMMUNICATION

Effect of Combined Reserpine and ECS on Electroshock Seizure Thresholds in Mice

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BLANK, D. L. *Effect of combined reserpine and ECS on electroshock thresholds in mice.* PHARMAC. BIOCHEM. BEHAV. 4(4) 485–487, 1976. – Recent evidence has suggested that electroshock seizure threshold is correlated with levels of brain biogenic amines. Reserpine, a drug that depletes serotonin and norepinephrine, has been shown to decrease seizure thresholds. ECS treatment has been shown to increase amine levels as well as seizure thresholds. Combined reserpine and ECS have been shown to produce an intermediate level of serotonin and norepinephrine, but seizure threshold data for this group is absent. It was the purpose of this study to examine the seizure thresholds for combined treatment and compare them with groups treated with reserpine alone, ECS alone, and a placebo control group. The results suggest that, if only maximal seizures are considered, the seizure threshold is lowest for the reserpine and highest for the ECS alone or control groups, with the combined treatment group falling intermediate. If both minimal and maximal seizures are considered, the reserpine and combined treatment groups do not differ from one another, but do show a lower threshold as compared to ECS or control groups.

Reserpine Electroconvulsive shock Seizure thresholds

IN recent years a number of reports have related seizure threshold to brain biogenic amine levels. Agents which are known to increase the levels of serotonin and norepinephrine tend to increase seizure threshold. Prolonged administration of electroconvulsive shock (ECS) which, likewise, is reported to increase the level of indole and catachol amines [4, 6, 7], also appears to increase seizure threshold [13]. On the other hand, drugs which deplete biogenic amines (by interferring with amine synthesis and/or retention) reduce the threshold to seizures induced by electroconvulsive shock [1, 3, 12]. This depletion of amines by drugs such as reserpine (RES) has been offered as the underlying biochemical cause of lowered threshold to seizures of either electrical or other origins [2, 5, 9, 10]. The effect on amine levels of ECS and RES treatment combined, investigated by one group [4], appears to depend upon the brain structure examined. In some structures the levels of indole and catachol amines are intermediate between those produced by RES alone and those observed in placebo injected controls. In other structures the levels are comparable to those produced by RES alone. Seizure threshold following combined treatment has not been previously reported.

The fundamental hypothesis generated by this research holds that seizure threshold is positively correlated with and, perhaps, determined by existing levels of biogenic amines. If this hypothesis is true the following electroshock seizure thresholds should be ordered as follows, based upon the above data: (1) Pretreatment with ECS alone should result in the highest threshold to ECS; (2) Normal untreated controls should exhibit a lower threshold; (3) Pretreatment with both ECS and RES should lead to a threshold lower than in controls; (4) Animals treated with RES alone should exhibit a threshold to ECS equal to or lower than that of the combined treatment group. The purpose of the present study was to examine all 4 of these groups in a single experiment to determine the viability of these research hypotheses.

METHOD

Animals

Two hundred ten female mice (TAC: SW fBR), obtained from Taconic Farms and approximately 4 to 5 weeks of age, weighing between 16 and 25 g, with a median weight of 20 g, were employed in this study. Each animal was briefly etherized and wound clips secured between the anterior portion of the pinna and the skin overlying the adjacent temporalis muscle. These clips served as contact points for ECS electrodes. All animals were permitted 2 days to recover from this minor surgery and were permitted food and water ad lib for the duration of the study.

Procedure

The animals were divided into 4 groups and pretreated for 6 days according to the following schedule. Group 1

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(RES) received an IP injection of reserpine (0.6 mg/kg) dissolved in 0.25 M sucrose at a concentration of 0.06 mg/ml. Group 2 (ECS) received a 0.2 ml IP injection of 0.25 M sucrose and, 2 hr later, were subjected to an 8 mA electroshock. Group 3 (ECS/RES) received reserpine followed 2 hr later by electroshock treatment. Group 4 (CON) received a daily injection of 0.2 ml of 0.25 M sucrose and served as controls. Although body weight was taken daily, no attempt was made to monitor food intake or body temperature. However, no marked loss in body weight was observed for the duration of the experiment.

Animals subjected to electroshock were placed in a restraining apparatus and alligator clips were attached to the wound clips in the head. Rectangular current pulses of 1.6 msec duration and a rate of 450 pulses/sec were delivered for 425 msec at a constant current intensity of 8 mA via Tektronix 2600 pulse and waveform generators and 3 cascaded Tektronix 2620 constant current stimulus isolation units. Current intensity was monitored on an oscilloscope by observing the voltage drop across a 100 ohm series resistor. All animals which received the 8 mA electroshock treatment exhibited *grand mal* (maximal) seizures, i.e., tonic and clonic contractions followed by a post ictal relaxation [13].

On the afternoon of the last pretreatment day, each of the groups listed above was randomly divided into 5 subgroups for the determination of ECS threshold. Each subgroup received an electroshock differing from another subgroup by a current intensity of 1 mA. Ranges of current were from 3 to 7 mA. All other parameters of the shock were as listed above. Behavioral response to shock was classified as: 1. no response; 2. minimal seizure, i.e., mild clonic movements [13], or 3. *grand mal.*

RESULTS

The results of the experiment are shown in Figs. 1 and 2. Figure 1 shows the percentage of mice which exhibited a *grand mal* seizure at the current indicated. A Chi square analysis [11] was significant ($p<0.05$) suggesting that different treatments had different effects with respect to seizure threshold. The expected increase in seizure threshold for the ECS alone group as compared to control animals was not, however, suggested by the data. Figure 2 also shows seizure thresholds, but includes those animals at each current intensity that showed a minimal threshold to ECS, i.e., each point represents the percentage of animals showing either a *grand mal* seizure or a minimal seizure. No differences were found between the ECS and CON groups or between the ECS/RES and the RES groups. However, arbitrarily selecting the middle current intensity (5 mA) a Fisher exact test [11] showed a significant difference between either the ECS/RES or RES and control (CON) groups ($p<0.05$).

DISCUSSION

As predicted, the *grand mal* seizure threshold was lowest for the RES group and highest for the ECS and CON groups, with the combined treatment group (ECS/RES) falling intermediate between RES treatment and ECS or CON. The prediction, however, that an ECS pretreatment group should have a threshold higher than the CON group was not supported. It should be noted, however, that the biochemical data on which this latter comparison was based [4] show only modest increases in norepinephrine or serotonin above control levels and that these differences do not occur in all brain structures examined. This point could be further examined with a much larger sample and/or by determining seizure threshold by implanting stimulating electrodes in those structures which showed changes in norepinephrine or serotonin following ECS pretreatment alone.

If one considers, in addition to those animals exhibiting *grand mal* seizures, those which exhibited minimal seizures, the results are somewhat different. Although the ECS/RES group and the RES group exhibited lower seizure thresholds compared to control animals, the 2 treatment groups were not different from one another. *A priori,* these results were equally as likely as the first considering that combined

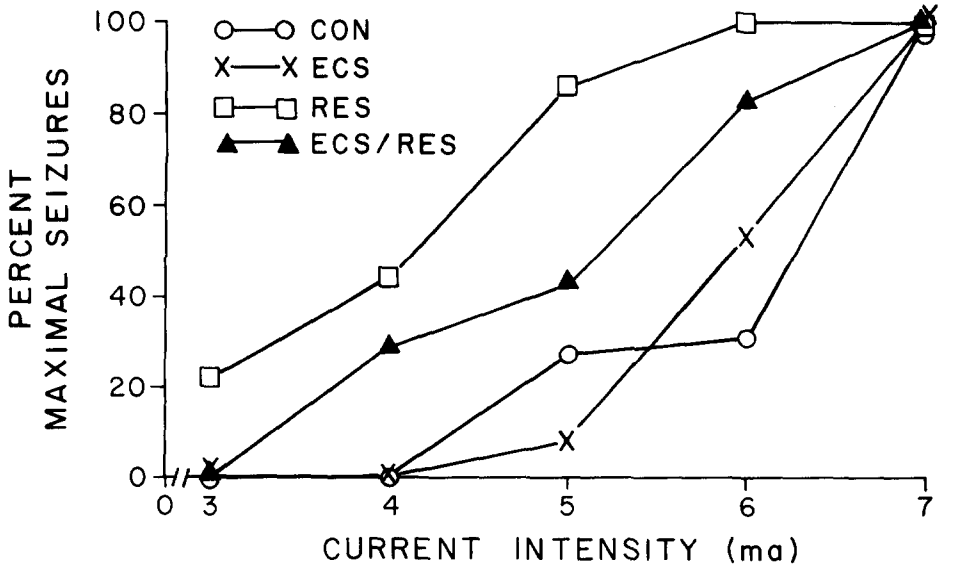

FIG. 1. Maximal seizure thresholds for the 4 treatment groups.

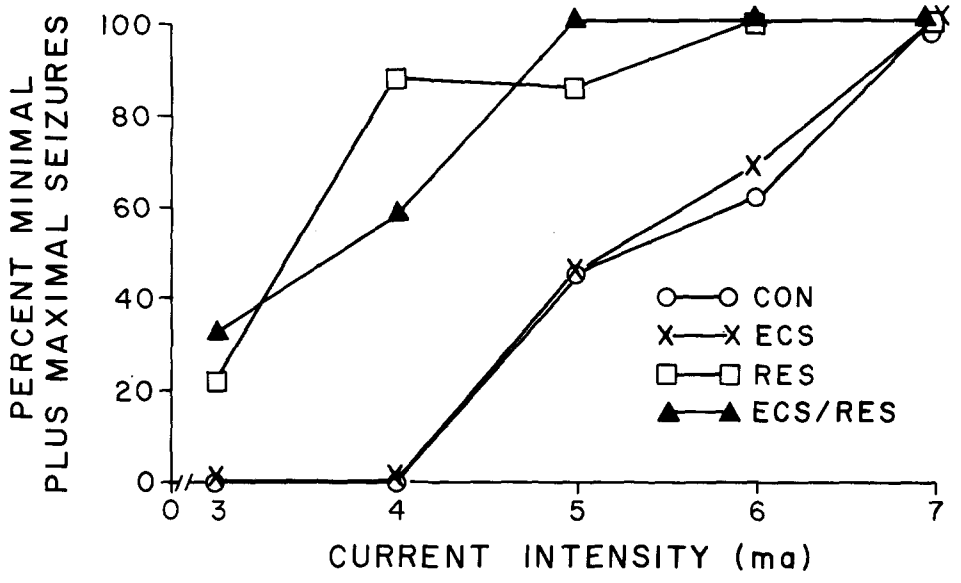

FIG. 2. Maximal plus minimal seizure thresholds for the 4 treatment groups.

treatment gives amine levels which are either intermediate between those for CON and RES groups or else comparable to those for RES alone treatment, depending upon brain structure. This, however, does not speak to the question of why the same results were not obtained for both the *grand mal* only and the *grand mal* plus minimal seizure animals. A number of explanations could account for this observation. (1) In the first place, the determination of a minimal seizure is far more subjective than a determination of a *grand mal* seizure [13] and, it is thus possible that animals which seemed to exhibit a minimal seizure were misclassified. (2) Alternately, assuming that the classification was correct, it is possible that the mechanisms underlying the production of minimal and *grand mal* seizures are not the same. For example, one mechanism might involve biogenic amine levels while another mechanism might be linked to other biochemical events such as changes in cerebral energy metabolism (Blank and Wayner, unpublished). In this behavioral experiment, of course, there was no way to distinguish between or among such mechanisms. (3) Since explanations 1 and 2 are not mutually exclusive, both could pertain.

Thus, the hypothesis that behavioral thresholds for electroconvulsive shock parallel previously reported levels of brain biogenic amines following similar treatments is given some support by the present study.

ACKNOWLEDGEMENT

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