Alterations in the behavioral and biochemical effects of electroconvulsive shock with nicotine[1]

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Mice treated with nicotine sulfate (1.0 mg/kg, i.p.) prior to training for a passive avoidance response showed antagonism toward the amnesic effect produced by a post-training electroconvulsive shock; this effect was particularly apparent when drug treatment was given 45 to 60 min prior to training. A reversal of the predicted effect of ECS upon brain serotonin level by nicotine suggested a possible corrolary of the drug-induced facilitation of memory consolidation.

Prior studies have indicated that the administration of electroconvulsive shock in close temporal proximity with training for the establishment of a response results in a significant degree of failure to perform that response when subsequent testing is carried out (Kopp et al, 1966; Essman, 1968a). This phenomenon has been interpreted as an experimentally-induced retrograde amnesia which has been related in several respects to physiological as well as biochemical changes in the central nervous system, produced by electroshock. Recent concern in this laboratory has been with several of the biochemical changes attending cerebral electroshock and its sequelae (Essman, 1968b, 1968c). Specifically, changes in the amnesic effect produced by post-training electroshock and several pharmacological agents, which have either acted to minimize the elevation in brain serotonin or alter its turnover rate as a consequence of electroshock, have also been indicated as means by which the ECS-induced amnesia is appreciably reduced (Essman, 1967). The purpose of the present study was to consider one such compound, nicotine sulfate, a central nervous system stimulant, that has been shown to alter the content of serotonin in the brain (Westfall et al, 1967). Under these conditions, therefore, it was hypothesized that the changes in brain serotonin resulting from nicotine treatment could impose rate-limiting conditions upon the brain serotonin alteration produced by electroshock, and thereby affect the degree to which such electroshock treatment would lead to a retrograde amnesia.

Method

Male CF-1s strain mice, weighing approximately 27 g, were assigned to five drug-treatment and two saline-treatment conditions, with 20 animals per group in the behavioral series and 10 animals per group in the biochemical series.

Four groups of Ss were each given 1.00 mg/kg of nicotine sulfate intraperitoneally, and the animals in the remaining group were treated with an equivalent volume of 0.9% saline. A single training trial in an apparatus designed to establish a passive avoidance response (Essman & Alpern, 1964) was given to Ss at either 15, 30, 45, or 60 min following injection, with the latency of entry into an inner chamber from an outer vestibule recorded. Ss received a 3 mA foot shock upon entering the inner chamber. Ten sec following the training trial all animals were given a single electroconvulsive shock (10 mA, 700 V, 200 msec), and were subsequently tested in the same apparatus at 24 h following training for the retention of the conditioned response, as indicated by a latency in excess of 25 sec after placement in the outer vestibule. Another group of mice (N = 20) was given an i.p. injection of 1.0 mg/kg of nicotine sulfate daily at 24 h intervals for three successive days. One h following the third daily injection these mice were trained, given ECS, and tested for retention 24 h later. Saline-treated control mice (N = 20), injected over the same three-day interval, were also trained and tested under the same experimental conditions. Parallel groups of animals (10/group) were given sham-ECS under each of the drug-treatment conditions described above, and a series of groups under both of the above-described drug and electroshock treatment conditions were killed by cervical section at 60 min following drug- or saline-injection, and in each case by 2 min following the administration of ECS or sham-ECS. The brain tissue of these latter groups of animals was assayed for serotonin and 5-hydroxyindoleacetic acid (Bogdanski et al, 1956; Udenfriend et al, 1958).

Results

The behavioral data are summarized in Table 1, and indicate that the amnesic effect of post-conditioning electroshock, as observed in both of the saline-treated groups, was significantly attenuated by prior treatment with nicotine sulfate ($\chi^2 = 36.34$, df = 6, $p < .001$). The drug-treated groups also differed significantly from one another ($\chi^2 = 16.80$, df = 3, $p < .001$), and this was largely accounted for by the difference between the 60 and 45 min pre-training groups and the 30 and 15 min pre-training groups ($\chi^2 = 7.20$, df = 1, $p < .01$); the former differed significantly from one another ($\chi^2 = 8.64$, df = 1, $p < .01$), whereas the latter did not ($\chi^2 = 0.96$, df = 1, $p > .50$) and were comparable in the incidence of retention with the saline-treated controls. It is of interest to note that the median response latency differences between the testing and training trials decreased as a function of a reduced drug-treatment-training trial time interval, suggesting reduced efficacy of the antagonism by nicotine sulfate of the amnesic effect of electroshock.

It is apparent that the three daily treatments of nicotine sulfate conferred no better antagonism toward the amnesic effect of ECS than did a single treatment 1 h prior to training.

The biochemical data are summarized in Table 2; for the saline-treated animals ECS was effective in elevating whole brain serotonin levels by approximately 12% ($t = 5.33$, df = 18, $p < .001$), with no significant alteracion in 5-HIAA level. In the mice treated with nicotine sulfate whole brain serotonin level was decreased 1 h following injection by approximately 6%, as compared with controls ($t = 2.00$, df = 1, $p < .07$); when nicotine-treated mice were given ECS there was an 8% decrease in whole brain serotonin level ($t = 2.50$, df = 18, $p < .05$); under these latter conditions whole brain 5-HIAA was significantly elevated ($t = 36.18$, df = 18, $p < .001$).

Discussion

The data indicate that mice treated with 1.0 mg/kg of nicotine sulfate at least 45 min prior to being given a single training trial show an appreciably attenuated incidence of retrograde amnesia, produced by post-training electroconvulsive shock; the high incidence of conditioned response retention shown by mice treated with nicotine sulfate 1 h prior to training, and given post-training ECS, was paralleled by an apparent change in the

Table 1

Median Response Latency Difference (Testing-Training Trial) and Per Cent Incidence of Conditioned Response Retention in Mice Treated with Nicotine Sulfate Prior to Training and Post-Training Electroconvulsive Shock

Condition	Median Response Latency Difference-Sec (Testing-Training)	Per Cent Incidence of CR Retention
Saline	1.0	10
Nicotine Sulfate (1.0 mg/kg) 60 min p.t.	21.0	66
Nicotine Sulfate 45 min p.t.	12.5	25
Nicotine Sulfate 30 min p.t.	9.0	20
Nicotine Sulfate 15 min p.t.	8.0	10
Saline (0.9%–3X)	2.5	10
Nicotine Sulfate (1.0 mg/kg–3X)	19.0	65

Table 2

Brain Serotonin (5-HT) and 5-Hydroxyindoleacetic Acid (5-HIAA) Levels in Saline- and Nicotine-Treated Mice Given Electroconvulsive Shock (ECS) or Sham-Electroshock ($\overline{ECS}$)

	$\overline{ECS}$		ECS	
CONDITION	5-HT (μg/g)	5-HIAA (μg/g)	5-HT (μg/g)	5-HIAA (μg/g)
SALINE (0.9%)	0.68 (0.03)	0.32 (0.15)	0.76 (0.04)	0.41 (0.16)
NICOTINE SULFATE (1.0 mg/kg)	0.64 (0.06)	0.36 (0.02)	0.59 (0.03)	0.78 (0.03)

level of whole brain serotonin level increase, as previously reported (Essman, 1967, 1968c). This change with ECS was reversed in the nicotine-treated mice. The change in indole levels in this latter case suggests an increased turnover rate for brain serotonin, whereas in the saline-treated animals the amine and its metabolite, as affected by ECS, do not warrant any judgment as to apparent metabolic alteration.

While the relationship between ECS-induced elevation in whole brain serotonin level and ECS-induced retrograde amnesia is not necessarily causal, the observation that attenuation of the amnesic effect of ECS and reversal of the serotonin alteration accompanying ECS, as brought about by nicotine treatment, does lend support to the argument that those conditions that prevent at least one of the neurochemical changes attending cerebral electroshock also minimize its amnesic effect. This observation is further supported by the observation (Essman, 1968c) that agents which interfere with the contact of serotonin with its receptor site, change the serotonin stores in the brain, and that such metabolic alterations presumably can affect the rate at which the memory trace is consolidated and/or interfered with by electroshock.

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