Facilitation of maze acquisition by mice with tricyanoaminopropene (TCAP) given during early postnatal development [1]

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Tricyanoaminopropene, a compound suggested as a stimulus to the synthesis of RNA in the brain, was administered to male neonate mice daily from 3 to 16 days of age. When drug-treated animals were compared with controls, given physiological saline during early development, the former showed significant facilitation in the acquisition of an escape response from a water maze.

The behavioral effects of the malononitrile derivative, tricyanoaminopropene (TCAP) have been demonstrated in several studies (Chamberlain et al, 1963; Essman, 1966), in which single or multiple treatments with this compound have apparently facilitated both learning and memory consolidation. The basis for this behavioral effect has been assumed to be related to the fact that this compound apparently facilitates the synthesis of ribonucleic acid (RNA) in Dieters' nerve cells of the rabbit (Egyhazi & Hyden, 1961) and in regional sites of the mouse brain (Essman, 1965, 1966), and that such increases in brain RNA may directly or indirectly represent a basis upon which the processes of learning and memory may be dependent. Brush et al (1965) have reported negative findings with respect to acquisition of avoidance responses and water maze acquisition in rats treated with TCAP, failing to confirm the previous findings of Chamberlain et al (1963) in rats, and also suggesting that previous facilitative effects of TCAP in adult mice treated with this compound for 80 consecutive days (Essman, 1965 —unpublished data) may have been a function of the duration of such chronic treatment. Aside from possible differences in the duration of TCAP adminstration in mice, another possible factor that may account for differences in the behavioral effects of this compound may be the age at which animals are treated. Since, during early development of the central nervous system, a variety of endogenous biochemical systems become critically involved in conferring the subsequent capacity for the animal to perform, learn, and retain, it seemed apparent that early postnatal development may represent a critical period within which drug-induced acceleration of the synthesis of RNA might well represent an interval within which TCAP treatment could lead to differences in cognitive behavior in the young adult mouse. It was the purpose of this experiment to determine whether postweaning differences in maze acquisition would result from chronic treatment with TCAP during early post partum development in mice.

Method

Eight female CF-1 strain mice, approximately 65 days of age, were bred in the laboratory, and from the resulting litters the male offspring were matched and randomly assigned to either an experimental or control group. Twenty-three mice constituted the experimental group and 21 mice constituted the control group. Beginning at three days post partum, and continuing daily for 13 consecutive days, mice in the experimental group were injected IP with 20 mg/kg of TCAP. The control mice were injected, over the same period, to 16 days of age, with an equivalent volume of 0.9% saline. During the injection period the animals were returned to their respective litters and were weaned at 21 days of age. At 25 days of age all animals were given four training trials in a simple water maze designed to provide for the acquisition of an escape response (Essman & Jarvik, 1961). The maze basically consisted of a tank (22.9 x 30.6 x 12.7 cm) filled with water (20°C) with an escape ramp which was randomly positioned for each animal on either the right or left side. Each trial consisted of dropping the animal into the water-filled tank at a point opposite to and midway between either the right or left side. An area equivalent to the base of the triangle formed by the escape ramp, on the opposite side to that on which the ramp was positioned, was designated as an error zone. On any trial, entry by an animal into this area was counted as an error. The successful entry onto the escape ramp terminated each of the four trials given, and the interval between placement of the animal into the water and entry onto the escape ramp (escape latency) was time for each trial. Trials were given at 15-min intervals, and, following a successful escape response, the animal was toweled dry and kept under a 60-W bulb during the intertrial interval to preclude temperature loss. For each trial response errors and escape latencies were recorded.

Results

The decrement in escape latency over the four training trials was transformed and the difference between these transformed latency decrements was tested and found to be significant ($t = 6.74$, $df = 62$, $p < .001$). The difference between drug- and saline-treated animals in the incidence of errorless performance during the acquisition trials was tested and also found to be highly significant ($X^2 = 94.19$, $p < .001$). The transformed latency decrement and percent incidence of errorless performance for the acquisition trials are shown for

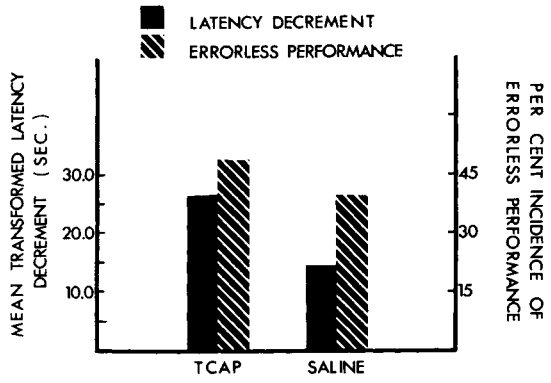

Fig. 1. Mean transformed latency decrement and percent incidence of errorless performance for TCAP- and saline-treated mice during water maze acquisition.

the TCAP- and saline-treated groups of mice in Fig. 1. For the four training trials the experimental group showed from 25% (on Trial 4) to 62.5% (on Trial 2) greater incidence of errorless performance on all trials, and for all trials the experimental group showed approximately 9% less total errors made during acquisition than did the control animals.

Discussion

The data indicate that mice chronically treated for 13 days during early post partum development with tricyanoaminopropene show maze acquisition at 25 days of age which, in all respects, is superior to that shown by control animals treated with physiological saline during the same period. The experimental animals showed a significantly greater decrement over controls in the latency to escape from the maze and also showed a significantly greater incidence of errorless performance. It may be noted that these differences in the acquisition of a simple maze response occurred 12 days following the discontinuation of drug treatment.

Previous studies have indicated that TCAP treatment increased the concentration of RNA in the brain, and it has been suggested that RNA synthesis may be accelerated by this compound. Behavioral studies have indicated that the compound facilitates the retention of avoidance conditioning in rats (Chamberlain et al, 1963) and serves to reduce the amnesic effect of postconditioning electroconvulsive shock (Essman, 1966); this latter study also indicated that TCAP treatment in mice for three days produced significant regional changes in brain RNA concentration, and the antagonism of the ECS-induced retrograde amnesia by TCAP was interpreted as a drug-induced facilitation of memory consolidation. Brush et al (1965) did not find any apparent behavioral effect of 15 mg/kg of TCAP administered IP to adult rats for nine or four days, or rats fed TCAP for 80 days; these authors suggested that the behavioral effects of the compound may be dependent upon the dosage or the duration of chronic administration. Species and task differences also limit the generality of these findings.

In the mouse, the first 16 days of post partum development have been indicated as being critical for the development of a variety of enzymes and substrates which play an important role in determining subsequent behavioral capacity of the animal. Since the synthesis and availability of RNA during this period, in which the brain becomes critically developed, has been linked in several respects to both behavioral as well as biochemical events, the facilitation of maze acquisition behavior, as demonstrated in the present study, may well represent a drug-induced acceleration of those processes upon which cognitive behavior is dependent.

The results of the present study suggest that drug-induced facilitation, in mice, of the acquisition of a simple task may be highly dependent upon the critical age period during which chronic administration of the drug is introduced. The suggestion by Brush et al (1965) that no obvious behavioral differences between TCAP-treated rats and saline-treated controls emerged after either nine or four days of chronic injection, may be quite true for the adult animal for which development of the central nervous system has proceeded beyond those critical periods wherein drug-induced changes in the developmental process may be effected. The present study, however, strongly suggests that the plasticity of the developing nervous system may be such that those biochemical effects resulting from TCAP treatment during early development may become more obvious in facilitating cognitive behavior of the young adult mouse.

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Note

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