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Dopa reversal of hypoxia-induced disruption of the conditioned avoidance response

Catecholamines play a role in mediating certain behaviour under stimulus control. The conditioned avoidance response (CAR) is disrupted by administration of reserpine (Seiden & Carlsson, 1964), which blocks monoamine incorporation into storage granules (see Carlsson, 1966), or α-methyl-*p*-tyrosine (Corrodi & Hanson, 1966) which prevents catecholamine synthesis by inhibiting tyrosine hydroxylase (Nagatsu, Levett & Udenfriend, 1964). The administration of 3,4-dihydroxyphenylalanine (dopa) prevents the disruption of the CAR by these agents (Seiden & Carlsson, 1964; Corrodi & Hanson, 1966). If the metabolism of dopa is prevented by a peripherally acting dose of a decarboxylase inhibitor such as Ro 4-4602 (Bartholini & Pletscher, 1968), the reversal shown by dopa alone is enhanced; however, if a centrally active dose of the inhibitor is used, the administration of dopa is not effective (Seiden & Martin, 1971). These data indicate that the dopa reversal is centrally mediated by a metabolite of dopa—probably noradrenaline, dopamine, or both.

Exposure to hypoxia has been shown to disrupt behaviour in man and experimental animals (Birren, Fisher & others, 1946; Adler, Burkhardt & others, 1950; Vacher & Miller, 1968; Hurwitz, Robinson & Barofsky, 1971). In man, exposure to 14% oxygen has been reported to produce behavioural disturbances (Birren & others, 1946; Adler & others, 1950). At this oxygen concentration there is no apparent alteration in cerebral oxygen consumption, high energy phosphate production or oxidative carbohydrate metabolism (McIlwain, 1966). The synthesis of catecholamines, as well as indoleamines, is dependent on oxygen, however, and mild levels of hypoxia are associated with a decrease in rat brain tyrosine and tryptophan hydroxylase activity *in vivo* (Davis & Carlsson, 1973). Since the conditioned avoidance behaviour is influenced by alterations in catecholamine metabolism, the effect of hypoxia on this behaviour was examined.

Male Sprague-Dawley rats, 250 to 350 g, were tested under low oxygen conditions in a shuttle box. The CAR apparatus consisted of a two compartment chamber and the appropriate response was to move from one compartment to the other. A trial consisted of presentation of a buzzer, the conditioned stimulus, for 10 s followed by the presentation of intermittent shock, the unconditioned stimulus, in the presence of the conditioned stimulus. The 700 V shock was delivered for 0·5 s every 2·5 s through a grid floor over a resistance of 270 kohm. A trial and the stimuli terminated for 60 s when the animal moved to the other compartment. A response was con-

sidered an avoidance if the rat reached the second compartment with all its four feet before the presentation of shock or an escape if the animal reached the second compartment after shock was introduced. If the animal failed to reach the second compartment 20 s after the presentation of unconditioned stimulus, the trial was terminated and recorded as a response failure. Six rats were given one session of 20 trials per day and when they reached a level of at least 90% avoidance for three consecutive days, they were given low oxygen and randomized drug treatments.

Oxygen and nitrogen were mixed after passing through two gas flow meters and the mixture was fed into the chamber at a rate of 4 litres min^{-1}. A rat was placed in the cage and the chamber was equilibrated with the gas mixture for 30 min before the first trial. The oxygen concentration during the session was 8·65%. Ro 4-4602[N^1(DL-seryl)-N^2-(2,3,4-trihydroxybenzyl)hydrazine] (50 mg kg^{-1}, i.p.) was given 1 h before the test session and L-dopa (100 mg kg^{-1}, i.p.) 30 min before the session.

Exposure to 8·65% oxygen reduced median avoidance responding to 25% (Fig. 1). At this oxygen concentration the general appearance of the animals was normal except for rapid respiration. Neither pretreatment with the peripheral decarboxylase inhibitor alone nor L-dopa alone restored responding. However, the combination of 50 mg kg^{-1} of Ro 4-4602 and 100 mg kg^{-1} of L-dopa was effective in counteracting the suppression of avoidance under hypoxic conditions ($P = 0{\cdot}05$ as determined by the Wilcoxon Matched-Pairs Signed Rank Test, Siegel, 1956). That dopa in the absence of the decarboxylase inhibitor did not reverse the effect of low oxygen is consistent with the data of Butcher & Engel (1969) who found that a dose of 100 mg kg^{-1} reduced responding on a Sidman avoidance paradigm although the same dose in the presence of Ro 4-4602 produced an increased rate of responding.

Under conditions of low oxygen with or without Ro 4-4602 alone or dopa alone, rats showed little activity. Between trials they would lie flat on the grid floor and upon presentation of the conditioned stimulus they would raise themselves but would remain stationary or move further back into the same compartment. After pretreatment with Ro 4-4602 and L-dopa the animals became active and showed considerable exploratory behaviour. The low avoidance behaviour shown by one animal (Fig. 1) after treatment with Ro 4-4602 and L-dopa was most likely due to this competing behaviour; when the dose of dopa was reduced to 50 mg kg^{-1}, this avoidance rate reached 80% (data not shown). Other animals performed less efficiently under a lower dose of dopa.

Dopamine-β-hydroxylase, also an oxygen-requiring enzyme, catalyses the conver-

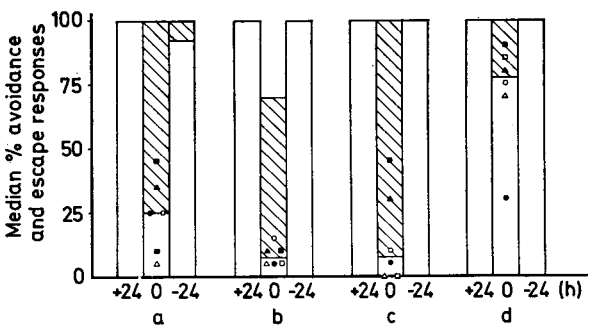

FIG. 1. Median avoidance and escape responses in rats during low oxygen (8·65%) and pretreatment with Ro 4-4602 and/or L-dopa. The figure shows the median avoidance (open columns) and escape (hatched columns) responses of six rats 24 h before, 24 h after, and during hypoxia at time 0. Animals were treated with Ro 4-4602, 50 mg kg^{-1}, 1 h before the first trial and/or with L-dopa, 100 mg kg^{-1}, 30 min before the first trial. Individual avoidance responses during the treatment session are shown by the symbols. Each rat has its own symbol. (a) No drug; (b) Ro 4-4602; (c) L-dopa; (d) Ro 4-4602 + L-dopa.

sion of dopamine to noradrenaline; yet, animals treated with Ro 4-4602 and dopa showed increased avoidance responding under hypoxic conditions. This would indicate (a) that the activity of dopamine β-hydroxylase is not greatly affected by low oxygen *in vivo*, (b) that noradrenaline was released onto receptors by the accumulating dopamine (see Rubenson, 1971; Andén, Engel & Rubenson, 1972), or (c) that noradrenaline is not the only factor in maintaining the CAR. Workers have presented evidence that it is dopamine as well as noradrenaline which is responsible for maintaining the CAR. Inhibition of dopamine β-hydroxylase by disulfiram or FLA-63 (Goldstein, Anagnoste & others, 1964; Svensson & Waldeck, 1969) did not prevent the dopa-reversal of a reserpine-induced suppression of the CAR (Seiden & Peterson, 1968; Ahlenius & Engel, 1971). However, these inhibitors did attenuate the reversal.

The present data show that the performance deficit resulting from hypoxia is alleviated by treatment with a peripheral decarboxylase inhibitor and dopa. This suggests that under conditions of low oxygen, central dopaminergic, and possibly noradrenergic, neurons are able to maintain conditioned avoidance behaviour when transmitter precursor is supplied so that synthesis by-passes the oxygen-requiring rate-limiting step. Moreover, the possible role of catecholamine metabolism for the altered behaviour of hypoxia merits further study.

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