THE COERULO-CORTICAL NOREPINEPHRINE SYSTEM AND LEARNING

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FROM observations that electrical self-stimulation responding is reduced or abolished by drugs which deplete monoamine stores or inhibit catecholamine synthesis, and is enhanced by the amphetamines and cocaine, several workers have suggested that this behaviour results from activation of central noradrenergic mechanisms. However, responding can continue after administration of the dopamine-β-oxidase inhibitor, disulfiram (ROLL, 1970), and self-stimulation can be obtained not only with electrode tips located in relation to the norepinephrine-containing cells of the locus coeruleus (CROW, SPEAR and ARBUTHNOTT, 1972), but also in relation to the dopamine-containing cells in the ventral mesencephalon (CROW, 1972a). A modified version of the original hypothesis is therefore that electrical self-stimulation results from activation of either of two catecholamine-containing systems, the dopamine neurones arising from the A9 and A10 cell body groups, or the noradrenaline neurones arising from the A6 group, the locus coeruleus (CROW, 1972b).

Recent observations on the effects of (+) and (−) amphetamine on self-stimulation response rates (PHILLIPS and FIBIGER, 1973) are consistent with the possibility that both dopaminergic and noradrenergic mechanisms are involved. An association between contraversive turning and self-stimulation through lateral hypothalamic (GRASTYAN *et al.*, 1969) and ventral mesencephalic (ARBUTHNOTT *et al.*, 1970; ANLEZARK *et al.*, 1971) electrodes, can be explained if activation of dopaminergic neurones underlies both stimulation-induced turning (ARBUTHNOTT and CROW, 1971) and some cases of electrical self-stimulation. On the other hand, the involvement of the coerulo-cortical norepinephrine system in self-stimulation with electrodes in the locus coeruleus is consistent with the observation that this behaviour is accompanied by increased norepinephrine turnover in the ipsilateral cortex (ANLEZARK *et al.*, 1973).

The motor behaviours associated with activation of these two catecholamine systems are, however, quite distinct. Marked increases in forward locomotor activity together with elements of the sniffing, licking, and gnawing syndrome accompany self-stimulation with electrodes in the A9 and A10 cell-body areas (CROW, 1972a), but are not seen with electrodes in the region of the locus coeruleus (CROW *et al.*, 1972). The functions of the two reward systems are thus clearly different, and the behavioural concomitants are compatible with a hypothesis (CROW and ARBUTHNOTT, 1972; CROW, 1973) that the dopamine neurones constitute a "motor activating" system which mediates the effects of rewarding environmental stimuli on the organisms immediate behaviour, while the noradrenaline neurones of the locus coeruleus register the success of preceding motor behaviours. According to

this hypothesis the dopamine system facilitates appetitive behaviours by transmitting the "incentive motivational" effects of rewarding stimuli, and the noradrenaline system conveys the "reinforcing" effects of such stimuli (for a historical review of the concept of "reinforcement" see WILCOXON, 1969).

IS CORTICAL NOREPINEPHRINE NECESSARY FOR LEARNING?

Recent experiments (ANLEZARK, CROW and GREENWAY, 1973a,b) have been designed to test whether learning is possible in the absence of the coerulocortical norepinephrine-containing system. Rats with bilateral lesions in the region of the locus coeruleus were compared with a group of rats with bilateral lesions in the cerebellum, a group with bilateral lesions in the brainstem ventral to the locus coeruleus, and a group with burr holes alone. Three weeks after operation all rats were food-deprived to 90 per cent of body weight, and were given five trials on each of sixteen consecutive days in an L-shaped runway. A food reward was available in the short-arm goal box, and the time taken to run the long initial arm was assessed by two photocells. Most rats showed a rapid decrease in running time with increasing runway experience.

After behavioural testing the rats were killed and the brains removed for brainstem histology and cortical norepinephrine assay. In the experimental group the

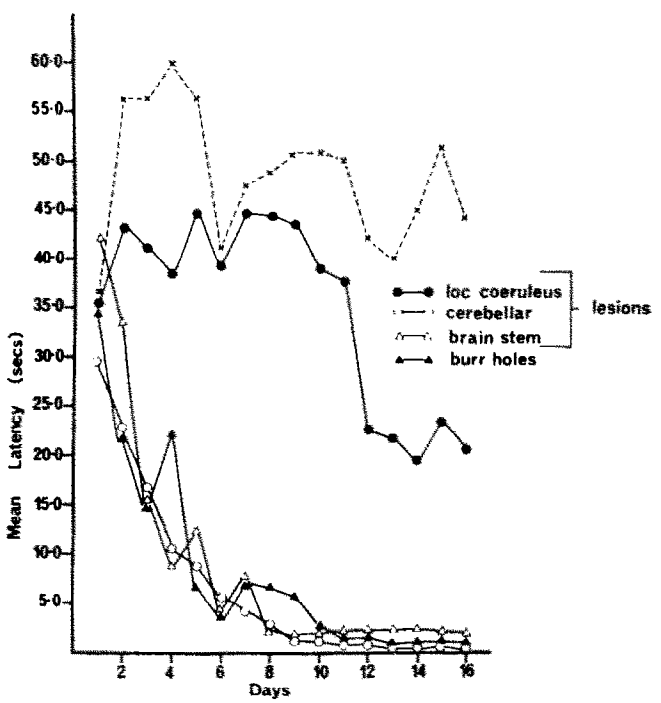

FIG. 1.—Mean running time in the initial arm of an L-shaped runway over the 16-day test period. The dotted line shows the performance of the three rats with apparently complete bilateral ablations of the locus coeruleus as assessed on histological examination. [From ANLEZARK G. M., CROW T. J. and GREENWAY A. P. (1973b) copyright, American Association for the Advancement of Science]

locus coeruleus was only partially ablated on one or both sides in many cases and a group of six rats with the most precise bilateral lesions was selected (from the total group of 28) for comparison with the six rats in each of the three control groups. In these rats cortical norepinephrine was substantially diminished by comparison with controls (mean 102ng/g vs. 325ng/g; $P < 0{\cdot}001$).

Behavioural testing (Fig. 1) showed a rapid decline in running time with increasing experience in each of the three control groups. The rate of decrease was much slower in the six rats with locus coeruleus lesions (analysis of variance; $F = 19{\cdot}629$, d.f. 3/20, $P < 0{\cdot}001$), and in three rats with apparently complete lesions of the locus coeruleus (dotted line) no decrease in running time was observed over the 16-day test period. In other experiments we have found that such rats do not differ from controls in exploratory activity, food intake or weight gain, nor in ability to discriminate sucrose solution from water. The deficit associated with loss of the cortical noradrenergic innervation therefore appears to be an impairment of the capacity to learn. In this respect the effects of ablations of the locus coeruleus may be contrasted with those of even large lesions of the cerebral cortex itself, which have little effect on the animal's ability to learn simple tasks (LASHLEY, 1929).

THE ROLE OF NOREPINEPHRINE IN LEARNING

KETY (1970) and I (CROW, 1968) independently proposed hypotheses concerning the possible role of the cortical adrenergic innervation in learning. The common element in these hypotheses is that the noradrenergic system is envisaged as acting upon particular configurations of recently-active cells to bring about some long-term change in their synaptic interconnexions.

Both hypotheses require the existence within the cortex of a "short-term trace" mechanism with a decay time of perhaps a few seconds. If norepinephrine release occurs within this time the synaptic interconnexions between the cells so identified will be permanently enhanced. Thus neural pathways which have led to "biologically satisfactory" motor outputs will be successively facilitated, and the role of the noradrenergic reinforcement system is to convert short-term trace changes into the structural synaptic alterations postulated to underly long-term memory. This conception of the action of a reinforcement mechanism is closely similar to THORNDIKE'S (1933) theory of "the action of the after-effects of a connection upon it", and to the theory developed by J. Z. YOUNG (1964) in relation to his studies on the octopus, of a neural mechanism for delivering a "results of action signal." Such a concept would account for the striking effects on the organism's learning capacity which we have observed following removal of the coerulo-cortical norepinephrine system.

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