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BRAIN STIMULATION REWARD: EVIDENCE FOR AN ADRENERGIC CONTRIBUTION IN THE RAT

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SUMMARY

Two centrally active inhibitors of phenylethanolamine-*N*-methyltransferase (PNMT: E.C. 2.1.1.28), the terminal enzyme for epinephrine biosynthesis in the brain, and a centrally active blocker of adrenergic synapses produced dose-related decreases in responding for intracranial reward. These decreases occurred at dosage levels which were free from measurable neurologic impairment. The present findings may indicate a possible role for epinephrine-containing neurons in the control of central reward processes.

Considerable evidence supports the involvement of the catecholamines norepinephrine (NE) and dopamine (DA) in brain stimulation reward. For example, there is a high degree of anatomical overlap between self-stimulation sites on the one hand and NE and DA cell bodies and fiber bundles on the other [3,5,8,16,19,20]. In addition, pharmacological manipulations which increase or decrease post-synaptic activation at NE and DA sites produce concomitant increases or decreases in self-stimulation rates [3,10,15,16,19, 20,21]. Finally, self-stimulation has been reported to produce changes in the release and turnover of central catecholamines and their metabolites [18, 19,23].

To date, most psychopharmacological investigations of reward have been primarily concerned with the roles of NE and DA, while less attention has focused upon any unique contributions of a third group of catecholamine-containing neurons (i.e. adrenergic neurons) which have recently been identified histochemically and neurochemically [9,11,12]. There is, however, some evidence that these systems may contribute to intracranial reward. For example, self-stimulation may be obtained from cell bodies which are close to the adrenergic C_2 nucleus [2] and intraventricular administration of exogenous epinephrine increases ongoing rates of self-stimulation [10].

If self-stimulation is adrenergic at least in part then interference with release of epinephrine should decrease responding for brain stimulation reward. The present experiment, therefore, examined the effects of two inhibitors of epinephrine biosynthesis and a blocker of adrenergic receptors upon this behavior.

The biosynthesis inhibitors were the benzylamine 2,3-dichloro-α-methyl benzylamine (Lilly, DCMB) [6,9,12] and the rigid conformation phenylethylamine analogue 5,6-dichloro-2-aminotetralin [7], while the synaptic blocker was yohimbine [9,14]. Drug effects were evaluated upon self-stimulation sessions of 14 or 4 h length, respectively, for the synthesis inhibitors and for the blocker. All drugs were injected at the start of a session at 1 ml/kg in 0.9% sodium chloride vehicle. A variety of dosages were employed (see Fig. 1). Injections were spaced 72 h or more apart, and dosages were based upon previous reports [6,7,9,12].

Fifteen adult male Sprague-Dawley rats weighing 350—500 g served as the subject pool. Subjects were obtained locally (Charles River, Portage, Mich.) and maintained upon ad libitum food (Wayne Lab blox) and water, and day/night cycles of 12 h each (light onset and offset 8 and 20 EST). The self-stimulation task of Wolf et al. [22] was used to assess the behavioral effects of drugs. Apparatus, parameters of stimulation, techniques of implantation and shaping procedures were essentially similar to published reports [22]. In the present experiment, displacement of a 14 × 16 cm overhead mounted steel plate resulted in the delivery of a 0.3 sec train of 60 cps sinusoidal current 50—350 μA in intensity through a unipolar electrode connected to a head-mounted brushing. In addition to the assessment of rate alterations, possible neurological impairment was evaluated upon a 1 m^2 grid located 1.5 m from the floor. Subjects were placed upon the grid in a horizontal position, and it was rotated 90° until perpendicular to the floor. Subjects were considered impaired if they fell from the rotated grid, and intact if they remained stationary or climbed towards its upper edge.

Fig. 1 presents the effect of vehicle (△——△) and drug (○——○) administration upon self stimulation. Five subjects were used for the determination of each data point, and all scores were percentage transformed, with the initial response to vehicle taken as 100%. Statistically significant ($P < 0.05$) differences based on *t*-tests for independent means [4] are indicated by asterisks. It may be seen that vehicle injections produced no consistent changes in baseline performance, while drug injections reduced responding in a dose-related fashion. Neurological impairment was observed only at the highest dosages employed in each of the drug tests. Thus, rate reductions at lower dosages may be a result of factors other than motor dysfunction. With regard to the observed rate decreases, it might also be noted that DCMB has been reported to produce signs of central stimulation [6] and we too have observed exophthalmos, piloerection and possible increases in startle with this drug. These behavioral effects do not suggest that the lowered self-stimulation rates resulted from sedation.

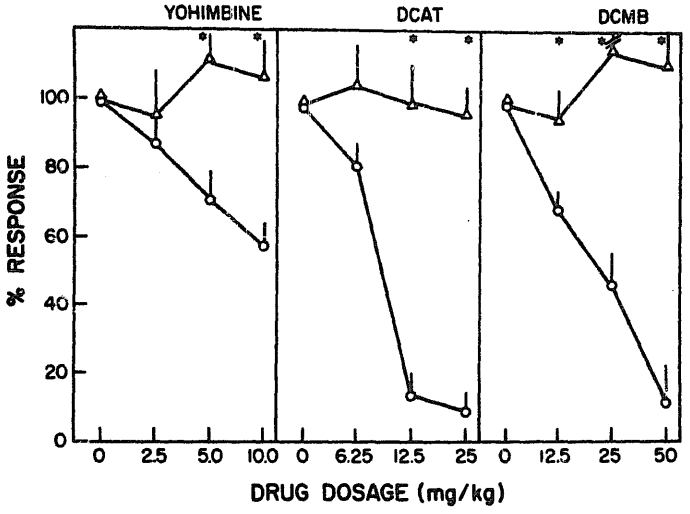

Fig. 1. Effects of adrenergically active agents upon brain stimulation reward; % mean and % S.E.M.; *$P < 0.05$.

At the close of the experiment all subjects were sacrificed with an overdose of pentobarbital and perfused initially with saline and subsequently with formal-acetic acid solution [13]. Brains were blocked, sectioned at 30 μm intervals and stained with cresyl violet for histologic examination. All sites were located in the caudal aspect of the medial forebrain bundle dorsal to the substantia nigra.

The results suggest that functional disruptions of central adrenergic systems may produce decreased responding for reward. The major evidence for this comes from the effects of two novel biosynthesis inhibitors which both produced significant rate decreases in the self-stimulation task. The effect of yohimbine, a centrally active inhibitor of epinephrine-sensitive adenylate cyclase [9], is also consistent with a role for adrenergic mechanisms in reward. The effect of yohimbine was not as powerful as synthesis inhibition in decreasing self-stimulation rates, but this drug also has other actions, such as blockade of receptors for serotonin and α-noradrenergic receptors [14].

The most sensitive site in the brain stem for self-stimulation is the locus coeruleus [5]. The rostral noradrenergic projections from this region are distributed widely to hypothalamus, limbic system and cerebral cortex, and have been implicated in a large number of critical behaviors other than self-stimulation. Our results, in conjunction with the anatomic evidence for C_2 adrenergic projections to the locus coeruleus [9,11], suggest that these adrenergic sites modulate the activity of the ascending noradrenergic system. In support of this view are the findings that self-stimulation [2], eating, grooming, arousal and aggression responses [1] can sometimes be elicited from sites which coincide with C_1 and C_2 cell bodies or fibers. Further studies are necessary to determine whether these behaviors elicited by C_1-C_2 stimulation are mediated through short projections to the locus coeruleus or through long ascending projections to the hypothalamus [9,11].

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REFERENCES

1 Berntson, G.G. and Hughes, H.E., Medullary mechanisms for eating and grooming in the cat, Exp. Neurol., 44 (1974) 255—265.
2 Carter, D.A. and Phillips, A.G., Intracranial self-stimulation at sites in the dorsal medulla oblongata, Brain Res., 94 (1975) 155—160.
3 Crow, T.J., Catecholamine-containing neurones and electrical self-stimulation, 1. A review of some data, Psychol. Med., 2 (1972) 414—421.
4 Dixon, W.J. and Massey, F.J., Introduction to Statistical Analysis (3rd ed.), McGraw-Hill, New York, 1969.
5 Ellman, S.E., Ackerman, R.F., Farber, J., Mattiace, L. and Steiner, S.S., Relationship between dorsal brainstem sleep sites and intracranial self stimulation, Physiol. Psychol., 2(1) (1974) 31—34.
6 Fuller, R., Roush, B.W., Snoddy, H.D. and Molloy, B.B., Inhibition of phenylethanolamine-*N*-methyltransferase by benzylamines 2: In vitro and in vivo studies with 2,3-dichloro-α-methyl benzylamine, J. med. Chem., 16 (1973) 106—109.
7 Fuller, R.W. and Molloy, B.B., In vitro inhibition of norepinephrine-*N*-methyltransferase by 2-aminotetralins — analogs of phenylethylamines with rigid conformation, Biochem. Pharmacol., 26 (1977) 446—447.
8 German, D.C. and Bowden, D.M., Catecholamine systems as the neural substrate for intracranial self-stimulation, Brain Res., 73 (1974) 381—419.
9 Goldstein, M., Lew, J.Y., Matsumoto, Y., Hökfelt, T. and Fuxe, K., The localization and function of PNMT in the central nervous sytesm. In M. Lipton, A. DiMascio and K. Killam (Eds.), Psychopharmacology: A Generation of Progress, Raven Press, New York, 1977, in press.
10 Hasegawa, K., Changes in the self-stimulation behavior by intraventricular injection of epinephrine, norepinephrine, isoproterenol and dopamine, Jap. J. Pharmacol., 25 (1975) 616—619.
11 Hökfelt, T., Fuxe, K., Goldstein, M. and Johansson, O., Immunohistochemical evidence for the existence of adrenaline neurons in the rat brain, Brain Res., 66 (1974) 235—251.
12 Lew, J.Y., Miyamoto, T. and Goldstein, M., Inhibition of PNMT activity in the adrenal glands and brain stem of the rat, Biochem. Pharmacol., 25 (1976) 1433—1434.
13 Luna, L.G., Manual of Histological Staining Methods of the Armed Forces Institute of Pathology, McGraw-Hill, New York, 1960.
14 Nickerson, M. and Collier, B., Drugs inhibiting adrenergic nerves and structures innervated by them. In L. Goodman and A. Gilman (Eds.), Pharmacological Basis of Therapeutics, MacMillian, New York, 1975, pp. 533—565.
15 Poschel, B.P.H. and Ninteman, F.W., Norepinephrine: a possible excitatory neurohormone of the reward system, Life Sci., 2 (1963) 782—788.
16 Rolls, E.T., The Brain and Reward, Pergamon, Oxford, 1975, pp. 73—89.
17 Saavedra, J.M., Palkovits, M., Brownstein, M.J. and Axelrod, J., Localization of phenylethanolamine-*N*-methyltransferase in the rat brain nuclei, Nature (Lond.), 248 (1974) 695.

18 St.-Laurent, J., Roizen, M.F., Milliaressis, T.E. and Jacobowitz, D.M., The effects of self stimulation on the catecholamine concentrations of discrete areas of the rat brain, Brain Res., 99 (1975) 194—200.
19 Stein, L., Chemistry of reward and punishment. In D.H. Efron (Ed.), Psychopharmacology: A Review of Progress, 1957—1967, U.S. Government Printing Office, Washington, D.C., 1968, pp. 105—123.
20 Stein, L., Norepinephrine reward pathways: role in self stimulation, memory consolidation and schizophrenia. In J.K. Cole and T.B. Sonderegger (Eds.), Nebraska Symposium on Motivation, University of Nebraska Press, Lincoln, Neb., 1975, pp. 113—161.
21 Wise, C.D. and Stein, L., Facilitation of brain self-stimulation by central administration of norepinephrine, Science, 163 (1969) 299—301.
22 Wolf, G., DiCara, L. and Simpson, W., The contact method: a simple technique for electrical self stimulation without external leads, Physiol. Behav., 11 (1973) 721—764.
23 Yuwiler, A. and Olds, M.E., Catecholamines and self stimulation behavior, effects on brain levels after stimulation and pretreatment with DL-α-methylparatyrosine, Brain Res., 50 (1973) 331—340.