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POTENTIATION OF L-DOPA INDUCED MOTOR ACTIVITY BY AN INHIBITOR OF PHENYLETHANOLAMINE-N-METHYLTRANSFERASE

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Abstract

1. Pharmacological inhibition of phenylethanolamine-N-methyltransferase (PNMT), the synthesizing enzyme for adrenaline, resulted in enhanced behavioral activation by 3,4,-dihydroxyphenylalanine (L-DOPA) in mice.
2. This suggests that an adrenergic system normally inhibits drug induced activation and
3. Points to an interaction between adrenaline and other catecholamines.

Keywords: adrenaline, DOPA, dopamine, epinephrine, PNMT, psychomotor, SKF 64139.

Abbreviations: adrenaline (A), catecholamines (CA), dopamine (DA), 3-4 dihydroxyphenylalanine (L-DOPA), noradrenaline (NA), phenylethanolamine-N-methyltransferase (PNMT).

Introduction

Catecholamines (CA) are known to be critically involved in motor activity. Both noradrenaline (NA) and dopamine (DA) appear to normally facilitate movement (Anden et al., 1973; Bartholini et al., 1969; Carlsson et al., 1957; Corrodi et al., 1970; Glick et al., 1975; Hornykiewicz, 1966; Stromberg, 1970; Stromberg and Svensson, 1971; Ungerstedt, 1974; Uretsky and Schoenfeld, 1971). L-DOPA, the immediate precursor to both DA and NA, enhances motor activation (Corrodi et al., 1970; Hornykiewicz., 1966; Stromberg, 1970; Uretsky and Schoenfeld, 1971) and both CA are involved in this effect, although an intact DA system is needed for all behavioral expression, including that of NA systems (Corrodi et al., 1970; Stromberg and Svensson, 1971).

While both NA and DA have been extensively investigated as mediators of the L-DOPA activation syndrome, only scant attention has been paid to adrenaline (A), a third CA neurotransmitter localized in medullary cell bodies (Goldstein et al., 1974; Hokfelt et al., 1974; Khalsa et al., 1977; Lew et al., 1977; Saavedra et al., 1974) which innervates both NA and DA rich areas of the nervous system (Lew et al., 1977; Pendleton et al., 1977; Saavedra et al., 1974). In a previous publication, we presented evidence that A neurons may both suppress and enhance activity, depending upon its behavioral and pharmacological characteristics. Normal exploration was reduced by an inhibitor of PNMT, while drug (amphetamine, morphine) induced activity conversely was facilitated (Katz et al., 1978).

In order to further characterize the behavioral effects of PNMT inhibitors, and to investigate the possible role of A in motor activation, we tested mice with varying amounts of L-DOPA pretreatment and PNMT inhibitor. Our findings suggest that A normally is inhibitory for L-DOPA activation, since PNMT inhibitors increase motor activity after precursor loading.

Methods

Subjects: Adult male outbred Swiss-Webster mice (25-35 g each; N=15) were obtained locally (Charles River, Portage, MI) and maintained upon ad libitum food (Teklad 4.0% fat diet #S-0836) and tap water. Subjects were individually housed throughout the experiment, and lighting cycles of 12 h light/12 h darkness were automatically programmed.

Drugs: The PNMT inhibitor, SKF 64139 (7,8,dichloro-1,2,3,4 tetrahydroisoquinoline HCl) (Khalsa et al., 1977; Pendleton et al., 1977) was administered in doses of 0, 10, and 40 mg/kg one hour prior to the injection of L-DOPA methyl ester HCl (Calbiochem #308055) 0, 300, or 600 mg/kg. All drugs were injected intraperitoneally 1 ml/kg in a 0.9% sodium chloride vehicle.

Apparatus: Motor activity was measured on electromagnetic field sensitive monitors (Stoelting, Chicago, SA 1566, 1562, 1570). Four monitoring platforms were used simultaneously and were calibrated to within 5% sensitivity of each other on a selective mode for the registration of gross body movement. The assignment of platforms to treatment groups was rotated systematically throughout the series of tests. Mice were tested individually in standard polypropylene containers (36 x 33 x 17 cm; Scientific Products, Series 50). Fresh pine chip bedding was added to cover the floor of each container.

Behavioral Procedure: All subjects were initially habituated to the experimental setting in four sessions each four hours in length. On the test day, subjects were placed in the apparatus and allowed a final 4 hour session in which to habituate. At hour five of the session the subjects were removed and injected with drug or vehicle, and returned to their cages for an additional hour of recording. At hour six, subjects were again removed for injection and were returned for a final 2 hour period in which drug effects and drug interactions were assessed. Subjects were used on more than one occasion, however, at least 4 days separated each test. Recovery from both drugs is considerably shorter than this period (Katz et al., 1978). All drug combinations were administered in a counterbalanced order across sessions.

Results

L-DOPA at both 300 and 600 mg/kg produced behavioral activation which was greater than control. The response to L-DOPA was dose related, and consisted largely of ambulation and sniffing. Subjects pretreated with the PNMT inhibitor prior to L-DOPA showed no consistent behavioral change over the next hour, but were facilitated in their DOPA responses (Fig 1 and Fig 2).

Visual observations of these animals indicated that initial injection of SKF 64139 induced considerable oral stereotypy, particularly at the highest dose. All animals showed chewing of the wood chips on their cage floor. No saline animals showed this chewing behavior. After L-DOPA, the 64139 subjects showed an explosive "jumping" behavior in which animals would remain by the cage walls and repeatedly jump towards the cage top. This movement was registered on the sensors. Friedman analysis of variance, on the final experimental period for both experiments, indicated the drug induced alterations were significant ($X^2r = 30$, $X^2r = 15.2$ for Figs 1 and 2 respectively df = 31, $p \leq 0.01$).

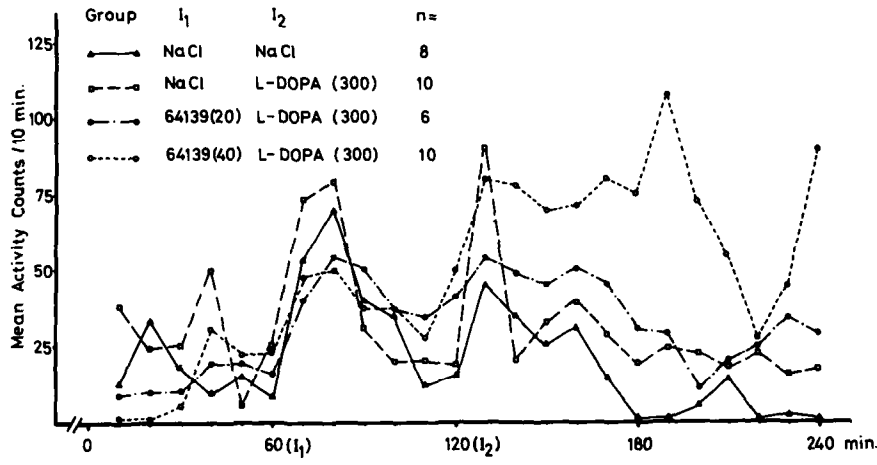

Fig. 1. Effects of SKF 64139 upon L-DOPA activation in mice (300 mg/kg). Minutes 0-60 are habituation; minutes 60-120 pretreatment with the PNMT inhibitor; minutes 120-240 the DOPA activation period.

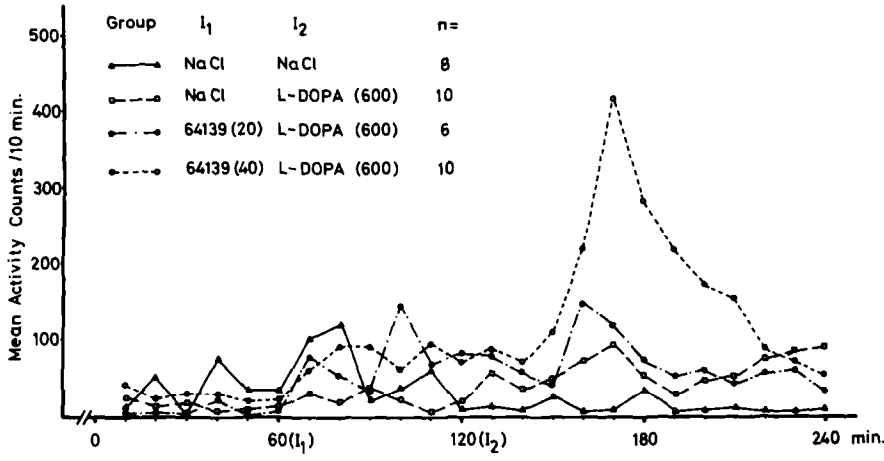

Fig. 2. Effects of SKF 64139 upon L-DOPA activation in mice (600 mg/kg). Minutes 0-60 are habituation; minutes 60-120 are pretreatment with the PNMT inhibitor; minutes 120-240 the DOPA activation period. Note change in ordinate in comparison with previous Figure.

Discussion

Initial injections of PNMT inhibitor produced no systematic changes in motor activity. In previous reports we have typically found motor inhibition after such treatment (Katz et al., 1978). These past reports utilized either individual rats or grouped mice, while the current report used individually housed mice. The present design additionally incorporated extensive habituation of subjects. It should be noted that we continue to obtain significant and dramatic reductions in motor activity both in rats and in grouped mice after all PNMT inhibitors, including SKF 64139 (Katz, unpublished observations). The present results suggest species and social differences may play some role in the observed differences.

While SKF 64139 itself had few effects upon gross movement, it did potentiate L-DOPA induced activation. Our results with L-DOPA are consistent with our previous report in which amphetamine and morphine were used to induce motor activation. All experiments suggest that CA-induced motor activity is inhibited by adrenergic neurons. Some reports have suggested that DOPA activation is largely DA mediated (Hornykiewicz, 1966) and only secondarily NA mediated (Stromberg, 1970; Stromberg and Svensson, 1971). Granted this, it follows the present results are interpretable as indicating an A-DA interaction. Since moderate amounts of PNMT are localized in DA containing brain nuclei and terminal areas (Goldstein et al., 1974; Hokfelt et al., 1974; Lew et al., 1977), this interpretation is consistent with the established histochemistry of these systems. Further supporting evidence for a tonic adrenergic inhibition of DA mediated behavior comes from the consistent oral stereotypy seen after SKF 64139 pretreatment (Katz et al., 1978; present findings). Other DA stimulants also induce oral stereotypy.

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