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EFFECT OF CENTRALLY-ACTING DRUGS ON MOBILIZATION OF FREE FATTY ACIDS (1)

BY

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Measurement of plasma free fatty acid (FFA) levels is an excellent means for studying the dynamics of lipid metabolism. Energy demands, nutritional status, hormonal and neurogenic influences are of prime importance in mobilizing lipids from depot fat (1). Neurogenic control is mediated through autonomic innervation of adipose tissue as well as indirectly through the neurohormones, epinephrine and norepinephrine (2). Central nervous system arousal from psychologically stressful stimuli causes marked and rapid mobilization of FFA, making this measurement a highly sensitive indicator of emotional stress. Very little is known concerning the effect on FFA of nervous system alterations from centrally-acting drugs. The present study observed the effects on FFA mobilization in man of selected types of antipsychotic, antidepressant and psychotomimetic drugs.

Methods

All subjects were men varying in age from 21 to 45 years. Their general health and nutrition was good; none was under treatment for any known illness. Each subject had been fasting for 12 to 14 hours prior to the drug trial. For at least one hour before the study and during the entire four-hour period of the study the subjects remained at rest.

Drugs were administered as follows : 1) benzquinamide, 300 mg intramuscularly (IM); 2) reserpine, 2.5 mg IM; 3) chlorpromazine 50 mg IM; 4) thioridazine, 50 mg IM; 5) imipramine, 50 mg IM; 6) des-

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methylimipramine 50 mg IM; 7) lysergic acid diethylamide (LSD-25) 1.5 mcg/K orally; 8) mescaline, 5 mg/K orally; 9) psilocybin, 225 mcg/K orally; 10) a combination of the last three drugs in one-third doses of each.

Plasma levels of FFA were determined by a slight modification of the Dole procedure (3). Blood was withdrawn just prior to administration of the drug and again one-half, one, two and four hours after. Clinical effects of the drugs were assessed by behavioral observations.

Results

Mean levels of plasma FFA at the various time periods following each drug are shown in Table I. Variations in the mean pre-treatment levels of FFA between drugs are due to different groups of subjects being used. For instance, the same subjects were used for tests with imipramine and desmethylimipramine, the mean pre-treatment levels of FFA being comparable. These subjects were different from those used in the trials of LSD-25, psilocybin, mescaline and the combination of these three drugs, the pre-treatment levels of FFA being different from the other group but comparable within the group. The same was true for reserpine and benzquinamide, and for chlorpromazine and thioridazine. Because of differences in base-line levels of FFA, the percent change from baseline was deemed a better index of drug effects than changes in actual values.

Table I

Mean Plasma FFA Levels (micromoles/L) *Prior to and Four Hours After Drugs*

Drug	N	Time Period					Percent Change
		0	½	1	2	4	
Imipramine	12	549	538	501	511	503	−9
Desmethylimipramine	11	564	537	520	677	793	+41
Chlorpromazine	12	392	432	523	598	592	+51
Thioridazine	12	402	414	434	494	575	+43
Reserpine	8	392	415	535	567	696	+78
Benzquinamide	11	389	724	803	904	919	+136
LSD-25	24	472	532	543	668	818	+73
Mescaline	25	493	606	718	740	1063	+115
Psilocybin	25	497	603	830	758	921	+85
Combined Psychotomimetics	25	463	585	700	718	840	+81

Mean levels of FFA were maximal at four hours for most drugs. Change from base-line for the antidepressants, imipramine and desmethylimipramine, was −9 and 41 percent respectively. Both drugs had sedative effects in normal subjects, that from imipramine being greater. Both phenothiazine antipsychotics, chlorpromazine and thioridazine, increased FFA levels by 51 and 43 percent respectively, each associated with marked clinical sedation. Two other types of antipsychotic drugs, reserpine and benzquinamide, increased FFA by 78 and 136 percent respectively. Both these drugs evoked clinical signs of excitement, which in the case of reserpine was not maximal until well after the four-hour test period. All three psychotomimetics, LSD-25, mescaline and psilocybin, as well as the combination of the three, increased FFA levels by 73, 115, 85 and 81 percent respectively. Excitement was characteristic of the clinical states produced by these drugs.

Especially in the case of the psychotomimetic drugs, an exhaustive attempt was made to correlate degree of FFA increase with clinical evidences of stress as measured by questionnaire data or self-report mood scales. Such correlations proved unfruitful, suggesting that nervous system stimulation shown physiologically may not necessarily be perceived psychologically in the same degree.

Discussion

Based on plasma FFA levels, phenothiazine antipsychotics and he dibenzazepine antidepressants appear alike. Both classes of drugs produce clinical sedation in normal subjects, that from the former being considerably greater. Free fatty acids continue to be mobilized, or their utilization is decreased, during sedation; at least their levels rise. An earlier study of the effects of 50 mg doses of chlorpromazine IM in 26 subjects also showed increased circulating FFA (4). Although adrenergic blockade effectively impairs FFA mobilization produced by epinephrine or norepinephrine, neither a moderate adrenergic blocker such as chlorpromazine, nor a strong one, such as phentolamine, decrease FFA mobilization when given alone. On the contrary, especially in the case of phentolamine, a fairly strong mobilizing effect occurs (5).

Other classes of antipsychotic drugs, as exemplified by reserpine and benzquinamide, increase FFA levels somewhat more than the phenothiazines, especially benzquinamide. Both drugs are attended by excitation soon after initial doses. In the case of reserpine, at least, catecholamines are released, providing a mechanism for the increased FFA

levels. Similar results with psychotomimetic drugs, which also cause excitation, suggests that FFA mobilization might be used to screen for drugs with directly stimulating effects.

Conclusions and Summary

Changes in plasma FFA levels following acute doses of a series of central nervous system drugs were used to group these agents. Each drug class used, antidepressants, antipsychotics, and psychotomimetics, increased FFA levels to some degree. Elevations were least with drugs having sedative effects, which included both the phenothiazine tranquilizers, chlorpromazine and thioridazine, as well as the dibenzazepine antidepressants, imipramine and desmethylimipramine. Increases were greater with excitant drugs, such as the antipsychotics, reserpine and benzquinamide, or the psychotomimetics, LSD-25, mescaline and psilocybin.

Effects of centrally-acting drugs on plasma FFA levels do not provide clues to their clinical therapeutic effects, though the degree of elevation of FFA levels seems related to stimulant as opposed to sedative properties.

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