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BRIEF COMMUNICATION

Similarity Between (+)-Amphetamine and Amfonelic Acid[1]

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ACETO, M. D., J. A. ROSECRANS, R. YOUNG AND R. A. GLENNON. *Similarity between (+)-amphetamine and amfonelic acid.* PHARMACOL BIOCHEM BEHAV 20(4)635–637, 1984.—Rats, trained to discriminate the CNS stimulant (+)-amphetamine (1.0 mg/kg) from saline in a two-lever drug administration task, were challenged with various doses of the structurally dissimilar CNS stimulant amfonelic acid. Amfonelic acid was found to substitute for the amphetamine stimulus and was found to be 1.5 times more potent than amphetamine.

(+)-Amphetamine Amfonelic acid Drug discrimination

AMFONELIC acid (7-Benzyl-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, AFA) has been shown to be a potent locomotor stimulant in a wide variety of animals [2]. Interest in the drug was heightened originally by the observation that the drug was not another disguised or masked phenethylamine, because none of the nitrogen atoms in the molecule were basic. Although AFA and (+)-amphetamine (AMPH) produced similar behavioral effects [4,11], their biochemical actions are quite different. Studies with α-methyltyrosine and reserpine indicated that the drugs did not act in the same manner, but their mechanisms involved catecholamines [1]. Other workers [12,14] showed that although AFA and AMPH released dopamine, they promoted mobilization of dopamine from different pools; AFA preferentially releases the older stored catecholamine while AMPH is dependent on the newly synthesized transmitter. Further, AFA enhances impulse-induced dopamine release and decreases dopamine neuronal impulse flow [14]. Another intriguing difference between the two stimulants has also been reported [1]. AFA does not produce aggregate group toxicity in mice, which has been shown for AMPH by many investigators [1, 5, 9]. In man, AFA and AMPH have been found to produce CNS stimulation, hallucinations, paranoid ideation and exacerbation of schizophrenic symptoms [14,15]. Clearly, additional studies with this interesting pharmacological tool are indicated.

This study focuses on the behavioral effects produced by AMPH and AFA in a drug discrimination task, which is a sensitive and specific paradigm for the study of CNS active agents [6,8]. In a previous investigation, Schechter [13] reported that AFA did not substitute for an apomorphine stimulus. In the present study, with rats trained to discriminate 1.0 mg/kg of AMPH sulfate from saline, we examine the ability of the AMPH stimulus to generalize (substitute, transfer) to AFA.

METHOD

Fourteen male Sprague-Dawley rats were trained to discriminate AMPH sulfate (1.0 mg/kg, IP) from saline (1.0 ml/kg) using standard (Coulbourn Instruments) two-lever operant chambers. The discrimination training procedure for these animals has been previously reported [8]. Briefly, the administration of saline or AMPH, 15 minutes prior to a variable internal 15-second (VI-15 sec) schedule of reinforcement served as the discriminative cue for the correct (reinforced) lever. Occasional periods (2.5 min) of non-reinforced lever responding were used to assess the degree

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TABLE 1
RESULTS OF GENERALIZATION STUDIES USING AMPH-TRAINED RATS

Agent	Dose (mg/kg)	N*	% AMPH Lever Responding† (±S.E.M.)	Mean† Res/Min (±S.E.M.)	ED_{50}‡ (mg/kg)
AMPH§	1.00	14/14	94% (3.1)	14.9 (1.4)	0.42 (0.29–0.62)
AFA	0.10	4/4	18% (8.6)	15.1 (1.2)	
	0.25	4/4	41% (17.0)	14.3 (2.3)	
	0.75	4/4	76% (12.6)	14.7 (2.8)	
	1.00	4/4	97% (2.3)	14.0 (1.8)	0.27 (0.07–1.02)
Saline 1 ml/kg		14/14	4% (1.2)	14.8 (1.7)	
Saline/Vehicle¶		14/14	3% (1.4)	15.1 (1.6)	

*Number of animals responding/number of animals receiving drug.
†Data obtained during 2.5 min extinction session.
‡Followed by 95% confidence limits.
§Data previously reported [8]; included for comparative purposes.
¶Saline plus one drop of Twen 80 per 10 ml was added.

of stimulus control exerted by saline and AMPH over behavior, and to evaluate the ability of AFA to substitute for the AMPH cue. Data collected during the 2.5 min extinction sessions included total responses (expressed as mean responses per minute) and percent drug appropriate responding (i.e., responses on the drug designated lever/total number of responses on both levers times 100). An ED_{50} value for AFA was determined by the method of Finney [7] and represents the calculated dose of AFA at which the animals would be expected to make 50% of their responses on the drug-appropriate lever.

RESULTS AND DISCUSSION

In the AMPH-trained rats, administration of AFA resulted in stimulus generalization (Table 1). A comparison of ED_{50} values reveals AFA to be approximately 1.5 times more potent than AMPH. Response rates under drug or non-drug conditions were similar.

Previous reports have indicated that AFA produces increases in locomotor activity, avoidance responses, and induces stereotyped behavior that are similar to that produced by AMPH [3, 4, 10]. That AMPH and AFA produce a similar behavioral effect in the discrimination paradigm is consistent with those investigations. Although AMPH and AFA share a common stimulus effect, it is unclear whether the effect is produced by the same mechanism of action. Based on the data derived from biochemical and other behavioral studies (e.g., [1, 12, 14]), it seems likely that the stimulus effects may be mediated by different catecholamine mechanisms. However, additional investigations involving AFA as training drug and detailed drug discrimination studies involving dopamine antagonists in combination with AFA and/or AMPH are needed to elucidate these differences.

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