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BRIEF COMMUNICATION

Antagonism of Behavioral Effects of Cocaine by Lithium

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FLEMENBAUM, A. *Antagonism of behavioral effects of cocaine by lithium.* PHARMAC. BIOCHEM. BEHAV. 7(1) 83–85, 1977. – Ten rats, serving as their own controls, were tested for hyperactivity (HyA) (by number of turns of an activity wheel cage) and stereotyped behavior (SB). The animals were given one week each of acclimation to the cages, saline, cocaine (19 mg/kg in 1 cc/kg saline), rest, two weeks on LiCl, and a week on LiCl plus the same dose of cocaine. LiCl produced a nonsignificant decrease of HyA and significantly decreased cocaine SB. The same procedure was duplicated using two different doses of cocaine in five animals each with identical results. The author concludes that Li seems to inhibit cocaine effects in animals and suggests a potential area of research for the use of Li in humans.

Lithium Cocaine Hyperactivity Stereotyped behavior

THE AUTHOR recently reported the Lithium (Li) inhibition of amphetamine hyperactivity (HyA) and stereotyped behavior (SB) in rats after having observed that Li blocked the amphetamine highs in three clinical cases [3]. Since this observation, we have duplicated these findings of Li-amphetamine in at least 20 more animals ([5], accepted for publication). Because cocaine has such a remarkable pharmacological similarity to amphetamine [8,9], it was considered important to obtain the same kind of data in animals utilizing cocaine.

MATERIALS AND METHOD

Male Sprague-Dawley rats of an initial weight of 200 g were tested. The animals were housed in pairs with food and water provided ad lib in a normal daylight photoperiod.

Every day at the same time, 8:00 a.m., the animals were taken from their housing and placed for two hours in the activity wheel cages. During the next six weeks, the animals were given the following schedule: one week of saline, one week of cocaine IP, one week of rest, two weeks of LiCl subcutaneously (SC), and one week of LiCl plus cocaine. All drugs were given dissolved in saline at 1 cc/kg. The drugs were given IP about five to ten minutes before the animals were put into an activity wheel cage. LiCl was given SC at a total dose of 3.0 meq/kg/day divided into two doses at 10 and 17 hr. The same schedule was followed throughout the study. In this way the animals could be utilized as their own controls since baseline of activity and SB differ from one animal to another. Initially, the study was done with ten animals at one dose of 19 mg/kg; then the process was duplicated utilizing two different doses for five animals each.

Activity was measured in a crude way utilizing the number of turns of the (activity) wheel for the two hr of elapsed time. SB was measured utilizing two standardized scales [2,6] given to the animals after a ten to fifteen sec evaluation every fifteen minutes for three times and then every twenty min. The numbers obtained for each one of the two scales were added across the six measures obtained in the two hr and averaged for each one of the animal groups.

RESULTS

The results are given utilizing *t*-test with weighted means. Table 1 gives the average values of number of wheel turns in the two hour period for each week and each one of the conditions. It also provides the SB given as the sum of both measurements obtained in each one of the two scales six times in the two hr period.

The table shows a slight decrease of activity by lithium alone which is not significant for the group as a whole and a decrease of cocaine HyA which also is not significant. On the other hand, the reduction of SB produced by lithium is always significant.

DISCUSSION

There are several anecdotal reports that suggest lithium alone decreases animal activity. However, the evidence is good that this decrease is not significant for activity wheel turns, jiggled cages, etc., and only significant for increased time to reach the wall in open field situations [10]. Besides, in our own lab more than 100 rats had shown no consistent decrease of activity as measured by activity

TABLE 1

COCAINE.

Condition/Number		ACTIVITY $\bar{X}$ Turns (SD)	T-Test Significance*	SB
10 mg/kg (5 animals)				
Saline	1	260.2 (149)	–	0
Cocaine	2	319.5 (167)	NS	6.44 (1.2)
Rest	3	240.1 (105)	NS	1.1 (0.2)
Li	4	113.3 (50)	S = 0.05	0
Li + Cocaine	5	270.9 (110)	NS	6.1 (0.9)
			(S = 0.07)†	(NS)‡
19 mg/kg (10 animals)				
Saline	1	204.7 (92.2)	—	0
Cocaine	2	537.6 (215.2)	S = 0.0025	16.16 (0.9)
Rest	3	307.1 (53.8)	NS	4.1 (0.9)
Li	4	143.3 (61)	NS	0
Li+Cocaine	5	400.3 (171.7)	S = 0.05	6.9 (1.2)
			(NS)†	(S = 0.000)‡
24 mg/kg (5 animals)				
Saline	1	260.4 (137.1)	—	0
Cocaine	2	444 (121.6)	S = 0.002	18.16 (0.6)
Rest	3	348.5 (56.4)	S = 0.05	4.6 (0.6)
Li	4	185.1 (21.2)	NS	0
Li + Cocaine	5	366.1 (110.5)	NS	8.7 (1.8)
			(NS)†	(0.001)‡

SB = Stereotyped Behavior.

* All *t*-test (one tail) compare wheel turn averages of each condition to Saline except when otherwise noted († or ‡).

†Level of significance for the differences in wheel turn averages between Li + active drug vs active drug alone.

‡Same as † but comparing SB averages.

wheels or photoelectric cell activity cages, and on occasion there has been an increase of activity. Thus, an additive effect by lithium alone cannot be utilized as an explanation for the results.

These results comprise a partial report of a larger study evaluating Li activity at the dopamine and norepinephrine receptor levels [5], but that is beyond the scope of this paper. As mentioned previously, the pharmacological mechanisms of action of cocaine are remarkably similar in many respects to those of amphetamine. Earlier, the author had reviewed evidence indicating that in many respects the pharmacology of Li is the opposite to that of amphetamine [3]. Thus, it is not surprising to find that Li also decreases the HyA and SB produced by cocaine. However, a reduction rather than a blocking of effects was observed.

Also, it is important to notice that other drugs block the effects of amphetamine (and probably cocaine), the most conspicuous of which agents are phenothiazines. This type of drug (phenothiazines) has been utilized in the clinic and emergency rooms to obtain clinical control of amphetamine (and cocaine) psychosis.

Although animal models do not always predict response in humans, the literature has been consistent in equating SB with an animal model of psychosis [11]. Although drug induced psychosis and drug induced highs are not pharmacologically identical, a dramatic behavioral effect of amphetamine (and cocaine) is the ability to greatly facilitate hypothalamic self-stimulation. There appear to be at least two distinct self-(pleasure)-stimulation systems in the brain, one in which the map for hypothalamic self-stimulation correlates clearly with norepinephrine fiber distribution. For this one it has been elegantly demonstrated [12] that norepinephrine release in the medial forebrain bundle, the hypothalamus, and the limbic system is responsible in part for the positive reinforcement of behavior. The second system is another area in the substantia nigra rich in dopamine cells [1,11]. Thus, amphetamine (and cocaine) psychosis and highs are both phenomena related to norepinephrine dopamine stimulation. Drug abusers on the street obtain the same kind of euphoria and high feelings with cocaine as with amphetamines. Thus, if Li does decrease cocaine induced SB in animals, in spite of the fact that animal models are not necessarily representative of human behavior and results, we can speculate that at the human level Li may also decrease cocaine highs, especially since cocaine highs, similar to amphetamine highs, are a prelude to cocaine psychosis [8,9].

The clinical implications of such a possibility are important because of a large body of evidence which indicates that a significant majority of young amphetamine abusers are vulnerable at priori. As much as seventy-five percent were depressed prior to drug abuse [7]. Also, the author has speculated that chemical dependence, in a significant number of patients, is secondary to a masked affective disorder that may be responsive to Li therapy [4]. The author now speculates that in such cases, the prophy-

lactic administration of Li would work in two ways(1) by improving the masked affective disorder, and (2) by decreasing the highs obtained from the drug. Therefore, Li would have a clinical advantage over other medications that are useful on an acute basis for the treatment of cocaine (or amphetamine) psychosis.

Still, these results are preliminary, and duplication by independent laboratories utilizing less crude methods in vivo and vitro is essential before a definite conclusion can be drawn. However, after duplication, there will be a definite indication for a trial in humans. This would be of remarkable importance because, if confirmed, these results would suggest a possible use of Li as a prophylactic for both amphetamine and cocaine abuse.

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