Pharmacology Biochemistry & Behavior, Vol. 5, pp. 701–704.

BRIEF COMMUNICATION

Cocaine and Morphine Self-Administration: Effects of Differential Rearing[1]

SHIRLEY Y. HILL[2] AND BARBARA J. POWELL[3]

Washington University School of Medicine, St. Louis, MO.

(Received 21 February 1976)

HILL, S. Y. AND B. J. POWELL. *Cocaine and morphine self-administration: effects of differential rearing.* PHARMAC. BIOCHEM. BEHAV. 5(6) 701–704, 1976. – Two groups of Wistar rats were reared in either enriched or impoverished conditions for 100 days postweaning. These two groups were further divided and tested for cocaine or morphine preference in a two-bottle choice (water alternative) for 16 days. Enriched and impoverished rearing has previously been found to alter emotionality, conditionability, and body weight of adult rats. Validating previous reports of differential rearing effects on body weight, the enriched animals in the present study weighed less than their litter mates reared in impoverished conditions. Animals reared in the enriched environment consumed significantly more cocaine than animals reared in an impoverished one. No significant differences were observed for morphine self-selection as a result of differential rearing.

Cocaine Morphine Differential rearing

A VARIETY of early experiences have been shown to affect the physiology and behavior of adult animals. The ability of adult animals to perform learning tasks and the degree of emotionality displayed in adulthood appear to be related both to genetic [5,15] and experiential factors [1, 3, 6]. Reduced emotionality is typically defined operationally in terms of fewer defecations and more ambulations in the open field.

The early experience received by rats during the preweaning period has been shown to be an important determinant of emotionality in the adult rat. Increased stimulation during the first week of life produces extensive effects in adult animals. These include increased activity, decreased defecation rate in the open field, and reduced plasma corticosterone levels [1, 3, 6] indicative of reduced emotionality. Similarly, characteristics of the post-weaning environment, such as increased stimulation, have been shown to affect the physiology, emotionality, and learning ability of adult rats [2, 3, 7, 10, 16, 17]. Physiological alterations include reduced ratios of cortical to sub-cortical cholinesterase activity and significantly lower body weights in animals reared in enriched environments [10]. Facilitation of learning in adult rats has been reported to occur as a result of exposure to enriched rearing [2, 7, 16].

Alterations in adult rats are typically brought about by varying environmental complexity and/or social grouping of animals. Environments having a high degree of stimulation, either in the form of greater visual stimuli or multiple housing conditions, are usually referred to as enriched or free environments. Those employing a lesser degree of visual stimulation or isolated housing are termed impoverished or restricted.

The effects of post-weaning rearing conditions has received little attention with respect to drug-seeking behavior in laboratory animals. One report [9] is available concerning alcohol consumption in rats reared in either enriched or impoverished environments. In that study, animals were handled on each day prior to weaning and reared in an enriched environment following weaning. No significant differences in alcohol consumption were found as a result of these experiences.

The present study was designed to determine if differential rearing conditions might alter self-selection of cocaine or morphine in adult animals. Changes in free-choice

[1] This research was supported in part by NIAAA Grant AA-00209 and by SAODAP Grant DA-4RG008.
[2] Send Reprint Requests to: Shirley Y. Hill, Department of Psychiatry, Washington University School of Medicine, 4940 Audubon Avenue, St. Louis, Missouri 63110.
[3] Presently at: Veterans Administration Hospital, Cooper Drive Division, Lexington, Kentucky 40509.

drinking might be expected to occur as a result of altered emotionality and/or learning ability as a result of differential rearing.

METHOD

Animals

Twenty-four male Wistar rats, bred in our laboratory, were used. At 20 days of age the animals were weaned and assigned to one of two living conditions. Fifteen animals were assigned to the enriched environment and nine to the impoverished one. Since the impoverished environment is most like standard laboratory conditions, it was of most interest to determine the effects of enriched rearing, and thus more animals were assigned to the enriched group.

The impoverished groups were individually housed in standard laboratory cages (17.8 x 24.1 x 17.8 cm), located in a room where quiet conditions could be maintained. The enriched groups were housed in a single large chamber (121.9 x 121.9 x 60.9 cm), covered with a removable screen. The chamber floor was covered with sand and contained two activity wheels, plastic toys, and small wooden platforms containing enclosures. This method of producing increased stimulation was modeled after that of Krech [10]. The animals had ad lib access to food and water from two water bottles fixed to each wall of the chamber, while food was scattered on the chamber floor.

When the animals had reached 100 days of age, all were individually housed in standard laboratory cages equipped with two Kimax graduated drinking tubes. During the next 5 days, they were adapted to a 7-hr/day drinking schedule. A single bottle of water was used for this purpose. Following the acclimation period and when 7-hr intakes had stabilized, the (E) animals were divided into two groups. One group (N = 9) was offered a choice between morphine sulfate (0.5 mg/ml) and water, the other group (N = 6) was offered a choice between cocaine hydrochloride (0.1 mg/ml) and water. Similarly, the (I) animals were divided into two groups. One group (N = 4) was offered a choice between morphine and water, while the other group (N = 5) was offered a choice between cocaine and water.

The two-bottle choice was available 7 hours a day from 9 a.m. until 4 p.m. each day for 16 days. This was the only time that fluid was available. The two bottles were rotated daily to avoid formation of position preferences. Animals were handled three times during the drinking period, on the first, eighth, and sixteenth days in order that body weights could be recorded.

RESULTS

In order to validate the efficacy of the differential rearing procedure, body weight data obtained before initiation of drug treatment were analyzed for the two groups. In agreement with previous reports [10], the enriched animals weighed less (mean of 298 g) than the impoverished animals (mean of 379 g), a statistically significant difference ($t = 4.56$, $df = 22$, $p<0.001$).

A two-way analysis of variance with repeated measures was performed on the mg/kg intake of the two morphine groups, (E) and (I) and the two cocaine groups, (E) and (I). The effects of increased exposure to the drugs was evaluated by grouping the sixtten choice days into four four-day periods. This variable will be referred to subsequently as "time."

The analysis of variance of the drug consumption measures showed a significant drug effect ($F = 181.2$, $df = 1$, $p<0.0001$) and a significant environment by drug interaction ($F = 25.0$, $df = 1$, $p<0.0002$). The significant interaction was found because of the significantly greater intake of cocaine by the enriched group.

The effects of repeated exposure to the drug (time) did not show significant effects. As may be seen in Fig. 1, consumption varied somewhat across time but not in a linear way. Interactions of time with environment or time with drug were also nonsignificant as was the three-way interaction of time x drug x environment.

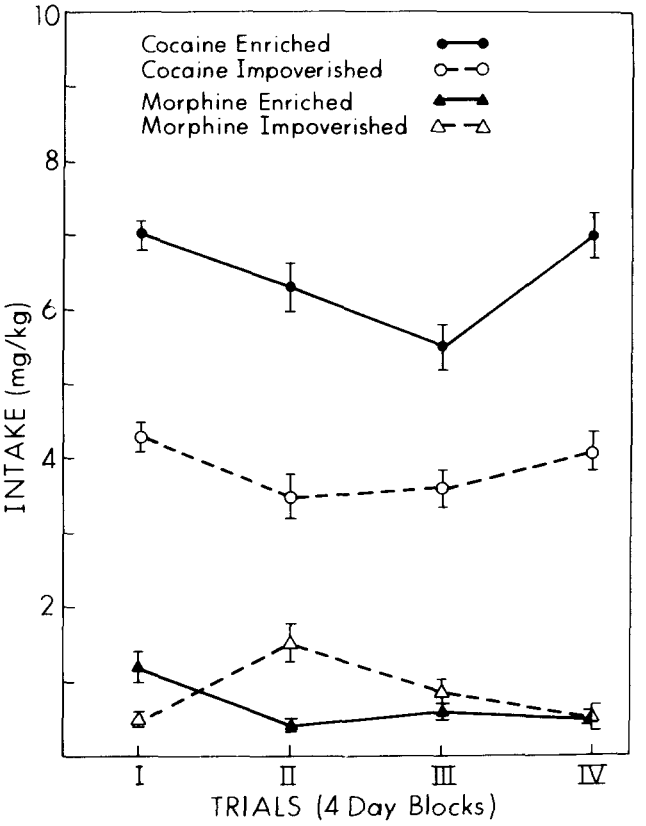

FIG. 1. The effect of differential rearing on free-choice drinking of cocaine and morphine. Intake is expressed in mg/kg of drug during four time periods. Each time period (I–IV) represents the mean of four 7-hr drinking trials. Vertical bars represent the standard error of the mean.

A comparison of the fluid intakes for the two groups was made to insure that the greater mg/kg intake of cocaine by the enriched group was not due to the smaller body weight of this group (Table 1). While the enriched animals weighed 22% less than their impoverished litter mates, their asymptotic intake of cocaine solutions (trial block IV) was approximately 42% greater (12 ml vs 17 ml).

DISCUSSION

Self-administration of morphine in animals has been amply demonstrated using both intravenous delivery contingent upon bar-pressing [18] and oral consumption [11, 12, 13, 19]. Cocaine self-administration has also been

TABLE 1

TOTAL FLUID CONSUMPTION (ml) OF MORPHINE AND COCAINE GROUPS. PROPORTION OF DRUG INTAKE TO TOTAL FLUID INTAKE IN PARENTHESES

		Trials (4-Day Blocks)			
		I	II	III	IV
Morphine	E	20.1 (1.9)	22.3 (5.3)	23.0 (1.5)	24.3 (1.9)
	I	20.2 (2.6)	25.1 (1.0)	24.2 (1.3)	23.7 (1.1)
Cocaine	E	19.0 (60.8)	20.9 (45.9)	25.4 (47.6)	22.1 (53.6)
	I	20.4 (79.5)	21.5 (57.5)	22.1 (53.6)	23.0 (71.6)

shown to occur both in rats and in monkeys [4,8] using the intravenous method.

Maintenance of drug-seeking behavior in animals may be presumed to be affected by the conditioning procedure employed. Oral methods of delivery generally have met with greater difficulties in establishing sustained drug-seeking. This may be due to the longer latency of the reward when drugs are consumed rather than delivered intravenously. The present study was undertaken to determine if environmental factors leading to reduced emotionality and superior conditionability would similarly affect the rapidity with which oral drug-seeking behavior is acquired.

The highly significant interaction of environment and drug condition in the present study indicates that differential rearing appreciably affects the free-choice consumption of cocaine solutions. The effect of environmental rearing on morphine consumption remains to be determined due to the small quantity of drug consumed during the 16 choice trials. Extensive training trials are often needed, however, to establish opiate-directed behavior in laboratory rats by the oral route [12,13].

The notable finding in this study is that enriched rearing increases free-choice cocaine consumption. This finding is open to a variety of interpretations. Enriched environments have been shown to reduce emotionality an facilitate conditioned learning. Reduced emotionality may have contributed to the initial acceptance of the novel taste of cocaine solutions. Further, enhanced conditionability may have served to sustain drug drinking behavior once it had commenced. Each of these factors alone or in combination may have contributed to the greater consumption of cocaine observed in enriched animals.

Although the present results are preliminary, it may be concluded that rats reared in an enriched environment consume significantly more cocaine than those reared in restricted ones. That pharmacological effects may have contributed to the increased consumption observed, is strongly suggested by the quantity of cocaine consumed, an asymptotic level of 6.45 mg/kg. In another study (Hill *et al.*, in press), this dose was administered to rats immediately preceding 7-hr sleep recordings, with significant changes resulting in total sleep time. Although the cocaine was consumed over a 7-hr period in the present study, whereas a single 6.0 mg/kg dose was administered in the sleep study, sleep recordings were monitored for 7-hr and alterations noted over the entire recording. It is quite probable, therefore, that cocaine in the dose range freely selected by these animals had pharmacological effects for several hours. That the effects of low doses of cocaine persist for several hours has also recently been demonstrated in humans [14] where 8-hr sleep recordings were obtained.

REFERENCES

1. Ader, R. Early experiences accelerate maturation of the 24-hour adrenocortical rhythm. *Science* **16**: 1225–1226, 1969.
2. Bingham, W. E. and W. J. Griffiths. The effects of differential environments during infancy on adult behavior in the rat. *J. comp. physiol. Psychol.* **45**: 307–312, 1952.
3. Denenberg, V. H. and J. R. C. Morton. Effects of environmental complexity and social groupings upon modification of emotional behavior. *J. comp. physiol. Psychol.* **55**: 242–246, 1962.
4. Dougherty, J. and R. Pickens. Fixed-interval schedules of intravenous cocaine presentation in rats. *J. exp. Analysis Behav.* **20**: 111–118, 1973.
5. Harrington, G. M. Strain differences in open-field behavior of the rat. *Psychon. Sci.* **27**: 51–52, 1972.
6. Hess, J. L., V. H. Denenberg, M. X. Zarrow and W. D. Pfeifer. Modification of the corticosterone response curve as a function of handling in infancy. *Physiol. Behav.* **4**: 109–111, 1969.
7. Hymovitch, B. The effects of environmental variations on problem-solving behavior in rats. *J. comp. physiol. Psychol.* **45**: 313–321, 1952.
8. Johanson, C. E. and C. R. Schuster. A choice procedure for drug reinforcers: Cocaine and Methylphenidate in the Rhesus monkey. *J. Pharmac. exp. Ther.* **193**: 676–688, 1975.
9. Kazmaier, K., R. E. Butcher, R. J. Senter and R. M. Stutz. Rearing conditions and ethanol consumption by rats. *Q. Jl Stud. Alcohol* **34**: 520–524, 1973.
10. Krech, D., M. R. Rosenzweig and E. L. Bennett. Effects of environmental complexity and training on brain chemistry. *J. comp. physiol. Psychol.* **53**: 509–519, 1960.
11. Kumar, R., I. P. Stolerman and H. Steinberg. Resumption of morphine self-administration by ex-addict rats. In: *Agonist and Antagonist Actions of Narcotic Analgesic Drugs*, edited by H. W. Kosterlitz, H. O. J. Collier and J. E. Villarreal. British Pharmacological Society, London: Macmillan Press Limited, 1973, pp. 255–265.
12. McMillan, D. E., J. D. Leander, T. W. Wilson, S. C. Wallace, T. Fix, S. Redding and R. T. Turk. Oral ingestion of narcotic analgesics by rats. *J. Pharmac. exp. Ther.* **196**: 269–279, 1976.
13. Nichols, J. R. A procedure which produces sustained opiate-directed behavior (morphine addiction) in the rat. *Psychol. Rep.* **13**: 895–904, 1963.

14. Post, R. M., J. C. Gillin, R. J. Wyatt and F. K. Goodwin. The effect of orally administered cocaine on sleep of depressed patients. *Psychopharmacologia* **37**: 59–66, 1974.
15. Powell, B. J., L. K. Martin and D. K. Kamano. Relationship between emotionality, drug effects, and avoidance responses in Tryon S_1 and S_3 strains. *Can. J. Psychol.* **21**: 294–297, 1967.
16. Schweikert, G. E. III, and G. Collins. The effects of differential post-weaning environments on later behavior in the rat. *J. Genet. Psychol.* **109**: 255–263, 1966.
17. Singh, D. and W. S. Maki, Jr. Effects of post-weaning rearing conditions on emotionality and social-seeking behavior in the rat. *Psychon. Sci.* **13**: 163–164, 1968.
18. Weeks, J. R. and R. J. Collins. Patterns of intravenous self-injection by morphine addicted rats. *Res. Publs Ass. Res. nerv. ment. Dis.* **46**: 288–298, 1968.
19. Wikler, A. and F. T. Pescor. Persistence of "relapse-tendencies" of rats previously made physically dependent on morphine. *Psychopharmacologia* **16**: 375–384, 1970.