Pharmacology Biochemistry & Behavior, Vol. 20, pp. 807–809, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

BRIEF COMMUNICATION

Effects of 6-OHDA Lesions in the Nucleus Accumbens on the Acquisition of Self Injection of Heroin Under Schedule and Non Schedule Conditions in Rats

GEORGE SINGER AND MEREDITH WALLACE[1]

Department of Psychology, La Trobe University, Bundoora, Australia, 3083

Received 21 March 1983

SINGER, G. AND M. WALLACE. *Effects of 6-OHDA lesions in the nucleus accumbens on the acquisition of self injection of heroin under schedule and non schedule conditions in rats.* PHARMACOL BIOCHEM BEHAV **20**(5) 807–809, 1984.—Acquisition of heroin self injection is enhanced in bodyweight reduced rats if a non contingent food delivery schedule is operating (schedule-induced self injection). Dopamine depletion of the nucleus accumbens septum (NAS) reduces nicotine self injection and a number of other schedule-induced behaviours. In the present experiment 6-OHDA lesions in the NAS significantly reduced the levels of heroin self injection in 7 rats on a food delivery schedule compared with sham lesioned controls. The reduced heroin intake did not differ from that of lesioned or sham lesioned rats with no schedule present. The results confirm previous reports that intact dopaminergic neurones in the NAS are necessary for schedule-induced behaviours to occur, and demonstrate that components of the same behaviour which are not schedule-induced can continue without disruption in the presence of the lesions.

6-OHDA Heroin self injection Schedule-induced self injection Nucleus accumbens septum
Dopamine Nicotine self injection

DATA from a series of experiments [2,5] show that the acquisition of nicotine self injection behaviour in naive rats is dependent on reduced body weight and the presence of a food delivery schedule. Recently we have shown that the acquisition of schedule-induced behaviours such as drinking, wheel running and nicotine self injection was diminished through 6-OHDA lesions of the nucleus accumbens septum (NAS) although these lesions did not affect deprivation induced drinking or spontaneous wheelrunning [7,8]. The schedule is a necessary condition for the acquisition of nicotine self injection behaviour, whereas heroin self injection behaviour can be acquired without the presence of the schedule but is accelerated if a schedule is operating [3].

If an intact catecholaminergic NAS system is necessary for schedule-induced behaviours to occur, the component of heroin self injection which is schedule-induced should be reduced by NAS lesions, but the component which occurs without the presence of the schedule should be unaffected.

In this paper we report an experiment showing the effects of 6-OHDA lesions in the NAS on the acquisition of heroin self injections with and without the presence of a food delivery schedule.

METHOD

Animals

Forty-two naive male Long-Evans rats were reduced to 80% of free feeding body weight 360–400 g. Rats were housed individually in temperature controlled conditions (22°C±1) with a 12 hour light/12 hour dark cycle. Water was freely available at all times.

Apparatus

The test chamber was made of clear perspex with a stainless steel barred floor, and measured 35×32×32 cm. A food pellet dispensing unit and a bar were attached to the same side wall. The bar operated a syringe infusion pump (Sage Instruments Model 341) which delivered 0.07 ml of drug solution when triggered. A timing device was incorporated into the system so that any further bar presses during the five second infusions could not initiate another infusion. Bar presses and infusions were recorded on a chart recorder during the sessions. Noyes food pellets (standard formula 45

[1]Requests for reprints should be addressed to Dr. Meredith Wallace.

mg) were delivered to the animal on a Fixed Time 60 sec (FT-60) non-contingent schedule.

Surgery

All animals were anaesthetized with an IP injection of Sagatal (60 mg/kg) (May and Baker, Victoria, Australia).

All animals were catheterised by implantation of a polyethylene (SP28) catheter into the right jugular vein. Catheters were held in place by leather jackets.

Prior to catheterisation 14 animals were lesioned by the bilateral stereotactic injection of 6-OHDA (2,4,5 trihydroxyphenylamine hydrochloride, Sigma) into the NAS. The co-ordinates of the NAS lesion site were 3.4 mm anterior to bregma, 1.7 mm lateral to the mid line and 7.2 mm below the dura at the point of penetration [4]. Stereotactic injections were made from a 10 μl Hamilton syringe through a 30 gauge stainless steel cannula. Each injection of 6-OHDA consisted of 2 μl of an 8 μg/μl solution, thus a total dosage of 16 μg was delivered into each site. The rate of injection was 1 μl/min. The 6-OHDA was dissolved in a 2 μg/μl solution of ascorbic acid and brought to isotonicity with sodium chloride. All solutions were prepared on the morning of surgery. Fourteen animals were sham lesioned using an ascorbate/NaCl mixture (vehicle) and 14 animals remained unlesioned.

Fluorescent Histochemistry

An aqueous aldehyde method was used for the fluorescence histochemical localization of catecholamines. The method used is a modification of the method of Furness, Heath and Costa [1] and is fully described in a previous paper [7].

Procedure

After two days' recovery from surgery all rats were given a daily 1 hour session in the test chamber. Seven unlesioned, seven 6-OHDA lesioned and six sham lesioned rats were placed on a FT-60 food delivery schedule while the remaining seven unlesioned, seven 6-OHDA lesioned and eight sham lesioned rats were given 60 pellets in a single amount at the beginning of each session. Freshly prepared heroin (diacetylmorphine hydrochloride, Victorian Health Department) was available to all animals (0105 mg/kg/infusion). Each animal was primed with an initial dose prior to each experimental session. After 10 days of testing the animals were perfused for fluorescence histochemistry.

RESULTS AND DISCUSSION

The heroin self injection rates for all six groups for the last two days of the acquisition period are shown in Fig. 1. ANOVA was carried out using the means of the last two days of the acquisition phase. These data show a significant effect for lesions, $F(2,36)=10.6$, $p<0.01$, also for schedule vs non-schedule, $F(1,36)=20.5$, $p<0.01$, and the interaction, $F(2,36)=7.7$, $p<0.01$. A main effects test showed that the number of self injections by the 6-OHDA lesioned scheduled group did not differ from the self injection rate of the three non scheduled groups but was different from the unlesioned scheduled and sham lesioned scheduled groups.

The data showed a reduced level of heroin self injection for the 6-OHDA group on a food delivery schedule. The lesion reduces the self injection level to that of the non-scheduled lesioned and unlesioned groups.

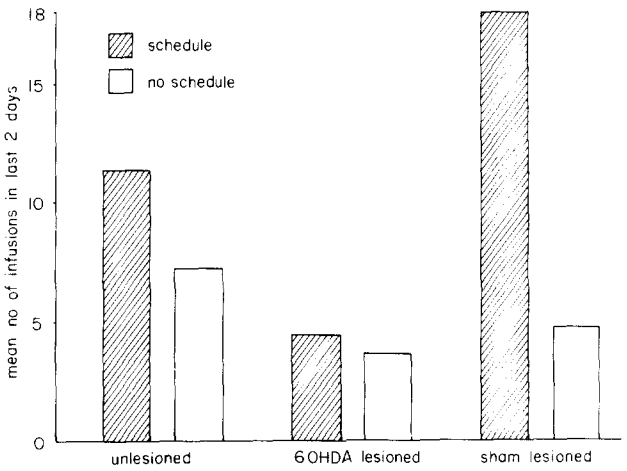

FIG. 1. Mean number of heroin infusions on days 9, 10 (last 2 days) for each group.

Self injections by the sham lesioned scheduled group were significantly higher than for the unlesioned scheduled group (see Fig. 1). The higher self injection level for the sham lesioned group is difficult to explain. Both these groups have significantly higher levels than the 6-OHDA groups and it is possible that postoperative stress-induced corticosterone release in interaction with the schedule promotes a faster acquisition rate of heroin self injection early in the acquisition period, which is maintained through the 10 days of the study. Data from a number of previous experiments [2] show that saline self injection levels over a period of 10 days are not significantly different from a mean of zero.

Histochemical verification indicated that the 6-OHDA lesioned groups showed considerable reduction in fluorescence of both right and left half of the NAS with possibly some smaller reduction in fluorescence in adjacent areas of the olfactory tubercle and caudate putamen. Only the amount of non specific damage was assessable in the tissues and was extensive. Fluorescence in the NAS of sham lesioned animals was of the same brightness as that of unlesioned animals. Since quantitative assessment of loss of fluorescence is unreliable, only qualitative statements about the intensity of fluorescence and location are possible and these are in accordance with our earlier reports [8].

The results of this experiment show clearly that intact catecholaminergic neurons in the NAS are necessary for schedule induced behaviours to occur and that components of the behaviour which are not schedule induced can continue without disruption when the lesions are present. Previous studies [8] have shown that pretreatment with desmethylimipramine does not change the effects of 6-OHDA on schedule induced drinking. Therefore it seems reasonable to suggest that dopaminergic and not noradrenergic neurons are involved in the mediation of schedule induced behaviours. The finding is in accordance with our earlier reports on schedule induced drinking, wheel running and nicotine self injection [6]. It considerably strengthens the concept of schedule induced behaviour since it provides specific biochemical and anatomical locations for the regulation of the acquisition of this behaviour, regardless of the final motor response.

It also supports our classification of psychoactive drugs in terms of acquisition patterns [6]. We have shown that the self administration of a group of drugs such as alcohol and heroin can be initiated without the schedule, but intake is enhanced if body weight is reduced and further increased if a schedule is operating. In contrast, self administration of a second group of substances including nicotine and Δ^9THC is initiated only if the schedule is present and body weight is reduced. The findings of this experiment reinforced the distinction between heroin self injection where the schedule is not an essential factor, and nicotine self injection, where the behaviour is dependent on reduced body weight and the presence of a food delivery schedule.

ACKNOWLEDGEMENTS

We wish to thank Lorraine Mackenzie, Debbie Wiselenski and Micheal Papasava for their assistance in collecting the data. This research was supported by ARGC Grant No. D18015288.

REFERENCES

1. Furness, J. B., J. W. Heath and M. Costa. Aqueous aldehyde (faglu) methods for the fluorescence histochemical localization of catecholamines and for ultrastructural studies of central nervous tissues. *Histochemistry* **57:** 285–295, 1978.
2. Lang, W. J., A. A. Latiff, A. McQueen and G. Singer. Self administration of nicotine with and without a food delivery schedule. *Pharmacol Biochem Behav* **7:** 65–70, 1977.
3. Oei, T. P. S., G. Singer and D. Jeffreys. The interaction of a fixed food delivery schedule and body weight on self administration of narcotic analgesics. *Psychopharmacology (Berlin)* **67:** 171–176, 1980.
4. Pellegrino, L. T. and A. J. Cushman. *A Stereotaxic Atlas of the Rat Brain*. New York: Appleton-Century-Crofts, 1967.
5. Singer, G., F. Simpson and W. J. Lang. Schedule induced self injections of nicotine with recovered body weight. *Pharmacol Biochem Behav* **9:** 387–389, 1978.
6. Singer, G. and M. Wallace. Schedule-induced self injection of drugs. *Prog Neuropsychopharmacol Biol Psychiatry*, in press, 1983.
7. Singer, G., M. Wallace and R. Hall. Effects of dopaminergic nucleus accumbens lesions on the acquisition of schedule induced self injection of nicotine in the rat. *Pharmacol Biochem Behav* **17:** 579–581, 1982.
8. Wallace, M., G. Singer, J. Finlay and S. Gibson. The effect of 6OHDA lesions of the nucleus accumbens septum on schedule induced drinking, wheel running and corticosterone levels in the rat. *Pharmacol Biochem Behav* **18:** 129–136, 1983.