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Asymmetrical Effect of Unilateral Cortical Lesions and Amphetamine on DRL-20: A Time-Loss Analysis

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KUBOS, K., J. V. BRADY, T. H. MORAN, C. H. SMITH AND R. G. ROBINSON. *Asymmetrical effect of unilateral cortical lesions and amphetamine on DRL-20: A time-loss analysis.* PHARMACOL BIOCHEM BEHAV 22(6) 1001–1006, 1985.—Male Sprague Dawley rats received unilateral 1.5 mm diameter focal suction lesions of either the left or right orbito-frontal cortex and were tested for response to 6 doses of amphetamine sulfate ranging from 0.5 to 1.5 mg/kg on a DRL-20 schedule of reinforcement. Right hemispheric lesion animals obtained a greater number of control reinforcements and were more sensitive to amphetamine's disruptive effects, showing a greater dose-related decrease in water rewards obtained than left lesion animals. An analysis method is introduced which combines the interactive effects of premature responses and their IRT value in a way that relates directly to reinforcement attainment. Calculated total session time made unavailable for reinforcement due to premature responding, correlated negatively (r=−.942) with the number of reinforcements obtained.

Laterality Cortical lesion Amphetamine Supersensitivity DRL-20 Accumbens Reinforcement omission

RECENT work has indicated an asymmetrical potency of right over left hemispheric cortical lesions in producing behavioral outcomes. For example, right hemispheric ischemic lesions [28–30] produce alterations in shock-induced aggression, open field behavior and spontaneous nocturnal locomotor activity while similar lesions of the homologous left hemisphere do not [28–30].

Biochemical investigations of various brain regions have shown that the hyperactivity resulting from right cortical insult is generally accompanied by an ipsilateral and contralateral depletion of cortical norepinephrine (NE) [25,29], as well as dopamine (DA) [15, 29, 31] in the A10 cell group and in the caudate/nucleus accumbens. Comparable left hemispheric lesions which are ineffective in producing hyperactivity, do not alter contralateral NE or DA concentrations.

Studies aimed at defining the mechanism underlying this phenomenon have focussed upon the orbito frontal cortex, the site of infarct formation attendant to middle cerebral artery ligation. Focal destruction of cortical NE neurons by unilateral microinjection of 6-OHDA [31] or the NE neurotoxin DSP-4 [14] reproduces the asymmetrical behavioral and biochemical effects of vascular or mechanical insult. Destruction of cortically resident cell bodies by microinjection of low doses of kainic acid [15] produces similar effects. Additionally, 2 mm diameter disc shaped knife cortical undercuts severing cortico subcortico communicating fibers at the level of the internal capsule produce the behavioral consequences of cortical injury without altering either ipsilateral or contralateral NE levels [16]. Taken together, these findings suggest that disruption of normal cortical noradrenergic influence upon the cell bodies of cortical efferents may represent the first link in a chain of events leading to hyperkinesis.

A possible subcortical termination site in the nucleus accumbens for these fibers has been suggested by experiments demonstrating that large fronto-cortical ablations result in a chronic enhancement of amphetamine stimulated locomotion [1, 4, 5, 6, 7, 19, 20]. An extensive body of evidence suggests that mesolimbic dopaminergic neurons innervating the nucleus accumbens control spontaneous activity as well as the expression of drug stimulated locomotion [3]. Lesions of the nucleus accumbens employing a wide variety of techniques have been reported to profoundly influence spontaneous locomotor activity in rats [9, 11, 12, 21, 22] and abolish or significantly inhibit the activity increasing effects of amphetamine [9–11]. It is therefore possible that the enhanced amphetamine response of fronto cortically lesioned rats may be due to the development of a denervation supersensitivity by dopaminergic accumbens neurons.

We therefore postulated that the hyperactivity resulting

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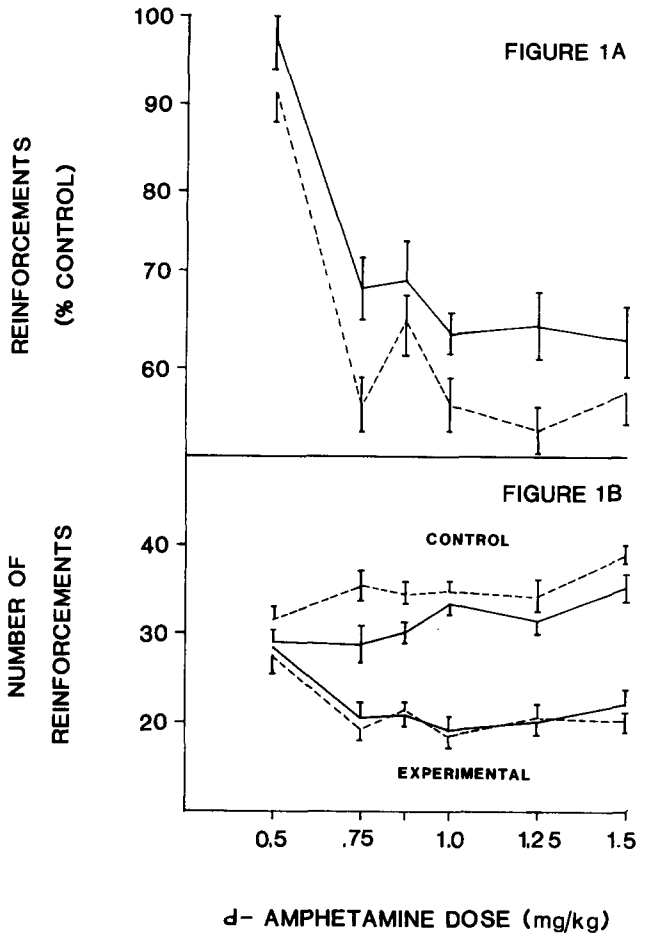

FIG. 1. The effect of varying d-amphetamine doses upon number of reinforcements as a percent of control (1A) and absolute numbers of rewards (1B). Solid lines denote left lesion animals and broken lines denote right lesions. "Control" refers to values derived from weekly saline trials. Bars represent ±SEM.

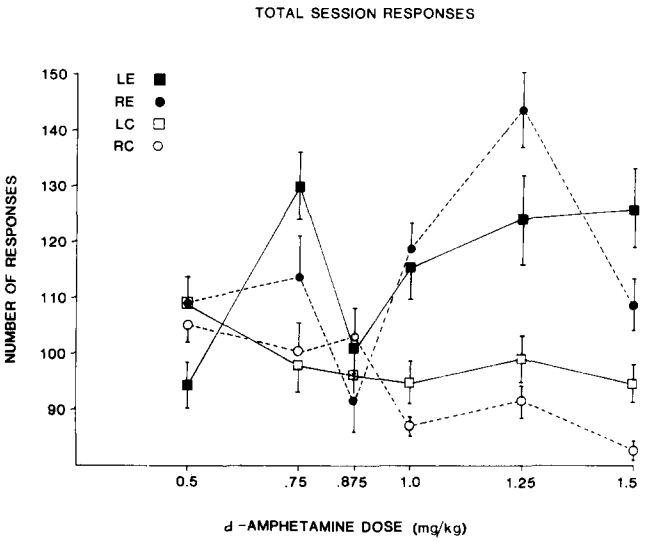

FIG. 2. The effect of amphetamine upon total number of responses omitted with a 30 min session. LC—left lesion, control responding. LE—left lesion experimental condition. RC—right lesion, control responding. RE—responding under d-amphetamine. Control responding is derived from experimental subjects' weekly saline trials. Bars represent ±SEM.

from our smaller, focal right fronto-cortical lesions might also be producing an increased sensitivity of the mesolimbic system. This supersensitivity might be seen as an increased amphetamine response similar to that produced by destruction of larger cortical areas. The first purpose of this experiment was to determine if the lateralized efficacy favoring right over left hemispheric injury in producing locomotor hyperactivity would be parallelled by a differential development of amphetamine sensitivity favoring right lesion animals.

In addition to stimulating locomotion, amphetamine alters reward motivated responding. This influence has long been known to be rate dependent [2], lowering high rates of responding while increasing the occurrence of low rate behavior. Amphetamine's ability to elevate low rates of responding is especially evident in schedules of reinforcement which encourage spaced responding, such as DRL (differential reinforcement for low rates of responding). Due to the intrinsic amphetamine sensitivity of responding maintained by DRL contingencies [2], and findings indicating that amphetamine's ability to decrease high response rates is significantly impaired by bilateral 6-OHDA lesions of the nucleus accumbens [27], it was postulated that DRL-20 sec might constitute an appropriate situation in which to test for a possible differential drug sensitivity between animals receiving either left or right focal cortical suction lesions. Thus, this experiment was designed as a test of left versus right hemispheric lesion induced differences by operant techniques.

Premature responding under DRL contingencies lowers reinforcement density in at least two ways. The first is to postpone reinforcement delivery. A response occurring prior to the contingency interval delays the availability of the next reward by a period of time equal to the contingency interval length. Secondly, the amount of non reinforced time elapsed from contingency interval start (last reinforced response) to any premature response subtracts from total session time, and therefore causes the omission of rewards. Thus, the opportunity to obtain future reinforcement is reduced by the product of the number of premature responses and their temporal occurrence within the DRL interval. We based an analysis of time loss upon the summation of these "subtractive products" over individual sessions. The final purpose of this experiment was to determine if a method explicitly addressing this interaction would be useful in the analysis of DRL responding.

METHOD

Subjects

Subjects were 21 male Sprague-Dawley rats weighing 250–350 g at the start of the experiment. Upon arrival, animals were randomly assigned to either left or right lesion

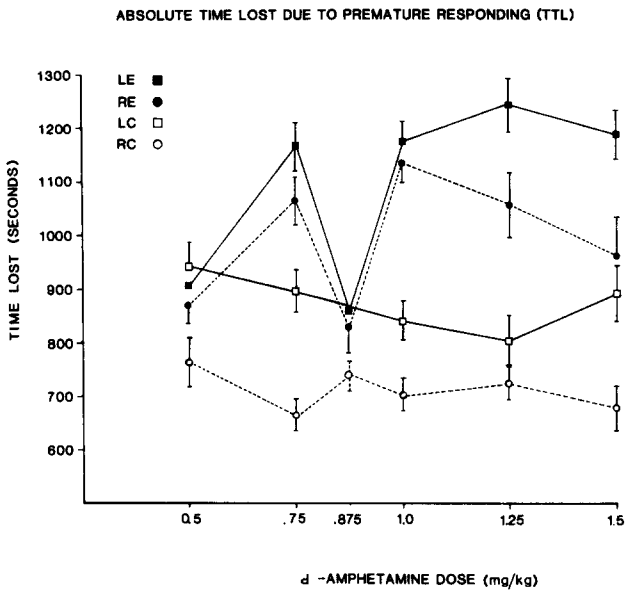

FIG. 3. Absolute number of seconds lost due to premature DRL responding from a total of 1800 sec available during a 30 min session. LC—left lesion, control responding. LE—left lesion experimental condition. RC—right lesion, control responding. RE—responding under d-amphetamine. Control responding was derived from experimental subjects during weekly saline trials. Bars represent ±SEM.

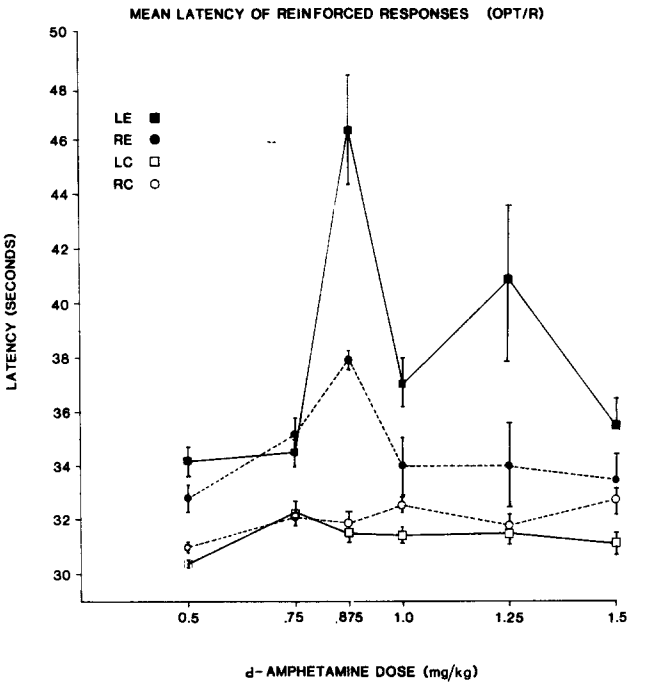

FIG. 4. Mean latency of reinforced responses (OPT/R). Also represents the mean reinforced IRT. LC—left lesion, control responding. LE—left lesion experimental condition. RC—right lesion, control responding. RE—responding under d-amphetamine. Control values are derived from experimental subjects during weekly saline trials. Bars represent ±SEM.

conditions. Subjects were housed on a schedule of lights on at 6 a.m., lights off at 6 p.m. For the DRL study, they were maintained on a 23 hr water deprivation schedule and were allowed food ad lib. Two weeks prior to and during locomotion testing, animals were placed on ad lib water as well. All training and testing was performed during the hours of 8:30 a.m. and 4 p.m.

Apparatus

Four standard operant chambers were individually housed in $^1/_2$" thick particle board sound attenuating enclosures equipped with fans. Each chamber was illuminated by a 28 V DC house light and a green cue light located above the bar (BRS). Appropriate responding resulted in the presentation of 0.01 ml water by a BRS electromechanical dipper with the cue light being extinguished for 2 sec.

Contingency programming, reinforcement presentation and data collection for all 4 chambers was performed by a 64K Apple II+ operating under assembly language control. Interfacing was accomplished by means of a DIO-9 I/O card and U-16 interface (Interactive Structures, Bala Cynwyd, PA) with system timing being supplied by a Time Machine II (Creative Software, West Valley City, UT) quartz clock card. Response data for each DRL-20 session was collected as the total number of responses occurring within 20 1-sec bins during the 30 min session. At the completion of each session the total number of reinforcements (number of IRT's > 20 sec) delivered was written to disk along with binned response data. Statistical analysis involved two- and three-way analysis of variance. Correlation significance was tested by the method of Jones [8].

Surgery

Surgery was carried out under Chloropent anesthesia (3.0 cc/kg) as described in detail elsewhere [24]. Briefly, a craniotomy was performed and a focal suction lesion measuring 1.5 mm in diameter was made in either the left or right fronto-orbital cortex using a blunt 18 ga hypodermic needle. Animals were sutured and returned to their cages where they were allowed to recover for 1 week prior to deprivation and training.

Training

Initially, animals were water deprived for 48 hr and hand-shaped to bar press. Once the response was acquired, a single 1-hr continuous reinforcement (CRF) session was instituted. Following the CRF session, 23 hr-deprived rats were placed in the operant chambers for daily 30 min sessions. Animals were then run 5 days per week with the Monday DRL requirement being equal to the preceeding Friday's value. Between Tuesday and Friday the timing requirement was increased at the rate of 2 sec per day until DRL-20 was attained. Following this training regimen, rats were run 5 days per week on DRL-20 until a criterion of no more than a 10% standard error in any response bin over Tues. through Thurs. occurred. Once criterion responding was attained, the Monday session was considered a "warm-up" and data was discarded. Sessions occurring between Tues. and Thurs. were saline control days with Fri. being the experimental day. D-amphetamine sulfate was administered IP once per week to both left and right lesion animals in an ascending series of 0.5, 0.75, 0.875, 1.0, 1.25 and 1.5 mg/kg. Doses

higher than 1.5 mg/kg were not employed because these doses totally disrupted bar pressing in 90% of the subjects. All injections were delivered 30 min prior to testing.

Four left and four right lesion animals participating in the experiment also served in a pilot study of this experiment 2 months prior to the beginning of the present study. Since statistical analysis failed to show differences between pilot data and data developed for the present study, pilot data was included in the present data set.

Data Analysis

Data were analyzed both in terms of absolute numbers of responses as well as drug responding as a percentage of control to correct for possible alterations in baseline response levels and to take into account individual response characteristics. Differences among the various measures obtained were tested employing 2- and 3-way analysis of variance. ANOVA significance was tested with appropriate planned comparisons. Subjects served as their own controls.

Time-Loss Analysis

For this analysis, the number of responses per interresponse time (IRT) bin was multiplied by the median bin value in seconds. Thus, a single response within the 1-second bin was numerically treated as 0.5 second lost from the total 1800 sec of session reinforcement availability while a response in the 20-sec bin subtracted 19.5 sec from session time. The measure of total time lost (TTL) due to premature responding was obtained by summing the response × bin weighting products across IRT bins for the entire session. The remaining time which presented an opportunity for reinforcement was calculated by subtracting TTL from the 1800 sec of total session time. A measure of response efficiency in this opportunity interval was obtained by dividing opportunity time by the number of reinforcements taken, yielding time/response (OPT/R), the mean interresponse time of those responses which directly produced reward.

RESULTS

Compared as percent of control, increasing doses of amphetamine significantly reduced the number of reinforcements obtained by the right lesion group, $F(1,160)=4.83$, $p<0.05$, to a greater extent than it did in the group receiving left orbito-frontal lesions (Fig. 1A). Total reinforcements obtained under the control condition by right lesion rats was significantly greater, $F(1,168)=7.46$, $p<0.01$, than that of left lesion animals while differences in total rewards obtained under the drug did not reach significance. Absolute numbers of responses under the drug were significantly greater in both groups than under the control condition, $F(1,224)=17.84$, $p<0.01$. Bar pressing of left and right lesion groups was found to be differentially affected when responding was compared across the entire dose range, $F(5,224)=3.07$, $p<0.05$. Increasing doses significantly reduced the number of reinforcements obtained by both groups, $F(5,160)=9.01$, $p<0.01$, relative to control. Absolute numbers of responses emitted by left and right groups were similar, except for control day responding during the weeks when 1.0, 1.25 and 1.5 mg/kg of amphetamine was administered (Fig. 1A). Right animals had generally lower control response rates (Fig. 2). Amphetamine reduced the number of water rewards obtained by both groups, $F(3,331)=55.48$, $p<0.001$, to approximately the same levels (Fig. 1B).

Time-Loss Analysis

Saline control day responding of right lesion rats led to significantly less total time loss (TTL), $F(1,163)=14.44$, $p<0.01$, and therefore significantly more remaining opportunity time (OPT) than rats receiving lesions of the left orbito frontal cortex. Both groups experienced a highly significant TTL increase, $F(1,295)=52.39$, $p<0.001$, in response to amphetamine (Fig. 3) and although right lesion subjects consistently produced lower TTL's than left lesion subjects, these group differences failed to reach significance, $F(1,132)=3.46$, $p>0.05$. A strong interaction of TTL with dose levels, $F(1,132)=4.26$, $p<0.01$, was noted for both groups as distance between the curves widened beyond 1.0 mg/kg with the maximum downward deflection in this measure seen at 0.875 mg/kg (Fig. 3).

As expected the total amount of session time made unavailable by premature responding, was negatively correlated with reinforcement attainment. Under control conditions, the correlation between time lost and the number of rewards obtained ranged from -0.797 to -0.995 with a mean of -0.942 ± 0.015 S.E.M.

The correlation of reward attainment and time lost in various interval segments was also investigated. Total time lost was divided into three batches, the first and third of which held the time lost during the first and last 5 seconds of the schedule, with the second batch containing data from the 10 middle 1-sec bins. Only time lost during the middle 10 1-sec intervals (IRT's 6–14) achieved a significant correlation with water presentations.

Opportunity time per response (OPT/R) represents the mean interresponse interval (the number of seconds since the preceeding response) of the bar presses which directly produced rewards. Under control conditions both groups behaved similarly on this measure with left rats waiting 30.41 sec and right animals having a mean latency of 30.98 sec (Fig. 4). Amphetamine had a profound overall influence upon this measure, $F(1,279)=47.66$, $p<0.001$. Amphetamine significantly increased the IRT's of reinforced responses in both groups. However, right lesion animals responded more efficiently, $F(1,130)=5.95$, $p<0.05$, across dose than left subjects, waiting a shorter 33.62 sec before emitting a reinforced response while left lesion latency was 37.10 sec. Again, the 0.875 mg/kg dose produced the greatest deviation from control values with a peak of 45.4 sec for the left group and 34.5 sec for rats with right lesions.

DISCUSSION

Amphetamine caused a significantly greater reduction in the number of reinforcers earned by right lesion rats in comparison with animals who received comparable 1.5 mm lesions of the homologous left orbito frontal cortex. Comparing individual animals' reinforcement density under the drug with the subject's own weekly control value, the enhanced right lesion amphetamine response was seen as a significant 10 percent greater reinforcement loss. This decrease was partially attributable to greater time loss due to increased responding in the middle IRT range. Thus, sensitivity to amphetamine's disruptive effect upon DRL-20 performance was asymmetrically developed on the basis of hemispheric lesion laterality.

Focally lesioned rats also responded differently in the absence of drug. Under control conditions, rats receiving approximately 1.5 mm diameter unilateral lesions of the right orbito frontal cortex responded more efficiently and earned

significantly more reinforcers than their counterparts with homologous lesions of the opposite hemisphere. Right lesion rats were also better able to withhold premature responding during the middle of the contingency interval which led to the omission of fewer reinforcers and contributed to their higher control reinforcement rates.

The amount of time lost due to premature responding was found to be highly correlated with reinforcement density. This was probably due to the fact that the time loss measure is directly derived from the nonreinforced IRT distribution. The utility of time loss analysis would seem to be that, in a single value, it expresses the combined effect of both numbers of responses, as well as their IRT value in a way that is directly related to reward attainment. That is, individual premature responses are transformed into values which explicitly recognize that response's contribution to overall reinforcer availability. Time loss calculations were found to be of significant descriptive value, but of limited analytical use with this particular data. In retrospect, a more appropriate application might have been in the quantification of more subtle data, e.g., where differences in IRT distributions were suspected, but where reinforcement densities were similar. In this case, time loss calculations could be employed to quantify the contributions of IRT ranges to the eventual reward density outcome even if intersubject or intergroup outcomes were the same.

Finally, TTL was discovered to have some unexpected methodological uses. First, it can be employed to derive the mean IRT of reinforced responses from nonreinforced IRT distribution data where this measure was not originally obtained. Secondly, its use decreases real time memory and computation demand upon small laboratory computers and conserves limited disk storage capacity.

Our previous studies investigating lateralized sensitivity to cortical insult have chiefly focused upon spontaneous nocturnal home cage wheel running activity as the dependent variable. This experiment represents our first demonstration of a lateralized influence upon (a) reward maintained behavior and (b) the development of drug sensitivity. Present results showing that operant behavior is influenced on the basis of lesion laterality indicates that such asymmetrical influences arising from small focal orbito frontal lesions extend to extrinsically motivated behavior as well.

The asymmetrical development of amphetamine sensitivity reported here suggests that one factor contributing to the development of post lesion hyperactivity may involve an asymmetrical induction of dopaminergic supersensitivity. Alternatively, equal amounts of subcortical denervation could be acting upon target sites with endogenously asymmetrical receptor concentrations or dopamine contents. Support for this view has come from studies demonstrating a 10% greater concentration of right hemispheric nucleus accumbens D2 receptors [32] and comparably greater right accumbens dopamine content [33]. Another possibility is that the postulated dopaminergic denervation supersensitivity effect may be due to an enhanced sensitivity of other structures or transmitter receptors which, in turn, influence accumbal function. Clearly, our lesions must have destroyed cortical glutamatergic and other efferents and similar supersensitivities would presumably develop among these denervated receptor populations as well. An interaction among these upregulated receptor populations may be an important factor to be considered. A parsimoneous model suggesting how such interactions might take place in the striatus has recently been proposed by Lehmann and Langer [17].

Our present results demonstrate that there are differences between left and right hemispherically lesioned rats which are revealed as differential DRL responding. Since animals were used as their own controls, it cannot yet be determined whether left hemispheric lesions reduced amphetamine's effects or whether both lesions potentiate the drug effect, but right hemispheric lesions do so to a greater extent.

In summary, focal cortical lesions asymmetrically affect a variety of behaviors on the basis of lesion laterality: shock-induced aggression [30], exploratory behavior [30] and spontaneous running wheel behavior [25,30] and nocturnal locomotion measured in computerized activity chambers [23]. The present study extends the documented lateralized influence to reward motivated behaviors and has provided evidence suggesting a possible mechanism for direct activity control which may involve a differential sensitivity of dopaminergic mesolimbic neurons.

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