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An Examination of the Intravenous Self-Administration of Phenylpropanolamine Using a Cocaine Substitution Procedure in the Baboon

R. J. LAMB,*[1,2] CHRISTINE A. SANNERUD* AND ROLAND R. GRIFFITHS*†[2]

**Department of Psychiatry and Behavioral Science and †Department of Neuroscience*
The Johns Hopkins University School of Medicine, Baltimore, MD 21205

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LAMB, R J , C A SANNERUD AND R R GRIFFITHS *An examination of the intravenous self-administration of phenylpropanolamine using a cocaine substitution procedure in the baboon* PHARMACOL BIOCHEM BEHAV **28**(3) 389–392, 1987 —Intravenous self-administration of phenylpropanolamine HCl (0 10 to 10 0 mg/kg/injection) was examined in baboons under conditions in which baseline responding was maintained by intravenous injections of cocaine HCl (0 32 mg/kg/injection) Drug was available under a FR 160-response schedule of intravenous injection Each drug injection was followed by a 3-hr time-out allowing a maximum of eight injections per day Phenylpropanolamine or phenylpropanolamine vehicle (saline) was substituted for cocaine for a period of 15 days followed by a return to the cocaine baseline Response rates after phenylpropanolamine substitution were similar to those maintained by saline substitution, and lower than those maintained under cocaine baseline conditions At the two highest doses of phenylpropanolamine tested (3 2 and 10 0 mg/kg/injection) concurrent food maintained behavior was suppressed

Phenylpropanolamine Self-administration Baboon

PHENYLPROPANOLAMINE is marketed as an over-the-counter drug for use as a nasal decongestant and as an anorectic. Structurally and pharmacologically there are a great number of similarities between phenylpropanolamine and amphetamine. Phenylpropanolamine differs structurally from amphetamine only by the introduction of a beta-hydroxyl group Both drugs can produce sympathomimetic effects and are anorectics [1] These and other similarities between phenylpropanolamine and amphetamine have raised concern that phenylpropanolamine, like amphetamine, might be a drug of abuse [4,7] This concern about the possible abuse potential of phenylpropanolamine might appear to be borne out by the frequent appearance of phenylpropanolamine in many counterfeit amphetamine preparations [7] However, it is unclear that these counterfeit amphetamine preparations or "look-alike" drugs are capable of maintaining abusive patterns of use. Even if these "look-alike" drugs maintained abusive patterns of use, it would be unclear that phenylpropanolamine would be the responsible ingredient. For instance caffeine and ephedrine are both frequent ingredients in these preparations [7] Caffeine is thought to play a role in the maintaince of coffee drinking [11] and ephedrine has been shown to serve as a reinforcer in animal studies [9]. Therefore it is likely that even if these counterfeit amphetamine preparations did maintain an abusive pattern of use phenylpropanolamine might not be the responsible ingredient

The present study was designed to examine the reinforcing properties of phenylpropanolamine in the baboon There have been, to our knowledge, only two previous reports on the reinforcing properties of phenylpropanolamine in nonhuman subjects The first report was a review article from this laboratory, which reported that phenylpropanolamine was not a reinforcer when substituted for cocaine, but provided no details of the experimental results The present report is a systematic and independent replication of this study The second report is a recent study by Woolverton and coworkers [20], which also reports that phenylpropanolamine is not a reinforcer when substituted for cocaine

METHOD

Three male baboons (*Papio anubis*) weighing 23–26 kg served as experimental subjects. Baboon RA had been studied in previous sedative self-administration experiments and baboon DI had been studied in antidepressant self-administration experiments Baboons were housed within standard primate squeeze cages, which also served as experimental chambers These cages were enclosed by sound and

[1]Present address R J Lamb, NIDA-Addiction Research Center, P O Box 5180, Baltimore, MD 21224
[2]Requests for reprints should be addressed to R J Lamb or R R Griffiths

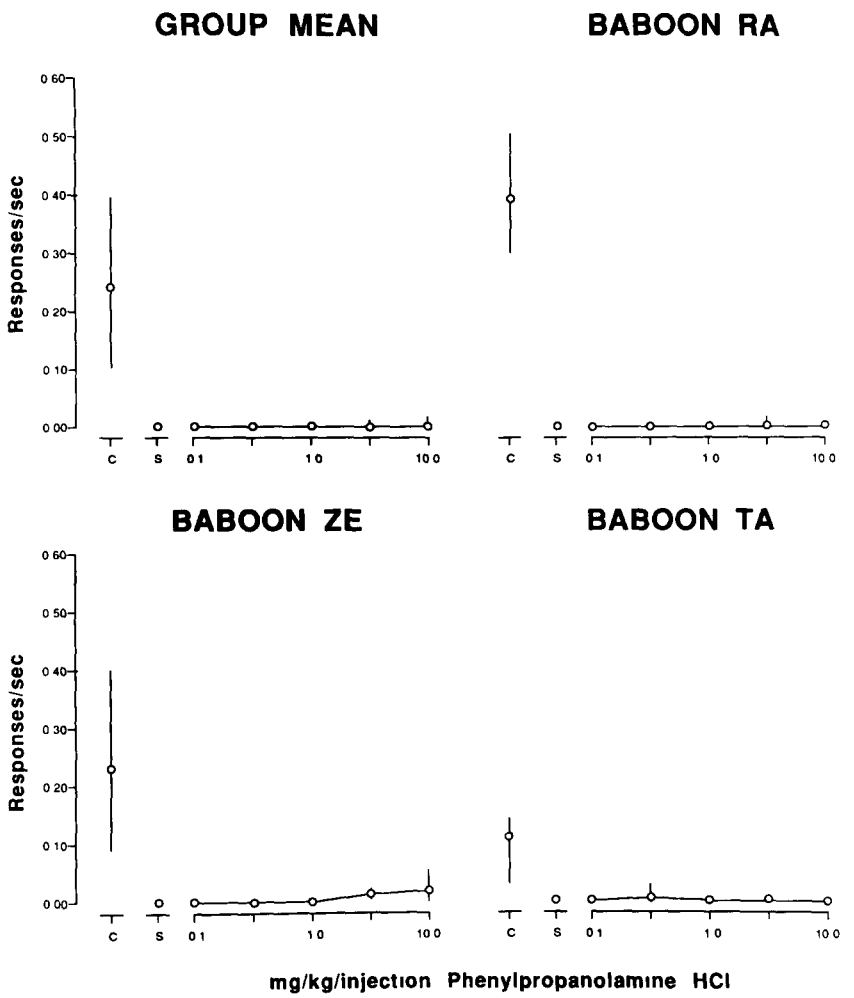

FIG 1 Mean rate of responding for days 11–15 of phenylpropanolamine or phenylpropanolamine vehicle (saline) substitution under a FR 160-response T O 3-hr schedule of intravenous injection Individual data for each of the 3 baboons studied as well as the grouped data are shown The vertical axes are response rate in responses/sec The horizontal axes are phenylpropanolamine HCl dose in mg/kg/injection plotted on a log scale The points above 'S' represent the data obtained during saline substitution The points above 'C' represent the mean of the mean from the three days of cocaine HCl (0 32 mg/kg/injection) availability that preceded each phenylpropanolamine or saline substitution Bars through each point represent the range of the values from which that point was calculated

light attenuating cubicles [16]. Intravenous catheters were implanted using sterile technique in either femoral or jugular veins under pentobarbital anesthesia using methods described in [16] Catheters were protected by a harness/tether system, which allowed baboons virtually unrestricted movement within the cage [16] The infusion system was similar to that described in [8]. Baboons had free access to water through a drinking tube and received daily rations of fruit and vitamin supplements.

A 0.7×1 0 m aluminum panel was mounted on one wall of the experimental chamber A Lindsley lever (Gerbrands, No. G6310) (lower left of panel) with an associated jewel light (approximately 1 5 cm diameter), a leaf lever (lower right of panel) with an associated jewel light, and a food hopper with an associated light (lower left or center of panel) were mounted on the aluminum panel. A 5×5 cm translucent panel which could be transilluminated was mounted on the aluminum panel in the upper left corner

Baboons could respond on the leaf lever under a fixed-ratio 30-response schedule of food pellet (1 g Noyes or BioServ banana flavored) delivery (i e., every thirtieth response delivered a food pellet and produced a brief flash of the hopper light) 24 hr per day The availability of an injection was indicated by a 5-sec tone followed by illumination of a jewel light over the Lindsley lever When the jewel light was illuminated, each response produced a brief feedback tone (approximately 0 1 sec) Upon completion of 160 responses on the Lindsley lever following illumination of the jewel light (FR160), the jewel light over the lever was extinguished, the drug injection was begun, the 5×5 cm translucent panel was illuminated for a 1-hr period and a time-out period of 3 hr was begun This schedule of drug availability

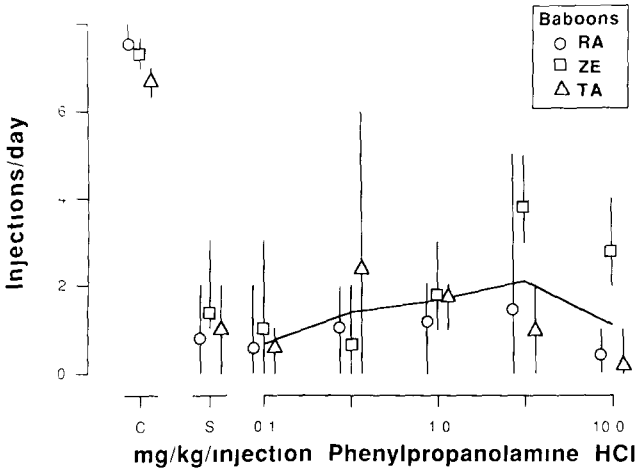

FIG 2 Mean number of injections per day for days 11–15 of phenylpropanolamine or phenylpropanolamine vehicle (saline) substitution under a FR 160-response T O 3-hr schedule of intravenous injection Individual data for each of the 3 baboons (RA, ZE, TA) studied as well as the grouped data (the line) are shown The vertical axis represents injections per day The horizontal axis represents phenylpropanolamine HCl dose in mg/kg/injection plotted on a log scale The points above 'S' represent the data obtained during saline substitution The points above 'C' represent the mean of the mean from the three days of cocaine HCl (0 32 mg/kg/injection) availability that preceded each phenylpropanolamine or saline substitution Bars through each point represent the range of values from which that point was calculated

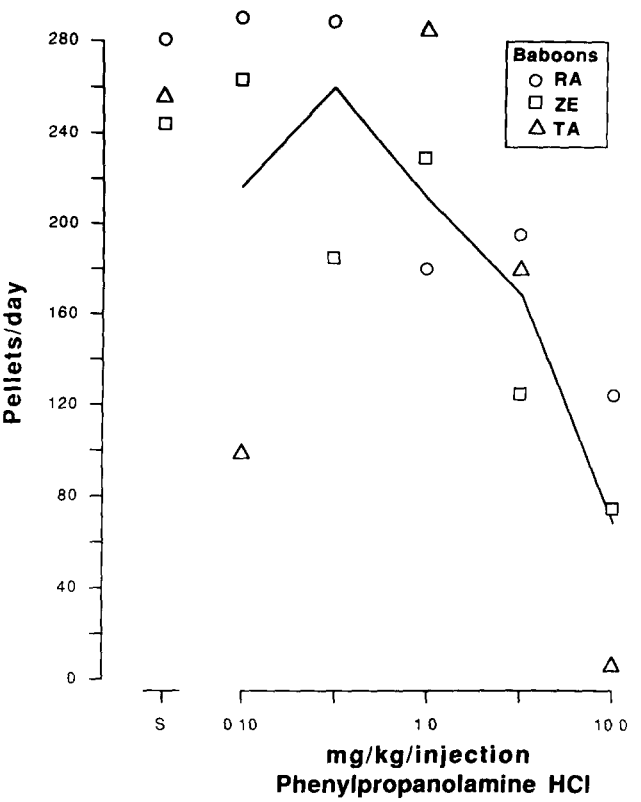

FIG 3 Mean number of food pellets per day for days 1–5 of phenylpropanolamine or phenylpropanolamine vehicle (saline) substitution under a FR 160-response T O 3-hr schedule of intravenous injection Food pellets were continuously available under a FR 30-response schedule of pellet delivery Individual data for each of the 3 baboons (RA, ZE, TA) studied as well as the grouped data (the line) are shown The vertical axis represents pellets per day The horizontal axis represents phenylpropanolamine HCl dose in mg/kg/injection plotted on a log scale The points above 'S' represent the data obtained during saline substitution

permitted a maximum of eight injections per day There was no time limit for completion of the fixed-ratio response requirement. Data were collected each day at approximately 8 a m. and drug changes were made at this time, if indicated

The self-administration of phenylpropanolamine was evaluated using a cocaine substitution procedure [12] Three days during which 0 32 mg/kg/injection cocaine HCl (dissolved in saline) maintained six or more injections per day preceded the substitution of each dose of phenylpropanolamine HCl or phenylpropanolamine vehicle (normal saline). Following substitution of phenylpropanolamine or saline for 15 days, cocaine was again available This procedure of replacing cocaine with a dose of phenylpropanolamine or saline was continued throughout the study. Experiments ran continuously 7 days per week Drug or vehicle injections were 5 ml and each injection was followed by a 5 ml flush of normal saline These injections each took about 90 sec to complete

RESULTS

As can be seen in Fig 1, neither the mean response rate for days 11–15 of phenylpropanolamine substitution for each baboon or for the group of three baboons is substantially different from that obtained on days 11–15 of saline substitution over a hundred fold range of phenylpropanolamine hydrochloride doses (0.10–10.0 mg/kg/injection). Only one dose of phenylpropanolamine in one baboon (ZE; 3.2 mg/kg/injection) maintained rates of responding which did not overlap those maintained by saline As can be seen in Fig. 2, the related measure of injections per day for days 11–15 of phenylpropanolamine substitution is also not maintained at a level substantially above that maintained by saline at the phenylpropanolamine doses tested All doses of phenylpropanolamine in every baboon had a range of the number of injections per day which did overlap those obtained by saline during days 11–15 of saline or phenylpropanolamine substitution

As can be seen in Fig 3, during the first five days of phenylpropanolamine substitution there was a dose related decrease in the number of food pellets obtained At 3 2 and 10 0 mg/kg/injection phenylpropanolamine, the number of food pellets obtained did not overlap the number of food pellets obtained during the same period with saline substitution

DISCUSSION

These studies indicate that intravenous phenylpropanolamine over a wide range of doses does not serve as an effective reinforcer in the baboon under conditions that other amphetamine-like anorectics do serve as reinforcers [9] Although phenylpropanolamine does not serve as a reinforcer, it does reduce food intake under these conditions like other amphetamine-like anorectics [10] These results agree with the results of a previous study from this laboratory that were reported in abbreviated form [10] These results also

agree with those obtained by Woolverton and coworkers [20] in the rhesus monkey In the rhesus monkey, as in the baboon, intravenous phenylpropanolamine does not serve as an effective reinforcer under conditions that other drugs such as amphetamine [20] are effective reinforcers and phenylpropanolamine does reduce food intake

Woolverton and coworkers [20], also, report that phenylpropanolamine can in some, but not all, monkeys set the occasion for amphetamine appropriate responding in monkeys trained to discriminate amphetamine from saline Similar results have been reported in rats [13,14] These results along with previous results reported in the literature indicate that the discriminative and reinforcing properties of the phenylisopropylamines may not covary (cf. [15])

The results obtained in this study as well as those obtained in previous studies in nonhumans indicate that phenylpropanolamine has a low potential for abuse This conclusion is in accord with the results available from controlled human studies Chait and coworkers [5] found no preference for phenylpropanolamine as compared to placebo in normal volunteers Similar results were obtained in patients being treated for obesity [3]

To what extent counterfeit amphetamine "look-alike" preparations maintain an abusive pattern of use is unknown. From the available experimental literature it would appear unlikely that phenylpropanolamine is serving as a reinforcer to maintain this behavior if it does occur Phenylpropanolamine may possibly increase the rate of this behavior due to the overlap in its discriminative stimulus properties with amphetamine, much in the manner that a stimulus associated with food presentation might increase the rate of behavior normally maintained by food when the behavior is undergoing extinction [2]. Alternatively if these counterfeit amphetamine preparations do maintain the behavior leading to their self-administration another ingredient may be responsible for the reinforcing effects of these preparations For example caffeine is a frequent component of these preparations and is thought to play an important role in the maintenance of coffee drinking [11] Likewise ephedrine is a frequent component of these preparations and has been shown to produce amphetamine-like subjective effects in drug abusers [17] and to serve as a reinforcer in baboons and dogs [9,19] Finally, it is important to note that while phenylpropanolamine may not be important for the reinforcing effects of counterfeit amphetamine preparations, phenylpropanolamine may contribute importantly to the adverse effects of these compounds especially when large doses are consumed, since phenylpropanolamine has been reported to produce psychotominetic effects [6,18] and adverse cardiovascular effects [6]

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