*Pharmacology Biochemistry & Behavior*, Vol 38, pp 375–377 © Pergamon Press plc, 1991 Printed in the U S A 0091-3057/91 $3 00 + 00

# Chlordiazepoxide Nonspecifically Enhances Consumption of Saccharin Solution

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Received 28 November 1989

PARKER, L A *Chlordiazepoxide nonspecifically enhances consumption of saccharin solution* PHARMACOL BIOCHEM BEHAV **38**(2) 375–377, 1991 —Following the establishment of a saccharin-amphetamine, saccharin-lithium or saccharin-saline association, rats were given a two-bottle test of preference for saccharin and water Thirty min prior to the test, half of the rats were pretreated with chlordiazepoxide (9 mg/kg) and half of the rats were pretreated with saline The results revealed that pretreatment with chlordiazepoxide (CDP) nonselectively enhanced saccharin consumption regardless of whether the flavored solution had been paired with amphetamine, lithium or saline. These results provide evidence that CDP enhances the palatability of flavored solutions

Chlordiazepoxide Amphetamine Lithium Palatability Conditioned taste aversions Taste reactivity test Psychopharmacology Conditioning

CHLORDIAZEPOXIDE (CDP) has been shown to attenuate conditioned taste avoidance (CTA) produced by shock (5), but its effect on CTAs produced by US drug states appears to be in controversy (2, 3, 5, 7, 13, 14). Delamater and Treit (5) reported that CDP enhances a CTA produced by lithium, while other investigators have reported that CDP attenuates a CTA produced by lithium (2, 6, 14). The former authors suggest that their results support the assumption that shock-based CTAs and lithium-based CTAs are produced by different neurological systems [see (7)]. That is, shock-based CTAs depend upon the action of the defensive system and the avoidance of the shock-paired flavor is the result of the flavor acquiring the capacity to signal danger [e.g., (12,15)]. On the other hand, lithium-based CTAs depend upon the action of the palatability system and the avoidance of the lithium-paired flavored solution is the result of the flavor becoming conditionally distasteful [e.g., (15)].

The traditional consummatory tests for assessing conditioned taste avoidance are ineffective in discriminating among the different associations produced by an unconditional stimulus (US) which affects the palatability system and a US which affects the defensive system, since the measure of learning is reduced consumption for both systems. However, the taste reactivity test devised by Grill and Norgren (9) effectively discriminates among flavor-lithium associations and flavor-shock associations (12). Lithium-paired flavored solutions elicit rejection responses similar to those elicited unconditionally by bitter quinine solution, but equally avoided (in the CTA test) shock-paired flavors do not elicit taste reactivity rejection responses. Furthermore, we (10, 11, 16) have reported that amphetamine-paired flavors, like shock-paired flavors, do not elicit rejection responses in the taste reactivity test which suggests that amphetamine-induced CTAs may not depend upon the palatability system. If amphetamine-paired flavors, like shock-paired flavors acquire the property of signalling danger, rather than becoming distasteful, then it is conceivable that CDP pretreatment will attenuate amphetamine-based CTAs in a similar manner as it attenuates shock-based CTAs.

## METHOD

### *Subjects*

Eighty male Sprague-Dawley rats weighing between 195–234 g were maintained on ad lib Rat Chow and housed in individual stainless steel cages. The experiment was conducted as two replications such that half of the rats in each condition were run about two weeks prior to the other half of the rats in each condition. The two replications were conducted identically and combined for data analysis.

### *Procedure*

One week after their arrival in the laboratory, the rats were deprived of water and given access to water for 15 min per day in graduated drinking tubes on each of three days. On the conditioning trial, the rats were presented 0.1% saccharin solution in a graduated drinking tube for 15 min immediately followed by an intraperitoneal (IP) injection of 3 mg/kg of d-amphetamine in solution with physiological saline, 50.2 mg/kg of 0 15 M lithium chloride in solution with distilled water or physiological saline solution. All injections were given in a volume of 8 ml/kg. On each of the following two days, the rats were given access to water for 15 min per day in graduated drinking tubes.

On the test day, the rats were injected with either 9 mg/kg of chlordiazepoxide in solution with physiological saline or physiological saline solution, in a volume of 1 ml/kg. Thirty min later, they were presented with two graduated drinking tubes containing a 0.1% saccharin solution and unflavored tap water The various groups were as follows: CDP-Amph (n = 14), Sal-Amph (n = 14), CDP-LiCl (n = 14), Sal-LiCl (n = 13), CDP-Sal (n = 13), Sal-Sal (n = 12). During the test trial, each rat was given an opportunity to taste each flavored solution, with the saccharin solu-

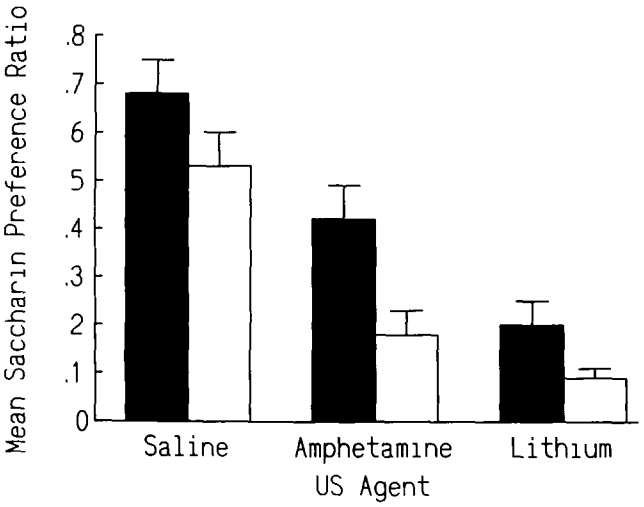


FIG 1 Mean preference for saccharin solution among the CDP-pretreated and the saline-pretreated rats conditioned with saline, amphetamine or lithium (standard errors are also presented) The solid bars represent CDP-pretreated groups and the open bars represent saline-pretreated groups

tion offered first, prior to placement of the drinking tubes on the cage. The side of saccharin tube placement was counterbalanced among the groups and the spouts of the bottles were within 3 cm of one another The amounts consumed from each bottle were measured.

The intake scores were converted to saccharin preference ratios. A preference ratio was obtained by dividing the amount of saccharin solution consumed by the total amount of fluid consumed from both bottles (saccharin + water). A value of 0.5, therefore, would indicate equal preference for both saccharin and water.

## RESULTS

Figure 1 presents the mean saccharin preference ratios for the various groups. A $2 \times 3$ ANOVA revealed a significant US Drug Condition effect, $F(2,74) = 32.2$, $p < 0.01$. Subsequent Newman-Keuls tests revealed that the saline-conditioned rats had higher preference ratios than the amphetamine- or lithium-conditioned rats ($p$'s $< 0.05$), but the amphetamine and lithium-conditioned rats did not differ from one another. Additionally, the pretreatment effect was significant, $F(1,74) = 11.8$, $p < 0.01$, the rats pretreated with chlordiazepoxide showed higher saccharin preference ratios than the rats that were pretreated with saline. Since the pretreatment condition $\times$ US condition interaction was not significant, the effect of CDP pretreatment on saccharin preference appears to be nonspecific, that is, enhancement of saccharin consumption by CDP is not dependent upon the conditioned properties of the solution.

## DISCUSSION

Chlordiazepoxide appears to nonspecifically enhance saccharin consumption regardless of the conditioned properties of the saccharin solution. This result provides further support for Berridge and Treit's (1) and Cooper's (3) suggestion that CDP enhances the positive palatability of flavored solutions. On the other hand, the results are not consistent with reports that CDP does not modify the relative preference for an amphetamine-paired flavored solution (13) and that CDP enhances the aversion of a lithium-paired flavored solution (5) Of course, variation in the CDP dose and/or the strength of the baseline CTAs could influence the effect of CDP pretreatment on the intake of saccharin solution. Riley and Lovely (13) employed a lower dose of amphetamine (2 mg/kg) during conditioning and tested the effect of CDP pretreatment in a two-bottle test after rats had previously received a single-bottle extinction test. On the basis of these procedural differences, the rats would be expected to have a weaker CTA than those in the present experiment Furthermore, in Experiment 2 of Delamater and Treit's (5) report, the rats received six CS preexposure treatments prior to conditioning as well as a weaker dose of lithium as the US treatment (25.6 mg/kg) than in the present experiment. It is thus conceivable that a sufficiently strong baseline CTA is necessary to demonstrate a CDP-induced attenuation of the CTA [see also (14)] Additionally, Riley and Lovely (13) employed a dose of CDP (3 mg/kg) which Roche and Zabik (14) have demonstrated to be ineffective in modifying a lithium-based CTA. In fact, although Riley and Lovely (13) reported that CDP did not significantly modify an amphetamine-induced CTA [with $t(10) = 2.01$, two-tailed, ns], the mean intake scores did vary in a direction consistent with the findings of the present experiment It is, therefore, probable that the dependent measure employed in the present experiment was simply more sensitive to the demonstration of attenuation of an amphetamine-based CTA by chlordiazepoxide pretreatment than was the measure employed by Riley and Lovely (13). Although our findings suggest that chlordiazepoxide attenuates both amphetamine-based and lithium-based conditioned taste aversions by enhancing their palatability, this does not detract from the significance of the report by Riley and Lovely (12) that chlordiazepoxide has nonspecific polydipsic effects that may influence a test of its ability to attenuate CTAs [e.g., (4)]. Because of this important report, investigators regularly employ two-bottle tests when assessing the effect of pharmacological agents upon CTAs [e.g , (8)]

The present results indicate that CDP, within the parameters employed in the present experiment, enhances the palatability of solutions that are conditionally distasteful (lithium-paired saccharin) as well as solutions that are not conditionally distasteful [saline-paired saccharin and amphetamine-paired saccharin (10, 11, 15)]. Therefore, it appears that CDP nonselectively enhances the positive palatability of tastants as suggested by Berridge and Treit (1) who demonstrated that CDP selectively increases the ingestive responding, without modifying the aversive responding, elicited by a variety of tastants. It is, of course, conceivable that modifications of the parameters employed in the present experiment would influence the enhancement of saccharin intake in CDP-pretreated rats However, since the saline-pretreated saline control group showed a mean preference ratio of 0.54, their saccharin preferences served as a good baseline from which to observe differences due to CDP pretreatment effects Another recent study (6) reported that CDP did not enhance lithium-paired or saline-paired saccharin (0 25%) preferences, however, the baseline saccharin preference ratios of saline-conditioned rats (derived from Table 4) was 0.72 suggesting that a ceiling effect may have masked any nonspecific enhancement of saccharin intake.

## ACKNOWLEDGEMENTS

This research was supported by a grant from the National Institute on Drug Abuse and Sam Houston State University Research Council The author is grateful to Hoffmann-La Roche for a donation of chlordiazepoxide

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