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Effect of Clonidine on Consummatory Negative Contrast and on Novelty-Induced Stress

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FLAHERTY, C. F., P. S. GRIGSON AND M. K. DEMETRIKOPOULOS. *Effect of clonidine on consummatory negative contrast and on novelty-induced stress.* PHARMACOL BIOCHEM BEHAV 27(4) 659–664, 1987.—In Experiments 1 and 1a rats were shifted from 32% to 4% sucrose solutions. The resultant negative contrast effect in consummatory behavior was not alleviated by clonidine (3.12, 6.25, 12.5, 25.0 and 50.0 μg/kg). The lower dose of the drug had no effect on behavior, the higher doses reduced consumption in shifted and unshifted rats in a dose dependent fashion. In Experiment 2 clonidine (6.25, 12.5 μg/kg) raised plasma glucose levels in a dose dependent fashion when the animals were exposed to a novel environment. These results are at variance with those obtained with chlordiazepoxide (and other anxiolytics in the case of contrast effects) and suggest limits on the degree to which clonidine can be considered to function as an anxiolytic.

Clonidine Plasma glucose Contrast effects Stress Novelty Anxiolytics

SHIFTING rats from 32% to 4% sucrose leads to a precipitous decrease in consumption—to a level considerably below that of animals that receive only the 4% sucrose solution. This negative contrast effect in consummatory behavior is alleviated in a dose dependent manner by chlordiazepoxide (e.g., [4,27], midazolam [3], ethanol [5], sodium amobarbital [22,25] and morphine [58]. These drugs differ in their effectiveness, with the benzodiazepines the most effective and morphine only marginally effective. Corresponding effects of benzodiazepines and barbiturates have been obtained on negative contrast in instrumental behavior [2, 56, 57]. These data, plus the fact that an elevation in corticosterone is correlated with negative contrast [23,33] indicate that negative contrast involves a stress or anxiety related state.

Consistent with this possibility is the finding that non-anxiolytic drugs tend to be without effect in the contrast procedure. Scopolamine, for example, does not affect contrast [3,28]. Contrast is not alleviated by methysergide [3], pyrilamine [3] or chlorpromazine and haloperidol [26, 55, 57].

The present series of experiments is concerned with the effects of clonidine on consummatory negative contrast and on novelty-induced stress. Clonidine has been effective in several animal models of anxiety. For example, clonidine reduces the magnitude of both the startle response and the potentiated startle response [12,13], it releases punished responding in the Geller-Seifter conflict test [10,41], and it blocks the anxiogenic effect produced by an injection of yohimbine into monkeys [53].

Data derived from clinical trials also suggest that clonidine might be effective in reducing contrast. That is, clonidine has been reported to have anxiolytic and antipanic effects [48,66] and to reduce the anxiety-like symptoms correlated with opiate withdrawal [32, 65, 68] and ethanol withdrawal [7]. However, the results in some of these clinical trials have been variable, often no effect being found [52, 66, 67].

Finally, there are also theoretical reasons for expecting an effect of clonidine on contrast. Gray [34,35] has proposed a neural mechanism for anxiety in which noradrenergic activation plays a key role. Gray's model suggests that clonidine should act in an anxiolytic fashion (e.g., [34], p. 362).

EXPERIMENTS 1 AND 1a

These experiments examined the effects of clonidine in doses of 50, 25, 12.50, 6.25, and 3.13 (Experiment 1a) μg/kg on the negative contrast effect that occurs when rats are shifted from 32% to 4% sucrose solutions.

METHOD

Subjects

Male Sprague-Dawley derived rats purchased from Blue-Spruce were used as subjects. Sixty rats were used in Experiment 1 and 24 in Experiment 1a. The animals, approximately 100 days old at the start of the experiment, were

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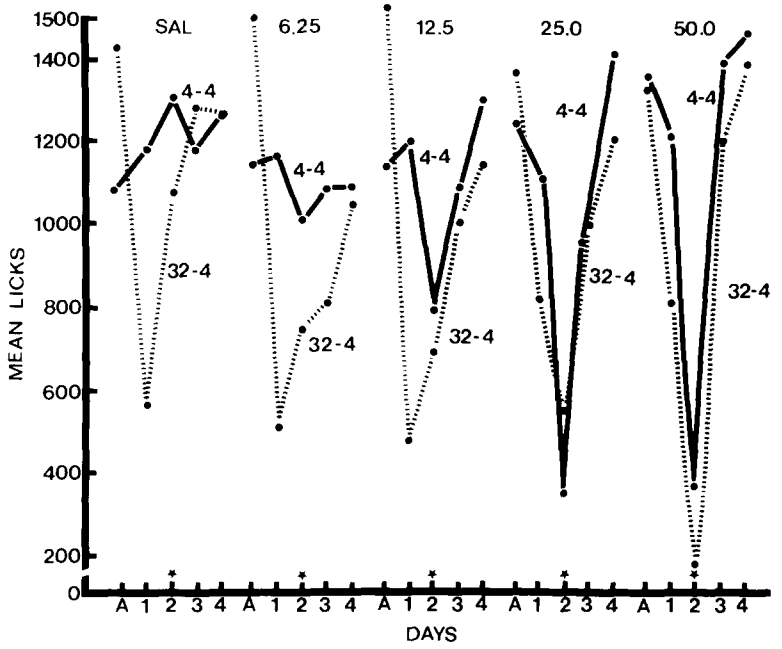

FIG. 1. Mean lick frequency in shifted (32–4) and unshifted (4–4) rats on the terminal acquisition day (A) and on each of the four postshift days. The clonidine injections (6.25, 12.5, 25.0 and 50.0 micrograms per kilogram) and saline injection (SAL) were administered on the second postshift day as indicated by the star.

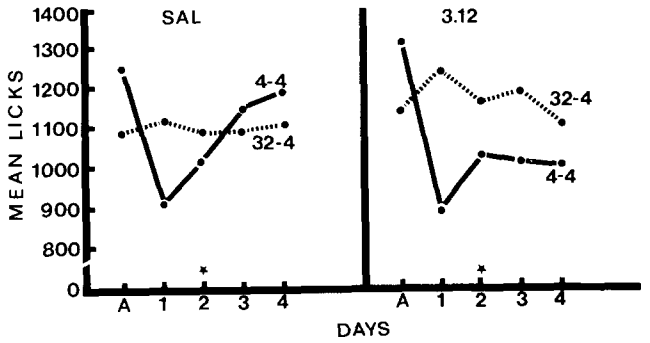

FIG. 2. Mean lick frequency in shifted and unshifted rats on the terminal acquisition day (A) and four postshift days. The saline (SAL) and clonidine (3.12 micrograms per kilogram) were administered on the second postshift day.

housed singly in metal cages and maintained on a 14 hr/10 hr light/dark cycle. The rats were kept at 82% of their free-feeding weight for the duration of the experiment. Water was always available in the home cage.

Apparatus

Testing was conducted in six identical metal grid cages (24.5×17.5×18 cm). A centrally located hole (1 cm in diameter) 7 mm above the floor was present in one wall of each cage. A graduated cylinder was placed outside of each chamber so that the orifice of the drinking spout was centered in the hole and flush with one wall of the chamber. Licking was recorded through a contact relay circuit by microprocessors.

Procedure

Half of the animals in each experiment (the Shifted Group) received a five minute access period to a 32% sucrose solution during a ten day preshift period. The remaining animals (the Unshifted Group) received access to a 4% sucrose solution during the preshift period. From the eleventh through the fourteenth day all animals were given the 4% sucrose solution.

The drug treatments were administered on day 12 (the second postshift day). In Experiment 1 separate groups of shifted and unshifted animals were injected with clonidine in doses of 50, 25, 12.5, or 6.25 μg/kg. Control animals were injected with isotonic saline (the drug vehicle). In Experiment 1a separate groups were injected with either 3.12 μg/kg of clonidine or with saline. The drug was injected IP 30 minutes prior to the beginning of the session. No injections were given on Day 11 or on Days 13 and 14.

The clonidine was purchased from Sigma, St. Louis, MO. The sucrose solutions were prepared by weight [sucrose/(sucrose + water)] from commercial grade cane sugar and tap water. The solutions were mixed 24 hours preceding each session and were presented at room temperature.

RESULTS

Terminal preshift and daily postshift lick frequencies obtained in Experiment 1 are presented in Fig. 1. At the end of preshift training (Day 10), the animals receiving the 32% solution licked more than the animals receiving the 4% solution, $F(1,49)=24.17$, $p<0.001$. The group that would receive the 50 μg/kg dose was an exception to this finding (see Fig. 1), but the interaction term (Solution × Drug Group) failed to reach reliability, $F(4,49)=2.36$, $p>0.066$.

Examination of the animals in the 50 μg/kg group showed

that the 4% group had a higher than usual average lick frequency and that two of the animals in the 32% group had atypically low lick frequencies. If the data were examined in terms of medians, rather than means, the normal 32%>4% ordering was present for the groups.

The animals shifted from 32% to 4% sucrose showed a substantial decline in lick frequency and, on the first postshift day, licked at a reliably lower level than the unshifted 4% group [Concentration × Drug × Day, $F(12,139)=2.83$, $p<0.002$, followed by least significant difference test, $p<0.05$]. The principal effect of clonidine was to reduce consummatory behavior. On Day 12 there was a reliable contrast effect in the saline and 6.25 μg/kg drug groups, but not in any of the other groups (least significant difference (LSD) test, $p=0.05$). The loss of contrast in the other groups was not due to a disinhibitory effect of the drug, but rather to a general decline in lick frequency. Thus, the lick frequencies of the drug-injected shifted and unshifted groups were all lower than the saline group on Day 12 (LSD test, $p=0.05$). This suppressant effect of clonidine was dose dependent (Fig. 1) with groups ranked as follows in terms of lick frequency: Sal > 6.25 = 12.50 > 25 = 50 for the unshifted groups, and sal > 6.25 = 12.50 = 25 > 50 for the shifted groups.

The results obtained with the 3.12 μg/kg dose of clonidine in Experiment 1a are presented in Fig. 2. This dose did not suppress intake nor did it influence contrast. The shifted rats licked less than the unshifted rats over the postshift period, $F(1,18)=9.65$, $p<0.01$, but there was no effect of drug or interactions between drug and other factors (all $Fs<1.00$).

DISCUSSION

Clonidine clearly did not reduce contrast. Degree of contrast was not influenced by the two lower doses of the drug (3.12, 6.25 μg/kg) and the three higher doses (12.5, 25.0, and 50.0 μg/kg) all had a suppressant effect on sucrose intake. These results are different than those obtained with anxiolytics such as chlordiazepoxide, midazolam, sodium amobarbital, ethanol, and morphine—all of which reduce contrast to a greater or lesser degree by selectively increasing the lick frequency of the rats shifted from the 32% to the 4% sucrose solution (references cited earlier). Chlordiazepoxide and sodium amobarbital have also been found to reduce contrast in instrumental tasks independent of their effect on consummatory behavior [2, 56, 57].

The results obtained in this study vary from those obtained in some other animal models of anxiolytic action. For example, clonidine has been reported to have anxiolytic effects in the Geller-Seifter conflict procedure [10,41], the potentiated startle procedure [12], and following an injection of yohimbine [53]. However, clonidine has not shown anxiolytic effects in exploratory and open-field related behaviors [11,39], nor does it block the anxiogenic-like effects of pentylenetetrazol [43]. These latter results are consistent with the failure of clonidine to influence contrast. The various animal models of anxiolytic action most likely capture different aspects of "anxiety" or emotionality and the systems influenced by clonidine are apparently not common to all these models.

Independent of the effects of clonidine on contrast, the effects of the drug on sucrose intake are suprising. Several studies have reported that clonidine enhances food intake, particularly carbohydrates—including sucrose pellets and sucrose chow [47, 49, 54, 59, 72]. These effects have been obtained in monkeys as well as rodents and have been obtained in deprived and nondeprived animals and with acute and chronic administration of clonidine. Two factors may be related to the different results obtained in the present study—the short test session (five minutes as compared to the typical one hour or longer session in other studies) and the fact that the sucrose was in solution and not a solid food substance. Of the two, the length of the test session seems likely to be more important. If this is the case, it would suggest that clonidine may enhance food intake by reducing satiation rather than stimulating intake per se. In this regard it is interesting that Yim *et al.* [71] reported that clonidine increased food intake in satiated rats but not in non-satiated rats.

However, it should be noted that the present results indicate that another factor may also be involved. Clonidine not only failed to increase sucrose intake, it substantially suppressed it. These results are suggestive of the disrupting effects that clonidine has on a variety of operant schedules including FI [37,69], FR [19,50], DRL [64], and tandem schedules [18]. This schedule disruption effect, and the decrease in consumption obtained in the present experiment (and some others [1, 45, 46]), may be related to the sedative effects of clonidine [6, 15, 17, 40, 44, 62, 63, 70]. It remains undetermined when intake stimulating effects and when sedative effects of clonidine will predominate. A review of the cited literature suggests that drug dose is not related to these different effects in a simple fashion since all have been obtained within the same dose range.

EXPERIMENT 2

Exposing rodents to a novel environment is a substantial stressor leading to elevations in epinephrine, norepinephrine, corticosterone, thyroid stimulating hormone, prolactin, and plasma glucose [16, 20, 21, 24, 29, 38, 42]. The novelty-induced rise in plasma glucose is reduced by pretreatment with chlordiazepoxide [20, 21, 29] in a dose range that would be sufficient to eliminate negative contrast. The present experiment was conducted to examine the effects of clonidine in the same novel environment conditions that were previously used to investigate the effects of CDP [29].

METHOD

Subjects

Twenty-seven male Sprague-Dawley derived rats were used as subjects. The animals were maintained on a 14 hour/10 hour light/dark cycle and had free access to food and water. The animals weighed approximately 400 grams at the start of the experiment.

Apparatus

The novel environment was the same as that described as "Environment A" in previous experiments [29]. Briefly, the animals were transported from their colony room and placed into black plastic wastebaskets (0.36 m^3) with hardware cloth covers. The wastebaskets had woodchips on the floor and were permeated with a menthol odor. The room in which the wastebaskets were contained was dimly illuminated (1 foot candle) with incandescent light and white noise was constantly present.

This room contrasted with the animals' colony room where the animals were housed in standard hanging metal cages with bright fluorescent lighting and no white noise.

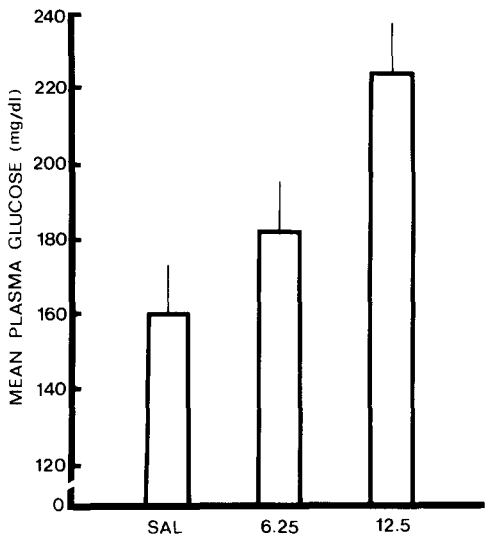

FIG. 3. Mean plasma glucose level as a function of saline or clonidine administration. The clonidine doses are in terms of micrograms per kilogram.

Procedure

Nine animals were randomly assigned to each of three groups which differed in terms of drug injection: isotonic saline; clonidine 6.25 μg/kg; or clonidine 12.5 μg/kg. The injections were made IP 30 minutes prior to exposure to the novel environment.

The animals were transported to the novel environment, left there for 20 minutes, and then returned to the colony room. In the colony room the animals were placed on a table and, while gently restrained by one experimenter, a second experimenter removed the tip of the rat's tail with a scalpel and extracted 75 microliters of blood into a heparinized microhematocrit tube. The blood was centrifuged and plasma glucose levels determined by spectrophotometer (Spectronic 88) using the Statzyme Glucose kit manufactured by Worthington Diagnostics, Freehold, NJ.

RESULTS

Clonidine raised plasma glucose levels, $F(2,21)=14.55$, $p<0.001$. Analyses of these data (shown in Fig. 3) with the least significant difference test ($p<0.05$) indicated that the plasma glucose levels of the animals injected with the 12.5 μg/kg dose were reliably higher than the plasma glucose levels of the saline and 6.25 μg/kg clonidine group. This latter group did not differ reliably from the saline injected animals.

DISCUSSION

The fact that systemically administered clonidine raised plasma glucose levels in the present experiment is consistent with other findings showing that clonidine releases ACTH from rat pituitary cells in culture [31]; increases plasma concentrations of immunoreactive beta-endorphin in rats [51]; raises corticosterone levels in rats [8]; raises plasma glucose levels in cats when administered through the left vertebral artery [9]; blocks the release of insulin [60]; and sometimes [36,39], but not always [61], has a hyperglycemic effect in humans administered clonidine for therapeutic reasons.

However, this hyperglycemic effect of clonidine means that, in a situation in which CDP had been previously shown to moderate increases in plasma glucose level, clonidine exacerbated them. Thus, clonidine failed to produce a benzodiazepine-like effect in negative contrast and in novelty stress, two situations which have a degree of empirical and theoretical validity as animal models of stress and/or anxiety. In considering the several animal models in which anxiolytic drugs have been investigated, clonidine functions in an anxiolytic fashion in the Geller-Seifter conflict test, and the potentiated startle test, but does not function in an anxiolytic fashion in the incentive contrast procedure, when the animals are exposed to novel environments including open-field tests of exploratory behavior, and when the animals are administered pentylenetetrazol.

It may be possible to reconcile this pattern of results. The Geller-Seifter test and the potentiated startle test both involve shock, the other paradigms do not. Thus, clonidine may have anxiolytic action under conditions of stress produced by physical pain or the anticipation of such pain, but not under conditions elicited by the "psychological" stressors of reward loss or novelty.

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