

Selective Effects of the δ -Opioid Receptor Agonist DPDPE on Consummatory Successive Negative Contrast

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Two experiments explored the role of the opioid system in a situation involving a surprising reduction in reward magnitude: *consummatory successive negative contrast*. Rats received access to 32% sucrose solution (preshift Trials 1–10) followed by 4% solution (postshift Trials 11–15). Independent groups received an injection of either the vehicle or the δ -receptor agonist [D-Ala²-,N-Me-Phe⁴,Gly-ol] enkephalin (DPDPE; 24 μ g/kg). DPDPE attenuated the contrast effect when injected before Trial 11 but not when injected before Trial 12. An additional experiment showed that the attenuating effect of partial reinforcement on the recovery from contrast was reduced by DPDPE injections administered before nonreinforced preshift trials.

Rats exposed in daily trials to a sweet 32% sucrose solution later drank a less-sweet 4% solution significantly less often than did a control group exposed to only the 4% solution (Vogel, Mikulka, & Spear, 1968). This effect, known as *consummatory successive negative contrast* (cSNC), involves a sharp suppression of consummatory behavior in the first trial after the downshift, followed by a recovery of behavior in subsequent trials. There is evidence that consummatory suppression is controlled by different mechanisms in the first versus the second trial after the downshift. For example, benzodiazepine anxiolytics (e.g., chlordiazepoxide, flurazepam, midazolam) reduce the size of cSNC when administered on the second postshift trial but not when administered on the first postshift trial (e.g., Becker, 1986; Flaherty, Grigson, Demetrikopoulos, Weaver, Krauss, & Rowan, 1990; Flaherty & Rowan, 1989). One interpretation (Flaherty, 1996) relies on the idea that benzodiazepine anxiolytics reduce the influence on consummatory behavior of the conflict between rejecting the downshifted solution (which is frustrating given the expectation of a large reward) and consuming it (given that the rat is deprived of food). Of course, the conflict arises only after the rat has had some experience with the downshifted solution. Thus, if the first postshift trial is longer than usual (e.g., more than the typical 5-min duration), then anxiolytics do reduce cSNC (e.g., Flaherty, Grigson, & Rowan, 1986; Mustaca, Bentosella, & Papini, 2000). These data are consistent with the hypothesis that the mechanisms underlying the initial impact of the downshift are dissociable from those underlying the recovery of consummatory behavior that follows.

If this hypothesis is correct, then it should be possible to find manipulations that affect primarily the initial reaction to the downshift without disrupting the recovery process. There are a few drug treatments that reduce the initial impact of reward downshift in the

cSNC situation, but none appears to be selective. For example, Rowan and Flaherty (1987) reported that morphine (4 and 8 mg/kg; a nonselective opioid agonist), administered 20 min before the first postshift trial significantly reduced the size of the cSNC effect, without affecting consummatory behavior per se. However, the same doses also reduce cSNC when administered on the second postshift trial. Similarly, cyproheptadine (3 and 6 mg/kg; a drug that binds to several receptors, including serotonin, acetylcholine, and histamine receptors), administered 30 min before the first postshift trial significantly reduced cSNC (Grigson & Flaherty, 1991). Again, however, cyproheptadine also attenuates cSNC when administered on the second postshift session (Becker, 1986). Grigson and Flaherty (1991) explored the potential contribution of serotonergic and histaminergic pathways to the effects of cyproheptadine on the first postshift trial without success. Thus, the mechanism by which cyproheptadine reduces the initial impact of reward downshift remains undetermined.

On the basis of the available evidence, Flaherty (1996) suggested a multistage model of cSNC involving a series of transitions from detection to rejection, search, and recovery. The initial impact of the downshift involves three components: detection, rejection, and search. Thus, rats downshifted from a large to a small reward exhibit significant increases in general activity and rearing, two behaviors that might be interpreted as reflecting searching patterns (Flaherty, Blitzer, & Collier, 1978; Pecoraro, Timberlake, & Tinsley, 1999; Pellegrini & Mustaca, 2000). According to Flaherty (1996), this “early reaction to reward reduction might be considered to be cognitive—a search for the ‘missing’ substance” (p. 95), whereas the recovery stage may involve stress and conflict. An alternative interpretation may be phrased in terms of Amsel’s (1992) frustration theory. According to frustration theory, a discrepancy between the expectancy of a larger reward and the presentation of a small reward induces an unconditioned internal state of primary frustration characterized by being hedonically aversive and by facilitating dominant responses (Daly, 1974; Stout, Boughner, & Papini, 2003). An association between prevailing cues and primary frustration allows those cues to subsequently elicit an expectancy labeled *secondary frustration*. Evidence from instrumental training situations suggests that the effects of primary and secondary frustration on behavior are dis-

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sociable (for a review, see Papini, 2003). When applied to the cSNC situation, frustration theory suggests that the initial response to the downshift may be predominantly dependent on primary frustration (an unconditioned internal state), whereas recovery from contrast may depend predominantly on the conflict induced by reward consumption and secondary frustration (a conditioned internal state).

Gray (1987) noticed that many of the factors that modulate behavioral effects that involve secondary frustration (including instrumental SNC) are similar to those that modulate performance in situations involving fear conditioning (including learning avoidance; see also Gray & McNaughton, 2000). On that basis, it was suggested that the same brain network is engaged by situations involving the surprising omission of appetitive reinforcers (frustration) and the presentation of aversive reinforcers (fear). This was labeled the *fear = frustration hypothesis*. Because the unconditioned response supporting fear conditioning in most experiments is peripheral pain induced by electric shock, then one may generalize Gray's view in the following manner: If fear = secondary frustration, then pain = primary frustration. This is consistent with the attenuating effects of morphine on the initial reaction to reward downshift (see above) and suggests that a more detailed analysis of the role of opioids in the cSNC situation is warranted. The present experiments provide information on the effects of a more selective opioid-receptor agonist, D-Ala²-,N-Me-Phe⁴,Gly-ol (DPDPE), on cSNC in rats. DPDPE was selected because, in addition to being more selective in its receptor effects (Cotton, Kosterlitz, Paterson, Rance, & Traynor, 1985; Goldstein, 1987), it has also been shown to have a variety of effects on pain-induced behavior (see Bodnar & Hadjimarkou, 2003). For example, DPDPE attenuated the behavioral effects of a subcutaneous injection of formalin (Fanselow, Calcagnetti, & Helmstetter, 1989) and impaired the acquisition of one-way active avoidance based on electric shock (Martinez, Hernandez, & Rodriguez, 1992).

Experiment 1

This experiment sought to answer the following question: Is the δ -opioid receptor selectively involved in the initial response to a surprising reduction in reward magnitude? Unpublished research from our lab indicated that DPDPE attenuates cSNC in a dose-dependent manner (Castro, 2000). Rats that had received 10 daily trials of access to a 32% sucrose solution followed by 5 trials of access to a 4% solution received i.p. injections of 0 (saline), 6, 12, 24, 48, or 96 $\mu\text{g}/\text{kg}$ of DPDPE before Trials 11 and 12—the first and second postshift trials. Consummatory performance, measured in terms of fluid intake, exhibited least suppression in Trial 11 at the 24 $\mu\text{g}/\text{kg}$ dose. Moreover, similar doses were used in other experiments in which DPDPE had a behavioral effect (e.g., Shulteis, Martinez, & Hruby, 1988). On the basis of these results, the 24 $\mu\text{g}/\text{kg}$ dose was chosen for the present experiments. Experiment 1 was designed to isolate the potentially differential effects of DPDPE on Trials 11 and 12. Three groups of rats received injections before each of these two trials. A drug control group was injected both times with distilled water (vehicle), a second group received a DPDPE injection before Trial 11 and a vehicle injection before Trial 12, and a third group received a vehicle injection before Trial 11 and a DPDPE injection before Trial 12. Three additional groups received the same drug treatments, except they

had access to the 4% sucrose solution throughout the 15 training trials (unshifted controls). Because this experiment was designed to evaluate the extent to which DPDPE reduced the size of the cSNC effect, the key comparisons involved Groups 32–4 versus Groups 4–4 at each drug treatment.

Method

Subjects. Forty-eight Long-Evans hooded rats, approximately 90 days old, were used in this experiment. Rats were bred and housed in the Texas Christian University vivarium under a 12 hr light:12 hr dark cycle (lights on at 07:00 hr), and were deprived of food to 80%–85% of the free-food weight. Water was continuously available in each individual wire mesh cage. Animals were trained during the light phase of the daily cycle.

Apparatus. Training was conducted in four conditioning boxes (MED Associates, St. Albans, VT) constructed of aluminum and Plexiglas and measuring 29.3 cm in length, 21.3 cm in height, and 26.8 cm in width. The floor was made of steel rods 0.4 cm in diameter and 1.6 cm apart running perpendicular to the feeder wall. A bedding tray filled with corncob bedding was placed below the floor to collect fecal pellets and urine. Against the feeder wall was an elliptical hole 1-cm wide, 2-cm high, and 4 cm from the floor. A sipper tube, 1 cm in diameter, could be inserted through this hole. When fully inserted, the sipper tube protruded 1.5 cm into the box. A computer located in an adjacent room controlled presentation and retraction of the sipper tube. The computer also detected contact with the sipper tube by way of a circuit involving the steel rods in the floor. Each conditioning box was placed in a sound-attenuating chamber that contained a speaker to deliver white noise and a fan for ventilation. Together, the speaker and fan produced noise with an intensity of 80.1 dB (Scale C). Animals were trained in the dark.

Procedure. Training lasted for a total of 17 daily trials. All the rats included in this experiment were trained at the same time. Each rat was assigned to one of the four conditioning boxes and always trained in that box. Rats were trained in squads of four; squads were constant, but the order of training of the squads was varied across days. After each trial, conditioning boxes were cleaned with a damp paper towel, feces were removed when present, and bedding material was replaced as needed. The first two trials served to familiarize animals with the training context. Rats were placed in the box for 5 min; the white noise and fan were constantly on. No solution was presented during these two initial trials.

The following 15 trials were divided into a preshift phase (10 trials) and a postshift phase (5 trials). Rats were randomly assigned to one of six groups ($n = 8$). For Group 32/V/V (where V stands for vehicle), the 10 preshift trials involved access to a 32% sucrose solution (wt/wt, prepared by mixing 32g of commercial sugar for every 78g of distilled water), whereas the 5 postshift trials involved access to a 4% solution (wt/wt, 4g of sugar for every 96g of distilled water). Vehicle injections (distilled water, 1 ml/kg) were administered 6 min before Trial 11 (first postshift trial) and Trial 12 (second postshift trial). Group 4/V/V received the same treatment, except the 4% sucrose solution was presented throughout the 15 training trials.

Groups 32/DPDPE/V and 4/DPDPE/V received the same training described for the previous two equivalent groups, except that DPDPE (24 $\mu\text{g}/\text{kg}$ at a volume of 1 ml/kg) was administered 6 min before Trial 11. Similarly, Groups 32/V/DPDPE and 4/V/DPDPE received the same treatment, except that the DPDPE injection was administered 6 min before Trial 12.

Each trial started with a variable pretrial interval of 30 s (range: 15–45 s). At the end of this interval, the sipper tube was automatically presented. A trial started when a rat maintained contact with the sipper tube for a cumulative total of 5 s during any 30-s interval. This criterion was introduced to avoid initiating a trial after an accidental contact with the sipper tube that did not involve drinking. The trial lasted a minimum of 5 min; if a rat was drinking when the 5-min period ended, the solution remained available until the rat spontaneously interrupted drinking. This was done to

avoid retracting the sipper tube while the rat was drinking from it, a "punishment" contingency that could potentially affect drinking behavior. Trial duration was longer than 5 min for 16 of the 48 rats. A total of 53 trials were longer than 5 min, out of a total of 720 trials (7%) administered to all the rats in the course of this experiment. Of these 53 trials, 21 occurred during the postshift phase. The average duration of these longer trials was 404.2 s. Retraction of the sipper tube was followed by a posttrial interval averaging 30 s (range: 15–45 s). The dependent variable was the cumulative amount of time in contact with the sipper tube, measured in 0.05-s units. This variable, labeled *goal tracking time*, was shown in separate studies to correlate positively and significantly with the amount of fluid ingested during 5-min long trials (Mustaca, Freidin, & Papini, 2002). Data were lost as a result of equipment malfunction in four preshift trials, in different rats assigned to four different groups (Groups 32/DPDPE/V, 32/V/DPDPE, 32/V/V, and 4/DPDPE/V), and in 1 rat for Trial 11 (in Group 4/V/DPDPE). Missing preshift values were replaced by the average of the preceding and following trial of that particular rat. The missing Trial 11 value was replaced by the group average for that trial.

DPDPE (Sigma-Aldrich Chemicals, St. Louis, MO) was prepared by mixing 1 mg of DPDPE powder with 1 ml of distilled water. The stock solution was then diluted to obtain the desired dosage of 24 $\mu\text{g}/\text{ml}$. The drug was prepared before Trial 11. All injections were administered 6 min before the start of Trials 11 and 12.

Results

Figure 1 shows the main results of this experiment in terms of

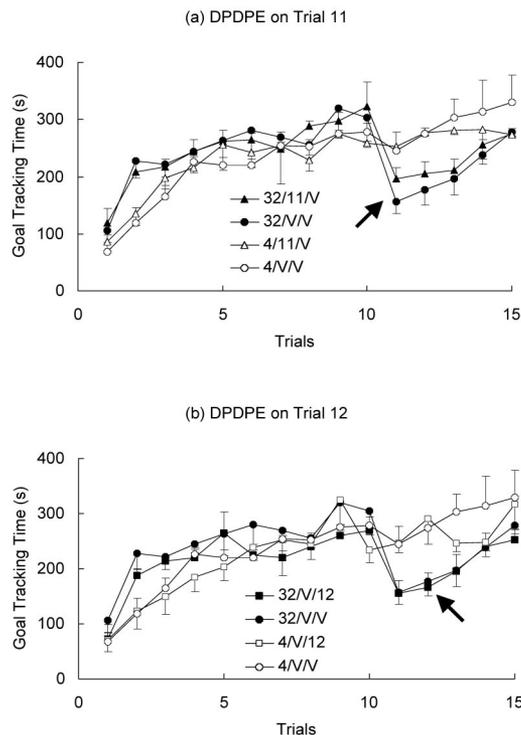


Figure 1. Results of Experiment 1. a: Performance of the groups injected with [D-Ala2-,N-Me-Phe4,Gly-ol] enkephalin (DPDPE) on Trial 11 (see arrow). b: Performance of the groups injected with DPDPE on Trial 12 (see arrow). These four groups received a vehicle injection on Trial 12 or 11, respectively. The two injection controls that received vehicle injections on both Trials 11 and 12 are reproduced in both panels. The downshift from 32% to 4% sucrose solution occurred on Trial 11 for all the groups. V = vehicle injection.

the group average of goal tracking time for each daily trial. The groups receiving access to 32% solution tended to develop drinking behavior faster than the groups given 4% solution. A Sucrose (32%, 4%) \times Trial (1–10) analysis of variance (ANOVA), with groups pooled irrespective of drug treatment in the subsequent postshift phase indicated that the 32% groups were significantly above the 4% groups, $F(1, 46) = 5.21, p < .03$, and their behavior changed significantly across trials, $F(9, 414) = 43.11, p < .001$. The interaction between these factors fell short of statistical significance, $F(9, 414) = 1.86, p < .06$.

Figure 1 also shows consummatory performance in the postshift phase (Trials 11–15). These results may be summarized into three main comparisons. First, a comparison of Groups 32/V/V versus 4/V/V provides good evidence of a cSNC effect. There was a substantial drop in goal tracking times in Group 32/V/V on Trials 11 and 12, followed by a recovery of consummatory behavior in the subsequent trials. Second, DPDPE diminished the size of the consummatory suppression on Trial 11 in the downshifted rats (Group 32/DPDPE/V), without affecting performance in the unshifted controls (Group 4/DPDPE/V). Thereafter, consummatory performance recovered to normal levels in the downshifted rats. Third, DPDPE had no observable effect when administered before Trial 12, either in Group 32/V/DPDPE or in Group 4/V/DPDPE.

These data were subjected to independent one-way ANOVAs followed by LSD multiple comparisons. Two sets of four groups were selected for analysis. First, to determine the effects of DPDPE administered before Trial 11, one-way ANOVAs on Trial 11 and 12 were computed on Groups 32/DPDPE/V, 4/DPDPE/V, 32/V/V, and 4/V/V. There was a significant group effect on Trial 11, $F(3, 28) = 4.09, p < .02$. Pairwise comparisons indicated a significant cSNC effect in the vehicle groups ($p < .01$) but not in the DPDPE-treated groups ($p < .10$). Group 32/DPDPE/V was also not different from Group 4/V/V ($p < .15$). The difference between the two downshifted groups also failed to reach significance ($p < .19$). A similar set of analyses, on the same groups, was computed for Trial 12 with the following results: The group effect was significant, $F(3, 28) = 7.92, p < .01$. Pairwise comparisons revealed significant cSNC effects for both the vehicle groups ($p < .001$) and the DPDPE groups ($p < .01$). The latter effect is attributed to a minimum amount of recovery in the downshifted group combined with an increase in the consummatory behavior of the unshifted control. Group 32/DPDPE/V also differed from Group 4/V/V ($p < .01$) but not from Group 32/V/V for a small margin ($p < .30$). Thus, DPDPE administered before Trial 11 had an attenuating effect on cSNC on that trial, but the effect was not present on Trial 12.

Second, to determine the effects of DPDPE administered before Trial 12, one-way ANOVAs on Trial 11 and 12 were computed on Groups 32/V/DPDPE, 4/V/DPDPE, 32/V/V, and 4/V/V. There was a significant group effect on Trial 11, $F(3, 28) = 4.47, p < .02$. On Trial 11, and as one might expect because no treatment had been administered at this point, the cSNC effect was significant in both the vehicle and DPDPE pairwise comparisons ($ps < .02$). Furthermore, there were no significant differences between the two shifted groups or between the two unshifted groups ($ps < .96$). The group effect was also obtained on Trial 12, $F(3, 28) = 4.62, p < .02$. It is interesting to note that DPDPE had no detectable effect when administered on Trial 12. The same statistical results just described for Trial 11 were also obtained on Trial 12 for the pairwise comparisons: The two cSNC effects ($ps < .04$) and the

lack of differences among the two shifted and the two unshifted groups ($ps < .81$).

Discussion

To our knowledge, Experiment 1 provides the first evidence of any drug that attenuates performance on only the first postshift session in a cSNC situation (see Flaherty, 1996, for a detailed review). An interpretation of these results requires the guidance of some behavioral theory, and, as mentioned previously, we adopt frustration theory for this purpose (Amsel, 1992). Figure 2 displays a schematic representation of the theory's application to the first postshift trial (Trial 11 in Experiment 1). Frustration theory assumes that during the preshift trials (Trials 1–10) the rat develops an expectancy of obtaining the 32% solution (e_{32}) when placed in the conditioning box or when in contact with a portion of the box, such as the area around the sipper tube (S) and that either S or e_{32} instigate the drinking response (R_D). On Trial 11, the detection of a discrepancy between e_{32} and $S_{4\%}$ (the actual solution encountered in the box) induces an internal unconditioned state of primary frustration (R_F), which is hedonically aversive. We add to this picture the additional assumption that the detection of a discrepancy between expected and obtained reward also changes the hierarchy of dominant responses, reducing the dominance of drinking (hence the inhibitory link from R_F to R_D in Figure 2) and increasing the dominance of other responses (R_O), such as activity and rearing (e.g., Pellegrini & Mustaca, 2000). Although R_F is hedonically aversive, we assume that it does not involve conflict. As shown in Figure 2, there are at least seven ways in which DPDPE could have disrupted consummatory behavior, but only some of them can account for the selective attenuation of cSNC observed in Experiment 1.

Hypothesis 1: Deflation of the incentive value of the 32% solution expectancy. This would be functionally equivalent to reducing the concentration of the preshift solution. For constant postshift concentrations, the lower the preshift magnitude of the

sucrose solution the smaller the impact of reward downshift (Pellegrini & Papini, 2004). Thus, DPDPE could have attenuated cSNC by deflating the value of the memory for the 32% solution. To the extent that consummatory suppression on Trial 12 is also partly dependent on a discrepancy between expected and obtained magnitudes, this account predicts that cSNC should be also attenuated by DPDPE on Trial 12—an effect that was not observed in Experiment 1. Furthermore, there is no evidence that DPDPE can reduce the incentive value of sucrose solutions; if anything, it does just the opposite, as will be discussed in hypothesis 3.

Hypothesis 2: Facilitation of consummatory behavior. There is evidence that a variety of opioid receptor agonists, including DPDPE, increase consumption of sucrose solutions, whereas opioid antagonists decrease it (e.g., Ruegg, Yu, & Bodnar, 1997). Thus, it is possible that the attenuating effect of DPDPE on cSNC on Trial 11 is a consequence of drug-induced drinking of the solution and has no connection to the reward downshift manipulation. One problem with this hypothesis is that it also predicts an increase in consummatory behavior in Group 4/DPDPE/V on Trial 11 and of Groups 32/V/DPDPE and 4/V/DPDPE on Trial 12 relative to their respective vehicle controls, none of which was observed in Experiment 1.

Hypothesis 3: Inflation of the incentive value of the 4% solution experienced on Trial 11. Rats administered DPDPE and exposed to a distinct context later develop a preference for that context, relative to a place paired with vehicle injections (Shippenberg, Bals-Kubik, & Herz, 1987). DPDPE may have the potential to inflate the incentive value of a 4% sucrose solution, just as it does for places (see Stromberg, Meister, Volpicelli, & Ulm, 1997). This would be functionally equivalent to increasing the magnitude of the postshift solution (i.e., shifting to a solution that is higher than 4% in concentration). For constant preshift concentrations, the higher the postshift concentration the smaller the size of the cSNC effect (Pellegrini & Papini, 2004). But if this were the case, then DPDPE should have also inflated the value of the 4% solution on Trial 12, thus causing a similar attenuation of cSNC on that trial.

Hypothesis 4: Inhibition of primary frustration. Opioid activation may diminish the intensity of the aversive state of primary frustration induced by the discrepancy between expected and obtained magnitudes, thus reducing the suppression of drinking behavior. This effect could be direct, affecting a system responsible for primary frustration, or it could be indirect. An example of an indirect effect is provided by Konorski's (1967) theory of reciprocal inhibition between general motivational systems. Konorski suggested that stimuli with hedonic value activate either appetitive or aversive motivational systems that, in turn, inhibit each other. Thus, DPDPE could be enhancing an appetitive system that inhibits its activity in an aversive system at a time when the rat experiences primary frustration. Whether the inhibitory effect of DPDPE on primary frustration is direct or indirect, it follows that primary frustration should be relatively strong on Trial 12 for Group 32/DPDPE/V when rats are no longer under the influence of the opioid agonist, thus leading to a similar or even stronger consummatory suppression than on Trial 11. As seen in Figure 1, the degree of suppression on Trials 11 and 12 in Group 32/DPDPE/V was about the same, thus providing some support for the hypothesis that opioid system activation may reduce primary frustration. Because consummatory suppression on Trial 12 is assumed to be predominantly determined by secondary frustration, the absence of a DPDPE effect on this trial is consistent with the idea that a

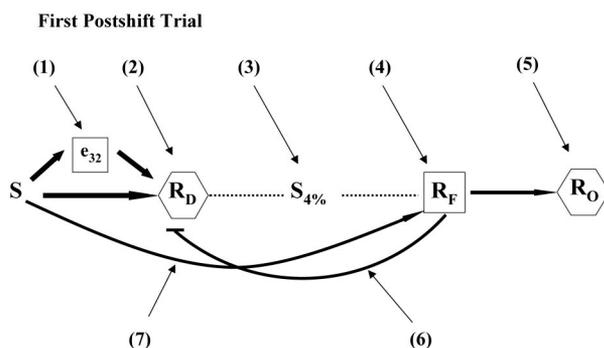


Figure 2. A theoretical representation of consummatory performance during the first postshift trial in a consummatory successive negative contrast situation. Numbers with arrows reflect potential mechanisms of action of [D-Ala2-,N-Me-Phe4,Gly-ol] enkephalin (see text for extensive description of these mechanisms). Solid arrows represent facilitatory links; the dashed arrow (6) represents an inhibitory influence; dashed lines represent the passage of time; internal events are enclosed in squares; responses are enclosed in hexagons. S = contextual stimuli; e_{32} = expectancy of the 32% sucrose solution; R_D = drinking response; $S_{4\%}$ = 4% sucrose solution; R_F = primary frustration; R_O = other responses.

δ -opioid receptor pathway may be selectively engaged during the initial reaction to surprising reward loss.

Hypothesis 5: Interference with other responses. An attenuation of cSNC may be the consequence of DPDPE interfering with the expression of responses other than drinking. However, DPDPE can actually enhance exploratory behavior in rats (Morelli, Fenu, & Di Chiara, 1989). In addition, this hypothesis would predict also an attenuation of cSNC on Trial 12, an effect that was not observed in Experiment 1.

Hypothesis 6: Interference with the inhibition of drinking behavior by primary frustration. According to frustration theory, a site associated with primary frustration becomes aversive and the animal tends to withdraw from it (e.g., Papini & White, 1994). An application of this hypothesis to the results of Experiment 1 would suggest that punishment of the drinking response by surprising reward reduction leads to response inhibition. That is, approaching the sipper tube and tasting the (now reduced) solution is followed by an emotionally aversive state that tends to suppress approach and licking responses. The hypothesis that DPDPE attenuates frustration-induced inhibition of drinking is consistent with the results of Trial 11 but not necessarily with the lack of effect on Trial 12. However, the lack of DPDPE effect on Trial 12 could be accommodated on the basis of the following two assumptions: First, that consummatory suppression on this trial is mainly driven by secondary frustration (an assumption based on the selective effects of benzodiazepine anxiolytics on Trial 12; see introduction for references), and, second, that secondary frustration does not engage a δ -receptor opioid system (an assumption based on the lack of a DPDPE effect on Trial 12). Thus, DPDPE could selectively disinhibit response suppression caused by primary frustration, whereas it may not affect the response suppression dependent on secondary frustration.

Hypothesis 7: Interference with the acquisition of secondary frustration. According to frustration theory, the aversive state of primary frustration becomes conditioned to contextual cues (presumably, cues surrounding the sipper tube in the conditioning box) or to the taste of the 4% solution in the course of Trial 11. This is assumed here to be an instance of simple Pavlovian conditioning occurring by temporal-spatial contiguity between external cues and an internal aversive state acting as the unconditioned stimulus (see, e.g., Wagner, 1963). It was suggested previously that the performance of a downshifted rat on Trial 11 predominantly depends on primary frustration. It is plausible, however, that some amount of conditioning of secondary frustration taking place during this trial contributes in some measure to consummatory suppression, assuming that conditioning is relatively rapid and occurs in less than the 5 min of trial duration. If DPDPE interferes with this conditioning it may lift a source of suppression for drinking and attenuate the cSNC effect. The lack of a DPDPE effect on Trial 12 can be accommodated by suggesting that DPDPE interferes with the acquisition of secondary frustration, but not with its retrieval once acquired. Of course, this conditioning mechanism is not a factor in the 4% unshifted control condition, which shows no observable DPDPE effect.

In summary, some of the possible mechanisms of action of DPDPE in the cSNC situation can be discarded on the basis of the results provided by Experiment 1. Hypotheses numbered (1), (2), (3), and (5) in Figure 2 are not consistent with some aspects of the results. In contrast, hypotheses numbered (4), (6), and (7) are consistent with the results of Experiment 1 and merit further study.

Experiment 2

Experiment 2 was designed to distinguish between some of the viable theoretical alternatives evaluated previously. Theoretically, because primary (hypothesis 4) and secondary frustration (hypothesis 7) are sequentially linked, it would be difficult to identify whether a given factor is interfering with one of them selectively. Anything that interferes with primary frustration should also diminish the amount of secondary frustration conditioned to contextual cues, thus leading to behavioral consequences similar to a direct interference with secondary frustration. However, interference with the inhibition of drinking behavior (hypothesis 6) should be relatively easy to assess. Experiment 2 was designed to test the hypothesis that DPDPE interferes directly with frustration (either primary or secondary) by using a design involving partial reinforcement of consummatory behavior.

Pellegrini, Muzio, Mustaca, and Papini (2004) exposed independent groups of rats to trials in which they had either continuous access to the 32% sucrose solution (continuous reinforcement; CR), or to a random mixture of the 32% sucrose solution and water (partial reinforcement; PR). Notice that PR in this case refers to the availability of the reinforcer in the entire trial rather than to the relationship between each licking response and reinforcement. Along the lines of frustration theory (Amsel, 1992), PR training should induce an expectation of the 32% solution acquired during reinforced (R) trials and also the primary and secondary frustration acquired during nonreinforced (N) trials. Occasionally, as rats experience pairings between secondary frustration and reinforcement during some late R trials, the disruptive consequences of frustration are counterconditioned and the response develops persistence. This account predicts that PR training should attenuate cSNC and also that such an attenuating effect should be eliminated by administration of anxiolytic drugs such as chlordiazepoxide before N trials. Both of these predictions were confirmed (Pellegrini et al., 2004). Experiment 2 uses this basic design to tease out the mechanism by which DPDPE attenuates cSNC.

In the present experiment, rats trained under a PR schedule received an injection of DPDPE before each of the 10 N trials, mixed randomly with 10 R trials during the preshift phase. Two control groups received vehicle injections on the same days, one running on a PR schedule and the other running on a CR schedule. All groups received 20 preshift trials; thus, in this experiment, the first and second postshift trials were Trials 21 and 22, respectively. Because the present experiment was concerned with the modulating role of DPDPE on recovery from incentive downshift, unshifted behavioral controls were not included. Two alternative predictions were derived from the theoretical analysis developed from Figure 2.

First, consider hypotheses 4 and 7 in Figure 2. Frustration theory makes specific predictions for the postshift phase of this experiment depending on the mechanism of action assumed for DPDPE. Because rats were not injected before the first postshift trial, it was predicted that the DPDPE-treated group trained under PR would show a level of suppression equal to that of the vehicle group trained under CR. This prediction follows from the assumption that DPDPE either attenuates primary frustration (hypothesis 4) or disrupts the acquisition of secondary frustration (hypothesis 7). Such effects are equivalent to reducing the impact of N trials, that is, of making the PR schedule more similar to a CR schedule. However, the results of Experiment 1 suggest that DPDPE atten-

uates, but does not completely eliminate, the cSNC effect. For example, DPDPE injected before Trial 11 eliminated any statistical evidence of cSNC but did not result in any additional degree of suppression on Trial 12 (see Figure 1a). If DPDPE had completely eliminated the emotional reaction to reward downshift in Trial 11, consummatory performance would have dropped significantly as if the rats were experiencing the downshift for the first time on Trial 12—an expectation contradicted by the data. Thus, it was assumed that DPDPE-treated rats would still experience some amount of primary frustration during N trials and, also, that some amount of secondary frustration would be conditioned to external cues. As a result, some degree of counterconditioning of secondary frustration was predicted in DPDPE-treated rats; such counterconditioning should speed up recovery during the postshift trials. It is interesting, then, that frustration theory predicts that PR rats receiving DPDPE before N trials should exhibit an initial response to the downshift typical of the CR condition (on Trial 21) but a recovery typical of the PR condition (Trials 22–25).

Second, consider hypothesis 6 in Figure 2. In contrast to the previous prediction, if DPDPE acts by reducing the inhibition of drinking behavior induced by primary frustration, without interfering with the recruitment of primary frustration, then DPDPE-treated and vehicle-treated rats given PR training should exhibit similar drinking levels during all postshift trials when DPDPE was not administered.

Concerning consummatory performance during N preshift trials, when water was offered to the rats, there are two issues that make it difficult to formulate predictions. First, on the basis of previous results that were obtained by using a similar procedure (Pellegrini et al., 2004), it was expected that rats would exhibit very low goal tracking scores. Low goal tracking scores create a floor effect that could possibly obscure differences in water drinking induced by DPDPE. Second, because these rats were not specifically deprived of water, it is unclear whether they would be motivated to drink water even if DPDPE were to reduce the inhibition of drinking behavior induced by primary frustration.

Method

Subjects and apparatus. Twenty-four Sprague–Dawley rats, purchased from Harlan (Indianapolis, IN) were housed in individual cages upon arrival. Rats were about 30 days old on arrival and about 90 days old when training started. Maintenance, deprivation conditions, housing, training apparatus, and drug preparation were as described in Experiment 1.

Procedure. The complete experiment lasted 27 days, and all the rats were trained simultaneously. The initial two daily trials were administered to familiarize the animals with the training context (see description in Experiment 1). Thereafter, rats received 25 daily trials, 20 preshift and 5 postshift. As described in Experiment 1, the sipper tube remained accessible after 5 min when a rat was in contact with it. As a result, some trials lasted longer than 5 min. Trial duration was longer than 5 min for 16 of the 24 rats and always during the preshift phase. A total of 40 trials were longer than 5 min, out of a total of 600 trials (7%) administered to all the rats during this experiment. The average duration of these longer trials was 5 min 64 s.

The training procedure was identical to that described in Experiment 1, except for the following. The animals were randomly assigned to three groups ($n = 8$). For all the groups, the final five postshift trials were identical: 5 min of access to a 4% sucrose solution. The groups differed in the preshift treatment. Group CR/V received 20 preshift trials of access to the 32% sucrose solution (i.e., the CR group). Group PR/V received 10 trials of access to a 32% solution randomly mixed with 10 trials of access

to distilled water (i.e., 50% PR group). Group PR/DPDPE also received 10 reinforced (32% solution) and 10 nonreinforced (distilled water) preshift trials, mixed randomly. R and N trials were administered according to the following sequence for all the rats: RRRRNNRRRNNRRRNNRR. Because the sucrose was considered to provide reinforcement, nonreinforced trials involved only the presentation of the vehicle (distilled water) in which the sucrose was diluted (rats were not explicitly deprived of water in this experiment).

All animals were injected 6 min before each of the N trials of the preshift phase. There were 10 injections in total. For Groups CR/V and PR/V, a vehicle injection was administered before each N trial (distilled water, 1 ml/kg). For Group PR/DPDPE, the injection contained 24 $\mu\text{g/kg}$ of DPDPE, at a volume of 1 ml/kg, as described in Experiment 1.

Data were lost as a result of equipment malfunction in 8 preshift trials, 3 in Group PR/DPDPE, 2 in Group CR/V, and 3 in Group PR/V. In all cases, the values were replaced by an average of the rat's scores on the preceding and following trials. There was one missing value for Trial 12, for a rat assigned to Group PR/V. This value was replaced by the group average for that day.

Results and Discussion

Figure 3 displays the results of this experiment. As was expected (Pellegrini et al., 2004), the presence of water during N trials in the preshift phase led to a drastic reduction of goal tracking times in the two PR groups. Whether PR rats had received DPDPE before the N trials made no difference. Statistical analyses confirmed this description. First, a Group \times Trial ANOVA restricted to the 10 R trials indicated significant effects across trials, $F(9, 189) = 57.94$, $p < .001$, and a significant interaction effect, $F(18, 189) = 2.17$, $p < .01$, but a negligible group difference ($F < 1$). The interaction effect probably reflects a relatively faster acquisition of consummatory behavior in Group CR/V than in the two PR groups. Second, a Group \times Trial analysis restricted to the 10 N trials indicated a highly significant group difference, $F(2, 21) = 197.72$, $p < .001$, and also a significant interaction effect, $F(18, 189) = 1.84$, $p < .03$, but consummatory performance did not differ across trials ($F < 1$). Follow-up pairwise tests on the group factor confirmed that Group CR/V was significantly different from the two PR groups ($ps < .001$), which in turn did not differ from each other ($p < .60$). Therefore, DPDPE had no detectable effect during the preshift trials, either when administered before N trials or by carry over on R trials.

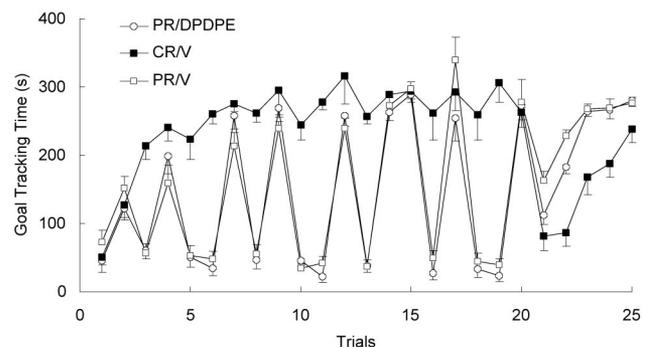


Figure 3. Performance of the three groups from Experiment 2 downshifted from 32% to 4% sucrose solution on Trial 21. DPDPE = [D-Ala²-, N-Me-Phe⁴, Gly^{-ol}] enkephalin; CR = continuous reinforcement; PR = partial reinforcement; V = vehicle injection.

The main results were obtained during the postshift trials. As can be seen in Figure 3, DPDPE combined with PR training during preshift trials led to an initial reaction to the downshift (Trial 21) that was intermediate between the two vehicle groups but to a rate of recovery of consummatory behavior (Trials 22–25) that was very similar to that of the group trained under PR. Statistical analyses confirmed these conclusions. A Group \times Trial analysis of the 5 postshift trials revealed significant differences among the groups, $F(2, 21) = 16.75, p < .001$, a significant recovery across trials, $F(4, 84) = 52.14, p < .001$, and also a significant interaction effect, $F(8, 84) = 2.40, p < .03$. This significant interaction points to differential rates of recovery across groups. One-way ANOVAs followed by pairwise LSD tests were computed at each postshift trial to determine the source of the global interaction. There were significant group effects for Trials 21–24, $F_s(2, 21) > 4.70, p_s < .03$, with the following pairwise results. For Trial 21, Group CR/V performed significantly below Group PR/V ($p < .01$), replicating the attenuating effects of PR training, but did not differ from Group PR/DPDPE ($p < .30$). However, although the difference between Groups PR/DPDPE and PR/V was relatively larger, it failed to reach significance ($p < .08$). Thereafter (Trials 22–24), the pattern was the same in all pairwise comparisons: Group CR/V differed from the two PR groups ($p_s < .01$), which, in turn, did not differ from each other ($p_s < .91$). The statistical evidence just described confirms the results predicted on the basis of frustration theory, providing support for hypotheses 4 and 7, as outlined in Figure 2.

General Discussion

The cSNC effect appears to be a relatively uncomplicated phenomenon, but its underlying causality is far from simple. The transient suppression of drinking caused by a downshift in reward magnitude engages different mechanisms depending on the extent of the experience with the new reward (first vs. second postshift trials). It was previously known that several drugs could affect consummatory contrast on the second postshift trial without interfering with the initial response to the downshifted solution—most notably benzodiazepine anxiolytics (see introduction for references). It was also known that certain drugs could affect consummatory behavior on the initial postshift trial, including morphine and cyproheptadine (see introduction for references); but these drugs also reduced cSNC on the second postshift trial, so their effects were not selective. The results reported in this article complete (albeit only across experiments) a picture of first versus second postshift trial that can be described as a double-dissociation effect. Benzodiazepines affect performance on the second but not on the first postshift session, and at least one drug, the selective δ -opioid receptor agonist DPDPE, affects performance on the first but not the second postshift trial. Up to now, there were no known examples of a drug (or any other treatment) that could affect the initial reaction to reward downshift without interfering with the recovery process. Experiment 1 provided clear evidence of such a selective effect by administering the opioid agonist DPDPE on either the first or the second postshift trials. DPDPE attenuated the initial reaction to the downshift in sucrose solution, without affecting consummatory performance on the second postshift session.

The selectivity of this effect is incompatible with a variety of nonspecific effects that DPDPE could have on this preparation. For

example, potential effects on the motor system, on the detection of sucrose solutions, on the elicitation of drinking behavior, on the general motivation to consume fluids, or on the induction of a general appetitive state can be safely eliminated because these factors should affect consummatory performance with equal strength on the first and second postshift trials. Therefore, the effect of DPDPE must relate to some specific feature of the cSNC situation.

The present experiments were inspired by an extended version of Gray's (1987) fear = frustration hypothesis. Given the sort of experimental evidence reviewed by Gray and considered as a basis for his hypothesis, both "fear" and "frustration" are referred to as *conditioned (anticipatory) responses*, as obtained in either Pavlovian or instrumental learning situations. The extension, thus, simply suggests that a similar relationship exists among the unconditioned responses that support the conditioning of fear and frustration. In the typical experiments reviewed by Gray (1987; Gray & McNaughton, 2000), fear conditioning is usually established by pairing a signal, whether in a Pavlovian or instrumental (escape-avoidance) situation, with peripheral pain usually induced by electric shock. Similarly, the conditioning of frustration is usually measured in an instrumental learning situation in which the organism experiences a surprising omission or reduction in reward magnitude or quality. Following Amsel's (1992) theory, these two kinds of frustrative responses, the unconditioned and conditioned ones, are referred to as *primary* and *secondary frustration*. Then, the extended analogy suggests that pain is to primary frustration as fear is to secondary frustration. It follows, therefore, that factors modulating the organism's response to painful stimuli should also modulate its response to a surprising reduction in reward magnitude that triggers primary frustration.

Several potential effects of DPDPE can be envisioned when one frames the events of the first postshift trial, in a cSNC situation, in terms of frustration theory (see Figure 2). These options were discussed in detail previously and three of them were found to be consistent with the results of Experiment 1. These were the possibility that DPDPE affects the intensity of the primary frustration state (hypothesis 4 in Figure 2), that it affects the inhibition of drinking behavior by primary frustration (hypothesis 6), and that it affects the establishment of a Pavlovian association between some external cue surrounding the sipper tube and the primary frustration state (hypothesis 7). Whereas hypotheses 4 and 7 are difficult to distinguish, Experiment 2 helped discriminate them against hypothesis 6.

Experiment 2 sought to distinguish between the effects of DPDPE on frustration (whether primary or secondary) versus the effects of DPDPE on frustration-induced suppression of drinking behavior by implementing a PR schedule during the preshift phase. This manipulation was also attractive because it allowed, at least in theory, for the drug to have an effect on performance that could be detected at a point in training when the rats were not being injected. From previous research (Pellegrini et al., 2004), we knew that PR training during the preshift phase attenuates cSNC and that injecting rats with the anxiolytic chlordiazepoxide before every nonreinforced preshift trial eliminates this attenuation. Experiment 2 was modeled on the same predicament, except that DPDPE was assumed—on the basis of Experiment 1 data—to affect some aspect related to the frustrative state induced by reward downshift. As a result, two alternative predictions were derived.

First, if DPDPE reduces the intensity of primary or secondary frustration, without eliminating either of these two processes (hypotheses 4 and 7 in Figure 2), then DPDPE-treated rats should undergo some degree of counterconditioning of secondary frustration, which it is assumed to underlie the attenuating effects of PR on cSNC (Mikulka, Lehr, & Pavlik, 1967; Pellegrini et al., 2004). As a result, when tested in the absence of DPDPE during postshift trials, DPDPE-treated rats were expected to exhibit the following features: (a) a degree of suppression in the first postshift trial similar to the CR group. DPDPE administered before nonrewarded trials was expected to reduce the impact of nonreinforcement, making the PR schedule be more like a CR schedule; and (b) a rate of recovery in the second and subsequent postshift trials similar to that of a group given PR during preshift trials. This prediction follows from the expectation that the effect of DPDPE administered before nonreinforced trials was to reduce either the intensity of primary frustration or its ability to support conditioned frustration, without completely eliminating either. Therefore, some amount of counterconditioning of secondary frustration was expected to occur during PR training (Amsel, 1992). The second alternative prediction held that if the DPDPE mechanism of action is to attenuate frustration-induced inhibition of drinking behavior (hypothesis 6 in Figure 2), then DPDPE-treated rats were expected to show a postshift performance similar to that of the PR group. This latter prediction follows from the fact that, in this experiment, rats were scheduled to experience all the postshift trials without receiving DPDPE treatment.

The results of Experiment 2 were consistent with the first hypothesis, that is, that the DPDPE action in the cSNC situation consists of either selectively reducing the unconditioned state of primary frustration or of impairing the establishment of the state of secondary frustration through Pavlovian conditioning. Recent research on fear conditioning has come to a similar conclusion regarding the role of opioids (McNally, Pigg, & Weidemann, 2004; McNally & Westbrook, 2003). In one experiment (McNally & Westbrook, 2003), rats receiving tone–shock acquisition pairings that led to an increase in freezing responses, were then shifted to tone-only extinction trials. Prior to each extinction session, one group of rats received injections of the opioid antagonist naloxone, whereas the other was treated with a saline injection. Naloxone increased resistance to extinction, suggesting that the opioid system is normally engaged during extinction of fear conditioning. An additional experiment demonstrated that postextinction treatment with naloxone failed to reinstate already extinguished freezing behavior, suggesting that the opioid system is critical for the learning changes that occur during the extinction of fear, but not for the expression of freezing responses. McNally et al. (2004) suggested that opioids are involved in attenuating a hypoalgesia response that normally regulates unconditioned stimulus (US) processing (shock-induced pain), thus preserving the novelty of unconditioned stimulus presentations.

None of the hypotheses considered in Figure 2 are equivalent to McNally et al.'s (2004) hypoalgesia hypothesis for fear conditioning. There is, of course, an obvious procedural difference between cSNC and fear conditioning, namely, the frequency of occurrence of the aversive event. Whereas shock is presented several times in the fear conditioning situation, reward downshift occurs only once in the cSNC situation. However, multiple downshifts (as in the PR schedule used in Experiment 2) do attenuate the size of contrast, thus suggesting that a compensatory response analogous to hy-

poalgesia in fear conditioning may also develop in situations involving frustrative outcomes. Whereas, theoretically, hypoalgesia could be thought of as analogous to Amsel's (1992) mechanism of frustration counterconditioning, the two are notoriously different. Counterconditioning is assumed to involve a hedonic shift in an antecedent event by virtue of its pairing to a subsequent event of an opposite and stronger hedonic value. In Pavlov's (1927) original experiments, a dog exposed to shock–food pairings eventually acquired “a well-marked alimentary conditioned reflex,” responding to the shock by “turning its head to where it usually received the food and smacking its lips, at the same time producing a profuse secretion of saliva” (pp. 29–30). Thus, anticipatory frustration must be paired several times with food presentation for the counterconditioning of frustration to develop. In contrast, hypoalgesia is thought of as part of the (compensatory) unconditioned response to pain—although hypoalgesia can also be conditioned (Grau, Salinas, Illich, & Meagher, 1990). In addition, there is no evidence suggesting that frustrative reactions undergo a sort of tolerance with repeated exposure to surprising nonreward. In one experiment (Ludvigson, McNeese, & Collerain, 1979), rats received partial reinforcement training during hundreds of trials. These so-called *donor rats* were placed in a goal box where they either found food on a random half of the trials or found nothing on the other half of the trials. It was known that rats exposed to surprising nonreward emit a frustration odor that other rats, called *observer rats*, can detect and use as discriminative stimuli (for reviews, see Ludvigson, 1999; Papini & Dudley, 1997). The effects of these goal-box placements were assessed by the ability of observer rats to respond to the odors emitted by donor rats by either approaching or avoiding the location in a T maze situation (no reinforcement was provided for observer rats). Even after 570 trials, a new set of observer rats responded to the odors just as the original set of observers had done, by avoiding the location in which a donor rat had previously experienced a surprising nonreward event. These results suggest that the donors were emitting frustration odors of about the same intensity throughout their extensive exposure to partial reinforcement. Thus, to the extent that these odors reflect an internal state of primary frustration, it may be argued that counterconditioning affects the behavioral expression of frustration (e.g., goal-avoidance responses), but not the intensity of the internal affective state per se.

It is possible, therefore, that the effects of DPDPE described in the present situation are not mediated by the induction of a compensatory response, but rather represent direct influences on the affective states of frustration induced by reward downshift. Whether the opioid system is normally engaged in the cSNC situation remains to be determined by a systematic study of the effects of specific opioid antagonists (for negative results with naloxone, see Rowan & Flaherty, 1987).

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