The effect of chlordiazepoxide and propranolol on glycemic conditioning in rats

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A tendency toward conditioned hyperglycemia occurred in rats with a history of insulin administration in a novel environment. This response was accentuated in rats that received propranolol (5 mg/kg) pretreatment either during the conditioning phase only or both during the conditioning phase and on the test day. Pretreatment with chlordiazepoxide (CDP; 10 mg/kg) either during the conditioning phase only or on the test day only eliminated conditioning, whereas in a previous experiment, pretreatment with CDP (same dose) during both the conditioning phase and on the test day reversed the conditioned hyperglycemic response to one of conditioned hypoglycemia. Other results included the following: (1) CDP pretreatment reduced the novelty-induced elevation of plasma glucose, but not of corticosterone; (2) CDP pretreatment reliably interfered with insulin-induced hypoglycemia; (3) first-time administration of propranolol on the test day for conditioning raised plasma glucose levels; (4) a shift from CDP to saline pretreatment on the test day for conditioning raised corticosterone levels; (5) habituation to environmental novelty was evident in the corticosterone measure, but not in the plasma glucose measure.

Many studies have demonstrated that the repeated administration of insulin in a particular stimulus context will result in a conditioned change in blood glucose when the animals are exposed to that context and given a placebo instead of insulin. However, there is little agreement on the direction of the conditioned glycemic response. There have been numerous reports of conditioned hypoglycemia (Alvarez-Buylla & DeAlvarez-Buylla, 1975; Matysiak & Green, 1984; Woods, 1972; Woods & Kulkosky, 1976; Woods & Shogren, 1972), some reports of conditioned hyperglycemia (Siegel, 1972, 1975), and some reports of both conditioned hypoglycemia and conditioned hyperglycemia (Flaherty et al., 1980; Storlien, Smith, Atrens, & Lovibond, 1985).

The factors that are responsible for these different results are not well understood, but there is considerable evidence that the relative novelty of the conditioning context may be important for the occurrence of the hyperglycemic conditioned response (Flaherty & Becker, 1984; Flaherty, Grigson, & Brady, 1987; Flaherty, Rowan, & Pohorecky, 1986; Storlien et al., 1985). Novelty may function to enhance the salience of the conditioning context (Storlien et al., 1985), and/or it may function as a stressor (Hennessy & Levine, 1978; Mormede, 1983) that, in conjunction with insulin-induced stress, may promote the development of conditioned hyperglycemia (Flaherty et al., 1987).

It has been shown that the anxiolytic chlordiazepoxide (CDP) reduces the plasma glucose elevation produced by exposure to a novel environment (Flaherty et al., 1986). In addition, the conditioned hyperglycemic response that usually follows insulin conditioning in a novel context is reversed to one of hypoglycemia when the animals are pretreated with CDP during both the conditioning and the test phase (Flaherty, Becker, Rowan, & Voelker, 1984). However, since in this experiment CDP was administered during both the conditioning and the test phase, it was not possible to determine whether the anxiolytic action of CDP blocked acquisition of the conditioned hyperglycemic response, or simply its expression. Propranolol, an adrenergic blocker that acts primarily at the beta-2 receptor, has mixed effects as a tranquilizer in several animal models of anxiety (Davis, Redmond, & Baraban, 1979; Durel, Krantz, & Barrett, 1986; Flaherty, in press; Sepinwall, Grodsky, Sullivan, & Cook, 1973). It has been found clinically effective in "panic-attack" anxiety (Bonn & Turner, 1971; Granville-Grossman & Turner, 1966) and, more recently, in patients with chronic anxiety (Meibach, Dunner, Wilson, Ishiki, & Dager, 1987). Although the effectiveness of dl-propranolol as an anxiolytic agent is controversial, pilot studies in our laboratory suggested that pretreatment with dl-propranolol (5 mg/kg) may serve to reverse the hyperglycemic conditioned response to one of hypoglycemia following insulin conditioning in a novel context.

In the present experiment, we were concerned with the further investigation of the effect of the anxiolytic CDP and the beta adrenergic blocker dl-propranolol on the acquisition or the expression of the conditioned hyperglycemic response. In the previous study, CDP (10 mg/kg) was administered both during conditioning

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and on the test day for conditioning. In the present study, separate groups of rats were pretreated with CDP (10 mg/kg), either during conditioning or on the test day for conditioning only, while other groups were pretreated with dl-propranolol (5 mg/kg) during conditioning, on the test day for conditioning, or during both the conditioning phase and on the test day for conditioning.

METHOD

Subjects

The subjects were 108 male Sprague-Dawley rats purchased from Blue Spruce Farms at approximately 90 days of age. They were housed in suspended metal cages and maintained on Purina Rat Chow and water ad lib, with a 14:10-h light:dark cycle. The rats' body weights ranged from 365–610 g.

Apparatus

The conditioning environment, which we have previously referred to as the "novel environment" or "Environment A" (Flaherty et al., 1980), consisted of a black wastebasket (0.36 m³) with fresh cedar woodchips on the bottom and a menthol odor. The wastebaskets were contained in a dimly illuminated room (10.76 lx), different from the animals' colony room, which was brightly illuminated (538.19 lx). White noise was present in the conditioning room.

Procedure

The experiment was conducted as three complete replications, with 36 subjects per replication. The animals were housed in the colony room for approximately 30 days prior to the start of the experiment. During this time, they were handled and weighed eight times. They were run in four groups of 9 between 1400 and 1730 h every other day. The running times of the four groups were rotated to control for time serving as a possible conditioned stimulus. Light onset was at 0800 h.

The experiment involved three pretreatment drug conditions and two conditioning drug manipulations. The pretreatment drug was dl-propranolol (5 mg/kg) administered i.p. 20 min prior to entry into the conditioning environment, CDP (10 mg/kg) administered i.p. 30 min prior to entry into the conditioning environment, or isotonic saline administered i.p. either 20 or 30 min prior to entry into the conditioning environment. The treatment drug, administered in the conditioning context, was either a subcutaneous (s.c.) injection of regular, porcine insulin (2.5 IU/kg) or isotonic saline.

Six subgroups of animals received the pretreatment drug (dl-propranolol, CDP, or saline) at different stages of the experiment (i.e., during the conditioning phase and/or on the test day). These subgroups ($n = 12$ in all cases) were as follows: Group S-S, a saline pretreatment group that received saline during both the conditioning phase and on the test day; Group P-P, a propranolol pretreatment group that received the drug during both the conditioning phase and on the test day; Group P-S, a group given propranolol pretreatment during the conditioning phase and saline on the test day; Group S-P, a group given saline pretreatment during the conditioning phase and propranolol on the test day; Group C-S, a group given CDP pretreatment during the conditioning phase and saline on the test day; Group S-C, a group given saline pretreatment during the conditioning phase and CDP pretreatment on the test day.

Half of the animals ($n = 6$) in each of these groups received insulin as the conditioning drug and half received saline.

The conditioning phase consisted of six trials, one every other day. On each trial, the rats were removed from their home cages, weighed, given the appropriate pretreatment injection (dl-propranolol, CDP, or saline), and returned to their home cages. At the culmination of this time period, the rats were placed in a

Plexiglas carrying cart and transported to the conditioning environment. Immediately upon entry, each rat was injected subcutaneously with the appropriate treatment drug (saline or insulin) and placed in a wastebasket. A hardware cloth screen was placed on top of each wastebasket. Following the 25-min conditioning session, the rats were removed and returned to the colony room. They were placed on a table that was covered with newspapers and were free to roam for 1 min. They were then returned to their home cages.

A test trial for conditioning was given 48 h after the sixth conditioning trial. On this test trial, all procedures remained as described above, except that all rats were injected with placebo (saline), rather than insulin, in the conditioning context.

Immediately following the 1st and the last day of the experiment, when the animals were placed on the table, 150 μ l of blood were collected from the tip of the tail into two 75-microhematocrit capillary tubes. The blood was centrifuged for 14 min. For the first and second replication, plasma glucose was assayed using the Worthington Statzyme kit, and for the third replication, a kit purchased from Fisher Scientific was used. A Spectronic 88 spectrophotometer was used to obtain the absorbance readings. Corticosteroid levels were determined by a Radioimmune Assay kit, using iodinated corticosterone. The data were analyzed with the analysis of variance procedure. Body weight, as determined on the test day for conditioning, was used as a covariate for the analysis of the plasma glucose data obtained on the test day for conditioning.

RESULTS

Day 1

Plasma glucose. The administration of insulin on the first conditioning day suppressed plasma glucose levels (PGLs) [$F(1,89) = 596.24, p < .001$]. There was no reliable overall effect of pretreatment drug administration ($F < 1.00$), but the interaction of pretreatment drug $\times$ conditioning drug was reliable [$F(2,89) = 5.66, p < .01$]. These data are illustrated in Figure 1. Subsequent anal-

Figure 1. Mean plasma glucose levels on initial exposure to the conditioning context. Different groups were pretreated with saline, dl-propranolol (PROP; 5 mg/kg), or chlordiazepoxide (CDP; 10 mg/kg). Subgroups were injected with either insulin (2.5 IU/kg) or saline in the conditioning context.

ysis with Fisher's least significant difference (*LSD*) test ($p = .05$) indicated that CDP pretreatment reliably suppressed PGLs in the group injected with saline in the conditioning environment, but raised PGLs in the animals injected with insulin in the conditioning environment.

Corticosterone. Insulin treatment reliably elevated circulating corticosterone levels [$F(1,84) = 11.28, p < .001$] (see Figure 2). Neither the main effect of pretreatment nor the pretreatment $\times$ conditioning drug interaction was significant ($p > .05$).

Day 7: Test Day

Plasma glucose. The group with a history of insulin administration had reliably higher PGLs relative to the saline-treated controls overall [$F(1,71) = 4.16, p < .045$]. However, this suggestion of an overall hyperglycemic conditioned response must be qualified, because different results were obtained with the various subgroups defined by pretreatment drug administration [pretreatment drug $\times$ conditioning drug interaction; $F(5,71) = 2.36, p < .05$]. These data are presented in Figure 3.

Subsequent analysis indicated that a history of insulin administration led to a conditioned hyperglycemic response in the animals that were administered propranolol pretreatment both during conditioning and on the test day (Group P-P) and the animals administered propranolol during the conditioning phase only (Group P-S), but the conditioned hyperglycemia in the saline pretreatment group failed to reach statistical reliability. There was no evidence for conditioned hyperglycemia in any other group.

Independent of conditioning effects, propranolol pretreatment administered on the test day only (Group S-P) elevated PGLs in the animals given saline as a conditioning drug relative to all other groups—with the exception of the saline subgroup, which was shifted from CDP to saline as the pretreatment drug (Group C-S). This

Figure 2. Mean corticosterone levels (nanogram/milliliter) on initial exposure to the conditioning context. Values represent means across all pretreatment conditions.

Figure 3. Mean plasma glucose levels (PGLs) on the test day for conditioning (Day 7) as a function of pretreatment drug saline (S), propranolol (P), or chlordiazepoxide (C) and treatment drug saline or insulin. Labels on the abscissa (S-S, etc.) represent pretreatment conditions during the conditioning phase (first letter) and on the test day for conditioning (second letter).

shift from CDP pretreatment to saline pretreatment on the test day (Group C-S) also tended to elevate PGLs in rats given saline as the conditioning drug, relative to Groups P-P and S-C ($p < .05$). Finally, CDP administered on the test day only (Group S-C) suppressed PGLs in animals with a history of insulin relative to all other insulin treatment groups, as well as in animals with a history of saline as the conditioning drug, relative to Groups C-S and S-P (see Figure 3).

Thus, conditioned hyperglycemia, or a tendency toward hyperglycemia, occurred in three groups (P-S, P-P, and S-S), and it was totally absent in three groups (S-P, C-S, and S-C). A shift to propranolol pretreatment (S-P), or away from CDP pretreatment (C-S), tended to elevate PGLs in animals with a history of saline as the conditioning drug. The administration of CDP on the test day for conditioning (Group S-C) tended to lower PGLs overall.

Corticosterone. A history of insulin administration tended to elevate circulating corticosterone levels overall, but the effect was not reliable [$F(1,70) = 2.8, p < .07$].

Animals shifted from CDP pretreatment during the conditioning phase to saline pretreatment on the test day (C-S), had higher corticosterone levels than did all other groups [$F(5,70) = 5.89, p < .01$, followed by *LSD* tests]. In addition, the animals shifted to CDP on the test day (S-C) showed higher corticosterone levels than did the animals shifted to propranolol on the test day (S-P) (*LSD* test) (see Figure 4).

Habituation

Finally, with respect to the plasma glucose measure, neither the placebo group pretreated with saline (S-S) nor

Figure 4. Mean corticosterone (CS) levels (nanogram/milliliter) on Day 7, as a function of pretreatment condition, collapsed across conditioning drug (i.e., saline and insulin). S: saline. P: propranolol. C: chlordiazepoxide.

the placebo group pretreated with propranolol (P-P) became habituated to environmental novelty stress from the 1st to the 7th conditioning day ($p > .05$). Habituation to environmental novelty stress, however, was evidenced by the corticosterone measure in both the saline-pretreated placebo group [S-S: $t(8) = 2.38$, $p < .05$] and the propranolol-pretreated placebo group [P-P: $t(8) = 3.78$, $p < .01$] (see Figure 5).

DISCUSSION

Day 1

Administration of insulin on the 1st acquisition day suppressed PGLs to approximately 54% of control values. This degree of suppression should have approximated a

reduction sufficient to activate an adrenocortical response (Zukoski, 1966), and the elevated corticosterone levels on the 1st day in the insulin-treated animals suggests that such an activation occurred.

The reduction of PGLs in the placebo group given CDP pretreatment on Day 1 is consistent with earlier studies which showed that CDP reduces the glycemic indicants of novelty-induced stress (Flaherty et al., 1986). The failure of the same dose of CDP to reduce corticosterone elevation may indicate differential sensitivity of the two stress measures.

The finding that CDP interfered somewhat with the insulin-induced hypoglycemia on Day 1 may be related to a (nonreliable) tendency for CDP to raise corticosterone levels on Day 1—an effect that could tend to offset the hypoglycemia induced by insulin. It is also possible that benzodiazepine treatment may lead to insulin resistance, as has been reported with ethanol treatment, which could potentially interfere with the effectiveness of insulin (Avogaro et al., 1987).

Day 7: Test Day

In the case of plasma glucose, the conditioned response was in the direction of hyperglycemia in animals given saline as a pretreatment drug (Group S-S), and it was statistically reliable in animals given propranolol pretreatment during the conditioning phase only (Group P-S) and in the animals that were administered propranolol during both the conditioning and the test phase (Group P-P).

Although the magnitude of the conditioned hyperglycemic response in the saline-pretreated controls was marginal in this experiment, this effect has been reliably obtained in a number of other studies (Flaherty et al., 1984; Flaherty et al., 1987; Flaherty et al., 1980). The dose of insulin used in the present study was lower than that used in our previous studies (either 2.7 or 5.4 IU/kg), but this difference does not likely explain the marginal conditioned response, because Siegel (1972) has obtained

Figure 5. Mean plasma glucose levels (PGLs, left panel) and mean corticosterone levels (CS, right panel) on Day 1 and Day 7 in groups given saline as the conditioning drug and administered either saline (Group S-S) or propranolol (Group P-P) as the pretreatment drug throughout the experiment.

a conditioned hyperglycemic response with a dose of 2.4 IU/kg or lower. It might be suggested that, although the conditioned hyperglycemic response is small relative to the unconditioned response (as is usually the case), it may serve at least two important functions. First, it may serve a metabolic function by augmenting the supply of energy available for response to a stressor. Second, it may serve a "cognitive" function, since some evidence suggests that circulating glucose plays an important role in learning and memory (Lee, Graham, & Gold, 1988).

The fact that the conditioned hyperglycemic response was more pronounced when propranolol was administered during the conditioning period (Groups P-P and P-S) may be related to a reduction in the endogenous release of insulin (which mediates conditioned hypoglycemia (Woods, 1972; Woods, Alexander, & Porte, 1972) via blockade of the pancreatic beta-2 receptors (Woods & Porte, 1974). Such a blockade should serve to facilitate the development of the conditioned hyperglycemic response. Furthermore, if propranolol blocks the endogenous release of insulin, it could be predicted that propranolol pretreatment would interfere with, rather than accentuate, the development of a conditioned hypoglycemic response. Such opposing effects of propranolol pretreatment on the development of the conditioned hyperglycemic and the conditioned hypoglycemic response would provide additional evidence that the two responses are indeed mediated by distinct mechanisms (Flaherty et al., 1987).

Conditioning was not apparent in the animals given propranolol pretreatment on the test day only (S-P). Thus, the administration of propranolol for the first time on the test day blocked the expression of conditioning—an effect that was apparently due to the selective elevation of PGLs in the placebo group, rather than to changes in the PGLs of animals with a history of insulin administration. Propranolol pretreatment, however, did not elevate PGLs on Day 7 in the animals with a history of insulin administration, nor did it elevate PGLs in any group on the 1st day of the experiment.

Some studies have reported elevated PGLs following propranolol administration (Dornhorst, Powell, & Pensky, 1985; Frishman & Silverman, 1984; Lawrence, Aglouni, & Hagan, 1984). Lundquist (1972) suggested that the effect of propranolol treatment on PGLs may be dependent on the state of the organism, since propranolol treatment led to hyperglycemia in free-feeding nonstressed mice, but abolished catecholamine-induced hyperglycemia. Given that there was some evidence for habituation to the novel environment in the placebo group (with respect to the corticosterone measure), first-time propranolol administration on the test day for conditioning (Day 7) may have been expected to elevate, rather than suppress, plasma glucose levels.

No conditioning at all was apparent in the two treatments involving CDP administration. These results differ from those of a previous experiment, in which pretreatment with CDP (same dose) both during the conditioning phase and on the test day reversed the conditioned

hyperglycemic response to one of conditioned hypoglycemia (Flaherty et al., 1984). In the present study, the change in drug state (resulting from either the removal or the addition of the drug on the test day) apparently interfered with the expression of the conditioned response. Thus, the failure to obtain conditioning here may be due to a change in the state of the organism from the conditioning to the test phase.

State-dependent learning has been reported previously when benzodiazepines have been used in both appetitive and aversive conditioning tasks (Colpaert, 1986; Iwahara, 1972; Patel, Ciofalo, & Iorio, 1979). In two reports, however, state-dependent learning did not occur. Davis (1979) reported that diazepam interfered with the expression of conditioned fear in the potentiated startle paradigm, but not with the acquisition of conditioned fear. Also, Tenen (1967) reported evidence inconsistent with the state-dependency hypothesis with CDP treatment. Both Davis (1979) and Tenen (1967) conducted training and testing in different contexts, which is not typical of state-dependency experiments. Given the importance of contextual cues for the expression of tolerance to the analgesic effects of morphine (Siegel & MacRae, 1984) or the sedative effects of CDP and midazolam (File, 1982; King, Bouton, & Musty, 1987), the conditioned stimulus complex (including the state of the organism) may be a necessary cue for the elicitation of the conditioned response associated with drug administration. However, whether the results obtained in this experiment represent a true state-dependent effect, or a generalization decrement resulting from context change (both the addition and the removal of CDP on the test day produced noticeable changes in corticosterone and/or PGLs) cannot be ascertained with the present data.

In the case of plasma corticosterone, the conditioned elevation of corticosterone in animals with a history of insulin administration in a novel environment was marginal relative to the conditioned hyperglycemic response overall. The reason for the absence of a reliable conditioned corticosterone response is not clear, but it may be related to the temporal parameters selected for conditioned glycemia, or perhaps to the period of the light:dark cycle during which conditioning occurred.

In summary, it was previously demonstrated that a history of insulin administration can lead to the development of either a conditioned hypoglycemic or a conditioned hyperglycemic response, depending on the relative novelty of the conditioning context (Flaherty et al., 1987; Flaherty et al., 1980). The conditioning of a glycemic response (in either direction), however, is likely made difficult by the competitive relationship between the mechanism mediating conditioned hypoglycemia (the endogenous release of insulin) and that mediating conditioned hyperglycemia (activation of the adrenocortical axis). This suggestion is supported by the finding that propranolol pretreatment, which should block the mechanism mediating conditioned hypoglycemia, accentuates the conditioned hyperglycemic response, whereas CDP pre-

treatment, which should block the mechanism mediating conditioned hyperglycemia, actually reverses the conditioned hyperglycemic response to one of hypoglycemia (Flaherty et al., 1984). Thus, the present study provides further evidence for the occurrence of conditioned hyperglycemia following a history of insulin administration in a novel environment, and suggests that the accentuation of this response by propranolol pretreatment might be advantageous for the investigation of other aspects of conditioned hyperglycemia.

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