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Chronic 2-Deoxy-D-Glucose Treatment: Adaptation of its Analgesic, But Not Hyperphagic Properties

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BODNAR, R. J., D. D. KELLY, M. BRUTUS AND M. GLUSMAN. *Chronic 2-deoxy-D-glucose treatment: Adaptation of its analgesic, but not hyperphagic properties.* PHARMAC. BIOCHEM. BEHAV. 9(6)763–768, 1978.—Given that acute administration of 2-deoxy-D-glucose (2-DG), an antimetabolic glucose analogue, induces elevations in both food intake and pain thresholds, the present study examined whether chronic 2-DG administration would result in adaptation of either its analgesic or hyperphagic effects. Seven rats were trained on an operant psychophysical liminal escape (LE) procedure, and after placebo baseline, were administered on alternate days 60 min prior to LE determinations eight 2-DG (600 mg/kg) injections. Food intake was measured for 6 hr after each injection. Twelve additional animals were tested for alterations in reflex flinch-jump thresholds 30 min following placebo, acute 2-DG (350 mg/kg) and chronic (14th day) injections. Whereas the first three 2-DG injections induced profound elevations in LE thresholds, the final 3 injections failed to alter thresholds above baseline. In contrast, both acute and chronic 2-DG injections increased food intake. Reflex flinch-jump thresholds, like LE thresholds, were elevated above baseline following acute 2-DG injections, but unchanged following the chronic treatment. These data suggest that the analgesic and hyperphagic properties of 2-DG are experimentally dissociable, and offer further evidence that 2-DG may increase pain thresholds via a stress-induced activation of pain inhibitory mechanisms.

Pain inhibition 2-Deoxy-D-glucose Analgesia Food intake Adaptation Stress Rats

ANIMALS exposed to novel environmental stressors such as inescapable foot shock, rotation, intraperitoneal injections of hypertonic saline, cold-water swims or abrupt food deprivation display significant behavioral analgesia [1, 7, 9, 11, 18, 20, 30]. That it is the stressful properties of these stimuli that are responsible for the pain threshold elevations is suggested by the observations that repeated exposures to either cold-water swims or severe inescapable foot shock result in adaptation of the analgesic effects [1, 9, 10, 20] in the same manner that other stress-induced physiological responses such as pituitary-adrenocortical activation adapt [26].

The antimetabolic glucose analgoue [34], 2-deoxy-D-glucose (2-DG) has usually been employed as a regulatory challenge that induces increased food intake in rats [14, 27, 33], primates [27,28] and humans [32]. 2-DG's effects may be related to its ability to cross selectively cell membranes and to interfere with normal cellular metabolism. However, 2-DG induces in addition many stress-related physiological responses including marked glucoprivation, peripheral sympatho-medullary and pituitary-adrenal discharge and hyperglycemia [15, 19, 34]. These latter effects prompted our initial investigations into the potential analgesic properties of 2-DG. We found that acute 2-DG injections produced a systematic, dose-dependent and time-dependent increase in both a reflex pain threshold, the tail-pinch test and an operant psychophysical pain threshold, the liminal escape test. Moreover, the temporary analgesia following acute administration of 2-DG was potentiated if the animal was concurrently food deprived [3,6].The purpose of the present study was to determine whether the analgesic and hyperphagic effects of 2-DG might dissociate during a chronic regimen of repeated 2-DG injections. Since stress-induced analgesia normally shows adaptation following repeated exposure to the same stressor, the analgesic properties of 2-DG might be expected to decline with chronic administration if the analgesia were stress-related. On the other hand, since the increased food intake is apparently not a stress response [31], this effect of 2-DG might not show adaptation or tolerance. Therefore, in the present study, the acute and chronic effects of 2-DG upon gross 6-hr post-injection food intake and upon liminal escape (LE) pain thresholds in the same animals were ascertained. Additionally, the acute and chronic effects of 2-DG upon flinch-jump thresholds were studied to extend the scope of any nociceptive threshold alterations to a reflex pain test.

METHOD

Liminal Escape Threshold and Food Intake Determinations

Seven male albino Holtzman Sprague-Dawley rats (350–500g)served in the experiment. Behavioral sessions were conducted in a standard operant chamber (BRS/LVE) 26.5 cm high with a 30×24 cm grid floor composed of 14 grid bars (0.6 cm dia.) spaced 1.9 cm apart. A lever, mounted 7 cm above the floor and protruding 2 cm into the chamber, served as the response manipulandum and required a dead weight

force of 24 g for closure. Constant current, square wave shocks with a 200 Hz frequency were delivered via a 14 pole scrambler through the grids.

Initially each rat was shaped by the method of successive approximations to depress the lever to terminate a train of pulsed foot shocks delivered at a rate of 300 msec on/300 msec off. Following this shaping session, each animal was exposed over a 9-session sequence to an identical series of increasingly stringent escape contingencies which gradually approached the fixed-ratio LE schedule [3,6], in which shocks were delivered for up to 10 sec unless the rat depressed the lever 3 times and initiated a 20-sec intertrial interval. A session consisted of 100 such trials distributed over 5 shock intensities: 0.2, 0.4, 0.6, 0.8, 1.0 mA. The shock intensity was switched every 4 trials so that every 20 trials the rat was exposed to all 5 intensities. The order of shock intensities within successive 20-trial blocks was determined by a Latin Square design in which each intensity occupied a given ordinal position only once and in which no transition was ever repeated. The first 20 trials of each session were recorded separately to allow for warm-up effects and are analyzed separately. From the last 80 trials of each session, the probability of escape and the amount of time spent in shock for each shock intensity were recorded, as well as the time spent depressing the lever and the number of extra, or ineffective, responses made during the intertrial interval.

After 10 daily 100-trial liminal escape sessions, all rats entered a 44-day paradigm in which they were exposed to 20 sessions on alternate days. The first 7 and last 7 liminal escape sessions served as the placebo baseline and recovery conditions, respectively. On these days, intraperitoneal injections of 2 ml sterile water/kg body weight preceded the liminal escape sessions by 60 min. During the intervening 8 sessions, each animal received an injection of 2-DG (600 mg 2-DG/2 ml sterile water/kg body weight, IP) and was tested for liminal escape thresholds 60 min thereafter on the first 3 (Days 1–3) and the last 3 (Days 6–8) days of 2-DG administration. Food and water were available at all times except during liminal escape sessions. Body weight and food intake during the 6 hr following each injection were measured daily.

Flinch-Jump Threshold Determinations

Twelve additional naive male rats were tested for flinch-jump thresholds using a modification of the Evans procedure [16]. Electric shocks were delivered through a 30×24 cm floor composed of 14 grids by a 60 Hz, constant current shock generator and an electromechanical grid scrambler. Using an ascending method of limits of successively more intense shocks, the flinch threshold was defined in mA as the lowest intensity that elicited a withdrawal of a single paw from the grids. The initial-jump threshold was defined as the lowest intensity that elicited simultaneous withdrawal of both hindpaws from the grids. The jump threshold was defined as the lowest of two consecutive intensities that elicited a jump as above. Each trial began with the animal receiving a 300-msec foot shock at a current intensity of 0.1 mA. Subsequent shocks occurred at 10-sec intervals and were increased in equal 0.05 mA steps until all three nociceptive thresholds were determined. After each trial, the current intensity was reset to 0.1 mA for the next trial until 6 trials were completed. Daily flinch, initial-jump and jump thresholds were each computed as the mean of these 6 trials; three days of stable baseline thresholds were determined for each animal. Fourteen daily injections of 2-DG (350 mg/2 ml sterile water/kg body weight, IP) followed with flinch-jump determinations made 30 min after the first (acute) and fourteenth (chronic) injections.

RESULTS

Figure 1 displays the profound elevations in LE thresholds caused by the initial three exposures to 2-DG, the significantly less severe effects of the last three 2-DG exposures and the subsequent return to normal baseline thresholds during the recovery period. Two-way analyses of variance across placebo, 2-DG injections and recovery conditions revealed significant increases in time spent in shock, $F(19,480)=19.0$, $p<0.01$, and complementary significant decreases in escape probability, $F(19,480)=20.8$, $p<0.01$, across all shock intensities. The Scheffé post-hoc comparisons summarized in Table 1 show that 2-DG's analgesic effects as compared to placebo occurred following the first three injections and that only minor increases in nociceptive thresholds remained following chronic 2-DG administration. Indeed, significant decreases in escape probability and significant increases in the time spent in shock were observed across shock intensities for the first three as compared to the last three 2-DG injections (escape probability: 0.4 mA: $F=6.39$, $p<0.05$; 0.6 mA: $F=13.40$, $p<0.01$; 0.8 mA: $F=11.39$, $p<0.01$; 1.0 mA: $F=11.44$, $p<0.01$; time spent in shock: 0.2 mA: $F=4.24$, $p<0.05$; 0.4 mA: $F=5.70$, $p<0.05$; 0.6 mA: $F=11.09$, $p<0.01$; 0.8 mA: $F=11.28$, $p<0.01$; 1.0 mA: $F=11.10$, $p<0.01$). The intensity-dependent pattern of escape responding in all animals remained consistent over all experimental conditions with the probability of escape always showing a systematic increase as a function of stimulus intensity. This suggests that orderly shifts in escape thresholds, rather than random fluctuations, occurred following acute 2-DG injections. An additional analysis of the first 20 warm-up trials of the LE sessions revealed an identical pattern of effects in that acute 2-DG injections significantly elevated LE thresholds over both placebo and chronic 2-DG treatments.

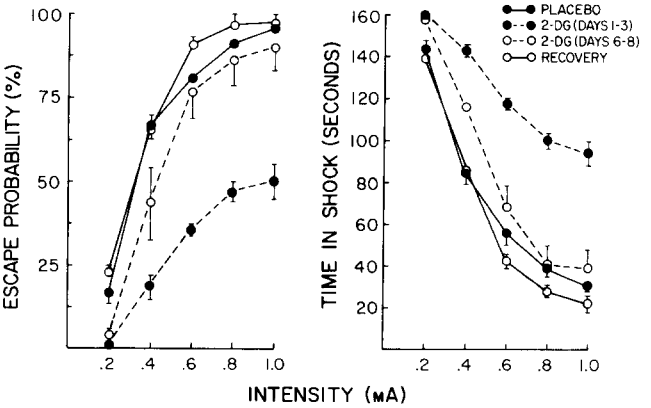

FIG. 1. Alterations in liminal escape thresholds (± SEM) across shock intensities 60 min following initial (Days 1–3) and repeated (Days 6–8) 2-deoxy-D-glucose (2-DG) injections as compared to placebo baseline and recovery sessions.

TABLE 1

SCHEFFE ANALYSIS OF ALTERATIONS IN LIMINAL ESCAPE PAIN THRESHOLDS FOLLOWING ACUTE AND CHRONIC 2-DG ADMINISTRATION

Condition	Escape Probability (%) Shock Intensities (mA)					Time Spent in Shock (sec) Shock Intensities (mA)				
	0.2	0.4	0.6	0.8	1.0	0.2	0.4	0.6	0.8	1.0
Placebo Baseline										
Mean	16.7	66.6	80.6	90.8	95.1	143.7	84.0	55.9	39.7	30.3
2-DG (Days 1–3)										
Mean	0.3	18.4	35.7	46.8	50.0	160.0	143.2	118.3	100.7	94.1
F	7.83	36.19	28.18	36.86	42.33	8.65	34.19	30.17	35.87	41.17
p	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
2-DG (Days 6–8)										
Mean	3.9	43.4	76.5	85.7	89.6	157.7	116.0	68.0	40.7	39.2
F	4.55	6.93	0.30	1.08	2.02	4.91	7.77	1.24	0.02	1.97
p	<0.05	<0.05	NS	NS	NS	<0.05	<0.01	NS	NS	NS
Recovery										
Mean	22.6	65.1	90.7	96.8	96.9	139.4	85.7	42.7	27.5	22.1
F	1.18	0.05	4.53	5.51	0.99	0.62	0.03	3.35	7.54	5.47
p	NS	NS	<0.05*	<0.05*	NS	NS	NS	NS	<0.01*	<0.05*

*Liminal escape thresholds are lower than baseline.

Similar differences in the effects of acute and chronic 2-DG injections occurred in intertrial behaviors of all animals. Both the time spent holding onto the lever, $F(19,120)=2.24$, $p<0.01$, and the number of extra intertrial lever presses, $F(3,136)=11.49$, $p<0.01$, showed significant variations across the experimental paradigm. Table 2 shows that the initial 2-DG injections caused a decline in both intertrial bar-holding time and in extra intertrial responses, but that chronic 2-DG did not. However, the relative apportionment of extra responses during intertrial intervals subsequent to escape trials as opposed to non-escape trials remained relatively constant throughout the experimental sequence, $F(3,136)=2.37$; see Table 2. Again, the continued, systematic patterning of intertrial behaviors during the experimental phase indicated that acute exposure to 2-DG resulted in orderly, non-random alterations in liminal escape behavior.

The adaptation of liminal escape pain thresholds following chronic 2-DG exposure was clearly dissociated from 2-DG's hyperphagic effects. Table 3 shows that whereas food intake increased significantly during the 6 hr following both acute and chronic 2-DG administration, $F(19,120)=5.80$, $p<0.01$, the hyperphagia induced by these treatments did not differ significantly, $F(1,40)=2.55$. Food

TABLE 2

SCHEFFE ANALYSIS OF ALTERATIONS IN LIMINAL ESCAPE INTERTRIAL INTERVAL MEASURES FOLLOWING ACUTE ANND CHRONIC 2-DG ADMINISTRATION

Condition	Bar-Holding	Extra Responses	Extras/Opportunity Escape: Extras/Opportunity Non-Escape
Placebo Baseline			
Mean	71.6	56.4	8.43
2-DG (Days 1–3)			
Mean	36.7	22.7	19.40
F	29.31	25.64	—
p	<0.01	<0.01	NS
2-DG Days 6–8)			
Mean	62.5	47.2	12.85
F	2.97	2.00	—
p	NS	NS	NS
Recovery			
Mean	72.3	67.9	8.01
F	0.04	2.96	—
p	NS	NS	NS

TABLE 3

SCHEFFE ANALYSIS OF FOOD INTAKE AND BODY WEIGHT ALTERATIONS FOLLOWING ACUTE AND CHRONIC 2-DG ADMINISTRATION

Measure	Placebo Baseline	2-DG (Days 1–3)	2-DG (Days 6–8)	Recovery
Food Intake				
Mean	2.82	6.44	7.51	3.78
SEM	0.27	0.60	0.35	0.46
F	—	37.76	70.64	4.79
p	—	<0.01	<0.01	<0.05
Body Weight				
Mean	452.9	452.5	443.7	454.3

intake was still elevated above baseline during the recovery condition. These nonadapting effects of 2-DG upon food intake seemed specific to its glucoprivic properties since the 6 hr post-injection hyperphagia did not significantly alter body weight, $F(3,120)=0.38$.

Table 4 shows that the reflex flinch-jump threshold alterations following acute and chronic injections of 2-DG were identical to operant LE threshold shifts. One-way analyses of variance revealed that the significant changes in jump, $F(2,33)=49.65$, $p<0.01$, initial-jump, $F=33.67$, $p<0.01$ and flinch, $F=5.33$, $p<0.01$, thresholds were attributed to profound elevations in all three nociceptive measures following acute 2-DG administration as compared to both baseline and chronic values, rather than any alterations from baseline induced by chronic 2-DG administration.

TABLE 4

SCHEFFE ANALYSIS OF ALTERATIONS IN JUMP, INITIAL JUMP AND FLINCH REFLEX PAIN THRESHOLDS FOLLOWING ACUTE AND CHRONIC 2-DG ADMINISTRATION

Threshold	Baseline	2-DG Condition Acute	Chronic
Jump			
Mean	0.447	0.681	0.473
SEM	0.015	0.021	0.016
F	—	74.40*	1.35
Acute vs. Chronic F		57.06†	
Initial Jump			
Mean	0.417	0.608	0.455
SEM	0.013	0.018	0.018
F	—	65.72†	2.57
Acute vs. Chronic F		32.43†	
Flinch			
Mean	0.154	0.206	0.162
SEM	0.005	0.016	0.010
F	—	8.44†	0.50
Acute vs. Chronic F		4.67*	

*$p<0.05$; †$p<0.01$.

DISCUSSION

The present study demonstrates a dissociation of 2-DG's ability to induce hyperphagia and its ability to elevate both operant and reflex pain thresholds. Whereas acute administration of 2-DG elevated tail-pinch, liminal escape and flinch-jump thresholds (present study, [3,6]), chronic 2-DG administration resulted in adaptation of the analgesic response observed in the latter two tests. That these effects were the result of the adaptive influences of chronic 2-DG treatment, rather than temporal shifts in analgesic potency were confirmed by the near-normal reactivity to aversive shock observed both 30 min following chronic treatment in the flinch-jump test and during both the warm-up and test trials of the LE procedure. In contrast, 2-DG's effect upon gross 6 hr food intake remained undiminished over the same chronic regimen of injections, suggesting that the physiological mechanisms underlying the analgesic and hyperphagic effects of 2-DG differ. One explanation for the present results is that 2-DG exerts its acute analgesic response by acting as a stressor, thereby activating an intrinsic pain-inhibitory system. 2-DG administration induces a profile of physiological stress responses including marked glucoprivation and peripheral sympatho-medullary and pituitary-adrenal discharge [15, 19, 34]. In addition, it induces dose-dependent and time-dependent reflexive and operant pain threshold elevations, the potency and magnitude of which are similar to that of other stressors such as cold-water swims [7,9] and severe inescapable foot shock [1, 17, 18, 20]. Like the analgesia induced by these latter two stressors [1, 9, 10, 20], 2-DG adapts with repeated exposure in much the same way that other physiological stress responses adapt [26] and in much the same way that repeated administration of morphine results in tolerance [21].

Other observations have linked the various actions of 2-DG with that of inescapable foot shock and hypothermic stress. First, whereas animals acutely exposed to inescapable foot shock exhibit profound norepinephrine depletions, animals pretreated with chronic 2-DG injections fail to show such deficits following the identical procedure [25]. Second, whereas animals acutely exposed to either inescapable foot shock or hypothermic stress fail to display 2-DG-induced hyperphagia, animals chronically exposed to these two stressors exhibit the expected overeating response to 2-DG [24]. This study correlated such effects to hypothalamic norepinephrine loss in the acutely-stressed animals and its subsequent adaptation following chronic stress exposure.

Third, full and reciprocal cross-tolerance develops between cold-water swim-induced and 2-DG-induced analgesia, indicating that the pain inhibitory consequences of one stressor can be altered by prior administration of another [29]. The complementary relationship between the nociceptive elevations induced by 2-DG and those induced by inescapable foot shock or cold-water swims is not total since: (a) hypophysectomy attenuates the analgesia induced by foot shock and cold-water swims, but not that induced by 2-DG [2, 4, 5, 23]; (b) morphine-tolerant rats display full analgesia following acute exposure to cold-water swims, but not following 2-DG injection [13,30]; and (c) in keeping with the latter data, high naloxone doses only partially reverse inescapable foot shock-induced or cold-water swim-induced analgesia [1, 8, 9, 12, 17, 18].

Yet given these differences, the analgesic properties of 2-DG following acute exposure and its subsequent adaptation following chronic treatment appear to be specific to respective activation of and adaptation of pain-inhibitory mechanisms subserving nociceptive modulation since the hyperphagic aspects of 2-DG administration fail to adapt. However, other alternative explanations should be addressed. First, undetected temporal shifts in the hyperphagic response could have occurred in the present study following chronic 2-DG treatment, indicating an adaptation to the induced overeating. The entertainment of such a possibility still demonstrates dissociation of 2-DG's effects upon nociception and feeding since differential time courses for the full expression of the adaptive influences exist. Second, performance during the LE procedure may have affected subsequent 2-DG induced hyperphagia given that acute but not chronic inescapable foot shock reduces this effect [24]. Neither the methodology nor the data support this notion since: (a) the foot shock was lower (maximum: 1 mA) in intensity and could be terminated in the present study; (b) hyperphagia occurred following acute 2-DG-injections despite the endurance of more time spent in shock; and (c) similar hyperphagia occurred following chronic 2-DG injections despite the lower amount of shock endured. Though these findings [24] do not explain the present data, they are not themselves in dispute since chronic exposure to shock occurred during initial training and baseline along with the subsequent, expected hyperphagic response to 2-DG. Third, sensory inattention rather than analgesia might account for the nociceptive threshold elevations following acute 2-DG injections since impaired cerebral metabolism and EEG synchronization are observed following intravenous 2-DG in monkeys [22] and since rats injected with a 2-DG dose of 700 mg/kg exhibit ataxia in the LE test 30 min later [3,6]. Again the present methodology and data do not support this hypothesis since: (a) a 600 mg/kg 2-DG dose was employed in conjunction with a LE test 60 min thereafter; (b) orderly intensity-dependent shifts in escape thresholds occurred rather than random fluctuations following acute 2-DG injections; and (c) the ability to ingest solid food pellets with all attendant sensory-motor integration was intact as was the ability to make the escape response.

In summary, exposure to stressful situations has long been known to induce a profile of physiological adaptations, or stress reactions. The present and other recent data suggest that a temporary decline in sensitivity to pain may also be one of the body's normal responses to a wide range and variety of acute stressors. Thus, in addition to well-documented central neural changes in sympathetic arousal and pituitary-adrenal activation, another coping response used by the neuroendocrine system may be the activation of a heterogeneous and complex pain-modulating system which dampens normal reactions to pain during periods of stress.

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