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2-Deoxy-D-Glucose-Induced Decrements in Operant and Reflex Pain Thresholds

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BODNAR, R. J., D. D. KELLY, M. BRUTUS, A. MANSOUR AND M. GLUSMAN. *2-Deoxy-D-glucose-induced decrements in operant and reflex pain thresholds*. PHARMAC. BIOCHEM. BEHAV. 9(4) 543–549, 1978.—Acute exposure to many environmental stressors induces significant analgesia. The present study examined whether 2-deoxy-D-glucose (2-DG), an antimetabolic glucose analogue, which induces glucoprivation and peripheral sympatho-adrenal discharge, would also produce analgesia as measured by either an operant liminal escape or a reflex tail-pinch procedure. In the liminal escape paradigm, 9 rats were tested at weekly intervals in 6 randomly selected testing conditions: 30 min pre-test injections of four 2-DG doses (100, 225, 350 and 700 mg/kg, IP) and 180 min pre-test injections of the 2 higher doses. Moderate analgesia occurred at the lower 2-DG doses 30 min after injection, while profound analgesia occurred at the higher doses. After 180 min, only the 700 mg/kg 2-DG dose produced moderate analgesia, which was further enhanced by food deprivation. Rats tested in the tail-pinch paradigm displayed a similar dose-dependent analgesia course. These results demonstrate that 2-DG decreases nociceptive sensitivity, possibly through stress-induced activation of an intrinsic pain-inhibitory system.

Pain-Inhibition 2-Deoxy-D-glucose Analgesia Stress Rats

RATS exposed to severe, novel environmental stressors such as inescapable foot shock, rotation, intraperitoneal injections of hypertonic saline, cold-water swims or food deprivation display a transient though profound behavioral analgesia [5, 7, 9, 26, 27, 46]. Repeated exposures to these same stressors result in adaptation to the analgesic effects [1, 7, 8, 37] in the same manner that other stress-induced physical responses such as pituitary-adrenocortical activation adapt [43]. On a neural level, acute exposure to either inescapable foot shock or cold-water swims has also been shown to deplete brain norepinephrine levels in the rat, while repeated exposures or cross-treatment between the 2 conditions does not [3, 47, 48, 55]. Recently, Ritter and Ritter [41] have reported that prior chronic exposure to 2-deoxy-D-glucose (2-DG), an antimetabolic glucose analogue [57], prevented depletion of brain norepinephrine induced by acute inescapable foot shock, suggesting that 2-DG and inescapable foot shock may exert similar physiological effects upon the central nervous system. Like many noxious stimuli, acute administration of 2-DG also induces many stress-related physiological responses, including marked glucoprivation, peripheral sympatho-adrenal discharge and hyperglycemia [15, 29, 57]. These responses are thought to be caused by 2-DG's ability to selectively cross cell membranes and interfere with normal cellular metabolism. This mechanism is also thought to account for the increased intake of food following 2-DG administration in rats [14, 44, 50], primates [44,45] and humans [49].

The purpose of the present study was to test whether 2-DG, because of its stress-like properties, might also induce analgesia. Since stressors induce a level and duration of analgesia proportional to their severity [4], 2-DG might also be expected to produce an analgesia that was both dose-dependent and time-dependent. Like narcotic-, non-narcotic-, and stimulation-induced analgesia, stress-induced analgesia has been shown to be active on a wide variety of both reflex and operant pain threshold tests [5, 7, 31, 32, 33]. Accordingly, in the present experiment, the analgesic potential of 2-DG was assessed with a reflex tail-pinch test and with an operant liminal escape procedure, that has been shown to be sensitive to both an animal's evaluation of the relative aversiveness of a given stimulus and its motivation to respond, or not, to terminate its presence [31, 32, 33]. The tail-pinch procedure is a rapid reflex test which yields a point estimate of the threshold and thus allows the close temporal tracking of an analgesic time course. The liminal escape test is a discrete trial variant [25, 34, 36] of the shock titration schedule devised by Weiss and Laties [51,54], but it has the advantage of being behaviorally more stable since the programing of shock intensities is not left under the control of the animal [35,52], and thus the derived complementary psychophysical functions appear to reflect the integrated response of the organism across a broad continuum of aversiveness represented by different shock intensities. Nevertheless, since titration and liminal escape both appear to tap the sensory-discriminative and emotional aspects of the pain

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response, the two procedures have been found to display a similar profile of pharmacologic sensitivities [22, 31, 33, 38, 39, 53, 56].

METHOD

Liminal Escape Testing

Nine male albino Holtzman Sprague-Dawley rats (350–500 g) served in the operant liminal escape procedure. 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 terminal fixed ratio liminal escape schedule. Pulsed foot shocks were delivered for 10 sec unless the rat depressed the lever 3 times to abbreviate the shock train and initiate 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 over 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 and these less stable data are not included in the present analysis. 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 during the intertrial interval.

After 10 daily 100-trial sessions, rats were placed on a 2 session per week schedule for 7 weeks. Each pair of sessions occurred on successive days, the first always programmed as a placebo or control day, the second as an experimental drug session. On successive weekly drug days, animals were injected intraperitoneally with 1 of 4 doses of 2-DG (100, 225, 350 or 700 mg 2-DG/2 ml sterile water/kg body weight). On 4 of the test weeks, one at each dose, liminal escape sessions were begun 30 min following injections. On 2 other weeks, sessions were programmed 180 min following injections of 350 and 700 mg/kg. On the paired control days, placebo injections (2 ml sterile water/kg body weight, IP) preceded test sessions by similar periods. Normally food and water were available to the animals at all times, except during liminal escape sessions. However, on 1 test week, food was explicitly denied the animal during the interval between an injection of 2-DG at 700 mg/kg and a test session 180 min later. The weekly order of these 7 test conditions was randomly selected for each animal.

Tail-Pinch Threshold

The tail-pinch thresholds for 6 naive male albino rats were determined by delivering pressure 8 cm proximal from the tip of the tail at a linearly increasing rate with a motor-driven analgesy meter (Ugo-Basile, Milan). The minimal pressure which elicited either tail withdrawal and/or hindlimb struggling in the experimenter's grasp served as the dependent variable. During each experimental session, threshold determinations were made immediately prior to and 30, 60, 120 and 180 min following an injection. On 6 successive weekly sessions, each rat was injected with either 1 of 4 doses of 2-DG (100, 200, 400 or 600 mg/2 ml sterile water/kg body weight, IP) or 2 placebo conditions. The order of the 6 conditions was randomly determined and the experimenter conducting the tail-pinch procedure was uninformed as to the specific experimental condition.

RESULTS

2-DG elevated operant liminal escape thresholds in an orderly dose-dependent fashion 30 min following injection. Figure 1 displays the decrease in escape probability 30 min following each of the four 2-DG dose levels; similar, complementary increases in the time spent in shock were observed. It is clear that this dose-dependent analgesic relationship was transient as Fig. 2 shows a return toward placebo levels 180 min following the two highest 2-DG doses. An analysis of variance, using the 9 rats in each injection condition as a repeated measure, showed significant decreases in escape probability across 2-DG injection dose and time conditions, $F(8,360)=18.37$, $p<0.01$, across liminal escape shock intensities, $F(4,360)=140.53$, $p<0.01$, and for the injection × intensity interaction, $F(32,360)=2.07$, $p<0.01$. Significant, complementary increases in time spent in shock were observed across 2-DG injection conditions, $F(8,360)=p<0.01$, across shock intensities, $F(4,360)-158.27$, $p<0.01$, and for their interaction, $F(32,360)=2.30$, $p<0.01$. A posteriori Tukey comparisons, as summarized in Table 1, indicated that whereas the 2 lower 2-DG doses induced mild decrements in escape responding 30 min following injection, the 350 and 700 mg/kg 2-DG doses produced significant reductions in escape responding. Despite the escape decrements at the latter doses, normal motor (ambulation and posture) was noted following the 350 mg/kg dose, while moderate ataxia was observed at 700 mg/kg. Even so, this 2-DG induced ataxia did not interfere with ongoing operant escape responding, since all rats displayed an intensity-dependent pattern of escape responding 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 and is not indicative of severe non-specific motor deficits which would induce random escape behavior independent of stimulus intensity tracking.

The 2-DG-induced decrease in nociceptive sensitivity was time-dependent as well as dose-dependent. The 350 mg/kg 2-DG dose, which induced profound analgesia across all shock intensities 30 min following injection, produced no discernable changes in nociceptive sensitivity when administered 180 min prior to testing. Similarly, the 700 mg/kg dose which produced severe escape decrements 30 min following injection, induced significant, yet moderate residual analgesia when administered 180 min prior to testing.

Further enhancements of liminal escape deficits were produced in the food-deprivation and 700 mg/kg of 2-DG (700 mg/kg)-injection condition, suggesting a synergy between

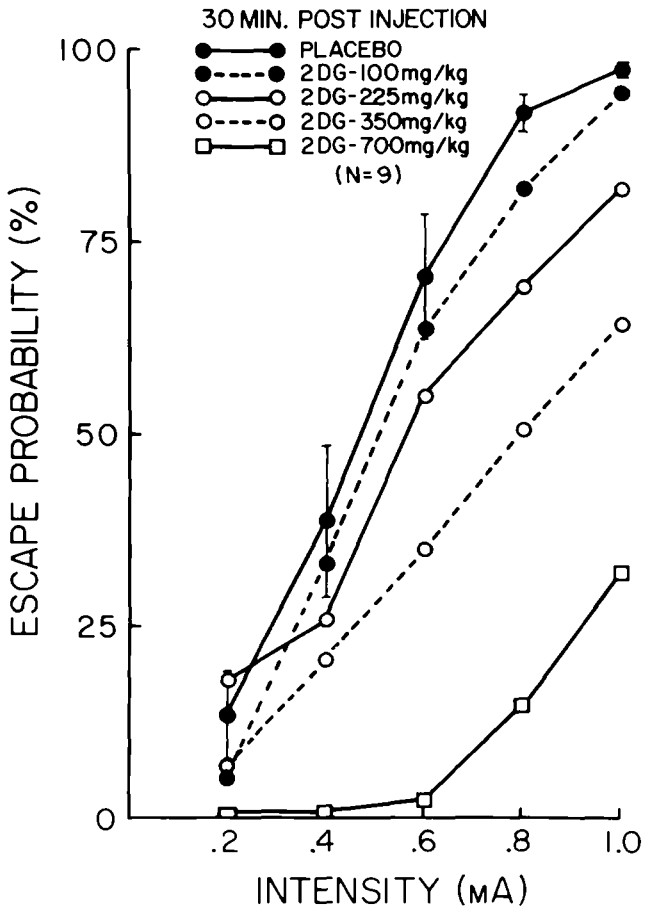

FIG. 1. Dose-dependent alterations in liminal escape probability across shock intensities 30 min following 2-deoxy-D-glucose (2-DG) administration. The mean (±SEM) of all placebo conditions is displayed as a standard.

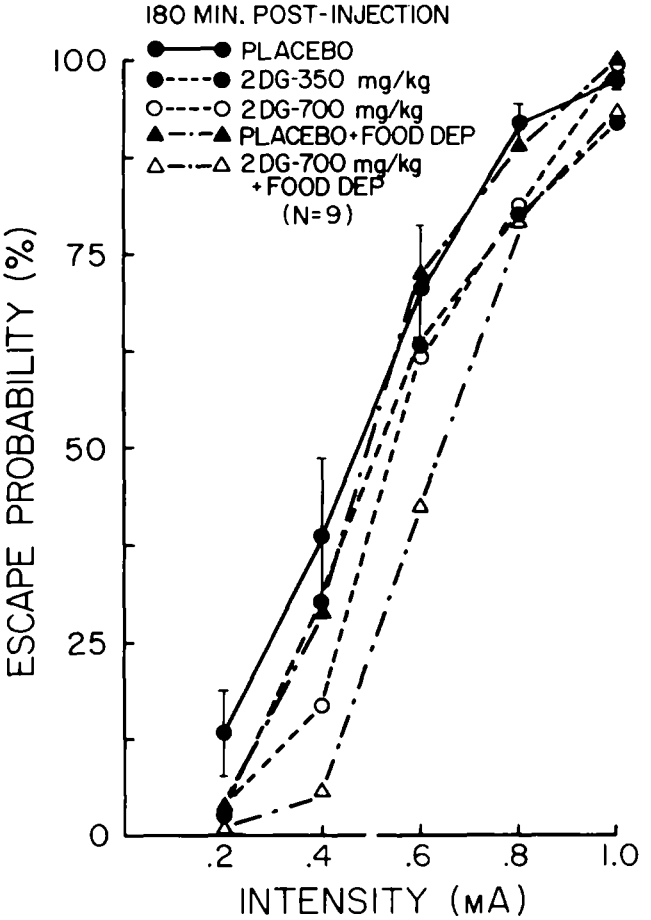

FIG. 2. Alterations in liminal escape probability across shock intensities 180 min following administration of 350 mg/kg and 700 mg/kg of 2-deoxy-D-glucose (2-DG). The effects of food deprivation during the 180 min between 0 or 700 mg/kg 2-DG injections and the test session are also shown. The mean (±SEM) of all placebo conditions is displayed as a standard.

endogenous (2-DG) and exogenous (deprivation) hunger signals. Significant decreases in escape responding following this manipulation were observed across intermediate shock intensities as compared to placebo control, the food-deprivation placebo control, 0.4: $t(8)=3.21$, $p<0.05$; 0.6: $F(8)=3.21$, $p<0.05$, and the 2-DG (700 mg/kg) injected alone, 0.4: $t(8)=2.04$, $0.1>p>0.05$; 0.6: $t(8)=2.54$, $p<0.05$; 0.8: $t(8)=1.92$, $0.1>p>0.05$ conditions.

The percentage of time spent by the rats depressing the lever during the intertrial interval also differed following 2-DG injections, $F(8,72)=2.35$, $p<0.05$. This intertrial depression on the lever is typical of escape performance in the albino rat [20] and is normally interpreted as either a preparatory response [17,21], a perseverative response [30], or a species-specific defense reaction [12,13]. Averaged across all placebo sessions the rats spent half of their time between shock trials in continuous contact with the lever (50.28%). Table 2 summarizes the percentages across drug conditions. In general, the decreased bar-holding noted following 2-DG injections did not correspond with the analgesia induced by the same injections. For instance, at 30 min following 2-DG administration, rats receiving the non-analgesic 100 mg/kg dose and the analgesic 350 mg/kg dose both displayed significant decreases in bar-holding. Also, at 180 min following 2-DG administration, both the analgesic 700 mg/kg rats and the analgesic 700 mg/kg plus food deprivation rats showed normal bar holding patterns, $t(8)=0.25$.

Figure 3 displays the similar dose-dependent elevations in reflex tail-pinch thresholds following acute 2-DG administration. A two-way analysis of variance, using the pre-injection difference scores at each test interval, revealed significant elevations in the amount of pressure necessary to elicit a withdrawal response across 2-DG and placebo injection conditions, $F(3,120)=2.38$, $p<0.05$, but not for the post-injection time course, $F(3,120)=0.51$. Tukey post-hoc comparisons demonstrate that whereas the 2 lower 2-DG doses induced mild, though nonsignificant elevations, 100 mg/kg: $t(23)=1.06$; 200 mg/kg: $t(23)=1.27$ in tail-pinch thresholds, the 2 higher 2-DG doses induced profound and significant tail-pinch threshold elevations, 400 mg/kg: $t(23)=2.89$, $p<0.01$; 600 mg/kg: $t(23)=2.37$, $p<0.05$ that persisted over the 3-hr post-injection time course.

DISCUSSION

It is apparent from the present results that 2-DG produces dose-dependent elevations in both operant liminal escape

TABLE 1

DOSE-DEPENDENT AND TIME-DEPENDENT ALTERATIONS IN LIMINAL ESCAPE THRESHOLDS FOLLOWING ADMINISTRATION OF 2-DEOXY-D-GLUCOSE (2DG)

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
1. Placebo	x	13	39	71	92	98	149.7	119.4	73.4	41.2	29.1
Post 30 Min											
2. 2-DG (100	x	5	33	64	82	94	155.7	127.6	89.4	60.9	32.4
mg/kg)	t	1.42	0.69	0.98	1.03	0.83	1.58	2.70	0.54		
	p	NS	NS	NS	NS	NS	NS	NS	NS	0.05	NS
3. 2tDG (225	x	18	26	55	69	82	146.6	135.2	97.2	75.9	57.3
mg/kg)	t	0.85	1.28	1.03	1.80	1.32	1.18	1.55	1.27	2.06	1.60
	p	NS	NS	NS	NS	NS	NS	NS	NS	0.10	NS
4. 2-DG (350	x	7	21	35	51	64	155.5	146.8	123.0	107.7	85.0
mg/kg)	t	1.25	1.75	2.79	3.76	3.42	1.26	2.62	3.13	4.96	4.35
	p	NS	NS	0.05	0.01	NS	0.05	0.0	0.01	0.01	
5. 2-DG (700	x	0	0	2	14	32	161.0	160.2	159.2	148.6	124.2
mg/kg)	t	2.40	3.94	9.11	17.93	6.06	2.26	3.58	7.38	26.04	12.00
	p	0.05	0.01	0.001	0.001	0.001	0.10	0.01	0.001	0.001	0.001
Post 180 Min											
6. 2-DG (350	x	3	30	63	80	92	158.0	127.9	82.0	58.5	34.5
mg/kg)	t	2.39	1.40	1.46	0.98	1.90	1.11	0.81	1.49	0.56	
	p	0.05	NS	NS	NS	NS	0.10	0.01	0.05	NS	NS
7. 2-DG (700	x	4	17	62	81	99	159.0	145.8	92.0	60.8	28.6
mg/kg	t	2.04	3.05	1.32	1.17	1.67	2.18	3.43	2.35	1.43	0.13
	p	0.10	0.02	NS	NS	NS	0.10	0.05	NS	NS	
8. Placebo ·	x	4	29	73	89	100	158.6	140.5	76.7	45.3	23.0
Food	t	2.61	1.93	0.18	0.44	0.98	2.08	3.57	0.42	0.41	2.38
Deprivation	p	0.05	0.10	NS	NS	NS	0.10	0.01	NS	NS	0.05*
9. 2-DG (700	x	1	6	43	79	93	160.4	157.1	118.9	74.2	43.9
mg/kg ·	t	2.22	3.58	2.74	1.32	0.86	2.08	3.44	3.72	2.52	1.43
Food	p	0.10	0.01	0.05	NS	NS	0.10	0.01	0.05	NS	
Deprivation											

*Significantly less than baseline values.

and reflex tail-pinch pain thresholds. The similarity and orderliness of 2-DG's dose-dependent effects upon the 2 measures suggests that these threshold shifts, particularly those at the 350 mg/kg dose 30 min following the injection and at the 700 mg/kg dose 180 min post-injection, were more likely due to a decrease in pain sensitivity than to a non-specific behavioral effect such as impaired motor performance, which might induce more random fluctuations. Non-specific ataxia, however, seemed to be responsible for liminal escape alterations at the 700 mg/kg dose administered 30 min earlier. Time-dependent alterations were also observed for liminal escape, but less so for tail-pinch thresholds.

Inasmuch as 2-DG fulfills many of the physiological criteria of a stressor, including intense activation of the

TABLE 2

ALTERATIONS IN LEVER-HOLDING BEHAVIOR FOLLOWING 2-DEOXY-D-GLUCOSE (2-DG) ADMINISTRATION

	Conditions							
		Post 30 Min			Post 180 Min			
	Placebo	2-DG (100 mg/kg)	2-DG 225 mg/kg)	2-DG 350 mg/kg)	2-DG (700 mg/kg)	2-DG (350 mg/kg)	2-DG (700 mg/kg)	Placebo · Food Deprivation	Placebo · Food Deprivation
x%	50.28	43.56	38.22	28.78	7.33	45.22	45.89	45.00	43.22
t		2.31	1.27	4.98	7.00	0.79	0.82	0.24	1.00
p		0.05	NS	0.01	0.001	NS	NS	NS	NS

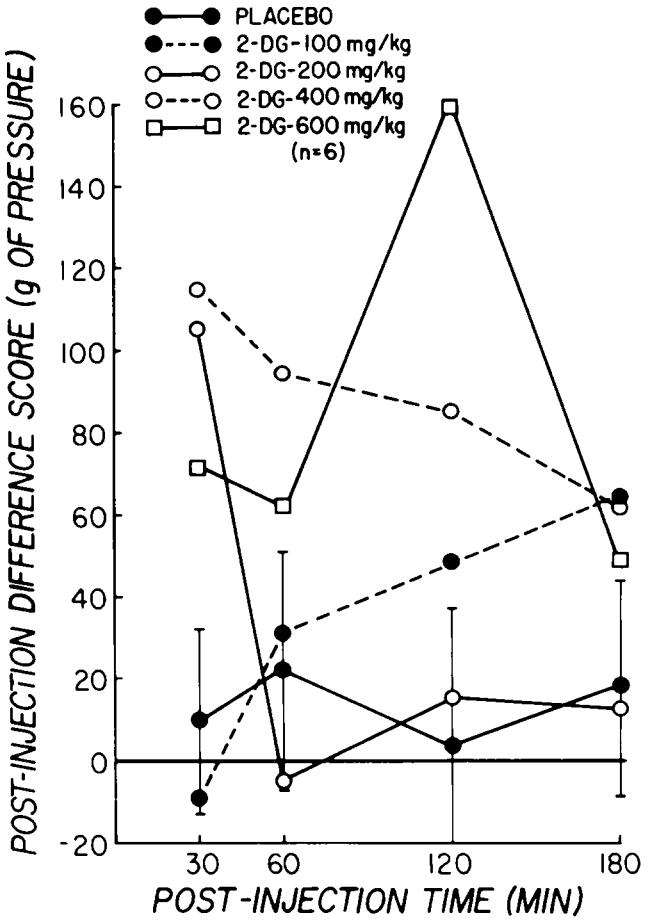

FIG. 3. Dose-dependent alterations in tail-pinch thresholds as a function of post-injection time course following 2-deoxy-D-glucose (2-DG) administration. Each data point represents the difference score of each post-injection test point minus its pre-injection (baseline) counterpart. The mean (+SEM) of the two placebo conditions is displayed as a standard.

pituitary-adrenal and sympatho-medullary axes [15, 29, 57] the present data are consistent with previous observations that acute exposure to physiological stressors produces analgesia [1, 5, 7, 9, 26, 27, 37, 46]. However, 2-DG does not seem to be a painful stressor in the same sense as cold-water swims, forced rotation and inescapable foot shock, yet it still induces a comparable level and time course of analgesia. Thus, along with the elevations in pain thresholds induced by unexpected food deprivation [9,46], these data suggest that stressors need not be painful to prompt analgesia. Indeed, from the present data, it also appears that these latter stressors can potentiate each other's analgesic effects when combined and suggest a synergy between exogenous and endogenous means of inducing the stress-related and pain-inhibitory consequences of hunger signals.

It is especially compelling that 2-DG and other stressors which induce analgesia share the property of activating both the central hypothalamic and peripheral pituitary-adrenal axes. The mechanism by which analgesia might be produced by activating this intrinsic pain-inhibitory system is still unclear, but several recent empirical observations have narrowed the possibilities. First peripheral endorphins may be involved since, in response to severe injury stress, adrenocorticotropin and β-endorphin are released concomitantly by the pituitary [24]. Moreover, following inescapable foot shock stress, β-endorphin levels increase in blood, but not brain tissue [42]. However, stress-induced alterations in central opiate activity and their subsequent role in stress-induced analgesia have been less clear cut. Some studies have reported increased brain opiate receptor binding factor [1, 18, 37] and decreased ^{3}H-leu-enkephalin binding [19] following inescapable foot shock while another has reported unaltered ^{3}H-met-enkephalin levels in brain [23] following the identical stressor. Further behavioral evidence suggests that stress-induced analgesia may not be opiate-related: (a) cold-water stress-induced and morphine-induced analgesia fail to develop cross-tolerance [11]; (b) naloxone only partially reverses inescapable foot shock-induced and cold-water swim-induced analgesia [1, 6, 7, 10, 27] and (c) dorsolateral spinal cord lesions, which attenuate both opiate and stimulation-induced analgesia [2, 28, 40] fail to alter foot shock-induced analgesia [28,40]. Second, hypophysectomized animals display a sharply attenuated analgesia following acute exposure to cold-water swims [4] and to inescapable foot shock (A. Pert, personal communication, 1978). Third, other data from our laboratory indicate that whereas chronic 2-DG administration is still accompanied by an increased food intake, adaptation develops to the pain threshold elevations, in much the same manner that both cold-water swim-induced and inescapable foot shock-induced analgesia adapt and that the array of other physiological responses to stress adapt [16].

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 stress. Thus, in addition to well-documented central neural changes in sympathetic arousal and pituitary-adrenal activation, another coping response cued by the nervous system may be the activation of a pain-modulating system which dampens normal reactions to pain during periods of stress.

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