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Opiate and Non-Opiate Mechanisms of Stress-Induced Analgesia: Cross-Tolerance Between Stressors

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SPIAGGIA, A., R. J. BODNAR, D. D. KELLY AND M. GLUSMAN. *Opiate and non-opiate mechanisms of stress-induced analgesia: Cross-tolerance between stressors.* PHARMAC. BIOCHEM. BEHAV. **10**(5) 761–765, 1979.—Acute exposure to severe stressors induce profound analgesia. Repeated exposures to the same stressors result in adaptation in much the same way that repeated administration of opiates results in tolerance. The present study investigated whether two qualitatively different stressors, cold-water swims (CWS) and injections of 2-deoxy-D-glucose (2-DG) share common pain-inhibitory mechanisms by determining whether cross-tolerance developed to their analgesic effects. Cross-tolerance was also examined between 2-DG and morphine. Flinch-jump thresholds were determined in six groups of six rats each. Analgesia was observed 30 min following acute exposure to CWS (2°C for 3.5 min), 2-DG (350 mg/kg) and morphine (10 mg/kg), but not following placebo injections or warm water swims. Chronic exposure to all three analgesic treatments resulted in tolerance and adaptation. Complete and reciprocal cross-tolerance developed between the analgesia induced by CWS and by 2-DG. Complete cross-tolerance to 2-DG analgesia also developed in morphine-tolerant rats, but only partial cross-tolerance to morphine analgesia developed in 2-DG adapted rats. These results support the concept that stressful events induce analgesia through specific activation of an intrinsic pain-inhibitory system which has both opiate and non-opiate branches.

Pain-inhibition Analgesia Stress Cross-tolerance Cold-water swims 2-Deoxy-D-glucose Morphine Rats

ACUTE exposure to stressful events has long been known to induce a profile of physiological stress responses including pituitary-adrenal activation and sympatho-medullary discharge [37]. Recent evidence suggests that a temporary decline in sensitivity to pain may also be one of the body's normal responses to stress. A number of effective analgesia-inducing stressors, including inescapable foot shock (FS), cold-water swims (CWS), rotation, food deprivation and injections of either hypertonic saline, 2-deoxy-D-glucose (2-DG), or insulin, have been identified using a wide range of reflex and operant nociceptive measures [1, 4, 6, 10, 12, 15, 20, 26, 27]. Although initial exposure to either FS, 2-DG or CWS produced analgesia, chronic long-term exposure over 12–14 days does not [1, 9, 11, 25, 27]. Thus analgesic effects of stress adapt in a manner similar to its neuroendocrine and autonomic correlates.

Several investigators have linked endorphin activity to the mediation of stress-induced analgesia, since adrenocorticotrophic hormone (ACTH) and β-endorphin are released concomitantly by the pituitary [19] in increased concentrations into plasma [34] following either FS stress or severe trauma. In addition, FS analgesia correlates well with increases in brain opiate receptor activity and decreases in ^{3}H-leu-enkephalin activity [1, 15, 16, 27, 35]. However, considerable evidence exists which is contrary to this contention: (a) ^{3}H-met-enkephalin activity is unaltered following acute exposure to FS [18]; (b) naloxone, which is capable of completely eliminating opiate analgesia at low doses [28] can only partially reverse FS or CWS analgesia across a wide dose range [1, 8, 20, 26]; (c) dorsolateral spinal cord lesions, which attenuate both opiate and stimulation-induced analgesia [3,21], fail to alter FS analgesia [21]; and (d) cross-tolerance fails to develop between morphine and CWS analgesia [13,16]. The latter finding contrasts with the full development of cross-tolerance between intracerebral micro-injections of morphine and endorphin fragments [39,44], and between the former and systemic morphine injections [24]. It also contrasts with partial development of cross-tolerance between stimulation-induced and morphine analgesia [29].

Given the number and range of novel environmental events that increase nociceptive thresholds following acute exposure and adapt following repeated exposure, it seems unlikely that non-specific factors peculiar to the individual stressors account for the analgesia. Rather, a common pain-inhibitory system may exist that is activated during times of

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stress, and that adapts after repeated exposure. Therefore, one might expect that repeated activation of this system by one stressor would make it refractory to subsequent activation by a second stressor. To examine this possibility, the present study investigated whether cross-tolerance would develop between the analgesia induced by two qualitatively different stressors, CWS and 2-DG, and also between 2-DG and morphine. CWS qualifies as a stressor in that acute, but not chronic exposure activates the pituitary-adrenal axis and depletes hypothalamic norepinephrine [38, 40, 41]. Acute administration of the antimetabolic glucose analogue 2-DG [42], induces many stress-related physiological responses, including marked glucoprivation, peripheral sympathoadrenal discharge and hyperglycemia [14, 22, 42], while repeated 2-DG injections prevent FS-induced brain norepinephrine depletions [33].

METHOD

Thirty-six Holtzman Sprague-Dawley rats (280–380 g) were tested for flinch-jump thresholds using a modification of the Evans procedure [17]. Electric shocks were delivered through a 30-cm by 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. The experimenter conducting the flinch-jump test was uninformed of the purpose of the experiment. Stable baseline flinch-jump thresholds were determined over 3 days. It should be noted that such thresholds remain stable over trials within a session as well as over sessions and seem not to be subject to adaptation [6, 8, 9, 11, 13, 17], possibly because of both the shock's short duration and liminal intensity.

Based on these data, rats were assigned into six matched groups of six rats each. Then, Group 1 was administered 14 daily injections of 2-DG (350 mg/2 ml sterile water/kg body weight, IP) followed on the fifteenth day by a single forced CWS at 2°C for 3.5 min (2-DG/CWS group). Group 2 underwent the reverse sequence: 14 daily CWS followed on the fifteenth day by a single injection of 2-DG (CWS/2-DG group). Group 3 received 14 daily injections of morphine (10 mg morphine sulfate/ml buffered solution/kg body weight, SC) followed on the fifteenth day by a single injection of 2-DG (MOR/2-DG group); Group 4 underwent the reverse sequence (2-DG/MOR group). Group 5 received 14 daily placebo injections (2 ml saline/kg body weight, IP) followed on the fifteenth day by CWS (PLA/CWS group), while Group 6 underwent 14 daily warm-water control swims (28°C for 3.5 min) followed on the fifteenth day by an injection of 2-DG (WWC/2-DG group).

Flinch-jump thresholds were tested for three days prior to the experimental sequence (baseline condition), then on the 1st (acute condition), 14th (chronic condition) and 15th (cross-treatment) experimental days, and subsequently for four more days (recovery condition). All experimental treatments occurred 30 min prior to flinch-jump testing. Twenty days following the last experimental (cross-

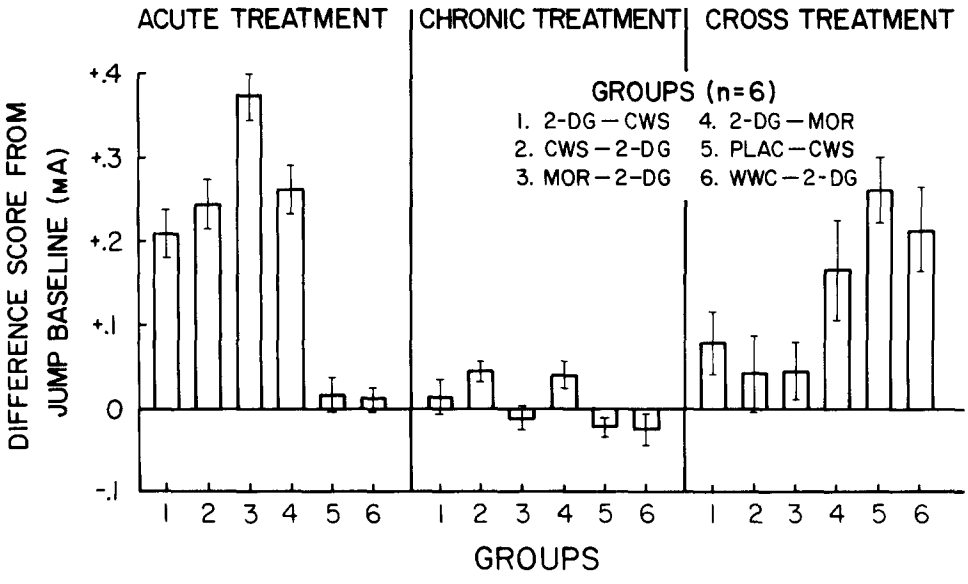

FIG. 1. Mean alterations (± SEM) in jump threshold from baseline values as a function of acute, chronic or cross-treatments for the six experimental groups. Abbreviations: 2-DG—2-deoxy-D-glucose; CWS—cold-water swims; MOR—morphine; PLA—placebo; WWC—warm-water control. The first designation signifies the agent used in the acute and chronic treatments while the second was used in the cross-treatment.

TABLE 1

A POSTERIORI SCHEFFE COMPARISONS BETWEEN THE JUMP THRESHOLDS OF BASELINE AND EXPERIMENTAL TREATMENTS ACROSS GROUPS

Group	Baseline	Treatment					
		Acute		Chronic		Cross	
	mA	mA	F	mA	F	mA	F
1. 2-DG/CWS	0.449	0.656	31.29†	0.461	0.11	0.528	1.58
2. CWS/2-DG	0.452	0.696	27.75†	0.497	1.39	0.494	0.66
3. MOR/2-DG	0.443	0.816	154.71†	0.431	0.31	0.488	1.17
4. 2-DG/MOR	0.445	0.707	42.40†	0.485	2.19	0.613	8.76*
5. PLA/CWS	0.444	0.418	0.25	0.422	0.13	0.706	24.55†
6. WWC/2-DG	0.439	0.450	0.13	0.415	0.88	0.654	14.82†

*$p<0.05$; †$p<0.01$.

treatment) day, all groups were reexposed to their original acute condition to determine if any long-term effects had resulted from the chronic experimental treatments. The means of the three baseline sessions and the four recovery sessions were ascertained for use in a two-way analysis of variance comprising the six experimental groups as one main effect and the experimental conditions within each group as the second main effect.

RESULTS

Figure 1 summarizes the analgesic effects of the three experimental manipulations upon jump thresholds following acute exposure (left panel) and the subsequent development of tolerance or adaptation following chronic exposure (middle panel). The further development of either full or partial cross-tolerance following cross-treatment is shown in the right panel. Initial-jump thresholds displayed an identical pattern of effects while flinch thresholds, as in prior experiments [13,17] showed somewhat less responsivity to the experimental manipulations. A two-way analysis of variance revealed significant differences across experimental groups, jump: $F(5,180)=2.78$, $p<0.05$; initial-jump: $F=3.29$, $p<0.01$; flinch: $F=10.00$, $p<0.01$, as well as between baseline and experimental conditions within groups, jump: $F(5,180)=13.50$, $p<0.01$; initial-jump: $F=56.29$, $p<0.01$; flinch: $F=28.67$, $p<0.01$. Since the normal matched baseline thresholds did not differ across groups, jump: $F(5,30)=0.03$; initial-jump: $F=0.10$; flinch: $F=0.68$, a posteriori Scheffe comparisons were made between the experimental and baseline days for each group. Table 1 summarizes the significant elevations in baseline following acute exposure to CWS, 2-DG or morphine. Chronic exposure to each experimental treatment resulted in a decline in their analgesic effectiveness and a return of flinch-jump thresholds to baseline values. Placebo injections and warm-water swims showed neither acute nor chronic analgesic effects.

Tables 1 and 2 compare the cross-treatment thresholds with the baseline, acute, and chronic conditions. 2-DG injections and cold-water swims (2-DG/CWS and CWS/2-DG groups) showed full, reciprocal development of analgesic cross-tolerance. Rats chronically exposed to 2-DG were subsequently found to be refractory to the acute analgesic properties of CWS. Similarly, rats chronically exposed to CWS were subsequently found to be refractory to the acute analgesic properties of 2-DG. Furthermore, 2-DG and morphine injections displayed some development of analgesic cross-tolerance. Rats made tolerant to morphine (MOR/2-DG group) were subsequently found to be refractory to the acute analgesic properties of 2-DG. In contrast, 2-DG pretreated rats acutely exposed to morphine (2-DG/MOR group) exhibited partial cross-tolerance; flinch-jump thresholds were significantly higher than the chronic morphine or baseline conditions yet significantly lower than the acute morphine condition. The specific experimental treatments rather than the injection or swim schedule per se were responsible for these effects because neither control group displayed any cross-tolerance with CWS or 2-DG.

Both 2-DG and CWS induced similar analgesia to acute exposure 20 days following the cross treatment condition: 2-DG—jump: $F(1,16)=0.15$; initial-jump: $F=0.32$; CWS-jump: $F(1,10)=0.29$; initial-jump: $F=0.13$. In contrast, morphine induced only residual analgesia. Retest thresholds were significantly lower than acute morphine effects, jump: $F(1,10)=38.11$, $p<0.01$; initial-jump: $F=19.98$, $p<0.01$, but significantly higher than chronic effects, jump: $F=9.53$, $p<0.05$; initial-jump: $F=10.19$, $p<0.01$.

DISCUSSION

The primary finding of the present study is that full and reciprocal cross-tolerance develops to the analgesic effects of two qualitatively different stressors, CWS and 2-DG. This provides further support for the contention that stressful events induce analgesia through activation of common pain-

TABLE 2

A POSTERIORI SCHEFFE COMPARISONS BETWEEN THE JUMP THRESHOLDS OF THE CROSS-TREATMENT AND RESPECTIVE ACUTE AND CHRONIC TREATMENTS ACROSS GROUPS

Group	Treatment				
	Cross	Acute		Chronic	
	mA	mA	F	mA	F
1. 2-DG/CWS	0.528	0.696	6.12*	0.497	0.23
2. CWS/2-DG	0.494	0.681	17.38†	0.473	0.30
3. MOR/2-DG	0.488	0.681	21.82†	0.473	0.17
4. 2-DG/MOR	0.613	0.816	11.44†	0.431	10.36†
5. PLA/CWS	0.706	0.696	0.01	0.497	22.80†
6. WWC/2-DG	0.654	0.681	0.32	0.473	18.46†

*$p<0.05$; †$p<0.01$.

inhibitory mechanisms, and not through effects specific to each stressor. These data suggest that repeated activation of this pain-inhibitory system by exposure to one stressor makes it refractory not only to its analgesic effects, but also alters its analgesic capability when activated by acute exposure to a second stressor.

Though CWS and 2-DG analgesia share full and reciprocal cross-tolerance effects, they differ in their respective interactions with opiate analgesia. The analgesia induced by CWS and that induced by morphine appear to be independent of each other since cross-toleance fails to develop and since high (20 mg/kg) naloxone doses only partially reverse CWS analgesia [8, 13, 25, 26]. Furthermore, while hypophysectomy attenuates CWS analgesia [4], the same procedure potentiates the analgesia induced by a 10 mg/kg dose of morphine [4, 23, 30]. By contrast, animals made tolerant to the 10 mg/kg dose of morphine fail to exhibit 2-DG analgesia. Correspondingly, the analgesia induced by the 10 mg/kg dose of morphine is attenuated significantly by 2-DG. Therefore, the same dose of morphine that fails to interact with CWS does interact with 2-DG, albeit partially for the 2-DG/MOR group. This latter effect could be due to 2-DG's inability to compete successfully with morphine in occupying and habituating common receptor sites. Alternatively, this partial effect may simply be an artifact of the capability of the 10 mg/kg dose of morphine to induce greater analgesia than the 350 mg/kg dose of 2-DG. If the morphine dose were lowered to reflect a lower degree of analgesia, 2-DG pretreatment might exert full cross-tolerance effects. 2-DG analgesia shares other common properties with morphine analgesia in that both effects are potentiated in hypophysectomized animals [4, 23, 30] and sub-analgesic doses of each agent interact to produce significant analgesia [7].

This is not to say that 2-DG analgesia is specifically linked to endogenous opiate influences. In addition to exhibiting full and reciprocal cross-tolerance with CWS, 2-DG analgesia is unaffected by naloxone. Whereas naloxone at 1 mg/kg completely eliminates opiate analgesia [32], it fails to alter 2-DG analgesia over a wide range (1–20 mg/kg) both before and after the 2-DG injection [7]. These seemingly paradoxical effects are similar to observations showing that morphine and stimulation-produced analgesia exhibit both synergy [36] and partial cross-tolerance [29]. Yet, while some studies report attenuation of stimulation-produced analgesia by naloxone [2,29], other studies find no effect [32,43].

These data taken together suggest the existence of at least two independent pain-inhibitory branches of a pain-modulatory system, one with opiate-like characteristics and activated by acute exposure to morphine, the other with non-opiate characteristics and activated by acute exposure to such stressors as CWS. Both branches share the common characteristic of analgesic adaptation following repeated exposures. It is apparent that some experimental manipulations, such as injections of 2-DG share common characteristics with both branches.

The present study demonstrated that two different stressors, each capable of inducing analgesia following acute exposure, can develop full and reciprocal cross-tolerance to each other's analgesic effects. This finding supports the contention that it is the stressful consequences per se of the environmental events that induce analgesia through activation of an intrinsic stress-sensitive pain-inhibitory system, and thus provides functional, biological significance for intrinsic pain inhibition in times of stress.

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