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Neuroleptic and Analgesic Interactions Upon Pain and Activity Measures

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BODNAR, R J AND N NICOTERA *Neuroleptic and analgesic interactions upon pain and activity measures* PHARMAC BIOCHEM BEHAV 16(3) 411–416, 1982 —Previous data in rats indicate that while dopamine receptor blockers like haloperidol (HAL) potentiate opiate analgesia, dopamine receptor stimulants like apomorphine reduce cold-water swim (CWS) and 2-deoxy-D-glucose (2-DG) analgesia Yet recently, HAL and chlorpromazine (CPZ) have been shown to reduce heat and immobilization analgesia To address these differences, the present study investigated whether HAL (10 50, 100 μg/kg) or CPZ (1, 3, 5 mg/kg) would potentiate or reduce the effects of morphine (MOR), CWS, 2-DG and chlordiazepoxide (CDP) upon analgesia and activity While HAL increased jump thresholds in a dose-dependent manner, CPZ doses exerted erratic effects MOR analgesia was potentiated by the two higher CPZ doses and by the highest HAL dose 2-DG analgesia was potentiated by only the highest HAL dose while CDP analgesia was potentiated by the moderate CPZ dose While all CPZ doses potentiated CWS-induced increases in jump thresholds, the lowest HAL dose reduced this effect These effects are considered in terms of the analgesic manipulation and its magnitude of effect, the neuroleptic and its dose, the pain test, and possibly concurrent effects upon activity

Pain Activity Chlorpromazine Haloperidol Morphine Cold-water swims 2-Deoxy-D-glucose Chlordiazepoxide

DOPAMINE appears to modulate analgesic processes while dopamine receptor blockers potentiate the effects of analgesic manipulations, dopamine stimulants reduce these effects The analgesic effects of morphine are potentiated by haloperidol pretreatment on the tail-flick [10], the hotplate [18], and the tail-withdrawal [9] tests By contrast, the analgesic effects of two stressful manipulations, 2-deoxy-D-glucose injections [3] and cold-water swims [4] are reduced by pretreatment with the dopamine receptor stimulant apomorphine [2] Yet, a recent study [14] reported that increased tail-flick latencies in rats and mice induced by 1 hr of heat exposure were eliminated by chlorpromazine pretreatment and that increased tail-flick latencies in mice induced by 1 hr of immobilization were eliminated by haloperidol pretreatment

Given these apparent discrepencies, the present study reevaluated whether pretreatment with neuroleptic dopamine receptor blockers would potentiate or reduce analgesic responses In the first experiment, a dose range of chlorpromazine and haloperidol was systematically administered before the analgesic manipulations of morphine, 2-deoxy-D-glucose, cold-water swims and chlordiazepoxide [11,19] In the second experiment, activity levels were measured following chlorpromazine or haloperidol injections, either alone or in combination with either morphine, 2-deoxy-D-glucose, cold-water swims or chlordiazepoxide The second experiment was done to determine whether activity alterations induced by neuroleptic pretreatment covaried with analgesic alterations

EXPERIMENT 1 NEUROLEPTICS AND NOCICEPTIVE MANIPULATIONS

METHOD

Forty-eight male, albino Sprague-Dawley rats (250–400 g) were tested for flinch-jump thresholds using a modification of the Evans procedure [8] Electric shocks were administered through a 30-cm by 24-cm chamber floor composed of 16 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 jump threshold was defined as the lowest of two consecutive intensities that elicited simultaneous withdrawal of both hindpaws from the grids 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 each nociceptive threshold was determined After each trial, the current intensity was reset to 0 1 mA for the next trial until 6 trials were completed Daily flinch and jump thresholds were each computed as the mean of these six trials and four days of stable baseline thresholds were determined for all animals

The first group of twelve rats received subcutaneous injections of haloperidol (HAL) at each of the following doses 0, 10, 50 and 100 μg HAL hydrochloride (McNeil Laboratories)/ml normal saline/kg body weight The order of experimental conditions was determined by an incomplete coun-

TABLE 1

ALTERATIONS IN JUMP AND FLINCH THRESHOLDS (±SEM) FOLLOWING SYSTEMIC ADMINISTRATION OF CHLORPROMAZINE (CPZ) AND HALOPERIDOL (HAL)

CPZ Group			HAL Group		
Dose (mg/kg)	Threshold (mA) Jump	Flinch	Dose (μg/kg)	Threshold (mA) Jump	Flinch
0	0 494(0 040)	0 239(0 027)	0	0 442(0 035)	0 226(0 029)
1	0 594(0 055)†	0 290(0 035)†	10	0 483(0 037)*	0 268(0 029)†
3	0 506(0 054)	0 244(0 034)	50	0 586(0 050)*	0 331(0 039)
5	0 560(0 057)*	0 226(0 020)	100	0 606(0 066)*	0 318(0 026)†

*$p<0$ 01 †$p<0$ 05

terbalanced design in a double-blind procedure [6] Flinch-jump thresholds were determined 20 min after each injection and a minimum of 48 hr elapsed between each experimental condition The second group of twelve rats received intraperitoneal injections of chlorpromazine (CPZ) at each of the following doses 0, 1, 3 and 5 mg CPZ hydrochloride (Carter-Glogau)/ml normal saline/kg body weight This group was treated as the first except that flinch-jump thresholds were determined 30 min after each injection

A third group of six rats received the following manipulations according to an incomplete counterbalanced design In four injection sequences, HAL (0, 10, 50 and 100 μg/ml normal saline/kg body weight, SC) was administered 20 min before a subcutaneous injection of morphine at a dose of 5 mg/kg (5 mg morphine sulfate/ml buffered solution/kg body weight) Flinch-jump thresholds were determined 30 min after opiate injection In four more injection sequences, the same HAL doses were administered 20 min before the animal was exposed to a 3 5 min swim in a 2°C water bath with flinch-jump thresholds determined 30 min following the swim The ninth sequence consisted of two vehicle injections spaced 20 min apart with flinch-jump thresholds determined 30 min after the second injection A minimum of 48 hr elapsed between each experimental condition The fourth group of six rats underwent the identical paradigm except that the HAL dose sequence was now paired with intraperitoneal injections of 2-deoxy-D-glucose (450 mg 2-deoxy-D-glucose (Sigma)/ml normal saline/kg body weight) and chlordiazepoxide (15 mg chlordiazepoxide (Hoffman-LaRoche)/ml normal saline/kg body weight) respectively

A fifth group of six rats underwent the same experimental design except that CPZ (0, 1, 3 and 5 mg/ml normal saline/kg body weight, IP) was administered 30 min before either the 5 mg/kg dose of morphine or the 3 5 min swim in a 2°C bath The sixth group of six rats underwent the same experimental design with the CPZ dose sequence paired with either the 450 mg/kg dose of 2-deoxy-D-glucose or the 15 mg/kg dose of chlordiazepoxide

RESULTS

Table 1 summarizes the jump and flinch thresholds following administration of either CPZ or HAL as compared to vehicle injections CPZ significantly altered both jump, $F(3,33)=5$ 41, $p<0$ 004, and flinch, $F(3,33)=3$ 68, $p<0$ 022, thresholds Post-hoc Scheffé comparisons revealed that while jump thresholds were signficantly increased relative to the vehicle injections following the 1 mg/kg, $F(1,11))=9$ 67, $p<0$ 010, and the 5 mg/kg, $F(1,11)=11$ 77, $p<0$ 006, CPZ doses, only the 1 mg/kg, $F(1,11))=7$ 38, $p<0$ 02, significantly increased flinch thresholds HAL also significantly increased jump, $F(3,33)=11$ 56, $p<0$ 001, thresholds over respective vehicle values at each of the three doses 10 μg/kg, $F(1,11)=7$ 97, $p<0$ 017, 50 μg/kg, $F(1,11)=18$ 28, $p<0$ 001, and 100 μg/kg, $F(1,11)=11$ 88, $p<0$ 006 Flinch thresholds, $F(3,33)=12$ 84, $p<0$ 001, displayed a similar significant pattern of effects 10 μg/kg, $F(1,11)=7$ 32, $p<0$ 02, 50 μg/kg, $F(1,11)=20$ 98, $p<0$ 001, and 100 μg/kg, $F(1$ 11)=31 37 $p<0$ 001

As summarized in Table 2, the combination of CPZ doses with the 5 mg/kg dose of morphine significantly altered jump, $F(4,20)=9$ 12, $p<0$ 001, but not flinch, $F(4,20)=2$ 43, thresholds Jump thresholds were significantly increased over vehicle values for all CPZ-morphine pairings However CPZ pretreatment significantly potentiated morphine analgesia following only the 3 mg/kg, $F(1,5)=6$ 91, $p<0$ 047, and 5 mg/kg, $F(1,5)=12$ 22, $p<0$ 017, doses By contrast, HAL and morphine produced significant changes in both jump, $F(4,20)=11$ 64, $p<0$ 001, and flinch, $F(4,20)=7$ 95, $p<0$ 001, thresholds with all morphine conditions increasing both thresholds over vehicle values HAL pretreatment, however, only potentiated morphine-induced increases in jump thresholds at the 100 μg/kg dose, $F(1$ 5)=6 93 $p<0$ 046

CPZ paired with the 450 mg/kg dose of 2-deoxy-D-glucose significantly altered both jump, $F(4,20)=3$ 86, $p<0$ 018 and flinch, $F(4,20)=3$ 20, $p<0$ 035, thresholds with all 2-deoxy-D-glucose conditions increasing both thresholds over vehicle values Yet, CPZ pretreatment failed to significantly potentiate 2-deoxy-D-glucose antinociception Similarly, HAL and 2-deoxy-D-glucose produced significant changes in both jump, $F(4,20)=4$ 86, $p<0$ 007 and flinch, $F(4,20)=5$ 59, $p<0$ 004, thresholds with all 2-deoxy-D-glucose conditions increasing both thresholds over vehicle values The 100 μg/kg HAL dose produced significant potentiations in 2-deoxy-D-glucose-induced increases of both jump, $F(1,5)=11$ 09, $p<0$ 021, and flinch, $F(1,5)=6$ 29, $p<0$ 05, thresholds

CPZ paired with the 3 5 min swim in a 2°C bath exerted significant changes in both jump, $F(4,20)=32$ 09, $p<0$ 001, and flinch, $F(4,20)=9$ 90, $p<0$ 001, thresholds with all swim conditions increasing both thresholds over vehicle values Swim-induced increases in jump thresholds were significantly potentiated by the 1 mg/kg, $F(1,5)=22$ 26, $p<0$ 005,

TABLE 2

JUMP AND FLINCH THRESHOLDS (±SEM) FOLLOWING ADMINISTRATION OF CHLORPROMAZINE (CPZ) OR HALOPERIDOL (HAL) IN COMBINATION WITH EITHER MORPHINE (MOR), 2-DEOXY-D-GLUCOSE (2-DG), COLD-WATER SWIMS (CWS) OR CHLORDIAZEPOXIDE (CDP)

	CPZ Pretreatment			HAL Pretreatment			
	CPZ Dose (mg/kg)	Condition	Threshold (mA) Jump	Flinch	HAL Dose (μg/kg)	Condition	Threshold (mA) Jump	Flinch
A	Morphine (5 mg/kg)							
	0	Placebo	0 507(0 040)	0 255(0 034)	0	Placebo	0 418(0 025)	0 208(0 029)
	0	MOR	0 687(0 030)	0 353(0 038)	0	MOR	0 638(0 040)	0 315(0 037)
	1	MOR	0 692(0 044)	0 314(0 038)	10	MOR	0 607(0 063)	0 289(0 029)
	3	MOR	0 772(0 056)†	0 338(0 048)	50	MOR	0 688(0 073)	0 371(0 042)
	5	MOR	0 874(0 074)†	0 408(0 057)	100	MOR	0 792(0 076)*	0 401(0 051)
B	2-Deoxy-D-Glucose (450 mg/kg)							
	0	Placebo	0 482(0 044)	0 222(0 018)	0	Placebo	0 467(0 043)	0 243(0 031)
	0	2-DG	0 604(0 086)	0 325(0 043)	0	2-DG	0 627(0 074)	0 394(0 041)
	1	2-DG	0 682(0 069)	0 351(0 032)	10	2-DG	0 595(0 066)	0 353(0 045)
	3	2-DG	0 730(0 071)	0 395(0 030)	50	2-DG	0 721(0 025)	0 383(0 019)
	5	2-DG	0 777(0 115)	0 458(0 111)	100	2-DG	0 771(0 077)†	0 519(0 061)†
C	Cold-Water Swims (2°C)							
	0	Control	0 507(0 040)	0 255(0 034)	0	Control	0 418(0 025)	0 208(0 029)
	0	CWS	0 865(0 054)	0 514(0 074)	0	CWS	1 024(0 033)	0 603(0 057)
	1	CWS	0 996(0 041)*	0 522(0 036)	10	CWS	0 871(0 068)†	0 417(0 024)†
	3	CWS	1 029(0 046)†	0 756(0 096)	50	CWS	0 965(0 039)	0 551(0 063)
	5	CWS	1 013(0 061)†	0 843(0 137)†	100	CWS	1 046(0 028)	0 760(0 065)
D	Chlordiazepoxide (15 mg/kg)							
	0	Placebo	0 482(0 044)	0 222(0 018)	0	Placebo	0 467(0 043)	0 243(0 031)
	0	CDP	0 613(0 065)	0 243(0 022)	0	CDP	0 660(0 047)	0 367(0 017)
	1	CDP	0 660(0 099)	0 287(0 048)	10	CDP	0 695(0 043)	0 325(0 027)
	3	CDP	0 771(0 091)†	0 408(0 073)†	50	CDP	0 717(0 039)	0 379(0 029)
	5	CDP	0 681(0 044)	0 311(0 048)	100	CDP	0 729(0 058)	0 390(0 047)

Significant differences between the experimental conditions in the presence and absence of the pretreatment drug are denoted by *($p < 0.01$) and †($p < 0.05$). Differences between the placebo/control and experimental conditions are detailed in the text.

the 3 mg/kg, $F(1,5)=7.90$, $p<0.038$, and the 5 mg/kg, $F(1,5)=11.00$, $p<0.021$, doses of CPZ. Only the 5 mg/kg dose of CPZ potentiated the swim-induced flinch increases, $F(1,5)=10.81$, $p<0.022$. HAL-swim pairings significantly altered jump, $F(4,20)=42.34$, $p<0.001$, and flinch, $F(4,20)=23.53$, $p<0.001$, thresholds with all swim conditions increasing both thresholds over vehicle values. Swim-induced increases in jump, $F(1,5)=7.91$, $p<0.038$, and flinch, $F(1,5)=10.79$, $p<0.022$, thresholds were significantly reduced by the 10 μg/kg dose of HAL, an effect that may be attributable to the high thresholds induced in these rats by the swim alone.

Finally, CPZ paired with the 15 mg/kg dose of chlordiazepoxide significantly altered jump, $F(4,20)=5.54$, $p<0.004$, and flinch, $F(4,20)=4.20$, $p<0.013$, thresholds. While jump thresholds were significantly increased over vehicle values following all chlordiazepoxide conditions, flinch thresholds were significantly increased over vehicle values when chlordiazepoxide was paired with the 3 mg/kg dose of CPZ. Moreover, this same CPZ dose potentiated chlordiazepoxide-induced increases in jump, $F(1,5)=12.80$, $p<0.016$, and flinch, $F(1,5)=7.18$, $p<0.044$, thresholds. HAL-chlordiazepoxide pairings significantly altered jump, $F(4,20)=14.45$, $p<0.001$, and flinch, $F(4,20)=4.07$, $p<0.014$, thresholds with all chlordiazepoxide conditions increasing both thresholds over vehicle values. However, HAL pretreatment failed to significantly potentiate chlordiazepoxide antinociception.

EXPERIMENT 2 NEUROLEPTIC AND ANTINOCICEPTIVE EFFECTS UPON ACTIVITY LEVELS

METHOD

The activity levels of six rats were assessed on an activity meter (Omnitech Instruments, Columbus, OH) in a sound-isolated room. During a typical test session, the rat and the sawdust from its home cage were transferred to a test cage where it was left undisturbed for 10 min to allow for adaptation. Then either CPZ at a dose of 5 mg/kg (5 mg CPZ/ml normal saline/kg body weight, IP), HAL at a dose of 100 μg/kg (100 μg HAL/ml normal saline/kg body weight, SC) or vehicle was administered and the animal was returned to the cage. After a 2 min interval to allow for handling, activity levels consisting of horizontal and vertical movements were recorded for 30 min in three equal 10 min blocks for CPZ and vehicle and for 20 min in two equal 10 min blocks for HAL.

TABLE 3

ACTIVITY LEVELS FOLLOWING ADMINISTRATION OF CHLORPROMAZINE (CPZ 5 mg/kg), HALOPERIDOL (HAL 100 μg/kg) OR VEHICLE (VEH), IN COMBINATION WITH EITHER VEH, MORPHINE (MOR 5 mg/kg), 2-DEOXY-D-GLUCOSE (2-DG 450 mg/kg), COLD-WATER SWIMS (CWS 2°C/3 5 min) OR CHLORDIAZEPOXIDE (CDP 15mg/kg)

First Injection	Second Injection	Post Second Injection (min) 10	20	30	40
VEH	VEH	465 5	246 3	349 0	207 8
CPZ	VEH	57 3†	150 0	59 0†	43 0†
HAL	VEH	7 8†	37 8†	19 2†	12 8†
VEH	MOR	173 7†	303 0	297 5	291 8
CPZ	MOR	13 8*†	3 0*†	9 3*†	28 7*†
HAL	MOR	14 0*†	22 7*†	40 0*†	31 8*†
VEH	2-DG	305 0†	86 8†	52 3†	9 7†
CPZ	2-DG	61 7*†	45 2†	19 5†	2 3†
HAL	2-DG	37 8†	4 3†	11 8†	1 7†
VEH	CWS	199 2†	99 7	42 2†	98 0
CPZ	CWS	22 2*†	4 7†	4 8†	5 7†
HAL	CWS	48 0†	37 0†	21 7†	37 5†
VEH	CDP	163 8†	5 7†	14 3†	39 3†
CPZ	CDP	63 0†	60 7†	61 8†	44 0†
HAL	CDP	20 5*†	8 7†	7 0†	6 7†

*Significant difference between neuroleptic and VEH pretreatment

†Significantly different from VEH/VEH

The sensitivity of the apparatus excluded small grooming and chewing movements as well as such autonomic measures as heart rate and respiration Following this initial monitoring period, the rats received either a 3 5 min swim in a 2°C bath or injections of either morphine at a dose of 5 mg/kg (5 mg morphine/ml buffered solution/kg body weight, SC), 2-deoxy-D-glucose at a dose of 450 mg/kg (450 mg 2-deoxy-D-glucose/ml normal saline/kg body weight, IP), chlordiazepoxide at a dose of 15 mg/kg (15 mg chlordiazepoxide/ml normal saline/kg body weight, IP) or vehicle (1 ml normal saline/kg body weight, IP) After another 2 min interval for handling effects, activity levels were monitored for 40 more min in four equal 10 min blocks The order in which the three initial injections were systematically paired with the second set of five manipulations was determined by an incompletely counterbalanced design [6] A minimum of 48 hr elapsed between conditions

RESULTS

A two-way analysis of variance comparing CPZ and vehicle revealed significant effects across the ten manipulations, $F(9,45)=10\ 20$, $p<0\ 001$, among the seven activity intervals, $F(6,30)=32\ 84$, $p<0\ 001$, and for the interaction between manipulation and interval, $F(54,270)=2\ 14$, $p<0\ 001$ Post-hoc Scheffé comparisons revealed that the 5 mg/kg dose of CPZ significantly reduced activity levels below vehicle values at 10 (CPZ 260 8, Vehicle 457 7, $F=37\ 6$, $p<0\ 01$), 20 (CPZ 133 3, Vehicle 455 3, $F=100\ 5$, $p<0\ 01$) and 30 (CPZ 90 0, Vehicle 347 2, $F=64\ 1$, $p<0\ 01$) min following the first injection Table 3 summarizes the alterations in activity following the pairing of either CPZ or vehicle with the five other manipulations CPZ pretreatment had the following significant interactive effects it suppressed the activity levels of morphine-treated rats across all four post-injection blocks and potentiated the hypoactive effects of 2-deoxy-D-glucose and cold-water swims in the first 10 min following these latter manipulations

A two-way analysis of variance comparing HAL and comparable vehicle blocks revealed significant effects across the ten manipulations, $F(9,45)=24\ 13$, $p<0\ 001$, among the six activity intervals, $F(5,25)=45\ 52$, $p<0\ 001$, and for the interaction between manipulation and interval, $F(45,225)=3\ 93$, $p<0\ 001$ While the 100 μg/kg dose of HAL failed to alter activity levels 10 min following the injection (HAL 452 3, $F=0\ 04$), it significantly reduced activity levels 20 min following the injection (HAL 59 4, $F=196\ 0$ $p<0\ 001$) As summarized in Table 3, HAL pretreatment, like CPZ, significantly suppressed the activity levels of morphine-treated rats across all four post-injection blocks It also potentiated the hypoactive effects of chlordiazepoxide in the first 10 min following the latter injection

GENERAL DISCUSSION

The present study was based upon the notion that while dopamine receptor blockers should potentiate the effects of analgesic manipulations [9, 10, 18] dopamine stimulants should reduce these effects [2] Yet, another study reported that CPZ and HAL respectively antagonized the elevations in tail-flick latencies observed following exposure to 1 hr of either heat or immobilization [14] The findings of the present study provide marginal support for the former view First, the neuroleptics themselves had variable effects upon pain thresholds While HAL increased jump thresholds in a dose-dependent fashion, the greatest effect upon flinch thresholds occurred at the 50 μg/kg dose The CPZ dose range employed in the present study produced erratic effects upon jump thresholds while the 1 and 5 mg/kg doses significantly increased jump thresholds, the 3 mg/kg dose did not Moreover, flinch thresholds were significantly increased only following the 1 mg/kg CPZ dose None of these nociceptive effects appeared to be due to any gross motor impairment since all animals responded appropriately at higher shock levels Therefore, although these data are in accord with previous studies indicating antinociceptive activity for HAL [10,12] and CPZ [7,16], these neuroleptic drugs do not appear to possess powerful intrinsic analgesic actions As for the activity levels, CPZ produced significant hypoactivity in the 30 min interval between the injection and the nociceptive test while HAL reduced activity during the last 10 min of the 20 min injection-test interval Although the antinociceptive and hypoactive effects of the two neuroleptics appear to be related, this should be tempered by the fact that both were not measured simultaneously

The analgesic effects of morphine have been shown to be potentiated by HAL pretreatment on the tail-flick [10], the hot-plate [18] and the tail-withdrawal [9] tests These effects were corroborated for jump, but not flinch, thresholds at some neuroleptic doses While the specific analysis of either synergy or additivity was not part of the present experimental design, the data suggest that pretreatment with the 3

and 5 mg/kg CPZ doses prior to the 5 mg/kg dose of morphine produced greater increases in jump thresholds than the mere addition of each respective antinociceptive response alone By contrast, the potentiation of morphine analgesia by HAL at a dose of 100 μg/kg was additive (see Tables 1 and 2) This agrees with the observation [9] that a 640 μg/kg HAL dose potentiated tail-withdrawal increases induced by morphine at doses of 10 and 5 mg/kg, but not 2 5 mg/kg Moreover, the latter morphine dose, when paired with a 160 μg/kg HAL dose failed to increase tail-withdrawal latencies Again neuroleptic effects upon opiate analgesia appear to be related to their effects upon activity Pretreatment with either the 5 mg/kg CPZ dose or the 100 μg/kg HAL dose significantly reduced activity in animals treated with morphine during the 30 min interval between the opiate injection and the nociceptive test Parallel potentiations in opiate analgesia and opiate hypoactivity were produced by HAL and CPZ pretreatment during the 10 min period in which flinch-jump determinations were typically made (see 40 min column, Table 3) These data should be tempered by the fact that both measures were not made simultaneously in the same animals but rather in two groups

Neuroleptic pretreatment marginally affected other analgesic manipulations Since chlordiazepoxide and 2-deoxy-D-glucose respectively develop analgesic cross-tolerance with morphine [5,17], one might expect that their interactions with neuroleptics would mimic opiate-neuroleptic effects Like its effects upon morphine analgesia, pretreatment with the 100 μg/kg HAL dose potentiated the increased jump thresholds induced by 2-deoxy-D-glucose, but failed to affect chlordiazepoxide analgesia By contrast, while 2-deoxy-D-glucose analgesia failed to be affected by CPZ pretreatment, the 3 mg/kg, but not the 5 mg/kg CPZ dose potentiated the increased jump thresholds induced by chlordiazepoxide Marginal effects were also observed on the activity measure while CPZ pretreatment reduced further 2-deoxy-D-glucose hypoactivity in the first 10 min following the 2-deoxy-D-glucose injection, HAL pretreatment exerted an identical effect upon chlordiazepoxide hypoactivity

It has been proposed previously (see review [1]) that the analgesic effects of 2-deoxy-D-glucose and cold-water swims were due to the stressful consequences of the manipulations and not the manipulations per se Though the analgesic effects of these two stressors differ in some respects (see review [1]), both effects are reduced by pretreatment with the dopamine receptor stimulant apomorphine [2] The present data provide both support and non-support for the view that dopamine receptor blockers should potentiate stress-induced analgesia For HAL, 2-deoxy-D-glucose analgesia is potentiated only by pretreatment with the 100 μg/kg dose Yet, a 10 μg/kg HAL dose reduced the analgesic effects of cold-water swims and a 1 mg/kg HAL dose, considered to be potentially cataleptic (see review [15]), reduced immobilization analgesia on the tail-flick test [14] For CPZ, pretreatment appears to produce differential effects upon stress-induced analgesia as a function of the stressor employed Pretreatment with the 1, 3 and 5 mg/kg CPZ doses respectively potentiated the increases in jump thresholds induced by cold-water swims, yet failed to affect 2-deoxy-D-glucose analgesia By contrast, a 3 mg/kg CPZ dose reduced heat analgesia on the tail-flick test [14]

The magnitude of the antinociceptive effects induced by a particular stressor may provide one possible explanation for the observed differences For those groups of animals where neuroleptic pretreatment reduced stress-induced analgesia, the increases in pain threshold induced by the stressor itself were pronounced (a) tail-flick latency increases of 223% in rats and 413% in mice following heat stress, (b) tail-flick latency increases of 205% following immobilization, and (c) jump threshold increases of 245% following cold-water swims By contrast, for those groups of animals where neuroleptic pretreatment potentiated stress-induced analgesia, the analgesic effect produced by the stressor alone increased jump thresholds between 125 and 171% of baseline responding Another possible explanantion for the differential effects may involve the nociceptive measure While the flinch-jump test is somewhat sensitive to the hypoalgesic action of neuroleptics, the tail-flick test is not (e g , [13]) Yet this cannot explain why HAL pretreatment reduced cold-water swim analgesia on the flinch-jump test In conclusion, the contention that dopamine receptor blockade potentiates the effects of analgesic manipulations must be considered in terms of the manipulation employed and its magnitude of effect, the neuroleptic employed and its dose, the pain test employed, and possibly all of their concurrent effects upon activity measures

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