Pharmacology Biochemistry & Behavior, Vol. 28, pp. 283–289. © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0091-3057/87 $3.00 + .00

Reversal of Opioid-Induced Muscular Rigidity in Rats: Evidence for Alpha-2 Adrenergic Involvement

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Received 15 December 1986

JERUSSI, T. P., J. F. CAPACCHIONE AND M. J. BENVENGA. *Reversal of opioid-induced muscular rigidity in rats: Evidence for alpha-2 adrenergic involvement.* PHARMACOL BIOCHEM BEHAV **28**(2) 283–289, 1987.—Compounds from several different pharmacological classes were tested for their ability to reverse the muscular rigidity induced by an intravenous dose of fentanyl that also caused loss of the righting reflex (LOR). Opioid antagonists reversed the entire syndrome—LOR and rigidity but, generally, rigidity could be reversed nonspecifically by doses of compounds that caused LOR by themselves (e.g., CNS depressants). Muscle relaxants and agonists of histamine, which appeared to be acting peripherally, were also effective. On the other hand, serotonergic drugs and dopamine agonists were not. However, dopaminergic antagonists with adrenolytic activity (i.e., chlorpromazine, haloperidol) reversed rigidity, whereas sulpiride did not. Moreover, rigidity reversed by neuroleptics could be restored by piperoxane, an alpha-2 adrenergic antagonist. In addition, clonidine and other alpha-2 agonists selectively reversed only rigidity following systemic or central administration at doses several orders of magnitude lower than other compounds tested. It is proposed that opioid-induced rigidity is reversed by inhibition of sympathoadrenal outflow which can be accomplished selectively, centrally, by alpha-2 agonists.

Opioid rigidity Alpha-2 agonists Clonidine

POTENT opioids administered intravenously (IV) in higher than analgesic doses are used clinically for anesthesia. However, their clinical popularity is marred by their propensity to cause muscular rigidity [8, 10, 15]. Opioid-induced muscular rigidity is also evident in laboratory animals and some investigators have proposed that it may model Parkinsonism [11,16] since rigidity appears to be reduced by dopaminergic agonists [31]. Moreover, morphine injected directly into the head of the caudate nucleus induces rigidity in rats [16,17]. However, Rackham [24] could not confirm a dopaminergic mechanism in rats, and dopamine agonists were reported to increase, not decrease, morphine-induced rigidity in mice [30]. In addition, it appears that neurochemicals other than dopamine and pharmacological agents which do not mimic dopamine can also affect rigidity because it can be induced in rats by injection of muscimol or the glutamate antagonist, glutamate diethylester, into the superior colliculus [13] or striatum [28], respectively. Moreover, the behavior can be reduced by centrally acting muscle relaxants [4,24], diazepam [4,29], and clinically to some extent, with general anesthetics [5].

The matter is further complicated by inconsistent terminology because "rigidity" and "catalepsy" are sometimes used interchangeably or described as components of "catatonia" [18], and in many studies "rigidity" is defined by electromyograph (EMG) patterns, which may not necessarily indicate similar behavioral phenomena. For example, morphine [31], haloperidol [14], and muscimol [13] all have been reported to induce tonic EMG activity. However, the behaviors produced are quite different. Rats receiving high doses of potent opioids (e.g., fentanyl) lose their righting and develop a "lead-pipe" rigidity—a behavior in marked contrast to the malleable or plastic nature (the so-called "waxy flexibility") of catalepsy induced by neuroleptics which, in addition, is not naloxone reversible (unpublished observations).

In the present pilot investigation, previously communicated as an abstract [6], various classes of drugs were tested for their potential to reverse the rigidity induced following the IV administration of fentanyl. It appears that the reversal is mediated, relatively selectively, by alpha-2 adrenergic agonists and that, in contrast to previous reports, dopaminergic mechanisms, per se, are not involved.

METHOD

Male Sprague-Dawley rats (Hilltop Farms, PA) weighing 230–290 g or 75–100 g were allowed free access to food and water and housed five per cage in a temperature (72°F) and humidity (50%) controlled vivarium with a light-dark cycle of 12 hours (0600–1800 hours light). Animals were weighed and allowed 30 minutes to adapt to the laboratory conditions prior to testing (between 0900 and 1600 hours).

All doses were calculated as the free base and drugs were dissolved in distilled water and injected IV, intraperitoneally (IP), intrathecally (IT), or intracerebroventricularly (ICV) in volumes of 1 ml/kg (IV, IP), 10 μl (IT), or 5 μl (ICV). Haloperidol and droperidol were dissolved first in glacial acetic acid (10 μl/mg) and then diluted with distilled water. Volatile anesthetics were vaporized in a sealed 3840 ml jar containing

TABLE 1

EFFECTS OF OPIOIDS ON FENTANYL-INDUCED MUSCULAR RIGIDITY

Drug*	Dose (mg/kg)	Causes LOR‡	Reverses Rigidity
morphine	20.0	–	–
fentanyl	0.005	–	–
pentazocine	0.05	–	–
	0.3	–	+
buprenorphine	0.05	–	–
	0.075	–	+
naloxone	0.005	–	–
	0.01	–	+
naltrexone methyl bromide	0.5	–	–

*Six rats were tested for LOR and rigidity at each dose of each compound and drug combination, except for bupivicaine (Table 2) were N=5.

†Drugs were administered IV (except where indicated) immediately following the induction of rigidity. Numbers in parentheses represent pretreatment (PT) times in minutes prior to injection of fentanyl (0.035 mg/kg, IV).

‡"+" and "–" indicate "yes" and "no," respectively, for *all* of the animals tested.

TABLE 2

EFFECTS OF SEDATIVE-HYPNOTIC-ANESTHETICS ON FENTANYL-INDUCED MUSCULAR RIGIDITY

Drug*	Dose (mg/kg)	Route (PT time)†	Causes LOR‡	Reverses Rigidity
Sedative-Hypnotic Anesthetic				
diazepam	0.3		–	–
	1.0		+	+
thiopental	5.0		–	–
	10.0		+	+
pentobarbital	15.0		+	+
ketamine	2.0		–	–
	4.0		+	+
chloral hydrate	125.0		–	–
	175.0		+	+
	190.0	IP (5)	–	–
	240.0	IP (5)	+	+
gamma hydroxy butyrolactone	700.0		+	+
Volatile Anesthetic				
diethyl ether	12.0%	inhalation	+	+
isoflurane	1.5%	inhalation	+	+
Local Anesthetic				
bupivacaine	0.067	IT	–	+

Footnotes as in Table 1.

100 percent oxygen. Rats were then placed in the jar and observed for 10 minutes. Approximate concentrations of 1.5% isoflurane and 12% diethyl ether at 20°C resulted from 0.3 and 2.0 ml of the respective liquids when calculated by the formula:

$$\text{ml of anesthetic} = \frac{\text{ml of container} \times \text{formula weight} \times \% \text{ vapor}}{\text{specific gravity} \times 8206 \times °\text{K}}$$

Intravenous injections were delivered through either a tail vein while the rat was restrained in a cylindrical holder (IITC, Landing, NJ), or through a left femoral venous catheter (PE-50) implanted under 1.5% isoflurane anesthesia four hours previously. Rats injected ICV were stereotactically implanted under methohexital anesthesia (40 mg/kg) with a stainless steel left ventricular guide cannula (16 mm × 20 gauge) at coordinates: 1.5 mm lateral, −3.6 mm ventral, 0.8 mm posterior to bregma [23]. A week following surgery the test drug was administered through the cannula, over a period of 10 seconds, with a 10 μl syringe. Placement of cannulae were verified histologically. The smaller rats (75–100 g) were used only for IT injections which were made with a 10 μl syringe, 30 gauge needle, inserted to one side of the L5 or L6 spinous process at approximately 20 degrees to the vertebral column. The angle was decreased to about 10 degrees as the needle was advanced until it penetrated approximately 0.5 cm into the intervertebral space [19].

Rigidity was induced by the IV administration of 0.035 mg/kg fentanyl, which was the lowest effective dose (i.e., ED100) to produce both immediate loss of righting (LOR) and rigidity (which lasted about 9 min) in 100 percent of the animals (unpublished observations). LOR was considered to be present when an animal remained supine for at least 30 seconds. Rigidity was indicated by extreme extensor muscle tone and the absence of hindlimb flexion while the stiff animal was supported in a vertical position. Rigidity was considered to be reversed if, within two minutes following the administration of the test drug, the animal bent spontaneously at the abdomen when held vertically and the hindlimbs could be flexed passively by pushing the rear paws. Other compounds injected immediately after the reversal of rigidity were assessed for their ability to restore rigidity. When animals were pretreated with drugs, reversal of rigidity was evaluated during the two minutes immediately following IV fentanyl. Generally drugs were administered IV immediately following the induction of rigidity. However, some were injected IV or IP at various times prior to fentanyl to ensure, hopefully, that those compounds would be evaluated during their peak effects on rigidity. Others were administered ICV in order to confirm the relative contribution of their cerebral effects. Spinal involvement was evaluated by IT administration.

In preliminary work with each compound, the doses were increased until either LOR occurred or the animal died. Subsequently, the lowest dose to induce LOR was investigated. If this dose also reversed rigidity, then generally a lower dose which did not cause LOR was evaluated. Only those doses (see Tables 1–5) that were efficacious in *all* of the animals were selected for further study.

The following compounds were obtained as generous gifts: carbidopa, kojic amine (Merck & Co., Inc.); methysergide, guanfacine (Sandoz, Inc.); baclofen, guanethidine, phentolamine (Ciba Pharmaceutical Co.); progabide (L.E.R.S. Synthelabo); gamma-acetylenic GABA (Merrell Dow Pharmaceuticals, Inc.); diazepam, sodium nitroprusside (Hoffman-LaRoche, Inc.); isoflurane (Anaquest); morphine (S. B. Penick Co.); buprenorphine (NIDA); naltrexone methyl bromide (Boehringer Ingelheim Ltd.); pancuronium (Organon Inc.); haloperidol (McNeil Pharmaceutical); droperidol (Janssen Pharmaceutica Inc.); prazosin (Pfizer, Inc.); metiamide, dimaprit (Smith, Kline & French Research Ltd.); piperoxane (Rhone-Poulenc, Inc.); idazoxan (Reckitt & Colman Products). Other compounds were purchased from the following suppliers: fentanyl (USP); diethyl ether (Fisher Scientific); methohexital (Rutgers University Pharmacy); all others were purchased from Sigma Chemical Co.

TABLE 3

EFFECTS OF DRUGS THAT INFLUENCE VARIOUS NEUROCHEMICAL SYSTEMS ON FENTANYL-INDUCED MUSCULAR RIGIDITY

Drug	Dose (mg/kg)	Route (PT time)†		Causes LOR‡	Reverses Rigidity
GABAergic					
baclofen	2.5			−	−
	5.0			+	+
kojic amine	5.0			+	+
progabide	5.0			−	−
	5.0		(15)	−	−
	150.0	IP	(15)	−	−
bicuculline	1.0			−	−
	2.0			−	−
gamma acetylenic GABA	20.0		(15) (30) (60)	−	−
Serotonergic					
l-tryptophan	30.0			−	−
5-hydroxytryptophan	100.0		(15)	−	−
+ Carbidopa	150.0		(15)	−	−
p-chlorophenylalanine	300.0	IP	(4320)	−	−
methysergide	2.0			−	−
Purinergic					
adenosine	25.0			−	−
	50.0			+	−
theophylline	50.0			−	−
dibutyryl cAMP	100.0			−	−
Miscellaneous					
H_2O				−	−
		ICV		−	−
sodium nitroprusside	1.0			−	−

Footnotes as in Table 1.

RESULTS

The compounds tested are classified in Tables 1–5 according to their use or the neurochemical systems involved. In some cases the classification may be arbitrary (i.e.,

TABLE 4

EFFECTS OF CHOLINERGICS AND HISTAMINERGICS ON FENTANYL-INDUCED MUSCULAR RIGIDITY

Drug*	Dose (mg/kg)	Route (PT time)†	Causes LOR‡	Reverses Rigidity
Cholinergic				
scopolamine methyl bromide	10.0		−	−
	15.0		+	+
oxotremorine	0.01		−	−
succinylcholine	0.2		−	+
pancuronium	0.1		+	+
physostigmine	0.05		−	+
	0.1		−	+
neostigmine	0.025		−	+
hemicholinium	0.25	(15)	−	+
hexamethonium	10.0		−	−
	25.0		−	+
Histaminergic				
histamine	50.0		−	+
	100.0	IP	−	+
imidazole	50.0		−	+
diphenhydramine	5.0		−	−
cimetidine	50.0		−	−
metiamide	12.0		−	−
histamine + diphenhydramine	50.0 + 5.0		−	+
histamine + diphenhydramine	100.0 + 10.0	IP IP	−	+
histamine + cimetidine	50.0 + 50.0		−	+
histamine + cimetidine	100.0 + 100.0	IP IP	−	+
histamine + diphenhydramine + cimetidine	50.0 + 2.5 + 25.0		−	+
histamine + piperoxane	50.0 + 0.5		−	+
imidazole + piperoxane	50.0 + 0.5		−	+
dimaprit	75.0		−	+
dimaprit + diphenhydramine	75.0 + 5.0		−	+
dimaprit + cimetine	75.0 + 50.0		−	+
dimaprit + metiamide	75.0 + 12.0		−	+

Footnotes as in Table 1.

TABLE 5

EFFECTS OF DOPAMINERGICS AND ADRENERGICS ON FENTANYL-INDUCED MUSCULAR RIGIDITY

Drug*	Dose (mg/kg)	Route (PT time)†		Causes LOR‡	Reverses Rigidity
Dopaminergic					
apomorphine	0.1			−	−
	5.0			−	−
	0.035	IP	(5)	−	−
	5.0	IP	(5)	−	−
	10.0	IP	(15)	−	−
L-DOPA + Carbidopa	150.0	IP	(30)		
	150.0	IP	(60)	−	−
d-amphetamine	1.0			−	−
	0.1		−	−	
haloperidol	0.5			−	+
	0.05	IP	(60)	−	+
	1.0	IP	(60)	−	−
	5.0	IP	(40)	−	−
haloperidol + piperoxane	0.05	IP	(60)		
	0.1			−	−
chlorpromazine	0.25			−	+
	5.0			+	+
	5.0	IP	(40)	−	+
chlorpromazine + piperoxane	0.25				
	0.25			−	−
l-sulpiride	25.0			−	−
	12.5	IP	(90)	−	−
	100.0	IP	(90)	−	−
Adrenergic					
clonidine	0.035			−	+
	0.175	IP		−	+
	0.0001	ICV		−	+
alpha methyl DOPA	0.05			−	+
	0.0004	ICV		−	+
guanfacine	0.05			−	+
guanethidine	5.0			−	+
alpha methyl p-tyrosine	150.0	IP	(120)	−	+
yohimbine	0.075			−	−
	1.0			−	−
piperoxane	0.1			−	−
idazoxan	0.035			−	−
phenylephrine	0.25			−	−
prazosin	0.1			−	−
	0.5			−	+
phentolamine	0.1			−	−
	10.0			−	−
isoproterenol	0.1			−	−
	20.0			−	−
propranolol	2.0			−	−
clonidine + piperoxane	0.035				
	0.1			−	−
clonidine + piperoxane	0.0001	ICV			
	0.0002	ICV		−	−
clonidine + idazoxan	0.035				
	0.035			−	−

Footnotes as in Table 1.

diazepam could be classified as sedative-hypnotic, anxiolytic, or GABAergic) but, nevertheless, convenient for descriptive purposes.

It can be seen from Table 1 that naloxone and the partial opioid antagonists (pentazocine, buprenorphine) did not cause LOR (in fact they were the only compounds that reversed LOR), yet they reversed rigidity. However, the peripheral antagonist naltrexone methyl bromide was without effect.

As a general rule, compounds at doses which caused LOR by themselves also reversed rigidity (see Table 2). This was true for volatile general anesthetics (i.e., isoflurane, diethyl ether) as well as barbiturates (i.e., thiopental, pentobarbital) and other drugs with sedative-hypnotic activity (i.e., chloral hydrate, diazepam, ketamine). However, spinally acting bupivacaine also reversed rigidity. Others not typically classified as sedative-hypnotics (i.e., baclofen, kojic amine, in Table 3) also reversed rigidity but only at doses which caused LOR. None of the serotonergic drugs induced LOR and they, too, were without effect in reversing rigidity. One anomaly was adenosine which caused LOR without reversing fentanyl-induced rigidity.

All compounds that could influence nicotinic activity reversed rigidity without inducing LOR (see Table 4). However, the muscarinic agonist, oxotremorine, was without effect, and the peripheral antagonist, scopolamine methyl bromide, reversed rigidity only at a dose that caused LOR. Histamine and its agonists (e.g., dimaprit) also reversed rigidity without causing LOR, but rigidity was not restored by either H1 (diphenhydramine) or H2 (cimetidine, metiamide) antagonists alone or in combination, or by piperoxane.

Dopamine agonists (apomorphine, amphetamine, L-DOPA) did not reverse rigidity, but the antagonists were effective (see Table 5). Haloperidol, however, reversed rigidity as long as the animals were tested immediately after an IV dose or an hour following pretreatment with a smaller IP dose. Chlorpromazine, on the other hand, was effective regardless of dose. Moreover, rigidity reversed by chlorpromazine or haloperidol could be restored by piperoxane, an alpha-2 antagonist. However the D2 antagonist, sulpiride, did not reverse rigidity regardless of dose or duration of pretreatment.

Decreasing adrenergic activity with guanethidine or alpha methyl p-tyrosine reversed rigidity, but beta (isoproterenol) or alpha-1 (phenylephrine) adrenergic agonists were ineffective. On the other hand, all alpha-2 agonists (clonidine, alpha methyl DOPA, guanfacine) were effective, generally, at lower doses than other compounds tested, and rigidity was restored by the alpha-2 antagonists (idazoxan, piperoxane). Rigidity was not reversed by the alpha (phentolamine) or beta (propranolol) antagonists, but prazosin, an alpha-1 antagonist, was effective.

DISCUSSION

The objective of the present study was to use a variety of compounds from different pharmacological classes to obtain a "yes-no" answer and not to assess quantitatively the reversal of opioid-induced rigidity. From the data presented it is clear that all compounds which caused LOR, with the exception of adenosine, also reversed rigidity induced by fentanyl. Moreover, the reversal was not limited to a specific pharmacological class because volatile anesthetics, sedative-hypnotics with different modes of action, GABAergic drugs, and an antimuscarinic were all effective. Serotonergic compounds, on the other hand, did not reverse rigidity but, then again, they did not cause LOR either. It is possible that each of these compounds reversed rigidity by its own unique mechanism, but since increasing doses of central nervous system (CNS) depressants usually result in LOR, general CNS depression appears to be a more parsimonious explanation.

The present evidence also indicates that the rigidity induced by fentanyl is centrally mediated because it was reversed by naloxone and partial opioid antagonists but not by the peripherally acting antagonist, naltrexone methyl bromide. In contrast, the effects of the cholinergic agents on fentanyl-induced rigidity appear to be peripheral and *not* central. Nicotinic, but not muscarinic drugs, were effective in reversing rigidity at sub-LOR doses perhaps by direct neuromuscular or ganglionic blockade since succinylcholine, pancuronium, or hexamethonium do not penetrate the CNS. Impaired neuromuscular or ganglionic transmission may also account for the reversal observed with physostigmine and hemicholinium because this same effect was produced with neostigmine, a quaternary anticholinesterase, or scopolamine methyl bromide, a quaternary antimuscarinic, which do not cross the blood brain barrier. On the other hand, the reversal obtained with IT bupivacaine was probably due to nonspecific inhibition of descending activity at the spinal level.

Similar to the cholinergic drugs, the reversal of rigidity observed with histamine and its agonists did not appear to be centrally mediated either, since these agents do not enter the CNS. Furthermore the histamine receptor, per se, did not seem to be involved because imidazole itself reversed rigidity and neither H1 or H2 antagonists alone or in combination with each other could restore the rigidity reversed by the agonists. Perhaps in the rat, as reported for the frog endplate [3], histamine acts as an antagonist to modulate nicotinic cholinergic transmission.

Direct and indirect acting dopamine agonists (i.e., apomorphine, d-amphetamine, L-DOPA) could not reverse rigidity, and since only those dopamine antagonists with alpha-adrenergic properties were effective, i.e., chlorpromazine and haloperidol, but not sulpiride, an adrenergic mechanism was suspected. Moreover, rigidity reversed by dopamine antagonists could be restored by piperoxane, an alpha-2 antagonist. The selective involvement of an alpha-2 mechanism was further indicated because unlike the opioid antagonists that reversed both muscular rigidity and LOR, clonidine and other alpha-2 agonists reversed only the rigidity at doses several orders of magnitude lower than other compounds tested; again, rigidity was restored by alpha-2 antagonists. It was also apparent that the reversal was not merely due to a nonspecific hypotensive effect because sodium nitroprusside, at a dose that lowers blood pressure in rats, did not reverse rigidity. Moreover, since the nonspecific alpha-antagonist, phentolamine, was not effective, the reversal observed with prazosin might be due to a relative predominance of central alpha-2 activity caused by this specific alpha-1 antagonist.

In contrast to the data of Wand [31] and Havemann and Kuschinsky [17], these results indicate that dopamine, per se, is not of prime importance and that opioid-induced muscular rigidity could be reversed rather selectively by alpha-2 agonists. Even though the behavior could be reversed by neuroleptics, it was restored by alpha-2 antagonists. Morover, whereas lower doses of haloperidol were effective in reversing rigidity, higher cataleptic doses were not. Rackham [24] also noted that haloperidol at doses two-fold greater than chlorpromazine were ineffective in reversing morphine-induced rigidity in rats and concluded, therefore,

that a dopaminergic mechanism was not involved. Perhaps the effects of the neuroleptics were actually a result of their peripheral alpha-blocking properties which, in the case of haloperidol, was masked by complete dopaminergic blockade at higher doses. In contrast, chlorpromazine, which has greater adrenolytic activity to dopaminergic blockade compared to haloperidol [1,20], was effective regardless of dose.

In general, compounds at doses that reversed rigidity seemed to have a common feature—they all tended to decrease sympathetic tone. In particular, clonidine has been reported to decrease stimulation-induced release of norepinephrine from central [27] and peripheral [26] adrenergic neurons, reduce norepinephrine turnover in brain and spinal cord [2], and inhibit the spontaneous firing of noradrenergic neurons of the locus coeruleus [7] leading to a profound decrease of sympathetic outflow [12, 21, 25]. On the other hand, opioids have been shown to increase norepinephrine turnover, indicated by elevated cerebral 3-methoxy-4-hydroxyphenylethylene glycol concentrations [22], and cause sympathoadrenal stimulation as evidenced by significant elevations of plasma catecholamines [9]. Therefore it is proposed that pharmacological reversal of opioid-induced rigidity is accomplished by a reduction of sympathetic tone which is selectively effected by alpha-2 agonists.

ACKNOWLEDGEMENTS

Special thanks to Linda J. Suarez for her expert technical assistance with intrathecal drug administration and to Dr. T. C. Spaulding and Alison Tannenbaum for their helpful comments in preparation of the manuscript.

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